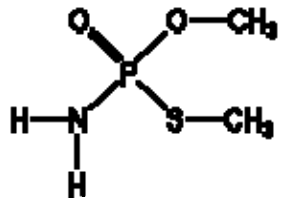
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

METHAMIDOPHOS

(CAS Reg. No. 10265-92-6)



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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels – AEGL-1, AEGL-2 and AEGL-3 – are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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SUMMARY

Technical methamidophos (CAS No. 10265-92-6) is a colorless to white crystalline solid organophosphate pesticide with a strong mercaptan-like odor. The solid material has a low vapor pressure and is readily soluble in water. Commercially, methamidophos is available as an aqueous liquid or emulsifiable concentrate. It is applied as a spray or by sprinkler irrigation to a variety of food crops.

Organophosphate pesticides such as methamidophos are neurotoxic in that they are inhibitors of cholinesterase enzymes. Inhibition of acetylcholinesterase, responsible for termination of the biological activity of the neurotransmitter acetylcholine at various nerve endings, results in sustained stimulation of electrical activity. Depending on concentrations administered, cholinergic signs following acute exposure of rats to methamidophos may include salivation, lacrimation, decreased activity, muscle fasciculation, ataxia, gasping, and tremors. In humans, inhibition of erythrocyte acetylcholinesterase activity, the form found in human erythrocytes, is used as a biomarker of exposure and effects of organophosphate pesticides. No inhalation studies involving human subjects were located.

No human inhalation data relevant to derivation of AEGL values were found. Acute inhalation toxicity studies with rats were available from two different laboratories. Both studies administered the test compound as liquid aerosols. Results of 4-hour inhalation LC_{50} values differed by a factor of approximately 3 between the two laboratories. In both studies, nominal concentrations were a poor indicator of analytical concentrations, indicating the difficulty in maintaining aerosols at these concentrations. A 6-hour inhalation study addressed non-lethal effects.

The study of Pauluhn (1986) was used for derivation of AEGL values. This study showed an adequate concentration-response curve, and cholinesterase activity was measured in plasma and erythrocytes. No clinical signs were observed following exposure of rats to 11.4 or 24.3 mg/m^3 for 4 hours or following exposure to 1.4 or 5.4 mg/m^3 for 6 hours. Clinical signs were observed at the next higher concentrations, 45.0 mg/m^3 for 4 hours and 33.1 mg/m^3 for 6 hours. At 11.4 mg/m^3, plasma cholinesterase activity was inhibited by approximately 50%, but erythrocyte acetylcholinesterase activity was unaffected. At 24.3 and 45.0 mg/m^3, plasma cholinesterase activity was 36 and 13% of the control value, respectively, and erythrocyte cholinesterase activity was 92 and 70% of the control value, respectively.

The exposure of rats to 24.3 mg/m^3 for 4-hours (Pauluhn 1986) was chosen as the point of departure for the AEGL-1. At this concentration, plasma and erythrocyte cholinesterase activity were depressed by 64 and 8%, respectively. Although there were no clinical signs at this concentration and the lower concentration of 11.4 mg/m^3, exposure to the next higher concentration of 45.0 mg/m^3 resulted in clinical signs consistent with the definition of the AEGL-2. Because of the apparent difficulty in maintaining liquid aerosols at these concentrations and the disparate data between the two available studies, the 24.3 mg/m^3 value was divided by a data base modifying factor of 2. Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies (Moser 1999; Garofalo et al. 1973). Therefore, an interspecies uncertainty factor of 3 was applied. Infants and juveniles may

be more sensitive to organophosphate pesticides than adults, but 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 (2006a) identified juveniles as being twice as sensitive as adults. Because there were no differences in sensitivity between adult and juvenile rats in the acute oral dosing study, and in keeping with intraspecies uncertainty factors derived for other organophosphate pesticides that did not show differences in sensitivity between adult and juvenile rats, an intraspecies uncertainty factor of 3 was considered adequate. The total uncertainty factor is 10. The 4-hour 24.3 mg/m^3 value was divided by a total modifying/uncertainty factor of 20 (2x10). In the absence of reliable time-scaling information, the resulting 4-hour value of 1.2 mg/m^3 was time-scaled ($C^n \times t = k$) using n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Because of uncertainty in scaling from 4 hours to 10 minutes, the 10-minute value 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. Mortality of 30% occurred at the next higher exposure of 195.5 mg/m^3. Because of the apparent difficulty in maintaining liquid aerosols at these concentrations and the disparity in data between the two available studies, the 45.0 mg/m^3 value was divided by a data base modifying factor of 2. Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies (Moser 1999; Garofalo et al. 1973). Therefore, an interspecies uncertainty factor of 3 was applied. 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 age-related differences in sensitivity to methamidophos (Moser 1999). Based on repeat-dose oral studies with adult and juvenile rats, the U.S. EPA (2006a) identified an uncertainty factor of 2 to protect the sensitive population of children. Because there were no differences in sensitivity between adult and juvenile rats in the acute oral dosing study, and in keeping with intraspecies uncertainty factors derived for other organophosphate pesticides that did not show differences in sensitivity between adult and juvenile rats, an intraspecies uncertainty factor of 3 was considered adequate. The total uncertainty factor is 10. The 4-hour 45.0 mg/m^3 value was divided by a total modifying/uncertainty factor of 20 (2x10). In the absence of reliable time-scaling information, the resulting 4-hour value of 2.3 mg/m^3 was time-scaled ($C^n \times t = k$) using n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Because of uncertainty in scaling from 4 hours to 10 minutes, the 10-minute value was set equal to the 30-minute value.

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 (see Appendix C for program output). 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. Because of the apparent difficulty in maintaining liquid aerosols at these concentrations and the disparity in data between the two available studies, the 101.54 mg/m^3 value was divided by a data base modifying factor of 2. Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies (Moser 1999; Garofalo et al. 1973). Therefore, an interspecies uncertainty factor of 3 was applied. 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 age-related differences in sensitivity to methamidophos (Moser 1999). Based on repeat-dose oral studies with adult and juvenile rats, the U.S. EPA (2006a) identified an uncertainty factor of 2 to protect children. Because there were no differences in sensitivity between adult and juvenile rats in the acute oral dosing study, and in keeping with intraspecies uncertainty factors derived for other organophosphate pesticides that did not show differences in sensitivity between adult and juvenile rats, an intraspecies uncertainty factor of 3 was considered adequate. The total uncertainty factor is 10. The 4-hour 101.54 mg/m^3 value was divided by a total modifying/uncertainty factor of 20 (2x10). In the absence of reliable time-scaling information, the resulting 4-hour value of 5.01 mg/m^3 was time-scaled ($C^n \times t = k$) using n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Because of uncertainty in scaling from 4 hours to 10 minutes, the 10-minute value was set equal to the 30-minute value.

The calculated values are supported by tested concentrations in a subchronic study with rats (Pauluhn and Cole 1988). No treatment related effects were observed in rats inhaling 1.1 mg/m^3 for 13 weeks. At 5.4 mg/m^3, erythrocyte and brain cholinesterase activities were inhibited by <30% throughout the treatment period. Rats inhaling 23.1 mg/m^3 showed clinical signs consistent with cholinesterase activity inhibition, but no deaths were reported. At study termination, brain acetylcholinesterase activity was inhibited by 45-47%.

The calculated values are listed in the table below.

TABLE ES 1. 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 BMC_{01} – rat (Pauluhn 1986)

*At the AEGL-1 point of departure, 24.3 mg/m^3 for 4 hours, plasma cholinesterase activity was 36% of the control value and erythrocyte acetylcholinesterase activity was 92% of the control value. At the AEGL-2 point of departure, 45.0 mg/m^3 for 4 hours, plasma cholinesterase activity was 13% of the control value and erythrocyte acetylcholinesterase activity was 70% of the control value.

1. INTRODUCTION

Technical methamidophos (CAS No. 10265-92-6) is a colorless to white crystalline solid organophosphate pesticide with a strong mercaptan-like odor (U.S. EPA 2006b). The presence of both an amine group and a sulfur atom single-bonded to phosphorus place it in the class

phosphoramidothioates. The solid material has a low vapor pressure and is readily soluble in water. Additional chemical and physical properties are listed in Table 1.

In 1972, methamidophos was registered in the United States under the trade name Monitor®. The application of methamidophos as an insecticide/acaricide is restricted to the food crops cotton, potatoes, and tomatoes and on the non-food crop alfalfa, grown for seed. Registered formulations include the technical grade liquid containing 60-72% a.i. (active ingredient) and an emulsifiable concentrate containing 40% a.i. Methamidophos is applied as a spray or by sprinkler irrigation (U.S. EPA 2006b).

Methamidophos is manufactured commercially by the reaction of sodium methyl phosphoroamidothioate and dimethyl sulfate or by the isomerization of O,O-dimethylthiophosphamidate (HSDB 2004). According to U.S. EPA (2006b), approximately 640,000 pounds of a.i. are used annually in the United States. Most usage is on potatoes. World production figures were not available.

Methamidophos is an environmental degradate of the organophosphate pesticide acephate ($C_4H_{10}NO_3PS$) and may be a metabolite of acephate following oral dosing of rats (Singh 1985; IPCS 2002). Acephate is the N-acetyl derivative of methamidophos.

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	O,S-Dimethyl phosphoramidothioate, Bayer 71628, Ortho 9006, Monitor, Tamaron	O'Neil et al. 2001a
Chemical formula	$C_2H_8NO_2PS$	O'Neil et al. 2001a
Molecular weight	141.1	U.S. EPA 2006b
CAS Reg. No.	10265-92-6	O'Neil et al. 2001a
Physical state	white crystalline solid thick clear liquid (75% technical solution)	U.S. EPA 2006b Sangha 1983
Solubility in water	2 kg/L	IPCS 1993
Vapor pressure	1.7×10^{-5} mm Hg 3×10^{-4} mm Hg at 30ºC	U.S. EPA 2006b O'Neil et al. 2001a
Vapor density, saturated (air =1)	1.7 mg/m^3 at 30ºC	Pauluhn 1986
Liquid density (water =1)	1.3 at 44.5ºC	O'Neil et al. 2001a
Melting point	44.5ºC (pure); 37-39 ºC (technical)	IPCS 1993
Boiling point	thermally unstable	IPCS 1993
Flammability limits in air	Not available	
Conversion factors	1 ppm = 5.77 mg/m^3 1 mg/m^3 = 0.17 ppm	Calculated

2. HUMAN TOXICITY DATA

No inhalation studies other than reports of accidental exposures were located. These reports lacked information on concentration and exposure duration. Symptoms of cholinesterase activity inhibition have been observed following ingestion of food containing methamidophos residue (HSDB 2004). Methamidophos has been implicated in causing organophosphate-

induced delayed neurotoxicity in humans; however, these incidents involved accidental or suicidal exposure to excessively high levels (Costa 2008).

In a clinical study, seven male and seven female volunteers, ages 21-48 years, were administered combinations of methamidophos (Monitor) and acephate (Orthene) at doses of 0.1, 0.2, 0.3, or 0.4 mg/kg/day in a gelatin capsule containing corn oil (Garofalo et al. 1973; reviewed in U.S. EPA 1988; 2000a).[1] A group of three males and three females received methamidophos/acephate in a 1:9 ratio (equivalent to 0.01, 0.02, 0.03, or 0.04 mg/kg/day methamidophos). A second group of two males and two females was given 0.1 or 0.2 mg/kg/day of a 1:4 mixture (equivalent to 0.02 or 0.04 mg/kg/day methamidophos). The controls (two males and two females) received gelatin capsules containing corn oil. Volunteers were blind to the dose administered. The daily dose was administered in three equally divided doses. Dosing was continued over a 37-73 day period (maximum administration of 21 days) until plasma cholinesterase activity inhibition reached two standard deviations below mean pretest activity for two successive cholinesterase assays. These mixtures had no effect on erythrocyte cholinesterase activity, hematology, blood chemistry, blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor, or finger tremor. After 16 days, plasma cholinesterase activity was significantly inhibited in all subjects in the 1:4 ratio group that received 0.2 mg/kg/day of the mixture. Significant plasma cholinesterase activity inhibition occurred after 21 days of dosing only in males in the group receiving the 1:9 ratio at 0.3 mg/kg/day. In the group that received 0.4 mg/kg/day (1:9 ratio), two of three females showed significant plasma cholinesterase activity inhibition after 10 days of dosing. Plasma cholinesterase activity returned to pretest values during a 7-day recovery period. Pre-test erythrocyte acetylcholinesterase activity values were similar in male and female volunteers. Pre-test plasma cholinesterase activity in females was approximately one-half of that in males.

The U.S. EPA relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide. The human oral dosing studies, contained in the Pesticide Handlers Exposure Database, "have been reviewed by the Agency and found on the basis of available evidence to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted" (U.S. EPA 2008).

3. ANIMAL TOXICITY DATA

Using standard protocols, methamidophos was tested for acute oral and dermal toxicity and skin irritation and sensitization (U.S. EPA 2006b). The acute oral LD_{50} was 15.6 mg/kg in male rats and 13.0 mg/kg in female rats. The acute dermal toxicity in rabbits was 118 mg/kg. Instillation into the eye resulted in corneal opacity and death of one of six rabbits (dose not reported). Methamidophos was moderately irritating to the eyes and mildly irritating to the skin of rabbits. Methamidophos was not a skin sensitizer in guinea pigs.

3.1. Acute Toxicity

All acute studies were conducted with rats. These studies are summarized in Table 2.

[1] The oral LC_{50} values in male and female rats for acephate and methamidophos are 700 mg/kg (O'Neil et al. 2001b) and 14 mg/kg (U.S. EPA 2006b), respectively.

Groups of ten male and ten female young-adult Sprague-Dawley rats inhaled an aerosol of technical methamidophos (purity 75.1%), head-only, for 1 hour (Sangha 1983). Liquid aerosol atmospheres were generated by pumping the test material through a fine nozzle and then mixing the spray with compressed, filtered and dried air. The compressed air finely atomized the test material. A constant air flow was maintained through the exposure chamber. Particles, collected on a cascade impactor averaged 1.1-2.1 μ; 90% of particles were <5 μ. Atmospheres were measured by collecting samples on filters and analyzing by gas chromatography. Cascade impactor sample values correlated better with nominal concentrations than filter samples and therefore were the basis for concentration measurements. Male rats were exposed to analytical concentrations of 160, 163, 253, or 319 mg/m^3 and female rats were exposed to analytical concentrations of 60, 160, 168, 196, 259, or 319 mg/m^3. Nominal concentrations which ranged from 550-1390 mg/m^3 did not correlate with analytical concentrations. Control groups were run with most exposures and were exposed to room air. During exposure and for up to 5 days post-exposure, all methamidophos-exposed rats showed cholinergic signs including salivation, lacrimation, decreased activity, muscle fasciculation, ataxia, gasping, tremors, tearing, and rhinorrhea. Deaths occurred either during exposure or within 5 days post-exposure. For male rats that inhaled 160, 163, 253, or 319 mg/m^3, mortality was 3/10, 1/10, 5/10, and 8/10, respectively. For female rats that inhaled 60, 160, 168, 196, 259, or 319 mg/m^3, mortality was 1/10, 7/10, 5/10, 5/10, and 9/10, respectively. The author calculated 1-hour LC_{50} values of 377 mg/m^3 (95% confidence limits of 301 to 502 mg/m^3) for male rats and 241 mg/m^3 (95% confidence limits of 205 to 280 mg/m^3) for female rats. From post-exposure days 2-7, mean body weights for both sexes were reduced compared to controls. Congested nasal passages, congested lungs, and congested cervical lymph nodes were observed in many of the rats that died.

TABLE 2. Acute Toxicity of Methamidophos Liquid Aerosol to Rats

Concentration (mg/m^3)	Exposure Duration	Effect/LC_{50} (mg/m^3)	Reference
	1 hour	Clinical signs, all exposures;	Sangha 1983
60		Mortality: 1/10 females[a]	
160		Mortality: 3/10 males; 7/10 females	
163		Mortality: 1/10 males	
168		Mortality: 0/10 females	
196		Mortality: 5/10 females	
253		Mortality: 8/10 males	
259		Mortality: 5/10 males; 5/10 females	
319		Mortality: 9/10 females	
		Calculated LC_{50} (males): 377 mg/m^3	
		Calculated LC_{50} (females): 241 mg/m^3	
	4 hours	Cholinergic signs at all concentrations	Sangha 1984
19		Mortality: no mortality (0/20)	
33		Mortality: 1/10 males; 0/10 females	
56		Mortality: 5/10 males; 4/10 females	
57		Mortality: 3/10 males; 4/10 females	
63		Mortality: 6/10 females	
83		Mortality: 8/10 males; 5/10 females	
173		Mortality: 10/10 females	
		Calculated LC_{50} (males): 63.2 mg/m^3	
		Calculated LC_{50} (females): 76.5 mg/m^3	

11.4 24.3 45.0 195.5 241.7 350.3	4 hours	No clinical signs, no mortality No clinical signs, no mortality Tremor, reduced motility, no mortality Tremor, additional clinical signs; mortality: 1/5 males, 2/5 females Tremor, additional clinical signs; mortality: 3/5 males, 5/5 females Tremor, additional clinical signs; mortality: 5/5 males, 4/5 females Calculated LC_{50}: 213 mg/m^3	Pauluhn 1986
1.4 5.4 33.1	6 hours, 5 days[b]	No clinical signs No clinical signs Slight tremor following exposure	Pauluhn 1986

[a] At some concentrations, only one sex was tested.

[b] Clinical signs were recorded after one 6-hour exposure.

Groups of ten male and ten female young adult Sprague Dawley rats inhaled a liquid aerosol of technical methamidophos (a.i. 70.5%), head only for four hours (Sangha 1984). The protocol and generation and measurement of the test atmospheres followed the same methods as in the 1-hour study described above. Particles, collected on a cascade impactor ranged from 0.13-1.0 µ and averaged 0.53 µ. Male and female rats inhaled analytical concentrations of 19, 33, 56, 57, or 83 mg/m^3. Additional groups of females were exposed to 63 or 173 mg/m^3. Mortalities occurred within five days postexposure. All rats exhibited clinical signs including salivation, lacrimation, muscle fasciculations, tremors, decreased activity, pilo erection, and hypothermia. Ocular and nasal irritation were observed on occasion. Body weight was decreased in some groups up to day 14. Mortality in male rats inhaling 19, 33, 56, 57, or 83 mg/m^3 was 0/10, 1/10, 5/10, 3/10, and 8/10, respectively. Mortality in female rats inhaling 19, 33, 56, 57, 63, 83, or 173 mg/m^3 was 0/10, 0/10, 4/10, 4/10, 6/10, 5/10, and 10/10, respectively. The 4-hour LC_{50} for male rats was 63.2 mg/m^3 (52-79 mg/m^3), and the 4-hour LC_{50} for female rats was 76.5 mg/m^3 (62-128 mg/m^3).

In a range-finding study, groups of 10 male and 10 female young-adult Wistar rats inhaled a liquid aerosol of technical methamidophos (75.7%), head-only, for 6 hours/day, for 5 days (Pauluhn 1986). The test material was vaporized in a polyethylene glycol E 400-ethanol mixture as vehicle. Measured concentrations were 0 (vehicle control), 1.4, 5.4, and 33.1 mg/m^3 Measured concentrations, determined by capillary gas chromatography/flame ionization, were a factor of 5 less than nominal concentrations (measured concentrations refer to the 75.7% a.i.). Measured concentrations were taken in the area of the rats' inhalation air. The low analytical concentrations were attributed to precipitation of larger particles in the baffle chamber. Particle size averaged 1.5 µ; 98% were inhalable. Air exposed and water aerosol control groups were non-concurrent. Clinical signs were recorded after each exposure. No clinical signs were observed in the groups at 1.4 or 5.4 mg/m^3 after any exposure. Both sexes of rats in the 33.1 mg/m^3 group showed slight tremors after the first and second exposures; with subsequent exposures, the rats appeared un-groomed and showed reduced motility and weakness of the rear extremities. These signs were reversible during a 14-day post-exposure observation period. No deaths were recorded. Blood samples taken from male rats for cholinesterase activity inhibition were taken within 10-20 minutes post-exposure and analyzed within one hour post-exposure; measurement of activity was by a modified Ellman method. Erythrocyte, plasma, and brain cholinesterase activity were unaffected at the lower two concentrations, after both one and five

exposures (Table 3). Relative to control values, erythrocyte and plasma cholinesterase activity were inhibited by 21 and 82% after one exposure to 33.1 mg/m^3 and by 19 and 84% after five exposures. These values indicate no progressive increase in cholinesterase activity inhibition with repeat exposure. In the group that inhaled 33.1 mg/m^3, brain cholinesterase activity, measured only after the fifth exposure, was reduced by 67% relative to the control value.

Following the range-finding study described above, Pauluhn (1986) exposed groups of five male and five female young-adult Wistar rats, head-only, to measured liquid aerosol at methamidophos concentrations of 11.4, 24.3, 45.0, 195.5, 241.7, or 350.3 mg/m^3 for 4 hours. The protocol was the same as described for the range-finding study above. There were no clinical signs observed in the vehicle control or groups exposed to 11.4 or 24.3 mg/m^3. Moderate tremor, staggering and high gait, reduced motility, bristling, and un-groomed coats were observed in rats exposed to 45.0 mg/m^3. These clinical signs were more marked in the groups that inhaled 195.5, 241.7, or 350.3 mg/m^3; additional signs in the groups exposed to 350.3 mg/m^3 included exophthalmos, reddened and bloody eyelids, corneal opacity, and dyspnea. No rats died in the lower three exposure groups. Mortality was 30% (1 male, two females), 80% (3 males and five females), and 90% in the groups exposed to 195.5, 241.7, and 350.3 mg/m^3, respectively (Table 2). The calculated LC_{50} for the sexes combined was 213 (174.6-260.7) mg/m^3. Rats that died during exposure showed reddened noses, lung edema, pale organs, and hemorrhagic areas in the gastrointestinal tract. Rats that were sacrificed following the 14-day observation period showed no apparent organ effects. Pulmonary function tests showed lung resistance increased in a concentration-related manner, but only following acetylcholine challenge. The effect of methamidophos on pulmonary function of rats exposed to 24 mg/m^3 is more fully discussed in Pauluhn et al. (1987). Blood was sampled for cholinesterase activity approximately one hour after exposure. Plasma cholinesterase was inhibited by approximately 50% at 11.4 mg/m^3, but erythrocyte acetylcholinesterase activity was unaffected in this group (102% of pre-exposure value) (Table 3). Erythrocyte acetylcholinesterase activity was inhibited by 9% and 30% relative to pre-exposure values in the 24.3 and 45.0 mg/m^3 groups, respectively. Groups exposed to higher concentrations were not tested.

TABLE 3. Plasma, Erythrocyte, and Brain Cholinesterase Activity in Rats Following Acute and Repeat Exposure (percent of control value)

Concentration (mg/m^3)	Plasma	Erythrocyte	Brain[a]
Six hour, 5-day repeat exposure			
0	86[b]	96	–
1.4	114, 113[c]	109, 109	118
5.4	95, 87	99, 101	103
33.1	18, 16	79, 81	33
Four-hour exposure			
0	84	119	–
6.4	85	116	–
11.4	53	102	–
24.3	36	92	–
45.0	13	70	–

Source: Pauluhn 1986 (data taken from pp. 45 and 79-80).

[a] Brain cholinesterase values are activity inhibition relative to the control group on day 5.

[b] Control values for plasma and erythrocyte cholinesterase activity are before and after sham exposure.

[c] Values for plasma and erythrocyte cholinesterase activity are after one and five exposures.

n = 5-10 rats.

In an unpublished study, rats inhaled the vapors of Monitor (95% technical) which was heated to 140ºC to enhance vaporization (U.S. EPA 1976). The exposure duration was four hours. No deaths occurred although plasma and erythrocyte cholinesterase activity was depressed by 20-30%. No further details were reported.

3.2. Repeat-Exposure Studies

The five-day repeat inhalation toxicity study conducted by Pauluhn (1986) is discussed in the previous section. In a subchronic inhalation toxicity study, groups of 10 Wistar rats/sex/concentration inhaled an aerosol of methamidophos, 73.4%, for three months (head/nose only) (Pauluhn and Cole 1988). Exposures were for 6 hours/day, 5 days/week. Methamidophos was aerosolized in polyethylene glycol E 400:ethanol (1:1). The mean analytical concentrations in the exposure chambers were 0, 1.1, 5.4, and 23.1 mg/m^3. These concentrations are similar to those used in the five-day repeat-exposure study. The mean mass aerodynamic diameters of the methamidophos particles in the groups were 1.52±0.13, 1.26±0.04, and 1.53±0.09 µ, respectively. Treatment-related effects were not observed in the low-concentration group. Relative to the vehicle control values, cholinesterase activities in erythrocytes and plasma were inhibited by 7-28% and 38-63%, respectively, throughout the treatment period in the mid-concentration group. At the end of the study, brain cholinesterase activity was inhibited by 25-29% in the mid-concentration group. There was no substantive difference in the magnitude of the response on plasma or erythrocyte cholinesterase inhibition from week 1-13. The following effects were observed in males and females in the 23.1 mg/m^3 concentration group: slight to moderate muscle tremors, aggressive behavior, decreased food consumption (5-28%) accompanied by decreased body weight gain (53%), increased plasma lactate dehydrogenase and glutamate oxaloacetate transaminase activities (males only), small decreases in some clinical chemistry values, decreased absolute and relative spleen weight, and inhibition of cholinesterase activities in erythrocytes (15-44%) plasma (53-93%) throughout the treatment period, and brain (45-47%) at study termination. There was no substantive difference in the magnitude of the response on plasma or erythrocyte cholinesterase activity inhibition from weeks 1-13. When treatment was discontinued, cholinesterase activities in erythrocyte and plasma returned to pretreatment values (brain was not determined).

3.3. Neurotoxicity

Acute toxicity studies showed that methamidophos is neurotoxic. Signs of acetylcholinesterase activity inhibition were observed in rats inhaling methamidophos for 1 to 6 hours (Sangha 1983; 1984; Pauluhn 1986). Cholinergic signs were also observed in oral studies of developmental and reproductive toxicity. See Section 4.2 for mechanism of toxicity of organophosphate pesticides. Doses below the LD_{50} failed to instill delayed polyneuropathy in hens (IPCS 2002).

3.4. Developmental/Reproductive Toxicity

No inhalation studies were conducted that addressed the developmental or reproductive toxicity of methamidophos. Reproductive and developmental toxicity studies that used the oral route of administration were reviewed by IPCS (2002) and HSDB (2004). These studies are

briefly reviewed here to show that methamidophos is not a teratogen. In a two-generation reproductive toxicity study, male and female CD rats received diets containing technical methamidophos (70.5% purity) at a concentration of 0, 3, 10, or 33 ppm (equivalent to 0, 0.15, 0.5, or 1.6 mg/kg body weight per day) for at least 100 days before mating. Females were treated throughout gestation and lactation. Methamidophos at 33 ppm increased the incidence of clinical signs in both parental rats and pups, generally reduced body weight of parental rats, reduced litter and pup weights, decreased the viability of pups, and reduced the proportion of fertilized females giving birth to second generation pups. The NOAEL was 0.5 mg/kg/day. Similar effects were found in a second two-generation study of reproductive toxicity with CD rats. The NOAEL for parental and developmental toxicity was 1 ppm in the diet (0.1 mg/kg/day) on the basis of >20% inhibition of plasma, erythrocyte and brain cholinesterase activity and an 8% reduction in body weight. The NOAEL for reproductive toxicity was 30 ppm in the diet, equivalent to 2.4 mg/kg/day.

Developmental studies with mice, rats and rabbits showed developmental toxicity at high oral concentrations but no teratogenicity. Developmental delay occurred in mice at all doses administered to the dams from day 16 of gestation through day 21 of lactation (0.4 to 4 mg/kg/day). Several FOB parameters were affected in weaned pups and neurons in the brain showed structural changes. Rat dams that received methamidophos (70.5%) orally at doses of 0. 0.3, 1, or 3 mg/kg body weight on days 6-17 of gestation showed typical signs of cholinergic toxicity at 3 mg/kg/day. The maternal and developmental NOAEL was 1 mg/kg/day. Fetal and litter weight were adversely affected at the 3 mg/kg/day dose. There were no fetal anomalies. In another study with rat dams treated with 0, 1, or 2 mg/kg/day on days 6-15 of gestation, fetotoxicity and increased anomalies were observed at both test concentrations. Rabbit dams administered 0, 0.1, 0.5, or 2.5 mg/kg/day showed reduced weight gain only at the highest dose. There was no developmental toxicity and no external, visceral, or skeletal anomalies occurred.

3.5. Genotoxicity

The genetic toxicology of methamidophos was reviewed by IPCS (2002) and HSDB (2004). An extensive range of studies has been performed with methamidophos in bacteria and mammalian cells *in vitro* and in mammals *in vivo*. Unless otherwise stated, technical methamidophos was tested. Assay results were negative in two studies of reverse mutation in *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537), one study of DNA repair in *Escherichia coli*, one study of unscheduled DNA synthesis in rat primary hepatocytes, two studies of point mutation in Chinese hamster ovary cells, one study of chromosomal aberration in Chinese hamster ovary cells (results were equivocal without metabolic activation), and one study of sister chromatid exchange in Chinese hamster ovary cells. An assay for chromosomal aberrations in mouse spleen cells was positive for the pure compound.

In *in vivo* tests for micronucleus formation in bone marrow cells of male and female mice, two tests with the technical material, delivered orally or intraperitoneally, were negative, and one test with the pure chemical was positive following intraperitoneal injection. Tests for chromosomal aberrations in bone marrow cells of mice and rats following oral or subcutaneous delivery were negative. Two assays for dominant lethal mutation in male mice following oral administration of the technical material were negative. A single assay for sister chromatid

exchange in the same system (intraperitoneal delivery) was positive when the pure compound was delivered intraperitoneally.

3.6. Chronic Toxicity/Carcinogenicity

Long-term studies of toxicity and carcinogenicity were conducted with dogs, rats, and mice. These unpublished oral studies were reviewed by the IPCS (2002) and HSDB (2004). Four groups of six male and six female beagle dogs consumed diets containing methamidophos (70% pure) at concentrations of 0, 2, 8, or 32 ppm, equivalent to 0, 0.06, 0.24, or 0.96 mg/kg/day for one year. At the end of one year, there were no deaths and no effects on body weight, food consumption, blood chemistry, hematology and urine parameters, or gross or microscopic changes of tissues or organs. At concentrations of 8 and 32 ppm, erythrocyte acetylcholinesterase activity was inhibited in both sexes by >20% and 84-87%, respectively. The NOAEL was 2 ppm in the diet and the LOAEL was 8 ppm on the basis of erythrocyte and brain cholinesterase activity inhibition.

Technical methamidophos was tested for chronic toxicity and carcinogenicity in a two-year dietary study with male and female F344 rats. Groups of 50 rats of each sex were administered methamidophos in the diet at concentrations of 0, 2, 6, 18, or 54 ppm, equivalent to 0, 0.01, 0.29, 0.85, or 2.9 mg/kg/day for two years. Interim sacrifices of 10 rats of each sex took place at 6 and 12 months and at one year. Clinical signs, food consumption, body weight, hematology, and clinical chemistry were monitored throughout the study. At sacrifice, major organs were weighed and organs and tissues were examined grossly and microscopically. Plasma, erythrocyte, and brain cholinesterase were assayed. After about 20 weeks, clinical signs of rough coat, urine staining, loose stools, and skin lesions increased in male and female rats that received 18 and 54 ppm in the diet. Body weight was depressed in males at 18 and 54 ppm and in females at 54 ppm. The relative weight of the testes was decreased in male rats that received 18 or 54 ppm, and the relative brain weight was increased in both sexes at 54 ppm. No neoplasms related to treatment were observed. Cholinesterase activity was inhibited by treatment in a dose-related manner (time of sampling not clearly stated). At 6, 18, and 54 ppm, plasma cholinesterase activity was inhibited by 26-47%, 70-71%, and 91%, respectively. At the respective concentrations, brain cholinesterase activity was inhibited by 31-39%, 64%, and 75-79%, and erythrocyte cholinesterase activity was inhibited by 32-36%, 65-68%, and 75-81%. The NOAEL was 2 ppm in the diet, equivalent to 0.1 mg/kg/day.

Technical methamidophos was tested for chronic toxicity and carcinogenicity in a two-year dietary study with male and female CD1 mice. Groups of 50 mice of each sex were administered methamidophos in the diet at concentrations of 0, 1, 5, or 25 ppm, equivalent to 0, 0.14, 0.67, or 3.5 mg/kg/day for males and 0, 0.18, 0.78, and 4 mg/kg/day for females. The protocol was the same as in the study with rats described above, except that cholinesterase activity was not measured. Mortality rate, clinical signs, hematology, and gross pathological appearance were not affected by treatment. At 25 ppm in the diet, food consumption and body weight gain were significantly decreased in both sexes. At 25 ppm, relative organ weights were affected in one or both sexes, and males showed diffuse interstitial pneumonia. There were no neoplasms that could be attributed to treatment. The NOAEL was 5 ppm in the diet; decreased weight gain was seen at the higher concentration.

3.7. Summary

Acute inhalation lethality studies were conducted with the rat. Studies conducted in two different laboratories, both with liquid aerosols and conducted over the same exposure duration, produced different results. The 4-hour LC_{50} values were 63.2-76.5 mg/m^3 (Sangha 1984) and 213 mg/m^3 (Pauluhn 1986). In both studies, nominal concentrations were up to 8-10 times greater than analytical concentrations, indicating difficulty in sampling and measuring methamidophos. The 1-hour LC_{50} was 377-241 mg/m^3 (Sangha 1983). In both studies, cholinergic signs including salivation, lacrimation, decreased activity, muscle fasciculation, ataxia, gasping and dyspnea, tremors, tearing, and exophthalmos, cornea opacity, and rhinorrhea were observed. Concentrations of 1.4, 5.4, and 33.1 mg/m^3, administered for 6 hours were non-lethal; no clinical signs were observed at the lower two concentrations (Pauluhn 1986).

The majority of evidence indicates that methamidophos is not genotoxic, carcinogenic, or a reproductive or developmental toxicant. Delays in development were associated with maternal toxicity.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Inhalation studies with methamidophos that addressed metabolism were not located. Dermal absorption in humans is estimated at 4.8% (IPCS 2002). Following oral administration to rats, radiolabeled methamidophos (S-methyl-^{14}C) was rapidly absorbed, distributed evenly throughout the body (due to its high aqueous solubility), metabolized, and excreted (Crossley and Tutass 1969, reviewed in IPCS 2002). Excretion was mainly via the urine in the form of acid metabolites and through expired air as carbon dioxide. Greater than 50% of the administered dose was excreted within 3 days. Biotransformation involved hydrolysis at the P-N bond and at the O- and S-ester bonds. Several intermediate metabolites were found in the urine, with the ultimate metabolite being phosphoric acid. A postulated metabolite, methyl mercaptan, was metabolized to carbon dioxide. Methamidophos does not contain aryl or carboxyl groups and so is not metabolized by A-esterases or carboxylesterases, enzymes that show age-related dependency in detoxification (Moser 1999; Padilla et al. 2000).

The metabolism of methamidophos was followed in lactating goats (studies reviewed by WHO 2003). ^{14}C-Methamidophos was administered orally for 1-7 days. Methamidophos was not detected in tissues following sacrifice at 18 hours post-dose. Most of the radioactive residues were associated with the metabolic pool including proteins and amino acids, specifically methionine. Only trace amounts were secreted in the milk. The proposed metabolic pathway included hydrolysis to form desamino methamidophos and desmethyl methamidophos and methyl transfer from the S-methyl moiety to form methionine with subsequent transformation to form choline and phospholipids. Oxidation of small carbon fragments formed by the ester/thioester hydrolysis of methamidophos and /or methionine may lead to production of CO_2 and incorporation of ^{14}C into the metabolic pool.

Following intravenous administration of 8 mg/kg (considered a near-toxic dose) $^{14}CH_3S$-labeled methamidophos to female Sprague-Dawley rats, cholinergic signs of tremors, salivation, and lacrimation were most severe at 20-60 minutes which correlated with peak inhibition of

acetylcholinesterase activity in the brain of 15-20% of control (Gray et al. 1982). Peak levels of radioactivity were achieved in the tissues within 1-10 minutes. Within 24 hours, 47% of the radioactivity was recovered in the urine and 34% as $^{14}CO_2$.

In rats, the maximally tolerated dose following either intravenous or oral dosing was the same, 8 mg/kg (Gray et al. 1982; Moser 1999). The intravenous route of administration can be used as a surrogate for the inhalation route. Because the same dose results in similar toxicity following intravenous and oral administration, oral toxicity should reflect inhalation toxicity.

4.2. Mechanism of Toxicity

Methamidophos is an organophosphate ester pesticide containing both an amide group and a sulfur group single bonded to a pentavalent phosphorus. The presence of an oxygen double-bonded to the phosphorus (oxon group) indicates that methamidophos does not need to be bioactivated *in vivo* to its oxygen analogue to exert its toxic action. The mode of action of organophosphate pesticides involves inhibition of the B-esterase, acetylcholinesterase (Costa 2008). Organophosphate esters attach to the serine hydroxyl group of the active site of acetylcholinesterase, the enzyme responsible for the destruction and termination of the biological activity of the neurotransmitter acetylcholine. When unbound acetylcholine accumulates at the cholinergic nerve endings, there is continual stimulation of electrical activity. The resulting signs of toxicity from stimulation of the muscarinic receptors of the parasympathetic autonomic nervous system are manifest as increased secretions, bronchoconstriction, miosis, gastrointestinal cramps, diarrhea, urination, and bradycardia. Stimulation of the parasympathetic junctions of the autonomic nervous system as well as the junctions between nerves and muscles cause tachycardia, hypertension, muscle fasciculation, tremors, muscle weakness, and flaccid paralysis. Symptoms resulting from effects on the central nervous system include restlessness, emotional lability, ataxia, lethargy, mental confusion, loss of memory, generalized weakness, convulsion, cyanosis, and coma. Acute toxicity of the organophosphate pesticides does not correspond with anticholinesterase potency (Chambers et al. 1990), indicating that metabolism is an important factor in determining overall toxicity.

Inhibition of acetylcholinesterase activity and other cholinesterases by organophosphate esters is generally long lasting, hours to days (Costa 2008). In the case of methamidophos; the blood and brain cholinesterase activity of rats administered an oral maximum tolerated dose recovered partially within 24 hours and nearly completely within 72 hours (Moser 1999). Preweanling rats (post-natal day 17) recovered faster than adult rats; at 24 hours post-exposure, both blood and brain cholinesterase activity were approximately 30-50% of control in adult rats and approximately 65-70% of control in preweanling rats. *In vitro*, methamidophos was found to be a weak to moderate inhibitor of cholinesterase in tissues of several species including humans (IPCS 2002). In these assays, enzyme activity was rapidly and spontaneously reactivated.

Organophosphate pesticides also inhibit butylcholinesterase, the primary form of cholinesterase found in blood plasma. The toxicological significance of butylcholinesterase activity inhibition is unknown. Acetylcholinesterase is the primary form of cholinesterase found in erythrocytes and is present at neuromuscular and nerve-nerve junctions. Due to human variability, it is difficult to measure cholinesterase activity inhibition of <20% (U.S. EPA

2000b). At greater than 30% erythrocyte acetylcholinesterase activity inhibition or 50% plasma activity inhibition, workers are withdrawn from pesticide application areas (U.S. EPA 2000b; ACGIH 2008).

4.3. Structure-Activity Relationships

Organophosphate and carbamate pesticides have a common mode of action (Costa 2008). Compared to carbamic acid esters which are poor substrates for cholinesterase-type enzymes, the organophosphate ester pesticides form a stable bond with acetylcholinesterase.

Information is available on the relative oral toxicity of multiple organophosphate pesticides (U.S. EPA 2006a; 2007). The relative toxicity of methamidophos and the related pesticide acephate as indicated by calculated oral benchmark dose values, BMD_{10} and $BMDL_{10}$, is summarized in Table 4. The benchmark doses were based on rat brain cholinesterase activity inhibition following repeated oral administration. Chronic toxicity as determined by benchmark doses does not correlate with acute oral toxicity values (Section 2), indicating the role of metabolism in toxicity. If methamidophos is assigned a potency of 1.00 for all routes of administration, then the relative potency for acephate is 0.08 (oral), 0.0025 (dermal), and 0.208 (inhalation) (U.S. EPA 2007).

4.4. Other Relevant Information

4.4.1. Species Variability

Inhalation studies with usable data were conducted only with rats. The route and rate of biotransformation of organophosphate pesticides is highly species-specific and dependent on the substituent chemical groups attached to the parent ester (Costa 2008). Baseline erythrocyte acetylcholinesterase activity is higher in humans than in other species (Ellin 1981). Oral dosing studies with methamidophos were available for rats, but the human oral dosing study used both acephate and methamidophos. An acute oral dose of 1 mg/kg methamidophos to male and female Long-Evans rats decreased whole blood cholinesterase activity to 40-50% of the control value (Moser 1999). In the human study, a 0.2 mg/kg/day oral dose of methamidophos and acephate in a 1:4 ratio (0.04 mg/kg/day methamidophos or 2.8 mg/kg/day for a 70-kg person) had no effect on erythrocyte cholinesterase activity but significantly inhibited plasma cholinesterase activity (raw data not provided) after 16 days of dosing (Garofalo et al. 1973).

In an *in vitro* study, the concentration of methamidophos required to inhibit 50% of the activity of cholinesterase from rat and mouse brain was the same, 2.0×10^{-5} M (Hussain et al. 1985). The concentration required to inhibit acetylcholinesterase activity in human erythrocytes was 2.3×10^{-5} M. No useful data on species variability could be gleaned from this study.

4.4.2. Susceptible Populations

Humans vary by gender, age, and genetic make-up in their sensitivity to cholinesterase inhibitors. The erythrocyte acetylcholinesterase activity of adults (153±24 activity units; acetylthiocholine substrate) is greater than that of healthy newborn infants (97±15 activity units) by a factor of 1.6 (Herz et al. 1975). Following *in utero* exposure to organophosphate pesticides, dams exhibit greater cholinesterase inhibition than fetuses (U.S. EPA 2006a). Developmental

neurotoxicity studies with methamidophos showed that protection of the rat dam against cholinesterase activity inhibition is protective against pup acetylcholinesterase activity inhibition *in utero*.

The U.S. EPA (U.S. EPA 2006a) identified infants and juveniles as populations susceptible to the toxicity of organophosphate pesticides. In the absence of human data on age-related sensitivity, the sensitivity to cholinesterase activity inhibition in adult and juvenile rats to methamidophos can be used as a surrogate for humans. The U.S. EPA used a dose-response modeling approach for evaluating quantitatively the relative sensitivity between juvenile and adult rats. For organophosphate pesticides, only repeated dosing exposure studies were considered. In this approach, benchmark dose values (BMD) were calculated for inhibition of juvenile and adult brain cholinesterase data. The ratio of juvenile and adult BMDs for each organophosphate pesticide was calculated and used as a chemical-specific uncertainty factor to protect the young. For methamidophos, the BMDs for adult and juvenile female rats were 0.18 and 0.09 mg/kg/day, respectively (Table 4). For adult and juvenile male rats, the BMDs were 0.10 and 0.08 mg/kg/day, respectively. The U.S. EPA assigned an factor of 2 to methamidophos. For AEGLS, this factor corresponds to an intraspecies uncertainty factor. Data on the related chemical, acephate, are also summarized in Table 4.

TABLE 4. Adult and Juvenile Rat BMD_{10} and $BMDL_{10}$ Values for Brain Acetylcholinesterase Activity Following Repeated Oral Dosing with Methamidophos or Acephate

Age and Sex	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Methamidophos		
Adult male	0.10	0.08
Adult female	0.18	0.11
Juvenile male	0.08	0.06
Juvenile female	0.09	0.08
Acephate		
Adult male	0.27	0.22
Adult female	1.25	0.30
Juvenile male	0.42	0.47
Juvenile female	1.13	0.60

The BMD values were based on a 10% response relative to the control.
Source: Table I.B-6, U.S. EPA 2006a.

A study of the sensitivity of pre-weanling and adult rats to methamidophos neurotoxicity following an acute oral exposure showed little age-related difference (Moser 1999). Using the oral route of exposure, the authors evaluated the acute age-related differences in sensitivity to methamidophos among preweanling (post-natal day 17; PND 17) and adult (PND 70) Long Evans rats of both sexes. Control data for cholinesterase activity (nmol ^{3}H-labeled acetylcholine iodide hydrolyzed/min/mg/tissue) were (a) male brain: PND 17, 4.8, adult 9.0; male blood: PND 17, 0.69, adult, 0.56; (b) female brain: PND 17, 5.2, adult 9.7; female blood: PND 17, 0.75, adult, 0.66. Range-finding studies determined the maximally tolerated dose of 8 mg/kg in both PND 17 and adult rats. Tested doses were 1.0, 2.0, 5.0, 10, and 15 mg/kg. The tested dose of 10 mg/kg resulted in severe cholinergic signs and weight loss. Doses for the definitive study were 1, 4, and 8 mg/kg. The time of peak effect of blood cholinesterase activity inhibition (measured in whole blood) was 1.5 hours in both groups. Recovery was faster in PND 17 rats than in adults. PND 17 and adult rats were similarly sensitive to methamidophos as measured by blood

and brain cholinesterase activity inhibition. Blood cholinesterase activity inhibition, reported as percent of control activity, was greater than that of brain. The lowest dose of 1 mg/kg produced brain and blood cholinesterase activity inhibition of 30-40%, but there were no behavioral effects observed in that dose group. A U.S. EPA standard functional observational battery (FOB) and motor activity observations were carried out. ED_{50} values for tremors were approximately 5 mg/kg in PND 17 rats and 6 mg/kg in adult rats. The respective values for gait changes/ataxia were approximately 4.3 and 6.0 mg/kg. Based on the Moser data, methamidophos toxicity failed to show age-related sensitivity.

Although age-related sensitivity is not apparent based on the acute and repeat-exposure oral studies with rats, humans are known to differ in sensitivity to the toxic effects of organophosphate pesticides. Although there is no data on differences among humans regarding metabolism of methamidophos, the oral dosing study of Garofalo et al. (1973) did not reveal differences within the range of tested doses. Therefore, an intraspecies uncertainty factor of 3 is considered appropriate.

4.4.3. Concentration-Exposure Duration Relationship

Toxicity studies were performed with exposure durations of 1, 4, and 6 hours, but the disparate data made time-scaling calculations inappropriate. The concentration-time relationship for a single endpoint for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$ (ten Berge et al. 1986). In the absence of empirical data, the time scaling factors of n = 3 and n = 1 are used to scale to shorter and longer exposure durations, respectively (NRC 2001)

4.4.4. Concurrent Exposure Issues

Dermal absorption may occur, but percutaneous toxicity is low compared to inhalation exposure as indicated by 4.8% skin absorption in humans (IPCS 2002).

The pesticide acephate is partially metabolized to methamidophos (Singh 1985). In *in vitro* studies with tissues from dogs, methamidophos was 75 to 100 times more potent than acephate in inhibiting acetylcholinesterase activity in brain and erythrocytes and cholinesterase activity in plasma. As indicated by a 4-hour LC_{50} in rats of 2130 mg/m^3 (MSDS 2003), acephate is a factor of 10- to 33-fold less toxic than methamidophos. However, benchmark dose calculations following repeat oral dosing (Table 4) indicate that methamidophos is a factor of 3 - to12 times more toxic, indicating the role of metabolism following inhalation.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human inhalation studies were located in the available literature. Occupational monitoring data involved dermal contact and consumer exposure involved oral intake of crop residues. In a 21-day repeat-oral dosing study of methamidophos combined with acephate, a dose of 0.04 mg/kg/day methamidophos (2.8 mg for a 70-kg person) did not inhibit erythrocyte acetylcholinesterase activity of male or female volunteers (Garofalo et al. 1973, reviewed in U.S.

EPA 1988; 2000a). Plasma cholinesterase activity was significantly inhibited, but the data were not provided in the review.

5.2. Summary of Animal Data Relevant to AEGL-1

Pauluhn (1986) exposed rats to several concentrations of methamidophos delivered as a liquid aerosol for 4 and 6 hours. No clinical signs were observed following 4-hour exposures to 11.4 or 24.3 mg/m^3, and no clinical signs were observed following 6-hour exposures to 1.4 or 5.4 mg/m^3. In each case the next higher concentration, 45.0 mg/m^3 for 4 hours and 33.1 mg/m^3 for 6 hours produced tremors, but no mortality. At the 11.4 mg/m^3 concentration, plasma cholinesterase activity was 53% of the control value and erythrocyte acetylcholinesterase activity was 102% of the control value. At the 24.3 mg/m^3 concentration, plasma cholinesterase activity was 36% of the control value and erythrocyte acetylcholinesterase activity was 92% of the control value.

In a second study, cholinergic signs were observed during the 4-hour exposure of rats to 19 mg/m^3 (Sangha 1984). The data of Sangha (1984) neither followed an adequate concentration-response curve nor correlated with nominal values, probable indications of the difficulty in sampling and measuring the liquid aerosol. Cholinesterase activity was not measured.

5.3. Derivation of AEGL-1

The study of Pauluhn (1986) was chosen for AEGL derivations. The data showed a good concentration-response curve, and measured cholinesterase activity correlated with clinical signs. The exposure of rats to 24.3 mg/m^3 for 4-hours was chosen as the point of departure for the AEGL-1. There were no clinical signs at this exposure. Clinical signs of tremor and reduced motility were observed during the 4-hour exposure to the next higher concentration of 45.0 mg/m^3. Plasma cholinesterase activity was 36 percent of the control value and erythrocyte cholinesterase was slightly inhibited (92% of the control value). Because of the apparent difficulty in maintaining liquid aerosols at these concentrations and the disparate data between the two available studies, the 24.3 mg/m^3 value was divided by a data base modifying factor of 2. Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies in both rats and humans (Moser 1999; Garofalo et al. 1973). Therefore, an interspecies uncertainty factor of 3 was applied. 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 (2006a) identified a toxicity ratio between adults and juveniles of 2. 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. The total uncertainty factor is 10. The 4-hour 11.4 mg/m^3 value was divided by a total modifying/uncertainty factor of 20 (2x10). In the absence of reliable time-scaling information, the resulting 4-hour value of 1.2 mg/m^3 was time-scaled ($C^n \times t = k$) using n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Because of uncertainty in scaling from 4 hours to 10 minutes, the 10-minute value was set equal to the 30-minute value. Values are listed in Table 5. Calculations are in Appendix A and a graph of the AEGL values in relation to toxicity data is in Appendix B.

TABLE 5. AEGL-1 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

The AEGL-1 values are supported by the subchronic study of Pauluhn and Cole (1988). In that study no treatment related effects were observed in rats inhaling 1.1 mg/m^3 for 13 weeks. At 5.4 mg/m^3, erythrocyte and brain cholinesterase activities were inhibited by <30% throughout the treatment period.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human inhalation studies relevant to development of AEGL-2 values were located in the available literature.

6.2. Summary of Animal Data Relevant to AEGL-2

Pauluhn (1986) exposed rats to several concentrations of methamidophos delivered as a liquid aerosol for 4 and 6 hours. No clinical signs were observed following 4-hour exposures to 11.4 or 24.3 mg/m^3, and no clinical signs were observed following 6-hour exposures to 1.4 or 5.4 mg/m^3. In each case the next higher concentration, 45.0 mg/m^3 for 4 hours and 33.1 mg/m^3 for 6 hours produced tremors, but no mortality. At 45.0 mg/m^3 plasma cholinesterase activity was 13% of the control value and erythrocyte cholinesterase activity was 70% of the control value. In a second study, cholinergic signs were observed during the 4-hour exposure of rats to 19 mg/m^3 (Sangha 1984). The data of Sangha (1984) did not follow a good concentration-response curve nor correlate with nominal concentrations, probable indications of the difficulty in sampling and measuring the liquid aerosol. Cholinesterase activity was not measured.

6.3. Derivation of AEGL-2

The 4-hour exposure of rats to 45.0 mg/m^3 was chosen as the point of departure for the AEGL-2. Clinical signs consisted of tremor and reduced motility. Cholinesterase activity was inhibited to 13 percent of control in plasma and 70% of control in erythrocytes. Because of the apparent difficulty in maintaining liquid aerosols at these concentrations and the disparate data between the two available studies, the 45.0 mg/m^3 value was divided by a data base modifying factor of 2. Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies (Moser 1999; Garofalo et al. 1973). Therefore, an interspecies uncertainty factor of 3 was applied. 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 age-related differences in sensitivity to methamidophos (Moser 1999). Based on repeat-dose oral studies with adult and juvenile rats, the U.S. EPA (2006a) identified an uncertainty factor of 2 to protect children. 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. The total uncertainty factor is 10. The 4-hour 45.0 mg/m^3 value was divided by a total modifying/uncertainty factor of 20 (2x10). In the absence of reliable time-scaling information, the resulting 4-hour value of 2.3 mg/m^3 was time-scaled ($C^n \times t = k$) using n values of 3 and 1 for

shorter and longer exposure durations, respectively (NRC 2001). Because of uncertainty in scaling from 4 hours to 10 minutes, the 10-minute value was set equal to the 30-minute value. Values are summarized in Table 6. Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 6. AEGL-2 Values for Methamidophos

10-min	30-min	1-h	4-h	8-h
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

The AEGL-2 values are supported by the subchronic study of Pauluhn and Cole (1988). In that study no treatment related effects were observed in rats inhaling 1.1 mg/m^3 for 13 weeks. At 5.4 mg/m^3, erythrocyte and brain cholinesterase activities were inhibited by <30% throughout the treatment period. At study termination following treatment with 23.1 mg/m^3, brain acetylcholinesterase was inhibited by 45-47%.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human inhalation studies relevant to derivation of AEGL-3 values were located in the available literature.

7.2. Summary of Animal Data Relevant to AEGL-3

The 4-hour exposure 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) followed an adequate concentration-response curve. Mortalities for rats inhaling 11.4, 24.3, 45.0, 195.5, 241.7, or 350.3 mg/m^3 for 4 hours were 0/10, 0/10, 0/10, 3/10, 8/10, and 9/10, respectively. Using U.S. EPA's Benchmark Concentration (BMC) program (V2.8), Benchmark concentration were calculated. The 4-hour $BMCL_{05}$ was 56.27 mg/m^3, and the 4-hour BMC_{01} was 101.54 mg/m^3 (see Appendix C for program output).

7.3. Derivation of AEGL-3

Both the 4-hour $BMCL_{05}$ of 56.27 mg/m^3 and the 4-hour BMC_{01} of 101.54 mg/m^3 were considered as points of departure for developing AEGL-3 values for methamidophos. 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 $BMCL_{05}$ of 56.27 mg/m^3 appeared unrealistically low based on 30% mortality when the concentration was increased more than 4-fold to 195.5 mg/m^3. This value is also close to the 45.0 mg/m^3 value that resulted in effects considered consistent with the AEGL-2. The 4-hour BMC_{01} for methamidophos delivered as a liquid aerosol was considered the threshold for mortality of rats. Because of the apparent difficulty in maintaining liquid aerosols at these concentrations and the disparate data between the two available studies, the 101.54 mg/m^3 value was divided by a data base modifying factor of 2. Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies (Moser 1999; Garofalo et al. 1973). Therefore, an interspecies uncertainty factor

of 3 was applied. 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 age-related differences in sensitivity to methamidophos (Moser 1999). Based on repeat-dose oral studies with adult and juvenile rats, the U.S. EPA (2006a) identified an uncertainty factor of 2 to protect the sensitive population of children. 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. The total uncertainty factor is 10. The 4-hour 101.54 mg/m^3 value was divided by a total modifying/uncertainty factor of 20 (2x10). In the absence of reliable time-scaling information, the resulting 4-hour value of 5.1 mg/m^3 was time-scaled ($C^n \times t = k$) using n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Because of uncertainty in scaling from 4 hours to 10 minutes, the 10-minute value was set equal to the 30-minute value. Values are summarized in Table 7, calculations are in Appendix A, and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 7. AEGL-3 Values for Methamidophos

10-min	30-min	1-h	4-h	8-h
10 mg/m^3	10 mg/m^3	8.1 mg/m^3	5.1 mg/m^3	2.5 mg/m^3

The AEGL-3 values are supported by the subchronic study of Pauluhn and Cole (1988). In that study, treatment of rats with 23.1 mg/m^3 for 90 days produced clinical signs of tremor; plasma, erythrocyte, and brain cholinesterase activity were substantially inhibited, but no deaths were reported.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 8. Derivation summaries are in Appendix D.

TABLE 8. Summary of AEGL Values for Methamidophos

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
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
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
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

8.2. Comparison with Other Standards and Guidelines

No standards or guidelines for methamidophos in air were found (Table 9). The American Conference of Government Industrial Hygienists (ACGIH) has not derived a Threshold Limit Value-Time Weighted Average for methamidophos. The ACGIH has calculated a Biological Exposure Index for acetylcholinesterase inhibiting chemicals (ACGIH 2008). The value, based on erythrocyte cholinesterase activity inhibition, is 70% of an individual's baseline.

TABLE 9. Standards and Guidelines for Methamidophos

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	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-2	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
AEGL-3	10 mg/m^3	10 mg/m^3	8.1 mg/m^3	5.1 mg/m^3	2.5 mg/m^3
ERPG-1 (AIHA)[a]			—		
ERPG-2 (AIHA)			—		
ERPG-3 (AIHA)			—		
IDLH (NIOSH)[b]		—			
REL-TWA (NIOSH)[c]					—
OSHA PEL (NIOSH)[d]					—
TLV-TWA (ACGIH)[e]					—
WEEL (AIHA)[f]					—
MAK (Germany)[g]					—
MAC (The Netherlands)[h]					—
LLV (Sweden)[I]					—

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association**
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[c]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA.

[d]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[e]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f]**WEEL (Workplace Environmental Exposure Level Guide)** (AIHA 2009) is the 8-hour time-weighted average that is expected to be without adverse health effects during a normal 8-hour day and 40-hour workweek.

[g]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] is defined analogous to the ACGIH-TLV-TWA.

[h]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands is defined similar to the ACGIH TLV.

[i]**LLV (Level Limit Value)** Occupational Exposure Limit of the Swedish National Board of Occupational Safety and Health, Solna, Sweden is defined similar to the ACGIH.

8.3. Data Adequacy and Research Needs

Methamidophos has a low vapor pressure and no usable studies involving inhalation exposure of humans were located in the available literature. An oral dosing study with human volunteers addressed effects consistent with cholinesterase activity inhibition. Inhalation studies with rats as the test species involving several exposure durations produced disparate results. Atmospheres were difficult to maintain and sample or measure as indicated by large differences in nominal and measured concentrations. AEGL values were based on an adequately conducted study with application of a data base modifying factor to account for the disparate results in the available studies. Acute and repeat-dose oral studies involving comparisons of cholinesterase activity inhibition between juvenile and adult rats addressed derivation of a chemical-specific intraspecies uncertainty factor. Compared to some organophosphate pesticides, metabolism in mammalian species appears to be fairly rapid. Metabolism pathways and mode of action are well understood.

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APPENDIX A: Derivation of Methamidophos AEGLs

Derivation of AEGL-1 Values

Key Study:	Pauluhn, J. 1986. Study for Acute Inhalation Toxicity to the Rat to OECD Guideline No 403. Report No. 15661, Bayer AG Institute of Toxicology, Wuppertal, Germany.
Toxicity endpoint:	No clinical signs; inhibition of plasma (64%) and erythrocyte (8%) cholinesterase activity in rats inhaling 24.3 mg/m^3 for 4 hours. The next higher concentration of 45.0 mg/m^3 resulted in tremors and greater inhibition of cholinesterase activity.
Time scaling	$C^n \times t = k$, where n = 3 and 1 for shorter and longer exposure durations, respectively (ten Berge et al. 1986)
Modifying factor:	2, based on disparate data
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973). Intraspecies: 3, based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats in an acute oral study (Moser 1999).
Calculations:	$24.3\ mg/m^3/20 = 1.22\ mg/m^3$ $k = (1.22\ mg/m^3)^3 \times 240\ min = 430.47\ mg/m^3 \bullet min$
10-min AEGL-1:	Set equal to the 30-minute value (2.4 mg/m^3) based on the 4-hour exosure duration
30-min AEGL-1:	$C = \sqrt[3]{(430.47\ mg/m^3 \bullet min/30)} = 2.4\ mg/m^3$
1-h AEGL-1:	$C = \sqrt[3]{(430.47\ mg/m^3 \bullet min/60)} = 1.9\ mg/m^3$
4-h AEGL-1:	$C = 1.2\ mg/m^3$
8-h AEGL-1:	$C = (1.2\ mg/m^3 \times 240)/480\ min = 0.61\ mg/m^3$

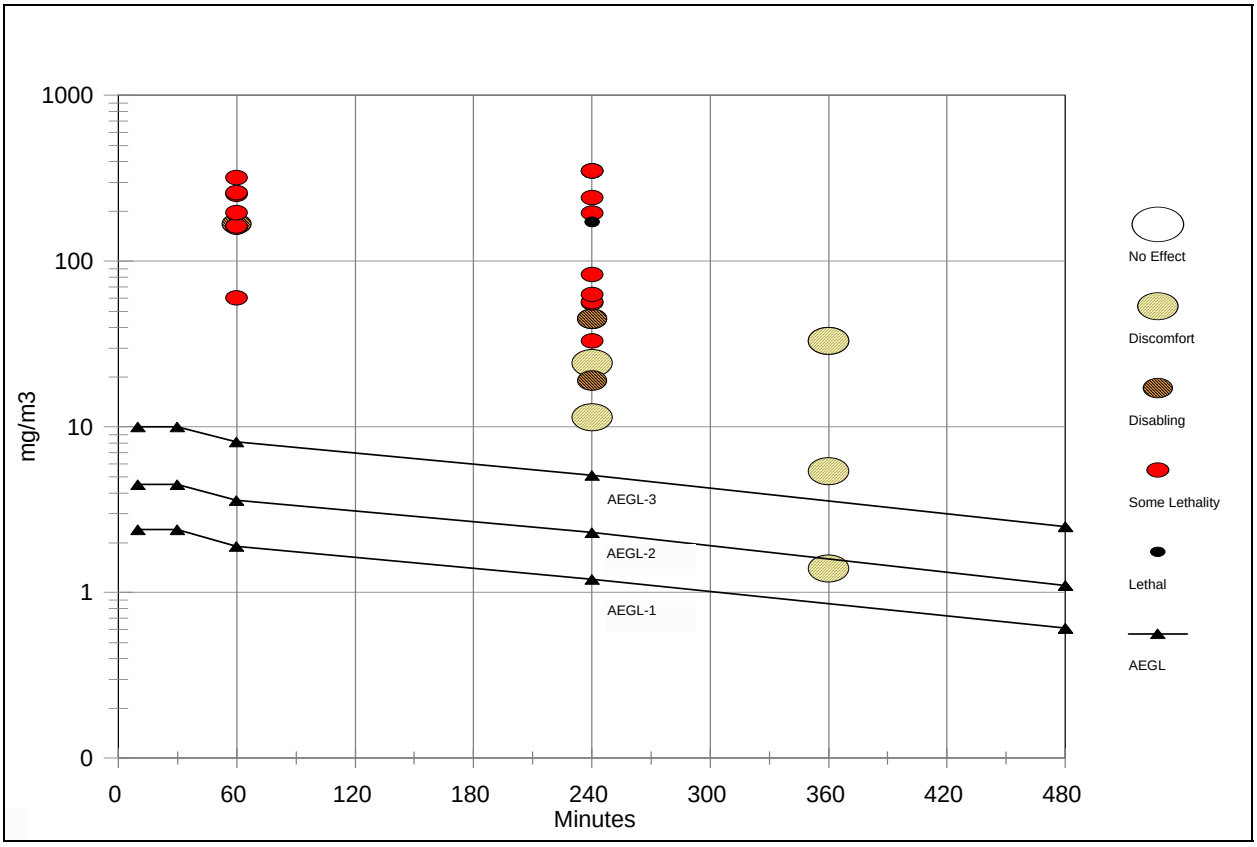
Derivation of AEGL-2 Values

Key Study:	Pauluhn, J. 1986. Study for Acute Inhalation Toxicity to the Rat to OECD Guideline No 403. Report No. 15661, Bayer AG Institute of Toxicology, Wuppertal, Germany.
Toxicity endpoint:	Tremors and inhibition of plasma (87%) and erythrocyte (30%) cholinesterase activity inhibition in rats inhaling 45.0 mg/m^3 for 4 hours
Time scaling	$C^n \times t = k$, where n = 3 and 1 for shorter and longer exposure durations, respectively (ten Berge et al. 1986)
Modifying factor:	2, based on disparate data
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973). Intraspecies: 3, based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats in an acute oral study (Moser 1999).
Calculations:	45.0 $mg/m^3/20 = 2.25\ mg/m^3$ (rounded to 2.3 mg/m^3 in summary tables) $k = (2.25\ mg/m^3)^3 \times 240\ min = 2733.75\ mg/m^3 \cdot min$
10-min AEGL-2:	Set equal to the 30-minute value (4.5 mg/m^3) based on the 4-hour exosure duration
30-min AEGL-2:	$C = \sqrt[3]{(2733.75\ mg/m^3 \cdot min/30)} = 4.5\ mg/m^3$
1-h AEGL-2:	$C = \sqrt[3]{(2733.75\ mg/m^3 \cdot min/60)} = 3.6\ mg/m^3$
4-h AEGL-2:	$C = 2.3\ mg/m^3$
8-h AEGL-2:	$C = (2.25\ mg/m^3 \times 240)/480\ min = 1.1\ mg/m^3$

Derivation of AEGL-3 Values

Key Study:	Pauluhn, J. 1986. Study for Acute Inhalation Toxicity to the Rat to OECD Guideline No 403. Report No. 15661, Bayer AG Institute of Toxicology, Wuppertal, Germany.
Toxicity endpoint:	Threshold for lethality in rats at the BMC_{01} of 101.54 mg/m^3 calculated from the rat lethality data of Pauluhn (1986). The $BMCL_{05}$ of 56.27 mg/m^3 appeared unrealistically low based on 30% mortality when the concentration was increased more than 4-fold to 195.5 mg/m^3.
Time scaling	$C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations, respectively (ten Berge et al. 1986).
Modifying Factor:	2, based on disparate data
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973). Intraspecies: 3, based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats in an acute oral study (Moser 1999).
Calculations:	101.54/20 = 5.08 mg/m^3 (rounded to 5.1 in the summary tables) (5.08 mg/m^3)^3 x 240 minutes = 31407.45 mg/m^3•min
10-min AEGL-3:	Set equal to the 30-minute value (10 mg/m^3) based on the 4-hour expoure duration
30-min AEGL-3:	$C = \sqrt[3]{(5345.05 \text{ mg/m}^3\text{•min} / 30)} = 10 \text{ mg/m}^3$
1-h AEGL-3:	$C = \sqrt[3]{(5345.05 \text{ mg/m}^3\text{•min} / 60)} = 8.1 \text{ mg/m}^3$
4-h AEGL-3:	C = 56.27/20 = 5.1 mg/m^3
8-h AEGL-3:	C = (5.08 x 240 min)/480 min = 2.5 mg/m^3

APPENDIX B: Category Graph of AEGL Values and Toxicity Data



Data:

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**mg/m^3**	**Minutes**	**Category**
NAC/AEGL-1		2.4	10	AEGL
NAC/AEGL-1		2.4	30	AEGL
NAC/AEGL-1		1.9	60	AEGL
NAC/AEGL-1		1.2	240	AEGL
NAC/AEGL-1		0.61	480	AEGL
NAC/AEGL-2		4.5	10	AEGL
NAC/AEGL-2		4.5	30	AEGL
NAC/AEGL-2		3.6	60	AEGL
NAC/AEGL-2		2.3	240	AEGL
NAC/AEGL-2		1.1	480	AEGL
NAC/AEGL-3		10	10	AEGL
NAC/AEGL-3		10	30	AEGL
NAC/AEGL-3		8.1	60	AEGL
NAC/AEGL-3		5.1	240	AEGL

NAC/AEGL-3		2.5	480	AEGL
Sangha 1983	rat	60	60	SL, 1/10 females
	rat	160	60	SL, 3/10 males, 7/10 females
	rat	163	60	SL, 1/10 males
	rat	168	60	SL, 0/10 females
	rat	196	60	SL, 5/10 females
	rat	253	60	SL, 8/10 males
	rat	259	60	SL, 5/10 males, 5/10 females
	rat	319	60	SL, 5/10 males, 9/10 females
Sangha 1984	rat	19	240	2, cholinergic signs
	rat	33	240	SL, 1/10 males, 0/10 females
	rat	56	240	SL, 5/10 males, 4/10 females
	rat	57	240	SL, 3/10 males, 4/10 females
	rat	63	240	SL, 6/10 females
	rat	83	240	SL, 8/10 males, 5/10 females
	rat	173	240	3, 10/10 females
Pauluhn 1986	rat	11.4	240	1, no clinical signs
	rat	24.3	240	1, no clinical signs
	rat	45.0	240	2, tremor
	rat	195.5	240	SL, 1/5 males, 2/5 females
	rat	241.7	240	SL3/5 males, 5/5 females
	rat	350.3	240	SL, 5/5 males, 4/5 females
	rat	1.4	360*	1, no clinical signs
	rat	5.4	360*	1, no clinical signs
	rat	33.1	360*	1, slight tremor

* The 6-hour exposures were repeated for 5 days.

APPENDIX C: Benchmark Concentration Calculation for Methamidophos

Pauluhn 1986, Methamidophos; rats $BMCL_{05}$

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                Mon Jul 13 14:03:22 2009
==========================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the probability function is:
  P[response] = Background + (1-Background) *
  CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal
  distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 7
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background          =          0
              Intercept    =     -4.36719
                 Slope             =     0.872461

       Asymptotic Correlation Matrix of Parameter Estimates
       ( *** The model parameter(s)  -background have been estimated at a boundary point, or have been
specified by the user,  and do not appear in the correlation matrix )

          intercept       slope
 intercept              1           -1
    slope              -1            1

                      Parameter Estimates
                                    95.0% Wald Confidence Interval
     Variable       Estimate       Std. Err.    Lower Conf. Limit   Upper Conf. Limit
   background             0            NA
    intercept        -16.834        6.7935          -30.149           -3.51897
        slope        3.13988        1.2412           0.707169          5.57258

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no
standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-14.3635	7			
Fitted model	-15.1945	2	1.66197	5	0.8937
Reduced model	-41.8789	1	55.0307	6	<.0001

AIC: 34.389

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
11.4000	0.0000	0.000	0	10	-0.000
24.3000	0.0000	0.000	0	10	-0.000
45.0000	0.0000	0.000	0	10	-0.002
195.5000	0.3938	3.938	3	10	-0.607
241.7000	0.6542	6.542	8	10	0.969
350.3000	0.9408	9.408	9	10	-0.547

Chi^2 = 1.61 d.f. = 5 P-value = 0.9003

Benchmark Dose Computation

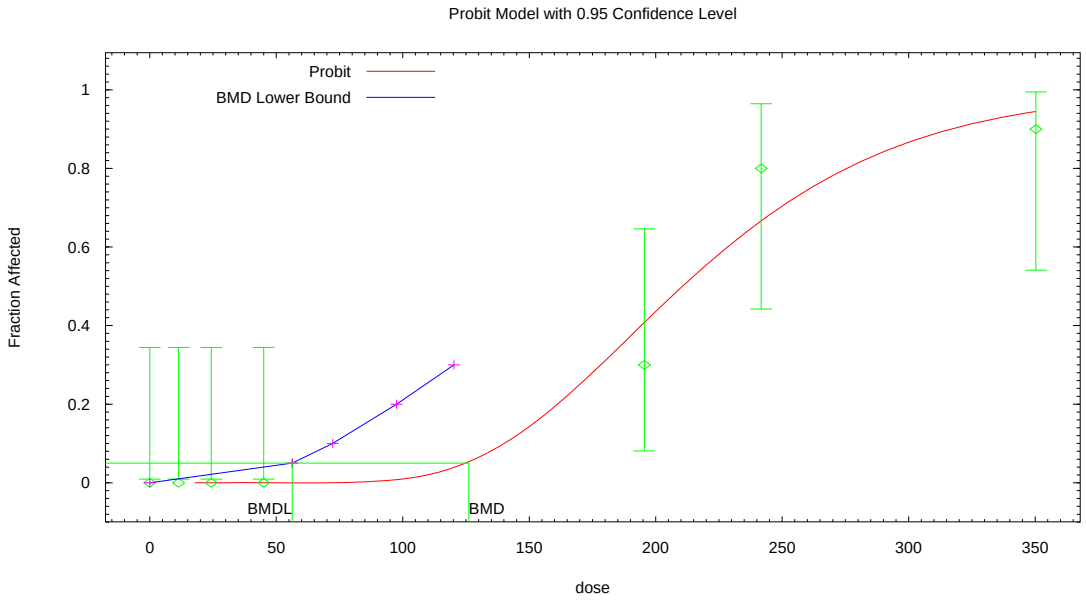
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMC = 126.153

$BMCL_{05}$ = 56.2749



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Pauluhn 1986, Methamidophos; rats BMC_{01}

==========

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Mon Jul 13 14:11:17 2009

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BMDS MODEL RUN

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The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -4.36719
Slope = 0.872461

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-16.834	6.7935	-30.149	-3.51897
slope	3.13988	1.2412	0.707169	5.57258

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table
~~~~~~~~~~

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-14.3635	7			
Fitted model	-15.1945	2	1.66197	5	0.8937
Reduced model	-41.8789	1	55.0307	6	<.0001

AIC: 34.389

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
11.4000	0.0000	0.000	0	10	-0.000
24.3000	0.0000	0.000	0	10	-0.000
45.0000	0.0000	0.000	0	10	-0.002
195.5000	0.3938	3.938	3	10	-0.607
241.7000	0.6542	6.542	8	10	0.969
350.3000	0.9408	9.408	9	10	-0.547

Chi^2 = 1.61 d.f. = 5 P-value = 0.9003

Benchmark Dose Computation

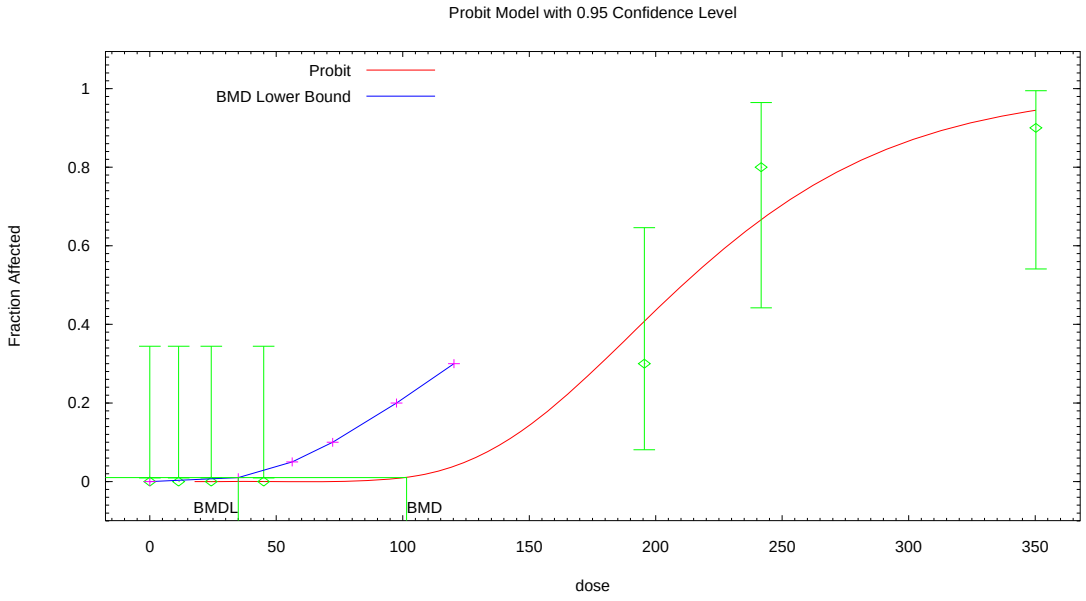
Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMC_{01} = 101.54

BMCL = 34.977



14:11 07/13 2009

APPENDIX D: Derivation Summary for Methamidophos AEGLs
Acute Exposure Guideline Levels For Methamidophos
(CAS Reg. No. 10265-92-6)

AEGL-1 VALUES				
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

Key Reference: Pauluhn, J. 1986. Study for Acute Inhalation Toxicity to the Rat to OECD Guideline No 403. Report No. 15661, Bayer AG Institute of Toxicology, Wuppertal, Germany.

Test Species/Strain/Sex/Number: Rat/Wistar/groups of 5 per sex

Exposure Route/Concentration/Duration: Inhalation/11.4, 24.3, 45.0, 195.5, 241.7, 350.3 mg/m^3/4 hours

Effects: 11.4 mg/m^3 – no clinical signs; approximately 50% inhibition of plasma cholinesterase activity.
24.3 mg/m^3 - no clinical signs; plasma cholinesterase activity was 36 percent of the control value and erythrocyte cholinesterase was slightly inhibited (92% of the control value).
45.0 mg/m^3 – clinical signs; inhibition of plasma and erythrocyte cholinesterase activity of 67 and 30%, respectively.

Endpoint/Concentration/Rationale: 24.3 mg/m^3 for 4 hours; no clinical signs, plasma cholinesterase activity was 36 percent of the control value and erythrocyte cholinesterase was slightly inhibited (92% of the control value).

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973).
Intraspecies: 3, based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats in an oral study (Moser 1999).

Modifying Factor: 2, conflicting data sets

Animal to Human Dosimetric Adjustment: Not applicable

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

Data Adequacy: The two inhalation studies, although well-conducted, provided conflicting data, indicating the difficulty in generating, sampling, and measuring liquid aerosols. For that reason a modifying factor was applied to the data set. The toxicity and mechanism of organophosphate pesticides is well understood. An oral human dosing study provides an estimate of human toxicity.

1

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
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

Key Reference: Pauluhn, J. 1986. Study for Acute Inhalation Toxicity to the Rat to OECD Guideline No 403. Report No. 15661, Bayer AG Institute of Toxicology, Wuppertal, Germany.

Test Species/Strain/Number: Rat/Wistar/groups of 5 per sex

Exposure Route/Concentration/Duration: Inhalation/11.4, 24.3, 45.0, 195.5, 241.7, 350.3 mg/m^3/4 hours

Effects: 11.4 mg/m^3 – no clinical signs; approximately 50% inhibition of plasma cholinesterase activity.
24.3 mg/m^3 - no clinical signs; plasma cholinesterase activity was 36 percent of the control value and erythrocyte cholinesterase was slightly inhibited (92% of the control value).
45.0 mg/m^3 – clinical signs; inhibition of plasma and erythrocyte cholinesterase activity of 67 and 30%, respectively.

Endpoint/Concentration/Rationale: 45.0 mg/m^3 for 4 hours – clinical signs of tremor and reduced motility; inhibition of plasma and erythrocyte cholinesterase activity of 67 and 30%, respectively.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973).
Intraspecies: 3, based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats in an oral study (Moser 1999).

Modifying Factor: 2, conflicting data sets

Animal to Human Dosimetric Adjustment: Not applicable

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

Data Adequacy: The two inhalation studies, although well-conducted, provided conflicting data, indicating the difficulty in generating, sampling, and measuring liquid aerosols. For that reason a modifying factor was applied to the data set. The toxicity and mechanism of organophosphate pesticides is well understood. An oral human dosing study provides an estimate of human toxicity.

2
3

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
10 mg/m^3	10 mg/m^3	8.1 mg/m^3	5.1 mg/m^3	2.5 mg/m^3
Key Reference: Pauluhn, J. 1986. Study for Acute Inhalation Toxicity to the Rat to OECD Guideline No 403. Report No. 15661, Bayer AG Institute of Toxicology, Wuppertal, Germany.				
Test Species/Strain/Number: Rat/Wistar/groups of 5 per sex				
Exposure Route/Concentration/Duration: Inhalation/11.4, 24.3, 45.0, 195.5, 241.7, 350.3 mg/m^3/4 hours				
Effect: Mortalities: 0/10, 0/10, 0/10, 3/10, 8/10, 9/10, respectively				
Endpoint/Concentration/Rationale: the 4-hour BMC_{01}, 101.54 mg/m^3, estimated as the threshold for lethality				
Uncertainty Factors/Rationale: **Total uncertainty factor**: 10 **Interspecies:** 3, based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973). **Intraspecies**: 3, based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats in an oral study (Moser 1999).				
Modifying Factor: 2, conflicting data				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n = 3 and 1 for shorter and longer exposure durations, respectively.				
Data Adequacy: The two inhalation studies, although well-conducted, provided conflicting data, indicating the difficulty in generating, sampling, and measuring liquid aerosols. For that reason a modifying factor was applied to the data set. The toxicity and mechanism of organophosphate pesticides is well understood. An oral human dosing study provides an estimate of human toxicity.				

2