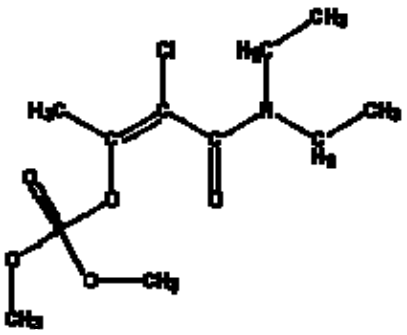
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

PHOSPHAMIDON

(CAS Reg. No. 13171-21-6)



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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:

A**EGL-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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EXECUTIVE SUMMARY

Technical phosphamidon (CAS No. 13171-21-6) is an organophosphate pesticide. At ambient temperatures, phosphamidon is a liquid with a low vapor pressure. In the past, phosphamidon was applied as a spray or by sprinkler irrigation to citrus fruits, cotton, and nuts. Phosphamidon is no longer registered for use in the United States.

Organophosphate pesticides including phosphamidon 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 may include salivation, lacrimation, decreased activity, muscle fasciculation, ataxia, gasping, and tremors. In humans, inhibition of erythrocyte acetylcholinesterase activity is used as a biomarker of exposure and effects of organophosphate pesticides. No inhalation studies involving human subjects were located.

No human data relevant to derivation of AEGL values were found. Acute inhalation toxicity studies with rats, mice, and guinea pigs were available. All acute studies were performed in the same laboratory. Results of 4-hour inhalation LC_{50} values differed among species. Analytically measured atmospheres were low compared to nominal concentrations, indicating difficulty in generating and sampling phosphamidon aerosols. All acute inhalation studies addressed lethality, with no data provided on tested concentrations.

No studies that addressed effects consistent with the definitions of the AEGL-1 or AEGL-2 were found. Based on the absence of data, AEGL-1 values are not recommended.

No human or animal data on a phosphamidon concentration that would result in effects consistent with the definition of an AEGL-2 were located. In the absence of empirical data, AEGL-2 values were calculated by dividing the AEGL-3 values by 3 (NRC 2001).

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 180 (2x3x3x10). The resulting 4-hour value is 0.57 mg/m^3. The 4-hour 0.57 mg/m^3 value 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 durations,

respectively (NRC 2001). Because of the disparate data and the uncertainty in time scaling from 4 hours to 10 minutes, the 10-minute AEGL-3 was set equal to the 30-minute AEGL-3 value.

The calculated values are listed in the table below.

TABLE S 1. 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	AEGL-3 values divided by 3
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	Four hour nose-only LC_{50} of 102 mg/m^3 in the rat divided by 3 (Sachsse et al. 1980)

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

1. INTRODUCTION

Phosphamidon (CAS No. 13171-21-6), an organophosphate insecticide, is a liquid with a low vapor pressure at ambient temperatures. It is miscible with water. The technical product Dimecron® contains 92% active ingredient. Dimercron consists of 73% *cis* isomer and 27% *trans* isomer. Formulations of Dimecron designate the percent active ingredient; thus, Dimecron 50 is a 50% solution (O'Neil et al. 2001; HSDB 2004). Additional chemical and physical properties are listed in Table 1.

The registration of phosphamidon in the United States was voluntarily cancelled by the manufacturer in 1990. Phosphamidon was applied as a spray or by sprinkler irrigation on citrus fruits, cotton, and nuts (HSDB 2004).

Phosphamidon is manufactured commercially by the reaction of trimethylphosphite with 2,2-dichloro-*N, N*-diethyl-3-oxobutyramide. The latter chemical is prepared from sulfuryl chloride and *N,N*- diethyl-3-oxobutyramide (HSDB 2004).

TABLE 1. Chemical and Physical Properties		
Parameter	**Value**	**Reference**
Synonyms	2-chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenhl dimethyl phosphoric acid ester; 2-chloro-*N,N*-diethyl-3-hydroxycrotoamide dimethyl phosphate; D-Cron; Dimercron; Dixon; Famphos; Kinadon; Merkon; Phosron; Pillacron ; Swat; Umedron	O'Neil et al. 2001' HSDB 2004
Chemical formula	$C_{10}H_{19}ClNO_5P$	O'Neil et al. 2001
Molecular weight	299.69	O'Neil et al. 2001
CAS Reg. No.	13171-21-6 (mixture) 207-99-4 (*trans* isomer) 23783-98-4 (*cis* isomer)	O'Neil et al. 2001 IPCS 2001
Physical state	Oily liquid, colorless to pale yellow	O'Neil et al. 2001; HSDB 2004
Solubility in water	Miscible	O'Neil et al. 2001
Vapor pressure	2.5×10^{-5} mm Hg at 20ºC	O'Neil et al. 2001
Vapor density, saturated (air =1)	Not available	
Liquid density (water =1)	1.21 at 25ºC	O'Neil et al. 2001
Melting point	-45ºC	O'Neil et al. 2001
Boiling point	120ºC	O'Neil et al. 2001
Flammability limits in air	Not available	
Conversion factors	1 ppm = 12.26 mg/m^3 1 mg/m^3 = 0.08 ppm	Calculated

2. HUMAN TOXICITY DATA

No inhalation studies other than accidental exposures were located. Reports of accidental exposures lacked information on concentration and exposure duration. Symptoms of cholinesterase activity inhibition have been observed in agricultural workers following spray treatment of fields with mevinphos and phosphamidon (Midtling et al. 1985). Symptoms included blurred vision, eye irritation, dizziness, weakness, headache, nausea, cramps, and vomiting. In a human exposure study, volunteers, ages 10-70 years, stayed in paddy fields during aerial spraying with phosphamidon and for one hour afterward (HSDB 2004). The application rate was 550 g/ha. The volunteers did not wear protective clothing. Most of the volunteers experienced eye irritation immediately after the application. No other symptoms were reported. Plasma cholinesterase activity was inhibited by 0-25% in 19 subjects, 26-50% in nine subjects and over 50% in two workers. There was no significant effect on erythrocyte acetylcholinesterase activity.

3. ANIMAL TOXICITY DATA

Phosphamidon has been tested for acute oral and dermal toxicity and skin and eye irritation. The acute oral LD_{50} and LD_1 values in male and female rats were 24 and 6.6 mg/kg, respectively (Gaines 1969). Acute oral LD_{50} values reported by Sachsse and Voss (1971) for the rat and mouse were approximately 30 mg/kg and 10 mg/kg, respectively. In the mouse, *cis*-phosphamidon delivered in 0.9% NaCl solution was more toxic than the *trans*-isomer by a factor

of 34, 6.5 mg/kg versus 220 mg/kg. Sachsse et al. (1980) reported the oral LD_{50} for Dimercron 100 SCW in male and female Tif:RAIf rats as 11.3 mg/kg. The metabolite desethylphosphamidon was equal in oral toxicity to the parent compound (Jaques and Bein 1960).

The dermal LD_{50} values in male and female rats were 143 and 107 mg/kg, respectively (Gaines 1969). Based on active ingredient, Sachsse and Voss (1971) cited dermal LD_{50} values of 125-640 mg/kg. The intraperitoneal LD_{50} values in mice and rats were 5.7 and 6.1 mg/kg, respectively (Agarwal et al. 1990). In a modified Draize test, undiluted technical grade phosphamidon was slightly irritating to both the intact and abraded skin of rabbits. A volume of 0.1 mL undiluted technical grade phosphamidon was moderately irritating to the eyes of rabbits.

3.1. Acute Toxicity

3.1.1. Rats

Acute inhalation studies are summarized in Table 2.

Groups of nine male and nine female rats (strain not identified) inhaled aerosols of phosphamidon, nose-only, for 1 or 4 hours (Sachsse et al. 1974). Phosphamidon was aerosolized by aerodynamic atomization; particles were collected on filters and concentrations were measured gravimetrically. Test concentrations were not provided. Particle size averaged 2 µ mass median diameter. Only 10% of the nominal test material atomized was recovered. Rats were observed for 7 days postexposure. The 1- and 4-hour LC_{50} measured concentrations were 160 and 180 mg/m^3, respectively.

Groups of male and female young-adult Tif:RAIf rats (number not specified) inhaled an aerosol of Dimecron 100 SCW for 4 hours; the post-exposure observation period was 14 days (Sachsse et al. 1980). About 70% of particles were 1-5µ in diameter. Rats were exposed either head-only or whole-body. Concentrations (not provided) were measured gravimetrically. Cholinergic signs were observed, but not described. The 4-hour LC_{50} values for head-only and whole-body exposure were 102 mg/m^3 (confidence limits, 84-122 mg/m^3) and 135 mg/m^3 (confidence limits, 113-170 mg/m^3).

TABLE 2. Acute Toxicity of Phosphamidon to Laboratory Animals

Species	Concentration (mg/m^3)	Exposure Duration	Effect/LC_{50} (mg/m^3)	Reference
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

Phosphamidon was delivered as a liquid aerosol.

3.1.2. Mice

Groups of nine male and nine female mice (strain not provided) inhaled aerosols of phosphamidon for 1 or 4 hours (Sachsse et al. 1974). The protocol was the same as that described in the study with rats above. The 1- and 4-hour LC_{50} values were 30 and <30 mg/m^3, respectively

3.1.3. Guinea Pigs

Groups of nine male and nine female Pirbright-White guinea pigs inhaled aerosols of phosphamidon for 1 or 4 hours (Sachsse et al. 1974). The protocol was the same as that described in the study with rats above. The 1- and 4-hour LC_{50} values were 2500 and 1300 mg/m^3, respectively

3.2. Repeat-Exposure Studies

In a 42-day repeat exposure inhalation study, groups of ten male and female Wistar rats inhaled concentrations of 0.05 or 0.5 mg/m^3 of phosphamidon for 4 hours/day, 5 days/week (Battelle Institute 1965). There was a temporary inhibition of erythrocyte cholinesterase (data not provided) but no mortality and no hematological, biochemical, or histopathological changes.

Groups of ten male and female Sprague-Dawley rats, ten male and female English guinea pigs, and two male and two female beagle dogs inhaled aerosols of phosphamidon for 6 hours/day, 5 days/week for 90 days (Industrial Bio-Test Laboratories, Inc. 1964). Concentrations were 0, 3, 16, or 125 mg/m^3. Particle size averaged 0.5 to 3 µ. There was no mortality and there were no effects on body weight, behavior, hematology or biochemical parameters, or histopathology. No information was provided as to whether these concentrations were nominal or measured.

3.3. Neurotoxicity

Acute toxicity studies showed that phosphamidon is neurotoxic. Undescribed signs of acetylcholinesterase activity inhibition were observed in rats inhaling phosphamidon for 1 or 4 hours (Sachsse et al. 1974; 1980). Cholinergic signs were also observed in oral studies of developmental and reproductive toxicity and chronic toxicity. See Section 4.2 for mechanism of toxicity of organophosphate pesticides.

3.4. Developmental/Reproductive Toxicity

No inhalation studies were conducted that addressed the developmental or reproductive toxicity of phosphamidon. Reproductive and developmental toxicity studies that used the oral route of administration were reviewed by IPCS (1986) and HSDB (2004). These studies are briefly reviewed here to show that phosphamidon is not a teratogen. In a two-generation reproductive toxicity study, male and female CD rats received diets containing technical phosphamidon (92.1% purity) at a concentration of 0, 5, 30, or 50 ppm (the latter reduced from 80 ppm 2 weeks into the study). Tremors, hyperactivity, unthriftyness, and ocular and nasal discharge were observed in animals treated with 30 and 50 ppm. Mean litter size and pup

survival were decreased in both generations at 50 ppm and lower pup weight was observed at 30 ppm. No treatment related malformations were found in pups. The NOAEL was 5 ppm in the diet.

Teratology studies were undertaken with rats and rabbits (IPCS 1986; HSDB 2004). Phosphamidon (92% purity) was administered by gavage at 0, 1, 2, or 4 mg/kg/day to rats and 0, 1, 3, or 10 mg/kg/day to rabbits. In rats, maternal toxicity at the higher doses led to subsequent developmental delay and reduced body weight in fetuses. Maternal toxicity in rabbits at 10 mg/kg/day did not affect reproductive parameters or fetal parameters including malformations.

Pregnant Swiss albino mice were treated during the gestational period with 15 or 35 ppm phosphamidon in the drinking water (Soni and Bhatnagar 1989). No toxic signs were observed and there was no mortality. The lower concentration did not produce significant effects. The higher concentration reduced the number of implants, litter size, and fetal weight and increased the number of resorptions. There were no fetal malformations. In a second part of the study, parental mice were treated for 30 or 60 days at 35 ppm in drinking water prior to mating. Following mating, females were treated throughout gestation. Treatment for 30 days prior to mating and during gestation also reduced the number of implants, litter size, and fetal weight and increased the number of resorptions. These effects were not seen in the group treated for 60 days. The authors suggested that the longer treatment induced resistance to the toxic effects of phosphamidon, thereby causing less embryotoxicity.

3.5. Genotoxicity

The genetic toxicology of phosphamidon was reviewed by IPCS (1986) and HSDB (2004). An extensive range of studies has been performed with phosphamidon in bacteria and mammalian cells *in vitro* and in mammals *in vivo*. Purity of phosphamidon, where stated, was 92%. Assay results were negative in the following *in vitro* test systems: reverse mutation in *Salmonella typhimurium* (TA100, TA1535, and TA1537), mitotic gene conversion in *Saccharomyces cerevisiae*, back mutation in *S. cerevisiae*, spot reverse mutation in *Escherichia coli*, forward mutation in mouse L5178Y Tk+/- lymphoma cells, DNA repair in human fibroblasts, and chromosome aberration in human lymphocytes.

In *in vivo* tests with oral administration, results were negative for sister chromatid exchange and nucleus anomalies in Chinese hamster bone marrow cells (results of two tests for nucleus anomalies were questionable), and chromosome aberrations in mouse spermatogonia and spermatocytes. Following oral administration, results were positive for micronucleus formation in mouse bone marrow cells. Following intraperitoneal injection, results were positive for chromosome aberrations in rat and mouse bone marrow cells, and in a host mediated assay with *S. typhimurium* in the mouse.

3.6. Chronic Toxicity/Carcinogenicity

Long-term studies of toxicity and carcinogenicity were conducted with dogs, rats, and mice. All long-term studies used the oral route of administration. Unpublished studies were reviewed by Sachsse and Voss (1971). Four groups of two male and two female beagle dogs were administered gelatin capsules containing 0, 0.1, 2.5, or 5 mg/kg/day for two years.

Mortality, clinical symptoms, body weight, food consumption, hematology parameters, and urinalysis were checked throughout the study. At sacrifice, major tissues and organs were examined grossly and microscopically. Dogs in the high-dose group died between the 100th and 600th days with death attributed to cholinesterase inhibition. Clinical signs included tremor, ataxia, salivation, emesis, etc. Dogs that ingested 2.5 mg/kg/day showed moderate signs of cholinesterase activity inhibition. The NOAEL was 0.1 mg/kg/day. No neoplasms attributed to the test material were observed. In a two-year study using the same protocol, the NOAEL for signs of cholinesterase activity inhibition in rats was 1.25 mg/kg/day. No tissue or organ abnormalities were observed.

Technical phosphamidon was tested for chronic toxicity and carcinogenicity in a two-year dietary study with male and female Osborne-Mendel rats and B6C3F1 mice (NCI 1979). Groups of 50 rats of each sex were administered phosphamidon in the diet at concentrations of 80 or 160 ppm for 80 weeks and then observed for 30-31 weeks. Matched controls consisted of groups of 10 rats of each sex (concurrent) plus 85 male and female controls from previous studies. Hyperexcitability and tremors were observed in dosed rats. In male rats, the incidence of hemangiomas and hemangiosarcomas in the spleen showed a dose-related trend, but incidences were not higher than in previous control groups. Females showed an increase in incidence of C-cell adenomas and carcinomas of the thyroid, but incidences in the high-dose group were not higher than in previous control groups. The evidence for carcinogenicity in male and female rats was considered equivocal.

Groups of 50 mice of each sex were administered phosphamidon in the diet at concentrations of 80 or 160 ppm (NCI 1979). Depending on dose group and sex, mice were fed for up to 80 weeks then observed for up to 31 weeks. The protocol was the same as in the study with rats described above. Hyperexcitability and tremors were observed in dosed mice. No tumor occurred at a higher incidence in treated mice than in controls.

3.7. Summary

Acute inhalation lethality studies were conducted with rats, mice, and guinea pigs. All studies were conducted in the same laboratory. Four-hour LC_{50} values for rats ranged from 102 to 180 mg/m^3 (Sachsse et al. 1974; 1980). Mice were more sensitive to the acute toxicity of phosphamidon than rats. The 4-hour LC_{50} for mice was <30 mg/m^3 (Sachsse et al. 1974). No explanation was provided for the fact that the 4-hour LC_{50} value for the nose-only exposure of rats was higher than the 1-hour LC_{50} in the study of Sachsse et al. (1974). In a 42-day repeat exposure inhalation study with rats, 0.5 mg/m^3 of phosphamidon for 4 hours/day, 5 days/week caused a transient inhibition of erythrocyte cholinesterase (Battelle Institute 1965). In a 90-day study with dogs, rats, and guinea pigs, 125 mg/m^3/day caused no untoward effects (Industrial Bio-Test Laboratories, Inc. 1964).

Developmental studies with mice, rats and rabbits showed developmental toxicity at high oral concentrations but no teratogenicity. The majority of evidence from oral studies indicates that phosphamidon is not genotoxic or carcinogenic.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Inhalation studies with phosphamidon that addressed metabolism were not located. Dermal absorption is low as indicated by LD_{50} values of >100 mg/kg in rats (Gaines 1969; Sachsse and Voss 1971). Phosphamidon is considered a non-cumulative pesticide; metabolism is principally by oxidation, hydrolysis by esterases, and reaction with glutathione (IPCS 2001). Following oral administration to rats and a lactating goat, both ^{32}P- and ^{14}C-labeled phosphamidon were metabolized and excreted primarily in the urine within 24 hours (Clemons and Menzer 1968). Only trace amounts of the parent chemical were found in the urine. Isolation of metabolites indicated that metabolism occurs by oxidation and hydrolysis. Non-toxic hydrolysis products (most not identified) account for about 90% of the metabolites (Lucier and Menzer 1971). Desethylphosphamidon was detected in urine and phosphamidon amide and deschlorophosphamidon amide were found in urine and milk. 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).

4.2. Mechanism of Toxicity

Phosphamidon is an organophosphate ester pesticide containing two methyl ester groups single bonded to pentavalent phosphorus. The presence of oxygen double-bonded to the phosphorus (oxon group) indicates that phosphamidon does not need to be bioactivated *in vivo* to its oxygen analogue to exert toxic action. The minor metabolite desethylphosphamide which retains the oxon group is nearly as toxic as the parent compound. 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. Signs and 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. According to Chambers et al. (1990), acute toxicity of the organophosphate pesticides does not correspond with anticholinesterase potency, 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 phosphamidon administered orally to rats, metabolism and excretion is 70% complete within 24 hours.

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 inhibition of <20% (U.S. EPA 2000). At greater than 30% erythrocyte acetylcholinesterase activity inhibition or 50% plasma activity inhibition, workers are withdrawn from pesticide application areas (U.S. EPA 2000; 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 more stable bond with acetylcholinesterase. No information on the toxicity of phosphamidon in relation to chemically similar organophosphate pesticides was found.

4.4. Other Relevant Information

4.4.1. Species Variability

Inhalation studies were conducted with rats, mice and guinea pigs. These studies indicate that the mouse is more sensitive to the toxicity of phosphamidon via the inhalation route than either rats or guinea pigs. As noted by Costa (2008), 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. In an acute oral study, the mouse was more sensitive to phosphamidon than the rat (Sachsse and Voss 1971). In subchronic and chronic oral studies, mice and rats were of equal sensitivity to the toxic effects of phosphamidon (NCI 1979). Both species tolerated 160 ppm in the feed for 6 weeks, but a concentration of 320 ppm in the feed was lethal to both species. The increased sensitivity of the mouse compared with the rat in the inhalation study of Sachsse 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).

Baseline erythrocyte acetylcholinesterase activity is higher in humans than in other species (Ellin 1981). No chemical-specific data on human sensitivity in relation to animal species were located.

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). Developmental neurotoxicity studies with phosphamidon

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 2006) identified infants and juveniles as populations susceptible to the toxicity of organophosphate pesticides. However, no information was provided for phosphamidon specifically.

4.4.3. Concentration-Exposure Duration Relationship

Toxicity studies were performed with exposure durations of 1 and 4 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 were used to scale to shorter and longer exposure durations, respectively (NRC 2001)

4.4.4. Concurrent Exposure Issues

Dermal absorption may occur, but toxicity would be low compared to inhalation exposure as indicated by dermal LD_{50} values of >100 mg/kg in the rat (Gaines 1969).

Sachsse and Voss (1971) reviewed studies on the potentiating effect of phosphamidon or its metabolite desethylphosphamidon on carbamates and other organophosphates. In all cases, the combined toxicity was additive.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were located in the available literature.

5.2. Summary of Animal Data Relevant to AEGL-1

Acute inhalation studies addressed lethal effects. No acute inhalation studies were located that addressed signs consistent with the definition of the AEGL-1.

5.3. Derivation of AEGL-1

No human or animal studies were located that addressed symptoms and signs consistent with the definition of the AEGL-1. Therefore, AEGL-1 values are not recommended (Table 3).

TABLE 3. AEGL-1 Values for Phosphamidon

10-min	30-min	1-h	4-h	8-hour
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

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

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

No animal studies relevant to deriving AEGL-2 values were located in the available literature. All studies reviewed in Section 3.1 involved mortality.

6.3. Derivation of AEGL-2

No human or animal data on a phosphamidon concentration that would result in effects consistent with the definition of an AEGL-2 were located. In the absence of empirical data, AEGL-2 values may be calculated by dividing the AEGL-3 values by 3 (NRC 2001). AEGL-2 values are summarized in Table 4. Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 4. AEGL-2 Values for Phosphamidon

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

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

All acute lethality studies were conducted in the same laboratory. Four-hour LC_{50} values for the rat, mouse, and guinea pig were 102-180 mg/m^3, <30 mg/m^3, and 1300 mg/m^3, respectively (Sachsse et al. 1974; 1980). These data indicate large species differences, and in addition, may reflect the difficulty in generating and measuring phosphamidon aerosol. The subchronic study of Industrial Bio-Test Laboratories, Inc. (1964) was not considered in development of AEGL-3 values because the non-lethal concentrations, up to 125 mg/m^3, appear unrealistic in comparison with the acute LC_{50} values.

7.3. Derivation of AEGL-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 was divided by a data base modifying factor of 2. In the absence of empirical data on non-

lethal concentrations, 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 considerably 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 on metabolism differences among humans. The total modifying/uncertainty factor is 180 (2x3x3x10). The resulting 4-hour value is 0.57 mg/m^3.

The 4-hour 0.57 mg/m^3 value 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 durations, respectively (NRC 2001). Because of the disparate data and the uncertainty in time scaling from 4 hours to 10 minutes, the 10-minute AEGL-3 was set equal to the 30-minute AEGL-3 value. Values are summarized in Table 5, calculations are in Appendix A, and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 5. AEGL-3 Values for Phosphamidon

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

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 6. Derivation summaries are in Appendix C.

TABLE 6. Summary of AEGL Values for Phosphamidon

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
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
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

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

8.2. Comparison with Other Standards and Guidelines

There are no standards and guidelines for phosphamidon (Table 7). The American Conference of Government Industrial Hygienists (ACGIH) has not derived a Threshold Limit Value-Time Weighted Average for phosphamidon. 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 7. Standards and Guidelines for Phosphamidon					
Guideline	**Exposure Duration**				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2	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
AEGL-3	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
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]					—
TEEL (SCAPA)[g] PAC-1 PAC-2 PAC-3			 0.15 mg/m^3 0.3 mg/m^3 60 mg/m^3		
MAK (Germany)[h]					—
MAC (The Netherlands)[i]					—

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

[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]**TEEL (Temporary Emergency Exposure Limits)** (SCAPA 2009) are based on AEGLs or ERPGs. Subcommittee on Consequence Assessment and Protective Action, U.S. Department of Energy. PAC = Protective Action Criteria.

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

[i]**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.

8.3. Data Adequacy and Research Needs

Phosphamidon has a low vapor pressure and no usable studies involving inhalation exposure of humans were located in the available literature. The data base of inhalation studies with animals is sparse, containing contradictory information and few details. Therefore, a conservative approach was taken to derive AEGL values.

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APPENDIX A: Derivation of Phosphamidon AEGLs

Derivation of AEGL-1 Values

No human or animal studies were located that addressed symptoms and signs consistent with the definition of the AEGL-1. Therefore, AEGL-1 values are not recommended.

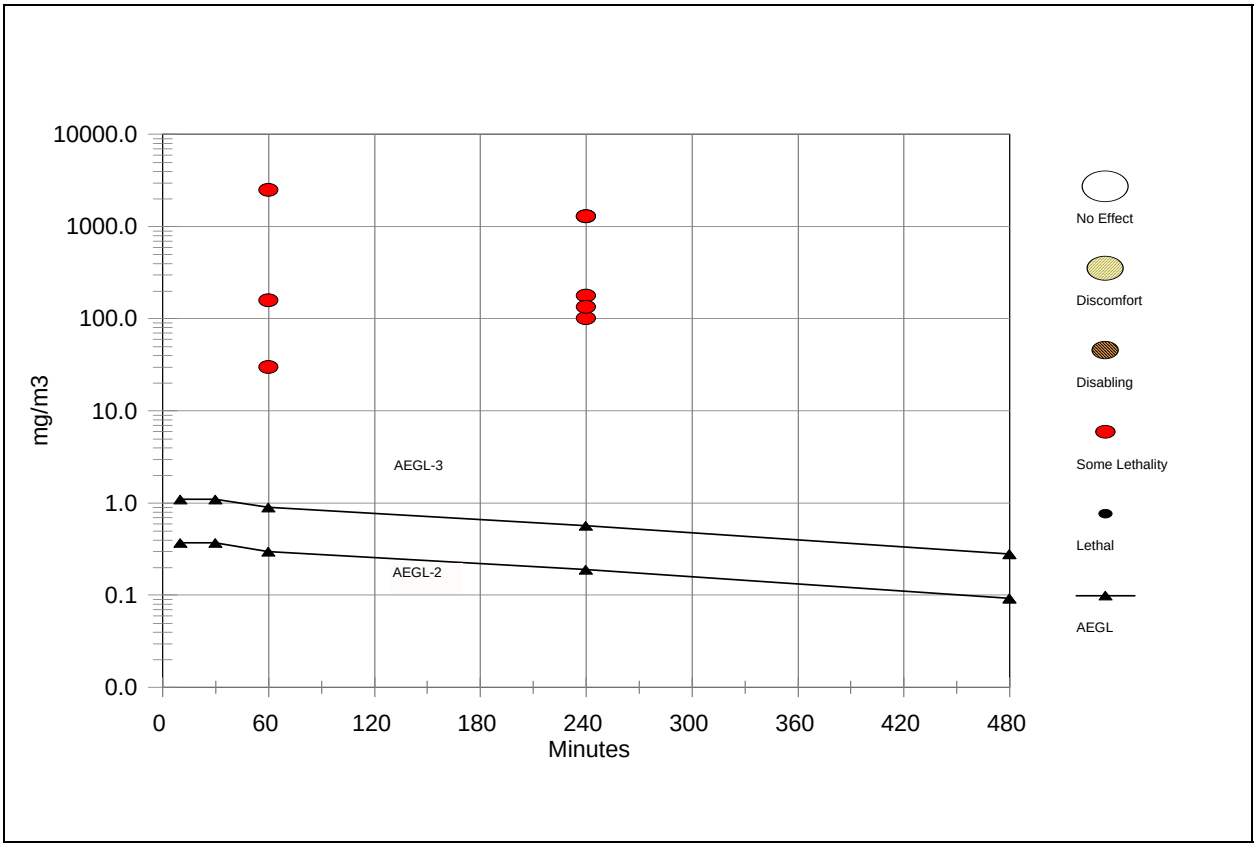
Derivation of AEGL-2 Values

Key Study:	Sachsse, K.R. K. Zbinden, and L. Ullmann. 1980. Significance of the mode of exposure in aerosol inhalation toxicity studies – head only versus whole body exposure. Arch. Toxicol. Suppl. 4:305-311.
Toxicity endpoint:	AEGL-3 values divided by 3 (NRC 2001).
Modifying factor:	2, based on the sparse and disparate data base (See AEGL-3 derivation)
Uncertainty factors:	Total uncertainty factor: 180 (See AEGL-3 derivation)
Time scaling	See AEGL-3 derivation
Calculations:	AEGL-3 values divided by 3
10-min AEGL-2:	C = 1.1 $mg/m^3/3$ = 0.37 mg/m^3
30-min AEGL-2:	C = 1.1 $mg/m^3/3$ = 0.37 mg/m^3
1-h AEGL-2:	C = 0.90 $mg/m^3/3$ = 0.30 mg/m^3
4-h AEGL-2:	C = 0.57 $mg/m^3/3$ = 0.19 mg/m^3
8-h AEGL-2:	C = 0.28 $mg/m^3/3$ = 0.093 mg/m^3

Derivation of AEGL-3 Values

Key Study:	Sachsse, K.R. K. Zbinden, and L. Ullmann. 1980. Significance of the mode of exposure in aerosol inhalation toxicity studies – head only versus whole body exposure. Arch. Toxicol. Suppl. 4:305-311.
Toxicity endpoint:	Four-hour LC_{50} value of 102 mg/m^3 in rats in a nose-only exposure divided by 3 as an estimate of the threshold for lethality in rats.
Modifying factor:	2, based on the sparse and disparate data
Uncertainty factors:	Total uncertainty factor: 30 Interspecies: 3, based on the rat being intermediate in toxicity between the mouse and guinea pig. Intraspecies: 10, based on the absence of information on differences in metabolism among humans.
Time scaling	$C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001).
Calculations:	102 mg/m^3/180 = 0.57 mg/m^3 (0.57 mg/m^3)^3 x 240 minutes = 43.67 mg/m^3•min
10-min AEGL-3:	C = set equal to the 30-minute value of 1.1 mg/m^3
30-min AEGL-3:	C = $\sqrt[3]{}$(43.67 mg/m^3•min/30) = 1.1 mg/m^3
1-h AEGL-3:	C = $\sqrt[3]{}$(43.67 mg/m^3•min/60) = 0.90 mg/m^3
4-h AEGL-3:	C = 0.57 mg/m^3
8-h AEGL-3:	C = (0.57 mg/m^3•min x 240 min)/480 minn = 0.28 mg/m^3

APPENDIX B: Category Graph of AEGL Values and Toxicity Data



1 **Data:**

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**ppm**	**Minutes**	**Category**
NAC/AEGL-1		NR	10	AEGL
NAC/AEGL-1		NR	30	AEGL
NAC/AEGL-1		NR	60	AEGL
NAC/AEGL-1		NR	240	AEGL
NAC/AEGL-1		NR	480	AEGL
NAC/AEGL-2		0.37	10	AEGL
NAC/AEGL-2		0.37	30	AEGL
NAC/AEGL-2		0.30	60	AEGL
NAC/AEGL-2		0.19	240	AEGL
NAC/AEGL-2		0.093	480	AEGL
NAC/AEGL-3		1.1	10	AEGL
NAC/AEGL-3		1.1	30	AEGL
NAC/AEGL-3		0.90	60	AEGL
NAC/AEGL-3		0.57	240	AEGL
NAC/AEGL-3		0.28	480	AEGL
Sachsse et al. 1974	rat	160	60	SL (LC_{50})
	rat	180	240	SL (LC_{50})
Sachsse et al. 1980	rat	102	240	SL (LC_{50})
	rat	135	240	SL (LC_{50})
Sachsse et al. 1974	mouse	30	60	SL (LC_{50})
Sachsse et al. 1974	guinea pig	2500	60	SL (LC_{50})
	guinea pig	1300	240	SL (LC_{50})

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

2

APPENDIX C: Derivation Summary for Phosphamidon AEGLs (CAS Reg. No. 13171-21-6)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Key Reference: Insufficient data				
Test Species/Strain/Sex/Number:				
Exposure Route/Concentration/Duration:				
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: **Total uncertainty factor:** **Interspecies**: **Intraspecies**:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy:				

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

1

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

Key References: Sachsse, K.R., K. Zbinden, and L. Ullmann. 1980. Significance of mode of exposure in aerosol inhalation toxicity studies – head only versus whole body exposure. Arch. Toxicol. Suppl. 4:305-311.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

Test Species/Strain/Number: Rat/Tif:RAIf/Number not provided

Exposure Route/Concentration/Duration: Inhalation/180, 135, 102, mg/m^3/4 hours (LC_{50} values)

Effects: Threshold for reversible effects estimated at 1/3 of the AEGL-3 values (NRC 2001).

Endpoint/Concentration/Rationale: One-third of the AEGL-3 value

Uncertainty Factors/Rationale: See AEGL-3 summary.

Total uncertainty factor: 30 applied to AEGL-3

Interspecies: 3

Intraspecies: 10

Modifying Factor: 2 applied to AEGL-3 based on sparse and disparate 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 data base is sparse. Details of the study were not provided.

2
3
4

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
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

Key References: Sachsse, K.R., K. Zbinden, and L. Ullmann. 1980. Significance of mode of exposure in aerosol inhalation toxicity studies – head only versus whole body exposure. Arch. Toxicol. Suppl. 4:305-311.
Rusch, G.M., C.B. Bast, and F.L. Cavender. 2009. Establishing a point of departure for risk assessment using acute inhalation toxicology data. Regul. Toxicol. Pharmacol. 54:247-255.

Test Species/Strain/Number: Rat/Tif:RAIf/Number not provided

Exposure Route/Concentration/Duration: Inhalation/180, 135, 102 mg/m^3 (4 hour LC_{50} values)

Effect: 4-hour LC_{50} (nose-only exposure): 102 mg/m^3 (most conservative value)

Endpoint/Concentration/Rationale: Estimated threshold for lethality: LC_{50} divided by 3 (Rusch et al 2009)

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
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

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. The 30-minute value was adopted as the 10-minute value due to uncertainty in extrapolating from a 4-hour exposure to 10 minutes.

Data Adequacy: The data base is sparse. Details of the study were not provided.

2