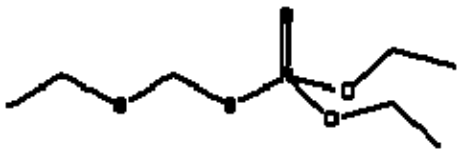
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
PHORATE
(CAS Reg. No. 298-02-2)

INTERIM



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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/m3]) 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/m3) 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/m3) 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

Phorate is an organophosphate cholinesterase inhibitor used as a systemic and contact insecticide. As a cholinesterase inhibitor, it phosphorylates cholinesterase and prevents the enzyme from deactivating acetylcholine. The result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors). Annual production in 1972 was approximately 3.6 million kg. Relative to dermal and oral exposure, inhalation is a relatively minor exposure route and this is reflected in the lack of inhalation toxicity data. No quantitative human inhalation studies are available.

Data to derive AEGL-1 values for phorate were not available, so AEGL-1 values are not recommended (Table S-1).

Newell and Dilley (1978) studied pregnant female rats (10/group) exposed to phorate at aerosol concentrations of 0.15, 0.40, and 1.94 mg/m^3 for one hr/day during days 7-14 of gestation. All high-dose rats exhibited tremors, lacrimation, and exophthalmos, and a total of five animals died at this exposure level during the eight days of exposure. No maternal deaths or cholinergic effects were reported for the two lower exposure levels. Organophosphate poisoning typically exhibits a steep exposure-response curve (NRC, 2003), and phorate appears to be no exception. [Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.] Although the clinical signs reported for pregnant rats following multiple exposures to phorate are appropriate for deriving AEGL-2 values, they were observed at an exposure level producing significant mortality. It is uncertain which effects, if any, would have occurred following a single exposure. The uncertainty of estimating acute effects from a multiple exposure study and the typically steep exposure-response for organophosphate poisoning justify estimating AEGL-2 values by a 3-fold reduction of the AEGL-3 values (NRC, 2001).

Information on the acute toxicity of phorate following inhalation exposure is limited to one report on rats (Newell and Dilley 1978). One-hour inhalation of phorate aerosol produced LC_{50} values of 60 mg/m^3 for male rats and 11 mg/m^3 for female rats. All animals that received "toxic or lethal doses" exhibited the common signs of cholinergic poisoning in a dose-dependent manner. However, no dose-response details were provided. Since detailed dose-response data are lacking, a three-fold reduction of the 1-hr LC_{50} of 11 mg/m^3 in female rats (3.67 mg/m^3) was used as an estimate of the phorate point-of departure (POD) for lethality (NRC 2001). This approach is justified by the steep concentration-response curve. [Organophosphate poisoning typically exhibits a steep exposure-response curve (NRC, 2003), and phorate appears to be no exception. Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.] Lethality data were not sufficient for empirical derivation of a time-scaling factor (n) for use in the equation $C^n \times t = k$ (ten Berge et al., 1986). Therefore, temporal scaling from the experimental duration of the respective POD to AEGL-specific durations was performed

using $n = 3$ when extrapolating to time points shorter than one hour and $n = 1$ when extrapolating to time points of an hour or longer using the $C^n \times t = k$ equation (NRC 2001). The total uncertainty factor adjustment for phorate AEGL-3 derivations is 30. The mechanism of action of organophosphate anticholinesterases is well understood and their action on cholinergic systems shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase activity and types of cholinesterase (humans having greater levels of plasma cholinesterase for protective detoxification than other species). Therefore, the interspecies uncertainty is limited to 3 as opposed to the default value of 10. The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify using the intraspecies default uncertainty factor of 10. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC, 2003).

Derived AEGL valued are presented in Table S-1.

S-1. AEGL Values for phorate (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL-2 (Disabling)	0.073	0.050	0.040	0.010	0.0050	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001; Newell and Dilley 1978)
AEGL-3 (Lethality)	0.22	0.15	0.12	0.031	0.015	Derived based on the 1-hr LC_{50} of 11 mg/m^3 in female rats (Newell and Dilley 1978); UF = 3 (interspecies) and 10 (intraspecies); n = 1or 3

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

1. INTRODUCTION

Phorate is an organophosphate insecticide used as a systemic and contact insecticide to protect potatoes, corn, peanuts, cotton, sugarcane, wheat, soybeans, beans, sorghum, and sugar beets from a number of pests. Annual production in 1972 was approximately 3.6 million kg (HSDB 2008). Phorate was the most toxic of five organophosphate insecticides given by inhalation for 1 hour to rats (Newell and Dilley (1978). All the animals that received toxic or lethal doses of these five organophosphate pesticides, exhibited the common signs of cholinergic poisoning: salivation, lacrimation, exophthalmos, defecation, urination, and muscle fasciculations. Cholinergic signs were dose dependent with each compound, and their duration varied among the compounds tested.

The physico-chemical properties of phorate are summarized in Table 1.

TABLE 1. Chemical and Physical Properties

Parameter	Value	References
Synonyms	Phosphorodithioic acid, O,O-diethyl S-(ethylthio)methyl ester; O,O-Diethyl ethylthiomethyl phosphorodithioate; Thimet; Rampart	O'Neil et al. 2001
Chemical formula	C_7-H_{17}-O_2-P-S_3	HSDB 2008
Molecular weight	260.34	HSDB 2008
CAS Reg. No.	298-02-2	HSDB 2008
Physical state	Liquid, light yellow	HSDB 2008
Odor	Skunk-like	HSDB 2008
Solubility in water	50 mg/ml @25°C	HSDB 2008
Vapor pressure	85 mPa @25°C	HSDB 2008
Liquid density (water =1)	1.156 @25°C	HSDB 2008
Melting point	-15°C	HSDB 2008
Boiling point	125-127 °C @2.0 mm Hg	HSDB 2008
Flash point	160 °C, open cup	HSDB 2008
Flammability limits	Combustible, does not readily ignite	NIOSH 2005
Conversion factors	1 ppm = 10.6 mg/m^3 1 mg/m^3 = 0.095 ppm	ACGIH 2005

2. HUMAN TOXICITY DATA

No controlled human studies relating phorate exposure with cholinergic responses were found.

2.1. Acute Lethality

2.1.1. Case Reports

Two workers experienced signs and symptoms of cholinesterase inhibition (confusion, dizziness, nausea, vomiting, constricted pupils, severe tachycardia, excessive salivation, respiratory distress, muscle fasciculation, and unconsciousness in one worker) in a pesticide

formulating plant where phorate concentrations ranged from 0.07 to 14.6 mg/m^3(ACGIH 2005). After appropriate treatment, recovery was prompt and uncomplicated.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

ACGIH reported a study in which 60% of a group of 40 workers engaged in the formulation of 10% phorate granules experienced cholinergic symptoms. Exposure levels were not reported.

2.3 Genotoxicity

ACGIH (2005) reported that no mutagenic response was found in an unscheduled DNA synthesis assay in human fibroblasts (WI-38 cells) at concentrations up to 10^{-3} mol/L. Garret et al. (1992) reviewed the genetic toxicity testing on 24 organophosphates, including phorate, and concluded the insecticide produced negative results. One exception was reported by Sobti et al. (1982) in which an increase in sister chromatid exchanges was noted using a transformed human lymphoblastoid cell line.

2.4. Carcinogenicity

No data on human carcinogenicity were found in the available literature.

2.5. Summary

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Studies were limited to one report in the available literature. Four groups of ten male and ten female Sprague-Dawley rats were exposed for 1 hour to atmospheres containing aerosols of phorate (1% in xylene) generated by a pneumatic aerosol generator (Newell and Dilley 1978; Table 2). The aerosol, averaging less than 1 μm in aerodynamic size, was in a highly respirable range. Average chamber concentrations, verified during exposure by gas chromatography, were 11, 21, 47, and 170 mg/m^3 and had a droplet mass median aerodynamic diameter of 0.44 μm (geometric standard deviation = 2.50). The animals were observed for toxic signs and mortality during exposure and for 14 days afterwards. Neither blood nor brain cholinesterase inhibition was measured. Detailed descriptions of the cholinergic signs of toxicity, their onset, and duration were not provided. Generally, all animals that received "toxic or lethal doses" exhibited the common signs of cholinergic poisoning in a dose-dependent manner (salivation, lacrimation, exophthalmos, defecation, urination, and muscle fasciculations). However, the investigators noted that rats surviving exposure recovered completely within 10 to 14 days afterward. Females were more sensitive to the acute toxic effects than were males. No concentration-specific lethality data were provided; however, LC_{50} values were reported. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. Histological examination of lungs from animals of the highest exposure concentration (time of death or sacrifice was not specified) showed pulmonary

irritation as evidenced by hemorrhage, edema, and congestion.

Newell and Dilley (1978) also reported the findings on groups of ten pregnant female rats exposed to phorate at aerosol concentrations of 0.15, 0.40, and 1.94 mg/m^3 for one hr/day during days 7-14 of gestation (Table 2). The animals exposed to 1.94 mg/m^3 (the highest concentration) exhibited toxic signs and mortality during the eight daily exposures. All high-dose rats exhibited tremors, lacrimation, and exophthalmos. A total of five animals died at this exposure level, one after the third, fourth, sixth, seventh, and eighth exposures, respectively. Two rats that died had bloody material in their intestines and bladder. One rat that died after the eighth exposure appeared to be resorbing her entire litter. No maternal deaths were reported for the two lower exposure levels. No differences in food consumption or weight gain were noted.

TABLE 2. Phorate Inhalation Toxicity in Animals

Species	Concentration (mg/m^3)	MMAD[a] (μm)	δg[b]	Exposure time	Endpoint	Reference
Rat 10/sex/group	11, 21, 47, 170	0.44	2.50	1 h	LC_{50} = 11 mg/m^3 for female rats (95% CL = 7-15 mg/m^3); LC_{50} = 60 mg/m^3 in male rats, 95% CL = 52-69 mg/m^3). Salivation, lacrimation, exophthalmos, defecation, urination, and muscle fasciculations were reported without dose-response details.	Newell and Dilley 1978
Rat 10 pregnant females/group	0, 0.15, 0.40, 1.94, and xylene solvent control	0.44	2.50	1 h/day, GD 7-14	0.15, 0.40 mg/m^3 = No maternal deaths; no significant fetal mortality. 1.94 mg/m^3 = Maternal toxicity (50% mortality; all had tremors, lacrimation, and exophthalmos); substantial fetal mortality (31% vs. 7.4% for xylene controls).	Newell and Dilley 1978

[a] mass median aerodynamic diameter
[b] geometric standard deviation

Acute dermal LD_{50} values of 9.3 mg/kg (95% CL = 7.9-11) for male rats and 3.9 mg/kg (95% CL = 3.4-4.4) for female rats were reported by Newell and Dilley (1978). The specific dose levels applied were not provided, but the findings indicate that phorate is readily absorbed and toxic following dermal exposure. However, in the circumstances of a whole body airborne exposure, the inhalation route would be a much greater hazard concern relative to dermal exposure.

3.2. Nonlethal Toxicity

No inhalation studies on the nonlethal effects of phorate were available in the literature. Rats and dogs were evaluated following oral administration of phorate for approximately 13 weeks (U.S. EPA 1998). Rats were fed diets containing 0, 0.22, 0.66, 2.0, 6.0, 12.0, or 18.0 ppm (equivalent to 0, 0.011, 0.033, 0.1, 0.3, 0.6, or 0.9 mg/kg/day/day). Mortality and reduced body

weight gain and food consumption were seen in both sexes fed either 12.0 or 18.0 ppm. Red blood cell (RBC) and brain cholinesterase activity were significantly inhibited at feeding levels of 2.0 ppm or greater; the NOEL was 0.66 ppm (0.033 mg/kg/day). Dogs were given capsules containing 0, 0.01, 0.05, 0.25, 1.25, or 2.5 mg/kg/day, 6 days/week for 13 to 15 weeks. Mortality was seen at the two highest levels with the dogs showing the typical cholinergic signs. RBC cholinesterase was inhibited by doses of 0.25 mg/kg/day in both sexes; the NOEL was 0.05 mg/kg/day.

3.3 Developmental/Reproductive Toxicity

Newell and Dilley (1978) exposed groups of ten pregnant female rats to phorate at aerosol concentrations of 0, 0.15, 0.40, and 1.94 mg/m^3 for one hr/day during days 7-14 of gestation (Table 2). A xylene control group was also included. The animals exposed to the highest phorate concentration exhibited toxic signs and mortality during the eight daily exposures. All high-dose rats exhibited tremors, lacrimation, and exophthalmos. A total of five animals died at the high concentration, one after the third, fourth, sixth, seventh, and eighth exposures, respectively. Two rats that died had bloody material in their intestines and bladder. One rat that died after the eighth exposure appeared to be resorbing her entire litter. No compound-related differences in food consumption or weight gain were noted. The highest exposure level produced notable maternal (50%) and fetal (31%) mortality rates. Also, the average fetal weight at the highest exposure was slightly greater than the other groups. No other fetal effects were seen. These observations were not the result of restricted food intake or solvent (xylene) toxicity.

3.4. Genotoxicity

ACGIH (2005) reviewed numerous genotoxicity assays on phorate and found no evidence of genotoxicity in a battery of tests. Phorate was negative in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA1538 in the presence and absence of metabolic activation. The outcomes were the same in assays with *Escherichia coli* in the presence and absence of metabolic activation, and in cultured Chinese hamster ovary cells (HGPRT locus) with and without metabolic activation. The chemical did not increase chromosomal aberrations in a dominant lethal test in mice and did not cause chromosomal aberrations in mammalian (rat) bone marrow cells at intraperitoneal doses up to 2.5 and 1.5 mg/kg/day in males and females, respectively. Phorate was negative in a mitotic recombination assay with *Saccharomyces cerevisiae* D3 with and without metabolic activation. Preferential toxicity assays in DNA repair proficient and deficient strains of *Eschericha coli* and *Bacillus subtillis* were negative, and preferential toxicity assays in DNA repair proficient and deficient strains of *B. subtilis* (strain H17 and M45, respectively) were also negative.

Garret (1992) reviewed the genetic toxicity testing on 24 organophosphates, including phorate, and concluded the insecticide produced negative results with the exception of one reported increase in sister chromatid exchanges using a transformed human lymphoblastoid cell line. Overall, the weight of evidence indicates that phorate is not genotoxic.

3.5. Chronic Toxicity/Carcinogenicity

No evidence of carcinogenicity occurred in rats given diets that contained 0, 1, 3, or 6 ppm phorate (about 0, 0.05, 0.15, or 0.3 mg/kg/day) for 2 yr. RBC and brain cholinesterase inhibition occurred at exposures of 3 and 6 ppm (Bingham et al., 2001). No evidence of carcinogenicity or other adverse effects occurred in mice given diets that contained 0, 1, 3, or 6 ppm phorate (about 0, 0.15, 0.45, or 0.9 mg/kg/day) for 78 weeks, other than a slight decrease in body weight gain in females that were fed 6 ppm.

3.6. Summary of Animal Toxicity

Information on the acute lethality of phorate following a single inhalation exposure is limited to one study in rats (Newell and Dilley 1978). One-hour inhalation of phorate aerosol produced LC_{50} values of 60 mg/m^3 for male rats and 11 mg/m^3 for female rats. All animals that received "toxic or lethal doses" exhibited the common signs of cholinergic poisoning in a dose-dependent manner. In another study by the same investigators, five of ten pregnant female rats exposed to 1.94 mg/m^3 (the highest concentration) died during the eight days of exposure, and all exhibited the signs of cholinesterase inhibition.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No metabolism and disposition studies following inhalation of phorate were available in the literature. Phorate is readily absorbed by the skin, as well as by the gastrointestinal tract, as evidenced by its high acute toxicity via these routes of exposure. A single oral dose of ^{14}C-phorate to male rats was readily absorbed and excreted with approximately 77.2% of the total administered ^{14}C in the urine and 11.7% in the feces within 24 hours (ACGIH 2005). Less than 1 % of the total radioactivity was found in tissues (highest level in blood) at 24 hours. Ten metabolites were present in the urine. Two nonphosphorylated metabolites comprised approximately 71% of the radioactivity present in the urine. About 19% of the urinary ^{14}C was associated with phosphorylated metabolites. Unchanged parent compound accounted for only 0.5% of the recovered urinary ^{14}C, and the remaining four phosphorylated compounds plus one unidentified metabolite together comprised less than 10% of the urinary radioactivity. These metabolites were formed following cleavage of the sulfur phosphorus bond associated with the carbon chain in phorate, from methylation of the liberated thiol group, and from oxidation of the resulting sulfide to sulfoxide and sulfone.

4.2. Mechanism of Toxicity

All organophosphate cholinesterase inhibitors have the same mechanism of action. These chemicals phosphorylate cholinesterase by reacting at the esteratic subsite of the enzyme which in turn prevents the enzyme from deactivating acetylcholine (Taylor, 2006). The overall result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors).

4.3. Structure Activity Relationships

Although all organophosphate cholinesterase inhibitors have the same mechanism of action, their potencies and physicochemical properties vary. The physicochemical differences will also affect environmental persistence and metabolic fate. Development of AEGL values by structure-activity analysis would be tenuous and uncertain without rigorous relative potency data.

4.4. Other Relevant Information

4.4.1. Species Variability

There are insufficient data to assess species variability in the toxic response to inhaled phorate *per se*. Variability in types of esterases and their respective activities is important regarding interspecies variability in organophosphate poisoning. This will affect susceptibility to organophosphates due to differences in detoxification potential (NRC, 2003). Baseline red blood cell acetylcholinesterase activity is slightly higher in humans (12.6 µmol/mL/min) than in monkeys (7.1 µmol/mL/min) and much higher compared to other species (4.7 µmol/mL/min for pigs; 4.0 µmol/mL/min for goats; 2.9 µmol/mL/min for sheep; 2.4 µmol/mL/min for mice; 2.0 µmol/mL/min for dogs; 2.7 µmol/mL/min for guinea pigs; 1.7 µmol/mL/min for both rats and rabbits; and 1.5 µmol/mL/min for cats) (Ellin, 1981). Similarly, humans tend to have greater plasma cholinesterase activity levels than other species (Wills, 1972). In humans, approximately 50% of the total blood cholinesterase consists of plasma cholinesterase. Plasma cholinesterase activity constitutes approximately 40% of the total blood cholinesterase in dogs, 30% in rats, 20% in monkeys, and only 10% in sheep, horses, and cows. Both of these findings suggest that humans will have greater potential for buffering the activity of organophosphate anticholinesterases by preventing interaction with red blood cell and brain cholinesterase as well as cholinesterase at neuromuscular junctions (NRC, 2003). Carboxylesterases known to occur in human erythrocytes, liver, lung, skin, and nasal tissue may also contribute to detoxification of organophosphates but the quantitative aspect of this has not been fully characterized (NRC, 2003).

The mechanism of action of organophosphates is well characterized (NRC, 2003) and is similar across species. Species variability in toxic response is more a function of variability in detoxification potential.

4.4.2. Susceptible Populations

Individual variability in plasma cholinesterase activity is well documented (NRC, 2003). This variability includes age-related differences (neonates are more susceptible than are adults), gender differences (females tend to have approximately 10% lower plasma and red blood cell cholinesterase activity), and genetically determined variations in plasma cholinesterase activity. This genetically determined variability, sometimes resulting in greatly reduced (64% of normal) activity of plasma cholinesterase may impart deficiencies in ability to detoxify organophosphates such as parathion. Additionally, polymorphic variability in A-esterases (i.e., paraoxonase/arylesterase) may also contribute to individual variability in organophosphate ester detoxification processes (NRC, 2003).

4.4.3. Concurrent Exposure Issues

Both concurrent exposure to other organophosphates and simultaneous exposure via other exposure routes would be of concern. Phorate may enter the body and be bioavailable by dermal, oral and inhalation pathways. Animal studies show that phorate is readily absorbed through the skin and gastrointestinal tract, as evidenced by its high acute toxicity via these routes of exposure (ACGIH 2005).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were available.

5.2. Summary of Animal Data Relevant to AEGL-1

There are no animal data on acute inhalation exposure to phorate demonstrating effects appropriate for deriving AEGL-1 values.

5.3. Derivation of AEGL-1

Data are insufficient for derivation of AEGL-1 values for phorate. The toxicity data reported in Newell and Dilley (1978) relate to multiple exposures over eight days, and detailed descriptions of the cholinergic signs of toxicity, their onset, and duration were not provided. Therefore, AEGL-1 values are not recommended (Table 3).

TABLE 3. AEGL-1 Values for Phorate

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

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

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values were available.

6.2. Summary of Animal Data Relevant to AEGL-2

The only data identifying nonlethal effects in animals following inhalation exposure to phorate are the results from a teratogenicity study in rats reported by Newell and Dilley (1978). Groups of ten pregnant female rats were exposed to phorate at aerosol concentrations of 0, 0.15, 0.40, and 1.94 mg/m^3 for one hr/day during days 7-14 of gestation. Rats exposed to the highest concentration exhibited tremors, lacrimation, and exophthalmos (onset and duration not provided). A total of five animals died at the high concentration, one after the third, fourth, sixth, seventh, and eighth exposures, respectively. No maternal deaths or cholinergic effects were reported for the two lower exposure levels. No compound-related differences in food consumption or weight gain were noted. It is uncertain which effects, if any, would have

occurred following a single 1-hour exposure.

6.3. Derivation of AEGL-2

Data were insufficient for empirical derivation of an AEGL-2 for phorate. Although the clinical signs reported for pregnant rats following repeated exposures to phorate (1.94 mg/m^3 for one hr/day, days 7-14 of gestation; Newell and Dilley, 1978) are appropriate for deriving AEGL-2 values, they were observed at an exposure level producing significant mortality. It is uncertain which effects, if any, would have occurred following a single exposure. A steep dose-response relationship is typical of the organophosphate cholinesterase inhibitors (NRC 2003). Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship. This relationship justifies estimating the AEGL-2 by a 3-fold reduction of the AEGL-3 values (NRC 2001). The AEGL-2 values are shown in Table 4 and Appendix A.

TABLE 4. AEGL-2 Values for Phorate[a]

10-min	30-min	1-h	4-h	8-h
0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3

[a] Derived from aerosol concentrations

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Newell and Dilley (1978) reported phorate acute LC_{50} values for single 1-hour exposures of rats of 60 mg/m^3 for males (95% CL = 52-69 mg/m^3) and 11 mg/m^3 for females (95% CL = 7-15 mg/m^3). The aerosol exposure levels used in the study were 11, 21, 47, and 170 mg/m^3 (mass median aerodynamic diameter = 0.44 μm, a highly respirable size), but detailed dose-response data were not provided. No other lethality data from single inhalation exposures were available.

7.3. Derivation of AEGL-3

Since detailed dose-response data are lacking for the only available acute inhalation lethality study, a three-fold reduction of the 1-hr LC_{50} of 11 mg/m^3 in female rats (3.67 mg/m^3) was used as an estimate of the phorate POD for lethality (NRC 2001). This approach is justified by the steep concentration-response curve. [Organophosphate poisoning typically exhibits a steep exposure-response curve (NRC, 2003), and phorate appears to be no exception. Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.] Lethality data were not sufficient for empirical derivation of a time-scaling factor (n) for use in

the equation C^n x t = k (ten Berge et al., 1986). Therefore, temporal scaling from the duration of the respective POD to AEGL-specific durations was performed using $n = 3$ when extrapolating to time points shorter than one hour and $n = 1$ when extrapolating to time points of an hour or more using the $C^n \times t = k$ equation (NRC 2001).

The total uncertainty factor adjustment for phorate AEGL-3 derivations is 30. As described in Sections 4.2 and 4.4, the mechanism of action of organophosphate anticholinesterases is well understood and their action on cholinergic systems shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase activity and types of cholinesterase. Humans have been shown to have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds. This decreases the availability of the compound to critical targets (e.g., brain cholinesterase). Therefore, the interspecies uncertainty is limited to 3 as opposed to the default value of 10. The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify using the intraspecies default uncertainty factor of 10. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC, 2003). The resulting AEGL-3 values are shown in Table 5 and Appendix A.

TABLE 5. AEGL-3 Values for Phorate[a]

10-min	30-min	1-h	4-h	8-h
0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3

[a] Derived from aerosol concentrations

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

TABLE 6. Summary of AEGL Values [a]

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3
AEGL-3 (Lethal)	0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3

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

[a] Derived from aerosol concentrations

8.2. Comparison with Other Standards and Guidelines

AEGL values for phorate are compared to other guidelines and standards for this compound in Table 7.

TABLE 7. Extant Standards and Guidelines for Phorate

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3
AEGL-3	0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3
ERPG-1 (AIHA)[a]					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					(0.05 mg/m^3)[c]
PEL-STEL (OSHA)[d]					(0.2 mg/m^3)[d]
IDLH (NIOSH)[e]					
REL-TWA (NIOSH)[f]					0.05 mg/m^3
REL-STEL (NIOSH)[g]					0.2 mg/m^3
TLV-TWA (ACGIH)[h]					0.05 mg/m^3
TLV Excursion Limit (ACGIH)[i]		0.15 mg/m^3			

[a] ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2007)
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] EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC)
is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c] OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (vacated by OSHA in 1989 but still used by some states; OSHA 2007). Defined as analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d] OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit) (vacated by OSHA in 1989 but still used by some states; HSDB 2008; OSHA 2007). Defined as analogous to the ACGIH-TLV-STEL.

[e] IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH, 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f] NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH, 2005) is defined analogous to the ACGIH-TLV-TWA.

[g] NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH, 2005)
is defined analogous to the ACGIH-TLV-STEL.

[h] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH, 2005) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect

[i] ACGIH TLV Excursion Limit) (ACGIH, 2005) is defined as a 30-minute TWA exposure which should not be exceeded provided that the 8-hour TWA is within the TLV-TWA. Exposures at 5-fold or above the TLV-TWA should not occur under any circumstances.

8.3. Data Adequacy and Research

Inhalation toxicity data on phorate are very limited. No quantitative data are available regarding human exposure. Animal data are limited to one species, the rat, and are primarily lethality data. Inhalation data that would permit more precision in the development of AEGLs would be more detailed dose-response lethality- and nonlethality data identifying effects appropriate for the derivation of AEGL-2 values.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Phorate

AEGL-1 values are not recommended for phorate due to insufficient data.

Derivation of AEGL-2 Values for Phorate

Data were insufficient for empirical derivation of AEGL-2 values for phorate. Due to the steep exposure-response relationship typical of the organophosphate cholinesterase inhibitors such as phorate (NRC 2003), the AEGL-2 values have been estimated as a 3-fold reduction of the AEGL-3 values (NRC 2001). [Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.]

10-minute AEGL-2 0.22 mg/m^3 /3 = 0.073 mg/m^3

30-minute AEGL-2 0.15 mg/m^3 /3 = 0.050 mg/m^3

1-hr AEGL-2 0.12 mg/m^3 /3 = 0.040 mg/m^3

4-hr AEGL-2 0.031 mg/m^3 /3 = 0.010 mg/m^3

8-hr AEGL-2 0.015 mg/m^3 /3 = 0.0050 mg/m^3

Derivation of AEGL-3 Values for Phorate

Key study:	Newell, G.W., Dilley, J.V. 1978. Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Stanford Research Inst. Report No. EPA-600/1-78-003; NTIS PB277077.
Critical effect:	3.67 mg/m^3 used as estimate of the lethality threshold based on the three-fold reduction of the 1-hr LC_{50} = 11 mg/m^3 in female rats (95% CL = 7-15 mg/m^3; LC_{50} = 60 mg/m^3 in male rats, 95% CL = 52-69). This approach is justified by the steep concentration-response curve. [Organophosphate poisoning typically exhibits a steep exposure-response curve (NRC, 2003), and phorate appears to be no exception. Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.]
Secondary support for derived values:	5/10 pregnant females died after 3-7 days of 1 hr exposures to 1.94 mg/m^3 in teratology study in rats. None died after 8 days of exposure to 0.40 mg/m^3 (Newell, G.W., Dilley, J.V. 1978).
Time scaling:	$C^n \times t = k$, where n = 1 or 3 The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). Extrapolations at all AEGL time points were based on the 1-hr exposure data.
Uncertainty factors:	Total uncertainty factor adjustment is 30. <u>Interspecies</u>: 3; the default value of 10 was considered unnecessary since variability in toxic response to phorate is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases than do other species. This decreases the dose to critical targets. <u>Intraspecies</u>: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify use of the default intraspecies uncertainty factor of 10.
Modifying Factor:	None

Calculation: AEGLs $\geq$ 1 hr: $(3.67\ mg/m^3)^1 \times 1\ hr = 3.67\ mg/m^3 \cdot hrs$
AEGLs < 1 hr: $(3.67\ mg/m^3)^3 \times 1\ hr = 49.4\ mg/m^3 \cdot hrs$

10-minute AEGL-3

$C^3 \times 0.167\ hrs = 49.4\ mg/m^3 \cdot hrs$
$C^3 = 296\ mg/m^3$
$C = 6.66\ mg/m^3$
$C = 6.66\ mg/m^3 / 30 = 0.22\ mg/m^3$

30-minute AEGL-3

$C^3 \times 0.5\ hrs = 49.4\ mg/m^3 \cdot hrs$
$C^3 = 98.8\ mg/m^3$
$C = 4.62\ mg/m^3$
$C = 4.62\ mg/m^3 / 30 = 0.15\ mg/m^3$

1-hour AEGL-3

$C^1 \times 1\ hr = 3.67\ mg/m^3 \cdot hrs$
$C = 3.67\ mg/m^3$
$C = 3.67\ mg/m^3 / 30 = 0.12\ mg/m^3$

4-hour AEGL-3

$C \times 4\ hrs = 3.67\ mg/m^3 \cdot hrs$
$C = 0.918\ mg/m^3$
$C = 0.918\ mg/m^3 / 30 = 0.031\ mg/m^3$

8-hour AEGL-3

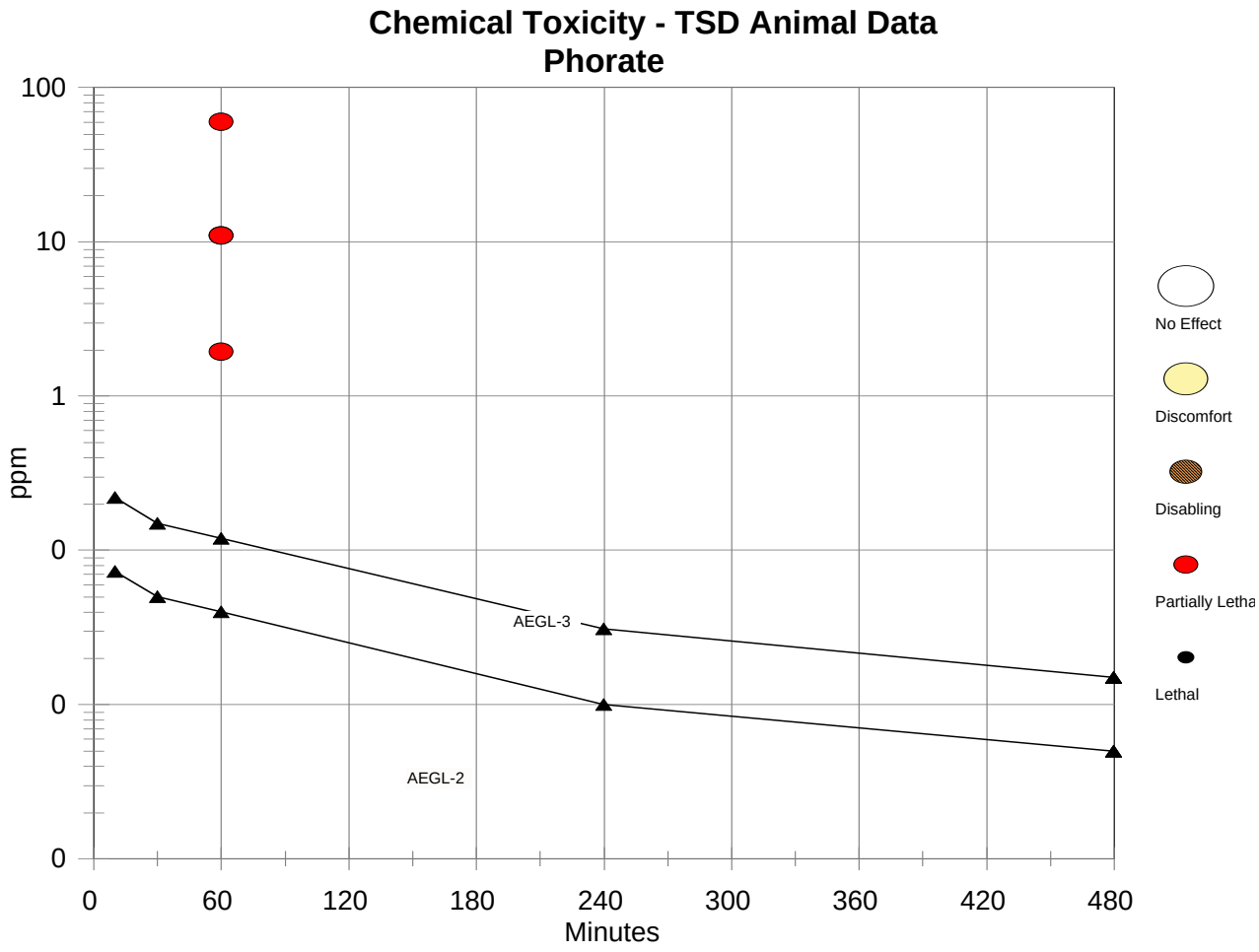
$C \times 8\ hrs = 3.67\ mg/m^3 \cdot hrs$
$C = 0.459\ mg/m^3$
$C = 0.459\ mg/m^3 / 30 = 0.015\ mg/m^3$

APPENDIX B: Time-Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically in the form of a linear regression analysis of the log-log transformation of a plot of C vs t. Ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

The available data do not allow for empirical derivation of a temporal scaling factor (n) for phorate. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to exposure time points shorter than the selected POD, and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.

APPENDIX C: Category Plot



Phorate

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Partially Lethal, 3 = Lethal

Source	Species	Sex	# Exp.	ppm	Min.	Category	Comments
NAC/AEGL-1				1	10	AEGL	
NAC/AEGL-1				1	30	AEGL	
NAC/AEGL-1				1	60	AEGL	
NAC/AEGL-1				1	240	AEGL	
NAC/AEGL-1				1	480	AEGL	
NAC/AEGL-2				0.073	10	AEGL	
NAC/AEGL-2				0.05	30	AEGL	
NAC/AEGL-2				0.04	60	AEGL	
NAC/AEGL-2				0.01	240	AEGL	
NAC/AEGL-2				0.005	480	AEGL	
NAC/AEGL-3				0.22	10	AEGL	
NAC/AEGL-3				0.15	30	AEGL	
NAC/AEGL-3				0.12	60	AEGL	
NAC/AEGL-3				0.031	240	AEGL	
NAC/AEGL-3				0.015	480	AEGL	
	rat	m	1	60	60	pl	*LD50 rats males (Newell and Dilley, 1978)
	rat	f	8	1.94	60	pl	*50% Maternally lethal dose (Newell and Dilley, 1978)
	rat	f	1	11	60	pl	*LD50 rats females (Newell and Dilley, 1978)

*Concentration-specific data were not reported. Therefore, category plot reflects LC_{50} values.

APPENDIX D: Derivation Summary Tables for Phorate AEGLs

AEGL-1 VALUES FOR PHORATE (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
NR	**NR**	**NR**	**NR**	**NR**
Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations : NA				
Effects: NA				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale : NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data Adequacy: Data are insufficient for derivation of AEGL-1 values for phorate, so values are not recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.				

1
2
3

AEGL-2 VALUES FOR PHORATE (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.073	**0.050**	**0.040**	**0.010**	**0.0050**
Reference: NA				
Test Species/Strain/Sex/Number: NA				
Exposure Route/Concentrations/Durations: One-third the AEGL-3 values. Supported by steep exposure-response relationship typical of the organophosphate cholinesterase inhibitors (NRC 2003), and phorate appears to be no exception (Newell and Dilley 1978). Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.				
Effects:				
Endpoint/Concentration/Rationale: : One-third the AEGL-3 values.				
Uncertainty Factors/Rationale: NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data Adequacy: Data available on AEGL-2 severity effects are only from a multiple exposure protocol study.				

4

1

AEGL-3 VALUES FOR PHORATE (mg/m^3)				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.22	**0.15**	**0.12**	**0.031**	**0.015**
Key Reference: Newell, G.W., Dilley, J.V. 1978. Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Stanford Research Inst. Report No. EPA-600/1-78-003; NTIS PB27707				
Test Species/Strain/Number: Sprague-Dawley rats (10/sex/group)				
Exposure Route/Concentrations/Durations: Inhalation ; aerosols at concentrations of 11, 21, 47, and 170 mg/m^3 with a droplet mass median aerodynamic diameter of 0.44 µm (geometric standard deviation = 2.50).				
Effects: LC_{50} = 11 mg/m^3 for female rats (95% CL = 7-15 mg/m^3)				
Endpoint/Concentration/Rationale: Lethality; 3.67 mg/m^3; three-fold reduction of LC_{50}. This approach is justified by the steep concentration-response curve. [Organophosphate poisoning typically exhibits a steep exposure-response curve (NRC, 2003), and phorate appears to be no exception. Even though the mortality incidence data on phorate are not reported, the 95% confidence levels for the LC_{50} (Newell and Dilley, 1978) values are narrow. The acute LC_{50} for a 1-hour exposure of phorate was 60 mg/m^3 (95% CL = 52-69 mg/m^3) for male rats and 11 mg/m^3 (95% CL = 7-15 mg/m^3) for female rats. These findings are indicative of a steep dose-response relationship.				
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 3; the default value of 10 was considered unnecessary since variability in toxic response to phorate is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases than do other species. This decreases the dose to critical targets. Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies use of the default intraspecies uncertainty factor of 10.				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: None				
Time Scaling: $C^n \times t = k$, where n = 1 or 3; n = 3 when extrapolating to shorter time points of <1 hr and n = 1 when extrapolating to longer time points (≥1 hr).				
Data Adequacy: Data are limited to one species but adequate for AEGL-3 derivation.				

2

3