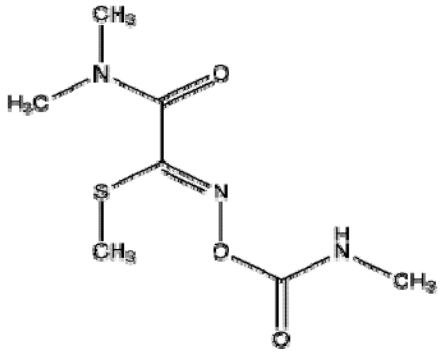
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

OXAMYL

(CAS Reg. No. 23135-22-0)



PROPOSED

PREFACE

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

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

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

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

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

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

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SUMMARY

Oxamyl (CAS No. 23135-22-0) is a crystalline solid *N*-methyl carbamate insecticide with a slightly sulfurous odor. Oxamyl is used as an insecticide, nematicide, and acaricide on field crops such as vegetables, fruits, and ornamentals. It is sold as a granule formulation or as a liquid formulation under the trade name Vydate™. Solid oxamyl is very stable and has a low vapor pressure. Oxamyl is manufactured commercially by chlorination of the oxime of methyl glycolate, reaction of that product with methanethiol and alkali, followed by reaction with dimethylamine, and conversion to the carbamate with methyl isocyanate. Approximately 800,000 pounds of active ingredient are applied annually in the United States. Application to cotton fields accounts for most of the usage.

Oxamyl and other carbamate pesticides are neurotoxic in that they are inhibitors of the enzyme acetylcholinesterase. Inhibition of acetylcholinesterase, responsible for termination of the biological activity of the neurotransmitter acetylcholine at various nerve endings, produces sustained stimulation of electrical activity. Depending on the concentration administered, signs following acute exposure of rats to oxamyl may include facial fasciculations, tremors, salivation, lacrimation, gasping and convulsions. In humans, inhibition of erythrocyte acetylcholinesterase activity is used as a biomarker of methyl carbamate exposure and effects. No inhalation studies involving human subjects were located. Given that methyl carbamate pesticides do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation, relative acetylcholinesterase activity inhibition levels measured from oral studies with humans and juvenile and adult rats were used to derive interspecies and intraspecies uncertainty factors.

The recent well-conducted study of O'Neil (2000, reviewed in U.S. EPA 2000) with rats inhaling oxamyl dust was chosen as the key study to derive AEGL-1 values. In that study, male and female rats inhaled 4.9 mg/m^3 of oxamyl dust for 4 hours. Erythrocyte acetylcholinesterase activity was inhibited by an average 28.5% and brain cholinesterase by an average 12% (sexes combined). Erythrocyte acetylcholinesterase activity inhibition of that magnitude may result in transient symptoms of discomfort in humans. Exposure to 24 mg/m^3 for 4 hours resulted in average erythrocyte and brain cholinesterase activity inhibition of 67-73%. Following exposure, rats showed ocular/nose discharge, diarrhea, tremors, and lethargy. Signs were similar in the control and 4.9 mg/m^3 exposure groups. The 4-hour 4.9 mg/m^3 value was divided by inter- and intraspecies uncertainty factors of 3 and 3.48, respectively, for a total of 10. The chemical-specific uncertainty factors were calculated by U.S. EPA (2007b). Their oxamyl-specific interspecies inhalation uncertainty factor was based on differences in modeled values for erythrocyte cholinesterase activity inhibition between rats and humans following oral dosing. Based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated an uncertainty factor of 3.48 to protect sensitive young. The resulting 0.49 mg/m^3 value was time-scaled ($C^n \times t = k$) from the 4-hour data point using an n value of 1.6 derived from three lethality studies involving exposure durations of 1 and 4 hours.

No studies that addressed effects consistent with the definition of the AEGL-2 tier were found. The concentration-response curve for lethality in rats is steep. As shown by the study of Kelly (2001), mortality went from 0% at 50 mg/m^3 to 100% when concentration was increased

2.4-fold (120 mg/m^3). Therefore, according to Standard Operating Procedures (NRC 2001), the AEGL-2 values were derived by dividing the AEGL-3 values by 3.

The study of Kelly (2001) with male and female rats was chosen as the basis for development of AEGL-3 values. The study was conducted according to U.S. EPA guidelines. The calculated 4-hour $BMCL_{05}$ for lethality for oxamyl dust was 22 mg/m^3. The 22 mg/m^3 value was divided by inter- and intraspecies uncertainty factors of 3 and 3.48 for a total of 10. U.S. EPA (2007b) derived an interspecies uncertainty factor of 3 for oxamyl based on differences in values for erythrocyte acetylcholinesterase activity inhibition between rats and humans. Based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated an uncertainty factor of 3.48 to protect sensitive young. The combined (rounded) uncertainty factor is 10. Although female rats appear to be slightly more sensitive to the toxic effects of oxamyl than male rats, the combined data with application of an uncertainty factor that protects sensitive juveniles provides a reasonable estimate of lethality. Values were time-scaled ($C^n \times t = k$) from the 4-hour data point using an n value of 1.6. The n value of 1.6 was based on three studies that encompassed exposure durations of one and four hours.

The calculated values are listed in the table below.

S 1. Summary of AEGL Values for Oxamyl

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL−1 (Nondisabling)	3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3	Slight symptoms of cholinesterase activity inhibition – rat (O'Neil 2000; U.S. EPA 2000)
AEGL−2 (Disabling)	5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3	AEGL-3 values divided by 3 based on steep concentration-response curve
AEGL−3 (Lethal)	16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 mg/m^3	4-hour $BMCL_{05}$ for lethality– rat data (Kelly 2001)

1. INTRODUCTION

Technical oxamyl (CAS No. 23135-22-0) is a crystalline solid *N*-methyl carbamate insecticide with a slight sulfurous odor. Oxamyl is used as an insecticide, nematicide, and acaricide on field crops such as vegetables, fruits, and ornamentals. It is sold under the trade names Vydate™ and Vydate L™. Technical grade oxamyl contains 89% a.i. (active ingredient). It is registered for use as liquid formulations (24 and 42% a.i.) and as a technical solid (42% a.i.). Vydate L is a water soluble liquid containing 24% oxamyl (Kennedy 1986a; HSDB 2004; U.S. EPA 2007a). Oxamyl is also commercially available as a granule formulation (10% a.i.) and as technical material in cyclohexanone/water at 42% a.i. Solid oxamyl is very stable (IPCS 1983). The chemical and physical properties of oxamyl are listed in Table 1.

Oxamyl is manufactured commercially by chlorination of the oxime of methyl glycolate, reaction of that product with methanethiol and alkali, followed by reaction with dimethylamine, and conversion to the carbamate with methyl isocyanate (HSDB 2004). Approximately 800,000 pounds of active ingredient are applied annually in the United States (U.S. EPA 2007a). Cotton accounts for most of the usage.

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Methyl N'N'-dimethyl-*N*-[(methylcarbamoyl)-oxy]-1-thiooxamimidate; 2-(dimethylamino)-*N*-[[(methylamino)]oxy]-2-oxoethanimodothioic acid methyl ester; N'N'-dimethyl-*N*-[(methylcarbamoyl)oxy]-1-thiooxaminidic acid methyl ester; N,N-dimethyl-ά-methylcarbamoyloxyimino-ά-(methylthio)acetamide: methyl 1-(dimethylcarbamoyl)-*N*-(methylcarbamoyloxy)thioformimidate; thioxamyl; DPX-1410; Vydate	O'Neil et al. 2001; U.S. EPA 2007a RTECS 2008
Chemical formula	$C_7H_{13}N_3O_3S$	O'Neil et al. 2001
Molecular weight	219.26	O'Neil et al. 2001
CAS Reg. No.	23135-22-0	O'Neil et al. 2001
Physical state	crystalline solid	O'Neil et al. 2001
Solubility in water	280 g/L	O'Neil et al. 2001
Vapor pressure	0.00023 mm Hg at 20-25ºC	HSDB 2004
Vapor density (air =1)	0.97 g/cm^2 at 25ºC	HSDB 2004
Liquid density (water =1)	No data	
Melting point	100-102ºC	O'Neil et al. 2001
Boiling point	Decomposes above melting point	HSDB 2004
Flammability limits in air	Not available	
Conversion factors	1 ppm = 8.97 mg/m^3 1 mg/m^3 = 0.11 ppm	Calculated

2. HUMAN TOXICITY DATA

No inhalation studies other than accidental exposures were located. These accidental exposures lacked information on concentration and exposure duration. No occupational monitoring data were presented by U.S. EPA (2007a). An oral dosing study was conducted by McFarlane and Freestone (1999; reviewed in U.S. EPA 2005). The Human Studies Review Board (HSRB 2006) reviewed the study and found it met ethical considerations (required by EPA's Human Subjects Protection Rule). Forty healthy male subjects, ages 19-39 years, in groups of five, ingested a gelatin capsule of oxamyl at doses of 0.005, 0.015, 0.03, 0.06, 0.09, or 0.15 mg a.i./kg body weight. Ten subjects received a placebo capsule. The dose was accompanied with a light breakfast. Clinical symptoms and signs were recorded pre-dose and at set times post-dose. Plasma and erythrocyte cholinesterase activity were assayed pre-dose and at set times post-dose. Clinical signs were reported by three subjects in the placebo group, three subjects in the 0.015 mg/kg dose group, one subject in the 0.03 mg/kg dose group, and one

subject in the 0.15 mg/kg dose group. Incidences of these signs did not show a dose-response relationship and did not correspond with cholinesterase activity inhibition in the dosed groups. The time of peak plasma and erythrocyte cholinesterase activity inhibition was 30-60 minutes after dosing, with recovery to baseline by 3 hours post-dose. Based on a 7% inhibition of erythrocyte cholinesterase activity, the U.S. EPA set the LOAEL at 0.09 mg/kg. The NOAEL was 0.06 mg/kg. Erythrocyte cholinesterase activity was inhibited by an average of 28% at 45 minutes post-dose in the 0.15 mg/kg dose group.

3. ANIMAL TOXICITY DATA

Using standard protocols, oxamyl has been tested for ocular and dermal irritation in the rabbit and dermal sensitization in the guinea pig (IPCS 2002). Oxamyl was not considered an ocular or dermal irritant and did not induce skin sensitization. The oral LD_{50} in male and female rats is 2.5-3.1 mg/kg (Kennedy 1986a).

3.1. Acute Lethality

All inhalation studies were conducted with rats (Table 2). In these studies, atmospheres of oxamyl were generated as dust or liquid aerosol. In an early study, groups of six young male ChR-CD rats inhaled 95% pure oxamyl dust, head-only, at concentrations of 140, 160, 180, or 210 mg/m^3 for one hour (Kennedy 1986a; see also DuPont 1969a for details of the study). Groups of six young female ChR-CD rats inhaled oxamyl (95% a.i.) at analytically-determined concentrations of 100, 120, or 140 mg/m^3, head-only, for one hour. All rats were two months old at initiation of the study. Particles were suspended by blowing air through a high velocity glass jet submerged in a mechanically-stirred reservoir of the test dust. Particle size, determined by cascade impactor sampling, averaged 3.5±2.1µ mass median diameter. All surviving rats were observed for 14 days post-exposure. During exposure, clinical signs included facial fasciculations, exophthalmos, lacrimation, red discharge around the nose and eyes, salivation, and gasping. Survivors lost weight during the first day, but showed normal growth thereafter. Calculated 1-hour LC_{50} values were 170 mg/m^3 for male rats and 120 mg/m^3 for female rats.

In a 4-hour study, groups of six male ChR-CD rats inhaled oxamyl dust (95% a.i.), head-only, at analytically-determined concentrations of 20, 53, 66, 77, or 90 mg/m^3 (Kennedy 1986a; DuPont 1969b). Particles were suspended in a 20-liter glass cylinder using a cyclone generator. Particle size (3.5±2.1µ) was determined by cascade impactor sampling. Male rats exposed to 20 mg/m^3 for 4 hours were sacrificed at 1, 2, and 7 days (two rats each day). Major tissues and organs of these rats were examined grossly and microscopically. Signs displayed during exposure were intense salivation, facial fasciculations, red discharge around the nose, lacrimation, exophthalmos, difficulty in breathing, and gasping. Signs were less severe at the lower concentrations. Deaths generally occurred within one day post-exposure. Following exposure, surviving rats were pale in color and lost up to 7% body weight. These signs resolved with no delayed deaths occurring. Except for mild congestion of some organs, results of the pathologic examinations of rats exposed to 20 mg/m^3 were unremarkable on all post-exposure days. The four-hour LC_{50} value for male rats was 64 mg/m^3.

In a GLP study that followed U.S. EPA guidelines for acute inhalation studies, groups of 5 male and 5 female Crl:CD rats were exposed, nose-only, to technical oxamyl (98% w/w) dust

at concentrations of 50, 54, 65, or 120 mg/m^3 for 4 hours (Kelly 2001). Chamber atmospheres of oxamyl were generated by suspending the particulate test substance with a jetmill. The test substance was metered into the jetmill with a bin feeder. Filtered, high-pressure air carried the atmosphere from the jetmill into a 29-L exposure chamber. Chamber concentrations were controlled by varying the test substance feed rate. Atmosphere concentrations were determined by gravimetric analysis; HPLC analysis was used to determine the percentage of active ingredient on the gravimetric filters. Particle size (mass median aerodynamic diameter) ranged from 3.2-4.2 µ.

Concentration-related deaths occurred either during exposure or within 2 days of exposure (Kelly 2001). All rats died at the highest exposure. The LC_{50} for the sexes combined was 56 mg/m^3. During exposure, red nasal discharge, gasping, and salivation were observed. There was a diminished response to an alerting stimulus. Immediately after exposure and during recovery, clinical signs included lethargy, decreased muscle tone, tremors, spasms, fasciculations, abnormal posture, abnormal gait, high carriage, and ataxia. Some clinical signs were seen in all groups. All clinical signs returned to normal in the second week after exposure. At necropsy, gross observations were unremarkable.

Groups of five male and five female CrL:CD rats inhaled aerosol atmospheres (not further defined) of a proprietary mixture of oxamyl at concentrations of 160, 220, 240, or 510 mg/m3 for 4 hours (U.S. EPA 1997). Chamber concentrations were based on measured aerosol concentrations and the reported purity of the active ingredient in the formulation. Rats died either during exposure or within three days following exposure. Fractional mortalities were 1/10, 2/10, 9/10, and 10/10 at the lowest through highest concentrations, respectively (gender not provided). Tremors and abnormal gait/mobility were observed in most surviving rats in the 160 and 220 mg/m^3 groups. Other clinical signs included gasping, lung noise, irregular respiration, lethargy, hunched posture, and diarrhea. No further details were provided in the summary document.

TABLE 2. Mortality of Rats Exposed to Oxamyl for 1 or 4 Hours

Exposure Duration/ Gender	Concentration (mg/m^3)	Mortality	LC_{50} (mg/m^3)	Reference
Dust or Powder Form				
1 hour (males)	140 160 180 210	0/6 2/6 4/6 5/6	170	DuPont 1969a; Kennedy 1986a
1 hour (females)	100 120 140	1/6 3/6 5/6	120	DuPont 1969a; Kennedy 1986a
4 hours (both sexes)	4.9 24	0/20 0/20	—	O'Neil 2000; U.S. EPA 2000
4 hours (males)	20 53 66 77 90	0/6 1/6 3/6 5/6 6/6	64	Dupont 1969b; Kennedy 1986a
4 hours (both sexes)	50 54	males: 0/5; females: 2/5 males: 1/5; females: 5/5	56	Kelly 2001

	65 120	males: 3/5; females: 4/5 males: 5/5; females: 5/5		
Aerosol				
4 hours (both sexes)	160 220 240 510	1/10 2/10 9/10 10/10	~230	U.S. EPA 1997

3.2. Acute Non-Lethal Toxicity

A study with oxamyl dust addressed non-lethal concentrations (Table 2). Two groups of rats, 10 per sex per group, inhaled 0, 4.9 or 24 mg/m^3 aerosolized oxamyl dust, nose-only, for 4 hours (O'Neil 2000; reviewed in U.S. EPA 2000). Test atmospheres were measured gravimetrically. Particle size ranged from 0.82 to 1.2 µ. Sacrifice took place immediately after exposure for cholinesterase activity determination. No deaths occurred during exposure. Wet stains, ocular/nose discharge and diarrhea were seen in all rats including the control groups. Tremors and lethargy were seen in the exposed groups, but incidences in the 4.9 mg/m^3 group were similar to those of the control groups (incidence data not reported). Compared to the pre-exposure values, plasma, erythrocyte and brain cholinesterase activity in males in the 4.9 mg/m^3 group were inhibited by 12, 28, and 15%, respectively. Respective values for males in the 24 mg/m^3 group were 72, 72, and 68%. Compared to the control values, plasma, erythrocyte and brain cholinesterase activity in females at 4.9 mg/m^3 were inhibited by 6.5, 29, and 9%, respectively. Respective values for females in the 24 mg/m^3 group were 76, 73, and 67%.

3.3. Repeat-Exposure Studies

No repeat-exposure inhalation studies were located. Repeated-dose oral studies with the rat show that oxamyl does not accumulate nor do the clinical signs of response change dramatically following multiple exposures at the same concentration (Kennedy 1986b; IPCS 2002; HSDB 2004).

3.4. Neurotoxicity

The studies described in Section 3.1 show that oxamyl is neurotoxic. Clinical signs included lethargy, decreased muscle tone, tremors, spasms, facial fasciculations, lacrimation, salivation, abnormal posture and gait, and ataxia. See Section 4.1 for the mode of action of carbamate insecticides.

In a study of gavage administration of oxamyl to male Long-Evans rats, motor activity in the period 15 to 35 minutes post-dosing was a reliable predictor of brain and erythrocyte cholinesterase activity inhibition (McDaniel et al. 2007). Doses were 0, 0.07, 0.10, 0.50, 1.00, and 1.50 mg/kg. Brain and erythrocyte acetylcholinesterase activity and motor activity were unaffected at doses of 0.07 and 0.10 mg/kg. Inhibited cholinesterase activity and decreased motor activity were dose related at >0.10 mg/kg, with brain acetylcholinesterase activity falling to approximately 40% of the control value and erythrocyte acetylcholinesterase activity and horizontal and vertical motor activity inhibited to <40% of control. One rat in the 1.00 mg/kg dose group and two rats in the 1.50 mg/kg dose group showed subtle cholinergic signs.

3.5. Developmental/Reproductive Toxicity

No inhalation studies were conducted that addressed developmental/reproductive toxicity of oxamyl. Reproductive and developmental toxicity studies that used the oral route of administration were reviewed in Kennedy (1986b), IPCS (2002) and HSDB (2004). These studies are summarized here, demonstrating that oxamyl is not a developmental or reproductive toxicant even at doses that are maternally toxic. In a two-generation reproductive toxicity study, male and female CrL-CD rats ingested oxamyl in the diet at doses of 0, 25, 75, or 15.8 ppm (approximately 0, 1.7, 5.2, or 11.6 mg/kg/day for males and 0, 2.0, 6.6, or 15.8 mg/kg/day for females). F_0 rats were mated 74 days after the beginning of treatment to produce the F_1 generation. The F_1 generation was treated for at least 105 days after weaning; dietary administration continued until weaning of the F_2 generation. The NOAEL for parental toxicity (F_0 and F_1 parental generation) was 25 ppm. Decreases in body weight, body weight gain, food consumption and efficiency, and increased relative testis weight were seen at 75 ppm. The NOAEL for developmental toxicity was also 25 ppm oxamyl in the diet. Reduced pup weight was seen at 75 ppm during lactation. The NOAEL for reproductive toxicity was 75 ppm.

Similar results were reported in a three-generation oral reproduction study with male and female CrL-CD rats. Dietary concentrations were 0, 50, 100, or 150 ppm. Oxamyl had no effect on the number of pregnancies or on gestation or fertility indexes. Dose-dependent reductions in litter size and body weight of weanlings at 100 and 150 ppm were observed consistently throughout the study. Individual data were not provided.

In a developmental toxicity study, groups of 25 pregnant Charles River CD BR rats received doses of 0, 0.2, 0.5, 0.8, or 1.5 mg/kg during gestation days 7-16. Doses were administered by gavage. The dams were killed on day 22 of gestation and the dams and fetuses were examined. There were no maternal deaths or abnormal gross changes in the dams. Maternal toxicity consisting of reduced body weight and reduced food consumption were observed at 0.8 mg/kg and above, and signs of cholinesterase inhibition were observed at 1.5 mg/kg. Fetal body weight was decreased at 0.8 mg/kg and above. There were no fetal malformations.

In a developmental toxicity study, groups of 17 pregnant New Zealand rabbits were gavaged with oxamyl at doses of 0, 1, 2, or 4 mg/kg/day on days 6-19 of gestation. On gestation day 22, all surviving dams were sacrificed and all fetuses were examined for malformations. One doe each in the 1 and 4 mg/kg/day groups died; these deaths were attributed to gavage error. Maternal body weight was reduced at 2 and 4 mg/kg/day, but necropsies were unremarkable. Although fetal resorptions were increased at 2 and 4 mg/kg/day, no fetal parameters (body weight, sex ratio, crown-rump length, or external or internal malformations) were statistically significantly affected.

3.6. Genotoxicity

Oxamyl has been tested in a range of *in vitro* genotoxicity assays (IPCS 2002; HSDB 2004). No studies addressed genotoxicity *in vivo*. Most assays were conducted with and without metabolic activation. Assay results were negative for reverse mutation in *Salmonella typhimurium* (TA97a, TA98, TA100, TA1535, TA1537) and *Escherichia coli* WP2 uvrA.

Results were negative for chromosomal aberrations and gene mutations in Chinese hamster ovary cells, chromosomal aberrations in human lymphocytes, and unscheduled DNA synthesis in rat hepatocytes. Test concentrations ranged up to 1200 µmol/L. Cytotoxicity was observed at the higher concentrations.

3.7. Subchronic and Chronic Toxicity/Carcinogenicity

Subchronic and chronic studies employed the dietary route of administration (Kennedy 1986b; IPCS 2002; HSDB 2004). These studies are only briefly described here in order to show the mode of action and species variability. Male and female CrL-CD Rats fed a diet containing oxamyl at concentrations of 0, 50, 100, 150, or 500 ppm for 90 days showed signs of cholinesterase activity inhibition and body weight loss within 2 days at 500 ppm. Dietary administration at 100 or 150 ppm resulted in reduced body weight gain (up to 7%) without other clinical signs. No effects were observed at 50 ppm. Feeding of oxamyl at 100 or 150 ppm for two years also resulted in depressed weight gain. Cholinesterase activity was inhibited only during the first week of feeding at 150 ppm. There was no tumor response. The NOAEL was 50 ppm (approximately 5 mg/kg/day).

In a similar 90-day feeding study, concentrations of 0, 10, 30, or 250 ppm were administered in the diet to male and female Crl:CD rats (U.S. EPA 1998). The systemic LOAEL was 250 ppm based on lower body weight. The LOAEL for neurotoxicity was based on decreases in brain, plasma, and erythrocyte cholinesterase activity inhibition, and impaired performance in a Functional Observational Battery at 250 ppm. The NOAEL was 30 ppm. These dietary concentrations corresponded to 2.1 and 2.4 mg/kg/day (NOAELs for males and females, respectively) and 14.9 and 19.9 mg/kg/day (LOAELs for males and females, respectively).

In a two year feeding study, male and female CrL-CD-1 mice were administered diets containing 0, 25, 50, or 100 ppm (the latter reduced to 75 ppm due to early mortalities). Body weight of mice fed 50 or 75 ppm was lower than that of controls during the first 6 months of the study. No other toxic response was seen. There was no evidence of a tumorigenic response. The NOAEL was 25 ppm in the diet (approximately 2.5 mg/kg/day).

Dogs fed oxamyl at 150 ppm for 2 years showed some clinical chemistry changes but no inhibition of cholinesterase activity. There were no deaths and no histological changes in major tissues and organs attributed to the test material. The NOAEL was 100 ppm in the diet (approximately 2.5 mg/kg/day).

3.8. Summary

Acute inhalation lethality studies were conducted with the rat. Toxicity was dependent on the form of the administered chemical, with the dust being more toxic than the aerosol. The 1- and 4-hour LC_{50} values for male rats inhaling the dust were 170 and 64 mg/m^3, respectively. Female rats were more sensitive to the inhalation toxicity of oxamyl dust. The 1- and 4-hour LC_{50} values for female rats were 120 and <50 mg/m^3, respectively. The 4-hour LC_{50} value for both sexes combined was 56 mg/m^3 (Kelly 2001). During exposure, rats showed signs indicative of acetylcholinesterase activity inhibition. The 4-hour LC_{50} for an aerosol of oxamyl particulates

was approximately 230 mg/m^3 (U.S. EPA 1997). The low vapor pressure of oxamyl (2.3 x 10^{-4} mm Hg at 20-25 ºC) makes vapor studies at ambient temperatures impractical.

No evidence of teratogenicity was observed in either the rat or rabbit treated in the diet with oxamyl (up to 150 ppm) even in the presence of maternal toxicity. A range of genotoxicity assays all provided negative results. In 2-year feeding studies with the dog, rat, and mouse at concentrations that approached toxic as indicated by reduced weight gain, there was no evidence of a tumorigenic response.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Inhalation metabolism studies with oxamyl were not located. The *N*-methyl carbamates do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation (U.S. EPA 2007b). Therefore, relative potency can be estimated from oral studies. Unlike some organophosphate pesticides that are metabolized by A-esterases which show great inter-individual variation, the biotransformation of the carbamate pesticides does not involve A-esterases. Studies of biotransformation *in vivo* and *in vitro* following administration by the oral route or intraperitoneal injection showed that oxamyl is metabolized in rats and mice via two major pathways: non-enzymatic hydrolysis to the oxime (methyl 2-dimethylamino)-*N*-hydroxy-2-ethanimidothioate or DMTO) and enzymatic conversion to dimethylamine(oxo)acetic acid (DMOA) (Harvey and Han 1978; IPCS 1983; 2002). Incubation of ^{14}C-labeled oxamyl with rat or mouse liver homogenate or liver microsomes showed the major fraction of label associated with the parent compound. Metabolites indicated metabolism by the routes described above.

When mice were injected intraperitoneally with ^{14}C-labeled oxamyl, urinary metabolites consisted of the parent compound (16%), DMTO (44%), and a number of other metabolites, many not identified (Chang and Knowles 1979). In rats treated orally, most radioactivity was excreted in the urine (Harvey and Han 1978; IPCS 2002). Most of the radioactivity in urine and feces was recovered as polar conjugates of DMTO, DMOA, and several other metabolites. According to Costa (2008), most metabolites of carbamic acid ester pesticides are devoid of biological activity.

Metabolism is fairly rapid as indicated by recovery of brain and erythrocyte cholinesterase activity following inhibition in rats. In adult Long-Evans rats dosed orally with 1 mg/kg oxamyl, brain and erythrocyte cholinesterase activity were approximately 50 and 20% of control, respectively at 0.5 hours post-dose; activities in both compartments returned to control values by 4 hours post-dosing (Padilla et al. 2007). The half-lives for recovery from erythrocyte cholinesterase activity inhibition in rats and humans are 0.8 and 2.4 hours, respectively, following oral dosing (U.S. EPA 2007b).

4.2. Mechanism of Toxicity

Oxamyl is an *N*-methyl carbamate insecticide/nematicide. The mode of action of carbamate pesticides involves cholinesterase inhibition (Costa 2008). Carbamic acid esters attach to the serine hydroxyl group of the reactive 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 result from stimulation of the muscarinic receptors of the parasympathetic autonomic nervous system and 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 resulting from effects on the central nervous system include restlessness, emotional lability, ataxia, lethargy, mental confusion, loss of memory, generalized weakness, convulsions, cyanosis, and coma. Inhibition of acetylcholinesterase activity is transient and reversible because there is rapid reactivation of the carbamylated enzyme in the presence of water.

Carbamates 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. A review of studies submitted to U.S. EPA (2007b) for pesticide registration shows that clinical signs and behavioral effects are not evident below 10% acetylcholinesterase activity inhibition. Due to human variability, it is difficult to measure inhibition of <20% from an individual's baseline (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). Other enzymes such as carboxylesterases are non-target enzymes to which cholinesterase activity inhibitors may bind.

4.3. Structure-Activity Relationships

Organophosphate and carbamate pesticides have a common mode of action (Costa 2008). Compared to organophosphate ester pesticides, the carbamic acid esters are poor substrates for cholinesterase-type enzymes. The carbamic acid esters which attach to the reactive site of acetyl cholinesterase undergo fairly rapid hydrolysis. The carbamylated (inhibited) enzyme is decarbamylated fairly rapidly with generation of the free, active enzyme.

Information is available on the relative oral toxicity of three carbamate pesticides (HSRB 2006; U.S. EPA 2007b). The endpoints were brain and erythrocyte cholinesterase activity inhibition in the rat and erythrocyte cholinesterase activity inhibition in humans. Raw data on erythrocyte cholinesterase activity inhibition were not provided for all three chemicals, but relative toxicity can be derived from the benchmark doses (BMD_{10} and $BMDL_{10}$) calculated by U.S. EPA (2007b) from a range of oral doses (Table 3). For methomyl and oxamyl, rat data on brain and erythrocyte cholinesterase activity are presented by McDaniel et al. (2007). If oxamyl is assigned a relative oral potency factor of 1, then the oral potencies of aldicarb and methomyl are 4 and 0.67, respectively (U.S. EPA 2007b).

TABLE 3. Adult Rat and Human BMD_{10} and $BMDL_{10}$ Values for Cholinesterase Activity Inhibition by *N*-Methyl Carbamate Pesticides (Oral Dosing)

Chemical	Rat				Human	
	Brain		Erythrocyte		Erythrocyte	
	Benchmark	Half-life	Benchmark	Half-life	Benchmark	Half-life

	Dose (mg/kg)	(h)	Dose (mg/kg)	(h)	Dose (mg/kg)	(h)
Aldicarb	BMD_{10}: 0.052 $BMDL_{10}$: 0.035	1.5	BMD_{10}: 0.031 $BMDL_{10}$: 0.020	1.1	BMD_{10}: 0.016 $BMDL_{10}$: 0.013	1.7
Methomyl	BMD_{10}: 0.486 $BMDL_{10}$: 0.331	1.0	BMD_{10}: 0.204 $BMDL_{10}$: 0.112	0.8	BMD_{10}: 0.040 $BMDL_{10}$: 0.028	1.6
Oxamyl	BMD_{10}: 0.165 $BMDL_{10}$: 0.127	0.9	BMD_{10}: 0.278 $BMDL_{10}$: 0.158	0.8	BMD_{10}: 0.083 $BMDL_{10}$: 0.068	2.4

Benchmark dose data for brain cholinesterase data for aldicarb and oxamyl are presented as the average of male and female rat values.
The $BMDL_{10}$ for 10% brain cholinesterase activity inhibition was used as the point of departure for U.S. EPA (2007b) risk assessment.
Source: Table 1.B-9, p. 50, U.S. EPA 2007b.

4.4. Other Relevant Information

4.4.1. Species Variability

The extent of hydrolysis of carbamate ester insecticides varies among species, ranging from 30 to 95%, and is chemical specific (Costa 2008). Baseline erythrocyte acetylcholinesterase activity is higher in humans than in other species (Ellin 1981).

Inhalation studies were conducted only with rats. Subchronic and chronic feeding studies with the rat, mouse, and dog showed little difference in toxicity among the species. Based on differences in modeled values for erythrocyte acetylcholinesterase activity inhibition between rats and humans, the U.S. EPA Office of Pesticide Programs calculated an oxamyl-specific inhalation interspecies uncertainty factor of 3 (U.S. EPA 2007b). Half-lives for enzyme regeneration of erythrocyte cholinesterase activity were 0.8 hours (adult rats) and 2.4 hours (humans).

4.4.2. Susceptible Populations

Humans vary by gender, age, and genetic make-up in 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 showed that protection of the rat dam against cholinesterase activity inhibition is protective against pup acetylcholinesterase activity inhibition *in utero*. The U.S. EPA (2007b) identified infants and juveniles as the most sensitive population to the anticholinesterase effects of *N*-methyl carbamate pesticides. In so doing, they evaluated the relative sensitivity of juvenile and adult rats to *N*-methyl carbamate pesticides including oxamyl. Based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated a Food Quality Protection Act (FQPA) uncertainty factor of 3.48 for children. This uncertainty factor corresponds to an AEGL intraspecies uncertainty factor.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship for a single endpoint for many irritant and systemically acting inhalational toxicants may be described by $C^n \times t = k$ (ten Berge et al. 1986). Data for time-scaling from three studies (DuPont 1969a; DuPont 1969b; Kelly 2001) and two

exposure durations (1 and 4 hours) provided consistent results. The least squares derived line describing the slope between the 1 and 4-hour values has an n value of 1.6 (Appendix A).

4.4.4. Concurrent Exposure Issues

No information relevant to concurrent exposure issues was located. Dermal absorption may occur, but toxicity is low compared to inhalation exposure as indicated by a dermal LD_{50} in rabbits of >2000 mg/kg body weight (IPCS 2002).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human inhalation studies were located in the available literature. No occupational monitoring data were presented by U.S. EPA (2007a).

5.2. Summary of Animal Data Relevant to AEGL-1

One study with oxamyl dust was available. In that study, groups of 10 rats/sex inhaled 4.9 or 24 mg/m^3 of oxamyl dust for 4 hours (O'Neil 2000; U.S. EPA 2000). Plasma, erythrocyte, and brain cholinesterase activity were inhibited at both concentrations. For the sexes combined, brain cholinesterase activity inhibition averaged 12% and erythrocyte acetylcholinesterase activity inhibition averaged 28.5% at the lower concentration. Respective values were 67.5% and 72.5% at the higher concentration.

5.3. Derivation of AEGL-1

The key study for AEGL-1 determination was O'Neil (2000; U.S. EPA 2000). Inhalation of 4.9 mg/m^3 oxamyl dust for 4 hours inhibited erythrocyte acetylcholinesterase activity by 28.5% (average of values in males and females) and brain cholinesterase by 12% (average of values in males and females). Erythrocyte acetylcholinesterase activity inhibition of that magnitude may result in transient symptoms of discomfort in humans. Wet stains, ocular/nose discharge and diarrhea were seen in rats exposed to 4.9 and 24 mg/m^3 as well as in the control groups. Additionally tremors and lethargy were seen in the exposed groups, but incidences in the 4.9 mg/m^3 group were reported as similar to those of the control groups (incidence data not reported). U.S. EPA (2007b) derived an interspecies uncertainty factor of 3 for oxamyl based on differences in modeled values for erythrocyte acetylcholinesterase activity inhibition between rats and humans (See section 4.4.1). Based on comparative brain cholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated an intraspecies uncertainty factor of 3.48 to protect sensitive young (See section 4.4.2). The combined uncertainty factor is 10.4 (rounded to 10). Female rats were not more sensitive to oxamyl exposure than male rats in this study. Values were time-scaled ($C^n \times t = k$) from the 4-hour data point using an n value of 1.6. Values are summarized in Table 4. Calculations are in Appendix B, and a category graph of the toxicity data in relation to AEGL values is in Appendix D.

TABLE 4. AEGL-1 Values for Oxamyl

10-min	30-min	1-h	4-h	8-hour
3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human inhalation studies 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 data on an oxamyl dust concentration that would result in effects consistent with the definition of an AEGL-2 were available in the open literature. Therefore, AEGL-2 values were derived by dividing the AEGL-3 values by 3. This approach is justified when there is a steep concentration-response curve (NRC 2001). As shown by the study of Kelly (2001) mortality went from 0% at 50 mg/m^3 to 100% when concentration was increased 2.4-fold (120 mg/m^3). AEGL-2 values are summarized in Table 5. Calculations are in Appendix B and a category graph of the toxicity data in relation to AEGL values is in Appendix D.

TABLE 5. AEGL-2 Values for Oxamyl

10-min	30-min	1-h	4-h	8-h
5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

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

7.2. Summary of Animal Data Relevant to AEGL-3

Because of its low vapor pressure, concentrations of oxamyl vapor high enough to induce mortality could not be attained. Three studies with oxamyl dust addressed lethality in the rat. In a 1-hour study LC_{50} values for male and female rats were 170 and 120 mg/m^3, respectively (DuPont 1969a). The 4-hour LC_{50} in male and female rats combined was 64 mg/m^3 (DuPont 1969b). A more recent study with rats reported a similar 4-hour LC_{50} value, 56 mg/m^3 (Kelly 2001).

7.3. Derivation of AEGL-3

Studies with oxamyl dust were chosen for development of AEGL values. The more recent, GLP study of Kelly (2001) was chosen as the basis for development of AEGL-3 values.

The calculated 1-hour $BMCL_{05}$ for lethality is 22 mg/m^3 and the BMC_{01} is 33 mg/m^3 (Appendix C). The NAC/AEGL Committee generally uses the $BMCL_{05}$ as the estimate at which lethality is not likely to be observed (NRC 2001). U.S. EPA (2007b) derived an interspecies uncertainty factor of 3 for oxamyl based on differences in values for erythrocyte acetylcholinesterase activity inhibition between rats and humans (See section 4.4.1). Based on comparative brain cholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated an uncertainty factor of 3.48 to protect sensitive young (See section 4.4.2). The combined uncertainty factor is 10.4 (rounded to 10) Although female rats appear to be slightly more sensitive to the toxic effects of oxamyl than male rats, the combined data with application of an uncertainty factor that protects sensitive juveniles provides a reasonable estimate of lethality. Values were time-scaled ($C^n \times t = k$) from the 4-hour data point using an n value of 1.6. Values are summarized in Table 6, calculations are in Appendix B, and a category graph of the toxicity data in relation to AEGL values is in Appendix D.

TABLE 6. AEGL-3 Values for Oxamyl

10-min	30-min	1-h	4-h	8-h
16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 mg/m^3

The 4-hour LC_{50} for rats in the key study (Kelly 2001) is 56 mg/m^3. A similar 4-hour LC_{50} value (64 mg/m^3) for rats was identified in a study conducted 30 years earlier in the same laboratory (DuPont 1969b).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 7. Derivations are summarized in Appendix E.

TABLE 7. Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3
AEGL-2 (Disabling)	5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3
AEGL-3 (Lethal)	16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 mg/m^3

8.2. Comparison with Other Standards and Guidelines

Other than AEGLs, no inhalation standards or guidelines for oxamyl have been established (Table 8). For acetylcholinesterase inhibiting chemicals in general, the American Conference of Governmental Industrial Hygienists has established a Biological Exposure Index based on erythrocyte cholinesterase activity (ACGIH 2008). Individuals should leave the area when their erythrocyte acetylcholinesterase activity falls to 70% of their baseline.

The U.S. EPA (2007b) calculated inhalation BMD_{10} values of 5 and 2 mg/m^3 for brain and erythrocyte cholinesterase inhibition, respectively, in humans. The endpoint was a 10% inhibition of erythrocyte cholinesterase activity.

TABLE 8. Standards and Guidelines for Oxamyl

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3
AEGL-2	5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3
AEGL-3	16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 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]					—
MAK (Germany)[f]					—
MAC (The Netherlands)[g]					—

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

[g]**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

Oxamyl has a low vapor pressure and no suitable inhalation exposure studies with humans were located in the available literature. An oral dosing study with human volunteers addressed effects consistent with cholinesterase activity inhibition. Inhalation studies with rats as the test species and involving two time points and dust and aerosol delivery were sufficient for derivation of three AEGL levels for five timepoints. Studies involving comparisons of cholinesterase activity inhibition between juvenile and adult rats and between rats and humans addressed chemical-specific uncertainty factors. Metabolism pathways and mode of action are well understood.

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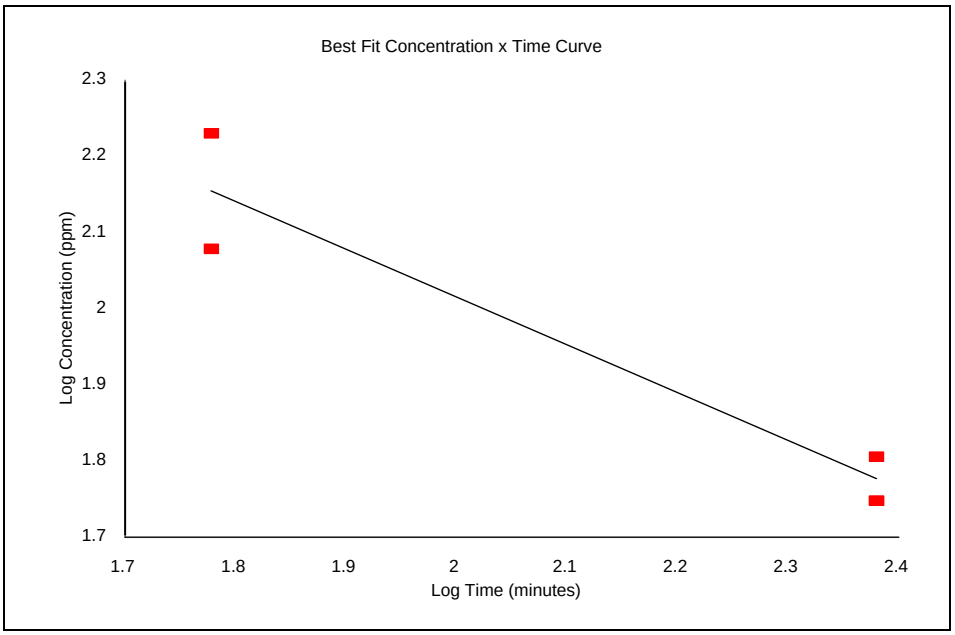
APPENDIX A: Time-Scaling Calculation for Oxamyl AEGLs



Time scaling of LC_{50} values was based on the 1-hour study of DuPont 1969a and the 4-hour studies of DuPont 1969b and Kelly 2001.

Time (minutes)	Concentration	Log Time	Log Concentration
60	170	1.7782	2.2304
60	120	1.7782	2.0792
240	64	2.3802	1.8062
240	56	2.3802	1.7482

Regression Output:	
Intercept	3.2701
Slope	-0.6272
R Squared	0.9157
Correlation	-0.9569
Degrees of Freedom	2
Observations	4

n = 1.59
k = 163526.7

APPENDIX B: Derivation of Oxamyl AEGLs

Derivation of AEGL-1 Values

Key Study:	O'Neil, A.J. 2000. Cholinesterase Inhibition determined in Rats Exposed to Inhalation Atmospheres of Oxamyl Technical (96.9%). Haskell Laboratory of Toxicology and Industrial Medicine, E.I. du Pont de Nemours Co. DuPont Study No. 4383. (Summarized in U.S. EPA 2000).
Toxicity endpoint:	Clinical signs of ocular/nasal discharge, diarrhea, tremors, and lethargy (the latter two signs also seen in control rats) following a 4-hour exposure of rats to 4.9 mg/m^3. For the sexes combined, brain cholinesterase activity inhibition averaged 12% and erythrocyte acetylcholinesterase activity inhibition averaged 28.5%.
Time scaling	$C^n \times t = k$ where n = 1.6 based on time scaling from the 1- and 4-hour rat data (three studies) with oxamyl dust.
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3 – The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation interspecies uncertainty factor of 3 based on differences in values for erythrocyte acetylcholinesterase activity inhibition between rats and humans. Intraspecies: 3.48 – The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation intraspecies uncertainty factor of 3.48 based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats.
Modifying factor:	None applied
Calculations:	$(4.9\ mg/m^3/10)^{1.6} \times 240\ minutes = 76.65\ mg/m^{3(1.6)}\bullet min$
10-min AEGL-1:	$C = \sqrt[1.6]{(76.65\ mg/m^{3(1.6)}\bullet min/10)} = 3.6\ mg/m^3$
30-min AEGL-1:	$C = \sqrt[1.6]{(76.65\ mg/m^{3(1.6)}\bullet min/30)} = 1.8\ mg/m^3$
1-h AEGL-1:	$C = \sqrt[1.6]{(76.65\ mg/m^{3(1.6)}\bullet min/60)} = 1.2\ mg/m^3$
4-h AEGL-1:	$C = 4.9\ mg/m^3/10 = 0.49\ mg/m^3$
8-h AEGL-1:	$C = \sqrt[1.6]{(76.65\ mg/m^{3(1.6)}\bullet min/480)} = 0.32\ mg/m^3$

Derivation of AEGL-2 Values

Key Study:	Kelly, D.P. 2001. Oxamyl (DPX-D1410) Technical (98%w/w): Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Laboratory Project ID: DuPont-6331.
Toxicity endpoint:	AEGL-3 values divided by 3. The steep concentration-response line shown by the Kelly (2001) data justifies deriving AEGL-2 values by dividing the AEGL-3 values by 3 (NRC 2001).
Time scaling	$C^n \times t = k$ where n = 1.6 based on time scaling from the 1- and 4-hour rat data (three studies) with oxamyl dust.
Uncertainty factors:	Total uncertainty factor: 10 (See AEGL-3 below)
Calculations:	AEGL-3 values/3
10-min AEGL-2:	C = 16/3 = 5.3 mg/m^3
30-min AEGL-2:	C = 8.2/3 = 2.7 mg/m^3
1-h AEGL-2:	C = 5.3/3 = 1.8 mg/m^3
4-h AEGL-2:	C = 2.2/3 = 0.73 mg/m^3
8-h AEGL-2:	C = 1.4/3 = 0.47 mg/m^3

Derivation of AEGL-3 Values

Key Study:	Kelly, D.P. 2001. Oxamyl (DPX-D1410) Technical (98%w/w): Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Laboratory Project ID: DuPont-6331.
Toxicity endpoint:	Threshold for lethality in rats at the $BMCL_{05}$ of 22.2692 mg/m^3 calculated from the rat lethality data of Kelly (2001).
Time scaling	$C^n \times t = k$ where n = 1.6 based on time scaling from the 1- and 4-hour rat data (three studies) with oxamyl dust.
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3 – The U.S. EPA Office of Pesticide Programs (2007b) calculated an oxamyl-specific inhalation interspecies uncertainty factor of 3 based on differences in values for erythrocyte cholinesterase activity inhibition between rats and humans. Intraspecies: 3.48 – The U.S. EPA Office of Pesticide Programs (2007b) calculated an oxamyl-specific inhalation intraspecies uncertainty factor of 3.48 based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats.
Modifying factor:	None applied
Calculations:	$(22.27\ mg/m^3/10)1.6 \times 240\ minutes = 864.05\ mg/m^{3(1.6)}\bullet min$
10-min AEGL-3:	$C = \sqrt[1.6]{(864.05\ mg/m^{3(1.6)}\bullet min/10)} = 16\ mg/m^3$
30-min AEGL-3:	$C = \sqrt[1.6]{(864.05\ mg/m^{3(1.6)}\bullet min/30)} = 8.2\ mg/m^3$
1-h AEGL-3:	$C = \sqrt[1.6]{(864.05\ mg/m^{3(1.6)}\bullet min/60)} = 5.3\ mg/m^3$
4-h AEGL-3:	$C = 22.27/10 = 2.2\ mg/m^3$
8-h AEGL-3:	$C = \sqrt[1.6]{(864.05\ mg/m^{3(1.6)}\bullet min/480)} = 1.4\ mg/m^3$

APPENDIX C: Benchmark Concentration Calculations for Oxamyl

Calculation of BMC_{01}: Data of Kelly 2001

```
==========================================================================
          Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
          Input Data File: C:\BMDS\OXAMYL _RAT.(d)
          Gnuplot Plotting File:  C:\BMDS\OXAMYL _RAT.plt
                                                  Wed Feb 25 13:36:33 2009
 ==========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background   + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function

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

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   User has chosen the log transformed model

               Default Initial (and Specified) Parameter Values
                 background =           0
                  intercept =      -9.7974
                      slope =      2.42048

         Asymptotic Correlation Matrix of Parameter Estimates

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

             intercept       slope
 intercept           1          -1
    slope           -1           1
                      Parameter Estimates
       Variable         Estimate          Std. Err.
     background                0             NA
      intercept           -17.86          8.42225
          slope          4.43819          2.09164

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

standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-17.8428			
Fitted model	-18.7358	1.78596	3	0.618
Reduced model	-34.6574	33.6292	4	<.0001

AIC: 41.4715

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	10	0
50.0000	0.3093	3.093	2	10	-0.748
54.0000	0.4379	4.379	6	10	1.033
65.0000	0.7475	7.475	7	10	-0.3458
120.0000	0.9996	9.996	10	10	0.05937

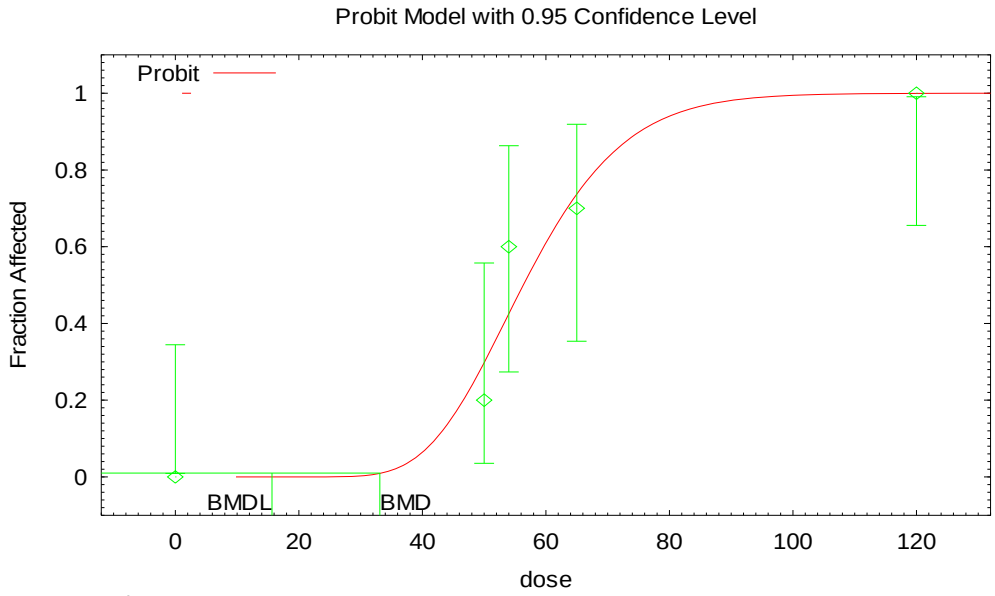
Chi-square = 1.75 DF = 3 P-value = 0.6260

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95

BMC_{01} = 33.1158

$BMCL_{01}$ = 15.6441



13:36 02/25 2009

Calculation of $BMCL_{05}$: Data of Kelly 2001

```
============================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: C:\BMDS\OXAMYL _RAT.(d)
        Gnuplot Plotting File:  C:\BMDS\OXAMYL _RAT.plt
                                                Wed Feb 25 13:36:33 2009
 ============================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the probability function is:  P[response] = Background + (1-Background) * CumNorm
(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

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

  Total number of observations = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              background =           0
               intercept =      -9.7974
                   slope =      2.42048

       Asymptotic Correlation Matrix of Parameter Estimates

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

            intercept       slope

intercept           1          -1

    slope          -1           1

                  Parameter Estimates

     Variable         Estimate          Std. Err.
   background                0             NA
    intercept           -17.86          8.42225
        slope          4.43819          2.09164

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

                  Analysis of Deviance Table
```

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-17.8428			
Fitted model	-18.7358	1.78596	3	0.618
Reduced model	-34.6574	33.6292	4	<.0001

AIC: 41.4715

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0
50.0000	0.3093	3.093	2	10	-0.748
54.0000	0.4379	4.379	6	10	1.033
65.0000	0.7475	7.475	7	10	-0.3458
120.0000	0.9996	9.996	10	10	0.05937

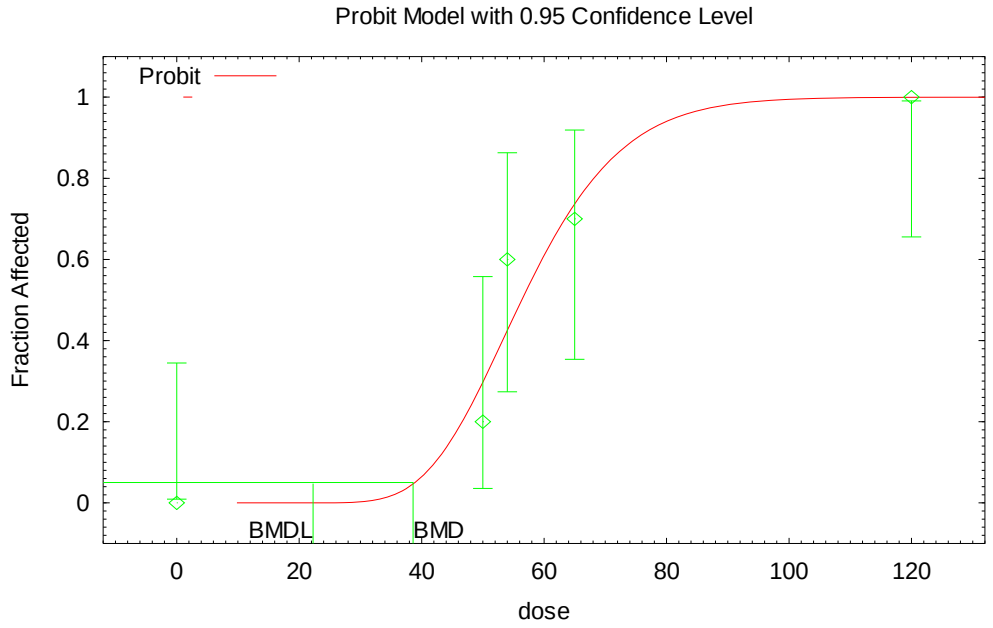
Chi-square = 1.75 DF = 3 P-value = 0.6260

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95

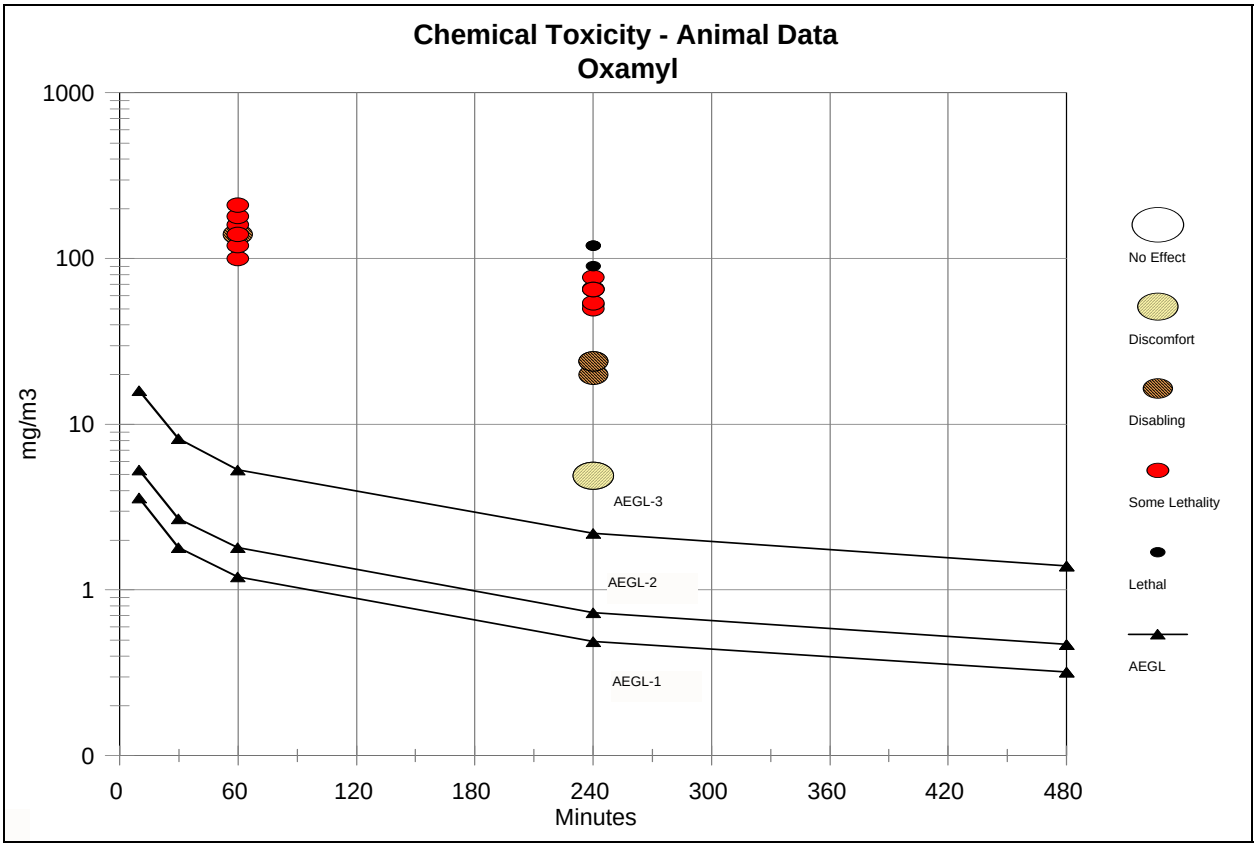
BMC_{05} = 38.612

$BMCL_{05}$ = 22.2692



13:42 02/25 2009

APPENDIX D: Category Graph of AEGL Values and Toxicity Data



Data:

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**mg/m^3**	**Minutes**	**Category**
NAC/AEGL-1		3.6	10	AEGL
NAC/AEGL-1		1.8	30	AEGL
NAC/AEGL-1		1.2	60	AEGL
NAC/AEGL-1		0.49	240	AEGL
NAC/AEGL-1		0.32	480	AEGL
NAC/AEGL-2		5.3	10	AEGL
NAC/AEGL-2		2.7	30	AEGL
NAC/AEGL-2		1.8	60	AEGL
NAC/AEGL-2		0.73	240	AEGL
NAC/AEGL-2		0.47	480	AEGL
NAC/AEGL-3		16	10	AEGL
NAC/AEGL-3		8.2	30	AEGL
NAC/AEGL-3		5.3	60	AEGL
NAC/AEGL-3		2.2	240	AEGL

NAC/AEGL-3		1.4	480	AEGL
DuPont 1969a	rat (male)	140	60	2 (clinical signs – facial fasciculations, salivation, lacrimation dyspnea, etc.)
	rat (male)	160	60	SL (mortality: 2 of 6)
	rat (male)	180	60	SL (mortality: 4 of 6)
	rat (male)	210	60	SL (mortality: 5 of 6)
DuPont 1969a	rat (female)	100	60	SL (mortality: 1 of 6)
	rat (female)	120	60	SL (mortality: 3 of 6)
	rat (female)	140	60	SL (mortality: 5 of 6)
DuPont 1969b	rat (male)	20	240	2 (clinical signs – facial fasciculations, salivation, lacrimation dyspnea, etc.)
	rat (male)	53	240	SL (mortality: 1 of 6)
	rat (male)	66	240	SL (mortality: 3 of 6)
	rat (male)	77	240	SL (mortality: 5 of 6)
	rat (male)	90	240	3 (mortality: 6 of 6)
Kelly 2001	rat (both sexes)	50	240	SL (mortality: 2 of 10)
	rat (both sexes)	54	240	SL (mortality: 6 of 10)
	rat (both sexes)	65	240	SL (mortality: 7 of 10)
	rat (both sexes)	120	240	3 (mortality: 10 of 10)

1

APPENDIX E: Derivation Summary for Oxamyl AEGLs

Acute Exposure Guideline Levels For Oxamyl

(CAS Reg. No. 23135-22-0)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3

Key Reference: O'Neil, A.J. 2000. Cholinesterase Inhibition Determined in Rats Exposed to Inhalation Atmospheres of Oxamyl Technical (96.9%). Haskell Laboratory of Toxicology and Industrial Medicine, E.I. du Pont de Nemours Co. DuPont Study No. 4383.

Test Species/Strain/Sex/Number: Rat/Crl:CD/male and female/groups of 10 of each sex

Exposure Route/Concentration/Duration: Inhalation/4.9 mg/m^3/4 hours

Effects: Clinical signs of ocular/nose discharge, diarrhea, tremors, lethargy (the latter two signs seen in control rats)

Endpoint/Concentration/Rationale: Clinical signs of slight acetylcholinesterase activity inhibition at 4.9 mg/m^3 for 4 hours meet the definition of an AEGL-1. Inhalation of 4.9 mg/m^3 oxamyl dust for 4 hours inhibited erythrocyte acetylcholinesterase activity by 28.5% (average of values in males and females) and brain cholinesterase by 12% (average of values in males and females).

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3, The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation interspecies uncertainty factor of 3 based on comparative erythrocyte cholinesterase activity inhibition in rats and humans.

Intraspecies: 3.48, The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation intraspecies uncertainty factor of 3.48 based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n = 1.6 calculated from three lethality studies

Data Adequacy: The key study was well-conducted, used adequate numbers of rats, and provided analytical concentrations.

1

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
5.3 mg/m^3	**2.7 mg/m^3**	**1.8 mg/m^3**	**0.73 mg/m^3**	**0.47 mg/m^3**
Key Reference: Kelly, D.P. 2001. Oxamyl (DPX-D1410) Technical (98%w/w): Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and industrial Medicine, Newark, DE; Laboratory Project ID: DuPont-6331.				
Test Species/Strain/Number: Rat/Crl-CD/groups of 5/sex				
Exposure Route/Concentration/Duration: 4 hours				
Effects: acetylcholinesterase activity inhibition, estimated at 1/3 of the AEGL-3 values.				
Endpoint/Concentration/Rationale: One-third of the AEGL-3 values, based on the steep concentration-response curve (1/3 of the 4-hour $BMCL_{05}$ for lethality, 22 mg/m^3)				
Uncertainty Factors/Rationale: **Total uncertainty factor**: 10 used for derivation of AEGL-3 **Interspecies:** 3 **Intraspecies**: 3.48				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n = 1.6 calculated from three lethality studies				
Data Adequacy: The key study was well-conducted, used adequate numbers of rats, and provided analytical concentrations. Values are supported by a second study (DuPont 1969b).				

2
3
4

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
16 mg/m^3	**8.2 mg/m^3**	**5.3 mg/m^3**	**2.2 mg/m^3**	**1.4 mg/m^3**
Key Reference: Kelly, D.P. 2001. Oxamyl (DPX-D1410) Technical (98%w/w): Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and industrial Medicine, Newark, DE; Laboratory Project ID: DuPont-6331.				
Test Species/Strain/Number: Rat/Crl-CD/groups of 5/sex				
Exposure Route/Concentration/Duration: 4 hours				
Effect: clinical signs consistent with acetylcholinesterase activity inhibition; lethality				
Endpoint/Concentration/Rationale: 4-hour $BMCL_{05}$, 22 mg/m^3, threshold for lethality				
Uncertainty Factors/Rationale: **Total uncertainty factor**: 10 **Interspecies:** 3, The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation interspecies uncertainty factor of 3 based on modeled values for erythrocyte cholinesterase activity inhibition between rats and humans. **Intraspecies**: 3.48, The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation intraspecies uncertainty factor of 3.48 based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: n value of 1.6 ($C^n \times t = k$) calculated from three lethality studies				
Data Adequacy: The key study was well-conducted, used adequate numbers of rats, and provided analytical concentrations. Values are supported by a second study (DuPont 1969b).				

2