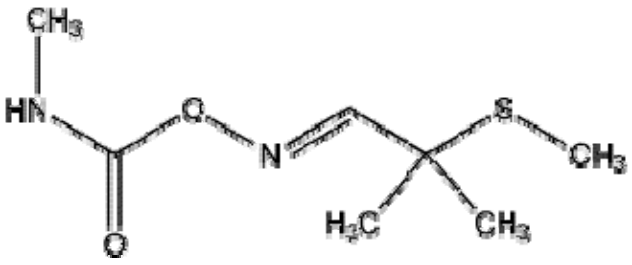
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

ALDICARB

(CAS Reg. No. 116-06-3)



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.

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Technical aldicarb (CAS No. 116-06-3) is a crystalline solid *N*-methyl carbamate pesticide with a slight sulfur smell. Aldicarb is registered as a systemic insecticide, acaricide, and nematocide for use on a wide range of crops. Aldicarb, sold under the trade name Temik™, is a granular formulation containing 5, 10, or 15% active ingredient. Temik™ is usually applied below the soil surface for absorption by plant root systems. Moisture is required to release the active ingredient from the granules. Two soil degradates, aldicarb sulfoxide and aldicarb sulfone, retain some of the toxic property of the parent compound. Approximately 4.5 million pounds of aldicarb are used annually in the United States.

Aldicarb and other carbamate pesticides are neurotoxic in that they are inhibitors of cholinesterase enzymes. Inhibition of acetylcholinesterase, responsible for termination of the biological activity of the neurotransmitter acetylcholine at various nerve endings, results in sustained stimulation of electrical activity. Depending on concentration administered, signs following acute exposure of rats to aldicarb may include facial fasciculations, tremors, salivation, lacrimation, gasping and convulsions. In humans, inhibition of erythrocyte acetylcholinesterase activity, the form found in human erythrocytes, is used as a biomarker of exposure to methyl carbamates. 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 adult and juvenile rodents are applicable for determination of interspecies and intraspecies uncertainty factors.

No human data relevant to derivation of AEGL values were found. No animal studies were located that addressed effects of aldicarb consistent with the definition of the AEGL-1. Therefore, AEGL-1 values are not recommended.

No studies that addressed effects consistent with the definition of the AEGL-2 were found. The concentration-response curve for lethality in rats is steep as shown by the studies of Risher et al. (1987) and UCC (1985). Mortality went from 0 to 83% with the doubling of exposure duration (Risher et al. 1987). Therefore, according to Standard Operating Procedures (NRC 2001), the AEGL-2 values were derived by dividing the AEGL-3 values by 3.

The study with aldicarb aerosol (UCC 1985) was chosen as the key study for AEGL-3 development. The 4-hour study used a sufficient number of rats and five concentrations. The calculated 4-hour $BMCL_{05}$ is 0.97 mg/m^3 and the BMC_{01} is 1.9 mg/m^3. The 4-hour $BMCL_{05}$ was chosen as the threshold for lethality. The 4-hour 0.97 mg/m^3 value was divided by inter- and intraspecies uncertainty factors of 2 and 3, respectively, for a total of 6. The aldicarb-specific interspecies inhalation uncertainty factor of 2 was based on differences in modeled values for red blood cell acetylcholinesterase activity inhibition between rats and humans (U.S. EPA 2007b). The intraspecies uncertainty factor of 3, derived by U.S. EPA (2007b) for the related methyl carbamates, oxamyl and methomyl, was applied. The intraspecies uncertainty factor was based on comparative brain acetylcholinesterase activity inhibition in juvenile and adult rats administered the pesticides by the oral route. The combined uncertainty factor is 6. No information was available for time-scaling. Values were time-scaled ($C^n \times t = k$) from the 4-hour

data point using n values of 3 and 1 for extrapolation to shorter and longer exposure durations, respectively (NRC 2001).

The calculated values are listed in the table below.

TABLE ES 1. Summary of AEGL Values for Aldicarb

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL−1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL−2 (Disabling)	0.16 mg/m^3	0.11 mg/m^3	0.087 mg/m^3	0.053 mg/m^3	0.027 mg/m^3	AEGL-3 values divided by 3
AEGL−3 (Lethal)	0.47 mg/m^3	0.32 mg/m^3	0.26 mg/m^3	0.16 mg/m^3	0.081 mg/m^3	$BMCL_{05}$ for lethality – rat - calculated from UCC (1985) data

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

1. INTRODUCTION

Technical aldicarb (CAS No. 116-06-3) is a white crystalline solid with a slight sulfur smell (AIHA 1993). Aldicarb is registered for use as a systemic insecticide, acaricide, and nematocide on a wide range of crops (O'Neil et al. 2001; U.S. EPA 2007a). Aldicarb is sold in the United States under the trade name Temik™, a granular formulation of aldicarb containing 5, 10, or 15% a.i. (active ingredient by weight) aldicarb in corn cob grit or gypsum; dichloromethane may be present up to 0.2% (UCC 1986). Temik™ is usually applied below the soil surface for absorption by plant root systems. Moisture is required to release the active ingredient from the granules. Two soil degradates, aldicarb sulfoxide and aldicarb sulfone retain anti-cholinesterase activity. Chemical and physical properties are listed in Table 1.

Aldicarb is manufactured commercially by the reaction of methyl isocyanate with 2-methyl-2-(methylthio) propionaldehyde (HSDB 2005). According to U.S. EPA (2007a), approximately 4.5 million pounds of aldicarb are used annually in the United States, primarily on cotton (64%). Other high use crops include peanuts, potatoes, sugar, beets, and citrus. World production figures are not available (IPCS 1991). Aldicarb is a restricted use pesticide and can be applied only by certified applicators.

TABLE 1. Chemical and Physical Properties		
Parameter	**Value**	**Reference**
Synonyms	2-Methyl-2-(methylthio)-propanal *O*-[(methylamino)carbonyl]oxime; 2-methyl-2-(methylthio)-propionaldehyde *O*-(methylcarbamoyl)oxime; Temik™	O'Neil et al. 2001
Chemical formula	$C_7H_{14}N_2O_2S$	O'Neil et al. 2001
Molecular weight	190.27	O'Neil et al. 2001
CAS Reg. No.	116-06-3	O'Neil et al. 2001
Physical state	Aldicarb: white crystalline solid Temik 15G pesticide: brown to black crystals	AIHA 1993 UCC 1986
Solubility in water	Soluble, 6 g/L at 25ºC	O'Neil et al. 2001; AIHA 1993
Vapor pressure, saturated	0.0001 mm Hg at 25ºC	AIHA 1993
Vapor density, saturated (air =1)	0.1 ppm at 25ºC	AIHA 1993
Liquid density (water =1)	1.195 at 25ºC	AIHA 1993
Melting point	99-100 ºC	O'Neil 2001
Boiling point	Decomposes	AIHA 1993
Flammability limits in air	No data	
Conversion factors	1 ppm = 7.78 mg/m^3 1 mg/m^3 = 0.13 ppm	Calculated

2. HUMAN TOXICITY DATA

No inhalation studies other than descriptions of accidental exposures were located. These reports lacked information on concentrations and exposure durations. Symptoms of cholinesterase activity inhibition have been observed following ingestion of food containing aldicarb or aldicarb degradates (HSDB 2005).

A double-blind human oral dosing study included 47 volunteers (38 men and 9 women) (Wyld et al. 1991, reviewed in U.S. EPA 1992). Groups of 4-8 males were administered doses of 0, 0.01, 0.025, 0.05, 0.06 (one subject), or 0.075 mg/kg of aldicarb in orange juice during a light breakfast. Females received 0, 0.025, or 0.05 mg/kg under the same protocol. Clinical signs and symptoms were observed by trained researchers. Blood plasma and erythrocytes were analyzed for cholinesterase activity at 1, 2, 4, 6, 8, and 21 hours after dosing; these values were compared with each subject's pre-exposure values taken at -16 and -3 hours and immediately predose. Peak effects were noted at 1 hour after the dose. Males, but not females developed symptoms consistent with acetylcholinesterase activity inhibition. In males, erythrocyte cholinesterase activity at one hour was inhibited by 3.8, 12, 29, and 38% in the 0.01, 0.025, 0.050, and 0.075 mg/kg dose groups, respectively. In females, the mean inhibition at one hour post-dose was 20% at 0.025 mg/kg and 36% at 0.050 mg/kg. The U.S. EPA noted that the erythrocyte cholinesterase activity inhibition may have been underestimated due to lack of measurement of some membrane-bound enzyme. The U.S. EPA considered the LOAEL 0.25 mg/kg based on sweating in one male. The NOAEL was 0.01 mg/kg. However, the Human Studies Review Board (HSRB 2006) considered acetylcholinesterase activity inhibition a more reliable endpoint than clinical signs. The HSRB (2006) reviewed the study and found it met ethical considerations (required by EPA's Human Subjects Protection Rule).

3. ANIMAL TOXICITY DATA

Using protocols that were standard at the time, aldicarb was tested for dermal and ocular irritation in the rabbit, and dermal sensitization in the guinea pig (IPCS 1991). Aldicarb was not irritating to the skin (500 mg moistened in saline solution) or eye (0.1 mL of a 25% suspension in propylene glycol). There was no sensitization response in male guinea pigs. Dermal LD_{50} doses in rats range from 2.5 to 3 mg/kg (Risher et al. 1987). Ranges for oral LD_{50} values for aldicarb, aldicarb sulfoxide, and aldicarb sulfone in the rat are 0.62-1.23, 0.49-1.13, and 20-25 mg/kg body weight, respectively (IPCS 1992). The LOAEL for acute oral neurotoxicity in rats was 0.05 mg/kg/day based on 23% and 10% inhibition of whole blood and erythrocyte cholinesterase activity, respectively in female rats (U.S. EPA 2005).

3.1. Acute Toxicity

Early inhalation studies were summarized in several reviews including Risher et al. (1987) and IPCS (1991). These summaries lacked details of exposure conditions and number and sex of animals. Carpenter and Smyth (1965) conducted inhalation studies with rats, mice, and guinea pigs. A concentration of 200 mg/m^3 aldicarb dust was lethal to all species within 5 minutes. Rats and mice were more sensitive than guinea pigs. Rats survived a dust concentration of 6.7 mg/m^3 for 15 minutes, but five of six rats died after a 30-minute exposure. All rats survived a saturated vapor concentration (not further described) for 8 hours. Two of six rats survived an 8-hour exposure to an aerosol concentration of 7.6 mg/m^3 (Weil and Carpenter 1970). Studies are summarized in Table 2.

Groups of five male and five female Sprague-Dawley rats inhaled an aerosol of aldicarb solution in dichloromethane for 4 hours (UCC 1985). Measured concentrations of aldicarb were 0.82, 2.0, 6.0, 8.7, and 46.3 mg/m^3. The respective mean dichloromethane concentrations for the same exposures were 43, 94, 183, 25, and 100 mg/m^3. The dichloromethane concentrations were considered low in toxicity compared to aldicarb [LC_{50} values of 57,000-60,000 mg/m^3 in rats and mice (NTP 1986)]. The mass median aerodynamic diameter ranged from 2.0 to 3.8 µ. Ataxia and tremors were seen at all concentrations during exposure. Additional signs of hypoactivity, increased respiration rate, lacrimation, exophthalmos, and periocular encrustation were observed at the two higher concentrations. Mortalities were seen at all concentrations except the lowest, 0.82 mg/m^3. Mortalities in males were 0/5, 0/5, 3/5, 5/5, and 5/5, respectively. Mortalities in females were 0/5, 1/5, 2/5, 5/5, and 5/5, respectively. The 4-hour LC_{50} was 3.9 mg/m^3 with confidence limits of 2.8-5.5 mg/m^3. At necropsy, discoloration of the lungs, perinasal encrustation and staining and eye abnormalities were observed. Survivors initially lost body weight, but body weight gains were observed by the end of the 14-day post-exposure observation period.

In studies conducted by Union Carbide Corporation from 1973-1977 (summarized in UCC 1992), rats were also exposed to the degradate aldicarb sulfone (Temik® sulfone). An aerosol of 120 mg/m^3, 0.5% in distilled water, for 8 hours failed to induce lethality in six rats. The LC_{50} for a 4-hour inhalation exposure to aldicarb sulfone dust was 420 mg/m^3. However, in the same summary report, a 4-hour LC_{50} for rats of 120 mg/m^3 was reported. Signs observed during exposure were indicative of cholinesterase activity inhibition and, at necropsy, congestion and hemorrhage of the lungs were noted.

Additional aerosol studies with aldicarb sulfone were conducted (UCC 1992). An aerosol of 6.9% technical aldicarb sulfone in dimethyl sulfoxide (approximately 2 mg/L) was lethal to half of tested rats in 47.6 minutes whereas an aerosol of 0.5% in DMSO (approximately 184 mg/m^3) was lethal to one of six rats in 4 hours. An aerosol of 0.5% in water (approximately 148 mg/m^3) was not lethal to any of six rats in 4 hours. Signs of cholinesterase activity inhibition were seen during exposure.

TABLE 2. Acute Toxicity of Aldicarb to Rats

Concentration (mg/m^3)	Exposure Duration	Effect/LC_{50} (mg/m^3)	Reference
Dust			
6.7	15 minutes 30 minutes	Survival: 6 of 6 mortality: 5 of 6	Risher et al. 1987
Liquid Aerosol			
0.82[a] 2.0 6.0 8.7 46.3 3.9	4 hours	No mortality mortality: 1 of 10 mortality: 5 of 10 mortality: 10 of 10 mortality: 10 of 10 calculated LC_{50}	UCC 1985
Vapor			
Saturated vapor	No mortality – 8 hours	—	Risher et al. 1987

[a] Aldicarb aerosol solutions in dichloromethane.

3.2. Repeat-Exposure Studies

No repeat-exposure inhalation studies with aldicarb were located. In a nine-day repeat-exposure inhalation study, groups of six male and six female Wistar rats inhaled 0, 1.4, 6, or 18 mg/m^3 of the metabolite aldicarb sulfone as particulates for 6 hours/day for 9 days (UCC 1977; U.S. EPA 1992). The test material was a 75% wettable powder. "Dust clouds" were generated by a baffled dust feed through which air was passed at 20 liters/minute. Airborne dust concentrations were measured gravimetrically. Exposure took place in a 120-L Plexiglas chamber. Body weight was measured and liver, kidney and brain were weighed. Plasma, erythrocyte, and brain were assayed for cholinesterase activity levels. No clinical signs were evident in rats inhaling 1.4 or 6 mg/m^3; there were no effects on body or organ weight. Rats inhaling 18 mg/m^3 displayed tremor and salivation. Body weight was decreased and blood cholinesterase activity was significantly inhibited at 19 hours following termination of the experiment (data not presented). Correction for percent active ingredient in the test material was not mentioned.

3.3. Neurotoxicity

Acute toxicity studies showed that aldicarb is neurotoxic. Ataxia and tremors were observed in rats inhaling aldicarb for 4 hours (UCC 1985). See Section 4.2 for mechanism of toxicity of *N*-methyl carbamates.

3.4. Developmental/Reproductive Toxicity

No inhalation studies were conducted that addressed the developmental or reproductive toxicity of aldicarb. Reproductive and developmental toxicity studies that used the oral route of administration were reviewed by Risher et al. (1987), IPCS (1991), and HSDB (2005). In developmental studies with the rat and rabbit, aldicarb showed neither developmental toxicity nor teratogenicity. Fetotoxicity manifest as reduced litter weight was apparent at maternally toxic doses in Sprague Dawley rats (0.5 mg/kg/day from gestation days 6-15). No congenital malformations were observed in offspring of rats administered aldicarb in the diet at concentrations up to 1.0 mg/kg throughout pregnancy, or in offspring of Dutch Belted rabbits administered aldicarb by gavage at doses up to 0.50 mg/kg on days 7 through 27 of gestation. No reproductive parameters were affected in any of three generations of rats fed aldicarb in the diet at doses up to 0.7 mg/kg body weight per day.

3.5. Genotoxicity

The genetic toxicology of aldicarb was reviewed by the National Toxicology Program (NTP 1979) and the International Program on Chemical Safety (IPCS 1991). Bacterial assays were conducted with and without metabolic activation. Assay results were negative for mutagenicity in *Salmonella typhimurium* (TA97, TA100, TA1535, and TA1537) and *Escherichia coli* WP2 uvrA. In an *in vitro* test for gene mutation in mouse L5178Y lymphoma cells, results were inconclusive in the absence of metabolic activation, but aldicarb induced mutations in the presence of S9 mix. Assays with aldicarb were negative for chromosome and chromatid breaks in human peripheral lymphocytes, but a significant increase in sister chromatid exchanges was seen in the same system. In *in vivo* clastogenicity assays, intraperitoneal injections with aldicarb induced damage in bone marrow cells in rats, but not in mice. There was no increased incidence of dominant lethal mutations in male rats treated with aldicarb in the diet and mated with untreated virgin females.

3.6. Chronic Toxicity/Carcinogenicity

Technical aldicarb was tested for chronic toxicity and carcinogenicity in two-year dietary studies with male and female F344 rats and B6C3F1 mice (NTP 1979). Groups of 50 rats and 50 mice of each sex were administered aldicarb in the diet at concentrations of 0, 2, or 6 ppm for 103 weeks and then observed for an additional 0 to 2 weeks. Body weight and survival were unaffected in both rats and mice. Dosed mice appeared hyperactive. No tumors occurred in either rats or mice at incidences that could clearly be related to administration of aldicarb.

Because the cholinesterase activity inhibition caused by aldicarb exposure is transient, the U.S. "EPA had concluded that the cumulative risks associated with the *N*-methyl carbamate pesticides are below the Agency's level of concern" (U.S. EPA 2007a).

3.7. Summary

Acute inhalation lethality studies were conducted primarily with the rat. The 4-hour LC_{50} value for an aerosol of aldicarb in dichloromethane was 3.9 mg/m^3 (UCC 1985). During exposure rats showed signs of cholinesterase activity inhibition. No rats died following a 15-

minute exposure to 6.7 mg/m^3 aldicarb dust, but mortality was 100% after 30 minutes (Risher et al. 1987). No details were available in the latter study.

Although considered highly acutely toxic, evidence indicates aldicarb does not affect fetal development, impair reproductive performance, conclusively induce genotoxic effects, or produce significant subchronic or chronic effects including cancer.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Inhalation studies with aldicarb that addressed metabolism 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). Oral absorption is rapid and nearly complete (Risher et al. 1987; IPCS 1991; AIHA 1993). The metabolic fate of aldicarb is similar in all species examined (IPCS 1992). Clinical signs in rats appear at approximately 5 minutes after administration. Unlike some organophosphate pesticides that are metabolized by A-esterases which show great inter-individual variation, the metabolism of the carbamate pesticide aldicarb involves both hydrolysis of the carbamate ester (to aldicarb oxime) and oxidation of the sulfur to the sulfoxide and sulfone derivatives. Hydrolysis is a minor pathway and results in compounds with little or no insecticidal activity (aldicarb oxime and aldicarb nitrile). Aldicarb is S-oxidized by flavin-containing monooxygenases to form aldicarb sulfoxide (Tang et al. 2006). Aldicarb sulfoxide is slowly degraded by both oxidative and hydrolytic mechanisms to yield the corresponding aldicarb sulfone and sulfoxide oxime. The sulfoxide and sulfone metabolites are active cholinesterase inhibitors. Excretion of these metabolites takes place via the urine (80-90%) within the first 24-hours post-exposure. The major urinary metabolites are aldicarb sulfoxide (40% of the dose) and aldicarb sulfoxide oxime and nitriles (over 30% of the dose). Only a small amount is expired as CO_2. Half-lives in rats and humans following oral dosing are 1.1 and 1.7 hours, respectively. Absorption through the skin can be extensive, and dermal LD_{50} doses in rats range from 2.5 to 3 mg/kg (Risher et al. 1987).

4.2. Mechanism of Toxicity

Aldicarb is an *N*-methyl carbamate insecticide. The mode of action of carbamate pesticides involves cholinesterase inhibition (U.S. EPA 2007b; Costa 2008). Carbamic acid esters attach to the serine hydroxyl group of the active site of acetylcholinesterase, the enzyme responsible for the destruction and termination of the biological activity of the neurotransmitter acetylcholine. When unbound acetylcholine accumulates at the cholinergic nerve endings, there is continual stimulation of electrical activity. The resulting signs of toxicity from stimulation of the muscarinic receptors of the parasympathetic autonomic nervous system are manifest as increased secretions, bronchoconstriction, miosis, gastrointestinal cramps, diarrhea, urination, and bradycardia. Stimulation of the parasympathetic junctions of the autonomic nervous system as well as the junctions between nerves and muscles cause tachycardia, hypertension, muscle fasciculation, tremors, muscle weakness, and flaccid paralysis. Signs and symptoms resulting from effects on the central nervous system include restlessness, emotional lability, ataxia, lethargy, mental confusion, loss of memory, generalized weakness, convulsions, cyanosis, and coma. Inhibition of acetylcholinesterase activity is transient and rapidly reversible (minutes to hours) because there is rapid reactivation of the carbamylated enzyme in the presence of water.

Maximum inhibition typically occurs between 15 and 45 minutes after exposure. The major metabolites of aldicarb, aldicarb sulfoxide and aldicarb sulfone are also cholinesterase inhibitors (Risher et al. 1987; U.S. EPA 2007a). Aldicarb sulfoxide is considered to have similar potency to the parent in terms of toxicity, while aldicarb sulfone is less potent. At the maximally tolerated oral doses of 0.18, 0.26, and 0.35 mg/kg for PND 17, PND 27, and adult rats, brain cholinesterase activity was 30-40% of the control value and blood cholinesterase activity was <10% of the control value (Moser 1999).

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 show that clinical signs and behavioral effects are not evident below 10% cholinesterase activity inhibition. Due to human variability, it is difficult to measure inhibition of <20% (U.S. EPA 2000). At greater than 30% erythrocyte acetylcholinesterase activity inhibition or 50% plasma activity inhibition, workers are withdrawn from pesticide application areas (U.S. EPA 2000; ACGIH 2008). Other enzymes such as carboxylesterases are non-target enzymes to which cholinesterase activity inhibitors such as aldicarb 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, i.e., the carbamylated (inhibited) enzyme is decarbamylated with the generation of the free, active enzyme.

Information is available on the relative oral toxicity of three carbamate pesticides (HSRB 2006; U.S. EPA 2007b). Aldicarb is considered the most toxic of the *N*-methyl carbamates. Based on an assigned potency of 1 for oxamyl, aldicarb is considered 4 times more toxic by the oral route. The endpoints for relative oral toxicity were brain and erythrocyte cholinesterase activity inhibition in the rat and erythrocyte acetylcholinesterase 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 from McDaniel et al. (2007).

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

Chemical	Rat				Human	
	Brain		Erythrocyte		Erythrocyte	
	Benchmark Dose (mg/kg)	Half-life (h)	Benchmark Dose (mg/kg)	Half-life (h)	Benchmark Dose (mg/kg)	Half-life (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	1.0	BMD_{10}: 0.204	0.8	BMD_{10}: 0.040	1.6

	$BMDL_{10}$: 0.331		$BMDL_{10}$: 0.112		$BMDL_{10}$: 0.028	
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, U.S. EPA 2007b.

The major metabolites of aldicarb also have anticholinesterase activity. Compared to oxamyl's potency of 1, aldicarb, aldicarb sulfone, and aldicarb sulfoxide were assigned potencies of 4, 3.44, and 3.68, respectively (U.S. EPA 2007b). These potencies were based on molecular weight conversions from aldicarb.

4.4. Other Relevant Information

4.4.1. Species Variability

Inhalation studies with usable data were conducted only with rats. 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). The U.S. EPA Office of Pesticide Programs (Taylor and Reaves 2006) compared erythrocyte cholinesterase activity inhibition in human and adult rat oral dosing studies following equivalent oral doses. Enzyme activity was assayed at 1 hour post-dose in humans and 0.75 hours post-dose in rats (Table 4).

TABLE 4. Comparison of Erythrocyte Acetylcholinesterase Activity Inhibition in Rats and Humans

Species	Oral Dose		
	0.01 mg/kg	0.025 mg/kg	0.05 mg/kg
Human (acute)			
Males	3.8%	12%	29%
Females	—	20%	36%
Rat (acute)			
Males	—	—	—
Females	—	—	10%
Rat (subchronic)			
Males	—	—	32%
Females	—	—	24%

Source: Taylor and Reaves 2006.

The U.S. EPA Office of Pesticide Programs (2007b) compared the toxicity (endpoint cholinesterase activity inhibition) of three *N*-methyl carbamate pesticides, oxamyl, methomyl, and aldicarb, using oral dosing in humans and in juvenile and adult rats. Most data were available for oxamyl which was used as the index chemical. Benchmark doses were calculated for brain and erythrocyte cholinesterase activity inhibition in juvenile and adult rats and erythrocyte cholinesterase activity inhibition in humans. Based on the comparative erythrocyte acetylcholinesterase activity inhibition for equal oral doses in adult rats and humans, the U.S. EPA calculated a chemical-specific interspecies uncertainty factor for aldicarb of 2. For most of the *N*-methyl carbamate pesticides, the interspecies uncertainty factor is used for all routes of exposure.

4.4.2. Susceptible Populations

Humans are known to 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 population most susceptible to the toxicity of carbamate pesticides. In the absence of human data, the relative sensitivity to cholinesterase activity inhibition of adult and juvenile rats to aldicarb can be used as a surrogate for a comparison of human adult and infant sensitivity. Using the oral route of exposure, Moser (1999) evaluated age-related differences in sensitivity to aldicarb among preweanling (post-natal day 17 [PND 17]), postweanling (PND 27) and adult (PND 70) Long Evans rats of both sexes. Control data for cholinesterase activity (nmol ^{3}H-labeled acetylcholine iodide hydrolyzed/min/mg/tissue) were (a) male brain: PND 17, 5.9; PND 27, 5.8; adult 7.0; male blood: PND 17, 0.44; PND 27; 0.49, adult, 0.43; (b) female brain: PND 17, 4.9, PND 27, 6.1; adult 6.9; female blood: PND 17, 0.50; PND 27, 0.52; adult, 0.59. Range-finding studies determined the maximally tolerated doses (0.18, 0.26, and 0.35 mg/kg in the PND 17, 27, and 70 groups, respectively) and time of peak effect of blood cholinesterase activity inhibition, 1 hour in all age groups. The U.S. EPA standard functional observational battery (FOB) and motor activity observations were carried out. Pre-weanling rats were twice as sensitive to aldicarb as adult rats, and dose-response data for brain acetylcholinesterase activity inhibition followed a similar pattern of age-related differences. Blood cholinesterase activity inhibition measured with a radiometric assay was greater than that of brain, with little age difference. At similar levels of brain cholinesterase activity inhibition, young rats generally showed fewer signs of toxicity as indicated by neurobehavioral parameters and motor activity than adult rats.

The U.S. EPA evaluated the relative sensitivity of juvenile and adult rats to *N*-methyl carbamate pesticides including aldicarb (U.S. EPA 2007b). The U.S. EPA calculated benchmark doses for brain cholinesterase activity inhibition in PND 17 and adult rats. The BMD_{10} and $BMDL_{10}$ in post-natal day 17 rats were 0.017 and 0.016 mg/kg, respectively. The BMD for adult rats was 0.033 mg/kg. Based on comparative brain acetylcholinesterase activity inhibition in aldicarb-treated post-natal day 17 juvenile rats and adult rats, the U.S. EPA calculated a Food Quality Protection Act (FQPA) uncertainty factor for children of 2.0. This uncertainty factor corresponds to an AEGL intraspecies uncertainty factor. A recovery half-life for brain cholinesterase activity was not available for rats, but recovery was complete in juvenile and adult rats by 24 hours (Moser 1999).

4.4.3. Concentration-Exposure Duration Relationship

No data were available for evaluating the relationship between ambient concentrations of aldicarb and exposure duration for a single endpoint. The concentration-time relationship for a single endpoint for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$ (ten Berge et al. 1986). In the absence of empirical data, the time scaling factors of n

= 3 and n = 1 are used to scale to shorter and longer exposure durations, respectively (NRC 2001).

4.4.4. Concurrent Exposure Issues

Dermal absorption may occur. Dermal LD_{50} values in rats range from 2.5 to 3.0 mg/kg (Risher et al. 1987). Concurrent exposure to other *N*-methyl carbamates in proportion to their potency indicates that they follow a dose-additive model of brain cholinesterase inhibition (Padilla et al. 2006; U.S. EPA 2007b).

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

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

5.3. Derivation of AEGL-1

No human or animal studies were located that addressed symptoms and signs consistent with the definition of the AEGL-1. Therefore, AEGL-1 values are not recommended (Table 5).

TABLE 5. AEGL-1 Values for Aldicarb

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

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

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

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

6.2. Summary of Animal Data Relevant to AEGL-2

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

6.3. Derivation of AEGL-2

No human or animal data on an aldicarb concentration that would result in effects consistent with the definition of AEGL-2 were located. Therefore, consistent with Standard Operating Procedures (NRC 2001), the 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. As shown by Risher et al. (1987) mortality went from 0 to 83% with the doubling of exposure duration. In the study reported by UCC (1985) mortality went from 10% at 2.0 mg/m^3 to 50% when concentration was increased 3-fold (6 mg/m^3). AEGL-2 values are summarized in Table 6. Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 6. AEGL-2 Values for Aldicarb

10-min	30-min	1-h	4-h	8-h
0.16 mg/m^3	0.11 mg/m^3	0.087 mg/m^3	0.053 mg/m^3	0.027 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

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

7.2. Summary of Animal Data Relevant to AEGL-3

A study with aldicarb dust lacked details of exposure and was of a short duration (Risher et al. 1987). Vapor concentrations high enough to induce mortality were not attained in a second study reported by Risher et al. (1987). One 4-hour study with aldicarb administered as an aerosol in dichloromethane presented concentration-response information (UCC 1985). In that study, mortality in rats inhaling 0.82, 2.0, 6.0, 8.7, or 46.3 mg/m^3 was 0/10, 1/10, 5/10, 10/10, and 10/10, respectively.

7.3. Derivation of AEGL-3

The study with aldicarb aerosol was chosen as the key study for AEGL-3 development (UCC 1985). The 4-hour study used a sufficient number of rats and five concentrations. The calculated 4-hour $BMCL_{05}$ is 0.97 mg/m^3 and the BMC_{01} is 1.9 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). The 4-hour 0.97 mg/m^3 value was divided by inter- and intraspecies uncertainty factors of 2 and 3, respectively, for a total of 6. U.S. EPA (2007b) derived an uncertainty factor of 2 for aldicarb based on differences in modeled values for red blood cell acetylcholinesterase activity inhibition between rats and humans (See section 4.4.1). Based on comparative brain cholinesterase activity inhibition in post-natal day 17 juvenile rats and adult rats, the U.S. EPA calculated an uncertainty factor of 2 to protect sensitive young (See section 4.4.2). In keeping with intraspecies uncertainty factors applied to the related carbamate pesticides, oxamyl and methomyl, the intraspecies uncertainty factor was raised to 3. The combined uncertainty factor is 6. No differences were found in sensitivity between male and female rats (UCC 1985). Values were time-scaled ($C^n \times t = k$) from the 4-hour data point using n values of 3 and 1 for extrapolation to shorter and longer exposure durations, respectively (NRC 2001). Values are summarized in Table 7, calculations are in Appendix A, and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 7. AEGL-3 Values for Aldicarb				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.47 mg/m^3	0.32 mg/m^3	0.26 mg/m^3	0.16 mg/m^3	0.081 mg/m^3

When AEGL-3 values are based on a 4-hour or longer exposure duration, the 10-minute value is usually set equal to the 30-minute value. However, the 15-minute value of 6.7 mg/mg^3 for aldicarb dust that resulted in no mortality in rats can be used as justification for not setting the 10- and 30-minute values equal. Application of a total uncertainty factor of 6 to the 6.7 mg/m^3 value results in a 15-minute value of 1.1 mg/m^3. The 15-minute value time-scaled to 10 minutes (n = 3) with application of an uncertainty factor of 6 is 1.3 mg/m^3, a value considerably larger than that derived from the 4-hour data.

The derived AEGL-3 values are based on an aerosol which may be less toxic than the dust. Because the 15-minute value derived from dust is larger than the calculated number using the aerosol, the use of the study with aerosol is justified. The dust study was not used for AEGL derivation because of the short exposure period and single concentration.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 8. Derivations summaries are in Appendix C.

TABLE 8. Summary of AEGL Values for Aldicarb					
Classification	**Exposure Duration**				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2 (Disabling)	0.16 mg/m^3	0.11 mg/m^3	0.087 mg/m^3	0.053 mg/m^3	0.027 mg/m^3
AEGL-3 (Lethal)	0.47 mg/m^3	0.32 mg/m^3	0.26 mg/m^3	0.16 mg/m^3	0.081 mg/m^3

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

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for aldicarb are listed in Table 9. The American Conference of Government Industrial Hygienists (ACGIH) has not derived a Threshold Limit Value-Time Weighted Average for aldicarb. The ACGIH has calculated a Biological Exposure Index for acetylcholinesterase inhibiting chemicals (ACGIH 2008). The value, based on erythrocyte cholinesterase activity inhibition, is 70% of an individual's baseline.

The American Industrial Hygiene Association Workplace Environmental Exposure Level Guide is 0.07 mg/m^3 (AIHA 1993). This value corresponds to an inhaled amount of aldicarb of 0.01 mg/kg/day if one assumes inhalation of 10 m^3 of air per 8-hour day by a 70-kg person. This dose is judged to provide sufficient protection from adverse health effects. A skin notation is recommended.

TABLE 9. Standards and Guidelines for Aldicarb

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2	0.16 mg/m^3	0.11 mg/m^3	0.087 mg/m^3	0.053 mg/m^3	0.027 mg/m^3
AEGL-3	0.47 mg/m^3	0.32 mg/m^3	0.26 mg/m^3	0.16 mg/m^3	0.081 mg/m^3
ERPG-1 (AIHA)[a]			—		
ERPG-2 (AIHA)			—		
ERPG-3 (AIHA)			—		
IDLH (NIOSH)[b]		—			
REL-TWA (NIOSH)[c]					—
OSHA PEL (NIOSH)[d]					—
TLV-TWA (ACGIH)[e]					—
WEEL (AIHA)[f]					0.07 mg/m^3 *
MAK (Germany)[g]					—
MAC (The Netherlands)[h]					—

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

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

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

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

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

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

[f]WEEL (Workplace Environmental Exposure Level Guide) (AIHA 1993) is the 8-hour time-weighted average that is expected to be without adverse health effects during a normal 8-hour day and 40-hour workweek.

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

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

8.3. Data Adequacy and Research Needs

Aldicarb has a low vapor pressure and no usable studies involving inhalation exposure of humans were located in the available literature. An oral dosing study with human volunteers addressed effects consistent with cholinesterase activity inhibition. Inhalation studies with rats as the test species involving several exposure durations and dust, aerosol, and vapor delivery were sufficient for derivation of two 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: Derivation of Aldicarb AEGLs

Derivation of AEGL-1 Values

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

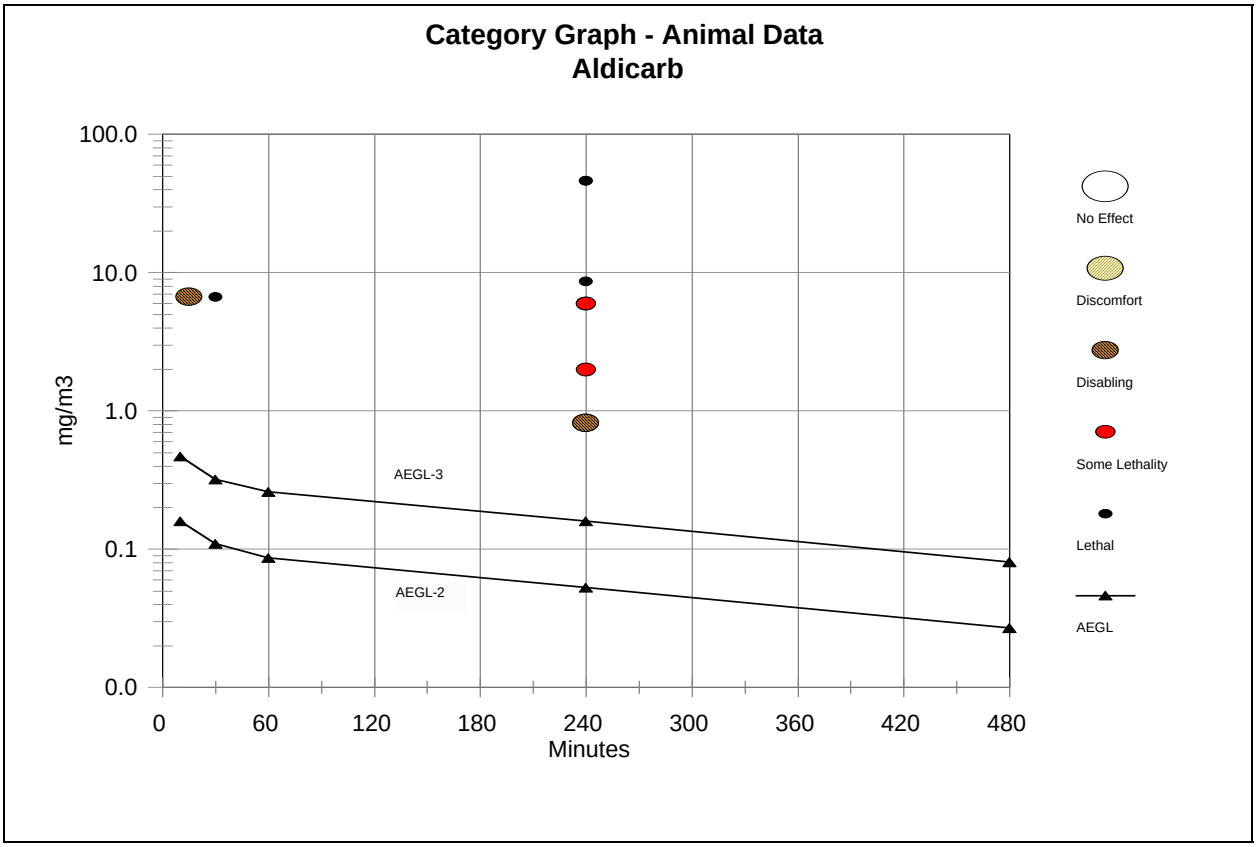
Derivation of AEGL-2 Values

Key Study:	UCC (Union Carbide Corporation). 1985. Aldicarb Solution (in DMC) LC_{50} Aerosol Acute Inhalation Toxicity Test. Bushy Run Research Center, Project Report 48-136, December 11, 1985.
Toxicity endpoint:	AEGL-3 values divided by 3. The steep concentration-response line shown by the Risher et al. (1987) and UCC (1985) data justifies deriving AEGL-2 values by dividing the AEGL-3 values by 3 (NRC 2001).
Time scaling	See AEGL-3 derivation, next page
Uncertainty factors:	Total uncertainty factor: 6 (See AEGL-3 derivation, next page)
Calculations:	AEGL-3 values divided by 3
10-min AEGL-2:	$C = 0.47\ mg/m^3/3 = 0.16\ mg/m^3$
30-min AEGL-2:	$C = 0.32\ mg/m^3/3 = 0.11\ mg/m^3$
1-h AEGL-2:	$C = 0.26\ mg/m^3/3 = 0.087\ mg/m^3$
4-h AEGL-2:	$C = 0.16\ mg/m^3/3 = 0.053\ mg/m^3$
8-h AEGL-2:	$C = 0.081\ mg/m^3/3 = 0.027\ mg/m^3$

Derivation of AEGL-3 Values

Key Study:	UCC (Union Carbide Corporation). 1985. Aldicarb Solution (in DMC) LC_{50} Aerosol Acute Inhalation Toxicity Test. Bushy Run Research Center, Project Report 48-136, December 11, 1985.
Toxicity endpoint:	Threshold for lethality in rats at the $BMCL_{05}$ of 0.973753 mg/m^3 calculated from the rat lethality data of UCC (1985).
Time scaling	$C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001).
Uncertainty factors:	Total uncertainty factor: 6 Interspecies: 2 – The U.S. EPA (2007b) Office of Pesticide Programs calculated an oxamyl-specific inhalation interspecies uncertainty factor of 2 based on differences in modeled red blood cell values for cholinesterase activity inhibition between the rat and humans. Intraspecies: 3 – The U.S. EPA (2007b) Office of Pesticide Programs calculated an aldicarb-specific inhalation intraspecies uncertainty factor of 2 based on comparative brain acetylcholinesterase activity inhibition in post-natal day 17 juvenile rats and adult rats. For consistency among the *N*-methyl carbamate pesticides, the chemical-specific intraspecies uncertainty factor of 3, derived for the both of the related *N*-methyl carbamate pesticides, oxamyl and methomyl, was applied to aldicarb.
Modifying factor:	None applied
Calculations:	$(0.973753\ mg/m^3/6)^3 \times 240\ minutes = 1.03\ mg/m^3 \bullet min$
10-min AEGL-3:	$C = \sqrt[3]{(1.03\ mg/m^3 \bullet min\ /10)} = 0.47\ mg/m^3$
30-min AEGL-3:	$C = \sqrt[3]{(1.03\ mg/m^3 \bullet min/30)} = 0.32\ mg/m^3$
1-h AEGL-3:	$C = \sqrt[3]{(1.03\ mg/m^3 \bullet min/60)} = 0.26\ mg/m^3$
4-h AEGL-3:	$C = 0.973753/6 = 0.16\ mg/m^3$
8-h AEGL-3:	$C = (0.16\ mg/m^3 \bullet min \times 240\ min)/480\ minn = 0.081\ mg/m^3$

APPENDIX B: Category Graph of AEGL Values and Toxicity Data



Data:

For Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**mg/m^3**	**Minutes**	**Category**
NAC/AEGL-1		Not recommended	10	AEGL
NAC/AEGL-1		Not recommended	30	AEGL
NAC/AEGL-1		Not recommended	60	AEGL
NAC/AEGL-1		Not recommended	240	AEGL
NAC/AEGL-1		Not recommended	480	AEGL
NAC/AEGL-2		0.16	10	AEGL
NAC/AEGL-2		0.11	30	AEGL
NAC/AEGL-2		0.087	60	AEGL
NAC/AEGL-2		0.053	240	AEGL
NAC/AEGL-2		0.027	480	AEGL
NAC/AEGL-3		0.47	10	AEGL
NAC/AEGL-3		0.32	30	AEGL
NAC/AEGL-3		0.26	60	AEGL
NAC/AEGL-3		0.16	240	AEGL
NAC/AEGL-3		0.081	480	AEGL

Risher et al. 1987	rat	6.7	15	2; survival of 6 of 6
	rat	6.7	30	SL; mortality of 5 of 6
UCC 1985	rat	0.82	240	2; ataxia and tremors
	rat	2.9	240	SL; mortality of 1 of 10
	rat	6.0	240	SL; mortality of 5 of 10
	rat	8.7	240	3; mortality of 10 of 10
	rat	46.3	240	3; mortality of 10 of 10

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

1

APPENDIX C: Benchmark Concentration Calculations for Aldicarb

Aldicarb $BMCL_{05}$ Derivation (data of UCC 1985)

```
==========================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: C:\BMDS\BCME_RAT.(d)
        Gnuplot Plotting File:  C:\BMDS\BCME_RAT.plt
                                                  Wed Apr 15 18:17:01 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 = 6
  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 =     -1.49047
                   slope =     0.948882

       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       -0.95
     slope      -0.95           1
                    Parameter Estimates
       Variable         Estimate          Std. Err.
     background                0             NA
      intercept         -2.82566          0.882065
```

slope 1.84829 0.513275

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	-10.1823			
Fitted model	-12.333	4.30146	4	0.3667
Reduced model	-41.0539	61.7432	5	<.0001

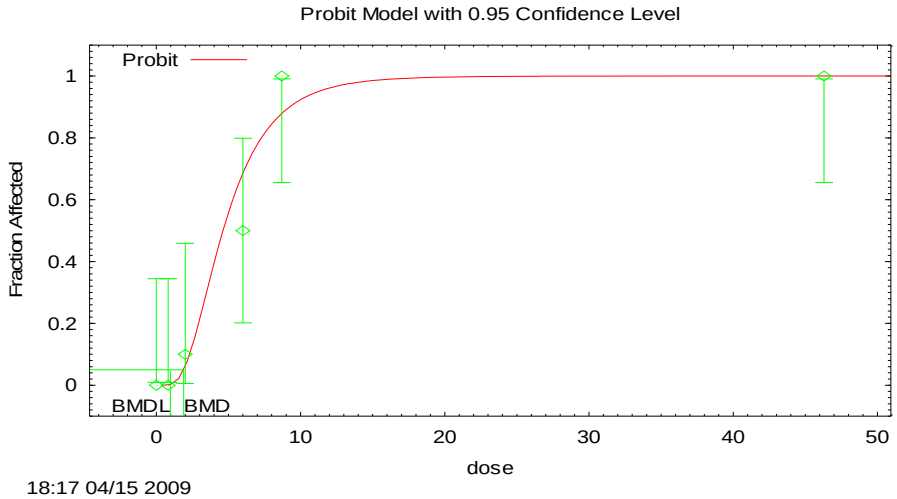
AIC: 28.6661

Dose	Est._Prob.	Goodness of Fit Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	10	0
0.8200	0.0007	0.007	0	10	-0.08401
2.0000	0.0612	0.612	1	10	0.5114
6.0000	0.6865	6.865	5	10	-1.271
8.7000	0.8796	8.796	10	10	1.17
46.3000	1.0000	10.000	10	10	0.01005

Chi-square = 3.25 DF = 4 P-value = 0.5161

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95

BMC_{05} = 1.89433
$BMCL_{05}$ = 0.973753



18:17 04/15 2009

Aldicarb BMC_{01} Derivation (data of UCC 1985)

==========

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Tue Mar 10 07:28:32 2009

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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 = 6
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 = -1.49047
slope = 0.948882

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	-0.95
slope	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-2.82566	0.882065	-4.55448	-1.09685
slope	1.84829	0.513275	0.842291	2.85429

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-10.1823	6			
Fitted model	-12.333	2	4.30146	4	0.3667
Reduced model	-41.0539	1	61.7432	5	<.0001

AIC: 28.6661

Goodness of Fit Scaled

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
0.8200	0.0007	0.007	0	10	-0.084
2.0000	0.0612	0.612	1	10	0.511
6.0000	0.6865	6.865	5	10	-1.271
8.7000	0.8796	8.796	10	10	1.170
46.3000	1.0000	10.000	10	10	0.010

Chi^2 = 3.25 d.f. = 4 P-value = 0.5161

Benchmark Dose Computation

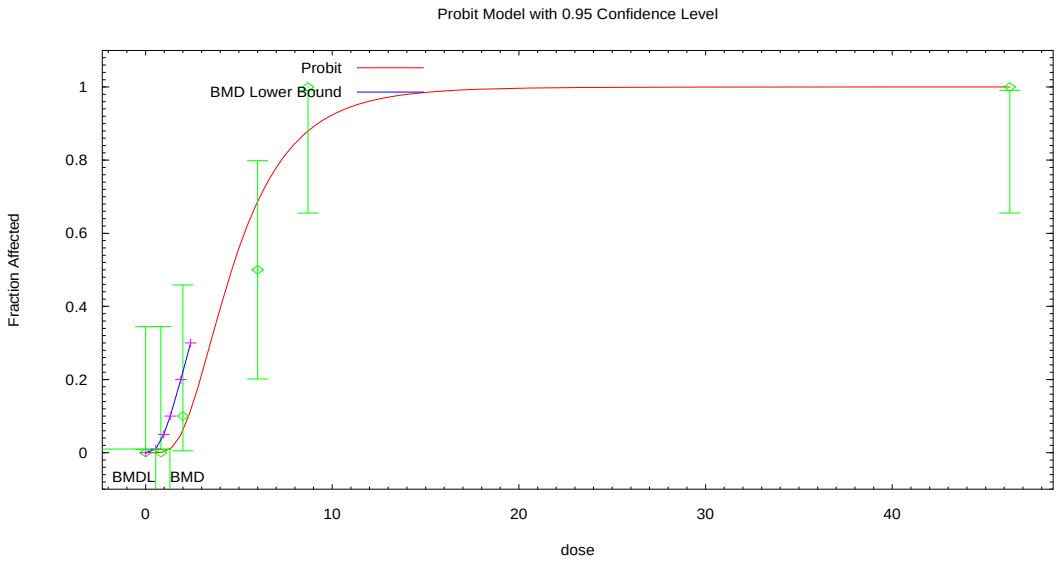
Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMC_{01} = 1.31016

$BMCL_{01}$ = 0.54285



APPENDIX D: Derivation Summary for Aldicarb AEGLs

Acute Exposure Guideline Levels For Aldicarb

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

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

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

1

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.16 mg/m^3	0.11 mg/m^3	0.087 mg/m^3	0.053 mg/m^3	0.027 mg/m^3
Key Reference: UCC (Union Carbide Corporation). 1985. Aldicarb Solution (in DMC) LC50 Aerosol Acute Inhalation Toxicity Test. Bushy Run Research Center, Project Report 48-136.				
Test Species/Strain/Number: Rat/Sprague-Dawley/groups of 5 per sex				
Exposure Route/Concentration/Duration: Inhalation/0.82, 2.0, 6.0, 8.7, 46.3 mg/m^3/4 hours				
Effects: acetylcholinesterase activity inhibition, estimate 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				
Uncertainty Factors/Rationale: **Total uncertainty factor**: 6 (used for derivation of AEGL-3) **Interspecies:** 2 **Intraspecies**: 3				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n = 3 and 1 for shorter and longer exposure durations, respectively				
Data Adequacy: The key study was well conducted, used adequate numbers of rats, and five concentrations.				

2
3
4

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.47 mg/m^3	0.32 mg/m^3	0.26 mg/m^3	0.16 mg/m^3	0.081 mg/m^3

Key References: UCC (Union Carbide Corporation). 1985. Aldicarb Solution (in DMC) LC_{50} Aerosol Acute Inhalation Toxicity Test. Bushy Run Research Center, Project Report 48-136.

Test Species/Strain/Number: Rat/Sprague-Dawley/groups of 5 per sex

Exposure Route/Concentration/Duration: Inhalation/0.82, 2.0, 6.0, 8.7, 46.3 mg/m^3/4 hours

Effect: Mortalities: 0, 1, 5, 10, and 10

Endpoint/Concentration/Rationale: $BMCL_{05}$, estimated as the threshold for lethality

Uncertainty Factors/Rationale:

Total uncertainty factor: 6

Interspecies: 2: The U.S. EPA (2007b) Office of Pesticide Programs calculated an aldicarb-specific interspecies uncertainty factor of 2 based on differences in values of modeled red blood cell cholinesterase activity inhibition between the rat and humans.

Intraspecies: 3: The U.S. EPA (2007b) Office of Pesticide Programs calculated an aldicarb-specific intraspecies uncertainty factor of 3 for the related chemicals oxamyl and methomyl based on comparative brain acetylcholinesterase activity inhibition in post-natal day 17 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 = 3 and 1 for shorter and longer exposure durations, respectively.

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

2