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Drinking Water Health Advisory for Oxamyl

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Lead EPA Scientist: Dr. Amal M. Mahfouz
Office of Water/OST/HECD (4304-T)
U. S. Environmental Protection Agency
Washington D.C.

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LIST OF ABBREVIATIONS

a.i.	Active Ingredient
AChE	Acetyl Cholinesterase
ADI	Acceptable Daily Intake
BW	Body Weight
CaEPA	California Environmental Protection Agency
CASN	Chemical Abstract Number
ChE	Cholinesterase
CHO	Chinese Hamster Ovary
CO_2	Carbon Dioxide
DMCF	N,N-Dimethyl-1-cyano-formamide
DMF	Dimethylformamide
DMOA	N,N-Methyloxamic acid
DMTO	Methyl N-hydroxy-N',N'-dimethyl-1-thiooxamimidate
DNA	Deoxyribonucleic Acid
DWEL	Drinking Water Equivalent Level
DWLOC	Drinking Water Level Of Comparison
F_0	Parental Generation
F_1	First Generation Offspring
F_2	Second Generation Offspring
FAO	Food and Agriculture Organization (of the United Nations)
FOB	Functional Observation Battery
GAC	Granular Activated Carbon
HA	Health Advisory
HED	Health Effects Division (U.S. EPA Office of Pesticides Program)
HSDB	Hazardous Substance Databank
IRED	Interim Reregistration Eligibility Decision
K_{ow}	Octanol-Water Coefficient
L/day	Liters Per Day
LC_{50}	Lethal Concentration - 50
LD_{50}	Lethal Dose - 50
LOAEL	Lowest Observed Adverse Effect Level
LOD	Level of Detection
MA	Motor Activity
MCL	Maximum Contaminant Level
mg/kg	Milligrms Per Kilogram
mg/kg/day	Milligrams Per Kilogram Per Day
mg/L	Milligrams Per Liter
：g/L	Micrograms Per Liter
：g/mL	Micrograms Per Milliliter
MRID	Master Record Identifier
MTD	Maximum Tolerated Dose
NaOH	Sodium Hydroxide
NAS	National Academy of Science

NOAEL	No Observed Adverse Effect Level
OPA	O-phthalaldehyde
OST	Office of Science and Technology (U.S. EPA, Office of Water)
OW	Office of Water (U.S. EPA)
p	Probability
PDP	Pesticide Data Program
ppb	Parts Per Billion
ppm	Parts Per Million
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision Document
RfD	Reference Dose
RSC	Relative Source Contribution
U.S. EPA	United States Environmental Protection Agency
UF	Uncertainty Factor
WHO	World Health Organization

1.0 INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the health effects, analytical methodology, and treatment technology that are useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for both short-term and long-term (Lifetime) exposure periods based on data describing non carcinogenic end points of toxicity. Short-term exposures can include one-day to ten-day exposure periods. In many cases, a longer-term value is included covering approximately 7 years, or 10 percent of an individual's lifetime. For those substances that are known or likely to be carcinogenic to humans, and for which a linear approach is used, Lifetime HAs are not recommended.

The Health Advisory evaluation of carcinogenic potential includes the U.S. EPA classification for the weight of evidence of the likelihood that the agent is a human carcinogen, conditions under which the carcinogenic effects may be expressed, and a quantitative estimate of cancer potency (slope factor) where available. The cancer slope factor is the result of the application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The Health Advisory includes the drinking water concentration equivalent to cancer risks of one-in-ten-thousand (10^{-4}), one-in-one-hundred-thousand (10^{-5}), and one-in-one-million (10^{-6}).

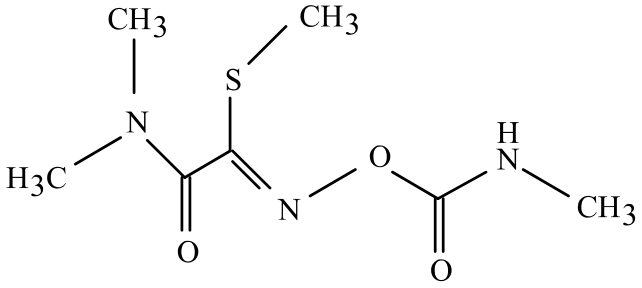
Cancer assessments conducted before 1996 used the five-category, alphanumeric system for classifying carcinogens established by the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986). After 1999, assessments were conducted using *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996, 1999a). Although the 1999 version of the *Guidelines for Carcinogen Risk Assessment* has not yet been finalized by the Agency, use of the 1986 guidelines ceased in 2001 with the publication of a directive from the administrator (U.S. EPA, 2001a) specifying that the 1999 guidelines are to be used on an interim basis for any new cancer assessment by the Agency. Between 1996 and 2001, assessments were conducted using both the 1986 and 1996 guidelines.

2.0 GENERAL INFORMATION AND PROPERTIES

2.1 Chemical Identity

CAS No. 23135-22-0

Structural Formula for Oxamyl is shown below:



Chemical Name: *N*,*N*-dimethyl-alpha-methylcarbamoyl)-*N*-(methylcorbamoyloxy)thioformimidate

Synonyms: Vydate®; Thioxamyl; and DPX 1410 (Budavari, 1989).

2.2. Uses

Oxamyl is a carbamate pesticide used to control insects, mites, and nematodes on fruits, vegetables, soybeans, and a variety of other crops. It also is used on tobacco and in plant nurseries. There are no approved residential uses for this pesticide. Oxamyl is a systemic and contact insecticide, acaricide, and nematocide used on a broad spectrum of agricultural pests. It is estimated that approximately 800,000 pounds of oxamyl active ingredient (a.i.) is used annually (U.S. EPA, 2000a).

2.3 Physical and Chemical Properties

Oxamyl is a crystalline solid that has a slightly sulfurous odor (Budavari et al., 1989). Its chemical and physical properties are presented in Table 2.1.

Table 2.1. Chemical and Physical Properties of Oxamyl

Formula	$C_7H_{13}N_3O_3S$
Molecular Weight	219.3 g/mole
Physical State (25/C)	Off-white; crystalline powder
Boiling Point (/C)	Decomposes on distillation
Melting Point (/C)	108-110/C
Vapor Pressure (25/C)	$2.3x10^{-4}$mmHg at 25/C
Specific Gravity (25/C)	0.97
Solubility (g/L) at 25/C: Water Acetone Ethanol Toluene	 280 670 330 10
Log Octanol/Water Partition Coefficient (Log K_{ow})	-0.47
Taste Threshold (Water)	Not Identified
Odor Threshold (Water)	Not Identified

Source: Budavari et al., 1989; HSDB, 2004; U.S. EPA, 1992a

3.0 OCCURRENCE AND EXPOSURE

3.1 Water

The U.S. EPA evaluated the occurrence of oxamyl in finished drinking water from approximately 13,000 public water systems in a sixteen-state cross section study (U.S. EPA, 2002a,b). Only one system had oxamyl levels that exceeded 0.02 mg/L. Based on the cross sectional data, EPA derived statistically generated, best estimate values for the occurrence of oxamyl in the United States public water systems. They concluded that no public water system in the United States is expected to have oxamyl levels that exceed 0.03 mg/L, and no more than 0.03% of the systems would have levels between 0.007 and 0.02 mg/L.

Oxamyl has been detected in ground water in Massachusetts, New York, New Jersey, and Rhode Island, North Carolina, and Maryland (U.S. EPA, 2000b, 1992b). The U.S. EPA conducted a study in Suffolk County, Long Island, NY and found that most samples had oxamyl levels that were between 1 to 2 ：g/L (U.S. EPA, 2000a). Three of the samples were >70 ：g/L, the highest being 395 ：g/L, but these higher levels were considered to be atypical. The U.S. EPA (2000a) estimates that environmental concentrations of oxamyl residues in surface and ground water are 1 and 4 ：g/L, respectively. Oxamyl was not detected in 1,370 wells sampled in 34 counties in California between July 1, 1995 and June 30, 1996 (CaEPA, 1997).

3.2 Food

Since oxamyl is used as a pesticide for food crops, it can be found in agricultural areas where various fruits and vegetables are grown, and it can be expected to be present on treated crops when purchased retail. Oxamyl typically is applied to field crops at an application rate that may range between 0.25 to 8 lb active ingredient (a.i.)/acre/day from one to 12 times a year, depending on the crop. Most crops, however, have a maximum seasonal application rate of 6 times a year or less (U.S. EPA, 2000b).

Data acquired by the U.S. Department of Agriculture through its Pesticide Data Program (PDP) and by the U.S. Food and Drug Administration show oxamyl to be present in/on only a few crops at relatively low levels. However, celery and apples have been found to have significant levels of oxamyl at 0.017-0.28 ppm and 0.014-0.32 ppm, respectively. PDP monitoring show residues above the Level of Detection (LOD; 0.14 ppb) in apple juice, green beans, spinach, tomatoes, pears, cantaloupe, and winter squash; however, the frequency of occurrence in/on these crops was <1%. Apples, pears, and peppers consistently demonstrate detectable residues from year to year.

3.3 Air

Information concerning the occurrence of oxamyl in ambient air was not found in the literature reviewed.

3.4 Soil

Information concerning the occurrence of oxamyl in soil was not found in the literature reviewed.

4.0 ENVIRONMENTAL FATE

Oxamyl is not considered to be a persistent pesticide. It dissipates in the soil environment by chemical degradation and microbial metabolism. The half-life of oxamyl in soil is estimated to be a few days to several weeks (U.S. EPA, 2000a). Groundwater studies show that significant contamination may result under certain conditions in vulnerable soils (e.g., muck, loamy sand, and silt loam) and acidic groundwater. Oxamyl may contaminate surface waters through spray drift or runoff.

Oxamyl's stability in water varies with pH. It degrades rapidly in neutral to alkaline environments, but persists in acidic conditions (U.S. EPA, 2000a). In a 1200-ppm solution, oxamyl has been reported to be stable for 11 days at $ pH 5, to have a half-life of 3 days at pH 9.1, and to have a half-life of 11 days at pH 6.9 (Harvey and Han, 1978a; Peebles, 1977).

Photolysis appears to be significant in acidic surface water but not in soil. When ^{14}C-oxamyl, at concentrations of 1 or 1000 ppm, in either distilled or river water, was exposed to ultraviolet radiation, its decomposition was rapid and extensive (Harvey and Han, 1978a). In the 1 ppm river water samples, 99% of the ^{14}C-oxamyl hydrolyzed in 48 hours. At the end of the first week of the study, 22-61% of the parent compound was recovered in the other samples. In a similar

study, the same authors were not able to detect any of the parent compound when river water spiked with 1 ppm ^{14}C-oxamyl was left outdoors and exposed to direct sunlight for 6 weeks. Oxamyl was hydrolyzed completely to the oximino product (identified below) by the end of the second study day. In the soil, oxamyl degrades with a half-life of 2 to 4 weeks under aerobic conditions and less than 1 week under anaerobic conditions (U.S. EPA, 2000a). In the field of most studies, half of the applied oxamyl dissipated from the surface within less than a week. Oxamyl's primary degradation products are an oximino derivative (methyl-N-hydroxy-N',N'-dimethyl-1-thiooxamimidate) and its isomer, and N,N-dimethyloxamic acid (U.S. EPA, 1992a).

Harvey and Han (1978a) demonstrated that under laboratory conditions, oxamyl was fairly mobile in four soils (muck, loamy sand, and two types of silt loam). Mobility increased as the amount of organic matter decreased in the soil; movement was slowest in muck and the most rapid in loamy sand. They also showed that oxamyl's downward movement in soil is not extensive. Over a 3- to 5-month period, very little ^{14}C-oxamyl penetrated to depths greater than 15 inches below the treated surface of silt loam, loamy sand, and fine sand soils. Only in sandy soil, after 3 months and 23 inches of rain, did more than 1% of the original carbon label reach the 15-inch depth. In another experiment, Harvey and Han (1978a) exposed ^{14}C-oxamyl-treated silt loam to 8.5 inches of artificial and natural rain over a 30-day period and detected radioactivity at depths of 30 inches.

Plants metabolize oxamyl after application. Harvey (1973) found that extracts from ^{14}C-oxamyl-treated peanuts and tobacco contained oxamyl and its oximino derivative; tobacco also had detectable levels of N,N-dimethyloxamic acid. The majority of radioactivity detected, however, was in a polar fraction of the extract, which consisted primarily of a glucoside conjugate of a hydrolyzed oximino compound. Harvey (1976) treated green tomatoes with ^{14}C-oxamyl and after ripening was able to detect the unchanged compound, its oximino derivative (methyl-N-hydroxy-N',N'-dimethyl-1-thiooxamimidate), a glucose conjugate, and N,N-dimethyl-1-cyanoformamide in the fruit and leaves.

5.0 TOXICOKINETICS

5.1 Absorption

There were no studies found in the available literature that assessed the toxicokinetics of humans exposed to oxamyl. An accidental ingestion case reported by Hayes and Laws (1991), however, resulted in the death of the victim and suggests that the pesticide was absorbed from the gastrointestinal tract.

After being administered orally or by injection, oxamyl was soon detected in various tissues and excretory products of experimental animals, indicating that the gastrointestinal tract absorbed it readily. Seventy-two hours after, two male Charles-River-CD rats were administered ^{14}C-oxamyl in peanut oil by gavage, 55% was recovered in urine and 19% in various other tissues, (Harvey and Han, 1978b). This indicates that at least 74% was absorbed from the gastrointestinal tract. After a single oral dose of ^{14}C-oxamyl at 1 mg/kg, 80-91% was absorbed

in rats as evidenced by detection of the radiolabel primarily in urine and lesser amounts in feces (< 3%) (Hawkins et al., 1990). Male Swiss-Webster mice given a single intraperitoneal injection of ^{14}C-oxamyl excreted 88.7% and 7.7% of the radiolabel in urine and feces, respectively, within 96 hours (Chang and Knowles, 1979).

Several 21-day dermal toxicity studies on male and female rabbits (Linda, 1999; U.S. EPA, 2000c) and an acute inhalation study with rats (O'Neil, 2000; Kennedy, 1986a; Tayfun, 1969) demonstrated that oxamyl lowered plasma, blood, and brain cholinesterase activity. These studies indicate that oxamyl also was absorbed through the skin and respiratory system. Kennedy (1986a) noted that when oxamyl was instilled in the eyes of rabbits, they exhibited hind-limb weakness, which suggests that the chemical is absorbed by this route of administration.

5.2 Distribution

Harvey and Han (1978b), described above, detected low levels of radioactivity in various parts of the rat 72 hours after administration. Ranges of 6.98 % to 12.55% were measured in the skin and hair, 6.34% to 4.18% in the carcass, 4.76% to1.32% in the gastrointestinal tract, 1.55% to 2.13% in blood, and 1.58% to 0.20% in the liver. Other tissues had no more than 0.36% of the radiolabel. Chang and Knowles (1979) also measured very low levels of radiolabel in the tissues of male mice injected with ^{14}C-oxamyl. Ninety-six hours after dosing, the levels detected ranged from 11.0 ppb in the testes to 37.0 ppb in the liver. Hawkins et al. (1990) did not detect tissue accumulation in rats after a single oral dose of ^{14}C-oxamyl.

5.3 Metabolism

Carbamate metabolism begins with hydrolysis to carbamic acid, which decomposes to carbon dioxide (CO_2) and the corresponding amine (WHO, 1986). The products of hydrolysis for N-dimethylcarbamates are alcohol and N-dimethyl substituted acid. Experimental studies demonstrate that rats and mice readily metabolize oxamyl. Rats can completely metabolize the chemical; however, mice only partially metabolize it and excrete some unchanged chemical in urine. Harvey and Han (1978b) described a possible metabolism scheme for oxamyl that involves two pathways. One pathway involves hydrolysis to methyl N-hydroxy-N',N'-dimethyl-1-thiooxamimidate (DMTO). Another mechanism is by enzymatic conversion to N,N-dimethyl-1-cyano-formamide (DMCF) and then to N,N-methyloxamic acid (DMOA), releasing CO_2.

Harvey and Han (1978b) recovered urine and feces from Charles River-CD rats 72 hours after they were given a single oral dose of ^{14}C-oxamyl. They recovered more than 70% of the radiolabel as DMTO, methyl N-hydroxy-N'-methyl-1-thiooxamimidate (MTO), DMOA, and N-methyloxamic acid (MOA). In a separate experiment, Harvey and Han (1978b) dosed one rat with ^{14}C-DMFC and detected DMOA and MOA in urine over a 72-hour period. In both studies 27-51% of the radiolabel was incorporated in amino acids. Ninety-six hours after being given a single intraperitoneal injection of ^{14}C-oxamyl, Swiss-Webster mice also had similar metabolites in their urine and feces (Chang & Knowles, 1979). In addition to DMTO, MTO, and MOA, the mice also excreted unchanged oxamyl and DMCF. *In vitro* studies by Harvey and Han (1978b),

using microsomal and/or cytosolic liver fractions from Charles River-CD rats and mouse liver subcellular fractions incubated with ^{14}C-oxamyl, supported their findings in the *in vivo* studies.

Carbamates also undergo conjugation (WHO, 1986). Hawkins et al. (1990) gave SD rats (5 animals/sex/group) a single oral dose of ^{14}C-oxamyl and recovered the radiolabel in urine as the ß-glucuronide of oxime (31 - 37%), in addition to oxime metabolite (13 - 18%), and unchanged oxamyl (7 - 11%).

5.4 Excretion

Oxamyl is eliminated rapidly by rats given the chemical orally and by mice that received it by injection. Hawkins et al. (1990) observed that after receiving a single oral dose of 1 mg/kg ^{14}C-oxamyl rats excreted 80% - 91% of the dose in urine and < 3% in feces. Rats given oral doses of 1 mg ^{14}C-oxamyl in 2 mL peanut oil excreted 63% to 72% of the radiolabel in urine and feces within 72 hours (Harvey and Han, 1978b). Most was found in the urine (4 to 61%) and smaller amounts were in feces (6 to 23%). A minute amount of radioactivity was found in the expired air (<0.3 %). Chang and Knowles (1979) demonstrated that male Swiss-Webster mice given a single injection of ^{14}C-oxamyl eliminated more than 75% of the radiolabel mostly in the urine after 6 hours.

5.4 Bioaccumulation

There was no information found in the available literature concerning oxamyl's bioaccumulation. Its rapid excretion and metabolism in mice dosed intraperitoneally (Chang and Knowles, 1979) suggest that bioaccumulation or retention should not be expected (U.S. EPA, 1992a). However, oxamyl may remain for longer periods in skin, hair, carcass, liver, and blood.

6.0 HEALTH EFFECTS DATA

There is limited information concerning human exposure to oxamyl. Information derived from experimental studies in mammals (rats, mice, and rabbits), however, is sufficient to determine its health effects. This section presents information primarily from studies where laboratory animals were exposed to oxamyl by an oral route, e.g., gavage or mixed in feed.

Oxamyl has been evaluated in short- and long-term exposure studies with rats, mice, and dogs. It has a low oral LD_{50} in rats and mice. It is not considered to be a skin sensitizer and caused marked pupillary constriction and conjunctival irritation when exposed to the eyes. Short-term and chronic effects in animals are similar. Neurotoxicity and depressed body weight and body weight gain are the major toxic effects observed in animal studies. Neurotoxic effects were characterized by statistically or biologically significant depression of plasma, blood and/or brain cholinesterase levels. Animals adversely affected by oxamyl also exhibited a regressive response in Functional Observational Battery (FOB) and Motor Activity (MA) assessments and neurotoxic clinical symptoms. Exposure-related clinical signs and FOB/MA effects included heavy breathing, tremors, abnormal gait or mobility, hunched-over posture, exophthalmus, ptosis, hyperactivity, piloerection, colored eye discharge, fasciculations, salivation, lacrimation,

pupillary response to light, and reduced hind limb grip strength. Several 21-day dermal toxicity studies with male and female rabbits (Linda, 1999; U.S. EPA, 2000c) and an acute nose only inhalation study with rats (O'Neil, 2000) demonstrated that oxamyl lowered plasma, blood, and brain cholinesterase activity by other exposure routes.

Oxamyl did not affect reproductive nor developmental indices in toxicity studies with rats and rabbits. It did not cause mutations, induce chromosomal aberrations, or affect DNA in genetic toxicity assays. In studies with rats, mice, and dogs after 1-2 years of exposure, oxamyl did not cause any increase in tumor incidence.

6.1 Human Studies

There was limited information found in the available literature concerning effects in humans from exposure to oxamyl.

6.1.1 Short-term Exposure

Hayes and Laws (1991) identified two cases of accidental ingestion of oxamyl. The doses were not specified. One exposure resulted in a fatality and had symptoms that included unconsciousness, incontinence, apnea, undetectable blood pressure, and pupillary constriction; the authors speculated that Sickle-cell disease related to the hemolytic crisis that caused the death was probably triggered by the exposure to oxamyl. The other person who accidentally ingested oxamyl survived.

6.1.2 Long-term Exposure

Nine months of cholinesterase activity measurements obtained from 542 California agricultural pesticide applicators were analyzed by Ames et al. (1989). Those who had plasma or RBC cholinesterase activity depressions of 70% or less of their baselines were identified, and a list of the pesticides handled by them 2 weeks prior to testing was acquired. Twenty-six workers (4.8%) had cholinesterase values at or below the California action level value for removal from exposure. Eight (31.5%) had pesticide related illnesses. Oxamyl was one of the pesticides that some of the workers were exposed to, but it was not the only one. The investigators were not able to determine specific exposures or the contribution of any one pesticide to cholinesterase (ChE) activity depression.

6.1.3 Reproductive and Developmental Effects

There were no studies of oxamyl reproductive or developmental effects in humans found in the available literature.

Bell et al. (2001) studied the potential association between fetal death and residential proximity to sites of agricultural pesticide application in selected California counties. Applying a case-cohort study design, they failed to prove a strong association between fetal death and pesticides exposure. They did show slightly elevated risks to women who lived near places where carbamate acetylcholinesterase inhibitors and other classes of pesticides were applied. This study evaluated carbamates and thiocarbamates as a single class, which included oxamyl in

addition to twenty-one other pesticides. It is for this reason and the lack of exposure/dose information that the contribution of oxamyl to the results observed from this investigation cannot be determined.

6.1.4 Carcinogenicity

There were no epidemiology, case reports, or other types of studies concerning oxamyl's carcinogenicity in humans found in the available literature.

6.2 Animal Studies

Oxamyl has been tested in several species of animal to assess its acute, chronic, and subchronic toxicity.

6.2.1 Acute Oral Studies

An acute oral LD_{50} of 2.5 mg/kg of body weight was calculated for female rats and 3.1 mg/kg for male rats (chemical purity was not reported) (Dashiell and Hinckle, 1980). Reinhardt (1971) gave oral doses of oxamyl (90% a.i.) to fasted male and female rats and non-fasted males. Clinical signs that were observed included heavy breathing, fasciculations, salivation and lacrimation. The oral LD_{50} for fasted animals was determined to be 4.0 mg /kg for males and 2.8 mg/kg for females. The LD_{50} for non-fasted males was 5.4 mg/kg. Similarly, Kennedy (1986a) determined that the oral LD_{50} for male rats was 3.1 mg/kg and 2.5 mg/kg for females. He also determined that the oral LD_{50} for male mice was 3.3 mg/kg and 2.3 mg/kg for female mice and 7.0 mg/kg for male guinea pigs. The oxamyl used in these studies was identified as technical grade supplied by E.I. duPont de Nemours and Company; the purity was not specified. However, a companion paper describing longer-term studies (Kennedy, 1986b) identifies oxamyl as being $95% pure. Also, other studies listed in a WHO (2002) document identify technical grade oxamyl supplied by the same manufacturer as being at least 95% pure.

6.2.2 Acute Intraperitoneal Studies

When a single injection of oxamyl (assumed to be $95% pure) was given to male rats by intraperitoneal injection, the LD_{50} was 4.0 mg/kg (Kennedy, 1986a). Both female mice and male guinea pigs died within 2 hours after being given oxamyl by intraperitoneal injection at doses $2.3 mg/kg and $5.1 mg/kg, respectively.

6.2.3 Acute Inhalation Studies

After 1-hour exposures to oxamyl in air, Kennedy (1986a) reported that the inhalation LC_{50} for male rats was 0.17 mg/L and 0.12 mg/L for females. He also showed that after a 4-hour inhalation exposure to rats the LC_{50} was 0.064 mg/L.

6.2.4 Acute Dermal Studies

A dermal application of oxamyl to the intact skin of rabbits resulted in a LD_{50} for males that was less than 5000 mg/kg and for females it was less than 2000 mg/kg (Brock, 1988). Kennedy (1986a) reported that the dermal LD_{50} for rats was >1200 mg/kg and for rabbits it was 740 mg/kg. He also reported that death occurred when oxamyl (50% a.i. in water) was applied at a

dose of 90 mg/kg to abraded rabbit skin. Oxamyl, in a dimethylformamide (DMF) vehicle, was applied to abraded or intact skin of male and female rabbits 6 hours daily for 15 days at doses of 50 or 100 mg/kg/day (Kennedy, 1986a). After each dose they exhibited fasciculations (muscle twitching), irregular breathing, reduced coordination, and salivation, which lasted approximately 4 hours; however, no effects were observed in animals given DMF only, and minimal effects were observed in male rabbits given the same doses of oxamyl in a methanol vehicle.

6.2.5 Dermal Sensitization

In a study by Wells (1968), oxamyl caused minor skin irritation in guinea pigs at the application site; one out of five animals died when challenged by intradermal injection of the chemical, and slight skin irritation was noted. However, severe toxicity developed if the skin was abraded, and four out of seven animals died when treated with 25% oxamyl. Although it may be concluded that oxamyl is not a skin sensitizer, this study is compromised by the noted high mortality (U.S. EPA, 2000a; HSDB, 2004).

6.2.6 Ocular Toxicity

Oxamyl is not considered to be an irritant to the rabbit eye (U.S. EPA, 2000c). In a primary eye irritation study oxamyl (concentration not reported in cited reference) caused marked pupillary constriction and conjunctival irritation, which was reversed in seven days. At high doses, however, Kennedy (1986a) noted that 10 mg of oxamyl instilled in the conjunctival sac of rabbits caused the pupillary constriction, as well as conjunctival swelling and discharge. All effects were reversed within 24 hours.

6.2.7 Acute Neurotoxicity

Experimental studies with rats and mice demonstrate that oxamyl can be acutely toxic because of its effect on blood and brain cholinesterase activity. Affected animals exhibit neurotoxic clinical symptoms and a gradually decreased response in the Functional Observational Battery (FOB) and the Motor Activity (MA) assessments.

Single doses of oxamyl (98.3% a.i.) in deionized water were given by gavage to groups of Crl:CD rats (42/sex/dose) in order to assess acute oral neurotoxicity (Malley, 1997a, b). The males were administered 0, 0.1, 1.0, or 2.0 mg/kg and females 0, 0.1, 0.75, or 1.5 mg/kg. Six of the rats/group were euthanized for *in situ* perfusion, and thirty rats/group were used to evaluate blood and brain cholinesterase levels. One high-dose male died on the first day of study, and this group had a significant ($p<0.05$) decrease in body weight gain. Blood and brain cholinesterase activity were decreased significantly statistically ($p<0.05$) and biologically (40% mean) in mid- and high-dose males and females on day 1 at the peak time of effect (30 - 60 minutes post-dosing). Decreases in cholinesterase activities were not biologically significant by the second day. Toxic decreases in cholinesterase activity were not observed in any animals after the first day or in low-dose males and females at any time.

Fayez and Kilgore (1992) administered a single dose of oxamyl (purity not reported) to groups of male Sprague-Dawley rats by stomach intubation at dose levels of 1, 2.1, and 3.5 mg/kg. Brain acetylcholinesterase was inhibited significantly for 2, 3, and 6 hours for the low-, mid-, and high-dose groups, respectively. The greatest inhibition, 46%, was seen in the high-dose group 2-hours after administration. Blood AChE was inhibited significantly for 2 hours in the low-dose group and 3 hours in the mid-, and high-dose groups. The greatest inhibition, 82%, was seen in the high-dose group 2-hours after administration. Clinical signs included salivation, ocular changes, tremors, fasciculation, and lacrimation. One high-dose rat died after 90 minutes. There was no significant brain or blood acetylcholinesterase inhibition beyond 6 hours.

When Kennedy (1986a) gave male rats 4.86 mg/kg of oxamyl (aqueous solution) by intragastric intubation, blood cholinesterase activity was decreased by 40% after 5 minutes and by 58% after 4 hours. The activity returned to normal after 24 hours. Activity returned to normal levels 24 hours after administration. When atropine (50 mg/kg) was administered intraperitoneally immediately after oral oxamyl doses at 4.86 mg/kg, there was little or no decrease in cholinesterase activity. Rats protected with atropine when treated with oxamyl (LD_{50} level) exhibited fasciculations, but no mortality (Kennedy, 1986a).

Male beagle dogs (21 months old) were given single oral doses of oxamyl ($95% purity assumed) in gelatin capsules at dose levels of 5, 10, 15, or 30 mg/kg and were observed for 21 days (Kennedy 1986a). The number of animals per dose group was not specified. One dog in the 30 mg/kg group died within an hour. All surviving treated dogs were reported to exhibit clinical signs of cholinesterase inhibition.

Repeated oral doses of 2.4 mg/kg of oxamyl given 5 days/ week for 2 weeks caused six male rats to exhibit mild fasciculations that lasted 2 to 4 hours during the first week and 1 to 2 hours during the second week. The animals also had slight body weight decreases. After the first two doses the rats exhibited salivation and slight pallor, but no clinical signs were noted afterwards (Kennedy, 1986a).

Reinhardt (1971) gave male rats 2.4 mg/kg oxamyl (90%+ technical) by gavage five times per week over a two-week period. The animals exhibited typical anticholinesterase symptoms such as fasciculations and salivation. However, there were no deaths or apparent cumulative toxicity reported.

In the studies by Malley (1997 a,b), twelve rats/group were given Functional Observational Battery (FOB) and Motor Activity (MA) assessments on days 1, 8, and 15. Oxamyl related clinical signs and FOB effects that were consistent with decreased cholinesterase activity, occurred 30-60 minutes after exposure in mid- and high-dose males and females. These included soiled fur, lacrimation, salivation, slow righting reflex, abnormal gait, tremors, impaired locomotion, no response to tail pinch, increased limb splay, incoordination, labored breathing,

and decreased forelimb and hind limb grip strength. Other effects included abnormal posture, palpebral closure, docile behavior, and decreased motor activity. No treatment-related gross effects or histopathology were observed. The LOAEL for this study was 1.0 mg/kg for male rats and 0.75 mg/kg for female rats based on clinical signs, FOB effects, and decreased blood and brain cholinesterase activity. The NOAEL was 0.1 mg/kg.

Oxamyl did not cause any delayed neurotoxicity in a study by Lee (1970). White, Leghorn adult chickens received single oral doses of oxamyl (1% suspension) at 20 and 40 mg/kg of body weight followed by intramuscular injections of 0.5 mg/kg atropine; the birds were observed for 28 days after treatment. Clinical signs of depression, lethargy, ataxia, ruffled feathers, incoordination, and slight respiratory difficulty were seen in the treated animals. These marked symptoms of cholinesterase inhibition disappeared 12 hours after dosing. The investigator reported that no compound related histological changes were seen, and there were no deaths or signs of delayed neurotoxicity in this study.

6.3 Subchronic Studies

Two subchronic studies in rats, which demonstrated clinical and behavioral neurotoxicity, were available in the literature.

Malley (1998) conducted a 90-day subchronic oral neurotoxicity study on Crl:CD(SD)BR rats. Male and female rats (42 /sex/exposure group) were fed oxamyl (98.3% pure) in the diet for 90 days at concentrations of 0, 10, 30, or 250 ppm (equivalent to 0, 0.564, 2.10, and 14.9 mg/kg/day for males and 0, 0.679, 2.40, and 19.9 mg/kg/day for females, respectively). The mid- and high-dose groups initially received 100 and 300 ppm, respectively, but these doses were reduced because of immediate toxicity. Serial sacrifices of the animals (10/sex/exposure group) were made on days 27, 55, and 90 to determine cholinesterase activity. Some of the rats (12/sex/exposure group) were given functional observational battery (FOB) and motor activity (MA) tests before exposure to oxamyl and during weeks 4, 8, and 13 of the study. At study termination six FOB-MA rats/sex/exposure group were perfused for neuropathology.

No animals died during the study. At the end of 90 days, body weights were decreased significantly ($p<0.05$) in the 250 ppm male (24%) and female rats (10%), which correlated with decreased food efficiency in both sexes and decreased food consumption in males. Exposure-related clinical signs and FOB/MA effects were observed in one or both sexes at 250 ppm. These included tremors, abnormal gait or mobility, hunched-over posture, exophthalmus, ptosis, hyperactivity, piloerection, colored eye discharge, hyperactivity, lacrimation, pupillary response to light, and hind limb grip strength. These effects were not observed in animals administered 30- or 10-ppm oxamyl diets. At the end of the study, the mean plasma, RBC and brain (cortical) cholinesterase levels were decreased by 24, 48, and 40%, respectively, in males and 60, 55, and 51%, respectively, in females, compared to controls. Decreases in brain and blood cholinesterase activity correlated with the presence of clinical signs and changes in FOB parameters in the 250-ppm group. Generally, the magnitude of cholinesterase inhibition was greater in females than males; and there was no cumulative effect with time. Motor activity was

not significantly affected at any concentration. No oxamyl-related neuropathological changes were observed in any exposure group (Malley, 1998).

The LOAEL for the study by Malley (1998) was 250 ppm (14.9 mg/kg/day and 19.9 mg/kg/day for male and female rats, respectively) based on decreased body weights and food efficiency, decreased plasma, RBC and brain cholinesterase activity, and clinical signs and changes in FOB parameters consistent with cholinesterase inhibition. The NOAEL was 30 ppm (2.10 mg/kg/day and 2.40 mg/kg/day for male and female rats, respectively).

In a 90-day oral feeding study, male and female weanling C7-1:CD rats (10/sex/exposure group) were given oxamyl (>95% pure) in the diet for 90 days at concentrations of 0, 50, l00, or 150 ppm (equivalent to approximately 0, 2.5, 5.0, and 7.5 mg/kg/day, respectively) (Kennedy, l986b). The first 4 days of study, the high-dose group was given 500 ppm, but due to immediate dose-related toxicity, it was decreased to 150 ppm. This dose (150 ppm) was administered from day 8 to study termination. Decreased body weight was the only toxic effect observed that was considered to be related to oxamyl ingestion. Weights were significantly ($p < 0.05$) lower than controls in males fed 100 or 150 ppm from days 28 to 91 of the study. In females receiving 100 and 150 ppm, lower body weight gains were only sporadically significant compared to controls. Proteinuria and occult blood appeared to be higher in the 100- and 150-ppm groups compared to controls, but the occurrence was inconsistent and the toxicological significance was determined to be unclear. There were no pathologic abnormalities observed (Kennedy, l986b).

There were no changes in body weight gain, food consumption, clinical signs, hematology, clinical chemistry, or pathologic indices observed in young adult beagle dogs (Kennedy, 1986b). The animals (4/sex/dose) were fed oxamyl (>95% pure) in the diet at levels of 0, 50, 100, or 150 ppm (equivalent to dose levels of approximately 0, 1.3, 2.5, and 3.8 mg/kg/day, respectively). The author reported sporadic occurrences of bloody mucoid diarrhea, eye discharge, inflammation, dehydration, thinning hair on chest, and cysts; however, these were not considered to be related to oxamyl administration.

6.4 Developmental and Reproductive Studies

Several single and multi-generation studies were conducted in rats and rabbits to identify and assess the potential effects that oxamyl might have on reproductive and developmental indices. When oxamyl was given to experimental animals orally by gavage or through feeding in the diet, limited adverse effects were observed. Generally the effects to treated male and female parents were limited to dose-related decreases in body weight, which usually were significant only at the higher dose levels. Exposure to oxamyl did not affect reproductive organs in male and female animals, and it did not adversely impact fertility indices in pregnant females. Oxamyl also did not adversely affect fetuses and pups up through three generations.

6.4.1 Developmental Studies

Oxamyl (97.2%) was administered to pregnant Charles River (CD) BR rats (25/dose group) by gavage from gestation days 7-16 to assess developmental toxicity (Rickard, 1988; U.S. EPA, 2000c). The dose levels were 0, 0.2, 0.5, 0.8, and 1.5 mg/kg/day. Fetuses were removed from dams on study day 22 and did not exhibit mortality or treatment-related gross abnormalities. Oxamyl had no apparent effect on reproductive parameters or fetal malformations or variations. Dams in the 0.8- and 1.5-mg/kg/day dose groups exhibited significant, dose-related decreases in body weight gain (2 1-30%; $p < 0.05$) and food consumption (10-16%; $p < 0.05$). There also was a dose-related increase in tremor incidence (4/25), which was attributed to cholinesterase inhibition. Dams in the 1.5-mg/kg/day dose group had a statistically significant ($p < 0.05$) increase in diarrhea, eye discharge, salivation, tremors, and wetness of the legs, perineum, and ventral part of the body. At doses $0.5 mg/kg, there was a statistically significant ($p < 0.05$), dose-related decrease in fetal body weights. It was determined, however, that the decrease in fetuses was not indicative of fetal susceptibility because reduced maternal weight gain was the contributing factor.

A NOAEL of 0.5 mg/kg/day and LOAEL of 0.8 mg/kg/day were identified for maternal toxicity based on decreased body weight gains, decreased food consumption, and increased incidence of tremors. A developmental toxicity NOAEL of 0.2 mg/kg/day and LOAEL of 1.5 mg/kg/day were based on dose-related decreases in the fetal body weight (Rickard, 1988; U.S. EPA, 2000c).

A teratogenicity study was conducted on groups of pregnant Crl:CD rats that were fed diets containing 0, 50, 100, 150, or 300 ppm of oxamyl on days 6 to 15 of gestation, corresponding to doses of 0, 2.5, 5.0, 7.5, and 15 mg/kg/day, respectively (Kennedy, 1986b). Dams' body weights and food consumption were decreased in a dose-related manner. By gestation day 20, mean body weights in the 150- and 300-ppm groups were 8% and 10%, respectively, lower than that of control animals. There were no apparent or significant differences in number of implantation sites, live fetuses, resorptions, fetal growth, fetal crown-to-rump length, and soft tissue and skeletal abnormalities.

Hoberman et al. (1980) presented the results of a developmental toxicity study conducted on pregnant New Zealand white rabbits (17/ dose group). Oxamyl (97.1% a.i.) was administered to New Zealand White rabbits by gavage at doses of 0, 1, 2, or 4 mg/kg/day on gestation days 6 through 19. After surviving, animals were sacrificed on gestation day 29, and the fetuses were removed, weighed, measured for crown-rump distance, and examined for external malformation/variations. All animals survived, except two that died from non-treatment related accidents. There were no oxamyl-related effects observed during necropsy, no clinical signs of toxicity, or changes to maternal absolute body weight and food consumption. During the treatment period, the mid- and high-dose groups had significantly reduced ($p < 0.05$) body weight gains that were 33%-39% that of controls; however, the weights recovered during the post-dosing period.

Oxamyl had no apparent or significant effect on the number of corpora lutea, resorption rates, implantations, preimplantation loss, litter sizes, fetal body weights and lengths, or fetal sex ratios. There also were no treatment-related external, visceral, or skeletal findings in any fetuses. Interpreting Hoberman et al. (1980) results, both Snyder (1980) and Kennedy (1986b) reported that the slight, but not significant, increase in the incidence of resorptions in the 4-mg/kg/day group indicates a slight embryotoxic effect. A maternal toxicity LOAEL of 2 mg/kg/day and the NOAEL of 1 mg/kg/day were determined based on reduced body weight gains. A developmental toxicity NOAEL was determined to be 4 mg/kg/day because no developmental toxicity was observed at the highest dose tested.

6.4.2 Reproductive Studies

Kennedy (1986b) described a three-generation reproduction study where female Crl:CD rats (16/sex/exposure group) were given oxamyl (95% purity) in their feed at dose levels of 0, 50, 100, or 150 ppm (equivalent to 0, 2.5, 5.0, and 7.5 mg/kg/day, respectively) for 12 weeks, Subsequently, they were mated with male rats. The F_{1b} and F_{2b} generations were mated at approximately 110 days of age to produce F_2 and F_3 generations (two litters each), respectively. Reproductive indices (i.e., fertility index, gestation length, pup viability, and lactation index) were not affected by oxamyl ingestion. Dams in the 100- and 150-ppm dose groups produced significantly ($p<0.05$) reduced litter sizes, and the weanlings' mean body weights were significantly ($p<0.05$) decreased in the majority of generations. Histopathological examination of parent animals and offspring from each generation revealed no abnormalities associated with oxamyl ingestion.

Sherman and Zapp (1971) also described a three-generation study where rats were fed the same dose levels of 95% pure oxamyl as described by Kennedy (1986b), but for a 90-day exposure period. Similarly, they observed that litter size and weanling body weights were lower at 100 and 150 ppm; viability and lactation indices also were lower. Fertility and gestation indices were not affected by oxamyl at any dose level. Some F_{3B} generation animals had slightly increased relative weights of their kidneys (100-ppm group) and testes (100-and 150-ppm groups). Oxamyl-related histopathological changes were not observed in any of the animals. The NOAEL for this study was determined to be the 50-ppm exposure, i.e., 2.5 mg/kg/day.

Male and Female Crl:CDRBR rats were given oxamyl (97.1% a.i.) in their diets to assess its toxicity in a two-generation reproduction study (Hurtt, 1990). The animals were fed diets containing 0, 25, 75, or 150 ppm. These feed levels were approximately equivalent to 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. The exposure period was not specified in the source document. Parental (F_0) and first generation offspring (F_1) males and females demonstrated signs of toxicity at the 75- and 150-ppm dose levels. Body weights and body weight gain decreased approximately 5-20% and 13-21%, respectively. Food consumption likewise was decreased by 14-17%. These animals that were in the 150-ppm dose group displayed clinical signs of toxicity, which included hyperactivity, skin sores and alopecia. Additionally, both offspring generations (F_1 and F_2) exposed to $75-ppm had 2-7.6% decreases

in body weight during lactation. In the 150-ppm dose group of both generations the number of live pups per litter and the viability index decreased by 15.7-16.4% and 21-43%, respectively.

A NOAEL for systemic/developmental toxicity was determined to be 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively), and the LOAEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively). A separate NOAEL was identified for offspring toxicity, which was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively); the LOAEL was 150 ppm (approximately 11.6 and 15.8 mg/kg/day for males and females, respectively).

Kennedy (1986b) summarized a one-generation reproduction study that was conducted with Crl:CD rats (6/sex/exposure level), which were given oxamyl in their feed at levels of 0, 50, 100, or 150 ppm (equivalent to doses of 0, 2.5, 5.0, and 7.5 mg/kg/day) continuously for 91 to 95 days. These animals were mated and produced two litters (F_{1a} and F_{1b}). Male parents in the 100- and 150-ppm dose groups had reduced body weights ($p < 0.05$) starting 28 days after the study began. Female parents in the same dose groups also had weight reductions; however, they were sporadically significant. Oxamyl did not appear to affect fertility, but the number of pups delivered to dams were slightly decreased in the 100- and 150-ppm groups. Pup survival was not affected during lactation, but the weanling body weights from the F_{1a} and F_{1b} litters associated with all dose groups were significantly (p $0.05) decreased.

6.5 Mutagenicity and Genotoxicity

Genetic toxicology studies indicate that oxamyl is not a mutagen. In several *in vitro* studies, oxamyl was not mutagenic in bacterial assay systems (i.e., *Salmonella* [Ames test] and *Escherichia coli*) and a mammalian cell culture (Chinese hamster ovary [CHO] cells). It did not induce chromosomal aberrations in CHO cells and was negative for inducing DNA damage and repair. Oxamyl also did not cause unscheduled DNA damage in primary rat hepatocytes.

Oxamyl was tested in bacterial cell (prokaryote) systems to assess its ability to cause gene mutations. A reverse gene mutation assay was performed on doses of oxamyl that ranged from 50 to 10,000 ：g/plate, with or without rat liver S9 activation, using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100. The test was negative in all strains and at all concentrations (Moriya et al., 1983; Arce, 1981; Shirasu et al., 1976). Oxamyl concentrations from 50 to 10,000 ：g/plate, with or without rat liver S9 activation, also were negative in tests with *Escherichia coli*, strain WP2 hcr (Moriya et al., 1983; Shirasu et al., 1976).

When tested in other *in vitro* gene mutation systems, oxamyl also was not mutagenic. It was tested in the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphoribosyltransferase (HGPRT) forward gene mutation assay (Rickard, 1987). The test was negative up to concentrations that caused less than an 80% decrease in cell viability (i.e., 1200 kM without S9 and 700 kM with S9). In a host-mediated assay with *S. typhimurium* strain G 46 hys, oral doses of oxamyl, totaling either 2 or 4 mg/kg, were administered to male ICR mice over a 24-hour period (Shirasu et al., 1976). It did not elicit a mutagenic response. When oxamyl

(concentrations not specified) was tested in Chinese hamster V79 target cells with or without activation (irradiated Syrian hamster fetal cells) for 72 hours, there was no significant effect on mutagenic frequency (Wojciechowski and Kaur, 1980).

Oxamyl was negative up to cytotoxic concentrations ($70 : g/mL without S9; 700 : g/mL with S9) in an *in vitro* CHO cell chromosome aberration assay (Vlachos, 1987).

The effect that oxamyl might have on DNA-damage and repair capability was evaluated in a *Bacillus subtilis* rec assay (U.S. EPA, 1999b; Shirasu et al., 1976). Oxamyl concentrations ranging between 20 and 2,000 : g/disk did not preferentially inhibit the repair-deficient bacterial strain compared to the repair-competent strain (H-17 Rec^+). In an *in vitro* unscheduled DNA syntheses assay, oxamyl was negative up to cytotoxic concentrations ($5 nM) (U.S. EPA, 1999b).

6.6 Chronic Studies

In a combined chronic toxicity/carcinogenicity study, oxamyl (97.1%, a.i.) was administered in the diet to 62 Crl:CDBR rats/sex/dose for 2 years (U.S. EPA, 2000c). The dose levels were 0, 25, 50, 100 or 150 ppm, which are equivalent to 0, 0.992, 1.97, 4.19, or 6.99 mg/kg/day for males and 0, 1.32, 2.69, 6.73 or 11.1 mg/kg/day for females, respectively. An interim sacrifice of 10 rats/sex/dose was conducted at 12 months.

Oxamyl did not affect mortality, food consumption, food efficiency, hematology, clinical chemistry, and urinalysis parameters. In the 100- and 150-ppm dose groups, there were significant increases ($p < 0.05$) in the incidences of hyperactivity (both sexes), swollen paws/legs (males), and skin sores (females). Compared to control animals the incidence of hyperactivity increased by 5-36% and 3-56% in males and females, respectively. Mid- and high-dose males and high-dose females had increased incidences of swollen legs and paws. Females rats also exhibited increased incidences of alopecia (high-dose group), and skin sores and scabs (mid- and high-dose groups). During the first year of study, mean body weights and body weight gains in the two higher dose groups were significantly lower ($p < 0.05$) in males (10% and 25%, respectively) and females (27% and 37%, respectively). These decreases were considered to be secondary to hyperactivity since neither the food consumption nor the food efficiency was affected in the test animals. At study termination, the high-dose females had a significantly ($p<0.05$) higher incidence of bilateral retinal photo cellular atrophy. Plasma cholinesterase levels were significantly decreased (both biologically and statistically) in both sexes of the 100- and 150-ppm dose groups. Plasma cholinesterase levels were reduced by 48% and 69% in males and females, respectively. Females exhibited these levels during the first month of treatment. Both red blood cell and brain cholinesterase levels were not affected at any dose level in either sex.

The NOAEL for this study was determined to be 50 ppm (1.97 mg/kg/day for males and 2.69 mg/kg/day for females), and the LOAEL was 100 ppm (4.19 mg/kg/day for males and 6.73

mg/kg/day for females). These effect levels were based upon the occurrence of hyperactivity, swollen legs and paws, skin sores, decreased body weights and body weight gains, increased incidence of pale ocular fundi, and inhibition of plasma cholinesterase levels (U.S. EPA, 2000c).

In a rodent study, male and female weanling Crl:CD rats (36/sex/exposure group) were given oxamyl (95% purity) at levels of 0, 50, 100, and 150 ppm in the diet for 2 years (Kennedy, 1986b). The control group of animals had 35 male and 36 female rats. Oxamyl levels in food were equivalent to 0, 2.5, 5.0, and 7.5 mg/kg/day. Cholinesterase activity reduction at the 150-ppm dose level was significant in male and female rats both statistically (p$0.05) and biologically (20% and 33%, respectively). The reductions occurred after 4 and 8 days, respectively, but after one month and through the duration of the study cholinesterase activity returned to normal. Significant (p$0.05) body weight reductions were evident in the mid- and high-dose groups throughout the study, but were only evident in the 50-ppm group at 24 months. Oxamyl ingestion in this study was not associated with mortality, clinical signs of toxicity, relative organ weights (liver, spleen, and kidneys), histopathology, or tumor incidence. The NOAEL for this study was identified as 50 ppm (2.5 mg/kg/day) of oxamyl.

Adamik et al. (1981) presented the results of a carcinogenicity study where oxamyl (97.1% a.i.) was administered to 80-88 CD-1 mice/sex/dose in their diet for 18 months (reported as a 2-year study by Kennedy (1986b)). The dose levels were 0, 25, 50, or 75/100 ppm, which were equivalent to 0, 3.75, 7.5 or 15/11.25 mg/kg/day for males and females, respectively. The 100 ppm dose was reduced to 75 ppm due to mortality in the mid- and high-dose groups during the initial phase of the study. Oxamyl did not affect food consumption, hematology, organ weights, or histopathology. Body weight decrements in males persisted throughout the study period, and during the 11^{th} week they were reduced significantly ($p < 0.05$) in the 50- and 75-ppm dose groups. In female mice, body weights decreased early in the study, but were sporadic and not statistically significant. The NOAEL for this study was determined to be 25 ppm (3.75 mg/kg/day), and the LOAEL was 50 ppm (7.5 mg/kg/day) based on decreased body weights in males and mortality in males and females during the initial phase of the study.

Two 1-year chronic feeding studies were conducted in order to assess the effects of oxamyl on dogs. In the first study, oxamyl (99%) was offered, once daily in the diet, to groups of male and female beagles (5/sex/exposure group) at dose levels of 0, 50, 150, or 250 ppm (equivalent to 0, 1.56, 4.60, or 8.0 mg/kg/day for males and 0, 1.46, 4.50, or 7.84 mg/kg/day for females, respectively) (Mebus, 1990; Dickrell, 1991; Van Pelt, 1999). Oxamyl did not produce any adverse effects in parameters assessed by urinalysis, ophthalmological examination, and gross pathology at any dose levels. Plasma and brain cholinesterase, however, was depressed at all dose levels in male dogs. In the 50-ppm dose group, plasma cholinesterase activity was significantly ($p<0.05$) reduced by 32% in males. At the higher dose levels, other oxamyl-related effects included tremors, vomiting, decreased body weight, and decreased food consumption and efficiency. In this study, a NOAEL for male dogs was not established due to depression of plasma and brain cholinesterase at all dose levels.

Subsequently, a repeat one-year study was conducted to establish a NOAEL in male dogs (5/dose) at dose levels of 0, 12.5, 20, 35 or 50 ppm (equivalent to 0, 0.372, 0.577, 0.930 or 1.364 mg/kg/day, respectively) (Dickrell, 1991). In this study food was offered *ad libitum*. In the 50 ppm group plasma, RBC and brain (cerebellum and medulla) cholinesterase levels were depressed by 11, 4, and 20%, respectively, compared to controls. The 20% brain cholinesterase inhibition was considered biologically relevant since tremors were observed at 150 and 250 ppm in males and at all doses in females in the first study. Plasma, RBC and brain cholinesterase levels were depressed 18, 5 and 2%, respectively, in the 35-ppm dose group. Therefore, 35 ppm (0.930 mg/kg/day) was determined to be the NOAEL based on decreased brain and plasma cholinesterase levels in males, and various toxicity symptoms observed in both sexes, e.g., vomiting, tremors, and decreased body weights and body weight gains.

A 2-year feeding study was conducted with male and female beagle dogs (4/sex/exposure group) (Kennedy, 1986b). Oxamyl (97.1% purity) was provided in the feed at 0, 50, 100, or 150 ppm, which were equivalent to mean doses of 0, 1.3, 2.5, and 3.8 mg/kg/day, respectively. Oxamyl did not cause mortalities, and it did not affect body weight, food consumption, clinical observations, histopathology, and hematological and urinalysis parameters. Serum alkaline phosphatase activity and cholesterol levels were increased by 2 standard deviations above pretest values in the 150-ppm dose compared to all other dose groups and controls; however, the significance of this effect was not determined.

6.7 Cancer Studies

In a combined chronic toxicity/carcinogenicity study (U.S. EPA, 2000c), oxamyl (97.1%, ad.) was administered in the diet to 62 Crl:CDBR rats/sex for 2 years. The dose levels were 0, 25, 50, 100 or 150 ppm, which is equivalent to 0, 0.992, 1.97, 4.19, and 6.99 mg/kg/day for males and 0, 1.32, 2.69, 6.73, and 11.1 mg/kg/day for females, respectively. Additional details of the study are presented in section 6.2.5. Based on the results of this study (body weights, eyes lesions, hyperactivity, plasma ChE inhibition, and retinal photo receptor cell atrophy), the highest dose tested (150 ppm) appeared to be the maximum tolerated dose (MTD) and sufficiently high to evaluate oxamyl's chronic toxicity and carcinogenicity. The results did not show any treatment-related increases in tumor incidence; therefore the study was negative for carcinogenicity.

Adamik et al. (1981) presented the results of a carcinogenicity study where oxamyl (97.1%, a.i.) was administered in their diet to 80-88 CD-1 mice/sex for 18 months. The dose levels were 0, 25, 50, or 75 ppm, which was equivalent to 0, 3.75, 7.5, and 15/11.25 mg/kg/day for males and females, respectively. Additional details of the study are presented in section 4.2.3. Based on the effects of body weights in males and mortality in both sexes during the initial phase of the study, the highest dose tested (75 ppm) appeared to be sufficiently high for testing oxamyl's carcinogenic potential. Exposure to oxamyl at any dose level did not increase tumor incidence; therefore the study was negative for carcinogenicity.

7.0 QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to seven years), and lifetime exposures if adequate data are available that identify a sensitive non-carcinogenic toxicity endpoint of toxicity. The HAs for non-carcinogenic toxicants are derived using the following formula:

$$HA = \frac{\text{NOAEL or LOAEL) x (BW)}}{\text{(UF) (\_\_\_L/day)}} = \text{\_\_\_\_mg/L (\_\_\_\_ : g/L)}$$

where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect Level (in mg/kg bw/day).
BW	=	assumed body weight of a child (10 kg) or an adult (70 kg).
UF	=	uncertainty factor (10, 100, 1,000 or 10,000) in accordance with NAS (1983,1994) or U.S.EPA (1994).
L/day	=	assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

7.1 Short-term Advisory Values

7.1.1 One-day Health Advisory

The study by Malley (1997a,b) is selected to serve as the basis for the One-day HA. Studies by Fayez and Kilgore (1992), Reinhardt (1971), and Kennedy (1986a) are of appropriate durations to consider for a One-day HA, but were not selected for the health advisory. This is because Fayez and Kilgore (1992) only evaluated male rats, Reinhardt (1971) identified a NOAEL that is larger in magnitude, and Kennedy (1986a) measured cholinesterase activity only in blood.

In the acute oral neurotoxicity study by Malley (1997a,b), single doses of oxamyl (98.3% pure) were administered by gavage to male (0, 0.1, 1.0, or 2.0 mg/kg) and female (0, 0.1, 0.75, or 1.5 mg/kg.) Crl:CD rats. Typical effects at mid and high doses included statistically significant decreased weight gain and food consumption. Clinical signs and FOB effects were consistent with decreased cholinesterase activity 30-60 minutes after exposure in the mid- and high-dose male and female animals. Statistically ($p<0.05$) and biologically significant, dose-related decreases in blood and brain cholinesterase activity (mean $ 40%) were observed in mid- and high-dose males and females on the first study day. Significant toxicologic decreases in cholinesterase activity were not observed in any animals after the first day or in low-dose males and females at any time. The LOAEL for this study was 1.0 mg/kg/day in males and 0.75

mg/kg/day in females based upon clinical and FOB effects, as well as decreased plasma, RBC, and brain cholinesterase activity. The NOAEL was 0.1 mg/kg/day.

The One-day HA for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(0.1 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.01 \text{ mg/L } (10 \text{ ：g/L})$$

where:

0.1 mg/kg/day	=	NOAEL, based upon RBC, plasma and brain cholinesterase inhibition, clinical signs of cholinesterase inhibition, and FOB effects
10 kg	=	assumed weight of a child.
100	=	uncertainty factor (UF), which includes a 10-fold UF for intraspecies variability, and another 10-fold UF to account for interspecies extrapolation as noted by NAS and EPA.
1 L/day	=	assumed drinking water consumption by a 10 kg child

7.1.2 Ten-day Health Advisory

The study by Malley (1997a,b) also is the basis for the Ten-day HA. A teratogenicity study in rats (Snyder, 1980) was reviewed, but the study's critical effect (decreased maternal body weight) and NOAEL (1 mg/kg/day) are not as sensitive as cholinesterase inhibition, which was observed by Malley (1997a,b). The NOAEL derived from the acute oral neurotoxicity study in Crl:CD rats by Malley (1997a,b) has been selected preferentially over other studies as being protective from the effects of chronic exposure (see discussion of Lifetime HA).

The One-day HA for a 10 kg child, 0.01 mg/L (10 ：g/L), also is used as a conservative estimate for the Ten-day HA to be protective of public health. The One-day HA also protects from chronic exposure effects, maternal, and developmental effects (U.S. EPA, 2000b).

7.1.3 Longer-term Health Advisory

No Longer-term value needs to be calculated for this contaminant since the endpoint of concern is cholinesterase depression, an acute effect. Therefore, the HA value of 0.01 mg/L is used for both short- and long-term advisories.

7.2 Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of non-carcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious health effects during a lifetime. The RfD is derived from the NOAEL (or LOAEL), which is identified from a chronic (or subchronic) study, and divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, non-carcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA in drinking water alone is determined in Step 3, by factoring in other sources of exposure, i.e., the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed.

For those substances that are “Known” or”Likely” to be carcinogenic to humans, and for which a linear approach is used, Lifetime HAs are not recommended.

Generally, a NOAEL or LOAEL from a lifetime, chronic, or subchronic study, is selected to establish a Lifetime HA. Accordingly, candidate studies for oxamyl are the 2-year rat feeding study by Kennedy (1986b), the 2-year combined chronic toxicity/carcinogenicity feeding study in Crl:CDBR rats (U.S. EPA, 2000c), and the 18-month feeding study in CD-1 mice (Kennedy, 1986b; Adamik et al., 1981). Several dog feeding studies, a 2-year study (Kennedy, 1986b) and two 1-year studies (Mebus, 1990; Dickrell, 1991), also were considered. Generally, clinical neurotoxicity and cholinesterase depression (brain, blood, plasma) were observed in the experimental dose range of all the species treated with oxamyl. High-dose rats and mice also had significant body weight depression, and oxamyl was fatal to high-dose mice (Kennedy, 1986b). The NOAELs from these studies are approximately 2 mg/kg/day for rats (Kennedy, 1986b), 3.75 mg/kg/day for mice (Kennedy, 1986b), and 1 mg/kg/day for dogs (Dickrell, 1991).

However, since the critical effect of oxamyl is an acute one, cholinesterase inhibition, a NOAEL from an acute neurotoxicity study (Malley (1997a,b) is selected. This is based on the weight of the evidence from the chronic toxicity studies in rats, mice, dogs, which yielded a higher NOAELs/LOAELs compared to the acute neurotoxicity study. Further, the measurement of cholinesterase inhibition was not conducted at the peak time in the chronic studies. Since the

acute NOAEL (0.1 mg/kg) is protective of any maternal or developmental effects and chronic exposure (repeated), there is high confidence in the chronic RfD derived from the acute neurotoxicity study in rat (U.S. EPA, 2000c).

The One-day HA for a 10 kg child also is used as a conservative estimate for the Lifetime HA to be protective of public health. The Lifetime HA is 0.01 mg/L (10 ：g/L).

7.3 Evaluation of Carcinogenic Potential

There were no human exposure or epidemiological studies found in the available literature to indicate that oxamyl is a human carcinogen. Furthermore, no evidence of oxamyl's carcinogenic potential has been demonstrated in long-term (1 and 2 years) dietary exposure studies with rats and/or mice (U.S. EPA, 2000c, 2002b; Kennedy, 1986b; Adamik et al., 1981). Additionally, oxamyl did not cause mutations, affect chromosomes, or damage DNA; therefore, it is negative for mutagenicity. Applying the criteria described in EPA's draft final guidelines for assessment of carcinogenic risk (U.S. EPA, 1999a), oxamyl may be classified as "not likely to be carcinogenic to humans." This group is for agents with animal evidence that demonstrates lack of carcinogenic effect in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects); extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans; convincing evidence that carcinogenic effects are not likely to occur by a particular exposure route; or convincing evidence that carcinogenic effects are not likely to occur below a defined dose range.

8.0 RISK CHARACTERIZATION

8.1 Hazard Identification

Oxamyl is a non-persistent carbamate pesticide. This chemical is a neurotoxicant known to inhibit cholinesterase, an essential enzyme for adequate neurotransmission. Therefore, the toxicity endpoint of concern for this contaminant for both acute and chronic exposures is based on the extent of blood and brain cholinesterase inhibition and the associated signs and symptoms of neurotoxicity. These effects were noted in all animal species tested including rats, mice and dogs.

Oxamyl did not affect reproductive or developmental indices in toxicity studies with rats and rabbits at levels below the levels noted for neurotoxicity. It did not cause mutations, nor induce chromosomal aberrations or affect DNA in genetic toxicity assays. In carcinogenic studies in rats and mice, oxamyl did not cause any increase in tumor incidence and therefore is not carcinogenic.

8.2 Dose-response

Clinical neurotoxicity and cholinesterase depression (brain, blood, plasma) were observed in the experimental dose range of all the species treated with oxamyl in both the acute and chronic studies. The NOAELs from the chronic feeding studies are approximately 2 mg/kg/day for rats

(Kennedy, 1986b), 3.75 mg/kg/day for mice (Kennedy, 1986b), and 1 mg/kg/day for dogs (Dickrell, 1991).

However, since the critical effect of oxamyl is an acute one, cholinesterase inhibition, a NOAEL was selected from the rat acute neurotoxicity study by Malley (1997a,b). This NOAEL, 0.1 mg/kg/day, was used for calculation of the health advisory values. The doses tested in this study were administered by gavage as single doses of oxamyl (98.3% pure) at 0, 0.1, 1.0, or 2.0 mg/kg for males and 0, 0.1, 0.75, or 1.5 mg/kg for females. Typical effects at mid and high doses included decreased weight gain and food consumption. Clinical signs and FOB effects were consistent with decreased cholinesterase activity 30-60 minutes after exposure in the mid- and high-dose male and female animals. Statistically ($p<0.05$) and biologically significant, dose-related decreases in blood and brain cholinesterase activity (mean $ 40%) were observed in mid- and high-dose males and females on the first study day; these effects were not detected after the first day of exposure. The LOAEL and NOAEL for these critical neurotoxicity endpoints were 1.0 mg/kg/day in males (0.75 mg/kg/day in females) and 0.1 mg/kg/day, respectively.

8.3 Exposure Assessment

The One-day HA value for a 10 kg child, 0.01 mg/L (10 ug/L), is used as a conservative estimate for all HAs to be protective of public health. The One-day HA also protects from chronic exposure effects, maternal, and developmental effects. Therefore, the Ten-day and Lifetime HA values also are using the same One-day HA value of 0.01 mg/L (10 ppb).

The U.S. Environmental Protection Agency (U.S. EPA, 2002a) determined that the estimated environmental concentrations (EECs) for oxamyl residues in surface and ground water are below the 1992 Drinking Water Standard (MCL) of 0.2 mg/L and the above calculated HA of 10 ppb (0.01 mg/L).

8.4 Sensitive Populations

Bell et al. (2001) found slightly elevated risk of fetal deaths in women who resided near sites where carbamates (acetylcholinesterase inhibitors) were applied. However, there were no direct measurement of the applied pesticides.

9.0 OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA (1992c) established a maximum contaminant level (MCL) of 0.2 mg/L for oxamyl in drinking water.
- The states of Arizona and Maine both have drinking water guidelines of 1.8 and 1.75 mg/L, respectively (FSTRAC, 1999).
- California developed a public health goal of 0.05 mg/L for oxamyl in drinking water based upon a NOAEL of 2.5 mg/kg/day derived from the chronic rat study by Kennedy (1986b) (CaEPA, 1997).
- The U.S. Food and Drug Administration adopted the U.S. EPA MCL of 0.2 mg/L as its standard for oxamyl in bottled water (21 CFR 165).

10.0 ANALYTICAL METHODS

Oxamyl is analyzed by a high performance liquid chromatographic procedure used for the determination of N-methyl carbamoyloximes and N-methyl carbamates in drinking water (Method 531.2; U.S. EPA, 2001b). In this method, the water sample is filtered and up to a 1000 ∶L aliquot is injected into a C-18 reverse phase HPLC column. After elution from the column, the analytes are hydrolyzed in a post-column reaction with 0.075 N sodium hydroxide (NaOH) at 80 to 100 /C to form methylamine. The methylamine is reacted with o-phthalaldehyde (OPA) and 2-mercaptoethanol (or N,N-dimethyl-2-mercaptoethylamine) to form a highly fluorescent isoindole, which is detected by a fluorescence detector. Analytes are quantitated using the external standard technique. The detection limit for this method has been estimated to be approximately 0.044 ∶g/L for oxamyl.

11.0 TREATMENT TECHNOLOGIES

The current best available technology to remove oxamyl from water is the use of granular activated carbon (GAC). Removal efficiency ranges from 85 to 95% depending upon design parameters (U.S. EPA, 2003).

Using solubility and vapor pressure data, the Henry's Law Constant for oxamyl has been estimated to be 2.37×10^{-7} atm x m^3/mole (ESE, 1984). This value suggests that aeration is not likely to be a suitable water treatment technique for removal of oxamyl. Adsorption of oxamyl by montorillonite clay has been demonstrated (Bansal, 1983); adsorption mechanisms were thought to include covalent bonding, coordination, protonation, hydrogen bonding and van der Waal forces. The demonstrated adsorption of oxamyl by clay suggests that adsorption may be a suitable technique for the removal of oxamyl from water (ESE, 1984). However, further studies are needed to confirm the effectiveness of adsorption techniques and to define the optimal conditions for use.

12.0 REFERENCES

Adamik, E.R.; M.K,.Criswell, S.C. Mahler, et al. 1981. Long term feeding study in mice with oxamyl: Project No. WIL-77033; HLO-252-81. (Unpublished study prepared by WIL Research Laboratories, Inc., submitted by E.I . du Pont de Nemours & Co., Wilmington, Del.; CDL:070136-A; 070137; 070138; 070139; 070140; 070141; 070142; 070143). MRID (Master Record Identifier) 00076813. As cited in: U.S. EPA, 2000c.

Ames RG, S.K. Brown, D.C. Mengle, E. Kahn, J.W. Stratton, R.J. Jackson. 1989. Cholinesterase activity depression among California agricultural pesticide applicators. *Am. J. Ind. Med*. 15(2):143-50.

Arce, G. 1981. Mutagenicity evaluation of IND1410-196 in *Salmonella typhimurium*. Haskell Laboratory Report No. 614-81: Medical Research No.4253-001. Unpublished study prepared by

E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory. 18 p. MRID 40606509. As cited in: U.S. EPA, 2000c.

Bansal, O.P. 1983. Adsorption of oxamyl and dimecron in montmorillonite suspensions. Soil Sci. *Soc. Am. J.* 47:877-882.

Bell, E.M., I. Hertz-Picciotto, J.J. Beaumont. 2001. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *Am. J. Epidemiol*. 154(8): 702-10.

Brock, W. 1988. Acute dermal toxicity study of IN D1410-196 in rabbits. Medical Research No. 4581-572: Haskell Laboratory Report No. 114-88. Unpublished study prepared by E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory. 18 p. MRID 40606501. As cited in: U.S. EPA, 2000c.

Budavari, S. Editor. 1989. The Merck index, 11th edition. Rahway, N.J.: Merck & Co., Inc. p. 1094.

CaEPA. 1997. California Environmental Protection Agency. Public health goal for oxamyl in drinking water. Sacramento, CA: Office of Environmental Health Hazard Assessment.

CFR. Title 21 Code of Federal Regulations (CFR). Part 165. Beverages. 525-544. (Revised April 1, 2004.)

Chang K-M, C.O. Knowles. 1979. Metabolism of oxamyl in mice and two spotted spider mites. *Arch. Environ. Contam. Toxicol*. 8:499-508.

Dashiell, O.L., L.Hinckle. 1980. Oral LD_{50} test in rats- EPA proposed guidelines. Haskell Laboratory Report No. 775-80. (Unpublished study received Nov 21, 1980 under 352-371; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:099754-D). MRID 00063011. As cited in: U.S. EPA, 2000c.

Dickrell, L. 1991. 52-Week dietary toxicity study with IND-1410 (oxamyl) in male dogs. Hazleton Laboratories America, Inc., Madison, WI. Study No. HLO 555-90. Unpublished. MRID 42052701. As cited in: U.S. EPA, 2000e.

ESE. 1984. Environmental Science and Engineering, Inc. Review or treatability data for removal of twenty-five synthetic organic chemicals from drinking water. U.S. EPA. Office of Drinking Water.

Fayez, V., W.W. Kilgore. 1992. Acute toxic effects of oxamyl in the rat. *Fundam. Appl. Toxicol*. 18(1): 55-9.

FSTRAC. 1999. Federal-State Toxicology and Risk Analysis Committee. Summary of State and Federal Drinking Water Standards and Guidelines.

Harvey, J. Jr. 1976. Metabolism of oxamyl in tomato fruit. Unpublished material. E.I. du Pont de Nemours and Company, Inc. Wilmington, DE. U.S. EPA Accession No. 095326. As cited in: U.S. EPA, 1992a.

Harvey, J. Jr. 1973. Additional studies on the metabolism and biodegradation of oxamyl in plants. Unpublished material. E.I. du Pont de Nemours and Company, Inc. Wilmington, DE. U.S. EPA Accession No. 096301. As cited in: U.S. EPA, 1992a.

Harvey, J Jr., J. C –Y. Han. 1978a. Decomposition of oxamyl in soil and water. *J. Agric. Food Chem*. 26:539-541. As cited in U.S. EPA, 1992a.

Harvey, J. Jr., J. C –Y. Han. 1978b. Metabolism of oxamyl and selected metabolites in the rat. *J. Agric. Food Chem*. 26:902-910.

Hawkins, D., B. Mayo, A. Pollard, et al. 1990. Biokinetics and metabolism of [carbon 14]-oxamyl in rats.: Lab Project Number: AMR-1226-88: HRC/DPT-191/90608. Unpublished study prepared by Huntingdon Research Centre Ltd., Dept. of Chemical Metabolism and Radiosynthesis. 75 p. MRID 41520801. As cited in: U.S. EPA, 2000b.

Hayes, W.J., Jr., E.R. Laws, Jr. (eds.) 1991. Handbook of pesticide toxicology. volume 3. classes of pesticides. New York, NY: Academic Press, Inc., 1168 p. As cited in: HSDB, 2004.

Hoberman, A.M., P.A. Mossburg, G.W. Wolfe, et al. 1980. Teratology study in rabbits: Oxamyl. Project No. 201-545; HLO-0801-80. Final report. (Unpublished study prepared by Hazleton Laboratories America, Inc., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 099754-B). MRID 00063009. As cited in: U.S. EPA, 2000c. Also cited as Snyder, F.G. 1980 in U.S. EPA, 1992a.

HSDB. 2004. Hazardous Substance Databank. National Library of Medicine's Toxicology Network (TOXNET) system (http://toxnet.nlm.nih.gov), February 2, 2004.

Hurtt, M. 1990. Reproductive and fertility effects with oxamyl (IN D1410): Multi-generation reproduction study in rats. Lab Project Number: 423-90: 8433-88-001. Unpublished study prepared by Haskell Laboratory/ E. I. du Pont de Nemours and Company. 1090 p. MRID 41660801. As cited in: U.S. EPA, 2000c.

Kennedy, G.L., Jr. 1986a. Acute toxicity studies with oxamyl. *Fundam. Appl. Toxicol*. 6:423-429.

Kennedy, G.L., Jr. 1986b. Chronic toxicity, reproductive, and teratogenic studies with oxamvl. *Fundam. Appl. Toxicol*. 7:106-118.

Lee, K.P. 1970. Oral ALD and delayed paralysis test (white leghorn chickens). Haskell Laboratory Report No. 234-70. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-E) MRID 00066893. As cited in: U.S. EPA, 2000c.

Linda, A.M. 1999. 21-Day repeated dose dermal toxicity study in rabbits. E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. Laboratory report No. du Pont-1599, January 19, 1999. MRID 44751201. As cited in: U.S. EPA, 2000f.

Malley, L. 1998. Oxamyl technical: subchronic oral neurotoxicity study in rats: Lab Project Number: 10730: HL-1998-00708. Unpublished study prepared by du Pont Haskell Laboratory for Toxicology and Industrial Medicine. 457 p. As cited in: U.S. EPA, 2000g.

Malley, L. 1997a. Acute oral neurotoxicity study of oxamyl technical in rats: Lab Project Number: HLR 1118-96: 10730-001: 1118-96. Unpublished study prepared by du Pont Haskell Laboratory for Toxicology and Industrial Medicine. 629 p. (Relates to L0000163 and L0000168). MRID 44254401. As cited in: U.S. EPA, 2000d.

Malley, L. 1997b. Acute oral neurotoxicity study of oxamyl technical in rats: supplement No. 1: Lab Project Number: 11268-001: 10730-001: 1118-96. Unpublished study prepared by E.I. du Pont de Nemours and Company. 67 p. MRID 44420301. As cited in: U.S. EPA, 2000d.

Mebus, C.A. 1990. Chronic toxicity study with oxamyl (IND 1410-196): One year feeding study in dogs. Haskell Lab. Study No. 381-90. Unpublished. MRID 41697901. As cited in: U.S. EPA, 2000e.

Moriya M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato, Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reverse assay systems. *Mutat. Res*. 116:185-216. As cited in U.S. EPA, 1992a.

NAS. 1994. National Academy of Sciences (National Research Council). Science and Judgement in Risk Assessment. Washington, DC: National Academy Press.

NAS. 1983. National Academy of Sciences (National Research Council). Risk Assessment in the Federal Government: Managing the Process. Washington, DC: National Academy Press.

O'Neil, A.J. 2000. Cholinesterase inhibition determined in rats exposed to inhalation atmospheres of oxamyl technical (96.7%). The Haskell Lab of Toxicology and Industrial Medicine, E.l. du Pont de Nemours and Company, du Pont Study No. 4383 (6/27/2000). Unpublished. As cited in: U.S. EPA, 2000h.

Peebles, J.L. 1977. Effect of oxamyl on soil microorganisms. Unpublished material. Submitted to E.I. du Pont de Nemours, Inc. U.S. EPA Accession No. 096301. As cited in: U.S. EPA, 1992a.

Reinhardt, C.F. 1971. Toxicological information on DPX-1410. Haskell Laboratory for Toxicology and Industrial Medicine. EPA Accession No. 113391. As cited in: U.S. EPA, 1992a.

Rickard, L. 1988. Teratogenicity study of IN D1410-196 in the rat. Medical Research No. 8428-001: Laboratory Project ID: 473-88. Unpublished study prepared by E. I. du Pont de Nemours and Co., Inc. 206 p. MRID 40859201. As cited in: U.S. EPA, 2000c.

Rickard, L. 1987. Mutagenicity evaluation of IND1410-196 in the CHO/HPRT assay. Medical Research No. 4353-001: Haskell Laboratory Report No. 265-82. Unpublished study prepared by E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory. 22 p. MRID 40606510.

Shirasu, Y., M.Moritani, K. Watanabe. 1976. Oxamyl mutagenicity study using bacteria. *Mutat. Res*. 40:19-30. As cited in: U.S. EPA, 1992a.

Sherman H, N.W. Zapp. 1971. Three generation reproductive study in rats with 1-(dimethylcarbamoyl)-N-(methylcarbamoyloxy)thioformidic acid, methyl ester (IND-1410). Haskell Laboratory. Report No. 315-71. MR No. 1203. U.S. EPA Accession No. 66912. As cited in: U.S. EPA, 1992a.

Snyder, F.G. 1980. Teratology study in rats-oxamyl. Final Report. Hazleton Laboratory. MR No. 3724-001, HLO 0801-80. U.S. EPA Accession No. 63009. As cited in: U.S. EPA, 1992a.

Tayfun, F.O. 1969. Acute dust inhalation toxicity: Haskell Laboratory Report No. 280-69. (Unpublished study received Nov 29,1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-N) MRID 00066902. As cited in: U.S. EPA, 2000c.

U.S. EPA. 2003. U.S. Environmental Protection Agency. Water treatment technology feasibility support document for chemical contaminants; in support of EPA six-year review of national primary drinking water regulations. Washington, DC: Office of Water, Office of Ground Water and Drinking Water. EPA-815-R-03-004. June 2003.

U.S. EPA, 2002a. U.S. Environmental Protection Agency. Occurrence Summary and Use Support Document for the Six-Year Review of National Primary Drinking Water Regulations. Washington, DC: Office of Water, Office of Ground Water and Drinking Water. EPA-815-D-02-006. March 2002.

U.S. EPA, 2002b. U.S. Environmental Protection Agency. National Primary Drinking Water Regulations: Announcement of the Results of EPA's Review of Existing Drinking Water Standards and Request for Public Comment; Proposed Rule. *Fed. Reg*. 67(74):19076-19078. April 17.

U.S. EPA. 2001a. U.S. Environmental Protection Agency. Notice of Opportunity To Provide Additional Information and Comment. *Fed. Reg*. 66(230):59593-59594.

U.S. EPA, 2001b. U.S. Environmental Protection Agency. Method 531.2.Measurement of N-methylcarbamoyloximes and N-methylcarbamates in water by direct aqueous injection HPLC with postcolumn derivatization. Revision 1.0. Cincinnati,OH: Technical Support Center , Office of Ground Water and Drinking Water. EPA-815-B-01-002. September 2001.

U.S. EPA, 2000a. U.S. Environmental Protection Agency. Interim Reregistration Eligibility Decision (IRED), Washington, DC: Oxamyl. Office of Prevention, Pesticides and Toxic Substances, EPA-738-R-00-015. October 2000.

U.S. EPA, 2000b. U.S. Environmental Protection Agency. Oxamyl. The revised HED chapter of the reregistration eligibility decision document (RED). PC Code: 103801. Case # 0253. DP Barcode: D263842. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, EPA-738-R-00-015. March 2000.

U.S. EPA. 2000c. U.S. Environmental Protection Agency. Memorandum. Subject: Oxamyl: toxicology chapter for RED. March 31, 2000. MRID 44737501; MRID 41963101; MRID 40827601; MRID 41118201; MRID 00066984.

U.S. EPA, 2000d, U.S. Environmental Protection Agency. Data Evaluation Report, Oxamyl, Acute Oral Neurotoxicity, Rat (81-8ss). Washington, DC: Office of Pesticide Programs.

U.S. EPA, 2000e, U.S. Environmental Protection Agency. Data Evaluation Report, Oxamyl, Chronic (1-Year) Toxicity Study - Dog (83-1b). Washington, DC: Office of Pesticide Programs.

U.S. EPA, 2000f, U.S. Environmental Protection Agency. Data Evaluation Report, Oxamyl, 21-Day dermal toxicity - rabbit (OPPTS 870.3200) (§82-2). Washington, DC: Office of Pesticide Programs.

U.S. EPA, 2000g, U.S. Environmental Protection Agency. Data Evaluation Report, Oxamyl, Subchronic Oral Neurotoxicity – Rat (§82-7). Washington, DC: Office of Pesticide Programs.

U.S. EPA, 2000h. U.S. Environmental Protection Agency. Memorandum. Subject: PC#1003801; Presentation of issues on oxamyl to HIARC. Office of Prevention, Pesticides, and Toxic Substances, Washington, DC. July 5, 2000.

U.S. EPA. 1999a. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Review draft. Washington, DC: Office of Research and Development. NCEA-F-0644.

U.S. EPA, 1999b. U.S. Environmental Protection Agency. Memorandum. Subject: Oxamyl - report of the hazard identification assessment review committee. HED DOC. NO. 013711. August 31, 1999. MRID 40606508; MRID 00049594

U.S. EPA. 1996. U.S. Environmental Protection Agency. Proposed guidelines for carcinogen risk assessment. *Fed. Reg*. 61(79):17960-18011.

U.S. EPA. 1994. Environmental Protection Agency. Integrated Risk Information System. Washington, DC: US Environmental Protection Agency. Available online at http://www.epa.gov/iris/

U.S. EPA, 1992a. U.S. Environmental Protection Agency. Final drinking water criteria document for oxamyl (vydate). Washington, DC: Health and Ecological Criteria Division, Office of Science and Technology, Office of Water. PB92173434. January 1992.

U.S. EPA, 1992b. U.S. Environmental Protection Agency. Pesticides in ground water database: a compilation of monitoring studies; 1971-1991. Document No. 734-12-92-001. Washington, DC: As cited in: CaEPA's Public Health Goal for Oxamyl in Drinking Water, 1997.

U.S. EPA, 1992c. U.S. Environmental Protection Agency. National Primary Drinking Water Regulations: Announcement of the Results of EPA's Review of Existing Drinking Water Standards and Request for Public Comment. *Fed. Reg*. 57:31846. July 17.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. *Fed. Reg*. 51(85):33992-34003.

Van Pelt, C.S. 1999. DuPont's position on the NOEL in male dogs following chronic dietary exposure to oxamyl. DuPont Reports HLR 381-90 and HLO 555-90. Laboratory Project ID. DuPont-2019. January 18, 1999. Unpublished. MRID 44737503. As cited in: U.S. EPA, 2000e.

Vlachos, D. 1987. Mutagenicity evaluation of IND1410-196 in an in vitro cytogenitic assay measuring chromosome aberration frequencies in chinese hamster ovary (CHO) cells: Medical Research No.4253-001: LBI Project No. 20990. MRID 40606507.

Wells, L.A. 1968. Primary skin irritation and sensitization tests. Haskell Laboratory Report No. 146-68. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours and Company., Inc., Wilmington, DE.; CDL:092249-L) MRID 00066900. As cited in: U.S. EPA, 2000c.

WHO. 2002. Pesticide residues in food - 2002 - Joint FAO/WHO Meeting on Pesticide Residues, Oxamyl. Geneva, Switzerland: International Programme on Chemical Safety, World Health Organization.

WHO. 1986. World Health Organization, International Programme On Chemical Safety, Environmental Health Criteria 64: Carbamate Pesticides, A General Introduction. Geneva, Switzerland: World Health Organization.

Wojciechowski J.P., P. Kaur. 1980. Cell-mediated mutagenesis of V79 cells with four carbamates. *In Vitro* 16:235-236. As cited in: U.S. EPA, 1992a.