

**PUBLIC HEALTH GOALS FOR  
CHEMICALS IN DRINKING WATER**

**OXAMYL**

**April 2009**

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# **Public Health Goal for Oxamyl in Drinking Water**

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# **PREFACE**

**Drinking Water Public Health Goals  
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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Public Health (DPH) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DPH are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DPH shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DPH must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DPH, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at [www.oehha.ca.gov](http://www.oehha.ca.gov).

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# **PUBLIC HEALTH GOAL FOR OXAMYL IN DRINKING WATER**

## **SUMMARY**

A Public Health Goal (PHG) of 26 ppb is established for oxamyl in drinking water, which is decreased from the PHG value of 50 ppb that was developed by the Office of Environmental Health Hazard Assessment (OEHHA) in 1997. Oxamyl is a carbamate pesticide that is used to control insects on cotton and many types of fruits and vegetables. It is a potent inhibitor of cholinesterase enzymes. The PHG is based on an acute oral study in humans reported by McFarlane and Freestone (1999). The 40 male subjects aged 19-39 in the study were administered a gelatin capsule of oxamyl at 0 (placebo), 0.005, 0.015, 0.03, 0.06, 0.09, or 0.15 mg/kg. Apart from decreased cholinesterase activities and increased saliva production reported for the highest dose group, no other treatment-related health effects were reported. At 0.15 mg/kg and 0.09 mg/kg, statistically significant decreases in cholinesterase activity were observed in erythrocyte and plasma. For this reason, the 0.06 mg/kg dose was identified as the no observed adverse effect level (NOAEL).

The United States Environmental Protection Agency (U.S. EPA) Human Studies Review Board reviewed the scientific and ethical aspects of this human study (U.S. EPA, 2006b). The board identified no deficiencies that would have affected the outcome or conclusions of the study, and concluded that this intentional human dosing study was sufficiently robust that it can be used for reducing the 10-fold inter-species uncertainty factor. The board criticized the study for the lack of females and for not providing a clear discussion of risk and existing information on incidences of accidental exposures to the research subjects, but found no clear or convincing evidence that the research was fundamentally unethical – e. g., that the research was intended to seriously harm participants or that informed consent was not obtained. OEHHA agrees with the conclusion of the board.

This NOAEL of 0.06 mg/kg derived from an acute oral human study is lower than the NOAELs derived from all acute, subchronic and chronic rat and mouse studies and it is also lower than the NOAELs from two other gavage studies performed in pregnant rats and rabbits. All these studies cited inhibition of cholinesterase or clinical symptoms related to this effect (such as increased secretions) as the most sensitive endpoints for oxamyl. An uncertainty factor of 10 was applied to account for intra-individual variability to give an estimated acceptable daily dose (ADD) of 0.006 mg/kg-day.

The PHG value was derived from an exposure scenario of a toddler. It was assumed that a toddler would likely consume no more than one-third of their daily water intake during a short period of time (0.0457 L/kg), based on their usual eating patterns (3-4 meals/day). This value is derived from the upper 95 percent confidence limit for daily consumption of community water for this age group (0.137 L/kg-day), as estimated by U.S. EPA (2004a) from a nationwide survey. Furthermore, it was assumed that only 20 percent of the total oxamyl dose is from water consumption and the other 80 percent comes from other sources, such as food, which is the standard assumption for pesticides applied to foods.



Using an ADD of 0.006 mg/kg-day and the exposure assumptions described, OEHHA developed the PHG of 26 µg/L (ppb).

The current California state and federal Maximum Contaminant Levels (MCLs) for oxamyl are 50 ppb and 200 ppb, respectively. Both MCLs were calculated based in part on a chronic rat study with a NOAEL of 2.5 mg/kg-day. The state MCL was based on a child's water consumption rate and pattern, while the federal level was based on the water consumption of an adult.

## INTRODUCTION

The carbamate insecticide oxamyl is applied to a variety of crops in California; use averaged about 110,000 pounds on 133,000 acres over the last five years. Its environmental persistence is low, so it does not accumulate in soils and is rarely found in ambient water although its mobility in soil is rather high. Traces of oxamyl are often detected, however, in fruits and vegetables to which it has been applied. Fresh fruits and vegetables are the principal sources of exposure to oxamyl.

Available scientific information on oxamyl was searched in the Hazardous Substances Data Bank (HSDB), Toxline, PubMed, and U.S. EPA's Integrated Risk Information System (IRIS). Articles thought to be of relevance to PHG determination were selected for review. Many toxicological studies on oxamyl were conducted for the registration of oxamyl as a pesticide and are not published in the open scientific literature. Toxicological information and discussion of these studies were obtained from earlier U.S. EPA analyses (U.S. EPA 1992a,b, 2000a,b,c) and a recently published U.S. EPA document, titled "Drinking Water Health Advisory for Oxamyl" (U.S. EPA, 2004b).

In the "Drinking Water Health Advisory for Oxamyl" (U.S. EPA, 2004b), acute cholinesterase inhibition in male and female rats exposed to oxamyl by gavage (Malley, 1997) was identified as the critical effect. Based on a NOAEL of 0.1 mg/kg-day, an uncertainty factor of 100, a body weight of 10 kg for a child, and a drinking water consumption rate of 1 L/day, U.S. EPA established a one-day health advisory level of 0.01 mg/L or 10 ppb. Since the NOAEL derived from acute toxicity studies is lower than the NOAELs observed in developmental, subchronic, and chronic studies, the one-day health advisory was also used as the health-protective level for the ten-day health advisory and the lifetime health advisory. No relative source contribution was used in the determination of the lifetime health advisory.

The current California state and federal Maximum Contaminant Levels (MCLs) for oxamyl are 50 ppb and 200 ppb, respectively. U.S. EPA's MCL was based on a NOAEL of 2.5 mg/kg-day oxamyl for decreased body weight gain in a two-year feeding study in rats (duPont, 1972; Kennedy, 1986a). An MCL of 0.2 mg/L was calculated based on a 70 kg adult male consuming two liters of water/day, a relative source contribution of 20 percent and an uncertainty factor of 100. From this calculation, the value of 0.175 mg/L was rounded by U.S. EPA to give a final MCL of 0.2 mg/L (200 ppb).

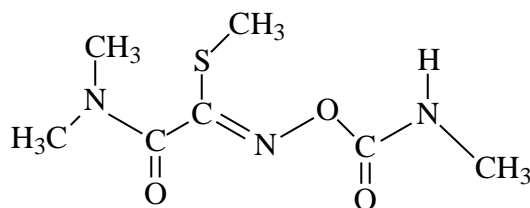
California's MCL for oxamyl of 50 ppb was based on the 1997 OEHHA PHG of 50 ppb that chose the same animal study used by the U.S. EPA, with a NOAEL of 2.5 mg/kg-day (Kennedy, 1986a). The calculation used an uncertainty factor of 100, a body weight of

10 kg for a child, a drinking water consumption rate of 1 L/day, and a relative source contribution of 20 percent.

## CHEMICAL PROFILE

### *Chemical Identity*

Oxamyl is a carbamate pesticide, CAS No. 23135-22-0. Its chemical name is *N,N*-dimethyl- $\alpha$ -methylcarbamoyloxyimino- $\alpha$ -(methylthio)acetamide, and its most common synonyms are: Vydate<sup>®</sup>; Thioxamyl; and DPX 1410 (U.S. EPA, 2004b). The chemical structure of oxamyl is shown below:



### *Physical and Chemical Properties of Oxamyl*

Oxamyl is a crystalline solid that has a slightly sulfurous odor. Chemical and physical properties of the chemical are provided in Table 1.

**Table 1. Physical and Chemical Properties of Oxamyl (HSDB, 2006; U.S. EPA, 2004b)**

Property	Value
Molecular weight	219.26 g/mole
Physical state	Off-white crystalline powder
Boiling Point (°C)	Decomposes on distillation
Melting Point (°C)	108-110°C
Vapor Pressure (25°C)	$2.3 \times 10^{-4}$ mm Hg at 20-25°C
Density	0.97 g/cm <sup>3</sup>
Solubility in water (25°C)	280 g/L
Solubility in organic solvents	Soluble in acetone and ethanol
Octanol-water partition coefficient (Log K <sub>ow</sub> )	-0.47

## ***Production and Uses***

Oxamyl belongs to a class of pesticide called carbamates; it is a contact and systemic insecticide, acaricide, and nematicide. Oxamyl is used to control chewing and sucking insects (including soil insects, but not wireworms), spider mites, and nematodes in ornamentals, fruit trees, vegetables, cucurbits, beets, bananas, pineapples, peanuts, cotton, soy beans, tobacco, potatoes and other crops. It is absorbed by the foliage and roots and translocated to other parts of the plant. There are no approved residential uses for this pesticide (U.S. EPA, 2004b; HSDB, 2006). According to the Pesticide Use Report Data published by the California Department of Pesticide Regulation (DPR, 2007), the annual usage of oxamyl in California in 2002 through 2006 was 80,300, 93,800, 112,600, 153,200, and 116,600 pounds, respectively. Most of this oxamyl is currently used on cotton.

## **ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE**

### ***Air***

No information concerning occurrence of oxamyl in ambient air was found in the literature reviewed.

### ***Soil***

Oxamyl is expected to be fairly mobile in soil; its mobility increases as the amount of organic matter decreases in the soil (Harvey and Han, 1978a). 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, 2004b).

In the soil, oxamyl degrades with a half-life of two to four weeks under aerobic conditions and less than one week under anaerobic conditions. In most field studies, half of the applied oxamyl dissipated from the soil surface within less than a week. The primary degradation products are an oximino derivative (methyl-N-hydroxy-N',N'-dimethyl-1-thiooxaminidate) and its isomer, and N,N-dimethyloxamic acid (U.S. EPA, 2004b).

### ***Water***

Oxamyl degrades rapidly in neutral to alkaline environments, but persists in acidic conditions. Half-lives ranging from three days to 11 days have been reported in slightly acidic (pH 5) or slightly alkaline (pH 9) water samples. Oxamyl is liable to photolysis. Harvey and Han (1978a) showed that ultraviolet radiation was able to destroy almost all of the oxamyl (1 ppm) in river water samples within 48 hours. In a similar study, the same authors were not able to detect any of the parent compound when river water spiked with 1 ppm oxamyl was left outdoors and exposed to direct sunlight for six weeks (U.S.

EPA, 2004b). However, oxamyl has been detected in a small percentage of runoff samples from agricultural fields in Florida (Wilson and Foos, 2006).

Oxamyl is not frequently detected in California drinking water sources (DHS, 2005). Oxamyl was not detected in any of 1,370 wells sampled in 34 counties in California between July 1, 1995 and June 30, 1996 (DPR, 1997). In sampling of approximately 11,000 groundwater sources and 800 surface water sources, oxamyl was not detected at levels above the California MCL from 1997 to 2004 (DHS, 2005). The state MCL for oxamyl was 200 ppb before June 2003, when it was lowered to 50 ppb (DPH, 2009).

### ***Food***

As oxamyl is used as a pesticide for food crops, it is not surprising that it has been detected on many food products. Monitoring data provided by the U.S. Department of Agriculture through its Pesticide Data Program showed low-levels of oxamyl (at a detection limit of 0.14 ppb) in apple juice, green beans, spinach, tomatoes, pears, cantaloupe, and winter squash. The frequency of occurrence in/on these crops was very low, <1 percent. 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 (U.S. EPA, 2004b).

Harvey (1973, as cited in U.S. EPA, 2004b) found that plants can metabolize oxamyl. A wide range of metabolites could be extracted from peanuts, tobacco, and green tomatoes treated with oxamyl. It was found that a majority of the pesticide was converted to water-soluble chemicals, such as conjugates of the metabolized oxamyl.

## **METABOLISM AND PHARMACOKINETICS**

### ***Absorption***

Animal studies show that oxamyl can be absorbed through oral, dermal, and inhalation routes. Harvey and Han (1978b) administered labeled oxamyl in peanut oil (1 mg/2 mL) to two male rats by gavage and monitored the exhaled air, urine, and feces for 72 hours. They estimated that over 70 percent of the dose was absorbed from the gastrointestinal tract. A similar study by Hawkins *et al.* (1990, as cited in U.S. EPA, 2004b) showed that rats absorbed 80-91 percent of a single 1 mg/kg oral dose of oxamyl, as most of the metabolites were found in urine and lesser amounts in feces (< 3 percent). Several sub-chronic dermal toxicity studies (Linda, 1999, as cited in U.S. EPA, 2004b) on rabbits showed that oxamyl lowered cholinesterase activity in blood and brain tissues, indicating the viability of dermal absorption. Similar findings were reported in an acute inhalation study in rats (O'Neil, 2000), demonstrating the potential of inhalation exposure.

## ***Distribution***

Harvey and Han (1978b) detected low levels of radioactivity in various tissues of the rat, 72 hours after administration of <sup>14</sup>C-labelled oxamyl (Table 2). This result does not indicate oxamyl is concentrated in any particular organ or tissue.

Chang and Knowles (1979) injected labeled oxamyl intraperitoneally into 20 male mice at approximately 1.16 mg/kg. Four groups of five mice were placed in metabolism cages and urine and fecal samples were collected up to 96 hour post-treatment. Mice were then killed and the radioactivity in blood and other tissues was measured. The levels of oxamyl in mouse tissues were low and ranged from 11 ppb (testes) to 37 ppb (liver). The data show most of the injected oxamyl was excreted in urine and feces in a few days (also see the section on Excretion).

**Table 2. Distribution of Radioactivity 72 Hours after Oral Treatment of Rats with Labeled Oxamyl (Harvey and Han, 1978b).**

<b>Tissue</b>	<b>Rat A, body weight 393 g % of original dose</b>	<b>Rat B, body weight 225 g % of original dose</b>
Skin and hair	6.98	12.55
Carcass	6.34	4.18
Gastrointestinal tract	4.76	1.32
Liver	1.58	0.20
Blood	1.55	2.13
Kidneys	0.19	0.27
Testes	0.13	0.09
Lungs	0.11	0.16
Other tissues	<0.15 each	<0.15 each
Total	22.0	21.5

## ***Metabolism***

Based on *in vitro* and *in vivo* study results, Harvey and Han (1978b) found oxamyl can be degraded through two pathways in rats. One pathway involves hydrolysis to methyl N-hydroxy-N',N'-dimethyl-1-thiooxamimidate (DMTO) and methyl N-hydroxy-N'-methyl-1-thiooxamimidate (MTO). Another route is through enzymatic conversion to N,N-dimethyl-1-cyano-formamide (DMCF) and N,N-methyloxamic acid (DMOA). Conjugates of these metabolites in urine and feces were the major (>70 percent) elimination products. No oxamyl or other organosoluble metabolites were detected in urine, feces, or tissues. Harvey and Han reported that incorporation of radioactive carbon into amino acids accounted for over half of the radioactivity retained in tissues.

Metabolism of oxamyl in mice has also been studied. In a study by Chang and Knowles (1979), it was reported that DMTO, MTO, DMCF, DMOA, as well as the parent compound, oxamyl, were detected in the urine of exposed mice. Similar metabolites were formed *in vitro* by incubating oxamyl with mouse liver subcellular fractions.

### ***Excretion***

Oxamyl is rapidly eliminated in rats and mice. Harvey and Han (1978b) administered 1 mg oxamyl in 2 mL peanut oil to rats by gavage and found that close to 50 percent of the dose was excreted within 24 hours. In 72 hours, most of the dose (68-72 percent) was excreted in urine and feces. Chang and Knowles (1979) administered oxamyl to mice by intraperitoneal injection (at 1.16 mg/kg) and found 76 percent of the dose was eliminated in six hours. In 96 hours, approximately 96 percent of the dose was eliminated, 89 percent in the urine and 8 percent in the feces. Hawkins *et al.* (1990, as cited in U.S. EPA, 2000b) reported that after receiving a single oral dose of 1 mg/kg oxamyl, rats excreted 80–91 percent of the dose in urine and < 3 percent in feces.

## **TOXICOLOGY**

### ***Toxicological Effects in Animals***

#### **Acute Toxicity**

Following acute oral exposure, oxamyl is highly toxic to rats, mice and guinea pigs. In rats, the oral (gavage) lethal dose (LD<sub>50</sub>) of technical oxamyl (estimated of 90-95 percent purity) ranged from 2.5 to 5.4 mg/kg depending on the sex and fasting condition (Reinhardt, 1971; Kennedy, 1986b). It was also reported that the oral LD<sub>50</sub>s of technical oxamyl in fasted mice and guinea pigs were 2.3 to 3.3 mg/kg and 7 mg/kg, respectively (Kennedy, 1986b). In all these test animals, clinical signs of cholinesterase inhibition such as lacrimation, salivation, and tremors were observed. When a single oral dose (gelatin capsule) of 5, 10, 15, or 30 mg/kg was given to 10-month-old male beagle dogs, clinical signs of cholinesterase inhibition were observed in all. The dog treated with the highest dose died within one hour, while the rest survived.

Kennedy (1986b) found the dose-response curve of oxamyl toxicity to be quite steep. Through oral exposure, no deaths occurred in female rats given 2.1 mg/kg and four of 10 died at 2.4 mg/kg. He also found that oxamyl does not accumulate nor do the clinical signs of response change dramatically following multiple exposures. He reported that repeated oral dosing (five daily doses per week for two weeks) of male rats at 2.4 mg/kg produced only mild clinical signs typical of anti-cholinesterase agents. Tissue pathology was not remarkable and no mortalities were observed although the dose level tested is one which produced mortality in females.

Kennedy (1986b) studied the ability of oxamyl to alter cholinesterase activity and the effectiveness of atropine as an antidote. It was reported that in rats given a single oral

dose of 4.8 mg/kg (approximately 90 percent of the lethal dose), cholinesterase activity in blood dropped to 2.6 ( $\mu\text{m}$  substrate hydrolyzed/mL/5 min) from a pretreatment value of 4.3 when sampled 5 min after treatment. This value dropped further to 1.8 after 4 hr and returned to a normal value of 5.7, 24 hr post-dosing. When atropine sulfate was given immediately after oxamyl treatment, the values were 4.5 (pretreatment), 3.7 (5 min), 5.0 (4 hr) and 5.3 (24 hr) (the beneficial effects of atropine in anticholinesterase poisoning are mediated through muscarinic receptor antagonism; it does not affect cholinesterase inhibition). In a similar experiment, it was shown that a single oral dose of 10.8 mg/kg killed 8 of 10 rats within 2 hr of treatment, while the same treatment, followed immediately by atropine, produced no deaths in 10 dosed rats.

Fayez and Kilgore (1992) administered single oral doses of oxamyl by gavage to male Sprague-Dawley rats at 0, 1, 2.1 or 3.5 mg/kg. Significant inhibition of brain acetylcholinesterase was observed in all exposed rats at 0.5 and 1 hr following the treatment. Similarly, significant inhibition of blood acetylcholinesterase was observed in all exposed rats at 0.5, 1, and 2 hr following the treatment. Most of the inhibition did not persist for more than 6 hr due to the instability of carbamylated acetylcholinesterase which leads to regeneration of the enzyme. Fayez and Kilgore also observed significant body weight gain reduction in all the exposed rats in the first two days following the treatment. A slight but not statistically significant reduction of body weight gain was noted in the 1 mg/kg dose group on the third day. The authors believed the reductions were related to reduced food consumption in the treated animals. They reported one rat out of 48 dosed with 3.5 mg/kg died after 1.5 hr.

Single doses of oxamyl in deionized water were given by gavage to groups of adult (35 days of age) Crl:CD<sup>®</sup>BR rats (42/sex/dose) in order to assess acute oral neurotoxicity (Malley, 1997). 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. Twelve rats/group were designated as the neurotoxicity subgroup, and clinical observations, body weights, and food consumption were recorded throughout the test period. A Functional Observational Battery and Motor Activity assessment were conducted prior to treatment, 30-60 minutes post-dosing on test day 1, and again on test days 8 and 15. Six rats/group of each sex from the neurotoxicity subgroup were sacrificed and tissues were fixed with in situ perfusion techniques on test day 16. Thirty rats/group per sex were designated as the clinical pathology subgroup. Cholinesterase activity in brain tissue, plasma, and erythrocytes was determined in 10 rats/gender/group 30-60 minutes post-dosing on test day 1, and again on test days 2 and 15. In addition, baseline plasma and erythrocyte cholinesterase activity were determined the day prior to treatment.

At the test day 1 sampling time, males and females in the mid- and high-dosed groups had statistically and biologically significant decreases (mean dropped by 40 percent or more) in blood and brain cholinesterase activity. By test day 2, male and female rats in these two groups had completely recovered from test substance-related, biologically adverse cholinesterase depression. No decreases in blood or brain cholinesterase activity in the low dosed group (0.1 mg/kg) were noted on days 1, 2, or 15 (Malley, 1997).

Observations for clinical signs were conducted on the clinical pathology subgroup rats (30/group of each sex) prior to blood and brain collection on test day 1. Approximately

30-60 minutes after dosing, males and females in the mid- and high-dosed groups showed clinical signs consistent with depression of cholinesterase activity such as soiled fur, lacrimation, salivation, change in pupillary response, slow righting reflex, abnormal gait, impaired locomotion, tremors, no response to tail pinch, splayed limbs, incoordination, labored breathing, increased urination, decreased forelimb and hindlimb grip strength and /or slightly increased hindlimb foot splay. By test day 2, no treatment-related clinical effects were observed in males and females in these dose groups. No treatment-related clinical effects were reported in either males or females administered 0.1 mg/kg.

One high-dose male died on the first day of study; there was no test substance-related mortality in female rats at any dose level. Decreases in body weight gain were noted in mid- and high-dosed males and in high-dosed females in the first two days of the study. In males, the lower body weight gain correlated with lower food consumption. However, this correlation was not observed in the females. Malley (1997) did not report any treatment related morphological changes in the nervous system of either males or females at any dose. Based on cholinergic signs and biochemical evidence of cholinesterase inhibition, a NOAEL of 0.1 mg/kg was determined.

U.S. EPA's National Health and Environmental Effects Research Laboratory analyzed the cholinesterase activity inhibition data in brain (Malley, 1997) and estimated benchmark doses (BMD<sub>10s</sub>) of 0.18 and 0.14 mg/kg for male and female rats, respectively (U.S. EPA, 2005).

Oxamyl administered by intraperitoneal injection was reported to have an LD<sub>50</sub> of 4 mg/kg in rats (Kennedy, 1986b). It caused death in mice given 2.3 mg/kg or greater and in guinea pigs given 5.1 mg/kg or greater. Death occurred within 2 hr after dosing and the clinical signs seen were those associated with cholinesterase inhibition (Kennedy, 1986b).

Oxamyl is also highly toxic via inhalation. It has a 1-hr lethal concentration (LC<sub>50</sub>) value of 0.12-0.17 mg/L in rats, and a 4-hr LC<sub>50</sub> value of 0.064 mg/L in male rats (Kennedy, 1986b). U.S. EPA (2005) evaluated cholinesterase activity inhibition data of an acute (single day, 4 hours) inhalation study in rats (MRID 45155801). The agency estimated that the BMD<sub>10s</sub> for inhibition of cholinesterase in brain and red blood cells are 0.0004 mg/L and 0.002 mg/L, respectively. U.S. EPA calculated that 0.0004 mg/L is equivalent to 0.083 mg/kg.

Kennedy (1986b) reported that oxamyl is a mild skin irritant. Its dermal toxicity in rats (LD<sub>50</sub> > 1,200 mg/kg) and rabbits (LD<sub>50</sub> of 740 mg/kg) is relatively high, suggesting limited dermal absorption.

### **Subchronic Toxicity**

Malley (1998) conducted a 90-day subchronic dietary neurotoxicity study on Crl:CD<sup>®</sup>BR rats. Adult male and female rats (42 /sex/exposure group) were fed oxamyl (98.3 percent pure) in the diet for 90 days at concentrations of 0, 10, 30, or 250 ppm. The mid- and high dose groups initially received 100 and 300 ppm, respectively, but these doses were reduced after seven days because of severe toxicity. Malley estimated that the mean daily oxamyl intakes for males at the low, medium, and high concentrations were 0.55,



1.69, and 15.3 mg/kg-day, respectively, and the mean daily oxamyl intakes for females at the low, medium, and high concentrations were 0.67, 2.03, and 20.3 mg/kg-day, respectively. Functional observational battery (FOB) and motor activity (MA) assessments were conducted prior to exposure, and during weeks 4, 8, and 13. Cholinesterase activity in brain tissue, plasma, and erythrocytes were determined in 10 rats/sex/group during weeks 4, 8, and 13. After 13 weeks, 6 rats/sex/group were randomly selected and sacrificed. Tissues from the high dosed rats and control rats were processed and examined for neuropathological effects.

Clinical signs of toxicity were reported in males and/or females at dietary levels of 100 ppm and above. They include tremors, abnormal gait or mobility, hunched over posture, hyperreactivity, hyperactivity, colored discharge from the eyes, and many others. During the FOB assessment, ptosis, piloerection, abnormal gait, absent pupillary response, and muscle fasciculations were observed in 250 ppm males and/or females. Motor activity in 250 ppm males and/or females was slightly lower compared to the controls. Changes in these neurobehavioral parameters and clinical signs were consistent with inhibition of cholinesterase activity, and were considered to be related to the treatment. These effects were not observed in animals dosed at 30 ppm or below.

Exposure to 250 ppm of oxamyl in diet resulted in statistically significant inhibitions of plasma, erythrocyte, and brain cholinesterase activities at each of the sampling times during the study. Generally, the magnitude of inhibition was greater in females than in males. Dietary exposure at 10 or 30 ppm did not result in toxicologically important inhibition of blood or brain cholinesterase activity in males or females. According to the researcher, any apparent changes were considered to be spurious either because of lack of statistical significance, lack of a dose-response relationship, or lack of consistent changes at multiple sampling times.

Decreases in body weight, weight gain, food consumption, and food efficiency were found in males and females exposed at 100 ppm or above. Some of these changes were biologically significant. No such effects were observed in either males or females at 30 ppm or below. No treatment-related morphological changes were reported in the nervous system of either sex at any dietary concentrations. Based on clinical signs and cholinesterase inhibition at 250 ppm in males and females, Malley (1998) identified 30 ppm as the NOAEL. This level corresponds to 1.69 mg/kg-day for male rats and 2.03 mg/kg-day for female rats (dose estimates were provided by Malley).

In a 90-day feeding study, male and female weanling albino rats (16/sex/exposure group) were given oxamyl in the diet for 90 days at concentrations of 0, 50, 100, or 150 ppm (Kennedy, 1986a). During the first four days of the study, the high-dose group was given 500 ppm, but due to apparent toxicity at this dose, it was stopped. This group was given control diet for three days, and then given 150 ppm of oxamyl in the diet from day eight to the end of the study. Clinical signs of toxicity were not observed in rats fed diets containing oxamyl at 150 ppm and below. Growth of male rats at both 100 and 150 ppm was significantly less than that of the controls. Ten rats/sex per group were sacrificed after 90 days. Results of the hematologic and enzyme studies did not show changes related to the treatment. Urine analysis revealed increased incidences of proteinuria and occult blood in the 100 and 150 ppm groups compared with the controls. Pathological

examination, including gross necropsy, evaluation of organ weight data, and micropathologic study of tissues from the control and highest dosed group was unremarkable. Based on the reduced weight gain data, a NOAEL of 50 ppm or 5 mg/kg-day (dose estimate provided by Kennedy) can be determined.

In another 90-day feeding study, oxamyl was added to the diet of beagle dogs at 0, 50, 100, or 150 ppm (Kennedy, 1986a). There were four male and four female dogs in each dose group. However, no intake estimates were provided by the paper. All dogs were normal with respect to appearance, behavior, appetite, and eliminations. In dogs receiving the test substance, infrequent, sporadic instances of bloody, mucoid diarrhea, eye discharge, inflammation, dehydration, thinning hair on the chest, and cysts were reported. The author did not find these observations were related to the treatment. Evaluation of organ weights, hematologic and blood chemistry studies, microscopic examination of tissues, and urine analysis also revealed no significant changes in the dogs fed oxamyl.

In a dermal toxicity study (MRID 40827601), oxamyl was applied dermally to male and female New Zealand White rabbits at dose levels of 0, 2.5, 50, or 250 mg/kg for 6 hours/day for 22 consecutive days. There were five animals/sex/group in the two low-dose groups and 10 animals/sex/group in the control and the high-dose groups. Blood samples were collected 9 days before the treatment and one hour after removal of bandages following the last treatment (U.S. EPA, 2000c). Hematology and clinical chemistry were done on the blood samples. Three high dose males died during the test, but the cause of death was considered unrelated to the treatment. There was a significant decrease in plasma, red blood cell, and brain cholinesterase activity in the 50 and 250 mg/kg-day male and female rabbits. A NOAEL of 2.5 mg/kg-day was determined (U.S. EPA, 2000c), based on the decrease in cholinesterase activity in plasma, red blood cell, and brain of the treated rabbits.

In a 21-day dermal toxicity study (MRID 44751201), groups of 6 animals/sex/group New Zealand White rabbits were treated with oxamyl at dermal doses of 0, 25, 40, 50 or 75 mg/kg-day, for 6 hours/day, 7 days/week. No mortality was recorded, and there were no clinical signs indicative of systemic toxicity at any treatment level. No treatment-related dermal irritation was produced. There were no treatment-related effects on body weight, food consumption or food efficiency in either sex of rabbits. Significant inhibition of plasma (29 percent) and brain (10.7 percent) cholinesterase was observed in female rabbits at 75 mg/kg-day. In male rabbits, there were no treatment-related changes in the plasma, red blood cell or brain cholinesterase activities at any dose level. A NOAEL of 50 mg/kg-day was determined (U.S. EPA, 2000c), based on the decrease in cholinesterase activity in plasma, red blood cell, and brain in female rabbits.

## **Developmental and Reproductive Toxicity**

### Reproductive toxicity

In an unpublished study, Sherman and Zapp (1971, as cited in U.S. EPA, 2004b) described a three-generation study where rats were given oxamyl in the diet at 0, 50, 100, or 150 ppm. They reported 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<sub>3B</sub> generation animals had slightly increased relative weights of their kidneys (100 ppm group) and testes (100 and 150 ppm). Oxamyl-related histopathological changes were not observed in any of the animals. The NOAEL for this study was determined to be 50 ppm, i.e., 2.5 mg/kg-day (dose estimate provided by U.S. EPA, 2004b).

In a one-generation reproduction study, male and female weanling albino rats (6/sex/exposure group) were given oxamyl in the diet at concentrations of 0, 50, 100, or 150 ppm (Kennedy, 1986a). During the first four days of the study, the high-dose group was given 500 ppm, but due to apparent toxicity at this dose, it was stopped. This group was given control diet for three days, and then given 150 ppm of oxamyl in the diet from day eight to the end of the study. Each of the females was placed with each of three separate males (from within the same group) for five days (one estrous cycle). After this 15-day mating period, females were transferred and examined twice daily for the birth of young (F<sub>1A</sub> generation). At postnatal day 4, litters of more than 10 pups were reduced to a number provided by a random number table. Each pup was weighed at weaning (21 days). This procedure was repeated approximately one week following weaning of the last F<sub>1A</sub> litter to produce the F<sub>1B</sub> generation.

The author reported that the treatment did not result in any adverse effects on fertility. The number of young delivered by rats fed 100 or 150 ppm in the F<sub>1A</sub> litter and by rats fed 150 ppm in the F<sub>1B</sub> litter was somewhat reduced (not statistically significant) but survival through the lactation period was unaffected. The average weanling body weights from all test groups were significantly lower than those of the controls (Table 3). It is not clear if the observed reduction in body weight resulted from in utero or post-partum exposure (via milk). Based on reduced weanling body weights, a lowest observed adverse effect level (LOAEL) of 50 ppm or 5 mg/kg-day can be identified (dose estimate provided by Kennedy).

**Table 3. Body Weights of Weanlings Derived from Oxamyl-fed Rats (Kennedy, 1986a).**

Dietary level (ppm)	Generation	Average number of pups/litter	Average body weight (g)
0	F <sub>1A</sub>	11.3	65
0	F <sub>1B</sub>	13.8	62
50	F <sub>1A</sub>	12.5	52*
50	F <sub>1B</sub>	12.8	57*
100	F <sub>1A</sub>	9.0	50*
100	F <sub>1B</sub>	11.0	46*
150	F <sub>1A</sub>	9.0	45*
150	F <sub>1B</sub>	9.8	47*

\* Statistically significant, p < 0.05.

In a three-generation reproductive toxicity study, Kennedy (1986a) exposed male and female rats to oxamyl in the diet at 0, 50, 100, and 150 ppm. There were 16 rats/sex per dose group (F<sub>0</sub> generation). Each of the females was placed with each of three separate males (from within the same group) for five days. After the mating period, females were transferred to semiclosed plastic cages and allowed to deliver their litters (F<sub>1A</sub> generation). Litters of greater than 10 were reduced to that number on lactation Day 4. After one week, matings were repeated to produce the F<sub>1B</sub> litter. When the F<sub>1B</sub> generation was approximately 110 days of age, they were mated as above to produce F<sub>2A</sub> and F<sub>2B</sub>. The process was repeated to yield F<sub>3A</sub> and F<sub>3B</sub> litters.

Rats fed either 100 or 150 ppm exhibited lower body weights relative to either control or the 50-ppm test group. These differences were apparent following one week on test diet and remained throughout the study. Indices of reproduction, including fertility, gestation, pup viability, and lactation, showed no meaningful differences between control and test groups. The litter size and average weanling weights in the 100 and 150 ppm groups were significantly ( $p < 0.05$ ) reduced. In contrast to an earlier one-generation reproductive toxicity study, body weights of weanlings in the 50 ppm group were not reduced compared to the controls. A cross-fostering study in which F<sub>3B</sub> generation pups from litters in the 150 ppm group were transferred at birth to mothers of the control group (and vice versa) resulted in growth superior to those pups remaining with their dams. This indicates that nutritional factors may play a role in the reduction of body weight gain of the pups. No pathologic changes were detected in any F<sub>3B</sub> generation weanlings that could be attributed to oxamyl feeding. It is not clear if any pathologic changes were found in other generations. Based on the reported results, a NOAEL of 50 ppm or 5 mg/kg-day (dose estimate provided by Kennedy) can be identified.

In an unpublished two-generation reproduction study (Hurtt, 1990, as cited in U.S. EPA 2004b), male and female rats were fed diets containing 0, 25, 75, or 150 ppm of oxamyl. The exposure period was not specified in the source document (U.S. EPA 2004b). Parental (F<sub>0</sub>) and first generation offspring (F<sub>1</sub>) males and females showed decreased food consumption and reduced body weight gain at the 75 and 150 ppm dose levels. The animals in the 150 ppm dose group displayed hyperactivity, skin sores, and alopecia. Additionally, both offspring generations (F<sub>1</sub> and F<sub>2</sub>) exposed to concentrations greater than 75 ppm had 2-7.6 percent 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 percent and 21-43 percent, 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) (dose estimates were provided by U.S. EPA, 2000c).

#### Developmental toxicity

In a teratogenic toxicity study reported by Kennedy (1986a), pregnant rats were given 0, 50, 100, 150, or 300 ppm oxamyl in their diet between gestation day 6 and day 15. On day 21, rats were sacrificed, and ovaries, uteri, and fetuses were removed and examined. Skeletal development and internal organs were examined only in the control, 150 and 300 ppm group fetuses.

Body weights of rats receiving oxamyl during pregnancy were significantly lower at feeding levels of 100 ppm and above. The reductions in the rate of weight gain were consistent with the reduced food intake observed in those groups. No gross changes in tissues and organs were observed in the dams at the time of sacrifice. There were no significant differences in the number of implantation sites, live fetuses, and resorptions per female between the control and the treated groups. Weight and length of fetuses were not affected by the treatment. External examination of all fetuses in all groups showed no major abnormalities. No major skeletal and internal abnormalities were detected in fetuses from dams receiving oxamyl at either 150 or 300 ppm. Based on the reduction of body weight observed in the dams, a NOAEL of 50 ppm or 5 mg/kg-day (dose estimate provided by Kennedy) can be identified.

In an unpublished study reported by Rickard (1988, as cited in U.S. EPA, 2004b), oxamyl was administered to pregnant Charles River rats (25/dose group) by gavage from gestation days 7 through 16. 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 (21-30 percent;  $p < 0.05$ ) and food consumption (10-16 percent;  $p < 0.05$ ). There also was a dose-related increase in tremor incidence, 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 equal or greater than 0.5 mg/kg-day, there was a statistically significant ( $p < 0.05$ ), dose-related decrease in fetal body weights. It was determined, however, that the decreased weight in fetuses was not necessarily indicative of fetal susceptibility because reduced maternal weight gain could be a contributing factor. A developmental toxicity NOAEL of 0.2 mg/kg-day was identified based on dose-related decreases in the fetal body weight (U.S. EPA, 2004b). This NOAEL is lower than the other NOAELs identified in this section. The difference in toxicity may be explained by the fact that rats were exposed to oxamyl by gavage in the Rickard study, while rats in the other studies were exposed through the diet.

In an unpublished study, Hoberman *et al.* (1980, as cited in U.S. EPA, 2004b) administered oxamyl to New Zealand white rabbits (17/dose group) by gavage at doses of 0, 1, 2, or 4 mg/kg-day on gestation days 6 through 19. Rabbits were sacrificed on gestation day 29, and the fetuses were removed, weighed, measured for crown-rump distance, and examined for external malformation/variability. No oxamyl-related effects were observed during necropsy, and there were no clinical signs of toxicity or changes to maternal absolute body weight or 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 percent lower than those of controls; however, the body weights recovered during the postdosing period. Based on the reduced body weight gains, a NOAEL of 1 mg/kg-day was determined. No treatment related developmental toxicity was observed in the study.

In a teratogenic toxicity study reported by Kennedy (1986a), pregnant rabbits were dosed orally with either distilled water or oxamyl at 1, 2, or 4 mg/kg-day, on gestation days 6

through 19. On day 29, all females were sacrificed and examined for visceral gross pathology, number of corpora lutea, implantations, resorptions, and fetuses. Fetuses were examined and weighed, and visceral structures and skeletal development were examined. The author found maternal survival, food consumption, pregnancy rate, implantation efficiency, gross pathology, ovarian and uterine weights, fetal viability, weight and length, and visceral and skeletal variations and malformations among test group does and fetuses were not different than in the controls. Body weight gain of rabbits treated with oxamyl at 2 or 4 mg/kg-day was reduced (it is not clear if the changes were statistically significant) during the dosing period with mean weight gains of 170, 154, 65, and 56 g in groups dosed at 0, 1, 2, and 4 mg/kg-day, respectively. The mean incidence of resorptions was highest in the 4 mg/kg-day group, but this value was not significantly different from that of the control group.

### **Immunotoxicity**

No data were located.

### **Neurotoxicity**

Neurotoxic effects of oxamyl in rats have been studied by Malley (1997 and 1998). The details of these results are presented in the Acute Toxicity and Subchronic Toxicity Sections.

Oxamyl did not cause any delayed neurotoxicity in an unpublished study by Lee (1970, as cited in U.S. EPA, 2004b). White, Leghorn adult chickens received single oral doses of oxamyl (1 percent 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 (U.S. EPA, 2004b).

### **Genetic Toxicity**

Venkat *et al.* (1995) tested genotoxicity of oxamyl using a modified SOS microplate assay in which the induction of  $\beta$ -galactosidase in *E. coli* PQ37 was used as a quantitative measure of genotoxic activity. For oxamyl, they reported activities of 1,202 unit/ $\mu$ mol in a 10 percent dimethylsulfoxide in saline solution and 605 unit/ $\mu$ mol in a micellar solution of sodium taurocholate. The purpose of the taurocholate solution was to simulate bile salt micelles in the gastrointestinal tract. For comparison, in taurocholate solutions, the activity of the positive control, 4-nitroquinoline oxide, was 16,734 unit/ $\mu$ mol, and activities of three naturally occurring compounds anethole (fennel), curcumin (turmeric), and capsaicin (capsicum peppers) were 4,594, 928, and 809 unit/ $\mu$ mol, respectively.

Oxamyl was reported as negative for mutation induction in Salmonella strains TA1535, TA1537, TA98, and TA100 with and without activation, at 0, 50, 100, 500, 1000, 5000,

or 10,000 µg/plate, using duplicate plates and two trials (Haskell Laboratory, 1981, as cited in DPR, 1998). In reports by Moriya *et al.* (1983), Arce (1981, as cited in U.S. EPA, 2004b), and Shirasu *et al.* (1976, as cited in U.S. EPA, 2004b), oxamyl was found to be negative in TA1535, TA1537, TA1528, TA98, and TA100 strains, with or without rat liver S9 activation.

Moriya *et al.* (1983) and Shirasu *et al.* (1976, as cited in U.S. EPA, 2004b) also found oxamyl to be negative for mutation induction in *Escherichia coli* strain WP2 hcr tests, with or without rat liver S9 activation. In another study reported by Shirasu *et al.* (1976, as cited in U.S. EPA, 2004b), oxamyl concentrations from 20 to 2,000 µg/disk did not preferentially inhibit the growth of a repair-deficient bacterial strain compared to a repair-competent strain.

Oxamyl gave negative results for mutagenicity in Chinese hamster ovary cells without activation, at concentrations from 50 to 1,200 µM. It also tested negative with activation, at concentrations from 25 to 700 µM (Haskell Laboratory, 1982a, as cited in DPR, 1998).

Oxamyl was negative for chromosomal aberrations in Chinese hamster ovary cells. The chemical was tested both with and without activation, at concentrations from 2.3 to 700 µg/mL (Litton Bionetics, 1982, as cited in DPR, 1998).

Oxamyl also tested negative for unscheduled DNA synthesis in rat hepatocytes *in vitro*. Oxamyl was tested with rat hepatocytes at concentrations from 10<sup>-5</sup> to 10 mM, with two cultures and two trials (Haskell Laboratory, 1982b, as cited in DPR, 1998).

Based on these test results, oxamyl is not considered to be a genotoxicant.

### **Chronic Toxicity/Carcinogenicity**

In a combined chronic toxicity/carcinogenicity study (MRID 41963201), oxamyl was administered in the diet to 62 rats/sex/dose for two years (U.S. EPA, 2000c). The dietary concentrations were 0, 25, 50, 100 or 150 ppm. An interim sacrifice of 10 rats/sex/dose was conducted at 12 months. In the 100 and 150 ppm groups, there were significant increases in the incidences of hyperactivity (both sexes), swollen paws/legs (males), and skin sores (females). Other signs of toxicity were also observed in animals exposed to high doses. During the first year of study, mean body weights and body weight gains in the two higher dose groups were significantly lower in males (10 and 25 percent, respectively) and females (27 and 37 percent, 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 statistically significantly higher incidence of bilateral retinal photoreceptor atrophy, presumably related to inhibition of retinal cholinesterase. Plasma cholinesterase levels were significantly decreased in both sexes of the 100 and 150 ppm groups. Red blood cell and brain cholinesterase levels were not affected at any dose level in either sex. No treatment-related increases in cancer incidence were noted. The NOAEL for this study was estimated to be 50 ppm (2.0 mg/kg-day for males and 2.7 mg/kg-day for females; dose estimates were provided by U.S. EPA, 2000c). The LOAEL was 100 ppm (4.2 mg/kg-day for males and 6.7 mg/kg-

day for females). These 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 plasma cholinesterase inhibition (U.S. EPA 2000c).

Kennedy (1986a) administered oxamyl in the diet to groups of rats (36/sex/exposure group) at 0 (control), 0 (second control), 50, 100, or 150 ppm for two years. Throughout the study period, rats fed either 100 or 150 ppm exhibited lower body weights relative to either control or the 50-ppm group. During the first year, a total of nine deaths occurred in the study, none of which were attributed to oxamyl feeding. An increase in mortality rate was seen in the second year among both control and test rats. A total of 58 male and 64 female (39 and 43 percent, respectively) rats died or were sacrificed with no apparent dose-response relationship. The authors reported no treatment-related changes in hematology or clinical blood chemistry. A decrease in cholinesterase activity was noted in some rats in the first eight days of the study. No compound-related pathologic changes were observed in rats fed up to 150 ppm oxamyl. The type and distribution of tumors were similar in the test and control rats. Based on the reduced body weight gain in male and female rats, a NOAEL of 50 ppm or 5 mg/kg-day (dose estimate provided by Kennedy) can be identified.

Kennedy (1986a) administered oxamyl in the diet to groups of mice (80/sex/exposure group) at 0, 25, 50, or 75 ppm for two years. The highest feed level, initially 100 ppm, was reduced to 75 ppm, beginning on the sixth test week. The administered oral oxamyl doses were estimated to be 3.75, 7.5, or 15 mg/kg-day for males and 3.75, 7.5, or 11.25 mg/kg-day for females (the doses were estimated by the U.S. EPA, 2004b). On Weeks three and four, an additional 22 mice were added to the groups exposed to oxamyl. Early mortality was noted in the first four weeks of the study, especially in the highest dose group. Body weights of mice fed either 50 or 75 ppm were less than those of the controls, particularly during the first six months of the study. No significant clinical signs of an adverse effect were noted in any of the test mice. At Week four, erythrocyte, hemoglobin, and hematocrit levels were reduced in males in the 75 ppm group. These values returned to normal by Week 13 and remained so for the duration of the test. There were no treatment related histopathological findings. The author reported that the type of tumors and tumor incidence in the treated groups were not different from those seen in controls. Based on the reduced body weight gain and the dose estimates made by U.S. EPA, a NOAEL of 25 ppm or 3.8 mg/kg-day can be identified. Kennedy also identified 25 ppm as the NOAEL, but estimated a corresponding dose of 2.5 mg/kg-day.

In a feeding study, oxamyl in the diet was fed to beagle dogs at 0, 50, 100, or 150 ppm for two years (Kennedy, 1986a). There were four male and four female dogs in each dose group. The treatment did not cause early death or a decrease in body weight or food consumption. No significant differences were observed between the controls and the treated dogs in clinical observations, hematologic and urine analysis results. Pathological examination of the organs did not detect any changes ascribable to the treatment.

Two unpublished one-year feeding studies in dogs showed that oxamyl at 50 ppm or above caused inhibition of cholinesterase activity and related clinical signs. In the first study, oxamyl (99 percent) 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 (Mebus,



1990; Dickrell, 1991; Van Pelt, 1999, all cited in U.S. EPA, 2004b). Oxamyl did not produce any adverse effects in parameters assessed by urinalysis, ophthalmological examination, and gross pathology at any of the dose levels. Plasma and brain cholinesterase, however, were 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 percent 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 (U.S. EPA, 2004b).

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, as cited in U.S. EPA, 2004b). In this study food was offered *ad libitum*. In the 50 ppm group, plasma, red blood cells, and brain (cerebellum and medulla) cholinesterase levels were depressed by 11, 4, and 20 percent, respectively, compared to controls. The 20 percent brain cholinesterase inhibition was considered biologically relevant since tremors were observed at 150 and 250 ppm in males. Plasma, red blood cells and brain cholinesterase levels were depressed 18, 5 and 2 percent, respectively, in the 35 ppm dose group. Therefore, 35 ppm (0.93 mg/kg-day; dose estimate provided by U.S. EPA, 2004b) 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 (U.S. EPA, 2004b).

## ***Toxicological Effects in Humans***

### **Acute toxicity**

A clinical case report described a 53 year old woman who drank a “swallow” of oxamyl by mistake and was semiconscious within 10 min. When she was brought to the hospital, she was unconscious, incontinent of feces, apneic, without detectable blood pressure, and her pupils were constricted. Despite prompt medical treatment, the woman died 12 hours later (Hayes, 1991).

McFarlane and Freestone (1999) conducted a randomized, double-blind, ascending oral dose study with oxamyl in humans. There were 40 healthy male subjects, aged 19-39 in the study. Each was given a single oral dose of oxamyl in a gelatin capsule at 0 (placebo), 0.005, 0.015, 0.03, 0.06, 0.09, or 0.15 mg/kg. The capsule was administered five minutes after a standard breakfast. With the exception of dose sessions 1 (2 placebos), 2 (1 placebo and 1 at 0.005), 7 (1 placebo and 4 at 0.09), 8 (1 placebo and 1 at 0.15), and 9 (1 placebo and 4 at 0.15), all other dose sessions had 1 placebo, 4 at current dose, and 1 at the next higher dose (U.S. EPA, 2006c). Blood samples for determination of erythrocyte and plasma cholinesterase activity were collected at screening, 2 days, 16 hr and 30 min before dosing, every 15 min for the first 2 hr after dosing and 3, 4, 6, 8, 12 and 24 hr and 7 ( $\pm 2$ ) days after dosing. Other clinical parameters indicative of

carbamate exposure, such as urinalysis, pupillometry, saliva increase etc. were also measured.

No treatment-related effects on the encephalogram, heart rate, pulse, blood pressure, respiratory rate, body temperature, haematological, clinical chemical (except cholinesterase activity) or urine parameters or on the pupils were observed (IPCS, 2002). At 0.15 mg/kg, plasma cholinesterase activity was decreased by 21-43 percent between 30 min and 2 hr after dosing, and cholinesterase activity in erythrocytes was decreased by 23-28 percent between 30 and 60 min after dosing. One hour after dosing, a significant increase (161 percent) in saliva production in the subjects was also reported. At 0.09 mg/kg, 7-12 percent plasma and erythrocyte cholinesterase inhibition was observed with three of five human subjects exhibiting greater than 20 percent plasma cholinesterase inhibition. For this reason, the 0.06 mg/kg dose was identified as the NOAEL.

The U.S. EPA Human Studies Review Board reviewed the scientific and ethical aspects of this human study. While the board acknowledged the lack of females in the study, it determined that there were no deficiencies identified that would have affected the outcome or conclusions of the study. Furthermore, the board believed that this intentional human dosing study was sufficiently robust that it can be used for reducing the 10-fold inter-species uncertainty factor. On ethical considerations, the board found the study failed to fully meet the specific ethical standards prevalent at the time the research was conducted; however, the board found no clear or convincing evidence that the research was fundamentally unethical – e.g., that the research was intended to seriously harm participants or that informed consent was not obtained (U.S. EPA, 2006b). OEHHA concurs with the U.S. EPA Review Board that the weaknesses of this study (not providing a clear discussion of risk and existing information on incidences of accidental exposures to the research subjects) do not preclude its use in risk assessment – especially since its use results in a decrease in estimated health-protective levels for oxamyl.

### **Subchronic and Chronic Toxicity**

Ames *et al.* (1989) reported a study that analyzed cholinesterase activity measurements for 542 California agricultural pesticide applicators under medical supervision during the first nine months of 1985. Twenty-six workers, 4.8 percent of the sample, had cholinesterase values at or below the California threshold values for removal from continued exposure to cholinesterase-inhibiting pesticides (60 percent of baseline for red blood cell cholinesterase and 50 percent of baseline for plasma cholinesterase activity). Eight of these 26 workers, 31.5 percent, had pesticide-related illnesses. Reliable exposure information was not available, and oxamyl was among the pesticides that the workers were exposed to.

### **Reproductive and Developmental Toxicity**

No studies were found in the scientific literature concerning reproductive or developmental effects of oxamyl in humans.

## Carcinogenicity

No epidemiology studies or case reports were found concerning carcinogenicity of oxamyl in humans.

## DOSE-RESPONSE ASSESSMENT

### *Noncarcinogenic Effects*

Oxamyl is a carbamate pesticide; it inhibits cholinesterase activity and causes neurotoxic effects in humans as well as test animals. The neurotoxic effects of oxamyl are evident within 30 minutes to an hour after dosing. In acute toxicity studies, cholinesterase activity of test animals usually recovers after 24 hours. In subchronic and chronic toxicity studies, besides the neurotoxic effects, the other adverse health effects are reduced body weight gain and reduced body weight. The human and animal oral studies considered for dose-response characterization are summarized in Table 4.

Based on the data presented, it is apparent that administration of oxamyl by bolus (gavage or capsule) is more toxic (gives a lower NOAEL) than exposure via the diet. This is likely a dose rate effect, because a bolus dose can be absorbed relatively quickly, while exposure through the diet spreads the dose over a longer time period. Also, the lower NOAEL for the acute versus chronic study suggests that the chemical does not accumulate from day to day and is rapidly eliminated. For the purpose of this assessment, the lowest NOAEL (0.06 mg/kg) of the values listed in Table 4 is used for the development of the PHG for oxamyl.

**Table 4. Oral Toxicity Studies Considered for Dose-response Characterization.**

<b>Study</b>	<b>Species and exposure</b>	<b>Adverse health effects</b>	<b>LOAEL or NOAEL</b>
Acute toxicity study by McFarlane and Freestone (1999)	Human (male adult) / oral via a capsule	Decreased cholinesterase activity in erythrocytes and plasma in less than 2 hours	NOAEL = 0.06 mg/kg
Acute toxicity study by Malley (1997)	Rat / gavage	Clinical signs, impaired motor activities, decreased blood and brain cholinesterase activity	NOAEL = 0.1 mg/kg
Subchronic (90 days) study by Malley (1998)	Rat (male)/ diet	Clinical signs, reduced body weight, decreased plasma, red blood cells, and brain cholinesterase activity	NOAEL = 1.7 mg/kg-day
Developmental study by Rickard (1988, as cited in U.S. EPA, 2004b)	Rat / gavage	Decrease in fetal body weight	NOAEL = 0.2 mg/kg-day

<b>Study</b>	<b>Species and exposure</b>	<b>Adverse health effects</b>	<b>LOAEL or NOAEL</b>
Reproductive and developmental study by Kennedy, 1986a	Rat / diet	Reduction of body weight gain in the neonates	LOAEL = 5 mg/kg-day
Developmental study by Hoberman <i>et al.</i> (1980 as cited in U.S. EPA, 2004b)	Rabbit / gavage	Reduced body weight gain in the dams	NOAEL = 1 mg/kg-day
Chronic toxicity study by Dickrell (1991, as cited in U.S. EPA, 2000d)	Dog / diet	Clinical signs, decreased plasma, red blood cells, and brain cholinesterase activity	NOAEL = 1 mg/kg-day
Chronic toxicity study by U.S. EPA, 2000c	Rat (male)/ diet	Reduced body weight gain, hyperactivity, swollen legs and paws, and skin sores	NOAEL = 2 mg/kg-day
Chronic toxicity study by Kennedy, 1986a	Mouse / diet	Reduced body weight gain	NOAEL = 3.8 mg/kg-day

The NOAEL in the human study conducted by McFarlane and Freestone (1999) is very similar to the NOAEL in the rat study of Malley (1997), indicating that the toxicokinetics for these acute (bolus) effects appear to be similar in the two species.

### ***Carcinogenic Effects***

No dose-response evaluation was performed for carcinogenicity as the chemical has not been shown to be either genotoxic or carcinogenic in animal or human studies.

## **CALCULATION OF PHG**

### ***Noncarcinogenic Effects***

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose of the chemical from all sources will first be calculated. This involves incorporation of appropriate estimates of uncertainty in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime daily dose for oxamyl that is unlikely to result in any toxic effects. For this purpose, the following equation will be used:

$$\text{ADD} = \frac{\text{NOAEL in mg/kg-day}}{\text{UF}}$$

where,

- ADD = acceptable daily dose, an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects;
- NOAEL = no-observed-adverse-effect level, which is identified as 0.06 mg/kg-day from the acute toxicity study reported by McFarlane and Freestone (1999);
- UF = an uncertainty factor of 10 to account for inter-individual differences in responses among humans, including potentially sensitive subpopulations.

Thus,

$$\text{ADD} = \frac{0.06 \text{ mg/kg-day}}{10} = 0.006 \text{ mg/kg-day}$$

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for non-carcinogenic endpoints:

$$C = \frac{\text{ADD mg/kg-day} \times \text{RSC}}{\text{WC/BW L/day}}$$

where,

WC/BW = volume of water consumed per kg body weight (L/kg-day); and

RSC = relative source contribution (usually 20 to 80 percent).

For the purpose of this evaluation, two separate exposure scenarios were developed, one for young infants (< 6 months old) and another for toddlers (< 2 years old). Our analysis of the U.S. EPA's evaluation of the National Health and Nutrition Examination Survey (NHANES) drinking water consumption rates (U.S. EPA, 2004a) suggests that appropriate health protective values for young infants and toddlers are 0.221 L/kg-day and 0.137 L/kg-day, respectively, based on the upper 95<sup>th</sup> percentiles of daily municipal water consumption. The intake values are normalized by body weight because water consumption is directly correlated with body weight. Since the ADD was derived from an acute (bolus) exposure, the daily water intake values are adjusted reasonable maximum acute intake values.

Infants are fed about every three hours, or about 8 meals/day. Considering the very short half-life of cholinesterase inhibition by oxamyl, we assumed that the maximum effective dose, based on consumption, would be the equivalent of any two meals combined. This is equivalent to one-fourth of their daily consumption volume, or 0.0552 L/kg-day. A toddler is fed only three or four times per day, so it seemed more logical that up to one-third of the daily water intake could be consumed within a short period of time (i.e., equivalent to a single bolus dose). The adjusted water intake estimates for toddlers would therefore be 0.0457 L/kg-day.

The RSC for young infants (< 6 months old) was assumed to be 1 because young infants get all their nutrients from formula or breast milk and are not exposed to other food products; a calculation based on this value is shown below. However, by the age of two, toddlers consume various meat and vegetable products which can represent important exposure pathways. The RSC for toddlers (< 2 years old) was therefore assumed to be the customary default value for pesticides used on foods, or 0.2. The two sets of exposure assumptions yield the following estimated health-protective concentrations for oxamyl in water:

$$C_{\text{infants}} = \frac{0.006 \text{ mg/kg-day} \times 1}{0.0552 \text{ L/kg-day}} = 0.109 \text{ mg/L}$$

$$C_{\text{toddlers}} = \frac{0.006 \text{ mg/kg-day} \times 0.2}{0.0457 \text{ L/kg-day}} = 0.026 \text{ mg/L}$$

Based on these calculations, OEHHA chooses the more health-protective exposure scenario (i.e., a toddler) to calculate a public health goal of 0.026 mg/L (26 ppb) for oxamyl in drinking water.

## RISK CHARACTERIZATION

Oxamyl is a carbamate pesticide that causes neurotoxicity in humans and laboratory animals via cholinesterase inhibition. Because carbamylation of acetylcholinesterase is spontaneously reversible, the inhibition is not cumulative with repeated daily exposures (Kennedy, 1986b; Fayez and Kilgore, 1992). In most of the short-term and long-term toxicity studies, reduced body weight gain, clinical signs related to cholinesterase activity inhibition, and behavioral changes were the main adverse effects. The available data indicate that oxamyl is not a mutagen, carcinogen or teratogen.

Cholinesterase inhibition data in an acute oral human study was selected for the development of a drinking water level for oxamyl. To account for intra-species variation, an uncertainty factor of 10 is used for calculating the PHG. The toxicity data for oxamyl are adequate and the observed acute toxicity NOAEL of 0.06 mg/kg-day in adult male subjects is consistent with data obtained from other rat, mice, rabbit, and dog studies, providing greater confidence in the NOAEL. Furthermore, this NOAEL is lower than many NOAELs derived from sub-chronic and chronic feeding studies of laboratory animals.

The most recent U.S. EPA (2004b) evaluation used a NOAEL of 0.1 mg/kg derived from the acute oral toxicity reported by Malley (1997) to determine a one-day health advisory level of 0.01 mg/L (10 ppb). The assumptions include an uncertainty factor of 100, a child's body weight of 10 kg, and a drinking water consumption rate of 1 L/day, without a relative source contribution. Although there are several differences in this approach from the OEHHA calculation, the most important is the use of a larger combined uncertainty factor, based on extrapolation from a non-human species. The human

NOAEL of 0.06 mg/kg that the PHG is based on is lower than the rat NOAEL in Malley (1997). OEHHA feels that the human data (McFarlane and Freestone, 1999) is more relevant than the Malley data for human risk assessment and that this evaluation therefore supersedes the U.S. EPA evaluation.

Children may ingest a large amount of water within a short period of time and thus have potential for high acute exposure. Also, because of the relatively large water consumption rate per body mass, the estimated dose (in mg/kg) can be larger for children. For these reasons, the PHG of 26 ppb has been based on toddlers' exposure. This PHG should also be low enough to protect all other potential sensitive subpopulations from adverse effects of a lifetime of exposures.

Available data suggest additive but not synergistic interactions of oxamyl with other organophosphate or carbamate pesticides (Iyaniwura, 1991). U.S. EPA has released its preliminary cumulative risk assessment for the N-methyl carbamate pesticides (U.S. EPA, 2005). In the assessment, oxamyl was selected as the reference chemical for the determination of relative potency factors for other carbamates. No correction for simultaneous exposures to other carbamates has been incorporated into this assessment because of the low frequency of occurrence of oxamyl and other carbamates in California drinking water (DHS, 2005).

## **OTHER REGULATORY STANDARDS**

U.S. EPA's MCL was based on a NOAEL of 2.5 mg/kg-day oxamyl for decreased body weight gain at higher levels from a rat chronic toxicity study (duPont, 1972). The IRIS reference dose (RfD) is based on the same study (U.S. EPA, 2006a, last updated 03/01/1991). U.S. EPA calculated an MCL and a maximum contaminant level goal (MCLG) of 0.2 mg/L based on a 70 kg adult male consuming two liters of water/day, an RSC of 20 percent and an uncertainty factor of 100. From this calculation, the value of 0.175 mg/L was rounded by U.S. EPA to give the final value of 0.2 mg/L (200 ppb), published in 1992. California developed the earlier PHG of 0.05 mg/L (50 ppb) (OEHHA, 1997) using a NOAEL of 2.5 mg/kg-day derived from a chronic rat study reported by Kennedy (1986a), a 100-fold UF, an RSC of 20 percent, and a consumption estimate of 1 L/day for a 10 kg infant. The current risk assessment is based on a study (McFarlane and Freestone, 1999) not available at the time of the earlier OEHHA assessment. The relative potency of oxamyl administered in a bolus is supported by a study in rats that was also not available at the time of the previous risk assessment (Malley, 1997).

In their "Drinking Water Health Advisory for Oxamyl," U.S. EPA (2004b) used a NOAEL of 0.1 mg/kg derived from the acute oral toxicity reported by Malley (1997) to determine a one-day health advisory (HA) level of 0.01 mg/L (10 ppb). In the calculation, assumptions include an uncertainty factor of 100, a child's body weight of 10 kg, and a drinking water consumption rate of 1 L/day. Furthermore, U.S. EPA regarded this one-day HA as a conservative estimate for all HAs to be protective of public health. Therefore, the ten-day and lifetime HA values are the same as the one-day HA value of 0.01 mg/L (10 ppb).

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