

Toxicologic Information About Insecticides Used for Eradicating Mosquitoes (West Nile Virus Control)

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Table of Contents

Executive Summary.....	1
Introduction	2
Fenthion	3
Malathion.....	13
Methoprene.....	34
Naled.....	42
Phenothrin.....	53
Permethrin	60
Resmethrin.....	69
Temephos	75
Conclusions	84
Recommendations for Avoiding Mosquito Bites	85

List of Acronyms and Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
aRfD	acute Reference Dose
CDC	Centers for Disease Control and Prevention
cRfD	chronic Reference Dose
DOT	US Department of Transportation
EPA	US Environmental Protection Agency
EXTOXNET	Extension Toxicology Network
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IPCS	International Program on Chemical Safety
IRIS	Integrated Risk Information System
LC ₅₀	Lethal Concentration, 50% mortality
LD ₅₀	Lethal Dose, 50% mortality
LOAEL	lowest-observed-adverse-effect level
MOE	Margin Of Exposure
MRL	Minimal Risk Level
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
PAD	populations-adjusted dose
RfD	Reference Dose
TOXNET	Toxicology Network
ULV	ultra-low volume
WHO	World Health Organization

Executive Summary

The Division of Toxicology of the Agency for Toxic Substances and Disease Registry (ATSDR) prepared this document in response to queries to the Centers for Disease Control and Prevention and ATSDR regarding environmental health issues associated with insecticide applications that have been or may be used for eradicating mosquitoes, particularly the mosquito that is a vector of West Nile Virus transmission. The insecticides summarized in this document are four organophosphates (fenthion, malathion, naled, and temephos); three of the pyrethroids (resmethrin, phenothrin, and permethrin); and the larvicide, methoprene.

The document provides health assessors within ATSDR and other public health officials with a single source of summaries of toxicologic issues of the insecticides of interest. Along with background information about insecticide use, environmental factors, the potential for human exposure, health effects/toxicity in humans and animals, toxicokinetics, and standards and guidelines for protecting human health, toxicity data are summarized in tables that provide no-observed-adverse-effect levels and lowest-observed-adverse-effect levels for endpoints for each study.

The organophosphate insecticides have varying degrees of acute toxicity, with temephos and malathion appearing to be the least toxic, followed by naled, and fenthion. The pyrethroids have relatively low mammalian toxicity, being typically used as insecticides for both home and commercial use. Methoprene is an insect growth regulator and is used as a larvicide. It has very low toxicity for animals and humans.

Introduction

The Division of Toxicology of the Agency for Toxic Substances and Disease Registry (ATSDR) prepared this document in response to queries to the Centers for Disease Control and Prevention and ATSDR about environmental health issues associated with insecticide applications that have been or may be used for eradicating mosquitoes, particularly the mosquito vector of West Nile Virus transmission. These insecticides are malathion, naled, permethrin, phenothrin, and resmethrin. In addition, the Division of Toxicology has included summaries for fenthion, methoprene, and temephos because they also have been used for mosquito control.

The purpose of the document is to provide health assessors within ATSDR and other public health officials with one source of summaries of toxicologic issues of the insecticides of interest. The individual summaries present brief background information about the insecticide use, environmental factors, potential for human exposure, health effects/toxicity in humans and animals, toxicokinetics, and standards and guidelines for protecting human health. Toxicity data are summarized in tables that provide no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) for endpoints for each study. Developmental and reproductive NOAELs and LOAELs also are presented. The tables are arranged by duration of exposure, route of exposure, and species.

Because of time constraints and the relative unavailability of unpublished studies submitted to the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide and Rodenticide Act, the summaries presented in this document were compiled primarily from secondary sources. These sources included EPA's registration documents and other EPA documents, the World Health Organization's (WHO's) International Programme on Chemical Safety (IPCS) data sheets, the Hazardous Substances Data Bank and others. The summaries for malathion, and the pyrethroids (resmethrin, phenothrin, and permethrin) were compiled from information in ATSDR's Toxicological Profiles for these insecticides.

Fenthion, malathion, naled, and temephos are organophosphate insecticides that act by inhibiting the activity of cholinesterase. They have varying degrees of toxicity. Organophosphates also inhibit cholinesterase activity of animals and humans and at high enough levels can produce symptoms of cholinergic poisoning ranging from mild (headache, drowsiness) to moderate (difficulty breathing, cardiac arrhythmias, confusion) to life-threatening (coma, seizures, paralysis) effects. The pyrethroids (resmethrin, phenothrin, and permethrin) are synthetic analogues of original pyrethrins, which are natural extracts in the flowers of the chrysanthemum plant and act by rapidly paralyzing flying insects. Methoprene is an insect growth regulator and is used as a larvicide. It is a synthetic analogue of the insect juvenile hormone that has very low toxicity for animals and humans.

Fenthion
(CAS Number 55-38-9)

Fenthion is an organophosphate used primarily as an insecticide and secondarily as an avicide and acaricide. It was used extensively preharvest on sugar cane, rice, field corn, beets, pome and stone fruit, citrus fruits, pistachio, cotton, olives, coffee, cocoa, vegetables, and vines. However, fenthion no longer has Food and Drug Administration approval because of an excess number of poisoning-related deaths (TOXNET 1985). Used as a contact and stomach insecticide, it is highly persistent. The Environmental Protection Agency (EPA) classifies it as a Restricted Use Pesticide because of the special handling warranted by its toxicity. Fenthion is effective against fruit flies, leaf hoppers, cereal bugs, weaver birds, animal parasites, mites, aphids, and codling moths. Fenthion has been used in mosquito control (Thomson 1976), but it was voluntarily pulled from the market as a mosquitocide in 2004 (EPA 2005). Fenthion was used on cattle and swine and for mosquito (adulticide) control in Florida only (EPA 1999). Approximately 222,400–333,600 pounds of the active ingredient was used annually, of which 74,400–111,600 pounds are specifically used for mosquito control.

Fenthion is applied as ear tags and used in spot treatments and pour-on applications for livestock. Application to control mosquitoes is both aerial and ground. Fenthion is not recommended for residual indoor application because of its high mammalian toxicity (i.e., it is highly toxic to birds and moderately toxic to mammals). As a spray, it is extremely effective at controlling mosquitoes. However, it is hazardous to birds, honey bees, beneficial insects, and fish. Fenthion should not be applied for mosquito control in areas containing fish, shrimp, crabs, or crayfish.

Section 1. Environmental Factors

Use of fenthion as an insecticide releases the compound directly to the environment through applications in sprays, dusts, and other application mechanisms. If released to the atmosphere, fenthion degrades rapidly in the vapor phase by reacting with photochemically produced hydroxyl radicals (half-life of about 5 hours). Particulate-phase fenthion is subject to wet and dry deposition (HSDB 2003).

When released to soil or water, fenthion degrades through photodegradation and biodegradation; in the presence of sunlight, photodegradation is likely to dominate. Hydrolysis occurs, but it usually is too slow to be a significant route; hydrolysis half-lives of 101 days in distilled water and 69 days in saltwater have been reported. Additionally, volatilization is expected to be relatively slow. The reported persistence half-life of fenthion in water under field conditions ranges from 2.9 to 21.1 days for various ocean, river, swamp, lake, and canal waters (HSDB 2003). However, it may persist longer in some environments, such as salt marsh sediments (below several mm deep), where light and oxygen are limited. In plants, fenthion oxidizes to sulfoxide and sulfone, which are both highly insecticidal (Worthing 1987).

Fenthion adsorbs strongly to soil particles. This adsorption makes fenthion less likely to move or leach through the soil with water percolating through the ground (Witt et al. 1985). In soil, residues of fenthion persist for approximately 4–6 weeks (Harding 1979). Biodegradation and photo-oxidation are the significant routes in soil, with photo-oxidation dominant under sunlit conditions. The U.S. Department of Agriculture's Pesticide Properties Database lists the soil half-life of fenthion as 34 days (HSDB 2003). This insecticide is susceptible to biodegradation through anaerobic or nonphotolytic organisms (HSDB 2003).

The persistence time of fenthion and its residues from the last application to the time residue levels are low enough to allow harvest is 1 week for tomatoes and strawberries; 10 days for pears; 2 weeks for onions; 3 weeks for beans, citrus, citrus juice, and plums; and 4 weeks for potatoes and sweet potatoes (OHM/TADS 2003). The interval between application and harvest is 4½ weeks for rice and rice straw. Lactating cows given a dose of 9 mg/kg excreted approximately 50% of the fenthion and its residues in 1 month. The maximum excretion of fenthion residues occurred in the first 24 hours. The residues excreted were primarily hydrolysis products. About 2% of the applied fenthion from a lactating cow was later found in the milk.

A measured, mean bioconcentration factor of 16,600 in guppies, a measured bioconcentration factor of 62 in tadpoles, and estimated bioconcentration factors of 760 and 200 based upon a log K_{ow} of 4.09 and a water solubility of 7.5 mg/L at 20 deg C, respectively, indicates that fenthion is likely to significantly bioconcentrate in aquatic organisms (HSDB 2003).

Section 2. Potential for Exposure

The general population is not likely to be exposed to large amounts of fenthion. Fenthion can be absorbed through dermal contact and by inhalation of dust particles. Occupational exposure to fenthion occurs through dermal contact and inhalation of dust and sprays, especially to workers applying the compound as an insecticide. Because fenthion has been detected in American foods, exposure to the general population can occur through consumption of foods containing fenthion residues. Ingestion is the important cause of severe poisoning with this compound (HSDB 2003).

Because of fenthion's use as a pesticide, EPA reviewed the likelihood of exposure to the public of unacceptable (i.e., high-risk) levels. In an extensive risk assessment, EPA (1999) identified the likelihood of such exposures in various scenarios, including dietary, residential, worker, drinking water, aggregate, and ecologic. For dietary risk assessments, the target exposure level above which risk is considered to be of concern is referred to as the populations-adjusted dose (PAD). An acute PAD (aPAD) and a chronic PAD (cPAD) are calculated by dividing the respective acute and chronic RfDs (aRfD and cRfD) by the Food Quality Protection Act Safety Factor. Because the Food Quality Protection Act Safety Factor was reduced to 1x for fenthion, the aPAD and cPAD are identical to the respective aRfD and cRfD. The margin of exposure (MOE) is defined as the ratio of the no-observed-adverse-effect level (NOAEL) to the estimated exposure dose. Low MOEs indicate that human levels of exposure are close to the levels for the NOAEL in animals. Regulatory agencies have used MOEs <100 as flags for further evaluation.

The *acute dietary risk* exceeds EPA's level of concern for the general U.S. population and all population subgroups, including infants and children. At the 99.9th percentile, the risk for the most highly exposed subgroup (children aged 1–6 years) is 800% of the aPAD. The risk falls below EPA's level of concern (100% aPAD) between the 90th and 95th percentiles. The *chronic dietary risk* exceeds EPA's level of concern for the general U.S. population and various population subgroups, *excluding* infants. The most highly exposed subgroup is children 1–6 years at 270% of the cPAD consumed. Beef fat and meat are the highest contributors to acute and chronic dietary risk for all population groups. Residue values for acute and chronic risk were extrapolated from data that do not represent the current label use pattern. Although these anticipated residues represent a best estimate by use of the limited data available, they are an overestimate.

Residential risk, of concern for toddlers, results from the use of fenthion as a wide-area mosquito adulticide. No risk concerns exist for exposure of adults associated with any treatment scenario.

Risks exceed EPA's level of concern (i.e., MOE <100) for toddlers at the maximum aerial label rate until 8 days post-treatment and until 2 days post-treatment at the average application rate.

Worker risk is of *concern* because of the use of fenthion as a wide area mosquito adulticide. MOEs <100 for short-term exposure and <300 for intermediate-term exposure exceed EPA's level of concern. Short-term risks exceed the level of concern for mixing/loading and applying liquids aerially (MOEs <55), ground ultra-low volume (ULV) applicators (MOEs <55), aerial application of granulars (MOEs <85), and flaggers during aerial application (MOEs <35). These MOEs include the use of engineering controls where appropriate. Intermediate-term risks exceed the level of concern for mixing/loading and applying liquids aerially (MOEs <20), ground mixing/loading and applying liquids (MOEs <85), aerial application of granulars (MOEs <230), ground-based granular application (MOEs <20), and flagging during aerial application (MOEs <10).

Drinking water risk is *low*. Little concern exists for adults and children from exposure to fenthion in drinking water because (1) the estimated environmental concentrations used in these calculations were derived from conservative, screening-level models; (2) only minor exposure to surface water is possible because of the application rate and method; and (3) the targeted treatment areas are residential and not significant contributors to drinking water derived from surface water sources.

There *is concern* for acute *aggregate risk* and short-term and intermediate-term aggregate risk associated with the use of fenthion.

Ecologic risk is *high* from use of fenthion as a wide-area mosquito adulticide. EPA's level of concern is exceeded for endangered bird species on an acute and chronic basis from the mosquito adulticide use. The level of concern is exceeded for endangered species of estuarine/marine invertebrates on an acute and chronic basis from the mosquito adulticide use.

Section 3. Health Effects/Toxicity

Health Effects in Humans

The principal toxicologic effect of fenthion and other organophosphate insecticides is cholinesterase inhibition. The following health effects can result:

- **Common early signs or mild symptoms** of acute cholinergic poisoning include miosis (pinpoint pupils), headache, nausea/vomiting, dizziness, muscle weakness, drowsiness, lethargy, agitation, and anxiety.
- **Moderate or severe poisoning** can result in chest tightness, difficulty breathing, bradycardia, tachycardia, hypertension, pallor, abdominal pain, incontinence, diarrhea, anorexia, tremor/ataxia, fasciculation, lacrimation, heavy salivation, profuse sweating, blurred vision, poor concentration, confusion, and memory loss.
- **Life-threatening or very severe signs and symptoms**, such as coma, seizures, respiratory arrest, pulmonary edema, loss of reflexes, and flaccid paralysis, can occur at high doses, such as in attempted suicide.

Fenthion has been used widely in many parts of the world to control household pests and mosquitoes. Twenty-seven of 28 workers who sprayed fenthion as residual indoor application for 15 days in a malaria-control operational trial without taking adequate precautions demonstrated various degrees of poisoning. These degrees included headaches, vertigo, blurred vision, muscle and abdominal pains,

cramps, diarrhea, and prolonged vomiting. Severe reduction of whole-blood cholinesterase activity was observed and remained reduced a month after the end of spraying. However, in a second smaller spraying operation when precautions were more stringent, only one of 12 men showed mild symptoms (IPCS 2003).

In mosquito larviciding operations, dermal exposure averaged 3.6 mg/h with both power and hard sprayers and 12.3 mg/h with a granular formulation dispersed by hand. Some workers showed some plasma cholinesterase depression, but in no case was erythrocyte cholinesterase depressed (IPCS 2003).

A woman who attempted suicide with fenthion at approximately 4 months' gestation survived the cholinergic crisis but remained unconscious for 96 hours. She eventually completely recovered and delivered a healthy baby at term (Karalliedde et al. 1988).

In a subchronic toxicity study, groups of four men given oral doses of 0.02 or 0.07 mg/kg/day for 4 weeks had no symptoms. No hematologic or clinical chemistry changes were seen, although at 0.07 mg/kg, significant plasma cholinesterase depression was noted (EPA 1998). Plasma cholinesterase was considered to be inhibited relative to group pretest values. In less than 24 hours after the initial dose, the level was depressed 8%, and levels reached 30% inhibition after 3 weeks. The group dosed with 0.02 mg/kg/day reached levels of 5%–12% inhibition starting 1 week after exposure. Inhibition in the control group was actually increased relative to pretest. The dose of 0.02 mg/kg/day is considered a threshold for inhibition because at least some statistical tests reported by the study author were significant compared with the control group. The threshold NOEL/LOEL is 0.02 mg/kg/day, and a NOEL is not considered definitely established for inhibition of plasma cholinesterase.

Health Effects in Laboratory Animals

Studies in laboratory animals exposed to fenthion dermally, orally, or by inhalation are summarized in Table 1, with NOAELs and lowest-observed-adverse-effect level (LOAELs) indicated.

A dermal LD₅₀ value of 330 mg/kg was reported for rats and oral LD₅₀ values in rats range from 190 to 615 mg/kg (Worthing 1983). No effects were observed in rats exposed by inhalation to 1197 mg/m³ for 1 hour (ACGIH 1991). Monkeys given fenthion by stomach tube for 2 years had inhibition of plasma and erythrocyte cholinesterase as early the first week at a dose of 0.2 mg/kg/day (EPA 1998). In rabbits exposed dermally to 5–400 mg/kg/day for 21 days, severe signs of cholinesterase inhibition were evident, and death occurred at 200 and 400 mg/kg/day. Clinical signs were seen at 150 mg/kg/day, but signs of neurotoxicity were seen at 100 mg/kg/day. Local dermal irritation occurred at \geq 50 mg/kg/day but not at 5 mg/kg/day (EPA 1998).

Several studies of animals treated orally with fenthion are available. Plasma cholinesterase was inhibited in beagles given fenthion in the diet for 1 year at 0.262 mg/kg/day and higher. No cholinesterase inhibition was seen at 0.056 mg/kg/day, whereas brain cholinesterase was inhibited at 1.228 mg/kg/day (EPA 1998). In monkeys dosed by stomach tube with fenthion for 2 years, plasma cholinesterase was frequently inhibited at the lowest dose tested of \geq 0.02 mg/kg/day, and erythrocyte cholinesterase was frequently inhibited at \geq 0.07 mg/kg/day (EPA 1998). Brain cholinesterase was not inhibited at any dose up to 0.2 mg/kg/day. In rats given fenthion in the diet for 2 years, plasma, erythrocyte, and brain cholinesterase was inhibited at the lowest doses (0.2 mg/kg/day for males and 0.3 mg/kg/day for females). No indication of systemic toxicity was found in this group, but the 0.8

mg/kg/day group had epididymal pathology (vacuolation), vacuolation of the nasolacrimal duct, pneumonia, lung weight change, skin lesions, ocular effects, and clinical signs (EPA 1998). Plasma cholinesterase was inhibited in mice given fenthion in the diet for 2 years at the lowest dose of 0.014 mg/kg/day and higher, whereas erythrocyte cholinesterase was inhibited at ≥ 0.71 mg/kg/day (EPA 1998).

Developmental toxicity in rats and rabbits and reproductive toxicity in rats also has been evaluated for fenthion (EPA 1998). In rats given 0, 1, 4.2, or 18 mg/kg/day by gavage on gestation days 6–16, the high-dose group displayed clinical signs that included tremors, lacrimation, exophthalmos, hypoactivity, urine-stained ventral surface and salivation, and decreases in body weight gain. The rate of resorptions (in excess of the historical control) also was slightly higher in the high-dose group. Plasma, erythrocyte, and brain cholinesterase were inhibited at 1.0 mg/kg/day and higher. Fetal brain cholinesterase also was inhibited in the high-dose group at day 20. Rabbits were treated with fenthion by gavage at doses of 0, 1, 2.75, or 7.5 mg/kg/day on gestation days 6–18. Dams had soft stools and brain cholinesterase inhibition at ≥ 2.75 mg/kg/day and decreased body weight at 7.5 mg/kg/day. Resorptions and unossified metacarpals in the high-dose group increased slightly. In a two-generation study, rats were fed fenthion in the diet at concentrations equivalent to 0, 0.05, 0.10, 0.70, or 5 mg/kg/day (EPA 1998). At 0.7 mg/kg/day, cytoplasmic vacuolization of the epithelial ductal cells of the epididymis, and inhibition of plasma and erythrocyte cholinesterase occurred. Decreased epididymal weight, decreased fertility, increased maternal weight during pre-mating, decreased weight gain during gestation, decreased pup weight gain during lactation, and inhibition of brain cholinesterase were observed at 5 mg/kg/day.

Carcinogenicity

One carcinogenicity test on fenthion indicated that this insecticide may be a carcinogen in male mice (NCI 1979). However, no carcinogenic effects were observed in other 2-year feeding studies of rats and mice (EPA 1998). The National Cancer Institute assessed the carcinogenicity of fenthion in Fischer 344 rats fed doses of 0, 10, or 20 ppm (equivalent to 0, 0.5, or 1 mg/kg/day). This study raised the question of possible compound-related increases in C-cell adenomas of the thyroid and interstitial-cell tumors of the testes. Evidence was not found of increases in these same tumor types in the more recent study at higher dose levels. Thus, fenthion is not considered carcinogenic in the rats in this study (EPA 1998). Fenthion did not demonstrate carcinogenicity in the 2-year feeding study in mice (EPA 1998). Data are insufficient to permit conclusions about the carcinogenicity of fenthion to humans.

Genotoxicity

Fenthion was not mutagenic when tested in a yeast assay (Simmon 1976). Tests on mice also did not show mutagenic effects from fenthion (ACGIH 1986). Fenthion was mutagenic in unscheduled DNA synthesis and mouse micronucleus assays. However, it did not result in postimplantation lethal effects in mice dosed with single doses of either 10 or 25 mg/kg in a previously run dominant lethal study. This study is considered very old, with associated uncertainties, and a new one is needed that follows current guidelines for dominant lethal testing (EPA 1998).

Table 1. Health Effect Levels of Fenthion in Humans and Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Acute Duration Toxicity							
dermal	once	rat		330 mg/kg	LD ₅₀		Worthing 1983
oral	24 hours	human		0.07 mg/kg/day	Marginal plasma cholinesterase inhibition	First day of a 28-day human feeding study	EPA 1998
oral	once	calf		40 mg/kg	LD ₅₀		IPCS 2003
oral	once	rat (male)		190–315 mg/kg	LD ₅₀		Worthing 1983
oral	once	rat (female)		245–615 mg/kg	LD ₅₀		Worthing 1983
oral (gavage)	1 week	monkey	0.07 mg/kg/day	0.2 mg/kg/day	Plasma and erythrocyte cholinesterase inhibition	First week of a 2-year monkey feeding study	EPA 1998
inhalation	1 hour	rats	1,197 mg/m ³		None	One hour of exposure to an airborne concentration of 1,197 mg/m ³ caused no visible effects in rats.	ACGIH 1991
Intermediate Duration Toxicity							
dermal	21 days	rabbit	50 mg/kg/day	100 mg/kg/day	Plasma and erythrocyte cholinesterase inhibition.	Neurotoxicity, body weight and muscle fasciculation, depressed motor activity, gait abnormalities, and slight tremors occurred at higher doses.	EPA 1998
dermal	21 days	rabbit	5 mg/kg/day	50 mg/kg/day	Dermal irritation		EPA 1998
oral	28 days	human		0.02 mg/kg/day	Plasma cholinesterase was inhibited by 5%–12% within 1 week.	Threshold dose for NOEL/LOEL. 3 groups of 4 males were dosed with caplets including corn oil. Dose levels were 0, 0.02, or 0.07 mg/kg/day.	EPA 1998
Chronic Duration Toxicity							
oral	2 years	monkey	0.02 mg/kg/day	0.07 mg/kg/day	Erythrocyte cholinesterase inhibition	Plasma cholinesterase was inhibited at 0.02 mg/kg/day, which EPA considered a threshold dose	EPA 1999
oral	2 years	rat		0.2 mg/kg/day (M); 0.3 mg/kg/day (F)	Plasma, erythrocyte and brain cholinesterase inhibition	At 0.8 mg/kg/day, epididymal pathology (vacuolation), lung weight change, skin lesions, and ocular effects occurred. At 5.2 mg/kg/day, body weight decreases, mineralization (stomach and other structures), and vacuolation of the nasolacrimal duct (males) occurred. Eye and optic lesions increased in females and became evident in males and included optic nerve pathology (atrophy and neovascularization).	EPA 1998

Table 1. Health Effect Levels of Fenthion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (diet)	1 year	beagle	0.056 mg/kg/day	0.262 mg/kg/day	Plasma and erythrocyte cholinesterase inhibition	Brain cholinesterase inhibited at 1.228 mg/kg/day.	EPA 1998
oral (diet)	2 years	mouse	0.014 mg/kg/day	0.71 mg/kg/day	Erythrocyte cholinesterase inhibition	Plasma cholinesterase inhibited at 0.014 mg/kg/day, but EPA considered the dose a threshold dose for cholinesterase inhibition. No carcinogenicity seen in this study.	EPA 1998
oral (drinking water)	5 generations	mouse		60 ppm	Statistically significant increase in mortality in some litters	No histopathologic change in liver or kidney. Slight increase in time from pairing to delivery of young.	Worthing 1983
oral	1 year	dog	50 mg/kg		No weight loss	No weight loss or decreased food consumption.	Worthing 1983
Developmental/Reproductive Toxicity							
oral (gavage)	gestation days 6–16	rat		1 mg/kg/day	Plasma, erythrocyte and brain cholinesterase inhibition		EPA 1998
oral (gavage)	gestation days 6–16	rat	4.2 mg/kg/day	18 mg/kg/day	Maternal and developmental toxicity	Clinical signs included tremors, lacrimation, exophthalmos, hypoactivity, urine-stained ventral surface, and salivation, and decreased body weight gain. Rate of resorptions and inhibition of fetal brain cholinesterase also increased slightly	EPA 1998
oral (gavage)	gestation days 6–18	rabbit	1.0 mg/kg/day	2.75 mg/kg/day	Brain cholinesterase inhibition	Maternal toxicity.	EPA 1998
oral (gavage)	gestation days 6–18	rabbit	2.75 mg/kg/day	7.5 mg/kg/day	Increased resorptions and unossified metacarpals.	Development and reproduction toxicity	EPA 1998
oral (diet)	2 generations	rat	0.1 mg/kg/day	0.7 mg/kg/day	Cytoplasmic vacuolation of the epithelial ductal cells of the epididymis and inhibition of plasma and erythrocyte cholinesterase.	At the high dose of 5 mg/kg/day, epididymal weight decreased, fertility decreased, maternal weight during pre-mating increased, weight gain during gestation decreased, pup weight gain decreased during lactation, and brain cholinesterase was inhibited.	EPA 1998

Section 4. Toxicokinetics

In animals, fenthion absorbs quickly into the bloodstream through the digestive tract, lungs, and skin and is systemically distributed (Gallo et al. 1991). It is eliminated through the urine and the feces (Thomson 1976). A single dose of the insecticide has prolonged action, suggesting that much of it is stored in body fat and later released for metabolism (HSDB 2003). Fenthion and its metabolites were found in the fat of steers slaughtered 3 days after dermal application of fenthion (Gallo et al. 1991). When 9 mg fenthion per kilogram was applied dermally to cows, 45%–55% of the dose was excreted in urine, 2.0%–2.5% was excreted in feces, and 1.5%–2.0% was recovered in milk (Gallo et al. 1991).

In rats, 86% of an oral dose is eliminated in 7 days (45% in urine and 40% in feces). Metabolites include the sulfone and disulfoxide of both the parent compound and its oxygen analogue (IPCS 2003). The toxicity of fenthion could be altered by interactions with chemicals that interfere with its detoxication, chemicals that have the same mechanism of action, or chemicals that induce hepatic microsomal enzymes.

Section 5. Standards and Guidelines for Protecting Human Health

Regulatory standards and guidance values are summarized in Table 2.

Table 2. Regulatory Standards and Guidance Values

Standard/Guidance	Value	Reference
Acute Reference Dose (aRfD)	0.0007 mg/kg/day*	EPA 1999
Chronic Reference Dose (cRfD)	0.00007 mg/kg/day*	EPA 1999
Voluntary Cancellation in 2004	None	EPA 2005
Occupational Standards: Occupational Safety and Health Administration, American Conference of Governmental Industrial Hygienists: Threshold Limit Value (TLV) 8-hour time-weighted average, skin	0.2 mg/m ³	ACGIH 1994
World Health Organization Acceptable Daily Intakes	0.001 mg/kg/day	Lu et al. 1995

* From EPA 1999 Revised Risk Assessment.

Section 6. References

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. Cincinnati: American Conference of Governmental Industrial Hygienists, Inc. (Cited in EXTOXNET 2003)

ACGIH. 1991. Documentation of the threshold limit values and biological exposure indices. Cincinnati: American Conference of Governmental Industrial Hygienists, Inc.

ACGIH. 1994. Documentation of the threshold limit values and biological exposure indices. Cincinnati: American Conference of Governmental Industrial Hygienists, Inc.

Budreau CH, Singh RP. 1973. Teratogenicity and embryotoxicity of demeton and fenthion in CF no. 1 mouse embryos. Toxicol Appl Pharmacol 24:324–32.

EPA. 1999. Overview of fenthion revised risk assessment. October 13, 1999. Washington, DC: US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Available at <http://www.epa.gov/oppsrrd1/op/fenthion/fenthionsum.htm>.

EPA 1998. Fenthion: The HED Chapter of the Reregistration Eligibility Decision Document (RED), Case #0290, PC Code 053301. Washington, DC: US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Available at <http://www.epa.gov/pesticides/op/fenthion/fenhed.pdf>.

EXTOXNET. 2003. Pesticide information Profile for Fenthion. Cooperative Extension Offices of Cornell University, Michigan State University, Oregon State University, and University of California at Davis. Available at <http://pmep.cce.cornell.edu/profiles/extoxnet/dienochlor-glyphosate/fenthion-ext.html>. Accessed February 10, 2003.

EPA. 2005. Fenthion voluntary cancellation requested. Washington, CD: US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Available at http://www.epa.gov/oppfod01/cb/csb_page/updates/fenthion-volcnl.htm.

Fytizas-Danielidou R. 1971. Effets des pesticides sur la reproduction des rats blancs. I. Lebaycide. Meded Fac Landbauwvet Rijkskuni v Gent 36:1146–50. (Cited in HSDB 2003)

Gallo MA, Lawryk NJ. 1991. Organic phosphorus pesticides. In: Hayes W J, Jr., Laws E Jr, eds. Handbook of pesticide toxicology. New York: Academic Press.

Harding WC. 1979. Pesticide profiles, part one: insecticides and miticides. University of Maryland, Cooperative Extension Service, Bulletin 267. (Cited in EXTOXNET 2003)

Hayes WJ. 1982. Pesticides studied in man. Baltimore: Williams and Wilkins. (Cited in EXTOXNET 2003)

HSDB. 2003. Hazardous Substance Data Bank: Fenthion. National Library of Medicine, National Toxicology Program. Available at <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> Accessed February 10, 2003.

IPCS 2003. Fenthion—Data sheets on pesticides No. 23. International Programme on Chemical Safety (IPCS, INCHEM); Sponsored jointly by FAO and WHO. Available at http://www.inchem.org/documents/pds/pds/pest23_e.htm. Accessed January 2003.

Joubert JPJ, Minne JA. 1979. The safety of fenthion 20% m/v when applied topically to pregnant cows. J S Afr Vet Assoc 50:47–8.

Karalliedde L, Senanayake N, Ariaratnam A. 1988. Acute organophosphorous insecticide poisoning during pregnancy. Human Toxicol 7:363–4.

Lu FC. 1995. A review of the acceptable daily intakes of pesticides assessed by the World Health Organization. Regul Toxicol Pharmacol 21:351–64.

NCI. 1979. Bioassay of fenthion for possible carcinogenicity. Technical report series no. 103. Bethesda, MD: US Department of Health, Education, and Welfare. Publication No. (NIH) 79-1353.

OHM/TADS (Oil and Hazardous Materials/Technical Assistance Data System). 2003. Developed by the Office of Water and Waste Management of the United States Environmental Protection Agency. 1985. Available at <http://csi.micromedex.com/DATA/OT/OT1072.HTM?Top=Yes>. Accessed January, 2003.

Shepard TH. 1986. Catalog of teratogenic agents, 5th Ed. Baltimore: Johns Hopkins University Press; 5–10.

Simmon V, Poole DC, Newell GW. 1976. In vitro mutagenic studies of twenty pesticides. Toxicol Appl Pharmacol 37:109.

Thomson WT. 1976. Insecticides, acaricides and avicides. In: Agricultural Chemicals, Book I. Fresno, CA: Thomson Publications. (Cited in EXTOXNET 2003)

TOXNET. 1985. National Library of Medicine's Toxicology Data Network. Hazardous Substances Databank. Bethesda, MD: US Department of Health and Human Services Public Health Service. National Institutes of Health, National Library of Medicine. (Cited in EXTOXNET 2003)

Tucker R, Crabtree DG. 1970. Handbook of toxicity of pesticides to wildlife. Washington, DC: US Department of Agriculture, Fish and Wildlife Service. Bureau of Sport Fisheries and Wildlife. (Cited in EXTOXNET 2003)

Witt JM. ed, 1985. Chemistry, biochemistry, and toxicology of pesticides. Proceedings of an extension service short course at Oregon State University. Eugene, OR: Pest Control Education Program. (Cited in EXTOXNET 2003)

Worthing CR. ed, 1983. The pesticide manual: A world compendium. Croydon, England: The British Crop Protection Council. (Cited in EXTOXNET 2003)

Worthing CR, Walker SB. 1987. The pesticide manual, 8th ed. Lavenham, Suffolk, England: Lavenham Press Ltd: 387 (Cited in HSDB 2003)

Malathion (CAS Number 121-75-5)

Malathion is an organophosphate insecticide used extensively in agricultural and horticultural applications. It also is used in regional pest eradication programs to control boll weevil, medfly, and mosquitoes (ATSDR 2001). The use of malathion by ground application and aerial spraying is generally the preferred method of eradicating adult mosquitoes associated with West Nile Virus because of its relatively low toxicity to humans, other mammals, and birds compared with other organophosphate insecticides (EPA 2000a,b). Because malathion is toxic to aquatic organisms, direct application to bodies of water is generally avoided.

Section 1. Environmental Factors

Malathion degrades rapidly in the environment (ATSDR 2001). Malathion in the open environment undergoes hydrolysis, biodegradation, and photolysis roughly in that order of importance. The rate of transformation depends heavily on pH and organic content of the environmental medium.

Hydrolysis is not significant in water at pH 5. At pH 7, malathion may completely hydrolyze in 6–7 days, whereas at pH 9, hydrolysis is complete in less than 12 hours (EPA 2000a; ATSDR 2001). Under least-favorable conditions (i.e., low pH and little organic content), malathion can persist with a half-life of months or even years. However, under most conditions typically encountered in the environment, the half-life for hydrolysis in water appears to be roughly 7–14 days (ATSDR 2001).

In soil, malathion is expected to be highly mobile, but it should not volatilize significantly. Biodegradation in soil is rapid, with 80%–95% biodegradation occurring in 10 days; it may be much faster, depending on soil content. Its half-life in soil is estimated by various authors from <1 day to 6 days, depending on the pH and the degradation pathway studied (ATSDR 2001).

If released to air, malathion should exist solely as a vapor in the ambient atmosphere and be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the estimated half-life for this reaction in air is ~5 hours. Malathion may also undergo photolysis (ATSDR 2001).

Section 2. Potential for Exposure

The general population is not likely to be exposed to large amounts of malathion. However, some exposure to residues of malathion is possible; as many studies show, malathion has been detected in foods and atmosphere samples. Populations living within or near areas of heavy malathion use are at increased risk for exposure to relatively larger amounts of malathion through dermal contact with contaminated plants, by inhalation of the mist formed from the applied insecticide, or by ingestion of water or foodborne residues. Dermal contact appears to be the major route of exposure. Ingestion also can be an important route, but inhalation has not been shown to be a significant route of exposure to malathion (ATSDR 2001).

Section 3. Health Effects/Toxicity

The data reviewed by ATSDR for this summary strongly support the hypothesis that health effects from malathion actually result either from the oxygen analogue, malaaxon (CAS # 1634-78-2; C₁₀H₁₂O₇PS), or phosphorus thionate impurities. Malaaxon is both a metabolite and an environmental degradation by-product. The phosphorus thionates are impurities, environmental degradation by-products, and possibly precursors for production. This hypothesis is being investigated under the authorities of the Federal Insecticide, Fungicide, and Rodenticide Act. In the
April 2005

interim, the chemical similarities of malathion to malaoxon and the thionates justify the use of malathion as a surrogate for these potentially more toxic metabolites and degradation products (EPA 2000a).

Health Effect in Humans Exposed to Malathion

The principal toxicologic effect of malathion and other organophosphate insecticides is cholinesterase inhibition. Information about health effects in humans exposed to organophosphate insecticides comes from case reports, case studies, statistical surveys, and epidemiologic studies. Many of the case reports cover people who have ingested malathion unintentionally or have attempted suicide by ingestion. Other case reports involve private residents who have applied malathion formulations improperly to their lawns and gardens or were exposed through inadequate packaging or spillage. In many cases, only minor symptoms developed, and were related more to the noxious odor than to the cholinergic effects. Most epidemiologic studies involve workers who were engaged in manufacturing, formulating, or applying malathion. A few surveys of populations in areas where malathion has been used to control mosquitoes or fruit flies also are available. Many of these studies have been reviewed by Blondell (1998) and generally are limited by such factors as inadequate documentation of exposure levels and reporting biases.

- **Common early signs or mild symptoms** of acute cholinergic poisoning include miosis (pinpoint pupils), headache, nausea/vomiting, dizziness, muscle weakness, drowsiness, lethargy, agitation, and anxiety.
- **Moderate or severe poisoning** can result in chest tightness, difficulty breathing, bradycardia, tachycardia, hypertension, pallor, abdominal pain, incontinence, diarrhea, anorexia, tremor/ataxia, fasciculation, lacrimation, heavy salivation, profuse sweating, blurred vision, poor concentration, confusion, and memory loss.
- **Life-threatening or very severe signs and symptoms**, such as coma, seizures, respiratory arrest, pulmonary edema, loss of reflexes, and flaccid paralysis, can occur at high doses, such as in the cases of attempted suicide.

Malathion also may be slightly irritating to the skin and eyes. In addition to acute poisoning, chronic effects such as peripheral neuropathy, neurobehavioral effects, and the development of allergic sensitivity have been reported, but these effects are not well documented (Blondell 1998).

Experimental Studies in Humans

Laboratory studies conducted by Milby and Epstein (1964) in 87 volunteers showed that a single exposure to 10% malathion (95% pure) induced contact sensitization in almost half the participants and that 0.1 and 0.01% concentrations of 99.3% malathion evoked positive responses in previously sensitized participants.

Moeller and Rider (1962) conducted a controlled study in which male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dosage of 0.11 mg malathion/kg/day for 32 days, 0.23 mg malathion/kg/day for 47 days, or 0.34 mg malathion/kg/day for 56 days. Plasma and erythrocyte cholinesterase was determined twice weekly before, during, and after administration of malathion. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or erythrocyte cholinesterase activity, nor did it induce clinical signs. In phase three, 0.34 mg malathion/kg/day for 56 days caused a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar depression in erythrocyte

cholinesterase was observed, but it occurred later. Routine blood counts conducted at the end of each study period did not detect any significant changes. No remarkable alterations in urinalyses were observed.

Male volunteers were exposed by inhalation to aerosol bombs that contained 0%, 5%, or 20% of malathion for 2 hours/day for 42 days (Golz 1959). Exposure concentrations were calculated as 0, 5.3, 21, and 85 mg/m³ by adjusting the application rate. These exposures did not result in changes in erythrocyte or plasma cholinesterase activity. The only effects noted were nasal and eye irritation at the highest concentration.

Health Effects Possibly Related to Municipal Use of Malathion for Mosquito Control

The Florida Department of Health attempted to evaluate adverse health effects potentially related to spraying to control the Mediterranean fruit fly outbreak of 1998 (CDC 1999). The estimated crude rate of malathion-related illnesses associated with the eradication effort was calculated at nine cases per 10,000 residents in the exposed areas. Of 230 reports of illness received, 34 (15%) were classified as probable, and 89 (39%) were classified as possible. Among these 123 cases, the acute signs and symptoms reported were respiratory (71%), gastrointestinal (63%), neurologic (60%), dermal (23%), and ocular (19%).

The report highlighted four cases in humans, two of whom were exposed after spraying:

- One person exposed while removing a pool cover with malathion residue.
- One person was exposed by direct contact with pesticide residue on fresh grass trimmings.
- One person worked outside on his roof during aerial spraying.
- One person suffered an acute exacerbation of a chronic asthmatic condition.

The California Department of Health Services conducted indirect assessments and symptom prevalence surveys to determine whether aerial application of malathion bait used to eradicate the Mediterranean fruit fly in Santa Clara County, California, posed a health hazard to the public (Kahn et al. 1992). In one indirect assessment, the records of a major hospital emergency department were compared during the first 5 weeks of spraying, the 2 weeks before spraying, and a corresponding 7-week period the year before. The number of visits did not differ significantly, and none of the hospital emergency departments in the county reported cases of pesticide poisoning. Another assessment of the frequency of ambulance calls in the same periods also showed no significant differences, but this assessment was relatively insensitive. An assessment for an increase in cases of asthma at a medical school hospital showed no increase, but the number of cases in this study were too small for definitive conclusions. In the symptom prevalence surveys—one an on-site home visit study, the other a telephone survey—no evidence was found that indicated the aerial spraying of malathion caused any detectable increase in symptoms.

Studies to determine whether an increase in fetal loss, low birthweight, and birth defects occurred in the same malathion program in Santa Clara County, California, were negative (Grether et al. 1987; Thomas et al. 1992). However, a statistically significant association between the incidence of gastrointestinal anomalies in offspring and exposure to malathion during the second trimester of pregnancy and a moderate association between stillbirths was reported by Thomas et al. (1992). When offspring of fathers exposed to malathion were examined, no increase in congenital malformations were found (Garcia et al. 1998).

Cases of possible immediate and delayed hypersensitivity reactions to malathion or to a corn syrup bait were investigated among 10 people who had developed dermatitis within a week of exposure to aerial application of malathion in Southern California (Schanker et al. 1992). The authors found one case of possible immediate IgE reaction to malathion bait and another case of irritant reaction to malathion and to the bait but no cases of delayed type hypersensitivity. Schanker et al. (1992) noted that, because of the low participation rate in the study, no specific conclusions could be drawn regarding the rate of sensitivity in the population.

Health Effects in Laboratory Animals

Studies in laboratory animals exposed to malathion dermally, orally, or by inhalation are summarized in Table 1, with no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) indicated.

At very high doses, malathion exposure can lead to death. Acute dermal and ocular exposure can cause slight irritation. Otherwise, most of the studies indicate that similar cholinergic effects, along with serious decreases in the plasma, erythrocyte, and brain cholinesterase, occur regardless of route of exposure or duration, depending on the dose. Inhibition of cholinesterase, however, did not necessarily result in overt signs of cholinergic toxicity. The levels of cholinesterase generally return to preexposure levels after exposure ceases. Therefore, decreased levels of the cholinesterases do not necessarily result in nervous system effects. One study in hens indicated that exposure to malathion was not associated with delayed neurotoxicity.

Other effects observed in laboratory animals that have been exposed to malathion for acute, intermediate, or chronic durations included evidence of liver or kidney toxicity, hematologic effects, and immunologic effects. Other effects after inhalation exposure to malathion included irritation and mild lesions in the nasal cavity, larynx, and lungs.

Fetal anomalies were found when pregnant rats or pregnant rabbits were given oral doses of malathion by gavage, although increased mean resorption sites were found in rabbits and fetal deaths were found in rats at maternally toxic doses. No effects on reproductive ability of male or female rats were found when they were given food containing malathion before, during, and after mating for two generations. However, parental body weight decreased during gestation and lactation, and pup body weights decreased in the F₁ and F₂ pups during late lactation. In addition, malathion produces reversible damage to spermatogenic tissue of male rats and minor histopathologic lesions in testes, ovaries, and uterus of rats.

Carcinogenicity

The International Agency for Research on Cancer (IARC) classifies malathion as Group 3, i.e., “not classifiable as to its carcinogenicity to humans” (IARC 1983, 2001), because of lack of evidence of carcinogenicity in experimental animals and lack of human data. In two recent studies of animals exposed to malathion in the diet, increased incidence of liver tumors was observed in male and female mice (Slauter 1994) and female rats (Daly 1996a) only at doses considered excessive (severe inhibition of cholinesterase activity and marked decreased body weight).

In addition, in a study in which malaoxon, the cholinesterase-inhibiting metabolite of malathion, was administered to rats in their diet, equivocal evidence of carcinogenicity was reported on the basis of increased incidence of thyroid C-cell neoplasms in both male and female rats (NCI 1979a, Huff et al.

1985). However, EPA concluded that this study was inadequate to provide a definitive determination of the carcinogenicity of malaoxon in the rats because of limitations of the study. In a recent study of rats exposed to malaoxon in the diet, mononuclear cell leukemia was observed in the male rats (Daly 1996b). However, the findings in this study are not considered treatment-related because statistical significance occurred only in males at a dose determined to be excessive (increased death rates and severe cholinesterase activity) because no dose-response resulted and because incidences were within the historical control range (EPA 2000c).

On the basis of these and earlier studies on malathion that provided inconclusive evidence of carcinogenicity (because of deficiencies in study design, evaluation, and reporting) (IARC 1983, NCI 1978, 1979b), EPA has classified malathion as indicating “suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential.” Specifically, the EPA evaluation is based on (1) liver tumors in rats and mice only at excessive doses of malathion; (2) a few rare tumors—oral palate mucosa in female rats and nasal respiratory epithelium in male and female rats exposed to malathion; however, these tumors cannot be determined as either treatment-related or the results of random occurrence; and (3) malaoxon is not carcinogenic in male or female rats (EPA 2000c).

Genotoxicity

Genetic toxicology studies indicate that malathion did not cause gene mutations in bacteria (Traul 1987) or unscheduled DNA synthesis in cultured rat hepatocytes (Pant 1989). Also, malathion was neither clastogenic nor aneugenic up to doses that showed clear cytotoxicity for the target tissues in vivo (Gudi 1990). Although other studies indicated that malathion was positive for chromosomal aberrations in in vivo and in vitro studies (Flessel et al. 1993), the relevance of these findings is not clear because the results were positive only at cytotoxic doses or the types of induced aberrations were asymmetric and therefore not consistent with cell survival. In addition, the purity of the test substance was an issue (Yang 2000). Results were weak but positive for sister chromatid exchange induction at high, cytotoxic doses (Galloway et al. 1987). According to EPA, the weight of evidence does not support a mutagenic hazard or a role of mutagenicity in the carcinogenicity associated with malathion (EPA 2000c).

Evaluation of data for malaoxon by EPA indicates that malaoxon is not mutagenic in bacteria but is a confirmed positive without S9 activation in the mouse lymphoma forward gene mutation assay (EPA 2000c). Malaoxon was not clastogenic in cultured Chinese hamster ovary cells. However, the findings from the mouse lymphoma assay suggest that malaoxon may induce both gene mutations and chromosome aberrations (Myhr and Caspary 1991). Nevertheless, malaoxon is not carcinogenic in rats (Yang 2000).

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
ACUTE DURATION TOXICITY							
dermal	once	human		0.01% concentration of 95% pure malathion	Contact dermatitis in previously sensitized people	A single exposure to 10% induced contact sensitization in almost 50% of 87 volunteers.	Milby and Epstein 1964
dermal	once	rat		>4,400 mg/kg	LD ₅₀	The LD ₅₀ was >4,400 mg/kg.	Gaines 1960; Kynoch 1986b; NIOSH 1976.
dermal	once	rat		2 mg/kg	Increased serum histamine levels 4 hours after dosing	Malathion (>99% pure) was applied in dimethylsulfide (DMSO) to the shaved skin under an occlusive bandage at 2–2,000 mg/kg.	Rodgers and Xiong 1997a
dermal	once	mouse	2 mg/kg	20 mg/kg	Increased serum histamine levels 4 hours after dosing	Malathion (>99% pure) was applied in DMSO to the shaved skin under an occlusive bandage at doses of 2–2,000 mg/kg.	Rodgers and Xiong 1997a
dermal	2 days 10 sec/day	mouse	2% malathion solution	8% malathion solution	Mild dermatitis and transient conjunctivitis; lethargy and anorexia	The mice were totally submerged in a solution of 2% or 8% malathion. No effects were found on cellular immune response to mitogens.	Relford et al. 1989
dermal		rabbit			Slight dermal irritation	Dose not reported	Liggett and Parcell 1985a
dermal		guinea pig			Not a skin sensitizer	Dose not reported	Kynoch and Smith 1986
dermal	3 days	dog		5% solution	34% Inhibition of erythrocyte cholinesterase, 36% inhibition of plasma cholinesterase	An unspecified amount of the solution was sprayed over the entire body.	Vestweber and Kruckenberg 1972
ocular		rabbit			Slight conjunctival irritation	Dose not reported	Liggett and Parcell 1985b

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral	once	rat		200–12,500 mg/kg	LD ₅₀ range	Reported LD ₅₀ values depend on the purity of the compound, with technical-grade malathion being more toxic than the pure compound. Young animals are more susceptible than older animals.	Hazelton and Holland 1953; Aldridge et al. 1979; NIOSH 1976; IARC 1983; HSDB 2002; Lu et al. 1965; Gaines 1969; Mendoza 1976; Umetsu et al. 1977.
oral	once	mouse		1,000–4,059 mg/kg	LD ₅₀ range	Reported LD ₅₀ values depend on the purity of the compound, with technical-grade malathion being more toxic than the pure compound.	Hassan and Dauterman 1968; Hazleton and Holland 1953; IARC 1983.; Rodgers et al 1986; Talcott et al. 1979; Umetsu et al. 1977
oral	once	rabbit		1,200 mg/kg	Death	Five of six rabbits died 6 hours after dosing.	Weeks et al. 1977
oral	once	rat		500 mg/kg	Increased activities of liver enzymes in serum indicative of liver toxicity	Technical-grade malathion (96%)	Enan 1983
oral	once	rat		4.4 mg/kg	Decreased hematocrit and platelet counts	Malathion 99%	Lox 1983
oral (corn oil)	once	rat	1,000 mg/kg	2,000 mg/kg	Neurotoxicity—decreased motor activity and clinical signs; decreased plasma and erythrocyte cholinesterase activity	No inhibition of brain cholinesterase at any dose. Technical-grade malathion (96.4%)	Lamb 1994a
oral	once	rat		1,950 mg/kg	Hemorrhage and hyperemia in the lungs; congestion and hemorrhage in the heart; liver necrosis, congestion and hemorrhage; kidney congestion, degenerative changes in tubular epithelium	Technical-grade malathion (95%)	Piramanayagam et al. 1996

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral	once	rat		600 mg/kg	Increased spontaneous motor activity; dose-related increase in inhibition of cholinesterase and neurotoxic esterase in brain and spinal cord	At the highest dose of 2,000 mg/kg, brain and spinal cord cholinesterase activities were inhibited by 56% and 47%, respectively.	Ehrich et al. 1993
oral	7 days	rat	163 mg/kg/day	411 mg/kg/day	Dizziness, recurrent convulsions, tremors; severe respiratory distress	The effects were more serious at the highest dose of 593 mg/kg/day, and tachycardia occurred at the highest dose.	Ojha et al. 1992
oral	8 days (gestation days 6–13)	rat	138 mg/kg/day	276 mg/kg/day	34% Inhibition of brain cholinesterase	Convulsions, tremor, and ataxia occurred at the high dose of 827 mg/kg/day. Also at 827 mg/kg/day, 47% inhibition of brain cholinesterase occurred in the pups.	Matthews and Devi 1994
oral (gavage)	3 day	rat		500 mg/kg/day	Dyspnea; decreased glutathione content and increased lipid peroxide in liver and kidney	Pregnant rats were treated on gestational days 6, 10, and 14.	Prabhakaran et al. 1993
oral (gavage)	6 days	rat		225 mg/kg/day	increased pituitary gland weight and serum prolactin levels, decrease in pituitary prolactin	Purity not specified.	Simionescu et al. 1977
oral (drinking water)	14 days	rat		89 mg/kg/day	Changes in clotting factors	At low dose, increase in fibrinogen and decrease in clotting factor XII; at 111 mg/kg/day, decrease in clotting factor II and XII and increase in factor X.	Lox 1985
oral	once	mouse		720 mg/kg	Tremors, fasciculation, 36% inhibition of brain cholinesterase; suppression of primary IgM response	The experimental result suggested that cholinergic stimulation plays a role in the organophosphate-induced suppression of the splenic antibody-forming cell. Erythrocyte and plasma cholinesterase were inhibited by 47% and 59% at 240 mg/kg.	Casale et al. 1983

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral	once	mouse		715 mg/kg	Increased proliferative response of splenocytes after exposure to metabolic activators	Metabolic activation was necessary for this response.	Rodgers and Ellefson 1990
oral	once	mouse		450 mg/kg	Stimulation of macrophage function	Mediators from cells may contribute to the increase in macrophage function.	Rodgers and Xiong 1996a
oral	once	mouse	1 mg/kg	10 mg/kg	Increased serum histamine levels	The consequences of the mast cell degranulation that results from malathion administration is not localized and symptoms such as lacrimation, rashes, and irritation of mucous membranes resulting from aerial malathion spraying may be systemic.	Rodgers and Xiong 1997b
oral (gavage)	14 days	mouse		0.1 mg/kg/day	Degranulation of mast cells associated with the small intestine	Malathion elevated macrophage function and led to mast cell degranulation in all tissues examined.	Rodgers and Xiong 1997c
oral	once	rabbit		188 mg/kg	50%–60% Inhibition of brain cholinesterase	Inhibition was observed in four brain areas—cerebral right frontal lobe, cerebral left frontal lobe, cerebellum lateralis, and cerebellum flocculus.	Vijayakumar and Selvarajan 1990
oral	once	rabbit	12 mg/kg	120 mg/kg	27% Inhibition of erythrocyte cholinesterase	Cholinesterase activity was inhibited by 61% at 600 mg/kg and 79% at 1,200 mg/kg.	Weeks et al. 1977
oral	once	hen	1,007.5 mg/kg		Acute delayed neurotoxicity	No signs occurred of delayed neurotoxicity. Technical-grade malathion (93.6%)	Fletcher 1988
inhalation	5–10 minutes	human	21 mg/m ³	85 mg/m ³	Nasal irritation	No other signs of toxicity occurred.	Golz 1959
inhalation	4 hours	rat			LC ₅₀	The LC ₅₀ was >5,200 mg/m ³ . Technical-grade malathion (96%/98%)	Jackson et al. 1986
inhalation	6 hours	rabbit	65 mg/m ³	123 mg/m ³	38% Inhibition of erythrocyte cholinesterase	No signs of toxicity or deaths occurred.	Weeks et al. 1977

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Intermediate Duration Toxicity							
dermal	30 days once/day	guinea pig		200 mg/kg/day	Death; 45%–52% inhibition of brain and erythrocyte cholinesterase at 200 and 400 mg/kg/day	Death occurred in 4/10 during days 20–30. Other effects included hyperkeratosis of the skin.	Dikshith et al. 1987
dermal	3 weeks 6 hr/day 5 d/wk	rabbit	50 mg/kg/day	300 mg/kg/day	Inhibition of erythrocyte, plasma, and brain cholinesterase at 300 and 1,000 mg/kg/day	No clinical signs of toxicity; no effects on body weight, food consumption, organ weights, hematologic, clinical chemistry parameters; no dermal reactions; gross and histologic examination unremarkable. Technical-grade malathion (94%)	Moreno 1989
oral (capsule)	32–56 days once a day	human	0.23 mg/kg/day	0.34 mg/kg/day	25% Depression of plasma and erythrocyte cholinesterase	No clinical signs of toxicity, no effects on blood counts or urinalyses. The malathion (purity not reported) was given in corn oil in a capsule.	Moeller and Rider 1962
oral (diet)	4–6 weeks	rat		62–68 mg/kg/day	50% Inhibition of brain, erythrocyte and plasma cholinesterase	No other adverse effects were noted.	NIOSH 1976; IARC 1983
oral (diet)	8–22 weeks	rat	2.3 mg/kg/day	5.8 mg/kg/day	Reduced humoral and cell-mediated immune response to antigens	No effect was seen on serum IgG or IgM levels.	Banerjee et al 1998
oral (diet)	90 days	rat	4 mg/kg/day	352–395 mg/kg/day	Inhibition of brain, erythrocyte and plasma cholinesterase	At higher doses (1,486 and 1,575 mg/kg/day), cholinergic signs of toxicity, greater inhibition of brain cholinesterase, and reduced body weight gain were observed. Technical-grade malathion (96.4%)	Lamb 1994b
oral (diet)	90 days	rat	38 mg/kg/day	75 mg/kg/day	Increased excitability as shown by changes in electroencephalogram and electromyogram	Running time was dose-dependent and indicated increased nervous excitability. Cholinesterase in the cerebral cortex was inhibited by 18% in rats sacrificed after 21 days.	Desi et al. 1978

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (drinking water)	6 months	rat		0.15 mg/kg/day	Prolonged prothrombin and partial thromboplastin times; hepatocyte degeneration	No effect was observed on fibrinogen, coagulation factors II, V, VII, or X, or on hematocrit or platelet counts	Lox and Davis 1983
oral (diet)	3–12 weeks	mouse	4.2 mg/kg/day	10.5 mg/kg/day	Decreased humoral and cell-mediated response to antigens	No effect was observed on serum IgG or IgM levels	Banerjee et al. 1998.
oral (gavage)	90 days	mouse		0.1 mg/kg/day	Increased macrophage function and mast cell degranulation	Malathion administration elevated some macrophage functions and led to mast cell degranulation in all tissues examined.	Rodgers and Xiong 1997d
oral (gavage)	15 weeks	rat		10 mg/kg/day	Significant decrease in serum cortisol and aldosterone levels, and congestion in zona reticularis of adrenal glands	No effects were observed on T3, T4, testosterone, estradiol 17-β levels.	Ozmen and Akay 1993
oral (gavage)	21 weeks	rabbit	0.5 mg/kg/day	2.5 mg/kg/day	Decrease in humoral and cell-mediated immunity	No effect was observed on serum IgG or IgM levels	Banerjee et al. 1998
oral (capsule)	6 weeks, 5 days/week	rabbit	10 mg/kg/day	25 mg/kg/day	25%–30% Inhibition of erythrocyte cholinesterase	The purity of malathion was not specified, and little detail was presented.	Desi et al. 1978
oral (capsule)	6 weeks, 5 days/week	rabbit		5 mg/kg/day	Decreased humoral immune response to <i>Salmonella</i> vaccine	The purity of malathion was not specified, and little detail was presented.	Desi et al. 1978
oral (capsule)	28 days	dog		125 mg/kg/day	Inhibition of plasma and erythrocyte cholinesterase	The dogs treated with malathion at ≥120 mg/kg/day had diarrhea.	Fischer et al. 1988
oral (capsule)	1 year	dog		62.5 mg/kg/day	Inhibition of plasma and erythrocyte cholinesterase	No deaths and no clinical signs of toxicity occurred at doses up to 250 mg/kg/day. Technical-grade malathion (95%)	Tegeris Laboratories, Inc. 1987
inhalation	42 days	human	21 mg/m ³	85 mg/m ³	Nasal and eye irritation	Irritation occurred during the first 5–10 minutes of each exposure. No effects were observed on erythrocyte or plasma cholinesterase activity.	Golz 1959

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
inhalation.	13 weeks 6 hrs/day 5 days/wk	rat		100 mg/m ³	Inhibition of plasma and erythrocyte cholinesterase; slight to moderate lesions in nasal cavity and larynx	Clinical signs (urogenital staining, excessive salivation, ungroomed fur) occurred mainly at the highest level (2,010 mg/m ³) but also at 100 and 450 mg/m ³ .	Beattie 1994
Chronic Duration Toxicity							
oral (diet)	2 years	rat	2.4 mg/kg/day	29–35 mg/kg/day	Inhibition of erythrocyte and plasma cholinesterase	Increased mortality in males occurred at 359 mg/kg/day and higher. At higher doses, other effects included decreased body weight gain, effects on hematologic and clinical chemistry parameters, and organ weights. Histopathologic effects included lesions in the nasal mucosa and nasal pharynx and chronic nephropathy. At the highest dose (868 mg/kg/day), incidence of combined hepatocellular adenoma and carcinoma increased in female rats.	Daly 1996a
oral (diet)	2 years	rat		166 mg/kg/day	Chronic inflammation of the stomach and stomach ulcers; fatty metamorphosis of the liver	No clear evidence was found of an association of tumor incidence with administration of malathion.	NCI 1979
oral (diet)	80 weeks	mouse		2980 mg/kg/day	Coughing and sneezing from week 72 until end of study; generalized body tremor from weeks 71–79	No histologic evidence was found of treatment-related non-neoplastic or neoplastic lesions.	NCI 1978

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (diet)	18 months	mouse	17.4–20.8 mg/kg/day	143–167 mg/kg/day	Inhibition of plasma and erythrocyte cholinesterase; increased incidence of non-neoplastic nasal lesions	At higher doses ($\geq 1,476$ mg/kg/day), effects included decreased body weight and food consumption, increased liver weight, and increased incidence of hepatocellular hypertrophy. Brain cholinesterase was inhibited at 2,978–3,448 mg/kg/day. At 1,476 and 2,978 mg/kg/day, male mice had increased incidence of combined hepatocellular carcinoma and adenoma.	Slauter 1994
Developmental/Reproductive Toxicity							
oral (gavage)	2 days	rat		40 mg/kg/day	Reversible damage of spermatogenic tissue	The damage included a reduced number of Sertoli and Leydig cells, reduced A-spermatogonia, and reduced pachytene spermatocytes.	Krause et al. 1976
oral (gavage)	20 days	rat		20 mg/kg/day	Reversible damage of spermatogenic tissue	The damage included reduced numbers of Sertoli cell, A-spermatogonia and pachytene spermatocytes.	Krause et al. 1976
oral	3 days, gestation days 28–30	rabbit		126 mg/kg/day	79% Decrease in fetal plasma cholinesterase, 66% decrease in fetal brain cholinesterase	The results show that malathion and/or metabolites cross the placenta.	Machin and McBride 1989
oral (gavage)	3 day	rat		500 mg/kg/day	Fewer implants per dam; reduced number of live fetuses per litter and fetal weight	Pregnant rats were treated on gestational days 6, 10, and 14.	Prabhakaran et al. 1993
oral (diet)	7 days	rat	18.5 mg/kg/day	163 mg/kg/day	Minor histopathologic lesion in testes, ovaries, and uterus	Similar effects with more severity occurred at higher doses.	Ojha et al. 1992
oral (gavage)	gestation days 6–15	rat	800 mg/kg/day		No indication of developmental toxicity in offspring	Maternal toxicity (urine staining, decreased body weight and food consumption) at 800 mg/kg/day, but not at 400 mg/kg/day. Malathion 94%	Lochry 1989

Table 1. Health Effect Levels of Malathion in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (gavage)	gestation days 6–18	rabbit	25 mg/kg/day	50 mg/kg/day	Increased mean resorption sites	Maternal toxicity (anorexia, soft stools) at 100 mg/kg/day, decreased body weight gain at 50 mg/kg/day. Malathion 92.4%. No effects observed on fertility, number of corpora lutea, or implantation sites.	Siglin 1985a
oral (gavage)	gestation days 6–18	rabbit	400 mg/kg/day		No gross abnormalities	Maternal toxicity at 200 and 400 mg/kg/day: increased mortality, tremors, reduced activity, increased salivation. Maternal NOAEL 100 mg/kg/day. Malathion 92.4%	Siglin 1985b
oral (gavage)	14 days	rat		10 mg/kg/day	Significant increase in serum FSH levels	No significant changes in serum LH and testosterone, testis and seminal vesicles weight; spermatogenic epithelium was normal.	Krause 1977
oral (gavage)	12 weeks	rats		44–45 mg/kg/day	Edema, congestion, and desquamation of lining cell of seminiferous tubules; decreased seminal vesicle pH, protein content, relative testes weight, and enzyme activities	Malathion was 90% pure.	Balasubramanian et al. 1987a, 1987b
oral (diet)	2 generations	rat	131–153 mg/kg/day	394–451 mg/kg/day	Decreased pup body weights in F1 and F2 pups during late lactation	Parental NOAELs were 394–451 mg/kg/day, and LOAELs were 612–703 mg/kg/day on the basis of decreased body weights during gestation and lactation and decreased F1 pre-mating body weights.	Schroeder 1990
oral (gavage)	15 weeks	rat		10 mg/kg/day	Hyperemia of the veins of the testes and degenerated testicular tubuli	No histopathologic effects on the ovaries were observed	Ozmen and Akay 1993.

Section 4. Toxicokinetics

Malathion appears to be readily absorbed after oral dosing and readily excreted, according to a study in orally dosed rats, where >90% of the dose was excreted (mostly in urine) within 72 hours, with most excretion in the first 24 hours (Reddy et al. 1989). Malathion does not appear to bioaccumulate in organs or tissues (HSDB 2002; Reddy et al. 1989). A dermal absorption study in humans determined that about 10% is absorbed dermally (Feldman and Maibach 1970). The major metabolites of malathion are malathion dicarboxylic acid and malathion monocarboxylic acid (Reddy et al. 1989). Although malaoxon is a minor metabolite, it is the active cholinesterase-inhibiting metabolite of malathion. Malathion's mode of toxic action is the inhibition of cholinesterase, which is caused by malaoxon. The toxicity of malathion could be altered by interactions with chemicals that interfere with its detoxication, with chemicals that have the same mechanism of action, or with chemicals that induce hepatic microsomal enzymes.

Section 5. Standards and Guidelines for the Protection of Human Health

Regulatory standards and guidance values are summarized in Table 2.

ATSDR has developed several minimal risk levels (MRLs) for malathion. An intermediate oral MRL of 0.02 mg/kg/day was derived on a NOAEL of 0.23 mg/kg/day for inhibition of plasma and erythrocyte cholinesterase activities in humans (Moeller and Rider 1962), using an uncertainty factor of 10 for the protection of sensitive humans populations. The LOAEL was 0.34 mg/kg/day. The chronic oral MRL of 0.02 mg/kg/day is based on a NOAEL of 2 mg/kg/day for inhibition of plasma and erythrocyte cholinesterase activities in male rats administered malathion in the diet for 2 years Daly (1996a) (Table 1), using an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for the protection of sensitive populations). The LOAEL was 29 mg/kg/day.

For inhalation exposure, an acute MRL of 0.2 mg/m³ was based on a NOAEL of 65 mg/m³ for inhibition of erythrocyte cholinesterase activity in rabbits (Weeks et al. 1977) (Table 1), using an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for the protection of sensitive populations). The LOAEL was 123 mg/m³. An intermediate inhalation MRL of 0.02 mg/m³ was based on a LOAEL of 100 mg/m³ for upper respiratory tract effects in rats (Beattie 1994) (Table 1). An uncertainty factor of 1,000 was applied (10 for animal to human extrapolation, 10 for the use of a LOAEL, and 10 for the protection of sensitive populations).

EPA (2000d) has proposed several risk assessment values in addition to the chronic oral reference dose (RfD) of 0.02 mg/kg/day based on the study by Daly (1996a). A proposed acute oral RfD of 0.5 mg/kg for 1-day exposure is based on a dose of 50 mg/kg/day, which resulted in decreased body weight in rabbits exposed on gestation days 6–18 in the study by Siglin (1985a). Although the 50-mg/kg/day dose was a LOAEL for decreased body weight during the 13 days of exposure, EPA considered this dose to be a NOAEL for decreased body weight for 1 day of exposure and applied an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability). EPA also proposed using an air concentration LOAEL of 100 mg/m³, 6 hours/day, 5 days/week, for 13 weeks in the study by Beattie (1994), converted to a dose of 25.8 mg/kg/day for short-, intermediate-, and long-term inhalation risk assessment. The uncertainty factor was 1,000 (10 for use of LOAEL, 10 for interspecies extrapolation, and 10 for human variability) to yield an inhalation risk assessment value of 0.03 mg/kg/day.

EPA also proposed a short- and intermediate-term dermal risk assessment value of 0.5 mg/kg/day on the basis of a NOAEL of 50 mg/kg/day for cholinesterase inhibition in rabbits exposed dermally for 6 hours/day, 5 days/week, for 3 weeks in the study by Moreno (1989).

Using these proposed values for the risk assessments for public health mosquito uses, EPA (2000d) concluded that the risk estimates for adults and toddlers for combined dermal and inhalation exposure did not exceed EPA's levels of concern for residential bystander inhalation and dermal exposure from truck fogger and aerial ULV mosquito-control applications. This assessment included incidental oral ingestion for hand-to-mouth activities. Given the low levels of malathion used to control mosquito-borne diseases, ATSDR finds this assessment reasonable.

Table 2. Regulatory Standards and Guidance Values for Malathion

Standard/Guidance	Value	Reference
Clean Water Act Maximum Contaminant Level(MCL)/Maximum Contaminant Level Goal(MCLG)	N/A	EPA 2002
Safe Drinking Water Act: 1- and 10-day Health Advisories (Child)	0.2 mg/L	EPA 2002
Reference Dose (RfD)	0.02 mg/kg/day*	EPA 2002
Safe Drinking Water Act: Drinking Water Equivalent Level (DWEL)	0.7 mg/L	EPA 2002
Safe Drinking Water Act: Lifetime Health Advisory	0.1 mg/L	EPA 2002
Occupational Standards: Occupational Safety and Health Administration Permissible Exposure Limit (PEL) 8-hour time-weighted average	15 mg/m ³ (skin)	OSHA 2003
National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention (NIOSH/CDC) Recommended Exposure Limit (REL)	10 mg/m ³ (skin)	NIOSH 2003
NIOSH/CDC Immediately Dangerous to Life or Health	250 mg/m ³	NIOSH 2003
ATSDR Oral Minimal Risk Level (MRL) Intermediate and Chronic	0.02 mg/kg/day	ATSDR 2001
ATSDR Inhalation MRL, Acute	0.2 mg/m ³	ATSDR 2001
ATSDR Inhalation MRL, Intermediate	0.02 mg/m ³	ATSDR 2001
Department of Transportation Reportable Quantity	100 pounds	DOT 2002
Environmental Protection Agency Reportable Quantity	10 pounds	ATSDR 2001

* EPA is reviewing the information in an application for reregistration of malathion and may shortly modify the RfD and establish an RfC.

Section 6. References

Aldridge WN, Miles JW, Mount DL, Verschoyle RD. 1979. The toxicological properties of impurities in malathion. Arch Toxicol 43:95–106. (Cited in IARC 1983)

ATSDR. 2001. Toxicological profile for Malathion. Draft for Public Comment. Atlanta: US Department of Health and Human Services, ATSDR.

Balasubramanian K, Ratnakar C, Ananthanarayanan PH, et al. 1987a. Histopathological changes in the testis of malathion treated albino rats. Med Sci Res 15:509–10.

Balasubramanian K, Vijayan AP, Ananthanarayanan PH, et al. 1987b. Effect of malathion on the testis of male albino rats. Med Sci Res 15:229–30.

Banerjee BD, Pasha ST, Hussain QZ, et al. 1998. A comparative evaluation of immunotoxicity of malathion after subchronic exposure in experimental animals. *Ind J Exp Biol* 36:273–82.

Beattie G. 1994. A 13-week toxicity study of aerosolized malathion administered by whole body inhalation exposure to the albino rat: Lab Project Number: 90729. Unpublished study prepared by Product Safety Assessment, Bio-Research Labs, Ltd. (Cited in Yang 2000)

Blondell J. 1998. Review of malathion incident reports. Memorandum from J Blondell to P Deschamp, Health Effects Division, Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency, Washington, DC.

Casale GP, Cohen SD, DiCapua RA. 1983. The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erythrocytes in inbred mice. *Toxicol Appl Pharmacol* 68:198–205.

CDC. 1999. Surveillance for acute pesticide-related illness during the medfly eradication program—Florida, 1998. *MMWR* 48:1015–18, 1027.

Daly I. 1996a. A 24-month oral toxicity/oncogenicity study of malathion in the rat via dietary administration: Final Report: Lab Project Number: 90-3641: J-11 90-3641. Unpublished study prepared by Huntingdon Life Sciences. (Cited in Yang 2000)

Daly I. 1996b. A 24-month oral toxicity/oncogenicity study of malaoxon in the rat via dietary administration: Final Report: Lab Project Number: 93-2234. Unpublished study prepared by Huntingdon Life Sciences. (Cited in EPA 2000b)

Desi I, Varga L, Farkas I. 1978. Studies on the immunosuppressive effect of organochlorine and organophosphoric pesticides in subacute experiments. *J Hyg Epidemiol Microbiol Immunol* 22:115–22.

Dikshith TSS, Srivastava MK, Raizada RB, et al. 1987. Interaction of hexachlorocyclohexane and malathion in male guinea pigs after repeated dermal application. *Vet Hum Toxicol* 29:138–43.

DOT. 2002. List of hazardous substances and reportable quantities. US Department of Transportation. Code of Regulations. 49 CFR 172.101, Appendix A. Available at <http://www.dot.gov/>. Accessed December 13, 2002.

Enan EE. 1983. Comparative biochemical effects of three aliphatic organophosphorus insecticides on white rats. *Int Pest Control* 25:42–4.

EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Washington DC: Office of Water, US Environmental Protection Agency. EPA 822-R-02-038

EPA. 2000a. Malathion Reregistration Eligibility Document. Washington DC: US Environmental Protection Agency.

EPA. 2000b. For Your Information. Malathion for Mosquito Control. 735-F-00-001.

EPA. 2000c. Cancer Assessment Document #2: Evaluation of the carcinogenic potential of malathion. Washington DC: US Environmental Protection Agency, Office of Pesticides Program, Health Effects Divisions.

EPA. 2000d. Malathion: Revisions to the Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Washington DC: Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency.

Ehrich M, Shell L, Rozum M, et al. 1993. Short-term clinical and neuropathologic effects of cholinesterase inhibitors in rats. *J Am Coll Toxicol* 12:55–68.

Feldman RJ, Maibach HI. 1970. Absorption of some organic compounds through the skin in man. *J Invest Dermatol* 54:399–404.

Fischer J. 1988. 28-Day oral toxicity study in beagles. Lab project No. 0852AX883L2116. Unpublished study prepared by American Cyanamid Co. 158 p. MRID 45077703. (Cited in IPCS 1998)

- Flessel P, Quintana PJE, Hooper K. 1993. Genetic toxicity of malathion: a review. *Environ Mol Mutagen*. 22:7–17.
- Fletcher D. 1988. 42-Day neurotoxicity study with AC 6,601 Technical in mature White Leghorn hens: Report No. BLAL 87 DN 109. Unpublished study prepared by Bio-Life Associates, Ltd. (Cited in Yang 2000)
- Gaines TB. 1960. The acute toxicity of pesticides to rats. *Toxicol Appl Pharmacol* 2:88–99.
- Gaines TB. 1969. Acute toxicity of pesticides. *Toxicol Appl Pharmacol* 14:515–34.
- Galloway SM, Armstrong MA, Reuben C, et al. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluation of 108 chemicals. *Environ Mol Mutagen*. 10:1–175. (Cited in Yang 2000)
- Garcia AM, Benavides FG, Fletcher T, et al. 1998. Paternal exposure to pesticides and congenital malformations. *Scand J Work Environ Health* 24:473–80.
- Golz HH. 1959. Controlled human exposures to malathion aerosols. *AMA Arch Ind Health* 19:53–59.
- Grether JW, Harris JA, Neutrons R, Kifer KW. 1987. Exposure to aerial malathion application and the occurrence of congenital anomalies and low birth weight. *Am J Public Health* 77:1009–10.
- Gudi R. 1990. Acute test for chemical induction of chromosome aberration in rat bone marrow cells in vivo with AC 6,601: Lab Report Number: 0125-1531. Unpublished study prepared by Site Research Laboratories. (Cited in Yang 2000)
- Hassan A, Dauterman WC. 1968. Studies on the optically active isomers of O,O-diethyl malathion and O,O-diethyl malaoxon. *Biochem Pharmacol* 17:14.
- Hazleton LW, Holland NG. 1953. Toxicity of malathion. Summary of mammalian investigations. *Arch Ind YG Occup Med* 8: 399–405. (Cited in IARC 1983)
- HSDB. 2002. Hazardous Substance Data Bank: Malathion. National Library of Medicine, National Toxicology Program. Available at <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> Accessed December 17, 2002.
- Huff, JE, Bates R, Eustace SL, et al. 1985. Malathion and malaoxon: histopathology reexamination of the National Cancer Institute's carcinogenic studies *Environ Res* 37, 154–73.
- IARC. 1983. Malathion. In: IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 3, Miscellaneous pesticides. Lyon, France: IARC.
- IARC. 2001. Malathion (Group 3). Available at <http://www-cie.iarc.fr/htdocs/monographs/vol30/malathion.html>
- Jackson G, Hardy C, Gopinath G, et al. 1986. Fyfanon (Malathion) 96/98% Technical: acute inhalation toxicity study in rats, 4-hour exposure: CHV 28/8640. Unpublished study prepared by Huntingdon Research Centre Ltd. (Cited in Yang 2000)
- Kahn E, Berlin M, Deane M, Jackson RJ, Stratton JW. 1992. Assessment of acute health effects from the medfly eradication project in Santa Clara County, California. *Arch Environ Health* 47:279–84.
- Krause W. 1977. Influence of DDT, DDVP and malathion on FSH, LH and testosterone concentration in testis. *Bull Environ Contam Toxicol* 18:231–42.
- Krause W, Hamm K, Weissmuller J. 1976. Damage to spermatogenesis in juvenile rat treated with DDVP and malathion. *Bull Environ Contam Toxicol* 15:458–62.
- Kynoch S, Smith P. 1986. Delayed contact hypersensitivity in the guinea-pig with malathion (Fyfanon) technical: 8666D/CHV 37/SS. Unpublished study prepared by Huntingdon Research Centre Ltd. (Cited in Yang 2000)
- Kynoch S. 1986a. Acute oral toxicity to rats of malathion (Fyfanon) Technical: 851341D/CHV 33/AC. Unpublished study prepared by Huntingdon Research Centre Ltd. (Cited in Yang 2000)

- Kynoch S. 1986b. Acute dermal toxicity to rats of malathion (Fyanon) Technical: 85133OD/CHV 34/AC. Unpublished study prepared by Huntingdon Research Centre Ltd. (Cited in Yang 2000)
- Lamb I. 1994a. An acute neurotoxicity study of malathion in rats: Final Report: Lab Project Number: WIL/206005. Unpublished study prepared by WIL Research Labs, Inc. (Cited in Yang 2000)
- Lamb I. 1994b. A subchronic (13-week) neurotoxicity study of malathion in rats: Final Report: Lab Project Number: WIL-206006. Unpublished study prepared by WIL Research Labs. 1729 p. (Cited in Yang 2000)
- Liggett M, Parcell B. 1985a. Irritant effects on rabbit skin of Malathion (Fyfanon) Technical: 851221D/CHV 35/SE. Unpublished study prepared by Huntingdon Research Centre Ltd. (Cited in Yang 2000)
- Liggett M, Parcell B. 1985b. Irritant effects on the rabbit eye of Malathion (Fyfanon) Technical: 851214D/CHV 36/SE. Unpublished study prepared by Huntingdon Research Centre Ltd. (Cited in Yang 2000)
- Lochry E. 1989. A development toxicity study with AC 6,601 in rats: Argus Research Laboratories Protocol 101-005. Unpublished study prepared by Argus Research Laboratories, Inc. (Cited in Yang 2000)
- Lox, CD. 1985. Short term malathion ingestion and blood clotting in the rat. *J Environ Pathol Toxicol Oncol* 6:51–5.
- Lox CD. 1983. Effects of acute pesticide poisoning on blood clotting in the rat. *Ecotoxicol Environ Saf* 7:451–45.
- Lox CD, Davis JR. 1983. The effects of long-term malathion or diazinon ingestion on the activity of hepatic synthesized clotting factors. *Ecotoxicol Environ Saf* 7:546–51.
- Lu FC, Jessup DC, Lavallee A. 1965. Toxicity of pesticides in young versus adult rats. *Fd Cosmet Toxicol* 3:591–6.
- Machin MGA, McBride WG. 1989b. Placental transfer of malathion in the rabbit. *Med Sci Res* 17:743–4.
- Matthews MS, Devi KS. 1994. Effect of chronic exposure of pregnant rats to malathion and/or estrogen and/or progesterone on xenobiotic metabolizing enzymes. *Pestic Biochem Physiol* 48:110–22.
- Mendoza CE. 1976. Toxicity and effects of malathion on esterases of suckling albino rats. *Toxicol Appl Pharmacol* 35:229–38.
- Milby TH, Epstein WL. 1964. Allergic contact sensitivity to malathion. *Arch Environ Health* 9:434–7.
- Moeller HC, Rider JA. 1962. Plasma and red blood cell cholinesterase activity as indications of the threshold of incipient toxicity of ethyl-p-nitrophenyl thionobenzenephosphonate (EPN) and malathion in human beings. *Toxicol Appl Pharmacol* 4:123–30.
- Moreno O. 1989. 21-Day dermal toxicity study with AC 6,601 in rabbits: Laboratory Report No. MB 88-9191. Unpublished study prepared by MB Research Laboratories, Inc. (Cited in Yang 2000)
- Myhr BC, Caspary WJ. Chemical mutagenesis at the thymidine kinase locus in L518Y mouse lymphoma cells: results for 31 coded compounds in the National Toxicology Program. *Environ Mol Mutagen* 18:51–83.
- NCI. 1978. Bioassay of malathion for possible carcinogenicity. Washington, DC: US Department of Commerce. (NCI-CG-TR-24; available from: National Technical Information Services, Springfield, VA 22161; PB-278 527, unpublished study; CDL:242903-A).
- NCI. 1979a.: Bioassay of malaoxon for possible carcinogenicity. Washington, DC: US Department of Commerce. (NCI-CG-TR-135; available from: National Technical Information Services, Springfield, VA 22161; PB-299 858, unpublished study; CDL:242903-C).

NCI. 1979b. Bioassay of malathion for possible carcinogenicity. Washington, DC: US Department of Commerce. (NCI-CG-TR-192; available from: National Technical Information Services, Springfield, VA 22161; PB-300 301, unpublished study; CDL:242903-B).

NIOSH. 1976. Criteria for a Recommended Standard—Occupational Exposure to Malathion. Washington, DC: US Department of Health, Education, and Welfare. (Cited in IARC 1983)

NIOSH. 2003. NIOSH pocket guide to chemical hazards. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/niosh/npg/npgd0375.html>.

Ojha S, Norton SP, Shrivastava N, et al. 1992. Toxic effect of malathion on the reproductive system of albino rats. *Environ Ecol* 10:833–6.

Ozmen G, Akay MT. 1993. The effects of malathion on some hormone levels and tissues secreting these hormones in rats. *Vet Hum Toxicol* 35:22–4.

Pant K. 1989. Test for chemical induction of unscheduled DNA synthesis in rat primary hepatocyte cultures by autoradiography with AC 6,601: Lab Project Number: 0125-5100. Unpublished study prepared by Site Research Laboratories. (Cited in Yang 2000)

Piramanayagam S, Manohar BM, Sundararaj A. 1996. Pathology of malathion toxicity in rats. *Indian Vet J* 73:734–7.

Prabhakaran S, Shameem F, Devi KS. 1993. Influence of protein deficiency on hexachlorocyclohexane and malathion toxicity in pregnant rats. *Vet Hum Toxicol* 35:429–33.

Reddy V, Freeman T, Cannon M. 1989. Disposition and metabolism of ¹⁴C-labeled malathion in rats (preliminary and definitive study). Midwest Research Institute. Study No. MRI 9354-B. Unpublished study. (Cited in EPA 2000b)

Relford RL, Ainsworth AJ, Harkness JE. 1989. Effects of a commercial malathion dip preparation on the cellular and humoral immune response of BALB/c mice. *Lab Anim Sci* 39:56–9.

Rodgers KE, Leung N, Ware CF, et al. 1986. Lack of immunosuppressive effects of acute and subacute administration of malathion on murine cellular and humoral immune responses. *Pestic Biochem Physiol* 25:358–65.

Rodgers KE, Ellefson DD. 1990. Modulation of respiratory burst activity and mitogenic response of human peripheral blood mononuclear cells and murine splenocytes and peritoneal cells by malathion. *Fundam Appl Toxicol* 14:309–17.

Rodgers KE, Xiong S. 1996. Contribution of mast cell mediators to alterations in macrophage function after malathion administration. *Fundam Appl Toxicol* 33:100–8.

Rodgers K, Xiong S. 1997a. Contribution of inflammatory mast cell mediators to alteration in macrophage function after malathion administration. *Int J Immunopharmacol* 19(3):149–156

Rodgers K, Xiong S. 1997b. Effect of acute administration of malathion by oral and dermal routes on serum histamine levels. *Int J Immunopharmacol* 19:437–41.

Rodgers K, Xiong S. 1997c. Effect of administration of malathion for 14 days on macrophage function and mast cell degranulation. *Fundam Appl Toxicol* 37:95–9

Rodgers K, Xiong S. 1997d. Effect of administration of malathion for 90 days on macrophage function and mast cell degranulation. *Toxicol Lett* 93:73–82

Schanker HM, Rachelefsky G, Siegal S, et al. 1992. Immediate and delayed type hypersensitivity to malathion. *Ann Allergy* 69:526–8.

Schroeder R. 1990. A two-generation (two litters) reproduction study with AC 6,601 to rats. Study No. 87-3243. Unpublished Study prepared by Bio/Dynamics, Inc. (Cited in Yang 2000)

Siglin J. 1985a. A resubmission of rabbit teratology study, FDRL Study No. 8171 (MRID 152569), with Appendix included. (Cited in Yang 2000)

Siglin J. 1985b. A teratology study with AC 6,601 in rabbits: FDRL Study No. 8171. Unpublished study prepared by Food and Drug Research Laboratories. (Incorporates a range-finding study) (Cited in Yang 2000)

Simionescu L, Oprescu M, Săhleanu V, et al. 1977. The serum and pituitary prolactin variations under the influence of a pesticide in the male rat. *Rev Roum Med* 15:181–8.

Slauter R. 1994. 18-Month oral (dietary) oncogenicity study in mice: Malathion: Lab Project Number: 668-001. Unpublished study prepared by International Research and Development Corp. (Cited in Yang 2000)

Talcott RE, Mallipudi NM, Fukuto TR. 1979a. Malathion carboxylesterase titer and its relationship to malathion toxicity. *Toxicol Appl Pharmacol* 50:501–4.

Tegeris Laboratories, Inc. 1987. One-year oral toxicity study in purebred beagles with AC6,601:Lab Number: 85010. Unpublished study. (Cited in Yang 2000)

Thomas D, Petitti D, Goldhaber M, et al. 1992. Reproductive outcomes in relation to malathion in the San Francisco Bay Area, 1981–1982. *Epidemiology* 3:32–9.

Traul K. 1987. Evaluation of CL 6601 in the bacterial/microsome mutagenicity test: Study No. 114. Unpublished study prepared by American Cyanamid Co. (Cited in Yang 2000)

Umetsu N, Grose FH, Allahyari R, et al. 1977. Effect of impurities on the mammalian toxicity of technical malathion and acephate. *J Agric Food Chem* 25:946–53.

Weeks MH, Lawson MA, Angerhofer RA, et al. 1977. Preliminary assessment of the acute toxicity of malathion in animals. *Arch Environ Contam Toxicol* 6:23–31.

Vestweber JG, Kruckenberg SM. 1972. The effect of selected organophosphorus compounds on plasma and red blood cell cholinesterase in the dog. *Vet Med Small Anim Clin* 67:803–6.

Vijayakumar TS, Selvarajan VR. 1990. Heterogeneity in response of different areas of rabbit brain to malathion. *Bull Environ Contam Toxicol* 44:721–8.

Yang YG. 2000. Malathion: The toxicology chapter for the RED. Memorandum from YG Yang to PA Decamp, Health Effects Division, Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency, Washington, DC

Methoprene (CAS Number 114-26-1)

Methoprene is an insect growth regulator used as a larvicide. It is a synthetic analogue of the insect juvenile hormone. Unlike conventional insecticides that act as direct poisons, methoprene disrupts the morphologic development of insects. It interferes with an insect's life cycle (metamorphosis) and prevents it from reaching maturity or reproducing. Methoprene is used in the production of foods, including meat, milk, eggs, mushrooms, peanuts, rice, and cereals. It is used as a feed additive for cattle to prevent breeding of hornflies in manure. It also is used in aquatic areas to control mosquitoes and several types of flies, moths, beetles, and fleas (EPA 1991).

Section 1. Environmental Factors

Methoprene rapidly biodegrades in soil, with a soil half-life of 10 days. Its half-life in water is <1 day in sunlight and >4 weeks in darkness. Methoprene rapidly degrades in plants, with a half-life of 1–2 days. If released to air, a vapor pressure of 2.36×10^{-5} mm Hg at 25°C indicates methoprene will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase methoprene degrades in the atmosphere by reaction with photochemically produced hydroxyl radicals and ozone; the estimated half-lives for these reactions in air are 1.5 hours and 48 minutes, respectively. Particulate-phase methoprene is removed from the atmosphere by wet and dry deposition. If released to soil, methoprene is expected to be immobile at an estimated K_{oc} of 23,000. If released into water, methoprene is expected to adsorb to suspended solids and sediment at the estimated K_{oc} . An estimated bioconcentration factor of 3,400 suggests that the potential for bioconcentration in aquatic organisms is very high (HSDB 2002). Methoprene is slightly toxic to fish but highly toxic to freshwater and estuarine invertebrates (EPA 1991).

Section 2. Potential for Exposure

People can be exposed to small amounts of methoprene through the food supply. However, the amount of methoprene in the U.S. consumer's diet is well below the level at which any adverse health effects could occur. People also can be exposed to methoprene while mixing, loading, or applying the pesticide and while working among treated crops (EPA 1991). Occupational exposure to methoprene can occur through inhalation and dermal contact with this compound where methoprene is produced or used. Methoprene's insecticidal applications suggest that the most probable exposure pathway for the general population is dermal contact with treated products (HSDB 2002).

Section 3. Health Effects/Toxicity

Studies in laboratory animals exposed to methoprene dermally, orally, or by inhalation are summarized in Table 1, with no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) indicated.

Methoprene has a very low acute oral and inhalation toxicity potential and is not an eye or skin irritant (EPA 1991). Technical-grade methoprene has a low irritant potential to skin in a primary dermal irritation study using New Zealand white rabbits (Hallesy and Hill 1973). Results of a skin sensitization study in guinea pigs showed that technical-grade methoprene was not a skin sensitizer (Zoecon 1975), and a primary eye irritation study in New Zealand white rabbits indicated that technical-grade methoprene was not an irritant to eyes (Hallesy and Hill 1973). In a 30-day study of rabbits exposed dermally (Nakasawa et al. 1975b), erythema at the application site was noted at ≥ 300 mg/kg.

Table 1. Health Effect Levels of Methoprene in Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
ACUTE DURATION TOXICITY							
dermal	once	rabbit		3,000 mg/kg	LD ₅₀		HSDB 2002
oral	once	rat		2,323 to >34,600 mg/kg	LD ₅₀		HSDB 2002
oral	once	mouse		2,285 mg/kg	LD ₅₀		HSDB 2002
oral	once	dog		5,000 mg/kg	LD ₅₀		HSDB 2002
oral (diet)	2 wks	rat	40,000 ppm		No gross abnormalities	Rats were fed technical-grade methoprene (68.9%) for 2 weeks and a control diet for an additional week. Gross pathologic examination in this top dosage group revealed no abnormalities. Some dose-related growth depression was attributed to palatability problems with the test material. Unpublished study	Jorgenson & Sasmore 1972a
inhalation	once	rat		>210 mg/L air	LC ₅₀		HSDB 2002
Intermediate Duration Toxicity							
dermal	30 day	rabbit	100 mg/kg	300 mg/kg	Erythema at application site	At ≥300 mg/kg, an increase occurred in neutrophil counts, weight loss, elevated leukocyte counts. Gross and histopathological examination indicated the only compound-related finding was confined to the treated skin sites. Unpublished study	Nakasawa et al., 1975b
oral (diet)	90 days	rat		1,000 ppm	Renal tubular regeneration; increase in liver and kidney organ/body weight ratio	Renal tubular regeneration in 3 (of 15) males at 1,000 ppm and 7 (of 15) males at 5,000 ppm. Increase in organ/body weight ratio of liver and kidney at 5,000 ppm. Slightly higher incidence in males at 5,000 ppm of a kidney lesion characterized by vacuoles within swollen convoluted tubules. A NOAEL could not be determined because no animals <1,000 ppm were subjected to histologic evaluation of kidney.	Jorgenson & Sasmore 1972b
oral (diet)	90 days	dog	500 ppm	5,000 ppm	Elevated serum alkaline phosphatase; increased organ/body weight ratio of liver	4 male and 4 female beagles were fed diets containing technical-grade methoprene (68.9%). No treatment-related changes seen in gross pathologic examination and microscopic evaluation of liver and other tissues. Unpublished study	Jorgenson & Sasmore 1972b

Table 1. Health Effect Levels of Methoprene in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (diet)	6 months	rat	400 ppm	2,000 ppm	Hypertrophy of liver parenchymal cells	400 ppm = 20 mg/kg/day	Nagano 1977
inhalation	4 hrs/day, 5 days/ wk, 3 weeks	rat	20 mg/L			Rats exposed by inhalation to an aerosol of technical-grade methoprene (purity 68.9%) at chamber concentrations of 0, 2, or 20 mg/L air. Alkaline phosphatase and bilirubin showed variations from controls at 2 and 20 mg/L but did not indicate a consistent pattern of toxicity. Gross necropsies and histologic evaluation of liver, lung, kidney, and trachea showed no treatment-related changes. Unpublished study	Olson & Willigan 1972
inhalation	6 days/ wk, 4 weeks	dog	0.0625 mg/kg/day			Groups of 3 male and 3 female beagles were exposed to technical-grade methoprene (in 2% ethanol solution) as aerosol at 0.0125, 0.0250, or 0.0625 mg/kg/day. No compound-related effects were found for body weight, food and water consumption, hematology, blood chemistry, urinalysis, or gross histopathologic findings. Unpublished study	Masao & Hiroyuki 1975
Chronic Duration Toxicity							
oral (diet)	2 years	rat	1,000 ppm	5,000 ppm	Increased incidence of hepatic lesions; increased liver weight	Increased hepatic lesions such as bile duct proliferation of portal lymphocyte infiltration in males at 5,000 ppm; elevated liver weight in 5,000 ppm females. No significant difference in incidence of any particular type of tumor. Unpublished study	Wazeter & Goldenthal 1975b
Developmental/Reproductive Toxicity							
oral (diet)	3 generations	rat	500 ppm	2,500 ppm	Reduced mean pup weight in F2 & F3 litters; elevated mean number of pups born dead per litter in F3 litters	Reduced mean pup weight in F2 litters on day 21 and in F3 litters on days 14 & 21. No compound-related effects observed in parental generations. No treatment-related effects on other tested parameters for offspring. Unpublished study	Killeen & Rapp 1974

Table 1. Health Effect Levels of Methoprene in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (diet)	78 weeks	mouse	250 ppm	1,000 ppm	Liver lesions	Dose-related increase in incidence and severity of liver lesions at $\geq 1,000$ ppm. Elevated frequency of amyloidosis of the small intestine in females at 2,500 ppm. No compound-related increase in incidence of any particular type of tumor; no evidence suggestive of carcinogenic activity. Unpublished study	Wazeter & Goldenthal 1975a
oral (intu- bated)	gestation days 7–114	mouse	600 mg/kg/d		No teratogenicity observed	No treatment-related effects observed on mean number of dead embryos or in sex ratio of fetuses. No internal or external abnormalities observed in fetuses. Fetuses of all treated groups displayed a statistically significant increase in number of caudal vertebrae. No compound-related effects reported. No evidence of teratogenicity observed under the conditions of the experiment. Unpublished study	Nakasawa et al., 1975a
oral	gestation days 7–18	rabbit	200 mg/kg/day	2,000 mg/kg/day	Fetotoxicity	Increased percentage of fetal deaths and increased proportion of female fetuses observed in high-dose group. No teratogenicity. NOAEL for fetal toxicity was 200 mg/kg/day on basis of increased percentage of fetal deaths. In top dosage group, 2 does aborted, and maternal weight gain was depressed. NOAEL for maternal toxicity was 200 mg/kg/day on basis of reductions in weight gain and abortions. Unpublished study	Nakasawa et al., 1975b

Methoprene has an inhalation LC₅₀ for rats of >210,000 mg/m³ air. No-effect inhalation values were 20,000 mg/m³ in a 3-week rat study and 0.0625 mg/kg/day in a 4-week dog study. Methoprene oral LD₅₀ values range from 2,323 to >34,600 mg/kg in rats, 2,285 mg/kg in mice, and 5,000 mg/kg in dogs. Mortality reached 20% in 4 months in rats receiving 232 mg/kg/day, but a dose of 116 mg/kg/day was without effect (HSDB 2002). A three-generation (one litter/generation) reproduction study in rats demonstrated a NOAEL on reproduction of at least 500 ppm in the diet (Killeen and Rapp 1974). A NOAEL of 500 ppm for dogs was seen in a 90-day feeding study (Jorgenson and Sasmore 1972b). Teratology studies in both mice and rabbits showed no evidence of teratogenicity under the conditions of the experiments. However, pregnant mice and rabbits were treated with methoprene from days 7 to 14 and from days 7 to 18 of gestation, respectively. The entire period of organogenesis, therefore, was not covered. Mutagenicity studies were negative, and a mouse and a rat oncogenicity study were negative (WHO 1984).

Section 4. Toxicokinetics

Methoprene is rapidly metabolized and eliminated by mammals. Mice (eight males and two females) intubated with an alcoholic solution of tritiated methoprene eliminated 63.6% of the administered radioactivity in urine and 12.3% in feces within 24 hours of dosing. Total cumulative recovery of tritium radioactivity at the end of 96 hours was 82% (68% in urine and 14% in feces). Autoradiographic studies showed a high concentration of radioactivity in the stomach and small amounts in the liver and kidneys at 0.5 hours post-treatment. At 6 hours, radioactivity occurred primarily in the small intestine, descending colon, and rectum. By 12 hours, radioactivity had essentially been eliminated from the body, and no residual radioactivity was found at 48 hours. Placental transfer of radioactivity was not evident in two pregnant mice (Cohen and Trudell 1972).

When ¹⁴C methoprene was administered orally to rats, slightly <20% was excreted within 5 days in the urine and a similar amount in feces, and almost 40% was excreted as ¹⁴CO₂. About 17% was retained in the body. Highest concentrations were in liver (84.5 ppm), kidneys (29 ppm), lungs (26 ppm), fat (36.5 ppm), and the adrenal cortex (12–13 ppm). About 12 labeled compounds were detected in the urine, but no unchanged methoprene was observed (Hawkins 1977).

In male and female rats (25 rats of each sex) given one oral radioactive dose of 25 mg methoprene/kg body weight, a total of 43.7% of the applied radioactive dose was excreted within 24 hours in urine (13%), feces (5.2%), and expired air (25.5%). During the next 48 hours, an additional 5.6%, 9.6%, and 10.1% (i.e., a total of 20.3%) was eliminated in the corresponding routes. By the end of a 5-day collection period, the cumulative ¹⁴C recovery from all three routes amounted to 76.4% of the administered dose (19.6% in urine, 18% in feces, and 38.8% in expired air). The maximum biologic half-life reported for about 60% of the radioactivity was about 10 hours and 107 hours for a further 15%. Plasma concentration of ¹⁴C in these rats peaked at 6 hours post-treatment, then declined slowly, with a half-life of about 48 hours during the 2nd–5th day after dosing. A sex difference in the rate of elimination of radioactive methoprene was not evident. Total amount of radioactivity in the plasma at 6 hours was 1.63% of the administered dose. Analyses of tissues from male rats sacrificed at various intervals showed highest ¹⁴C levels in liver, plasma, kidney, and lung during the first 6–12 hours post-dosing. Significant levels of ¹⁴C residues were later found in heart, adipose tissue, and adrenal glands. At all time intervals studied, ¹⁴C levels were low in the brain, eyes, and testes. Whole-body autoradiography showed that much of the ¹⁴C was located in organs concerned with absorption, biotransformation, and excretion (Chasseaud et al. 1974).

The metabolism of methoprene was studied in a guinea pig, a steer, and a cow (Chamberlain et al. 1975). In the guinea pig, 24% of the dose was excreted in the urine over 24 hours, 9.1% in the feces, and 17.2% in expired air. Highest tissue concentrations occurred in blood, muscle, and fat. In the steer, 21.6% of the dose was excreted in the urine after 2 weeks, 38.8% in the feces after 2 weeks, and 2.7% in the expired air after 96 hours. Highest tissue concentrations of radiolabel were found in the bile, gall bladder, liver, and kidney. In the cow, 15.1% of the dose was excreted in the expired air, 7.6% in the milk, 19.8% in the urine, and 30.2% in the feces. The highest levels of radioactivity were found in the bile, liver, skin, fetus, and udder. In all species, approximately 40% of the radioactivity in the feces was attributable to unchanged methoprene. No methoprene was found in the urine. Major metabolites identified in the steer and the guinea pig included 7-methoxycitronellic acid, 11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid, and 11-hydroxy-3,7,11-trimethyl-2,4-dodecadienoic acid.

The toxicity of methoprene could be altered by interactions with other chemicals that have the same mechanism of action, or with chemicals that affect its metabolism.

Section 5. Standards and Guidelines for Protecting Human Health

Methoprene can be used safely as a feed additive in accordance with the following prescribed conditions: (1) it is used as a feed additive in the form of mineral and/or protein blocks or other feed supplements in the feed of cattle at 22.7–45.4 mg per 100 pounds of body weight per month; (2) it is used to prevent the breeding of hornflies in the manure of treated cattle; (3) it is used to ensure safe use of the additive, the label and labeling of the pesticide formulation containing this additive shall conform to the label and labeling registered by EPA; (4) tolerances are established for residues of methoprene in or on the following feed additive commodities: cereal grain milled fractions (except flour and rice hulls)—10 ppm and rice hulls—25 ppm (HSDB 2002).

Tolerances have been established for residues of methoprene in or on the following raw agricultural commodities: barley—5 ppm; buckwheat—5 ppm; cattle fat—1 ppm; cattle meat—0.1 ppm; cattle meat by-products—0.1 ppm; corn (except popcorn and sweetcorn)—5 ppm; eggs—0.1 ppm; goat fat—1 ppm; goat meat—0.1 ppm; goat meat by-products—0.1 ppm; hog fat 1 ppm; hog meat—0.1 ppm; hog meat by-products—0.1 ppm; horse fat—1 ppm; horse meat 0.1 ppm; horse meat by-products—0.1 ppm; milk—0.1 ppm; millet—5 ppm; mushrooms—1 ppm; oats—5 ppm; peanuts—2 ppm; poultry fat—1 ppm; poultry meat—0.1 ppm; poultry meat by-products—0.1 ppm; rice—5 ppm; rye—5 ppm; sheep fat—1 ppm; sheep meat—0.1 ppm; sheep meat by-products—0.1 ppm; sorghum (milo) —5 ppm; and wheat—5 ppm (HSDB 2002).

Methoprene also is allowed for oral use in dogs aged ≥ 9 weeks and ≥ 4 pounds of body weight to prevent and control fleas (HSDB 2002).

No other regulatory standards or guidance values were located.

Section 6. References

Chamberlain WF, Hunt LM, Hopkins DE, et al. 1975. Absorption, excretion, and metabolism of methoprene by a guinea pig, a steer and a cow. *J Agric Food Chem* 23:736–42.

Chasseaud LF, Hawkins DR, Franklin ER, Weston KT. The metabolic fate of [5-14C]-isopropyl 11-methoxy-3,7,11-trimethyl dodeca-2,4-dienoate (Altosid) in the rat. Huntingdon Research Centre, England. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Cohen EN, Trudell J. 1972. Untitled letter report to Zoecon Corp. on metabolism of methoprene in mice. Stanford University Medical Center. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

EPA. 1991. Methoprene Reregistration Eligibility Document Facts. Washington, DC: US Environmental Protection Agency.

Hallesy DW, Hill R. 1973. Primary dermal irritation study of Altosid in rabbits. Syntex Research, USA. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Hawkins DR, Weston KT, Chasseaud LF, Franklin ER. 1977. Fate of methoprene (Isopropyl (2E,4E)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoate) in rats. *J Agric Food Chem* 25:398–403. (Cited in HSDB 2002)

HSDB. 2002. Hazardous Substance Data Bank: Methoprene. National Library of Medicine, National Toxicology Program. Available at <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> Accessed December 17, 2002.

Jorgenson TA, Sasmore DP. 1972a. Toxicity studies of ZR-515 (Altosid technical) (1) Acute 1P in rats (2) Repeated 1P in rats (3) Two-week, range-finding dietary studies in rats and dogs. Stanford Research Institute, USA. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Jorgenson TA, Sasmore DP. 1972b. Toxicity studies of Altosid Technical (1) Ninety-day subacute in rats (2) Ninety-day subacute in dogs. Stanford Research Institute, USA. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Killeen JC, Rapp WR. 1974. A three-generation reproduction study of Altosid in rats. Bio/dynamics Inc., USA. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Masao N, Hiroyuki M. 1975. Determination of subacute toxicity to Beagle dogs resulting from Altosid inhalation. Nomura Research Laboratory, Japan. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Nagano IK, et al. 1977. *Botyu Kagaku* 42(2):63–74. (Cited in HSDB 2002)

Nakasawa M, Matsumiya H, Ishikawa I. 1975a. Test of Altosid toxicity, III: determination of teratogenic potential of Altosid administration orally to rabbits. Nomura Research Institute, Japan. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Nakasawa M, Nomura A, Furuhashi T, Mihori J, Ikeya E. 1975b. Determination of teratogenic potential of Altosid administered orally to mice. Nomura Research Institute, Japan. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Nakasawa M, Shimizu T, Miyoshi K, Hasegawa R, Furuhashi T, Ogawa M, Mihori J. 1975c. Test of Altosid toxicity, II: rabbit subacute dermal toxicity of Altosid. Nomura Research Laboratory, Japan. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Olson WA, Willigan DA. 1972. Three-week inhalation exposure—rats. Altosid (Technical grade). Hazleton Laboratories, Inc., USA. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Wazeter FX, Goldenthal EI. 1975a. Eighteen month oral carcinogenic study in mice. Report No. 322-003. International Research and Development Corporation, dated 14 March. Submitted to WHO by Novartis Animal Health Australasia, Ltd, Pendle Hill, NSW, Australia. (Unpublished study cited in WHO 1984)

Wazeter FX, Goldenthal EI. 1975b. Chronic oral toxicity studies with Altosid technical. Report No. 322-001. International Research and Development Corporation, dated 14 March. Submitted to WHO by Novartis Animal Health Australasia, Ltd, Pendle Hill, NSW, Australia. (Unpublished study cited in WHO 1984)

WHO. 1984. Methoprene—Pesticide residues in food: 1984 evaluations. International Program on Chemical Safety. Geneva: World Health Organization.

Zoecon Corp. USA. 1975. Test of Altosid toxicity, V: skin sensitization of Altosid in guinea-pigs. Nomura Research Institute, Japan. Submitted by Zoecon Corp. USA to WHO. (Unpublished study cited in WHO 1984)

Naled (CAS Number 300-76-5)

Naled is an organophosphate insecticide registered since 1959 for use in the United States. Naled is used primarily to control adult mosquitoes but also is used on food and feed crops and in greenhouses. The mode of action of naled is as a nonsystemic contact and stomach poison (Hayes and Laws 1990). State and local authorities apply naled by truck-mounted or aircraft-mounted sprayers. Because of the very small quantities of pesticide applied, naled does not pose a moderate or serious health risk if applied according to the guidelines for use (EPA 2002).

Section 1. Environmental Factors

Naled and its degradation products are transformed primarily by abiotic hydrolysis, indirect photolysis in water, and biodegradation (Peckenpaugh et al. 1997). Naled and its degradation products dissipate rapidly under typical terrestrial, aquatic, and forestry field conditions, having half-lives of <2 days. Rapid hydrolysis and biodegradation help decrease the concentration of naled that remains in the environment shortly after treatment and thus lower the amount available for runoff (Peckenpaugh et al. 1997).

When naled is present in the atmosphere, it exists primarily in the vapor phase, where it degrades by reacting with hydroxyl radicals (Bidleman 1988; Meylan and Howard 1993). In atmospheric conditions, the estimated half-life of naled is 18 hours (Meylan and Howard 1993).

Naled degrades rapidly in aqueous media. The rate of degradation of naled in water by abiotic hydrolysis depends on pH, with an inverse relation between pH and half-life (Peckenpaugh et al. 1997). Estimated half-lives were 96 hours at pH 5, 15.4 hours at pH 7, and 1.6 hours at pH 9 (Valent USA 1993). Naled is nonvolatile from water, and it persists in water for up to 10 days without accumulation on sediment (Meylan and Howard 1991).

In the presence of a chemical photosensitizer (acetone), indirect photolysis contributed significantly to the photodegradation of naled in aqueous media. The rate of degradation in the presence of a photosensitizer was five times faster than when the photosensitizer was not used. The photodegradation of naled by indirect photolysis under environmental conditions will produce the by-product dichlorvos (Peckenpaugh et al. 1997).

In soil, the degradation of naled is aided not only by microbial populations, but also by hydrolytic processes. The mobility of naled in soil ranges from medium to high, based on K_{oc} values (Meylan et al. 1992; Lyman et al 1990; Wauchope et al. 1991; Gufstafson 1989). The estimated half-life of naled, based on exponential-decay calculations in soil, is 1 day (Wauchope et al. 1992). A more specific example from a persistence study shows that naled persisted in soil for only 3 days (Jain et al. 1987).

Section 2. Potential for Exposure

Major routes of exposure are by application from fog and mist sprayers. The use of application by aircraft increases the potential for exposure of humans and nontarget organisms to naled. Human exposure to naled during mixing, handling, application, and reentry operations can be minimized by use of approved respirators and other protective clothing. However, data are not available to fully assess such exposures. A reentry level of 24 hours for the use of naled on crops is required (Cornell University 1983).

EPA has estimated the exposure and risks to both adults and children posed by ULV aerial and ground applications of naled. Because of the very small amount of active ingredient released per acre of ground, the estimates found that for all scenarios considered, exposures were hundreds or even thousands of times below an amount that might pose a health concern. These estimates assumed several spraying events over a period of weeks, and they assumed a toddler would ingest some soil and grass in addition to experiencing skin and inhalation exposure (EPA 2002).

Section 3. Health Effects/Toxicity

One of the degradation products of naled is dichlorvos, another registered organophosphate. This is the only degradate of toxicologic concern for naled (food and water). Dichlorvos is included in the naled tolerance expression. Risks from naled-derived dichlorvos should be calculated in an aggregate assessment for dichlorvos. Because of the common metabolite, the risk assessment for naled cannot be considered complete until the assessment for dichlorvos has been considered (EPA 1999b).

Health Effects in Humans Exposed to Naled

The principal toxicologic effect of naled and other organophosphate insecticides is cholinesterase inhibition. Information on health effects in humans exposed to organophosphate insecticides comes from case reports, case series, statistical surveys, and epidemiologic studies. The most common human exposures to naled occur during mixing, handling, application and reentry procedures (Purdue University 1987).

Signs and symptoms of acute naled poisoning are as follows

- **Common early signs or mild symptoms** of acute cholinergic poisoning include miosis (pinpoint pupils), headache, nausea/vomiting, dizziness, muscle weakness, drowsiness, lethargy, agitation and anxiety.
- **Moderate or severe poisoning** can result in chest tightness, difficulty breathing, bradycardia, tachycardia, hypertension, pallor, abdominal pain, incontinence, diarrhea, anorexia, tremor/ataxia, fasciculation, lacrimation, heavy salivation, profuse sweating, blurred vision, poor concentration, confusion, and memory loss.
- **Life-threatening or very severe signs and symptoms**, such as coma, seizures, respiratory arrest, pulmonary edema, loss of reflexes, and flaccid paralysis, can occur at high doses, such as in the cases of attempted suicide.

Human Health Effects Possibly Related to Municipal Use of Naled for Mosquito Control

When a 1,376 hectare area was sprayed by aircraft with naled and temephos for mosquito control, the concentration of urinary metabolites of the compounds in persons who were indoors during spraying did not increase (Hayes 1982). During loading of an aircraft for naled spray treatments, naled entered through an unnoticed hole in the elbow-length gloves worn by a pilot. When discovered, the formulation was wiped off, not washed. The exposed area became red, with a burning sensation. When the blisters became dry, the skin itched. The man continued to work but reduced his exposure; recovery required 3 weeks (Hayes 1982).

A California study involved 542 agricultural pesticide applicators under medical supervision who had been exposed for >3 hours in a 30-day period to category I and II organophosphate and carbamate pesticides. The pesticides primarily responsible for lowered cholinesterase activity from those not responsible for lowered activity were not possible to distinguish in this study. Of the 26 workers with

April 2005 Page 43

cholinesterase depression, eight had pesticide-related illness. The frequency of naled inhibition of cholinesterase activity was 0 (<50% of baseline) for plasma and 1 to 2 (<70% and 60%, respectively) for erythrocytes (Ames et al. 1989).

In a study of people working with chrysanthemum plants, 12 women were exposed to a field that had been sprayed with a mixture containing naled at a concentration of 10.8%, captan (6%), and dicofol (2%). Nine of the 12 women complained of burning arms, face, neck, and abdomen. Four who were examined 4 days after the onset of symptoms had contact sensitization dermatitis. The results of a patch test 2 weeks after the exposure was negative. The results of all the tests strongly indicated that naled caused the symptoms (Hayes 1982).

Health Effects in Laboratory Animals

Laboratory animals have been exposed to naled dermally, orally, or by inhalation (Table 1). At high levels, naled can cause death in some animals. If the dose is lower, it may have muscarinic effects (including hypersalivation, lacrimation, sweating, and nasal discharge); nicotinic effects (fasciculation of muscles, weakness, and paralysis); and central nervous system effects (nervousness, apprehension, ataxia, convulsions, and coma). Death can result from respiratory failure or cardiac arrest (Clarke et al. 1981).

The most common effects at lower levels include decreases in blood, plasma, brain, and erythrocyte cholinesterase; body weight gain decreases; skin irritation; and other clinical signs. These effects occur regardless of route of exposure or duration. The effects are variable, but cholinesterase inhibition is always present if any effect is observed for acute to chronic exposures. Other effects accompany cholinesterase inhibition, but they are not consistent with either species or duration (EPA 1999a).

Serious effects can result from exposure to naled, but in many cases, brain cholinesterase is only slightly to moderately inhibited. No toxic effect was observed in rats that received 100 mg of 99% pure naled/kg for 84 days or in albino rats that received 100 mg of 91% pure naled/kg for 2 years (Worthing and Walker 1983).

Aside from mild cholinergic effects, some evidence indicated maternal and developmental toxicity in reproductive studies. Sprague-Dawley rats showed tremors, hypoactivity, and dyspnea when exposed to 40 mg/kg/day during gestation. Decreased body weight was also observed in pups, as were decreased survival rate and some moderate inhibition of development (Beaudoin and Fisher 1981; EPA 1999a).

The limited effects of naled on test subjects may depend on the route of exposure. Guinea pigs and rats exposed to ≥ 42 mg/m³ for 6 hours a day, 5 days a week for 5 weeks showed decreased cholinesterase activity and obvious discomfort and inactivity. In addition, male and female rats exposed to technical-grade naled in aerosol form at concentrations of 3.4–12.1 mg/m³ for 6 hours/day, 5 days/week for 3 weeks showed inhibition of cholinesterase and brain activity (ACGIH 1991).

Table 1. Health Effect Levels of Naled in Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
ACUTE DURATION TOXICITY							
dermal	once	rat (M)		800 mg/kg	LD ₅₀		Hayes 1982, Kidd and James 1991
dermal	once	mouse		600 mg/kg	LD ₅₀		NIOSH 2000
dermal	once	rabbit		1,100 mg/kg	LD ₅₀		Kidd and James 1991
oral	once	rat (M)		250 mg/kg	LD ₅₀		Hayes 1982
oral	once	rat (F)		281 mg/kg	LD ₅₀		Hayes 1982
oral	once	rat		430 mg/kg	LD ₅₀		Zenz et al. 1994
oral	once	mouse (M)		375 mg/kg	LD ₅₀		Hayes 1982
oral	once	mouse (F)		360 mg/kg	LD ₅₀		Hayes 1982
oral	once	mouse		222 mg/kg	LD ₅₀		NIOSH 2000
inhalation	6 hours	mouse		1,500 mg/m ³	LC ₅₀		Hartley and Kidd 1986
Intermediate Duration Toxicity							
dermal	28 days	Sprague-Dawley CD rat	1 mg/kg/day	20 mg/kg/day	Dermal irritation (erythema, edema, necrosis, and exfoliation). After 4 weeks, effects included acute ulcerative inflammation, necrosis, and epidermal hyperplasia. Systemic toxicity included plasma, erythrocyte, and brain cholinesterase inhibition and body weight gain and depression.	Most treatment-related effects resulted from 80 mg/kg/day. No treatment-related histopathologic changes other than skin effects were observed.	EPA 1999a (Based on unpublished data submitted to EPA)
oral	84 days	rat	100 ppm diet		No toxic effects	Technical-grade naled, given in diet, 99% pure	Worthing and Walker 1983
oral	27 days	rat	30 ppm diet			No depression of plasma, erythrocyte, or brain cholinesterase activities	ACGIH 1991

Table 1. Health Effect Levels of Naled in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (gavage)	28 days	rat	1 mg/kg/day	10 mg/kg/day	Cholinergic effects: 10 mg/kg/day produced mild cholinergic signs and reduction of plasma and brain cholinesterase by 50%; 1 mg/kg/day produced cholinesterase inhibition in plasma (no clinical signs)	Supplemental study, 100 mg/kg/day produced mortality and more significant cholinergic signs.	EPA 1999a (Based on unpublished data submitted to EPA)
inhalation	13 weeks, 6 hrs/day, 5 days/wk.	Fischer-344 rat	0.2 mg/m ³	1 mg/m ³	Cholinesterase inhibition	Based on 25%–30% depression of plasma during study and depression of erythrocyte cholinesterase (50%–60% early and 25%–20% at end of study)	EPA 1999a (Based on unpublished data submitted to EPA)
inhalation	13 weeks, 6 hrs/day, 5 days/wk.	Fischer-344 rat		6 mg/m ³	Tremors, salivation, nasal discharge, abnormal respiration, and anogenital staining. Inhibition of brain, plasma, and erythrocyte cholinesterase	No other effects related to treatment.	EPA 1999a (Based on unpublished data submitted to EPA)
inhalation	5 weeks, 6 hrs/day, 5 days/week,	guinea pig and rat		42 mg/m ³	Decreased cholinesterase activity, discomfort, inactivity	Aerosol composed of 65% naled, 25% xylene, and 10% emulsifier-surfactant	ACGIH 1991
Inhalation	3 weeks, 6 hrs/day, 5 days/week	rat		3.4 mg/m ³	Dose-dependent inhibition of the brain, erythrocyte, and plasma cholinesterase, effects noted at 7.2 and 12.1 mg/m ³	Effects observed at all concentrations and in both sexes.	ACGIH 1991
Chronic Duration Toxicity							
oral (gavage)	Lifetime, 1 dose/day	rat		2 mg/kg	Dose-related reduction in plasma, brain, erythrocyte cholinesterase	No other adverse effects; incidence of neoplastic lesions similar to that of controls.	ACGIH 1991
oral (gavage)	Lifetime, 1 dose/day	rat	0.2 mg/kg/day		No recordable effect	Incidence of neoplastic lesions similar to that of controls.	ACGIH 1991

Table 1. Health Effect Levels of Naled in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (gavage)	1 year	beagles	0.2 mg/kg/day	2 mg/kg/day	Plasma, erythrocyte, and brain cholinesterase activity depressed. Clinical signs included emesis, diarrhea, mineralization of lumbar spinal cord (M and F), anemia, erythrocyte count reduced, hemoglobin and hematocrit lowered.	Kidney and liver affected only at high dose (20 mg/kg/day)	EPA 1999a (Based on unpublished data submitted to EPA)
oral (gavage)	2 year	Sprague-Dawley CD rats	0.2 mg/kg/day		Cholinesterase inhibition, systemic toxicity	No effect.	EPA 1999a (Based on unpublished data submitted to EPA)
oral (gavage)	2 year	Sprague-Dawley CD rats		2 mg/kg/day	Cholinesterase levels lowered in plasma (4%–33%), erythrocytes (54%–60%), and brain (24%)	LOAEL for cholinesterase inhibition. No other treatment-related effects	EPA 1999a (Based on unpublished data submitted to EPA)
oral (gavage)	2 years	Sprague-Dawley CD rats		10 mg/kg/day	See above	LOAEL for systemic toxicity	EPA 1999a (Based on unpublished data submitted to EPA)
Developmental/Reproductive Toxicity							
oral (gavage)	gestation days 6–19	Sprague-Dawley rats	10 mg/kg/day	40 mg/kg/day	Maternal toxicity, tremors, hypoactivity, discharge from mouth and eyes, dyspnea	Dams sacrificed on day 20 of gestation, no developmental toxicity related to treatment. Resorption may have occurred at high dose that produced maternal toxicity.	EPA 1999a (Based on unpublished data submitted to EPA)

Table 1. Health Effect Levels of Naled in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (gavage)	gestation days 6–19	Sprague-Dawley rats			Maternal toxicity	.	Beaudoin and Fisher 1981; EPA 1999a (Based on unpublished data submitted to EPA)
oral (gavage)	gestation days 7–19	New Zealand rabbits	8 mg/kg/day		No maternal toxicity, pilot study used to determine dose level. 2 mg/kg/day produced mild cholinergic effects; 10 mg/kg/day produced high cholinergic effects.	Highest dose tested, no maternal or developmental toxicity related to treatment.	EPA 1999a (Based on unpublished data submitted to EPA)
oral (gavage)	2 generations	rats	6 mg/kg/day	18 mg/kg/day	Systemic effects in males of both generations; reproductive indices unaffected. Decreased body weight in both generations, survival of pups reduced, consistent decrease in pup weight during lactation, F0 and F1.	Parental systemic effects	EPA 1999a (Based on unpublished data submitted to EPA)

Carcinogenicity

No evidence exists of carcinogenicity in laboratory animals exposed to technical-grade naled (AMVAC 2002). IARC lists dichlorvos as possibly carcinogenic to humans, categorizing it in Group 2B, but states that evidence is inadequate for carcinogenicity (IARC 1991). IARC (1991) also notes that evidence is sufficient in experimental animals for the carcinogenicity of dichlorvos. This conclusion is based on two studies involving mice and three studies involving rats. Squamous-cell tumors (most often papillomas) were noted in mice fed dichlorvos. In rats fed dichlorvos, dose-related effects included mononuclear-cell leukemia and increased pancreatic adenomas (IARC 1991).

In 1999, at the Cancer Assessment Review Committee meeting for DDVP (dichlorvos), the committee determined that dichlorvos should be classified in category C as a carcinogen with "low dose risk extrapolation based on the incidence of forestomach tumor (squamous cell papilloma and/or carcinoma) in female mice" (EPA 2000). In this document, the IARC (1991) review of dichlorvos carcinogenicity is also included.

Genotoxicity

Naled causes mutations in microorganisms, apparently attributable to alkylation of DNA (Braun 1983). Mutation data exist for two bacterial species, *Bacillus subtilis* and *Salmonella enterica* serovar Typhimurium. Naled was more genotoxic in the absence of metabolic activation than in the presence of one, indicating that naled, not one of its metabolites, is responsible for the genotoxicity in microorganisms.

Section 4. Toxicokinetics

Naled can be absorbed into the body by inhalation, dermal contact, and ingestion. It does not accumulate in body tissues, but repeated exposure may have a cumulative effect on cholinesterase levels. Naled is hydrolysed rapidly in the body to produce a number of metabolites, including dichlorvos, dichlorbromoacetaldehyde, dimethyl phosphate, and an amino acid conjugate of degraded naled. In an experiment where 25 mg/kg of radiolabeled naled was fed orally to a cow, 9% was recovered in the urine and 34% was recovered in the fecal matter 1 week after dosing (INCHEM 1978). Residue of naled was not detectable (<0.01 ppm) in milk from Holstein cows that were subject to spray for 14 days with a 7.2-lb/gal EC formulation (HSDB 2002, Purdue University 1987). Because cows are ruminants, oral exposures of cows is not relevant to humans. As noted previously, risks from naled-derived dichlorvos should be calculated in an aggregate assessment for dichlorvos. The toxicity of naled could be altered by interactions with chemicals that interfere with its detoxication, with chemicals that have the same mechanism of action, or with chemicals that induce hepatic microsomal enzymes.

Section 5. Standards and Guidelines for the Protection of Human Health

Regulatory standards and guidance values are summarized in Table 2.

ATSDR has not derived MRLs for naled, and no toxicological profile exists for naled.

EPA has derived an oral RfD based on a chronic study in rats by Chevron Chemical Company. The rats were randomly divided and fed diets by gavage with 0, 0.2, 2, or 10 mg/kg/day. The noted effects were brain cholinesterase inhibition at 24% for the 2-mg/kg/day dosage group and 60% for the 10-mg/kg/day dosage group. Inhibition of erythrocyte cholinesterase at a very low level and moderate inhibition of plasma cholinesterase also were recorded for the dosage group fed 10 mg/kg/day.

Because brain cholinesterase inhibition was the effect used to determine the RfD, an uncertainty factor of 100 was used to account for both interspecies and intraspecies variation (EPA 2003).

Aside from the RfDs, EPA has derived a margin of exposure (MOE) from the dermal no-observed-adverse-effect level (NOAEL) of 1 mg/kg/day. Neither short- nor intermediate-term MOEs should be of concern for exposures of adults or children after mosquito applications by ULV spray methods, but applications for blackflies may be reason for concern because they nearly halve the MOE in both child and adult cases (EPA 1999). However, the dermal MOEs may be overestimated because they are based on the dermal NOAEL. This overestimation may result from the large difference between the dermal NOAEL and the LOAEL.

Table 2: Regulatory Standards and Guidance Values for Naled

Standards/Guidance	Value	Reference
National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention (NIOCH/CDC) Recommended Exposure Limit: (REL) 10-Hour TWA	3 mg/m ³	NIOSH 1992
Occupational Safety and Health Administration Permissible Exposure Limit (PEL)—8-Hour TWA	3 mg/m ³	OSHA 2002
American Conference of Governmental Industrial Hygienists Time Limit Value (TLV)—8-Hour TWA (inhalable fraction) (vapor and aerosol) (skin)	0.1 mg/m ³	ACGIH 2002
NIOSH/CDC Immediately Dangerous to Life or Health	200 mg/m ³	NIOSH 2002
Reference Dose (RfD)	0.002 mg/kg/day	EPA 1994
Department of Transportation Reportable Quantity	10 lbs. (4.54 kg)	DOT 2002

Section 6. References

ACGIH. 1991. Documentation of the threshold limit values and biological exposure indices. 6th ed. Volumes I, II, III. Cincinnati: 1061. (Cited in HSDB 2002)

Ames RG, Brown SK, Mengle DC, et al. 1989. Cholinesterase activity depression among California agricultural pesticide applicators. *J Ind Med* 15:143–50 (Cited in HSDB 2002)

AMVAC Chemical Corporation. 2002. Material safety data sheet, Dibrom 8 emulsive.

Beaudoin AR, Fisher DL. 1981. An in vivo/in vitro evaluation of teratogenic action. *Teratology* 23:57–61. (Cited in REPROTOX 2001)

Bidleman TF. 1988. Atmospheric processes wet and dry deposition of organic compounds are controlled by their vapor particle partitioning. *Environ Sci Technol* 22:361–7. (Cited in HSDB 2002)

Braun R, Schoeneich J, Weissflog L, et al. 1983 Activity of organophosphorus insecticides in bacterial tests for mutagenicity and DNA repair direct alkylation versus metabolic activation and breakdown. *Chem. Biol. Interact* 43:361–70. (Cited in REPROTOX)

Clarke ML, DG Harvey, DJ Humphreys. 1981. *Veterinary toxicology*. 2nd ed. London: Bailliere Tindall: 153. (Cited in HSDB 2002)

Cornell University. 1983. Naled chemical fact sheet. Available at <http://www.epa.gov/pesticides/citizens/naled4mosquitos.htm>.

DOT. 2002. List of hazardous substances and reportable quantities. US Department of Transportation. Code of Regulations. 49 CFR 172.101, Appendix A. Available at <http://www.dot.gov>. Accessed December 13, 2002.

EPA. 2003. Naled oral RfD summary. Available at <http://www.epa.gov/iris/subst/0175.htm> (Cited in IRIS (EPA 1995))

EPA. 2002. Naled for mosquito control. Washington, DC: US Environmental Protection Agency, Office of Pesticide Programs. Available at <http://www.epa.gov/pesticides/op/naled/naledsum.htm>. Accessed November 19, 2002

EPA. 2000. Cancer assessment document: evaluation of the carcinogenic potential of Dichlorvos (DDVP) (Sixth Review). Final Report. March 1, 2000. Washington, DC: US Environmental Protection Agency, Office of Pesticide Programs, Health Effects Division, Cancer Assessment Review Committee. Available at <http://www.epa.gov/pesticides/op/ddvp/carcprep.pdf>

EPA. 1999a. Naled human health risk assessment. Memorandum from S. Hummel to T. Myers, Washington, DC.: US Environmental Protection Agency, Office of Pesticide Programs, Health Effects Division. Available at http://www.epa.gov/pesticides/op/naled/hed_revassmt.pdf. Accessed February 19, 2003.

EPA. 1999b. Naled summary. Washington, DC: US Environmental Protection Agency, Office of Pesticide Programs. Available at <http://www.epa.gov/pesticides/op/naled/naledsum.html>. Accessed February 19, 2003.

EXTOXNET. 1993. Naled pesticide information profile. Available at <http://pmep.cce.cornell.edu/profiles/extoxnet/metiram-propoxur/naled-ext.html>. Accessed February 19, 2003.

Gustafson DI. 1989. Groundwater ubiquity score a simple method for assessing pesticide leachability Environ Toxicol Chem 8:339–57. (Cited in HSDB 2002)

Hartley D, Kidd H, eds. 1986. Agrochemicals handbook, with updates. Nottingham, England: Royal Society of Chemistry. (Cited in NIOSH 2000)

Hayes WJ, Jr. 1982. Pesticides studied in man. Baltimore/London: Williams and Wilkins: 172, 372. (Cited in HSDB 2002)

Hayes WJ, Laws ER, eds. 1990. Handbook of pesticide toxicology, v. 3, Classes of pesticides. New York: Academic Press, Inc. (Cited in EXTOXNET 1993)

HSDB. 2002. Hazardous Substance Data Bank: Naled. National Library of Medicine, National Toxicology Program. Available at <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> Accessed January 21, 2003.

IARC. 1991. IARC Monographs on the evaluation of carcinogenic risks to humans: occupational exposures in insecticide application, and some pesticides. Vol. 53. Lyon, France World Health Organization: 296.

INCHEM. 2002. Data sheets on pesticides No. 39: Naled. World Health Organization. Food and Agriculture Organization. Available http://www.inchem.org/documents/pds/pds/pest39_e.htm.

Jain HK, Agnihotri NP, Gupta AK. 1987. Persistence of naled and propetamphos in soil, water, and sediment. Pesticides 21:43–5. (Cited in HSDB 2002)

Kidd H, James DR, eds. 1991. The Agrochemicals handbook, Third Edition. Cambridge, UK: Royal Society of Chemistry Information Services (as updated).5-14 (Cited in EXTOXNET 1993)

Lyman WJ, Reehl WH, Rosenblatt DH. 1990. Handbook of chemical property estimation methods. Washington, DC: American Chemical Society: pp. 4–9. (Cited in HSDB 2002)

Meylan WM, Howard PH. 1991. Bond contribution method for estimating Henry's law constants. Environ Toxicol Chem 10:1283–93. (Cited in HSDB 2002)

Meylan WM, Howard PH. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26:2293–9. (Cited n HSDB 2002)

Meylan WM, Howard PH, Boethling RS. 1992. Molecular topology/fragment contribution method for predicting soil sorption coefficients. *Environ Sci Technol* 28:1560–7.

NIOSH, 2000. Registry of toxic effects of chemical substances: phosphoric acid, 1,2-dibromo-2,2-dichloroethyl dimethyl ester. Washington DC: US Department of Health and Human Services, Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/niosh/rtecs/tb903210.html>. Accessed January 22, 2003.

NIOSH, 2000. 2003. Pocket guide to chemical hazards: dimethyl-1,2-dibromo-2,2-dichloroethyl phosphate. Washington, DC: US Department of Health and Human Services, Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/niosh/npg/npg.html>. Accessed February 19, 2003.

Peckenpaugh J, Termes S, Laird C. 1997. EFED's Reregistration Chapter C for Naled. Memorandum to K. Monk, Reregistration Branch II, US Environmental Protection Agency, Washington, DC.
Purdue University. 1987. National Pesticide Information Retrieval System (Cited in HSDB 2002)

Reproductive Toxicology Center (REPROTOX). 2001 Report on naled. Available at <http://csi.micromedex.com/DATA/RX/RX1740.HTM>. Accessed January 23, 2003.

Valent USA Corporation. March 1993. Dibrom concentrate—for use in mosquito control programs. (Cited in EXTOWNET 1993)

Wauchope RD, Buttler TM, Hornsby AG, Augustijn-Beckers PWM, Burt JP. 1992. SCS/ARS/CES Pesticide properties database for environmental decision making. *Rev. Environ Contam Toxicol* 123:1–157. (Cited in HSDB 2002)

Worthing CR, SB Walker (eds.). 1983. *The pesticide manual—a world compendium*. 7th ed. Lavenham, Suffolk, Great Britain: The Lavenham Press Limited: 371. (Cited in HSDB 2002)

Zenz C, Dickerson OB, Horvath EP. 1994. *Occupational medicine*. 3rd ed. St. Louis, MO: 628 (Cited in HSDB 2002)

Phenothrin (CAS Number 260002-80-2)

Phenothrin, also known as sumithrin, is a synthetic pyrethroid. It is an insecticide registered for use against mosquitoes in swamps, and recreational areas. Phenothrin can be used to kill pests in aircrafts, ships, railroad cars and truck trailers, and for institutional non-food use. It can be used in homes, gardens, greenhouses and on pets (EPA 2005). Phenothrin is also formulated in powders, shampoos, and lotions to control human lice. In addition, it is used to protect stored grains. Racemic phenothrin was first synthesized in 1969 and is a mixture of four stereoisomers. d-Phenothrin is the 1:4 mixture of the [1R, cis] and [1R, trans] isomers and has been in use since 1977. d-Phenothrin is currently the only technical product commercially available (WHO 1990). Phenothrin breaks down rapidly in the environment and is expected to pose little risk to humans when used at low concentrations for mosquito control (EPA 2005).

Section 1. Environmental Factors

Phenothrin undergoes rapid photodegradation under outdoor conditions, with a half-life of less than 1 day on plants and other surfaces. It is transported to a very minor extent from the site of application on plants and in soils. Limited uptake of radiolabelled products into bean plants took place from soils treated with ¹⁴C-phenothrin. When soils were treated with phenothrin, it decomposed rapidly with initial half-lives of 1-2 days, but under flooded conditions the degradation was much slower from 2 weeks to 2 months. Very little movement was observed through soil columns when leaching was started immediately or 14 days after treatment with phenothrin (WHO 1990). If released into water, phenothrin is expected to adsorb to suspended solids and sediment based upon the estimated K_{oc}. Estimated volatilization half-lives for a model river and model lake are 7 and 81 days, respectively. However, volatilization from water surfaces is expected to be attenuated by adsorption to suspended solids and sediment in the water column (HSDB 2005). The degradative processes that occur in the environment generally lead to less toxic products (WHO 1990).

When phenothrin was applied to ponds at the rates of 28 or 56 g/ha to control mosquito larvae, mayfly naiads were most affected but no other arthropods were seriously affected. In fish, phenothrin has 96-hour LC₅₀ values of 17-200 µg/liter (WHO 1990).

Section 2. Potential for Exposure

Occupational exposure to phenothrin may occur through inhalation and dermal contact with this compound at workplaces where phenothrin is produced or used. The general population may be exposed to phenothrin via contact with insecticides containing phenothrin (HSDB 2005). Thus, the general population is exposed to phenothrin from conventional household aerosol spraying; when used to control lice; and from residues on stored wheat. Conventional household aerosol spraying is not expected to lead to aerial levels of phenothrin greater than 0.5 mg/m³. Residues of up to 4 mg/kg may be present in stored wheat, but this decreases after milling to 0.8 mg/kg in flour and to 0.6 mg/kg after baking (WHO 1990).

Section 3. Health Effects/Toxicity

Almost all systemic effects resulting from exposures to pyrethroids are related to their action on the nervous system. Pyrethroids exert their profound effect by prolonging the open phase of the sodium channel gates when a nerve cell is excited. In rodents, effects such as tremors are induced if the open state is prolonged for brief periods; effects such as sinuous writhing (choreoathetosis) and salivation occur if the open state is prolonged for longer periods. Neurologic signs typically result from acute

toxicity. Low-level chronic exposures to pyrethroids usually do not cause neurologic signs in mammals, largely because of rapid metabolism and elimination. Data from animal studies do not indicate that pyrethroids significantly affect end points other than the nervous system, although changes in liver weight and metabolism of chemicals sometimes have been used as an index of adverse effect levels for pyrethroids. A few recent animal studies indicate the potential for adverse neurodevelopmental, reproductive, and immunologic effects at exposure levels below those expected to result in overt signs of neurotoxicity. Data do not indicate that pyrethroids should be considered a carcinogenic concern to humans. No data in humans are available regarding the potential for pyrethroids to cross the placental barrier and enter a developing fetus. Limited data from animals indicate that transfer of pyrethroids across the placenta to the fetus may result in persistent effects on neurotransmitters later in life. Although pyrethroids have not been identified in human breast milk, very low levels of pyrethroids (<1% of an orally administered dose) are excreted into milk of lactating animals (ATSDR 2001).

Phenothrin has been used for many years and no toxic effects or cases of poisoning have been reported. In one human study by Hashimoto et al. (1980), phenothrin in a talc powder formulation was applied to the head hair and pudenda hair of 8 male human volunteers 3 times at intervals of 3 days at a dose of 32 mg/person per administration (0.44 to 0.67 mg/kg/day). Phenothrin powder was washed off 1 hour after application. There were no significant abnormalities observed in terms of dermal irritation, clinical signs, or blood biochemical and hematological parameters. The blood levels of phenothrin were below the detection limit of 0.006 mg/kg (WHO 1990).

Studies in laboratory animals exposed to phenothrin dermally, orally, or by inhalation are summarized in Table 1, with no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) indicated.

The acute toxicity of phenothrin is extremely low. The dermal LD₅₀ for phenothrin is >5,000 mg/kg in the rat and mouse. Oral LD₅₀ values for phenothrin in rats range from >500 to >10,000 mg/kg. The oral LD₅₀ for mice also range from >500 to >10,000 mg/kg. When phenothrin was given to Sprague Dawley rats orally for 5 consecutive days at 5,000 mg/kg/day, the authors concluded that phenothrin does not lead to the neurotoxic effects observed with several other pyrethroids (Okuno et al., 1978 in WHO 1990). The 4-hour inhalation LC₅₀ for phenothrin in rats ranged from >1,210 to 3,760 mg/m³ and from >1,210 to >1,180 mg/m³ in mice (WHO 1990). No adverse toxicological effects were observed when rats were exposed by inhalation to phenothrin at concentrations up to 210 mg/m³ (Kohda et al. 1979).

Several longer term studies of phenothrin have been conducted in rats and mice with exposure periods of 6 months (Murakami et al. 1981) to 2 years (Amyes et al. 1987; Hiromori et al. 19; Martin et al. 1987; Murakami et al. 1980,1981). The no-observed-effect levels from these studies were 300-1,000 mg/kg diet (approximately 40-160 mg/kg/day). A slight increase in liver weight and a significant difference in some clinical chemistry parameters from those of controls were observed at high doses in these studies. In the 2-year studies, phenothrin was not oncogenic to rats or mice at dietary levels of up to 3,000 mg/kg. Similar results were seen in two dog feeding studies with exposure periods of 26-52 weeks at doses of 100-3,000 mg/kg diet with a no-observed-effect level of 300 mg/kg diet (7-8 mg/kg/day) (Cox et al. 1987; Pence et al. 1981). Again, no tumorigenicity related to phenothrin was detected in these dog studies.

Table 1. Health Effect Levels of Phenothrin in Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Acute Duration Toxicity							
dermal	once	rat		>5,000 mg/kg	LD ₅₀		WHO 1990
dermal	once	mouse		>5,000 mg/kg	LD ₅₀		WHO 1990
oral	once	rat		>500 to >10,000 mg/kg	LD ₅₀		HSDB 2005
oral	once	rat		>5,000 to >10,000 mg/kg	LD ₅₀		WHO 1990
oral	once	mouse		>500 to >10,000 mg/kg	LD ₅₀		HSDB 2005
oral	once	mouse		>5,000 to >10,000 mg/kg	LD ₅₀		WHO 1990
oral	5 days	rat	5,000 mg/kg/day		No neurotoxic effects observed.	1 female rat died; signs of poisoning were noted in several rats, but signs disappeared rapidly at end of treatment and there were no other signs of poisoning.	Okuno et al. 1978 (WHO 1990)
inhalation	4 hr	rat		>1,210 to >3,760 mg/m ³	LC ₅₀		WHO 1990
inhalation	4 hr	mouse		>1,210 to >1,180 mg/m ³	LC ₅₀		WHO 1990
inhalation	4 hrs/day 5 wks	rat	210 mg/m ³			No adverse toxicological effects observed.	Kohda et al. 1979 (WHO 1990)
inhalation	4 hrs/day 5 wks	mouse	210 mg/m ³			No adverse toxicological effects observed.	Kohda et al. 1979 (WHO 1990)
Intermediate Duration Toxicity							
oral (diet)	6 months	rat	1,000 mg/kg	3,000 mg/kg	Elevated serum albumin level; elevated albumin-globulin ratio; increased absolute and relative liver weights.	No significant effect on mortality, clinical signs, ophthalmology, urinalysis, or gross and histopathological findings. 1 g/kg = 55.4 mg/kg/d Males; 1 g/kg = 63.3 mg/kg/d Females	Murakami et al. 1981 (WHO 1990)

Table 1. Health Effect Levels of Phenothrin in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (diet)	26 weeks	dog	300 mg/kg	1,000 mg/kg	Elevated alkaline phosphatase activity.	No abnormal findings in mortality, clinical signs, body weight, ophthalmology, gross or microscopic pathology, hematology, or urinalysis.	Pence et al. 1981 (WHO 1990)
Chronic Duration Toxicity							
oral (diet)	52 weeks	dog	300 mg/kg (M) 1,000 mg/kg (F)	1,000 mg/kg (M) 3,000 mg/kg (F)	Focal degeneration of the adrenal cortex; increased absolute and relative liver weights; decreases in erythrocytes, hemoglobin, hematocrit and total blood protein; histopathological alterations in adrenal glands and liver.	Focal degeneration of the adrenal cortex seen in 1 male dog fed 1,000 mg/kg and 4 dogs fed 3,000 mg/kg. Slightly enlarged hepatocytes in 1 male dog fed 1,000 mg/kg and 7 dogs fed 3,000 mg/kg. 300 mg/kg = 8.24 mg/kg/day - M 1,000 mg/kg = 26.77 mg/kg/day - F	Cox et al. 1987 (WHO 1990)
oral (diet)	18 months	mouse	300 mg/kg	1,000 mg/kg	Statistically significant difference in lung amyloidosis.	Increased liver weight at 3,000 mg/kg. No significant increase in tumors attributed to phenothrin.	Murakami et al. 1980 (WHO 1990)
oral (diet)	2 year	rat	2,000 mg/kg	6,000 mg/kg	Males showed a significant increase in serum glutamine-pyruvate aminotransferase activity.	No histopathological changes suggestive of oncogenicity found.	Hiromori et al. 1980 (WHO 1990)
oral (diet)	104 weeks	mouse	300 mg/kg (M) 1,000 mg/kg (F)	1,000 mg/kg (M) 3,000 mg/kg (F)	Increase in relative liver weights; higher incidence of periacinar hepatocyte hypertrophy with cytoplasmic eosinophilia in males.	No statistically significant increase in liver tumors. 300 mg/kg = 40 mg/kg/day (M) 1,000 mg/kg = 164 mg/kg/day (F)	Amyes et al. 1987 (WHO 1990)
oral (diet)	105 weeks	rat	1,000 mg/kg	3,000 mg/kg	Increase in relative liver weights; higher incidence of cystic dilatation of sinuses of mesenteric lymph nodes and periacinar hepatocytic hypertrophy in males.	No oncogenic activity.	Martin et al. 1987 (WHO 1990)
Developmental/Reproductive Toxicity							
oral	gestation days 6-18	rabbit	30 mg/kg		No apparent teratogenic effect.		Ladd et al. 1976 (WHO 1990)

Table 1. Health Effect Levels of Phenothrin in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (intubation)	gestation days 6-18	rabbit	1,000 mg/kg/day		No abnormalities observed		Rutter 1974 (WHO 1990)
oral	gestation days 7-12	mouse	3,000 mg/kg		No adverse teratogenic or embryotoxic effects.		Nakamoto et al. 1973 (WHO 1990)
oral (diet)	3 generation	rat	2,000 mg/kg		No reproductive effects.		Takatsuka et al. 1980 (WHO 1990)
oral (diet)	2 generation	rat	1,000 mg/kg	3,000 mg/kg	F ₀ and F ₁ females and selected F _{2B} male and female weanlings showed a slight but consistent increase in relative liver weights.		Tesh et al. 1978 (WHO 1990)

Neither teratogenicity nor embryotoxicity was observed in fetuses of rabbits and mice orally administered phenothrin at up to 1,000 and 3,000 mg/kg, respectively (Ladd et al. 1976; Rutter 1974; Nakamoto et al. 1973). In a 3-generation rat reproduction study, no reproductive effects were seen at 2,000 mg/kg (Takasuka et al. 1980). In a 2-generation rat reproduction study, the no-observed-effect level was 1,000 mg/kg diet, with a slight increase in relative liver weights observed at 3,000 mg/kg (Tesh et al. 1978)..

Phenothrin did not exhibit any mutagenic properties or cause chromosomal or DNA damage in a variety of *in vivo* and *in vitro* test systems (WHO 1990).

Section 4. Toxicokinetics

There have been a number of studies showing that after rats were given single or repeated oral exposure or dermal treatment with radiolabelled phenothrin, the radiolabel was rapidly and almost completely excreted in urine and feces within 3-7 days. The major metabolic pathways of phenothrin in rats were ester cleavage and oxidation at the 4'-position of the alcohol moiety or the isobutenyl group of the acid moiety (WHO 1990).

Section 5. Standards and Guidelines for Protecting Human Health

Regulatory standards and guidance values are summarized in Table 2.

An acceptable daily intake (ADI) of 0-0.07 mg/kg body weight has been established by WHO (1990).

Table 2. Regulatory Standards and Guidance Values for Phenothrin

Standard/Guidance	Value	Reference
World Health Organization acceptable daily intake (ADI)	0-0.07 mg/kg	WHO 1990

Section 6. References

Amyes SJ, Martin PA, Ashby R, et al. 1987. Sumithrin: Oncogenicity and toxicity study in mice. Suffolk, United Kingdom, Life Science Research. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)

Cox RH, Sutherland JD, Boelker RW, et al. 1987. Chronic toxicity study in dogs with Sumithrin technical grade. Vienna, Virginia, Hazleton Laboratories Inc. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)

EPA. 2005. Pesticides: Topical and Chemical Fact Sheets. Pesticides and Mosquito Control. US Environmental Protection Agency. Available at <http://www.epa.gov/pesticides/factsheets/mosquitocontrol.htm>.

Hashimoto T, Koyama Y, Okuno Y, et al. 1980. Human volunteer study with phenothrin and d-phenothrin powder. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)

Hiromori T, Koyama Y, Okun Y, et al. 1980. Two year chronic toxicity study of S-2539 in rats. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)

HSDB. 2005. Hazardous Substances Data Bank, National Library of Medicine. National Toxicology Program. Accessed March 15, 2005.

Kohda H, Nishimoto K, Kodota K, Miyamoto J. 1979. Acute and subacute inhalation toxicity studies of S-2539 Forte in rats and mice. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)

- Ladd R, Smith PS, Jenkins DH, et al. 1976. Teratogenic study with S-2539 in albino rabbits. Northbrook, Illinois, Industrial Bio-test Laboratories. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Martin PA, Amyes SJ, Ashby R, et al. 1987. Sumithrin: Combined toxicity and oncogenicity study in rats. Suffolk, United Kingdom, Life Science Research. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Murakami M, Hiromori T, Ito S, Hosokawa S. 1981. Six month oral toxicity study of S2539 Forte (Sumithrin (R)) in rats. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Murakami J, Ito S, Okuno Y, et al. 1980. Eighteen month chronic oral toxicity and tumorigenicity study of S-2539 in mice. Northbrook, Illinois, Industrial Bio-test Laboratories. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Nakamoto N, Kato T, Miyamoto J. 1973. Teratogenicity study of S-2539 Forte in mice. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Okuno Y, Kadota T, Miyamoto J. 1978. Neurotoxicity study of d-phenothrin in rats by repeated oral administration. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Pence DH, Hagen WH, Wilsaker RD, et al. 1981. Subchronic toxicity study of S2539-F in dogs. Vienna, Virginia, Hazleton Laboratories Inc. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Rutter HA. 1974. Teratogenicity study in rabbits: S-2539 Forte. Vienna, Virginia, Hazleton Laboratories Inc. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Takatsuka M, Okuno Y, Suzuki T, et al. 1980. Three-generation reproduction study of S-2539 in rats. Northbrook, , Illinois, Industrial Bio-test Laboratories. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- Tesh JM, Willoughby CR, Fowler JSL. 1987. Sumithrin: Effects upon reproductive performance of rats treated continuously throughout two successive generations. Suffolk, United Kingdom, Life Science Research. Unpublished report submitted to WHO by Sumitomo Chemical Co. (Cited in WHO 1990)
- WHO. 1990. Environmental Health Criteria 96: d-Phenothrin. International Programme on Chemical Safety. Geneva: World Health Organization.

Permethrin
(CAS Number 52645-53-1)

Permethrin is a synthetic pyrethroid that is used mostly for agricultural purposes. It has potential application in the protection of stored grain and it has been used in aerial application for forest protection and vector control, for the control of noxious insects in the household and on cattle, for the control of body lice, and in mosquito nets (WHO 1990). Permethrin is the most frequently used pyrethroid in the United States (ATSDR 2001).

Section 1. Environmental Factors

In laboratory studies, permethrin has been shown to degrade in soil with a half-life of 28 days or less. Studies to investigate the leaching potential of permethrin and its degradates showed that very little downward movement occurs in soil. Permethrin deposited on plants degrades with a half-life of approximately 10 days. In water and on soil surfaces permethrin is photodegraded by sun-light. In general, the degradative processes which occur in the environment lead to less toxic products. Permethrin disappears rapidly from the environment, in 6-24 hours from ponds and streams, 7 days from pond sediment, and 58 days from foliage and soil in a forest. From cotton leaves in a field, 30% of the compound was lost within 1 week. Under aerobic conditions in soil, permethrin degrades with a half-life of 28 days. There is very little movement of permethrin in the environment, and it is unlikely that it will attain significant levels in the environment (WHO 1990).

Direct releases to water are expected to be low for pyrethroids because these compounds are primarily applied aerially or from ground-based sprayers directly to crops and vegetation. Spray drift after application of these compounds, however, can contaminate nearby waters. Pyrethroids such as permethrin, which often is used in mosquito control, is prohibited from being applied to open water or within 100 feet of lakes, rivers, and streams because of its high toxicity to fish (EPA 2000). In addition, permethrin is highly toxic to bees.

Section 2. Potential for Exposure

Occupational exposure to phenothrin may occur through inhalation and dermal contact with this compound at workplaces where phenothrin is produced or used. Crop workers may be exposed during application and from contact with treated foliage. The general population may be exposed to permethrin via inhalation of ambient air after use, ingestion of food, and with the household use of insecticides containing permethrin (HSDB 2003). Exposure of the general population to permethrin is mainly via dietary residues. However, residue levels in crops grown according to good agricultural practice are generally low and the resulting exposure of the general population is expected to be low (WHO 1990).

Section 3. Health Effects/Toxicity

Almost all systemic effects resulting from exposures to pyrethroids are related to their action on the nervous system. These chemicals exert their profound effect by prolonging the open phase of the sodium channel gates when a nerve cell is excited. In rodents, effects such as tremors are induced if the open state is prolonged for brief periods; effects such as sinuous writhing (choreoathetosis) and salivation occur if the open state is prolonged for longer periods. Neurologic signs typically result from acute toxicity. Low-level chronic exposures to pyrethroids usually do not cause neurologic signs in mammals, largely because of rapid metabolism and elimination. Data from animal studies do not indicate that pyrethroids significantly affect end points other than the nervous system, although changes in liver weight and metabolism of chemicals sometimes have been used as an index of

adverse effect levels for pyrethroids. A few recent animal studies indicate the potential for adverse neurodevelopmental, reproductive, and immunologic effects at exposure levels below those expected to result in overt signs of neurotoxicity. Data do not indicate that pyrethroids should be considered a carcinogenic concern to humans. No data in humans are available regarding the potential for pyrethroids to cross the placental barrier and enter a developing fetus. Limited data from animals indicate that transfer of pyrethroids across the placenta to the fetus may result in persistent effects on neurotransmitters later in life. Although pyrethroids have not been identified in human breast milk, very low levels of pyrethroids (<1% of an orally administered dose) are excreted into milk of lactating animals (ATSDR 2001).

Permethrin has been used for many years, with no human poisoning cases reported. No indication exists that permethrin has a significant adverse effect on humans when used as recommended. It has induced skin sensations and paraesthesia in exposed workers, but these effects disappeared within 24 hours. Transient numbness, itching, tingling, and burning sensations have been reported in a small percentage of humans after dermal exposure to permethrin when it was used to treat head lice (WHO 1990).

Studies of laboratory animals exposed to permethrin are summarized in Table 2, with NOAELs and LOAELs indicated. Permethrin caused mild primary irritation of intact or abraded skin in rabbits. The dermal LD₅₀ is >4,000 mg/kg for rats, >2,000 mg/kg for rabbits, and >2,500 mg/kg for mice (HSDB 2003).

A 4-hour inhalation LC₅₀ for permethrin in rats is >23.5 mg/L (Exttoxnet 2003), and oral LD₅₀ values for permethrin in rats range from 410 to 6,000 mg/kg (HSDB 2003). The oral LD₅₀ for mice ranges from 250 to >4,000 mg/kg. Mortality also was observed during a 90-day oral exposure to permethrin in the diets of rats (DOD 1977). All 10 male and female rats in the projected 850 mg/kg/day exposure groups died during the study; actual doses were 505 and 870 mg/kg/day in males and females, respectively.

In acute and intermediate studies of oral toxicity in animals, permethrin caused tremors, weight loss, and increased liver and kidney weights at levels starting at 185 mg/kg/day. NOAELs in these studies ranged from 92 to 210 mg/kg/day (DOD 1977). Chronic studies on permethrin also showed increased liver weights in rats at levels starting at 25 mg/kg/day, with NOAELs at 5 mg/kg/day. One three-generation rat study showed hepatic effects in the offspring at doses of 25 mg/kg/day (FMC Corp. 1978), whereas another three-generation rat study showed no reproductive effects at 180 mg/kg/day (James 1979). No teratogenicity was seen in rats at doses up to 225 mg/kg (McGregor and Wickramaratne 1976). In another study, parent rats fed 50 mg/kg showed ataxia, tremor, and slight reduction in body weight, but no teratogenic effects were noted (Kohda et al. 1976). No oncogenicity was observed in rats and mice. Permethrin was not mutagenic in an Ames test and was negative in two reverse mutation tests in *Escherichia coli* (HSDB 2003).

Table 1. Health Effect Levels of Permethrin in Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Acute Duration Toxicity							
dermal	once	rat		>4,000 mg/kg	LD ₅₀		HSDB 2003
dermal	once	mouse		>2,500 mg/kg	LD ₅₀		HSDB 2003
dermal	once	rabbit		>2,000 mg/kg	LD ₅₀		HSDB 2003
dermal	once	rat	1.3 mg/kg		No effect on release of cytochrome C in rat brain		Abu-Qare & Abou-Donia 2001
oral	once	rat		410–6,000 mg/kg	LD ₅₀		HSDB 2003
oral	once	mouse		250 to >4,000 mg/kg	LD ₅₀		HSDB 2003
oral	14 day	rat	92 mg/kg/day (M) 114 mg/kg/day (F)	185 mg/kg/day (M) 218 mg/kg/day (F)	Muscle tremors; increased liver-to-body weight ratio in female rats		DOD 1977
oral	14 day	rat	186 mg/kg/day (M) 210 mg/kg/day (F)	379 mg/kg/day (M) 369 mg/kg/day (F)	Muscle tremors; increased liver-to-body weight ratio		DOD 1977
inhalation	4 hr	rat		>23,500 mg/m ³	LC ₅₀		Extoxnet 2003
Intermediate Duration Toxicity							
dermal	45 day	rat		0.13 mg/kg	Impairment in incline plane testing; increase in cortical and cerebellar cholinesterase activity; increase in ligand binding for M2-muscarinic acetylcholine receptor in the cortex		Abou-Donia et al. 2001b
dermal	60 day	rat	1.3 mg/kg		No effect on permeability of blood-brain barrier or blood-testes barrier		Abou-Donia et al. 2001a
dermal	60 day	rat		0.13 mg/kg	Diffuse neuronal cell death in the cerebral cortex, the hippocampal formation, and the cerebellum		Abdel- Rahman et al. 2001

Table 1. Health Effect Levels of Permethrin in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
inhalation	13 weeks, 6 hrs/day, 5 days/wk	rat	250 mg/m ³	500 mg/m ³	Neurologic—tremors, convulsions	Tremors and convulsions during first week of exposure but disappeared in the second week; hexobarbital-induced sleeping time significantly shortened after 500 mg/m ³ but not at lower doses.	Metker 1978
oral (diet)	21 days	rat		4,000 mg/kg	Severe trembling and weight loss	Some rats died at 9,000 mg/kg. No consistent histopathologic abnormalities	Dayan 1980
Oral	90 day	rat		505 mg/kg/day (M) 870 mg/kg/day (F)	Death		DOD 1977
Chronic Duration Toxicity							
oral (diet)	104 wks	rat	100 ppm (5 mg/kg/day)	500 ppm (25 mg/kg/day)	Increased liver weights		FMC Corp. 1977
Oral	2 yr	rat		500 mg/kg	Increased liver and kidney weights and hepatocyte vacuolation.	Increased liver and kidney weight and liver-to-body weight ratios in males; hepatocyte vacuolation in females; no oncogenic effects noted.	Ishmael and Litchfield 1988
oral (diet)	1 yr	dog	5 mg/kg/day	100 mg/kg/day	Increased alkaline phosphatase, increased liver weights, and hepatocellular swelling		ICI Americas Inc. 1982
oral (diet)	2 yr	rat	37.5 mg/kg/day	187 mg/kg/day	Slight whole-body tremors during first 2 weeks	No carcinogenic effects indicated.	Ishmael and Litchfield 1988
oral (diet)	2 yr	mouse	348 mg/kg/day		No signs of neurotoxicity, mortality, hematology and blood chemistry; no carcinogenic effects indicated.		Ishmael and Litchfield 1988
oral (diet)	2 yr	mouse	20 ppm (3 mg/kg/day)	500 ppm (75 mg/kg/day) (M) 2,500 ppm (375 mg/kg/day) (F)	Increased liver and lung weights; testis weight depression.	Liver and lung weight increases in females at 375 mg/kg/day; testis weight depression in males at 75 mg/kg/day; no significant carcinogenic effects noted.	FMC Corp. 1979

Table 1. Health Effect Levels of Permethrin in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Developmental/Reproductive Toxicity							
oral (diet)	3 generations	rat	180 mg/kg/day		No reproductive effects observed.	No effects on reproduction of rats; no effect on pregnancy rates, sex ratio, pup weight; no skeletal abnormalities.	James 1979
oral (diet)	3 generations	rat	100 mg/kg		No adverse reproduction effects seen.		Schroeder and Rinehart 1977
oral (diet)	3 generations	rat		500 ppm (25 mg/kg/day)	Offspring showed centrilobular hepatocyte hypertrophy and cytoplasmic eosinophilia and buphthalmos.	Body tremors in parents at 100 and 2,500 ppm and in offspring at 2,500 ppm.	FMC Corp. 1978
oral (diet)	gestation days 6–15	rat	4,000 mg/kg		No reproductive effects seen.	No significant dose-related effects on implantation sites/intrauterine fetuses observed.	Spencer and Berhance 1982
oral (gavage)	gestation days 6–16	rat	200 mg/kg		No maternal or fetotoxic effects evident.		FMC Corp 1976
oral	gestation days 9–14	rat	50 mg/kg		No teratogenic effects noted.	Parents fed 50 mg/kg showed ataxia, tremor, slight reduction in body weight.	Kohda et al. 1976
oral	gestation days 6–16	rat	225 mg/kg		No teratogenicity	No adverse toxicologic or teratogenic effects noted.	McGregor and Wickramaratne 1976

Section 4. Toxicokinetics

On the basis of the results of a study in which plasma permethrin concentrations were measured in an adult male who ingested permethrin in a suicide attempt, permethrin appears to follow a two-compartment model, with distribution half-times for the *trans* and *cis* compounds of 5.08 and 4.82 hours, respectively (Gotoh et al. 1998). After dermal application of permethrin to patients for treatment of scabies, the estimated absorption of permethrin was 0.5% of the applied dose, based on the urinary excretion of permethrin metabolites (van der Rhee et al. 1989). Urinary excretion of metabolites persisted for 7–10 days after one dermal application. A study using an *in vitro* preparation of human skin indicated that only a small fraction (approximately 0.7%) of a topically applied dose of permethrin fully penetrated the skin after a 48-hour exposure, with small amounts of permethrin identified in the epidermal and dermal layers (Franz et al. 1996).

Permethrin administered to mammals was rapidly metabolized and almost completely excreted in urine and feces within a short period of time. In rats, permethrin was distributed rapidly to nervous tissues after administration of an oral dose, with a distribution half-time of 4.85 hours (Anadón et al. 1991b). Concentrations of permethrin metabolites (*m*-phenoxy-benzyl alcohol and *m*-phenoxybenzoic acid) in nerve tissues were lower than those observed for the parent compound (Anadón et al. 1991a, 1991b). ¹⁴C-permethrin or its metabolites also are distributed rapidly to the kidney after oral administration to rats, with levels in the kidney peaking approximately 4 hours after dosing (Miyamoto et al. 1968). After oral exposure, permethrin or its metabolites also have been detected in fat of cows and rats up to 12 days after dosing (Gaughan et al. 1977, 1978). In rats exposed to single dermal doses of permethrin, >90% of the absorbed dose was excreted in urine and feces, with a urine-to-fecal ratio of approximately 4:1 (Shah et al. 1987). Percutaneous absorption of permethrin was also demonstrated in guinea pigs *in vivo* after a dermal application (Franz et al. 1996). The concentration of permethrin measured in brain tissue 24 hours after dosing was sevenfold higher than that of plasma. In this study, absorption was 20-fold greater than that measured in a preparation of human skin.

Section 5. Standards and Guidelines for the Protection of Human Health

Regulatory standards and guidance values are summarized in Table 2.

EPA has established an oral RfD for permethrin of 0.05 mg/kg/day based on a 2-year rat feeding study (FMC Corp. 1977), in which a NOAEL of 100 ppm (5 mg/kg/day) and a LOAEL of 500 ppm (25 mg/kg/day) for liver weight increases were identified. An uncertainty factor of 100 was used to account for interspecies and intraspecies differences (IRIS 2003).

The only other standards and regulations available are a World Health Organization (WHO) drinking water guideline for permethrin of 20 µg/L (WHO 2001) and a Food and Agriculture Organization/WHO accepted daily intake for permethrin of 0.05 mg/kg (HSDB 2003).

Tolerances are established for residues of permethrin and the sum total of its metabolites in or on the following animal commodities: cattle fat—3.0 ppm; cattle meat—0.25 ppm; cattle meat by-products—2.0 ppm; eggs—1.0 ppm; goat fat—3.0 ppm; goat meat—0.25 ppm; goat meat by-products—2.0 ppm; hog fat—3.0 ppm; hog meat—0.25 ppm; hog meat by-products—3.0 ppm; horse fat—3.0 ppm; horse meat—0.25 ppm; horse meat by-products—2.0 ppm; milk fat (reflecting 0.25 ppm in whole milk)—6.25 ppm; poultry fat—0.15 ppm; poultry meat—0.05 ppm; poultry meat by-products—0.25 ppm; sheep fat—3.0 ppm; sheep meat—0.25 ppm; and sheep meat by-products—2.0 ppm (HSDB 2003).

Table 2. Regulatory Standards and Guidance Values for Permethrin

Standard/Guidance	Value	Reference
World Health Organization (WHO) drinking water guideline	20 µg/L	WHO 2001
Food and Agriculture Organization/WHO accepted daily intake (ADI)	0.05 mg/kg	HSDB 2003
Environmental Protection Agency Reference Dose (RfD)	0.05 mg/kg/day	IRIS 2003

Section 6. References

Abdel-Rahman AA, Shetty AK, Abou-Donia MB. 2001. Subchronic dermal application of *N,N*-diethyl *m*-toluidamide (DEET) and permethrin to adult rats alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum. *Exp Neurol* 172:153–71.

Abou-Donia MB, Goldstein LB, Dechovskaia A, et al. 2001a. Effects of daily dermal application of DEET and permethrin, alone and in combination, on sensorimotor performance, blood-brain barrier and blood-testes barrier in rats. *J Toxicol Environ Health* 62:523–41.

Abou-Donia MB, Goldstein LB, Jones KH, et al. 2001b. Locomotor and sensorimotor performance deficit in rats following exposure to pyridostigmine bromide, DEET and permethrin, alone or in combination. *Toxicol Sci* 60:305–14.

Abu-Qare AW, Abou-Donia MB. 2001. Combined exposure to DEET (*N,N*-diethyl *m*-toluidamide) and permethrin induced the release of rat brain cytochrome c. *J. Toxicol. Environ Health Part A* 63:243–52.

Anadón A, Martínez-Larrañaga MR, Díaz MJ, et al. 1991a. Effect of deltamethrin on antipyrine pharmacokinetics and metabolism in rats *Arch Toxicol* 65:156–9.

Anadón A, Martínez-Larrañaga MR, Díaz MJ, et al. 1991b. Toxicokinetics of permethrin in the rat. *Toxicol Appl Pharmacol* 110:1–8.

ATSDR. 2001. Toxicological profile for pyrethrins and pyrethroids [Draft], Atlanta: US Department of Health and Human Services, ATSDR.

Dayan AD. 1980. 21-day neuropathological study in the Sprague-Dawley rat of permethrin (212732J) administered in the diet. Berkhamsted: Wellcome Research Laboratories. Report No. BP 80-48. Unpublished report submitted to WHO by Wellcome Foundation Ltd. (Cited in WHO 1990)

Department of Defense (DOD). 1977. Toxicological evaluation of 3-(phenoxyphenyl) methyl (+ or –)-*cis, trans*-3-(2,2-dichloroethenyl)-2,2-dimethyl cyclopropanecarboxylate (permethrin), December 1975–April 1977. Washington, DC: US Department of Defense. ADA047284.

EPA. 2000. Synthetic pyrethroids for mosquito control. Washington, DC: US Environmental Protection Agency. 735-F-00-004.

Extension Toxicology Network Exttoxnet. (EXTOXNET). 2003. Pesticide information profile. Available at <http://pmep.cce.cornell.edu/profile/exttoxnet>.

FMC Corporation. 1976. MRID No. 00029824, 00057099, 00070579. Available from EPA. (Cited in IRIS 2003)

FMC Corporation. 1977. MRID No. 00057105, 00070950, 00110686. Available from EPA. (Cited in IRIS 2003)

- FMC Corporation. 1978. MRID No. 00069702, 00120271. Available from EPA. (Cited in IRIS 2003)
- FMC Corporation. 1979. MRID No. 00027579, 00029495, 00044323, 00061901, 00062806, 92142033. Available from EPA. (Cited in IRIS 2003)
- Franz TJ, Lehman PA, Franz SF, et al. 1996. Comparative percutaneous absorption of lindane and permethrin. *Arch Dermatol* 132:901–5.
- Gaughan LC, Ackerman ME, Unai T, et al. 1978. Distribution and metabolism of *trans*- and *cis*-permethrin in lactating Jersey cows. *J Agric Food Chem* 26:813–8.
- Gaughan LC, Unai T, Casida JE. 1977. Permethrin metabolism in rats. *J Agric Food Chem* 25:9–17.
- Gotoh Y, Kawakami M, Matsumoto N, et al. 1998. Permethrin emulsion ingestion: Clinical manifestations and clearance of isomers. *Clin Toxicol* 36:57–61.
- HSDB. 2003. Hazardous Substances Data Bank (HSDB), National Library of Medicine. National Toxicology Program. <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> Accessed January 30, 2003.
- ICI Americas, Inc. 1982. MRID No. 00129600, 92142031. Available from EPA. (Cited in IRIS 2003)
- IRIS. 2003. Integrated Risk Information System (IRIS). US Environmental Protection Agency. Permethrin. Available at <http://www.epa.gov/iris/subst/0185.htm>.
- Ishmael J, Litchfield MH. 1988. Chronic toxicity and carcinogenic evaluation of permethrin in rats and mice. *Fundam Appl Toxicol* 11:308–22.
- James JA. 1979. A multigeneration reproduction study of 21Z73 (permethrin) in the rat. Report No. BPAT 79-3. Bechenham, Wellcome Research Laboratories. (Unpublished study cited in WHO 1990)
- Kohda H, Kadota T, Miyamoto J. 1976. Teratogenic evaluation with permethrin in rats. Unpublished report by Sumitomo Chemical Co. (Cited in WHO 1990)
- McGregor DB, Wickramaratne GA. 1976. Teratogenicity study in rats of ICI-PP557. Inveresk Research International Project No. 404898. Unpublished data by ICI Ltd. (Cited in WHO 1990)
- Metker LW. 1978. Subchronic inhalation toxicity of 3-(phenoxy-phenyl)methyl(+)-*cis, trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (permethrin), Aberdeen Proving Ground, Maryland: US Army Environmental Hygiene Agency. Report No. 75-51-0026-80. (Cited in WHO 1990)
- Miyamoto J, Sato Y, Yamamoto K, et al. 1968. Biochemical studies on the mode of action of pyrethroidal insecticides. Part I. Metabolic fate of phthalthrin in mammals. *Agric Biol Chem* 32:628–40.
- Schroeder RE, Rinehart WE. 1977. A three generation reproduction study of FMC33297 in rats. Bio-Dynamics Inc Project. Unpublished report from FMC Corporation. (Cited in WHO 1990)
- Shah PV, Fisher HL, Sumler MR, et al. 1987. Percutaneous absorption and pharmacokinetics of permethrin in young and adult rats. *Toxicology* 47:230–1.
- Spencer F, Berhance Z. 1982. Uterine and fetal characteristics in rats following a post-implantational exposure to permethrin. *Bull Environ Contam Toxicol*. 29:84–8. (Cited in WHO 1990)
- van der Rhee HJ, Farquhar JA, Vermeulen NPE. 1989. Efficacy and transdermal absorption of permethrin in scabies patients. *Acta Derm Venereol (Stockh)* 69:170–82.
- WHO. 1990. Environmental health criteria 94: Permethrin. Geneva: World Health Organization.

WHO. 2001. Guidelines for drinking water quality. World Health Organization. Available at <http://www.who.int/>. Accessed April 19, 2001.

Resmethrin
(CAS Number 10453-86-8)

Resmethrin is a synthetic pyrethroid used for control of flying and crawling insects in homes, greenhouses, indoor landscapes, mushroom houses, industrial sites, and for mosquito control. It is also used for fabric protection, pet sprays and shampoos, and it is applied to horses or in horse stables (Exotoxnet 2003). Resmethrin is currently used for mosquito control by aerial application (WHO 1989).

Section 1. Environmental Factors

Pyrethroids are rapidly degraded in the environment through photolysis, hydrolysis, and biodegradation. Resmethrin is released to the environment as a result of its use as an insecticide. Resmethrin is one of the least persistent pyrethroids because it rapidly degrades when exposed to air or light. Resmethrin is rapidly photodegraded; in sunlight, aqueous solutions have a half-life of 47 minutes in pure water and 20 minutes in sea water. A range of photoproducts is formed from ester cleavage and oxidation reactions. Resmethrin is also very rapidly degraded in soil, with 2% of the applied parent compound remaining after 16 days. Rapid degradation also occurs on plants; after 5 days, no resmethrin is detected on plants (WHO 1989).

Direct releases to water are expected to be low for pyrethroids because these compounds are primarily applied aerially or from ground-based sprayers directly to crops and vegetation. Spray drift after application of these compounds, however, can contaminate nearby waters. Pyrethroids such as resmethrin, which often are used in mosquito control, are prohibited from being applied to open water or within 100 feet of lakes, rivers, and streams because of their high toxicity to fish (EPA 2000). In addition, resmethrin is highly toxic to bees.

Section 2. Potential for Exposure

Occupational exposure to resmethrin may occur through inhalation and dermal contact with this compound at workplaces where resmethrin is produced or used. Since resmethrin is a widely used insecticide that can be employed for the control of a variety of insects, mosquitoes and in pet sprays and shampoos, the general population may be exposed to resmethrin through use of insecticides containing this compound (HSDB 2003). The general population may also be exposed to resmethrin to a minor extent via dietary residues (WHO 1989).

Section 3. Health Effects/Toxicity

Almost all systemic effects resulting from exposures to pyrethroids are related to their action on the nervous system. Pyrethroids exert their profound effect by prolonging the open phase of the sodium channel gates when a nerve cell is excited. In rodents, effects such as tremors are induced if the open state is prolonged for brief periods; effects such as sinuous writhing (choreoathetosis) and salivation occur if the open state is prolonged for longer periods. Neurologic signs typically result from acute toxicity. Low-level chronic exposures to pyrethroids usually do not cause neurologic signs in mammals, largely because of rapid metabolism and elimination. Data from animal studies do not indicate that pyrethroids significantly affect end points other than the nervous system, although changes in liver weight and metabolism of chemicals sometimes have been used as an index of adverse effect levels for pyrethroids. A few recent animal studies indicate the potential for adverse neurodevelopmental, reproductive, and immunologic effects at exposure levels below those expected to result in overt signs of neurotoxicity. Data do not indicate that pyrethroids should be considered a carcinogenic concern to humans. No data in humans are available regarding the potential for

pyrethroids to cross the placental barrier and enter a developing fetus. Limited data from animals indicate that transfer of pyrethroids across the placenta to the fetus may result in persistent effects on neurotransmitters later in life. Although pyrethroids have not been identified in human breast milk, very low levels of pyrethroids (<1% of an orally administered dose) are excreted into milk of lactating animals (ATSDR 2001).

Studies of laboratory animals exposed to resmethrin are summarized in Table 1, with no-observed adverse effect levels (NOAELs) and lowest-observed adverse effect levels (LOAELs) indicated.

The dermal LD₅₀ for resmethrin is 2,500 mg/kg for rats, 2,500 mg/kg for rabbits, and >5,000 mg/kg for mice. Oral LD₅₀ values for technical-grade resmethrin in rats range from 1,244 to >2,500 mg/kg. Its oral LD₅₀ for mice range from 300 to 940 mg/kg. The 4-hour inhalation rat LC₅₀ for resmethrin is >9,490 mg/m³; the inhalation LC₅₀ for dogs is >420 mg/m³, and for rabbits, >12,000 mg/m³ (HSDB 2003). However, the toxicity is influenced by the isomeric properties of the compound. For example, the oral LD₅₀ (rats) of 1R *cis* resmethrin is about 168 mg/kg, but the value for the 1R *trans* isomer is >8,000 mg/kg (Dorman and Beasley 1991). Resmethrin was found to be a slight dermal irritant in a 24-day dorsal/ventral rabbit ear test. However, it showed no compound-related lesions of the skin when applied twice a week for 3 weeks to the shaved skin of rabbits (WHO 1989).

In longer animal toxicity studies, resmethrin caused tremors, decreased body weights, and increased liver and kidney weights at levels ranging from 679 mg/kg/day to 5,000 mg/kg (Swentzel et al 1977; Miyamoto 1976). Skeletal development was delayed in rats at 80 mg/kg/day (Penwick Corp. 1979b), and a slight increase in pups cast dead and lower mean pup weight was seen at 25 mg/kg/day (Penwick Corp. 1979a). However, in another study, no teratogenicity was seen in rats at doses up to 1,500 mg/kg (Swentzel et al. 1977). In a 2-year rat study, minimal hypertrophy of hepatocytes and decreased spleen weights were seen at 39.5 mg/kg/day (Penwick Corp. 1980a). No oncogenicity was observed in rats and mice fed resmethrin. Resmethrin was not mutagenic to *Salmonella typhimurium* or Chinese hamster cells (WHO 1989).

Section 4. Toxicokinetics

In cows administered resmethrin orally, 43% of the administered dose was excreted in the urine as resmethrin metabolites (Ridlen et al. 1984). In rats administered resmethrin at 1 mg/kg, 53%–73% was excreted in the urine and feces in 6 days. When it was administered orally to rats at 500 mg/kg, it was absorbed rapidly from the gastrointestinal tract and was completely eliminated in the urine (36%) and feces (64%) in 3 weeks (HSDB 2003).

Table 1. Health Effect Levels of Resmethrin in Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Acute Duration Toxicity							
dermal	once	rat		2,500 mg/kg	LD ₅₀		HSDB 2003
dermal	once	rabbit		2,500 mg/kg	LD ₅₀		HSDB 2003
dermal	once	mouse		>5,000 mg/kg	LD ₅₀		HSDB 2003
oral	once	rat		1,244 to >2,500 mg/kg	LD ₅₀		HSDB 2003
oral	once	mouse		300–940 mg/kg	LD ₅₀		HSDB 2003
oral (diet)	14 days	rat	148 mg/kg/day (M), 180 mg/kg/day (F)	386 mg/kg/day	Tremor, increased hepatic/body weight ratios	Mortality and reduced body weight and food intake at ≥1,080 mg/kg/day.	Swentzel et al. 1977
inhalation	4 hours	rat		>9,490 mg/m ³	LC ₅₀		HSDB 2003
inhalation	1 hour	rabbit		>12,000 mg/m ³	LC ₅₀		HSDB 2003
inhalation	4 hours	dog		>420 mg/m ³	LC ₅₀		HSDB 2003
Intermediate Duration Toxicity							
oral (diet)	90 days	rat	67 mg/kg/day	679–724 mg/kg/day	Tremor, reduced body weight	Mortality at 2,400 mg/kg/day	Swentzel et al. 1977
oral (diet)	24 wks	rat	1,500 ppm (77.5 mg/kg/day (M), 86.6 mg/kg/day (F))	5,000 ppm	Tremor, decreased body weight, increased liver and kidney weights	Serum alkaline phosphatase activity also increased.	Miyamoto 1976
oral (diet)	6 months	dog	10 mg/kg/day	30 mg/kg/day	Increased liver weights		Gephart et al. 1980; Penwick Corp. 1980b
inhalation	90 days 6 hours/day, 5 days/week	rat	100 mg/m ³	300 mg/m ³	Minor effects on some clinical parameters and signs of irritation	At 1,000 mg/m ³ , clinical signs of irritation, minor neurobehavioral changes, reduced rate of weight gain; some changes in clinical pathology parameters.	Coombs et al. 1985
Chronic Duration Toxicity							
oral (diet)	2 year	rat		500 ppm (39.5 mg/kg/day M) (47 mg/kg/day F)	Minimal hypertrophy of hepatocytes; decreased spleen weights in females		Penwick Corp. 1980a
oral (diet)	85 wks	mouse	1,000 mg/kg		No oncogenicity	No oncogenicity observed	Cox et al 1979

Table 1. Health Effect Levels of Resmethrin in Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral (diet)	112 wks	rat	5,000 mg/kg		no oncogenicity	No oncogenicity observed; NOAEL of 500 mg/kg for hypertrophy of hepatocytes, which was not considered a definite toxic response	Knickerbocker et al. 1980
Developmental/Reproductive Toxicity							
oral (gavage)	gestation days 6–15	rat	80 mg/kg/day		No teratogenicity	No teratogenic effects seen	Machi et al. 1979
oral (diet)	gestation days 6–15	rat	40 mg/kg/day	80 mg/kg/day	Delay in skeletal development		Penwick Corp. 1979b
oral (intubation)	gestation days 6–18	rabbit	100 mg/kg/day		No teratogenicity	No teratogenic effects seen	Becci et al. 1979
oral (diet)	gestation days 6–16	rat	1,500 mg/kg		No teratogenicity	No gross abnormalities of fetal skeletons and soft tissues observed. Dams showed tremors and decreased food and water consumption at 1,500 mg/kg, and 2 dams died.	Swentzel et al. 1977
oral	gestation period	mouse	100 mg/kg		No teratogenicity	No significant adverse effects	Miyamoto 1976
oral (diet)	3 generations	rat		500 ppm (25 mg/kg/day)	Slight increase in pups cast dead and lower mean pup weight at weaning		Penwick Corp. 1979a

Section 5. Standards and Guidelines for the Protection of Human Health

Regulatory standards and guidance values are summarized in Table 2.

EPA has established an oral RfD for resmethrin of 0.03 mg/kg/day based on a three-generation reproduction rat study (Penwick Corp. 1980a), in which a LOAEL of 500 ppm (25 mg/kg/day) for increased pups cast dead and lower mean pup weight was identified. An uncertainty factor of 1,000 was used to account for interspecies and intraspecies differences and lack of an established NOAEL (IRIS 2003).

Table 2. Regulatory Standards and Guidance Values for Resmethrin

Standard/Guidance	Value	Reference
Environmental Protection Agency Reference Dose (RfD)	0.03 mg/kg/day;	IRIS 2003

Section 6. References

ATSDR. 2001. Toxicological profile for pyrethrins and pyrethroids [Draft], Atlanta: US Department of Health and Human Services, ATSDR.

Becci PJ, Knickerbocker M, Parent RA. 1979. Teratological evaluation of SBP-1382 in albino rabbits. Waverly, New York: Food and Drug Research Laboratories: 17 pp. Report No. 6288. Unpublished proprietary data supplied by Roussel Uclaf. (Cited in WHO 1989)

Coombs DW, Hardy CJ, Clark GC, et al. 1985. Resmethrin 90-day inhalation toxicity study in the rat. Huntingdon, UK: Huntingdon Research Centre, 80 pp. Report No. SBP 6/84997. Unpublished proprietary data supplied by Roussel Uclaf. (Cited in WHO 1989)

Cox GE, Knickerbocker M, Parent RA. 1979. Evaluation of dietary administration of SBP-1382 in CD-1 outbred albino mice over an 85-week period. Waverly, New York: Food and Drug Research Laboratories; Report No. 5270. Unpublished proprietary data supplied by Roussel Uclaf. (Cited in WHO 1989)

Dorman DC, Beasley VR. 1991. Neurotoxicology of pyrethrin and the pyrethroid insecticides. *Vet Hum Toxicol* 33:238–43.

EPA. 2000. Synthetic pyrethroids for mosquito control. Washington, DC: US Environmental Protection Agency. 735-F-00-004.

Extension Toxicology Network Extoxnet. (EXTOXNET). 2003. Pesticide information profile. Available at <http://pmep.cce.cornell.edu/profile/extoxnet>.

Gephart LA, Johnson WD, Becci PJ, Parent RA. 1980. 180-day subchronic oral dosing study with resmethrin in beagle dogs. Waverly, New York, Food and Drug Research Laboratories. Report No. 6289. Unpublished proprietary data supplied by Roussel Uclaf. (Cited in WHO 1989)

HSDB. 2003. Hazardous Substances Data Bank (HSDB), National Library of Medicine. National Toxicology Program. <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> Accessed January 30, 2003.

Integrated Risk Information System (IRIS). 2003. US Environmental Protection Agency. Resmethrin. Available at <http://www.epa.gov/iris/subst/0343.htm>.

Knickerbocker M, Becci PJ, Cox GE, Parent RA. 1980. A lifetime evaluation of the dietary administration of SBP-1382 to Wistar albino rats. Waverly, New York: Food and Drug Research Laboratories. Report No. 5271. Unpublished proprietary data supplied by Roussel Uclaf. (Cited in WHO 1989)

Machi RA, Kam C, Gallo MA, Stevens KR, Gagliardi JJ. 1979. Teratological evaluation of SBP-1382 technical in the albino rat. Florham Park, New Jersey: Booz, Allen & Hamilton Inc. Report No. 2054-066. Unpublished proprietary data supplied by Roussel Uclaf. (Cited in WHO 1989)

Miyamoto J. 1976. Degradation, metabolism and toxicity of synthetic pyrethroids. *Environ Health Perspect* 14:15–28. (Cited in WHO 1989)

Penwick Corporation. 1979a. MRID No. 00081276. Available from EPA. Write to FOI, EPA, Washington DC. 20460. (Cited in IRIS 2003)

Penwick Corporation. 1979b. EPA Accession No. 241765-66, 241768-70. Available from EPA. Write to FOI, EPA, Washington DC. 20460. (Cited in IRIS 2003)

Penwick Corporation. 1980a. EPA Accession No. 242782–242786. Available from EPA. Write to FOI, EPA, Washington DC. 20460. (Cited in IRIS 2003)

Penwick Corporation. 1980b. EPA Accession No. 244514. Available from EPA. Write to FOI, EPA, Washington DC. 20460. (Cited in IRIS 2003)

Ridlen RL, Christopher RJ, Ivie GW, et al. 1984. Distribution and metabolism of cis- and transresmethrin in lactating Jersey cows. *J Agric Food Chem* 32:1211–7.

Swentzel KL, Angerhofer RA, Haight EA. 1977. Toxicological evaluation of pyrethroid insecticide (5-benzyl-1,3-furyl) methyl-2,2-dimethyl-3-(2-methylpropenyl)cyclopropane-carboxylate (resmethrin). Aberdeen Proving Ground, Maryland: US Army Environmental Hygiene Agency. Report No. 51-0830-77. (Cited in WHO 1989)

WHO. 1989. Environmental health criteria 92: Resmethrins–Resmethrin, Bioresmethrin, Cisresmethrin. Geneva: World Health Organization.

Temephos
(CAS Number 3383-96-8)

Temephos (trade name Abate) is an organophosphate insecticide with such low toxicity to humans that it is occasionally used to treat potable water (HSDB 2003). Its primary use is as a larvicide for mosquitoes, midges, and blackflies on ponds, marshes, swamps, and neighboring ground. It also is used for cutworms, thrips, and lygus bugs on crops; for fleas on dogs and cats; and for lice on humans. Temephos has low toxicity for mammals but moderate toxicity for birds and high toxicity for certain aquatic organisms (HSDB 2003). Its low solubility in water (≤ 1 ppm; INCHEM 2002) and low human toxicity make it a candidate for (potable) water treatment, but its toxicity for certain aquatic organisms and the scarcity of information about its environmental fate may limit its appropriateness.

Section 1. Environmental Factors

An atmospheric half-life of 2.8 hours has been calculated on the basis of an estimated rate constant of 1.4×10^{-10} cm³/molecule-second for the vapor-phase reaction of temephos with photochemically produced hydroxyl radicals, given an average hydroxyl radical concentration of 5×10^5 molecules/cm³. However, because of temephos' very low vapor pressure (8.6×10^{-10} mm Hg at 25 °C), it probably will exist largely as a particulate when airborne, greatly lowering its rate of hydroxyl-radical reaction. Dry deposition is probably the dominant atmospheric removal process.

The soil adsorption coefficient for temephos is calculated to be 9,000–42,000, indicating it probably is highly immobile in soil and highly likely to partition out of water into sediment/soil (HSDB 2003). Temephos is practically insoluble in water (0.27 mg/L at 20 °C), a trait further supporting the likelihood of soil partitioning. Whether in water or soil, it is expected to volatilize extremely little. Its very low Henry's Law Constant (2×10^{-9} atm-m³/mole at 25 °C) indicates temephos would take thousands of days to volatilize from water (partitioning to soil instead), and its very low vapor pressure suggests it will not significantly volatilize from dry soil. It is expected to hydrolyze rapidly (within a few days) in highly basic or acidic conditions but to persist considerably longer at pH 5–7. When incubated in water from a sewage treatment lagoon, temephos slowly degraded after a lag period of 7 days. It did not biodegrade after 7 days in a natural pond water/sediment system. In the environment, a handful of studies found it to disappear rapidly from pond water and sediments (EPA 1999, also EXTOWNET 2002), but these data do not appear to be particularly thorough. When sprayed or dusted on vegetation, temephos has persisted for several days.

The estimated bioconcentration factor for Abate ranges from 1,300 to 20,000 according to its water solubility and octanol/water partition coefficient ($\log k_{ow}$) of 5.96 (HSDB 2003). This suggests that bio-uptake is an important process. In the few marine samples (mainly shellfish) that have been taken, however, temephos did not persist long (EPA 1999; EXTOWNET 2002; HSDB 2003). One study found that temephos bioaccumulated in fish during a 28-day exposure period, but by the 14th day after exposure, 75% of temephos had been eliminated (EPA 1999).

In summary, information about the environmental fate of temephos is sparse. On the basis of theoretical and laboratory calculations, it probably hydrolyzes quickly in highly acidic or basic conditions or in situations suitable for biodegradation, but in neutral-pH conditions it might persist for longer periods, probably tightly bound to soil. The few environmental studies have found it does not persist in sediment or in aquatic organisms.

Section 2. Potential for Exposure

Because temephos is used primarily as a larvicide to treat bodies of water, the potential for incidental dermal or soil/dust exposure during this usage is minimal (HSDB 2003). Furthermore, its human toxicity is so low that it is used for dermal application (human lice or pet flea topical treatment) as well as for potable water treatment (in combination with its very low solubility, which limits water concentrations). Because of its low human toxicity, low solubility, and use as topical treatment, unintentional toxic exposure is difficult to envision, except perhaps in the event of an occupational accident. The public could conceivably be exposed to repeated very low (<1 ppm) doses in situations where potable bodies of water are continually treated, but its low toxicity (see next section) and low solubility, indicate that little cause exists for concern about harm to humans. The possibility of injury to aquatic organisms might exist in that type of situation, however.

Section 3. Health Effects/Toxicity

Health Effect in Humans Exposed to Temephos

Few health-effect studies in humans have been conducted on temephos,, and no effects have been reported (HSDB 2003). Nevertheless, it acts as an organophosphate cholinesterase inhibitor, for which much literature is available. Health effects from a typical cholinesterase inhibitor are as follows:

- **Common early signs or mild symptoms** of acute cholinergic poisoning include miosis (pinpoint pupils), headache, nausea/vomiting, dizziness, muscle weakness, drowsiness, lethargy, agitation, and anxiety.
- **Moderate or severe poisoning** can result in chest tightness, difficulty breathing, bradycardia, tachycardia, hypertension, pallor, abdominal pain, incontinence, diarrhea, anorexia, tremor/ataxia, fasciculation, lacrimation, heavy salivation, profuse sweating, blurred vision, poor concentration, confusion, and memory loss.
- **Life-threatening or very severe signs and symptoms**, such as coma, seizures, respiratory arrest, pulmonary edema, loss of reflexes, and flaccid paralysis, can occur at high doses, such as in the cases of attempted suicide.

Effects of temephos on humans have not been reported in the literature, presumably because of its low toxicity.

Experimental Studies in Humans

Only three studies of humans were found in the literature.

A 19-month study was conducted of temephos added to all cisterns and other potable water containers in a community of approximately 2,000 people (Laws et al., 1968). The treatment occurred once a month and consisted of 1% temephos adsorbed to sand, in sufficient quantity to achieve a calculated concentration of 1 ppm (19 g of sand per 50 gallon/188 liter drum). Only one water sample ever had a temephos concentration >0.5 ppm, attributable to the combined effects of adsorption, solubility, and dilution over time. No significant change was measured in either plasma or erythrocyte cholinesterase of the villagers at any time during the study. Urinary excretion of temephos reached steady state after 4 months. No illness attributable to the insecticides occurred, and all of eight babies born were normal.

Humans who ingested 256 mg/day for 5 days or 64 mg/day for 4 weeks had no symptoms or any detectable effects on plasma or erythrocyte cholinesterase activity (Laws et al. 1967). At 70 kg for an adult, the doses are equivalent to 3.7 mg/kg/day for 5 days or 0.9 mg/kg/day for 4 weeks. When the standard water ingestion rate of 2 liters/day and the solubility of temephos (<1 ppm) are considered together, adult humans would be expected to receive <2 mg/day from drinking water treated with temephos. This scenario is extreme because daily water treatments are unlikely, so concentrations of temephos would decrease between treatments. The concentrations may be considerably below saturation (~1 ppm) even at their peak (the time of treatment). Given the no-observed-adverse-effect level (NOAEL) of 64 mg/day for 4 weeks, temephos is not expected to present a health hazard when used for larvicide water treatment.

A 2% formulation of temephos in pyrax powder was applied to participants and their bedding from a shaker (57 g, equivalent to 1.1 g of temephos) or to clothed subjects from a powder duster (31 g, equivalent to 0.62 g) (Steinberg et al. 1972). The treatment was safe and effective.

Health Effects Possibly Related to Municipal Use of Temephos for Mosquito Control

Temephos is not expected to pose a hazard to the public when used for mosquito control because (1) it would most likely be used for water (larvicide) treatment; (2) it has a low potential for toxicity in humans; and (3) it has a very low water solubility. In regard to people caught in aerial spray (or exposed to dust), temephos is used to treat lice on humans (and fleas on pets) in quantities on the orders of tens of grams. No instances were reported of human toxicity from temephos (HSDB 2003).

For these reasons, temephos is not expected to be of concern in municipal scenarios, barring an extreme occupational accident.

Health Effects in Laboratory Animals

Studies in laboratory animals exposed to temephos orally and dermally are summarized in Table 1, with NOAEL and lowest-observed-adverse-effect levels (LOAELs) indicated. Very high doses can cause death, but given the very low solubility of temephos, such doses would not be expected in humans (barring an occupational accident or intentional poisoning).

As expected, cholinesterase inhibition is a sensitive indicator. This effect was generally seen at approximately 10 mg/kg/day. Other effects also were noted at higher doses, including liver effects. However, a few chronic studies indicated organophosphate toxicity or other effects at 1 mg/kg/day.

Carcinogenicity

No studies or regulations regarding carcinogenicity were found. The handful of existing chronic-toxicity studies did not mention cancer.

Genotoxicity

The effect of temephos on several strains of bacteria has been tested (EXTOXNET 2002). Although one strain showed weak mutagenicity, the overall conclusion was that temephos is not mutagenic. Tests on rabbits also have shown no signs of mutagenicity.

Table 1. Health Effect Levels of Temephos in Humans and Laboratory Animals

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Acute Duration Toxicity							
dermal	once	human	1.1 g/person		Signs of toxicity	Used from a shaker or duster in topical treatment for lice. Concluded to be safe and effective.	Steinberg et al. 1972
dermal	once	rat (m)		>4,000 mg/kg	LD ₅₀	LD ₅₀	INCHEM 2002
dermal	once	rat (f)		>4,000 mg/kg	LD ₅₀	LD ₅₀	INCHEM 2002
dermal	once	dog		>5,000 mg/kg	LD ₅₀	LD ₅₀	EXTOXNET 2002
dermal	once	cat		>5,000 mg/kg	LD ₅₀	LD ₅₀	EXTOXNET 2002
dermal	once	rabbit		1,300 mg/kg	LD ₅₀	LD ₅₀	INCHEM 2002
dermal	5 days	rabbit		0.4 ml/kg/day (178 mg a.i./kg/day)	Cholinesterase inhibition; diarrhea	Both cholinesterase inhibition and diarrhea were noted.	INCHEM 2002
oral	5 days	human	256 mg/day (~3.7 mg/kg/day)		inhibition; clinical symptoms	No inhibition or symptoms observed.	Laws et al. 1967
oral	once	rat (m)		8,600 mg/kg	LD ₅₀ Cholinesterase	LD ₅₀	INCHEM 2002
oral	once	rat (f)		1,300 mg/kg	LD ₅₀	LD ₅₀	INCHEM 2002
oral	once	mouse		4,700 mg/kg	LD ₅₀	LD ₅₀	EXTOXNET 2002
oral	5 days	rabbit		100 mg/kg/day	Liver	Focal and diffuse hepatic necrosis noted.	HSDB 2003
oral	5 days	guinea pig	100 mg/kg/day		Organophosphate poisoning	No poisoning noted.	INCHEM 2002

Table 1. Health Effect Levels of Temephos in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
Intermediate Duration Toxicity							
dermal	3 weeks, 5 days/wk	rat	12 mg/kg/day	60 mg/kg/day	Lesions; tissue changes; body weight	When applied dermally as aqueous emulsion, half of rats had abraded skin. Decreased weight gain noted in 60 mg/kg/day group (intact and abraded skin), but no other effects seen.	INCHEM 2002
oral	28 days	human	64 mg/day (~0.9 mg/kg/day)		inhibition; clinical symptoms	No inhibition or symptoms observed.	Laws et al. 1967
oral	30 days	rabbit		10 mg/kg/day	Liver	Mild hepatic pathologic changes.	HSDB 2003
oral	44 day	rat	1 mg/kg/day	10 mg/kg/day	Erythrocyte cholinesterase inhibition	10 mg/kg/day resulted in 31% inhibition at 14 days and 47% at 44 days. No signs of organophosphate poisoning seen. Rats receiving 100 mg/kg/day showed signs of poisoning after 3 days (at 64% inhibition); gradual recovery from symptoms ensued, although inhibition progressed to 87% after 11 days.	INCHEM 2002
oral	35 days	rabbit	1 mg/kg/day	10 mg/kg/day	Cholinesterase inhibition; liver effects	No effects or significant inhibition were noted at 0.1 mg/kg/day or 1 mg/kg/day. The 10 mg/kg/day group developed 26% inhibition by day 7 and 47% inhibition by day 35. No animals showed signs of poisoning; no higher doses were used.	INCHEM 2002; HSDB 2003
oral	90 days	rat	6 ppm (0.3 mg/kg/day)	350 ppm (17.5 mg/kg/day)	Cholinesterase inhibition; clinical signs	Cholinesterase inhibition was the only effect noted.	INCHEM 2002; HSDB 2003
oral	35 days	rat	1 mg/kg/day		Cholinesterase inhibition	No cholinesterase inhibition was seen.	HSDB 2003
oral	186 days	sheep	5 mg/kg/day			No effects were noted.	HSDB 2003

Table 1. Health Effect Levels of Temephos in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral	99 days	rat		2,000 ppm (~100 mg/kg/day)	Death, clinical signs, and erythrocyte cholinesterase inhibition	8 of 10 died within 10 days; 100% erythrocyte cholinesterase inhibition; signs of poisoning.	HSDB 2003
Chronic Duration Toxicity							
oral (in drinking water)	19 months	human	0.5 ppm		Cholinesterase inhibition; clinical symptoms	No inhibition or symptoms observed in village of 2,000 when water containers were treated once a month with temephos; 0.5 ppm estimated maximum dose.	Laws et al. 1968
oral (diet)	2 years	rat	300 ppm		Not specified	No effects were noted.	HSDB 2003
oral	422 days	sheep	2.5 mg/kg/day		Not specified	No effects were noted.	HSDB 2003
oral	1 year	cow		1 mg/kg/day	Not specified	“Signs of poisoning” were noted.	HSDB 2003
oral	2 years	rat	1 ppm	10 ppm	Liver effects	Minor pathologic changes noted in liver.	EXTOXNET 2002
Developmental/Reproductive Toxicity							
oral (in drinking water)	19 months	human	0.5 ppm		Cholinesterase inhibition; clinical symptoms; reproduction	No symptoms observed in village of 2,000 when water containers were treated once a month with temephos; 0.5 ppm estimated max. dose. Eight normal births were observed.	Laws et al. 1968
oral (diet)	3 generations	rat	125 ppm		Fertility, gestation, reproduction, lactation, congenital defects	No effects were noted. Dietary exposure continued from weaning through reproductive age.	HSDB 2003

Table 1. Health Effect Levels of Temephos in Humans and Laboratory Animals (continued)

Route	Duration	Species	NOAEL	LOAEL	Organ/Effect	Comments	Reference
oral	unspecified	rat		500 ppm (25 mg/kg/day)	Number of litters, litter size, viability, congenital defects, cholinesterase inhibition; signs of toxicity	No developmental or reproductive effects were noted, but some cholinesterase inhibition and toxicity were seen.	EXTOXNET 2002; HSDB 2003
oral	1 year	cow		1 mg/kg/day	Fertility	Evidence indicated that it may affect the fertility in heifers.	HSDB 2003

Section 4. Toxicokinetics

The majority of an oral temephos dose in rats is excreted unchanged in the feces and urine (ExToxNet 2002; HSDB 2003; INCHEM 2002). 60% of the dose appeared in rat feces. Urinary excretion included sulfate ester and glucoside conjugates of phenolic hydrolysis. After oral administration of tritiated temephos in rats, radiation peaked in blood at 5–8 hours and then decreased, with a half-life of 10 hours. Radioactivity was found in the gastrointestinal tract and in fat. The mode of action of organophosphate cholinesterases is phosphorylation of the acetylcholinesterase enzyme at nerve endings. The toxicity of temephos could be altered by interactions with chemicals that interfere with its detoxication or with chemicals that have the same mechanism of action.

When temephos was applied dermally, <3% was absorbed across the skin in rats, rabbits, and dogs (HSDB 2003).

Section 5. Standards and Guidelines for the Protection of Human Health

Regulatory standards and guidelines are shown in Table 2.

Perhaps because of temephos' low toxicity and low expected concentrations, no agency has developed guidelines for chronic exposure. (Previous studies have indicated that its water concentration is not expected to be able to approach a level that would be toxic.) However, some occupational guidelines exist.

Table 2. Regulatory Standards and Guidance Values

Standard/Guidance	Value	Reference
National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention (NIOSH/CDC) Recommended Exposure Limit (REL): 10-hour time-weighted average (TWA, total dust)	10 mg/m ³	NIOSH 2003
NIOSH/CDC REL 10-hour TWA, respirable fraction	5 mg/m ³	NIOSH 2003
Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) 8-hour TWA, total dust	15 mg/m ³	NIOSH 2003
OSHA Permissible Exposure Limit (PEL): 8-hour TWA, respirable fraction	5 mg/m ³	NIOSH 2003

Section 6. References

EPA. 1999. Reregistration Eligibility Decision (RED) for Temephos: Revised environmental fate and effects assessment. Washington, DC: Environmental Protection Agency. Available at http://www.epa.gov/pesticides/op/temephos/rev_efed.pdf. Document is undated but hotlink from <http://www.epa.gov/pesticides/op/temephos.htm> says "Released 10/06/99."

EXTOXNET. 2002.: Pesticide information profile for temephos. Available at <http://pmep.cce.cornell.edu/profiles/extoxnet/pyrethrins-ziram/temephos-ext.html>. Accessed December 2, 2002; PIP "published" September 1993 and "last modified" December 19, 2001.

Hayes WJ Jr. 1982. Pesticides studied in man. Baltimore/London: Williams and Wilkins: 377.

HSDB. 2003. Hazardous Substances Databank: Temephos. National Library of Medicine, National Toxicology Program. Available at <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>. Accessed February 19, 2003.

INCHEM. 2002. Data sheets on pesticides. No. 8 Rev. 1: Temephos. Geneva: Food and Agricultural Organization, World Health Organization. Available at http://www.inchem.org/documents/pds/pds/pest8_e.htm. Accessed November 26, 2002; Data sheet revision date August 1978.

Laws ER Jr, Morales FR, Hayes WJ Jr, Joseph CR. 1967. Toxicology of Abate in volunteers. *Arch Environ Health* 14:289–91.

Laws ER Jr, Sedlak VA, Miles JW, Romney-Joseph C, Lacomba JR, Diaz-Rivera A. 1968. Field study of the safety of Abate for treating potable water and observations on the effectiveness of a control programme involving both Abate and Malathion. *Bull. World Health Org.* 38:439–45.

NIOSH. 2003. NIOSH pocket guide to chemical hazards: Temephos. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/niosh/npg/npgd0589.html>. Accessed April 1, 2003.

Steinberg M, Cole MM, Miller TA, Godke RA. 1972. Toxicological and entomological field evaluation of Mobam and Abate powders used as body louse toxicants (Anoplura: pediculidae). *J Med Entomol* 9:73–7.

Conclusions

The organophosphate insecticides (fenthion, malathion, naled, and temephos) summarized in this document are used as adulticides for agricultural and domestic control of insects. They are all effective in eradicating mosquitoes by inhibiting acetylcholinesterase in the targeted insects. Temephos is used as a larvicide for mosquito control. The persistence of organophosphate insecticides varies, by individual chemical and physical properties. Aerial application of these insecticides may result in oxidation in air to their more potent oxon analogs. The organophosphate insecticides also inhibit acetylcholinesterase in humans and animals, which can lead to cholinergic poisoning. Depending on the level and duration of exposure, symptoms can range from mild (headache, drowsiness) to moderate (difficulty breathing, cardiac arrhythmias, confusion) to life-threatening (coma, seizures, paralysis). The organophosphate insecticides have varying degrees of toxicity, with temephos and malathion appearing to be the least toxic, followed by naled, and fenthion. For example, although no MRLs or RfDs are available for temephos, humans tolerated doses as high as 256 mg/day for 5 days or 64 mg/day for 4 weeks with no symptoms and no effects on plasma or erythrocyte cholinesterase. Malathion has relatively low toxicity to humans, other mammals, and birds compared with other organophosphate insecticides. The chronic oral MRL and RfD for malathion are 0.02 mg/kg/day, whereas the RfD for fenthion is 0.00007 mg/kg/day.

Resmethrin, phenothrin, and permethrin are synthetic analogues (pyrethroids) of original pyrethrins, which are natural extracts in the flowers of the chrysanthemum plant. They typically are used as insecticides for both home and commercial use and are the most common pyrethroids used for mosquito control. They are not persistent in the environment. They act by rapidly paralyzing flying insects. Almost all systemic effects are related to the action of pyrethrins and pyrethroids on the nervous system. These chemicals exert their profound effect by prolonging the open phase of the voltage-gated sodium channels when a nerve cell is excited. They have relatively low mammalian toxicity, a rapid rate of degradation in the environment, and a typical use as insecticides for both home and commercial use. The RfDs for resmethrin and permethrin have the same order of magnitude as malathion: 0.03 mg/kg/day for resmethrin and 0.05 mg/kg/day for permethrin. There is not RfD for phenothrin, but WHO established an ADI of 0–0.07 mg/kg/day.

Methoprene is an insect growth regulator used as a larvicide. It is a synthetic analogue of the insect juvenile hormone that has very low toxicity for animals and humans. Unlike conventional insecticides that act as direct poisons, methoprene acts by disrupting the morphologic development of insects. It rapidly degrades in the environment, but it may accumulate in aquatic organisms. People may be exposed to small amounts of methoprene through the food supply, but the amount of methoprene in the U.S. consumer's diet is well below the level at which any adverse health effects could occur.

More than one of these or other insecticides may be used simultaneously, and exposure to several insecticides can occur simultaneously. Thus, joint toxic action, either by additivity or synergism may be a concern.

Recommendations for Avoiding Mosquito Bites

The Centers for Disease Control and Prevention provides recommendations for avoiding mosquito bites at <http://www.cdc.gov/ncidod/dvbid/westnile/index.htm>. Briefly, these include

- Apply insect repellent containing DEET (N,N-diethyl-meta-toluamide) to exposed skin whenever you are outdoors by following the directions on the insect repellent product
- When possible, wear long-sleeves, long pants, and socks when outdoors. Treating clothes with repellents containing permethrin or DEET will give extra protection, because mosquitoes can bite through thin clothing. Do not apply repellents containing permethrin directly to skin. Do not spray repellent containing DEET on the skin under your clothing.
- The hours from dusk to dawn are peak mosquito biting times. Consider avoiding outdoor activities during these times—or take extra care to use repellent and protective clothing during early evening and early morning.
- Mosquitoes lay their eggs in standing water. Limit the number of places around your home for mosquitoes to breed by getting rid of items that hold water.
- Check to see if an organized mosquito control program exists in your area. If no program exists, work with your local government officials to establish a program (see e.g., www.cdc.gov/ncidod/dvbid/westnile/city_states.htm).