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Malathion

Human Health and Ecological Risk Assessment

Final Report

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
ADI	acceptable daily intake
AEL	adverse-effect level
a.i.	active ingredient
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BMD	benchmark dose
$BMDL_{10}$	lower limit of the benchmark dose for 10% response
$BMDL_{20}$	lower limit of the benchmark dose for 20% response
bw	body weight
calc	calculated value
CBI	confidential business information
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
DTH	delayed-type hypersensitivity
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
ED_x	effective dose causing an X% response
ED_{10}	effective dose causing an 10% response
EHE	2-ethylhexyl ester
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IC_{50}	concentration causing 50% inhibition of a process
IgG	serum immunoglobulin G
IgM	serum immunoglobulin M
IMS	Intermediate syndrome
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient

K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LMI	leukocyte migration inhibition
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
m	meter
M	male
MDA	malathion dicarboxylic acid
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
MHV3	mouse hepatic virus 3
mL	milliliter
mM	millimole
MMI	macrophage migration inhibition
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPIDN	organophosphorus induced delayed neurotoxicity
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically based pharmacokinetic
PFC	plaque forming cells [splenic]
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SRBC	sheep red blood cell
TEP	typical end-use product
t.g.i.a.	Technical grade active ingredient
TRED	Tolerance Reassessment Eligibility Decision
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture

U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WHO	World Health Organization

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8 °C+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556 °F-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($\mu g/cm^2$)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	10,000
yards	meters	0.9144

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.

CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
1×10^{-10}	0.0000000001	One in ten billion
1×10^{-9}	0.000000001	One in one billion
1×10^{-8}	0.00000001	One in one hundred million
1×10^{-7}	0.0000001	One in ten million
1×10^{-6}	0.000001	One in one million
1×10^{-5}	0.00001	One in one hundred thousand
1×10^{-4}	0.0001	One in ten thousand
1×10^{-3}	0.001	One in one thousand
1×10^{-2}	0.01	One in one hundred
1×10^{-1}	0.1	One in ten
1×10^{0}	1	One
1×10^{1}	10	Ten
1×10^{2}	100	One hundred
1×10^{3}	1,000	One thousand
1×10^{4}	10,000	Ten thousand
1×10^{5}	100,000	One hundred thousand
1×10^{6}	1,000,000	One million
1×10^{7}	10,000,000	Ten million
1×10^{8}	100,000,000	One hundred million
1×10^{9}	1,000,000,000	One billion
1×10^{10}	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

PROGRAM DESCRIPTION

Malathion is an organophosphate pesticide used in Forest Service programs to control insect pests (e.g., thrips) in pine seed orchards and to control mosquitoes on lands managed by the Forest Service. Although either ground or aerial applications of malathion may be used in the programs to control mosquitoes, only ground equipment will be used to apply malathion in programs to control insects in pine seed orchards.

Of the many commercial formulations of malathion, Fyfanon ULV and Atrapa VCP are the formulations most commonly used for mosquito control in programs affecting lands managed by the Forest Service. Both products are adulticides—i.e., they are labeled for the control of adult mosquitoes. The Fyfanon and Atrapa formulations each contain about 96.5% malathion (9.9 lbs/gallon w/w). The remaining 3.5% of the formulations is listed as inerts on the product labels. The inerts seem to be impurities in technical grade malathion, the presence of which is an important issue that is addressed in the risk assessment. Fyfanon ULV and Atrapa ULV, which are designed for ultra-low volume application, can be applied using ground equipment or aircraft. In addition to the ULV formulations, various emulsifiable concentrate (EC) formulations of malathion have been used in ground applications. Two petroleum-based formulations, Hi-Yield 55% Malathion and Malathion 5, which are used only to control insect pests in pine seed orchards, are covered in this risk assessment.

Forest Service records indicate that ground application rates of malathion to control insect pests in pine seed orchards range from about 0.1 to 1.5 lb a.i./acre with an average application rate of about 0.3 lb a.i./acre. Labeled application rates for mosquito control are lower and range from 0.11 to 0.23 lb a.i./acre. For this risk assessment, the typical application rate for mosquito control is taken as 0.15 lb a.i./acre. Applications for mosquito control may be done repeatedly and as needed throughout the year. Neither the maximum cumulative annual application rate nor minimum application interval for mosquito control is specified on the product label. Most malathion use on lands managed by the Forest Service occurs in Region 8, the southern region. Based on the use statistics for Region 8, this risk assessment assumes a sequence of eight applications separated by 1-week intervals.

The use of malathion on lands managed by the Forest Service is miniscule compared with the total use of malathion in the United States. According to the use statistics summarized by the U.S. EPA, Forest Service use accounts for about 0.00017% (i.e., 1.7 in one million) of the total use in the United States.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification – Exposure to malathion can result in the inhibition acetylcholinesterase (AChE). The U.S. EPA uses AChE inhibition as the endpoint of concern for most dose-response assessments of malathion, and a similar approach is taken in this risk assessment. Depending on the degree of AChE inhibition, clinical effects can range from mild signs of toxicity (e.g., salivation or lacrimation) to convulsions and death. There are two types of AChE, one occurring

in nerve tissue and the other in red blood cells (RBC). In addition, plasma contains cholinesterases (ChE) that are different from and have broader substrate specificity than either RBC or nerve tissue AChE.

The malathion molecule itself does not cause AChE inhibition. AChE inhibition is induced by the metabolism of malathion to malaoxon in mammals and other species. Thus, the extent of metabolism from malathion to malaoxon is an important aspect for understanding the time-course of AChE or ChE inhibition. In most studies, inhibition of AChE or ChE by malathion is typically rapid in onset. Once exposure to malathion ceases, spontaneous reactivation of AChE proceeds relatively fast.

Some organophosphate pesticides cause other types of neurotoxic effects, specifically delayed toxicity and a condition known as *intermediate syndrome* (IMS). Delayed toxicity involves the inhibition of neuropathy target esterases (NTE) and is a neurological effect that is totally different from AChE inhibition. IMS appears to involve muscle fiber necrosis which occurs after acute AChE inhibition by organophosphate insecticides. Based on the available information, malathion does not appear to cause delayed toxicity or intermediate syndrome.

In terms of acute toxicity to humans and other mammals, malathion is among the least toxic of the organophosphate pesticides, with a very low order of acute toxicity resulting from oral, dermal, or inhalation exposure. A standard measure of acute lethal potency is the LD_{50} (i.e., the dose that is estimated to kill 50% of exposed individuals). In rat studies, the acute oral LD_{50} is more than 5000 mg/kg for technical grade malathion and up to 12,500 mg/kg for highly purified malathion. The dermal toxicity of malathion is so low that actual LD_{50} values have not been determined. Available studies indicate that the dermal LD_{50} of malathion is greater than 2000 mg/kg and report dermal NOAEL values of up to 5000 mg/kg. The inhalation LC_{50} values for technical grade malathion range from about 2000 to 5200 mg/m^3, concentrations far above any plausible levels of exposure.

The differences between the acute oral toxicity of technical grade malathion and highly purified malathion suggest that the impurities in technical grade malathion may contribute to toxicity. While an understanding of the impurities in malathion is important for assessing the relevance of some studies for the current risk assessment, the occurrence of these impurities in malathion has relatively little impact on the uncertainties that affect this risk assessment because all of the toxicology studies on malathion that are used quantitatively in this risk assessment involve a grade of malathion that is either identical to or comparable to the formulations used in Forest Service programs. Thus, the role of the impurities in technical malathion is likely to be encompassed by the available toxicity studies that investigate the effects of technical grade malathion.

Based on studies submitted to the U.S. EPA in support of the registration of malathion, U.S. EPA classifies malathion as non-irritating to the skin of rabbits (Category IV) and minimally irritating to the eyes of rabbits (Category III). This assessment is consistent with studies published in the open literature indicating that malathion may cause only transient eye irritation. There is one

early report in the literature of apparent contact dermatitis in humans exposed to technical grade malathion. Other studies associate contact dermatitis or delayed hypersensitivity with exposure to malathion bait sprays which involve the application of malathion with various adjuvants that may have contributed to the reports of delayed hypersensitivity.

There is a body of literature indicating that malathion may influence immune function, causing either enhancement or suppression of different endpoints under different exposure conditions and in different species. Immune enhancement can lead to transient inflammatory responses like irritation to the skin or respiratory tract. Oral exposure to malathion over a wide range of doses, from 0.1 to about 700 mg/kg/day, were shown to stimulate serum histamine release and macrophage activation. These effects, however, last for only a short period of time, usually from 2 to 4 hours after dosing. Several studies suggest that malathion may impair immune function based on decreased immune response indicators to foreign antigens. Only two studies, however, associate malathion exposures directly with increased susceptibility to infections which may suggest immunological impairment considered to be clinically significant. In both of these studies, tests for effects on immune function indicators were not performed. Thus, the potential clinical significance of the effects of malathion on immune function indicators is unclear.

There is a large, complex, and often controversial literature on the potential carcinogenicity of malathion as well as the potential mutagenicity of malathion and malaoxon. These studies were reviewed in detail by the U.S. EPA in the re-registration of malathion, and the U.S. EPA concluded that although there is suggestive evidence of carcinogenicity resulting from exposure to malathion, the evidence is not sufficient to support a quantitative risk assessment. Similar conclusions were reached by other organizations, including the Agency for Toxic Substances and Disease Registry (ATSDR) and the World Health Organization (WHO).

Malathion was tested for its ability to cause birth defects (i.e., teratogenicity) and its potential to cause adverse effects on reproductive performance. Teratogenicity studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Reproduction studies typically involve exposing animals for more than one generation, with each generation being allowed to reproduce. As a class, organophosphate pesticides appear to be toxic but not teratogenic in developing mammals, which appears to be the case with malathion.

Certain groups of individuals may be at increased risk when exposed to malathion. Based on toxicity studies, very young animals may be more sensitive than older animals to malathion. Because certain esterases in the liver play an important role in the detoxicification of malathion, individuals with liver disease who have abnormally low levels of endogenous liver malathion carboxylesterases may be at increased risk. There are no studies, however, that directly support this supposition. Similarly, animals on low-protein diets tend to have a number of changes in liver function that could impact susceptibility to compounds that are either activated or detoxified in the liver; however, there is limited experimental evidence to support this supposition.

Exposure Assessment –All exposure assessments for malathion are summarized in the EXCEL workbooks that accompany this risk assessment: Attachment 1 for eight applications at a typical rate of 0.15 lb a.i./acre with a ULV formulation for mosquito control and Attachment 2 for a single application at a typical rate of 0.3 lb a.i./acre with an EC formulation for insect control in pine seed nurseries. Nursery applications may entail multiple applications as is the case with ULV applications for mosquito control. Nonetheless, the assumption of single application for EC formulations applied to pine seed orchards is intended to bracket a plausible lower bound for the number of applications that may be used. EC formulations that involve multiple applications can be readily modeled using the EXCEL workbook for ULV formulations.

In the EXCEL workbooks, Worksheet E01 summarizes exposures for workers and Worksheet E03 summarizes exposures for the general public. The consequences of using a range of application rates, as detailed in the Program Description (Section 2), is considered in the risk characterization (Section 3.4).

Three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. In scenarios involving the ULV applications of malathion (i.e., non-accidental exposure), central estimates of exposure are approximately 0.002 mg/kg/day for aerial and backpack workers and about 0.003 mg/kg/day for broadcast ground spray workers. Upper bounds of exposures are approximately 0.022 mg/kg/day for broadcast ground spray workers and 0.012 mg/kg/day for backpack and aerial workers. The exposure levels for workers involved in the application of EC formulations are about twice those for workers involved in the application of ULV formulations. The differences in exposure levels reflect the differences in the typical application rates used for mosquito control (ULV formulations) and insect control in pine seed nurseries (EC formulations).

All of the accidental exposure scenarios for workers involve dermal exposure. The accidental exposure scenarios lead to dose estimates that are substantially greater than the general exposure levels estimated for workers. The greatest estimated exposure level is approximately 23 (15-35) mg/kg bw, which is associated with wearing contaminated gloves for 1 hour while applying ULV formulations. For emulsifiable concentrate (EC) formulations, the estimated dose levels associated with accidental exposures are far less. For the contaminated gloves scenario, the doses associated with a 1-hour exposure are only about 0.2 (0.01 to 3) mg/kg bw. The reason for this difference is that in the field, ULV formulations, unlike EC formulations, are not diluted prior to application. Consequently, the malathion concentration in the ULV formulation is about 1230 mg/mL, while the malathion concentration in field solutions of EC formulations is only about 3.6 (0.36 to 36) mg/mL.

Also, the difference in malathion concentrations in field solutions of ULV and EC formulations results in substantially different exposure levels for members of the general public in both accidental spray and accidental spill scenarios. For the general public (Worksheet E03), acute levels of exposures range from minuscule (e.g., less than 0.0001 mg/kg/day) to about 105 mg/kg bw for ULV formulations and 3 mg/kg bw for EC formulation. The maximum exposure levels for both the ULV and EC formulations are associated with the accidental spill of 200 gallons of a

field solution into a small body of water. The malathion concentration in the ULV formulation is much greater than that in field solutions of the EC formulation. Accordingly, even though the typical application rate for an EC formulation is twice that for a ULV formulation, accidental exposure levels associated with field solutions of ULV formulations are far greater than those associated with field solutions of EC formulations.

As expected, non-accidental acute exposure levels are much lower than accidental exposure levels for members of the general public. Estimated dose levels for EC formulations are somewhat higher than those for ULV formulations, based on the difference in typical applications rates—i.e., 0.15 lb a.i./acre for ULV and 0.3 lb a.i./acre for EC formulations. For both formulations, the highest non-accidental acute exposure levels are associated with the consumption of contaminated vegetation: 0.04 (0.009-0.3) mg/kg bw for ULV formulations and 0.05 (0.01-0.4) mg/kg bw for EC formulations. Although the application rate for EC formulations is twice that of ULV formulations, the exposure levels are comparable because the doses associated with the ULV formulations are based on residues immediately after the eighth application of malathion.

Differences in the number of applications between ULV and EC formulations also account for the similarity in longer-term exposure estimates. For both ULV and EC formulations, the highest estimated doses are associated with the consumption of contaminated vegetation: 0.007 (0.0008-0.3) mg/kg bw/day for ULV formulations and 0.004 (0.0009-0.036) mg/kg bw/day for EC formulations. All other longer-term exposure scenarios are associated with doses that are at least a factor of 10 less than the doses associated with the consumption of contaminated vegetation.

Dose-Response Assessment – The U.S. EPA recently proposed malathion RfD values of 0.14 mg/kg bw for acute exposures and 0.070 mg/kg bw/day for longer-term exposures. Both of these RfDs are based on $BMDL_{10}$ values from studies in rat pups. Following standard practice in Forest Service risk assessments, these most recent RfD values are adopted and used in the current risk assessment to characterize risks associated with acute and longer-term exposures. Several other RfD or equivalent toxicity values have been derived previously by the U.S. EPA, The Agency for Toxic Substances and Disease Registry (ATSDR), and the World Health Organization (WHO 1998). These alternate values are considered in the current risk assessment primarily in terms of defining dose-severity relationships.

As discussed in the exposure assessment, this risk assessment considers concurrent exposure to malathion and malaoxon on contaminated vegetation, by adopting the U.S. EPA conversion factor of 61—i.e., malaoxon is considered to be 61 times more toxic than malathion. Unlike the acute and chronic RfD values, which are based on relatively short-term exposure, the conversion factor is based on data from two dietary studies involving chronic exposure of adult rats to either malathion or malaoxon.

The dose-severity relationships for acute exposure to malathion are of considerable importance because several of the acute hazard quotients discussed in the risk characterization exceed 1 by a

substantial margin. The hazard quotients of greatest concern are those involving acute accidental exposure of workers or members of the general public to ULV formulations of malathion. For adults, there is minimal concern with hazard quotients of up to about 6. Based on a controlled human study, it is not clear that hazard quotients of up to about 110, corresponding to doses of 15 mg/kg bw, would be associated with overt signs of toxicity. It is not possible to clearly characterize the consequences of exposure to malathion levels greater than 15 mg/kg bw but less than about 56 mg/kg bw. Animal studies suggest that acute doses of up to 20 mg/kg bw might not be associated with severe adverse effects; however, their usefulness in characterizing human exposure is questionable. Moreover, the 20 mg/kg bw dose is quite close to the lowest reported lethal dose in humans—i.e., 56 mg/kg bw. Although individuals have survived doses of up to 1400 mg/kg bw, survival depended on prompt and effective medical intervention. Within the context of the current Forest Service risk assessment, doses greater than or equal to 56 mg/kg bw are regarded as potentially but not necessarily lethal.

Risk Characterization – Although malathion is more toxic to insects than to mammals, including humans, malathion effectively inhibits enzyme activity essential to the regulation of the human nervous system—i.e., AChE activity. Consequently exposure to malathion is potentially hazardous to workers as well as members of the general public.

Virtually all accidental exposure scenarios for workers and members of the general public lead to hazard quotients that are above the level of concern. Accidental exposure scenarios for ULV formulations lead to much higher hazard quotients than corresponding scenarios for EC formulations. The difference has to do with the much higher concentration of malathion in ULV formulations—i.e., 1230 mg/mL—relative to the concentration of malathion in field solutions of EC formulations—i.e., ranging from 0.36 to 36 mg/mL. For EC formulations, the maximum hazard quotient of 22 for workers is not expected to result in overt signs of toxicity. The most severe accidental worker exposure scenario for ULV formulations (i.e., wearing contaminated gloves for 1 hour) is associated with a hazard quotient of 161 with a range from 104 to 250. The central estimate and the upper bound are both in the range in which consequences of exposure cannot be well characterized. For members of the general public, the highest hazard quotients are associated with an accidental spill into a small pond from which water is consumed by a small child. This exposure scenario leads to hazard quotients of up to 1150 for ULV formulations and 110 for EC formulations. The accidental spill of malathion into surface water should be regarded as an emergency, and vigorous actions should be taken to limit the exposure of members of the general public, particularly children.

Non-accidental exposure scenarios lead to substantially lower hazard quotients. For ULV formulations, none of the hazard quotients for workers exceeds a level of concern. For EC formulations, the highest non-accidental hazard quotients for workers is 3. Based on dose-severity considerations, there is no apparent basis for asserting that these exposure levels would cause overt signs of toxicity. For members of the general public, many of the hazard quotients associated with acute non-accidental exposures are greater in magnitude than those for workers. The greatest hazards are associated with the consumption of contaminated vegetation (HQ values up to 14). For longer-term exposures, the hazard quotients are lower, and the level of concern—

i.e., an HQ greater than 1—is exceeded only for those exposures associated with the consumption of contaminated vegetation in which the upper bound of the hazard quotient is 3 for insect control in pine seed orchards and 7 for mosquito control. Hazard quotients for longer-term exposures associated with the contamination of surface water are substantially below the level of concern.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – The endpoints of concern in the ecological risk assessment are similar to those discussed in the human health risk assessment – i.e., AChE inhibition. Vertebrates including mammals, birds, reptiles, amphibians, and fish may be adversely affected by exposure to malathion because of its well-characterized neurotoxicity. Although standard toxicity studies may demonstrate other toxicological endpoints, neurotoxicity is the critical effect on which the ecological risk assessment is based.

The available information on the toxicity of malathion to experimental mammals is used to assess effects in nontarget terrestrial mammals for the ecological risk assessment. For mammals, there is no consistent relationship between body size and sensitivity to malathion. The variability of toxicity values within a given species (e.g., LD_{50} values for rats range from 390 to 2100 mg/kg bw) may obscure any relationship between body size and sensitivity to malathion.

The toxicity of malathion to birds is characterized in acute (gavage), subacute dietary (5-day and 8-day exposures), and chronic/reproduction studies. The acute oral LD_{50} values for malathion are highly variable, generally ranging from about 167 mg/kg for ring-necked pheasants to 1485 mg/kg for mallard ducks. As with mammals, the available data do not suggest any systematic relationship between acute oral LD_{50} values and body weights in birds. Several field studies indicate that adverse effects were not detected in birds after malathion was applied at rates greater than or comparable to those anticipated in Forest Service programs. Several studies investigate the effects of injecting malathion directly into eggs containing developing bird embryos. Although the results these studies are a useful index of general toxic potency, the route of exposure is not relevant to environmental exposure and cannot be used in dose-response assessments.

There is very little data regarding the toxicity of malathion to reptiles. An approximate LD_{50} of 2324 mg/kg for the green anole, which is within the range of toxicity values determined for relatively tolerant vertebrates and birds, suggests, albeit tenuously, that the available toxicity data on birds and mammals may be representative of malathion toxicity to reptiles. A more recent study indicates that lizards exposed to 200 mg/kg bw malathion demonstrated enhanced sprint performance; yet the dose level caused 20% mortality.

The toxicity of malathion to honeybees and earthworms is relatively well characterized. Malathion is highly toxic to the honeybee with 48- to 96-hour direct spray LD_{50} values ranging from 0.2 to 0.71 µg/bee. These direct spray LD_{50} values correspond to exposure levels of 2.15-7.6 mg/kg bw, factors of about 25-100 below the LD_{50} of approximately 200 mg/kg bw in small mammals. A feeding study in bees reports a the dietary NOAEL of 0.16 ppm.

Contact LD_{50} values are reported for two species of earthworms: *Eisenia foetida* [13.5 (8.0-22.8) $\mu g/cm^2$] and *Lumbricus rubellus* [0.27 (0.14-0.50) $\mu g/cm^2$]. These studies may be used to estimate potential effects in earthworms after direct spray applications of malathion. In an extensive study investigating the effects of soil contamination on earthworms, the most sensitive species native to North America appears to be *Enchytraceus albidus*, with a 21-day NOEC of 4.74 ppm. Other data indicate that certain tropical earthworm species may be more sensitive than *Enchytraceus albidus* to the effects of malathion; however the data are based on exposure to emulsifiable concentrate formulations, and it is not clear whether the apparent increase in sensitivity is due to formulation differences or differences in species sensitivity.

The database regarding the toxicity of malathion to aquatic organisms is quite extensive. As with mammals, the toxicity values for both technical grade malathion and emulsifiable concentrate formulations are highly variable, which may reflect differences in the purity of the malathion used in the various studies. LC_{50} values in fish range from about 100 to 10,000 ppb. In studies that explicitly compare technical grade malathion and emulsifiable concentrate formulations, there is no apparent difference in toxicity when exposures are expressed as malathion equivalents. In general, larger fish appear to be somewhat less sensitive than smaller fish to malathion exposure.

Exposure to malathion inhibits AChE in aquatic animals, as it does in mammals and terrestrial invertebrates. Sublethal exposure levels may cause reproductive effects in fish, including a failure to spawn, pathological changes to the ovaries, and degenerative changes in the testis. Many of the sublethal effects, however, are reported to occur in the high ppb range—i.e., from 100 to greater than 1000 ppb. Amphibians appear to be similar to fish in their sensitivity to malathion, with 24- to 96-hour LC_{50} values ranging from about 200 to greater than 3000 ppb. Some aquatic invertebrates are far more sensitive than fish or amphibians to malathion exposure. For example, reported 48-hour LC_{50} values for daphnids range from 0.69 to 1.2 ppb. As with fish, large invertebrates appear to be less sensitive than small invertebrates to malathion exposure, at least in terms of acute LC_{50} values. While very small arthropods like daphnids, scuds, and midge larvae are clearly sensitive to malathion exposure, the LC_{50} values for other groups invertebrates such as mollusks and worms are much higher, ranging from about 50,000 to greater than 200,000 ppb.

Exposure Assessment – Terrestrial animals can be exposed to pesticides after broadcast applications. The various exposure scenarios include the possibility of being sprayed directly (albeit unintentionally) with the pesticide, ingesting pesticide-contaminated media (vegetation, prey species, or water), grooming activities that result in the ingestion of the pesticide residue, or making contact with pesticide-contaminated vegetation. These scenarios are summarized in Worksheet G01 of the EXCEL workbooks that accompanies this risk assessment and address exposure to malathion, based on the typical application rate used for ULV formulations in mosquito control (Attachment 1) and EC formulations in insect control in pine seed orchards (Attachment 2). The consequence of using the range of application rates for both formulations is discussed further in the risk characterization.

In acute exposure scenarios, the highest exposure for terrestrial vertebrates involves the consumption of contaminated fish by a predatory bird after an accidental spill. In that scenario, the exposure levels would be approximately 3200 mg/kg bw for ULV applications and 94 mg/kg bw for EC formulations. As discussed in the exposure scenarios for the human health risk assessment, there is substantial difference between the malathion concentration in ULV formulations (1230 mg/mL), relative to the concentrations in field solutions of EC formulations (0.36 to 36 mg/mL). This difference accounts for the discrepancies in exposure levels for nontarget species in the accidental spray and accidental spill scenarios.

The range of exposure levels for the scenario involving the consumption of contaminated vegetation by terrestrial animals is broad and varies according to the malathion formulation (ULV or EC) applied, the rates of application, and the number of applications made. For ULV formulations, central estimates range from about 0.3 mg/kg (small mammal consuming fruit) to 0.5 mg/kg (large bird consuming grasses). Upper bound estimates for the consumption of contaminated vegetation range from about 0.68 mg/kg (small mammal consuming fruit) to 19 mg/kg (large bird consuming grasses). For EC formulations, central estimates range from about 0.4 mg/kg (small mammal consuming fruit) to 8 mg/kg (large bird consuming grasses). Upper bound estimates for the consumption of contaminated vegetation range from about 0.8 mg/kg (small mammal consuming fruit) to 33 mg/kg (small bird consuming contaminated insects).

The consumption of contaminated water based on expected environmental concentrations leads to much lower levels of acute exposure with peak doses of about 0.002 mg/kg bw for both ULV and EC formulations. Longer-term exposures associated with the consumption of contaminated water are very low for both types of formulations, with maximum doses of less than 0.00005 mg/kg bw. The accidental spill scenario leads to much higher estimates of exposure with upper bound doses of about 140 mg/kg bw for ULV formulations but only 4 mg/kg bw for EC formulations. As noted above, the substantial difference between spills of ULV and EC formulations relate to the much higher concentrations of malathion in ULV formulations, compared with EC formulations.

Although ULV formulations for mosquito control will be applied at lower application rates than EC formulations for insect control in pine seed orchards, longer-term exposures to contaminated vegetation are substantially higher for ULV formulations because the typical use of these formulations is modeled as 8 applications separated at 1-week intervals. Peak exposures for ULV applications are about 11 mg/kg bw for a large mammal and 17 mg/kg bw for a large bird. For ULV formulations, the corresponding exposure levels are lower by about a factor of 10—i.e., about 1.3 mg/kg bw for a large mammal and 2 mg/kg bw for a large bird. As with the acute exposures, doses associated with expected concentrations of malathion in surface water are very low—i.e., less than 0.00004 mg/kg bw for both ULV and EC formulations.

Exposure estimates for aquatic organisms are based on essentially the same information used to assess the exposure of terrestrial species to contaminated water. The estimated rates of contamination of ambient water associated with the application of ULV formulations are 0.02

(0.001-0.07) mg a.i./L per lb a.i. applied for peak exposures and 0.0002 (0.00002-0.0014) mg a.i./L per lb a.i. applied for longer-term exposures. For EC formulations, the corresponding values are 0.004 (0.0005-0.04) mg a.i./L per lb a.i. applied for peak exposures and 0.00002 (0.000002-0.0005) mg a.i./L per lb a.i. applied for longer-term exposures.

Dose-Response Assessment – The available toxicity data support separate dose-response assessments in six groups of organisms: terrestrial mammals, birds, nontarget terrestrial invertebrates, fish, amphibians, and aquatic invertebrates. Different units of exposure are used for different groups of organisms depending on how exposures are likely to occur and how the available toxicity data are expressed. An overview of the toxicity values used in the ecological risk assessment is given below.

Organism Group/Duration		Endpoint	Toxicity Value	Reference
Acute		**Terrestrial Organisms**		
	Mammals	BMD_{10} for AChE	17 mg/kg bw	Section 4.3.2.1
	Birds	Estimated NOEC	15 mg/kg bw	Section 4.3.2.2
	Honey Bee	LD_{50}	2.2 mg/kg bw	Section 4.3.2.3.
Longer-term				
	Mammals	BMD_{10} for AChE	11 mg/kg bw/day	Section 4.3.2.1
	Birds	NOEC	11 mg/kg bw/day	Section 4.3.2.2
Acute		**Aquatic Organisms**		
Amphibians				
	Sensitive	96-hour LC_{50} value	0.00059 mg/L	Section 4.3.3.2.
	Tolerant	16-day LC_{50} value	5.9 mg/L	Section 4.3.3.2.
Fish	Sensitive	LC_{50}	0.004 mg/L	Section 4.3.3.1
	Tolerant	LC_{50}	11.7 mg/L	Section 4.3.3.1
Invertebrates				
	Sensitive	LC_{50}	0.001 mg/L	Section 4.3.3.3
	Tolerant	LC_{50}	49 mg/L	Section 4.3.3.3
Algae	Sensitive	NOEC	0.5 mg/L	Section 4.3.3.4
	Tolerant	NOEC	200 mg/L	Section 4.3.3.4
Macrophytes		NOEC	24 mg/L	Section 4.3.3.4
Longer-term				
Amphibians	Sensitive	Estimated NOEC	0.00035 mg/L	Section 4.3.3.2.
	Tolerant	NOEC	0.75 mg/L (larvae)	Section 4.3.3.2.
Fish	Sensitive	Estimated NOEC	0.0024 mg/L	Section 4.3.3.1
	Tolerant	NOEC	0.021 mg/L	Section 4.3.3.1
Invertebrates	Sensitive	NOEC	0.0006 mg/L	Section 4.3.3.3
	Tolerant	NOEC	1.23 mg/L	Section 4.3.3.3

Theses toxicity values (TV) are used as the numerator in the derivation of the hazard quotients (HQ) used in the risk characterization where the hazard quotient is defined as the toxicity value divided by the exposure:

$$HQ = TV / Ex.$$

The use of these toxicity values in the ecological risk assessment is mathematically identical to the approach used in the human health risk assessment where the HQ is calculated as the acute or chronic RfD divided by the corresponding exposure. Unlike the human health risk assessment, however, the toxicity values used in the ecological risk assessment involve different endpoints for different groups of organisms and different durations of exposure. These differences are necessitated by the nature of the data that are available on the different groups of organisms.

For malathion, the different endpoints used in the dose-response assessment include doses associated with a 10% inhibition of acetylcholinesterase activity (BMD_{10} for AChE), estimated NOEC (no observed effect concentrations) for acute toxicity, developmental effects or reproductive effects, as well as doses or concentrations that are estimated to be lethal to 50% of the exposed organisms (LD_{50} or LC_{50} values). Because of the differences in the endpoints used to derive the HQ values, the interpretation of the HQ values in the risk characterization differs among the groups of organisms and durations of exposure.

Risk Characterization – Except for accidental exposures, most terrestrial vertebrates do not appear to be at substantial risk after applications of malathion. The risk characterization for mammals and birds are similar. The accidental spill of a large amount of malathion into a small pond leads to exposures that may exceed the level of concern for small mammals and fish-eating birds. For ULV formulations, the magnitude of the exceedance is much greater because of the higher concentration of malathion in ULV formulations, relative to concentrations in field solutions of EC formulations. Some scenarios for non-accidental acute exposures also exceed the level of concern, at least at the upper bounds of plausible exposures, for the consumption of contaminated vegetation and insects. For these scenarios, the magnitude of the exceedances at the upper bounds of exposure is substantially greater for EC formulations, relative to ULV formulations because of the higher application rates used for EC formulations. For the consumption of contaminated vegetation, the longer-term exposure scenarios for mammals and birds generally lead to hazard quotients that are below the level of concern. The only exceptions involve the upper bounds of the hazard quotients for large mammals and large birds consuming contaminated vegetation exclusively within an area treated with multiple applications of ULV formulations. Expected peak and longer-term concentrations of malathion in surface water lead to hazard quotients substantially below the level of concern.

Malathion is far more toxic to some invertebrates, particularly small insects, than it is to vertebrates. Adverse effects are expected in some terrestrial invertebrates, like insects and, perhaps, some other small arthropods. Malathion is an effective insecticide, and terrestrial insects, both target and nontarget, are likely to be adversely affected if sprayed directly with malathion at application rates used in Forest Service programs. Whether or not effects would be

seen in specific populations of terrestrial insects or other arthropods could be influenced by different behavioral patterns, food sources, or habitat. Malathion is not likely to cause adverse effects in earthworms, as they appear to be much less sensitive than other invertebrates to malathion exposure. While somewhat speculative, it seems plausible that other terrestrial arthropods, such as mites and some spiders, would be adversely affected by exposure to malathion. It seems less likely that other groups of terrestrial invertebrates, such as mollusks, would be adversely affected.

Generally, the risk characterization for aquatic species is much more severe than that for terrestrial species. Within each group of organisms for which hazard quotients are derived—i.e., fish, amphibians, aquatic invertebrates, and aquatic plants—the apparent differences between sensitive and tolerant species are substantial, and these substantial differences have a major impact on the risk characterization. Three types of exposure scenarios are used to assess risks in aquatic species: an accidental spill, expected peak concentrations, and expected longer-term concentrations of malathion in surface water. As in the assessment of terrestrial organisms, the accidental spill scenario for ULV formulations is associated with much higher concentrations of malathion in water than the corresponding scenario for EC formulations. Accidental spill scenarios for ULV formulation would likely result in substantial mortality in all groups of aquatic animals in both the sensitive and tolerant species within each group. Expected peak concentrations of malathion in surface water also exceed the levels of concern for fish, invertebrates, and amphibians at the upper bounds of the hazard quotients. Expected longer-term concentrations of malathion in surface water are below the level of concern for fish with both ULV and EC formulations. For sensitive species of amphibians, the longer-term hazard quotients modestly exceed the level of concern at the upper bounds of the application rates for both EC formulations (HQ=1.3) and ULV formulations (1.2). For sensitive species of invertebrates, the upper bound of the longer-term hazard quotient exceeds the level of concern only for EC formulations (HQ=1.3).

Some of the excursions above the level of concern for peak exposures suggest that lethality, and, perhaps, substantial lethality might be observed among some sensitive species of fish, amphibians, and invertebrates after the application of malathion. This risk characterization, however, is based on the selection of central estimates and upper bounds of water contamination rates (WCRs) that are intentionally conservative, reflecting applications in areas with clay soils and site conditions that favor high runoff. This approach is standard in general Forest Service risk assessments such as the current document. As a consequence of this conservative approach, site-specific or region-specific factors should be considered carefully in the preparation of site-specific or region-specific assessments. The application of malathion in some regions—e.g., areas with predominantly sandy or loamy soils—could lead to much lower expected peak and average concentrations in surface water than are suggested by the WCR values used in this risk assessment.

1. INTRODUCTION

The human health and ecological risk assessments that comprise this document address the health and environmental consequences of the Forest Service use of malathion to control insect pests (e.g., thrips) in pine seed orchards and to control mosquitoes. For mosquito control, the rationale for use includes both nuisance control and the control of the transmission of infectious diseases such as West Nile disease.

This document includes an introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with malathion and its commercial formulation, an assessment of potential exposure to the product, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These major sections represent the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2007a).

The series of human health and ecological risk assessments prepared for the USDA Forest Service are not, and are not intended to be, comprehensive summaries of all of the available information. This statement is particularly true for malathion, given the literature which includes a vast number of published studies as well as studies submitted to the U.S. EPA (most of which are unpublished) to support the reregistration of malathion (U.S. EPA/OPP 2000a,b,c).

The relevant published literature on malathion was reviewed by SERA (2001a) in a risk assessment conducted for APHIS to assess the consequences of using malathion in boll weevil control programs. While the exposures to malathion associated with boll weevil control are substantially different from those associated with mosquito control, the SERA (2001a) risk assessment evaluates more than 1000 published studies on malathion and is, therefore, useful in the current effort as a critical review of the available toxicological data on malathion through the year 2001. In the interest of economy, portions of the SERA (2001a) report are incorporated directly into the current risk assessment with the addition of recent studies. The SERA (2001a) review was updated with a literature search of TOXLINE (http://toxnet.nlm.nih.gov/ cgi-bin/sis/htmlgen?TOXLINE). Additional published literature was identified through a search of the ECOTOX database of published studies reviewed by the U.S. EPA (U.S. EPA/ORD 2006). ECOTOX is also the main ecotoxicity database used by the Pesticide Action Network (PAN 2006). Finally, numerous reviews regarding the toxicity and environmental fate of malathion were consulted in an effort to identify additional pertinent data (Arbuckle and Sever 1998; ATSDR 2000; ATSDR 2003; Davis et al. 2007; Flessel et al. 1993; Peterson et al. 2006;

Thompson 1996; Voccia et al. 1999; WHO 1998; WHO 2003). For the published literature, major reliance is placed on the 2003 review by the Agency for Toxic Substances and Disease Registry (ATSDR 2003), which is a comprehensive and critical review of the open literature up to 2003 and summarizes and reviews more than 600 citations.

The unpublished studies submitted to the U.S. EPA's Office of Pesticides in support of the reregistration of malathion are summarized in a human health risk assessment of malathion conducted by the Health Effects Division (HED) of OPP (U.S. EPA/OPP 2000a) as well as an ecological risk assessment of malathion conducted by the Environmental Fate and Effects Division (EFED) of OPP (U.S. EPA/OPP 2000b,c). An overview of these and other U.S. EPA risk assessments is provided in the Reregistration Eligibility Decision (RED) for malathion (U.S. EPA/OPP 2006). These and other related documents associated with the reregistration of malathion were prepared over the course of several years and subject to extensive public review.

The U.S. EPA/OPP analyses as well as public comments on these analyses are posted on the Internet at the E-Docket site (http://www.regulations.gov/fdmspublic/component/main, E-Docket ID *OPP-2004-0348*). The E-Docket contains 162 documents including updated risk assessments for human health (U.S. EPA/OPP 2005) and ecological risk assessments for threatened and endangered species (U.S. EPA/OPP 2004). Of these documents, 126 comprising approximately 31 megabytes of information were downloaded and reviewed in detail during the preparation of this risk assessment.

In addition to reviews published in the open literature, there is an immense amount of information about malathion on the Internet ─ e.g. more than a 1,150,000 hits at http://www.google.com/. Most of these data, however, are not well enough documented for use in this risk assessment.

The Forest Service will update this and other similar risk assessments on a periodic basis and welcomes input from the general public on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

Almost no risk estimates presented in this document are given as single numbers. Usually, risk is expressed as a central estimate and a range, which can be quite large. Because it is necessary to encompass many different types of exposure and to express the uncertainties inherent in the exposure assessments, the current risk assessment document contains numerous calculations. Many of the calculations are relatively simple and are included in the body of the document. Some of the calculations, however, are cumbersome. For those calculations, EXCEL workbooks are included as attachments to the risk assessment. Two workbooks are included, one for the use of malathion for mosquito control (Attachment 1) and the other for the use of malathion to control insect pests on vegetation (Attachment 2). The worksheets in these workbooks provide the detail for the exposure estimates and risk estimates cited in the body of this document. The EXCEL workbooks are divided into the following sections: general data and assumptions,

chemical specific data and assumptions, exposure assessments for workers, exposure assessments for the general public, and exposure assessments for effects on nontarget organisms. Documentation for using the EXCEL workbooks is provided in SERA (2005).

2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Malathion is an organophosphate pesticide used in Forest Service programs to control insect pests (e.g., thrips) in pine seed orchards and to control mosquitoes on lands managed by the Forest Service. Although either ground or aerial applications of malathion can be used in programs to control mosquitoes, only ground equipment is used to apply malathion in programs to control insects in pine seed orchards.

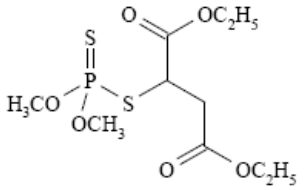
Of the many commercial formulations of malathion, Fyfanon ULV and Atrapa VCP are the formulations most commonly used for mosquito control in programs affecting lands managed by the Forest Service. Both products are adulticides—i.e., they are labeled for the control of adult mosquitoes. The Fyfanon and Atrapa formulations each contain about 96.5% malathion (9.9 lbs/gallon w/w). The remaining 3.5% of the formulations is listed as inerts on the product labels. The inerts seem to be impurities in technical grade malathion, the presence of which is an important issue that is addressed in the risk assessment. Fyfanon ULV and Atrapa ULV, which are designed for ultra-low volume application, can be applied using ground equipment or aircraft. In addition to the ULV formulations, various emulsifiable concentrate (EC) formulations of malathion have been used in ground applications. Two petroleum-based formulations, Hi-Yield 55% Malathion and Malathion 5, which are used only to control insect pests in pine seed orchards, are covered in this risk assessment.

Forest Service records indicate that ground application rates of malathion to control insect pests in pine seed orchards range from about 0.1 to 1.5 lb a.i./acre with an average application rate of about 0.3 lb a.i./acre. Labeled application rates for mosquito control are lower and range from 0.11 to 0.23 lb a.i./acre. For this risk assessment, the typical application rate for mosquito control is taken as 0.15 lb a.i./acre. Applications for mosquito control may be done repeatedly and as needed throughout the year. Neither the maximum cumulative annual application rate nor minimum application interval for mosquito control is specified on the product label. Most malathion use on lands managed by the Forest Service occurs in Region 8, the southern region. Based on the use statistics for Region 8, this risk assessment assumes a sequence of eight applications separated by 1-week intervals.

The use of malathion on lands managed by the Forest Service is miniscule compared with the total use of malathion in the United States. According to the use statistics summarized by the U.S. EPA, Forest Service use accounts for about 0.00017% (i.e., 1.7 in one million) of the total use in the United States.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

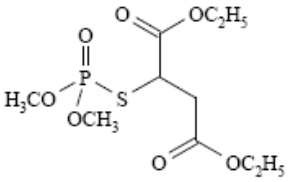
Malathion is the common name for diethyl [(dimethoxyphosphinothioyl)thio]butanedioate:



Other synonyms for malathion as well as an overview of its chemical and physical properties are given in Table 1. Malathion was initially registered as an insecticide in 1956 (U.S. EPA/OPP 2006c).

Malathion can exist as either the (R) enantiomer or (S) enantiomer [mirror images] or as a racemate, a mixture of both (R)- and (S)-enantiomers. Commercial grade malathion is the recemate [(RS)-malathion]. The available information regarding the toxicity of the enantiomers—(R)-malathion and (S)-malathion—is discussed in Section 3 and 4 (e.g., Polec et al. 1998).

Of the many organophosphate pesticides, only one other, dimethoate, has the phosphorodithioate structure (O,O-P=S(S)) (Nigg and Knaak 2000). The phosphorodithioate moiety is an important structural feature for malathion because the neurotoxicity of malathion is due to the oxidation of the P=S component of this moiety to P=O resulting in the formation of malaoxon,



the agent that inhibits cholinesterase (ChE). As discussed further in Sections 3 and 4, the formation of malaoxon occurs both *in vivo* (i.e., within an organism) and as a result of various biotic and abiotic oxidative processes in the environment. This characteristic complicates both the dose-response and the exposure assessments for malathion.

As summarized in Table 2, there are numerous commercial formulations of malathion labeled for forestry application and mosquito control. The information provided in Table 2, including brand name and composition, application rates, and inert ingredients, is taken from the product label for each of the specified formulations. The MSDS for each formulation was examined in order to identify the inert ingredients. The labels were identified from internet searches of www.greenbook.net, the Label Search at www.premier.cdms.net, and the Pan Pesticides Database—Pesticide Products at www.pesticideinfo.org.

Fyfanon ULV (registered to Cheminova Inc.) and Atrapa VCP (registered to Griffin LLC) are considered in this risk assessment for use on Forest Service managed lands. Both of these formulations are labeled for mosquito control as well as for the control of numerous other insect

pests. Both Fyfanon ULV and Atrapa VCP are ultra low volume formulations. As indicated in Table 2, Griffin LLC provides formulations that are named Atrapa VCP and Atrapa ULV. Based on a comparison of the product labels and material safety data sheets, Atrapa VCP and Atrapa ULV appear to be identical formulations.

The labels for both Fyfanon ULV and Atrapa VCP indicate that the formulations contain 96.5% malathion (9.9 lbs/gallon w/w). The remaining 3.5% of the material is specified on the product labels as *inerts*. The designation inerts is somewhat ambiguous. The term *inerts* typically refers to materials intentionally added to the active ingredients and is distinct from *impurities*, unintended contaminants that arise from the synthesis of the active ingredients. Technical malathion has a typical purity of about 96% (Contreras and Bustos-Obregon 1999). The 3.5% *inerts* listed on the product label appears to refer to impurities in the technical grade malathion. The presence of impurities in technical grade malathion, particularly isomalathion, is an extremely important issue, as discussed in Section 3.1.15.

As indicated in Table 2, many other commercial formulations of malathion are available. Based on use statistics from the Forest Service (Table 4), two additional formulations are considered in this risk assessment: Malathion 5 and Hi-Yield 55% Malathion. As indicated in Table 2, both of these formulations are petroleum-based formulations. While the precise composition of the petroleum products used in these formulations is not specified, both formulations appear to contain aromatic rather than aliphatic petroleum distillate fractions. These formulations are used on Forest Service managed lands only to control of insect pests in pine seed orchards.

Of the formulations covered by this risk assessment, only Malathion 5 is labeled for the control of mosquito larvae. Malathion 5 and some of the other formulations covered in Table 2 are applied directly to temporary standing bodies of water or intermittently flooded areas to control mosquito larvae; nevertheless, programs for mosquito control on Forest Service managed lands will not directly treat transient standing bodies of water. On the other hand, applications for adult mosquito control may involve the unintended overspray of small ponds and streams during aerial applications. These exposure scenarios are addressed both in the human health risk assessment (Section 3.2) as well as in the ecological risk assessment (Section 4.2).

2.3. APPLICATION METHODS

Fyfanon ULV and Atrapa VCP are labeled for both ground and aerial applications. Although both ground and aerial applications may be used in programs to control mosquitoes, only ground applications are used to control insect pests in pine seed orchards.

Ground applications may involve boom spray, mist blowers (nonthermal aerosols), air blast sprayers, or foggers. These methods are used primarily along roadways, rights-of-way, and other areas like campgrounds which are readily accessible by ground vehicles. Aerial applications can be conducted using either fixed-wing aircraft or helicopters. Formulations are applied through specially designed spray nozzles and booms. The nozzles are designed to reduce turbulence in order to minimize spray drift. Aerial applications may only be made under meteorological conditions that minimize the potential for spray drift. In aerial applications, approximately 40–100 acres may be treated per hour.

2.4. MIXING AND APPLICATION RATES

This section outlines the application rates and dilution volumes used in this risk assessment. These mixing and application rates are intended to reflect typical or central estimates as well as plausible lower and upper bounds. In the assessment of specific program activities, the Forest Service may use program-specific application rates to modify the worksheets included with this report to assess any potential risks for a specific proposed application.

2.4.1. Mosquito Control

For mosquito control, the maximum single application rate for both Fyfanon ULV and Atrapa VCP is 3 oz formulation per acre, which corresponds to 0.23 lb a.i./acre [3 oz / 128 oz/gallon x 9.9 lb/gallon]. The U.S. EPA/OPP (2006) indicates that typical application rates for the public health use of malathion as an insect adulticide range from 0.11 to 0.23 lb a.i./acre (U.S. EPA/OPP 2006, p. 6) but that most applications used for mosquito control are below the maximum labeled rate of 0.23 lb a.i./acre (U.S. EPA/OPP 2006, p. 89). Typical rates for mosquito control with handheld foggers are estimated at 0.1 lb a.i./acre (U.S. EPA/OPP 2006, p. 23).

For this risk assessment, the typical application rate for malathion in mosquito control programs is taken as 0.15 lb a.i./acre, which is more or less the average application rate reported for Forest Service managed lands in 2004 (Table 3). The maximum application rate is taken as 0.23 lb a.i./acre, the maximum labeled single application rate for mosquito control. The lower range of the application rate is taken as 0.11 lb a.i./acre, which, as discussed above, is the lower bound of labeled application rates for mosquito control. Also, it is close to the application rate estimated by the U.S. EPA for fogger applications.

Neither Fyfanon ULV nor Atrapa VCP indicates the maximum number of applications that can be made per year for mosquito control; furthermore, the U.S. EPA does not specify a maximum cumulative annual application rate (U.S. EPA/OPP 2006). For adult mosquito control, the product labels indicate that treatments should be repeated as necessary. In exposure assessments summarized in U.S. EPA/OPP (2006), the minimum application interval for crops treated with

malathion is set at 3 days with up to 25 applications per year (U.S. EPA/OPP 2006, p. 52); however, for mosquito control with malathion , neither minimum application intervals nor annual numbers of applications is specified.

The number of applications per season and the interval between applications is likely to vary substantially based on mosquito populations and any potential or perceived public health concerns. In the current risk assessment, the assumption is made that malathion sprays typically occur at 1-week intervals for no more than 8 consecutive weeks.

It is difficult to make generalizations about the timing of mosquito control programs, given the variability among mosquito species and populations over time (e.g., Zyzak et al. 2002). This is also true for applications of malathion intended to control other pests. The EXCEL workbooks that accompany this risk assessment are structured so that one or more applications can be modeled depending on program-specific objectives.

The ULV formulations of malathion are not mixed or otherwise diluted prior to application. Thus, exposure scenarios for ULV formulations involving spills, either spills onto the skin or spills into a small pond, are modeled for ULV formulations are spills of the undiluted formulation. As noted in both the risk assessments for human health (Section 3) and ecological effects (Section 4), this substantially increases the exposures associated with the spill scenarios for ULV compared to EC formulations.

2.4.2. Pest Control in Seed Orchards

Malathion 5 and Hi-Yield 55% Malathion may be used in Forest Service for the control of insect pests on pine see orchards. Various insect pests occur in pine seed orchards in the southern United States, including, among others, thrips (e.g., *Gnophothrips piniphilus* and *Gnophothrips fuscus*), coneworms (*Dioryctria* spp.), the Nantucket pine tip moth (*Rhyacionia frustrana*) as well as other *Rhyacionia* spp, red spider mites, aphids (*Cinara* spp.), midges (gall midge larvae), seedworms (*Laspeyresia* spp.), scale insects (*Chionaspis* spp.), ants, sawflies (*Neodiprion* spp.), black turpentine beetles (*Dendroctonus terebrans*), many insects in the order Orthoptera such as species of grasshoppers and crickets, Japanese beetles (*Popillia japonica*) (DeBarr 1971; DeBarr and Williams 1971; Otterbach 1963). Both Malathion 5 and Hi-Yield 55% Malathion are labeled for control of several of these insect pests at a maximum single application rate of 3 pints per acre (equivalent to 1.5 quarts or 0.375 gallons), which is equivalent to 1.875 lbs a.i./acre [0.375 gallon formulation x 5 lbs/gallon formulation]. As with applications for mosquito control, repeated applications may be made but the product labels do not specify application intervals, the maximum number of applications, or maximum annual application rates.

As discussed in Section 2.5, the major use of malathion in pine seed orchards occurs in Forest Service Region 8 (the southeast from Texas to the east coast from Virginia to Florida), and Table 4 provides annual use statistics from 1995 to 2004 for malathion on lands managed by the Forest Service. Based on these use statistics, the range of application rates for malathion is taken as 0.1-1.5 lb a.i./acre. The typical application rate is taken as 0.3 lb a.i./acre, which represents the average application rate over the 1995-2004 period rounded to one significant place. Although

only ground applications were conducted in pine seed orchards over this period, both ground and aerial applications are covered in this risk assessment in the event that aerial applications are considered in the future.

Malathion 5 and Hi-Yield 55% Malathion are mixed prior to application. For this risk assessment, the extent to which these formulations are diluted prior to application primarily influences dermal and direct spray scenarios, both of which are dependent on the 'field dilution' (i.e., the concentration of malathion in the applied spray). The greater the concentration of malathion in the field solution, the greater is the exposure. Based on the information in the product labels for Malathion 5 and Hi-Yield 55% Malathion, the minimum application volumes are 1 gallon per acre for aerial application and 3 gallons per acre for ground applications. For some pests on pine, up to 100 gallons per acre are recommended. Higher dilution volumes are recommended on for crops such as pecans, but these uses are not covered under the current risk assessment for Forest Service programs. For the current risk assessment, application volumes ranging from 1 to 100 gallons/acre used with the central estimate taken as10 gallons/acre. As noted above, program specific application volumes are used as inputs to the worksheets that accompany this risk assessment to evaluate specific Forest Service programs.

2.4.3. Other Pest Control Applications

While the current risk assessment is limited to mosquito control and insect pest control in pine seed orchards, malathion may be used by other organizations to control numerous other pest insects. Recent special local need Section 24(c) labels for Fyfanon ULV formulations indicate that up to 12 oz/acre of Fyfanon ULV may be applied 3 times/year for the control of grasshoppers on cottonwood and hybrid poplar plantation, which is equivalent to an application rate of nearly 1 lb a.i./acre [12 oz per acre / 128 oz/gallon x 9.9 lb/gallon = 0.928 lb a.i./acre]. While these applications are not explicitly considered in this risk assessment, the application rates are encompassed by the rates considered for seed orchard applications (Section 2.4.2).

2.5. USE STATISTICS

Based on information from the USDA/Forest Service, the U.S. EPA, the USGS, and the state of California, the use of malathion on lands managed by the Forest Service is very small relative to agricultural uses.

The USDA Forest Service tracks and reports the use of pesticides on Forest Service managed lands by use objectives and by geographical areas referred to as "*Regions*". The Forest Service classification divides the United States into nine regions designated from Region 1 (Northern) to Region 10 (Alaska) (Figure 1). [Note: There is no *Region 7* in the Forest Service system.]

Figure 1 summarizes the use of malathion in terms of total pounds applied to Forest Service managed lands during 2004, the most recent year for which statistics are available. As illustrated in Figure 1 and detailed further by region in Table 3, the great majority of malathion use (92% of the total) occurred in Region 8 (the southeast from Texas to the east coast from Virginia to Florida). Much smaller amounts were used in Region 9 (the northeastern section of the United States which accounted for 3% of total use) and in Region 5 (the Pacific Southwest including

California and Hawaii which accounted for 5% of total use). No malathion use was reported in other regions. The total amount of malathion used in all regions in 2004 was only 26.14 pounds.

Malathion is used on a number of crops, and a summary of its agricultural uses is presented in Figure 2 (USGS 2003). As indicated in this figure, somewhat greater than 5 million pounds of malathion were applied to agricultural crops, primarily cotton (80%), in 2002. The geographical distribution of the agricultural uses of malathion for 2002 are generally similar to those of the Forest Service (Figure 1) in that the largest area of agricultural use occurs in the southeast (Forest Service Region 8). For 2004, the use of malathion on all Forest Service managed lands was a factor of about 150,000 less than the amount used on cotton in 2002 [4,040,673 pounds / 26.14 pounds = 154,578] and a factor of about 190,000 less than the amount used on all agricultural crops [154,578 / 0.8066 = 191,642].

It is noteworthy that the statistics given for the Forest Service apply only to applications made on National Forests that are managed by the Forest Service and may not reflect the total use of malathion in all forestry applications. Similarly, the use statistics given by the USGS (2003) reflect only the agricultural use of malathion. The U.S. EPA estimates that about 15 million pounds of malathion are used annually in the United States in "commercial agricultural, industrial, governmental, and homeowner uses" (U.S. EPA/OPP 2006, p. 3) and that most of this, about 10.2 million pounds, involves the USDA/APHIS Boll Weevil Eradication Program (U.S. EPA/OPP 2006, p. 6). Based on the 15 million pound figure given by the U.S. EPA for total malathion use, the 26.14 pounds used on Forest Service managed lands is about 0.00017% (i.e., 1.7 in one million) of the total use in the United States.

The California Department of Pesticide Regulation provides very detailed pesticide use statistics (CDPR 2006). For 2004, the most recent year for which data are available, the total use of malathion in California was 492,308 lbs, and has declined gradually from 1994 to 2004 (Figure 3). In 2004, a total of 249,314 acres in California were treated with malathion for an average application rate of about 2 lbs/acre. The only use of malathion similar to applications made to Forest Service managed lands include applications for pest control (27,621 lbs) and applications to rights-of-way (945.1lbs) for a total of 28,566 lbs or about 5.8% of total use.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Exposure to malathion can result in the inhibition acetylcholinesterase (AChE). The U.S. EPA uses AChE inhibition as the endpoint of concern for most dose-response assessments of malathion, and a similar approach is taken in this risk assessment. Depending on the degree of AChE inhibition, clinical effects can range from mild signs of toxicity (e.g., salivation or lacrimation) to convulsions and death. There are two types of AChE, one occurring in nerve tissue and the other in red blood cells (RBC). In addition, plasma contains cholinesterases (ChE) that are different from and have broader substrate specificity than either RBC or nerve tissue AChE.

The malathion molecule itself does not cause AChE inhibition. AChE inhibition is induced by the metabolism of malathion to malaoxon in mammals and other species. Thus, the extent of metabolism from malathion to malaoxon is an important aspect for understanding the time-course of AChE or ChE inhibition. In most studies, inhibition of AChE or ChE by malathion is typically rapid in onset. Once exposure to malathion ceases, spontaneous reactivation of AChE proceeds relatively fast.

Some organophosphate pesticides cause other types of neurotoxic effects, specifically delayed toxicity and a condition known as *intermediate syndrome* (IMS). Delayed toxicity involves the inhibition of neuropathy target esterases (NTE) and is a neurological effect that is totally different from AChE inhibition. IMS appears to involve muscle fiber necrosis which occurs after acute AChE inhibition by organophosphate insecticides. Based on the available information, malathion does not appear to cause delayed toxicity or intermediate syndrome.

In terms of acute toxicity to humans and other mammals, malathion is among the least toxic of the organophosphate pesticides, with a very low order of acute toxicity resulting from oral, dermal, or inhalation exposure. A standard measure of acute lethal potency is the LD_{50} (i.e., the dose that is estimated to kill 50% of exposed individuals). In rat studies, the acute oral LD_{50} is more than 5000 mg/kg for technical grade malathion and up to 12,500 mg/kg for highly purified malathion. The dermal toxicity of malathion is so low that actual LD_{50} values have not been determined. Available studies report dermal NOAEL values of up to 5000 mg/kg. The inhalation LC_{50} values for technical grade malathion range from about 2000 to 5200 mg/m^3, concentrations far above any plausible levels of exposure.

The differences between the acute oral toxicity of technical grade malathion and highly purified malathion suggest that the impurities in technical grade malathion may contribute to toxicity. While an understanding of the impurities in malathion is important for assessing the relevance of some studies for the current risk assessment, the occurrence of these impurities in malathion has

relatively little impact on the uncertainties that affect this risk assessment because all of the toxicology studies on malathion that are used quantitatively in this risk assessment involve a grade of malathion that is either identical to or comparable to the formulations used in Forest Service programs. Thus, the role of the impurities in technical malathion is likely to be encompassed by the available toxicity studies that investigate the effects of technical grade malathion.

Based on studies submitted to the U.S. EPA in support of the registration of malathion, U.S. EPA classifies malathion as non-irritating to the skin of rabbits (Category IV) and minimally irritating to the eyes of rabbits (Category III). This assessment is consistent with studies published in the open literature indicating that malathion may cause only transient eye irritation. There is one early report in the literature of apparent contact dermatitis in humans exposed to technical grade malathion. Other studies associate contact dermatitis or delayed hypersensitivity with exposure to malathion bait sprays which involve the application of malathion with various adjuvants that may have contributed to the reports of delayed hypersensitivity.

There is a body of literature indicating that malathion may influence immune function, causing either enhancement or suppression of different endpoints under different exposure conditions and in different species. Immune enhancement can lead to transient inflammatory responses like irritation to the skin or respiratory tract. Oral exposure to malathion over a wide range of doses, from 0.1 to about 700 mg/kg/day, were shown to stimulate serum histamine release and macrophage activation. These effects, however, last for only a short period of time, usually from 2 to 4 hours after dosing. Several studies suggest that malathion may impair immune function based on decreased immune response indicators to foreign antigens. Only two studies, however, associate malathion exposures directly with increased susceptibility to infections which may suggest immunological impairment considered to be clinically significant. In both of these studies, tests for effects on immune function indicators were not performed. Thus, the potential clinical significance of the effects of malathion on immune function indicators is unclear.

There is a large, complex, and often controversial literature on the potential carcinogenicity of malathion as well as the potential mutagenicity of malathion and malaoxon. These studies were reviewed in detail by the U.S. EPA in the re-registration of malathion, and the U.S. EPA concluded that although there is suggestive evidence of carcinogenicity resulting from exposure to malathion, the evidence is not sufficient to support a quantitative risk assessment. Similar conclusions were reached by other organizations, including the Agency for Toxic Substances and Disease Registry (ATSDR) and the World Health Organization (WHO).

Malathion was tested for its ability to cause birth defects (i.e., teratogenicity) and its potential to cause adverse effects on reproductive performance. Teratogenicity studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Reproduction studies typically involve exposing animals for more than one generation, with each generation being allowed to reproduce. As a class, organophosphate pesticides appear to be toxic but not teratogenic in developing mammals, which appears to be the case with malathion.

Certain groups of individuals may be at increased risk when exposed to malathion. Based on toxicity studies, very young animals may be more sensitive than older animals to malathion. Because certain esterases in the liver play an important role in the detoxicification of malathion, individuals with liver disease who have abnormally low levels of liver carboxylesterases may be at increased risk. There are no studies, however, that directly support this supposition. Similarly, animals on low-protein diets tend to have a number of changes in liver function that could impact susceptibility to compounds that are either activated or detoxified in the liver; however, there is limited experimental evidence to support this supposition.

3.1.2. Mechanism of Action

The primary mechanism of action associated with malathion toxicity involves its direct effect on the nervous system. Malathion is metabolized to malaoxon which combines with and inhibits acetylcholinesterase (AChE). Detailed reviews of the neurotoxicity of organophosphates have been published by Abou-Donia (1995), Ecobichon (1994), Maroni et al. (2000), Osmundson (1998) and Taylor (1996). Much of the literature on the neurological effects of malathion was reviewed in some detail by CDHS (1991).

The biochemical basis for the toxic effects of malathion is related to the normal function of AChE. In the cholinergic system, neural impulses are transmitted between nerve cells or between nerve cells and an effector cell (such as a muscle cell) by the acetylcholine. When the acetylcholine reaches a certain level, the receptor cell is stimulated. Normally, the acetylcholine is rapidly degraded to inactive agents (acetate ion and choline) by AChE.

Organophosphorus insecticides, including malathion, form stable (and sometimes essentially irreversible) complexes with AChE (phosphorylation of the serine hydroxyl group at the ester site), suppressing the ability of the enzyme to degrade acetylcholine. When AChE activity is inhibited, acetylcholine persists and continues to accumulate at the synapse (the space between the two cells). Initially, this accumulation causes continuous stimulation of the cholinergic system, which may be followed by paralysis because of nerve cell fatigue. Depending on the degree of AChE inhibition, a broad spectrum of clinical effects may be induced ranging from mild signs of toxicity (e.g., salivation or lacrimation) to convulsions and death (Abou-Donia 1995; ATSDR 1993; O'Malley 1997).

There are two types of AChE, one occurring in nerve tissue and the other in red blood cells (RBC). In addition, plasma contains cholinesterases (ChE) that are different from and have broader substrate specificity than either RBC or nerve tissue AChE (Abou-Donia 1995). Although plasma ChE and RBC AChE are most often used as indices of exposure to cholinesterase inhibitors, these enzymes are not the receptors that lead to signs of toxicity (Anwar 1997; Banasik et al. 2003; Ecobichon 1991,1994; Gage 1967; Gallo and Lawryk 1991; Murphy 1980; Thompson 1999; Wills 1972); furthermore, there is a poor correlation between plasma ChE inhibition and the signs and symptoms of toxicity (Peedicayil et al. 1991).

Toxic effects are induced by the inhibition of AChE in nerve tissue (Abou-Donia 1995; Gage 1967; Wills 1972). The physiological functions, if any, of plasma ChE and RBC AChE are not

identified (Abou-Donia 1995). The inhibition of RBC AChE is generally regarded as a more clinically significant index of cholinesterase inhibition in the nervous system, compared with inhibition of plasma ChE (ATSDR 1993).

At least in RBC preparations, AChE inhibition by malathion follows a pure uncompetitive model (Kamal 1998; Datta et al. 1994). In purified brain cholinesterase, however, the inhibition of AChE by malathion appears to be competitive (Awad 1984). These kinetic differences probably reflect differences in the interaction of malathion with purified AChE versus membrane bound AChE (e.g., De Domenech et al. 1980).

The malathion molecule itself does not cause AChE inhibition. AChE inhibition is induced by the metabolism of malathion to malaoxon in mammals as well as other species. Thus, the extent of metabolism from malathion to malaoxon is an important aspect for understanding the toxicity of malathion, as discussed further in Section 3.1.3.

Not all adverse effects associated with exposure to malathion are directly related to neurotoxicity. Many chemicals, including malathion, induce or contribute to what is often referred to as *oxidative stress* or general oxidative damage that leads to increases in free radicals and/or a changes in enzyme systems (e.g., superoxide dismutase, or catalase) or naturally occurring antioxidants (e.g., GSH) that are designed to reduce oxidative damage. In patients admitted to hospitals with malathion poisoning, decreases were noted in blood GSH levels and increases were noted in the activity of several blood enzymes that reduce oxidative damage (Banerjee et al. 1999). Similarly, signs of oxidative stress (decreased RBC superoxide dismutase and glutathione peroxidase activities) were observed in mice exposed to dietary doses of malathion at 100, 500, or 1500 mg/kg/day over periods ranging from 15 to 120 days (Yarsan et al. 1999). At somewhat lower doses—i.e., 25, 50, 100, and 150 mg/kg administered by i.p. injections—malathion is associated with general sings of oxidative stress in brain tissue and cerebrospinal fluid (Fortunato et al. 2006). At even lower doses—i.e., 20 ppm in the diet of rats, equivalent to about 2 mg/kg bw /day—malathion exposure is associated with general signs of oxidative stress such as increased lipid peroxidation (Ahmed et al. 2000). *In vitro* studies using fibroblast cultures suggest that malathion may induce apoptosis (i.e., programmed cell death) by damaging mitochondria at concentrations below those associated with neurological effects (Masoud et al. 2003).

3.1.3. Pharmacokinetics

3.1.3.1. Overview of Information

Pharmacokinetics involves the quantitative study of the absorption, distribution, metabolism, and excretion of a compound. The metabolism of malathion is particularly important because malathion itself is not neurotoxic. Malaoxon, a metabolite of malathion, is the primary neurotoxic agent. The metabolism of malathion in mammals is further discussed in detail in Section 3.1.15.1. This section and the following subsection focus on aspects of the absorption and elimination of malathion that directly impact the risk assessment.

Malathion residues bind to skin (Menczel et al. 1983) and can persist on contaminated skin for periods of up to 7 days; however, on day 7, the proportion that is removable from the skin is only 0.01-0.02% of values obtained immediately after application (Kazen et al. 1974). In autoradiographic studies using rats, Saleh et al. (2000) noted that a substantial (≈80%) proportion of dermally applied malathion appears to bind tightly to skin and that skin may act as a reservoir for malathion. Conversely, if the malathion remains on the skin for only a brief period of time—i.e., 15 minutes—virtually all of the applied malathion can be removed by isopropanol extraction/washing (MRI 1992, pp. 22-25).

Reddy et al. (1989) examined the disposition of malathion in rats. In this study, rats were dosed by gavage with C^{14}-malathion (98% purity) at single doses of 40 or 800 mg/kg or with a single dose of 40 mg/kg C^{14}-malathion after being dosed with unlabelled malathion (94.6%) at a rate of 40 mg/kg bw/day for 15 days. No accumulation of radioactivity was found in any organs, and, at the 40 mg/kg dose, 90% of the radioactivity was excreted 72 hours after dosing. The highest concentrations of malathion were found in the liver, however, the amount of malathion in this organ was only a small fraction of the administered dose (0.3%). While the oral absorption coefficient was not calculated in this study, the appearance of most of the administered dose in the urine 24 hours after dosing suggests that oral absorption and excretion are rapid.

The rapid absorption and excretion of malathion was observed also in humans. Aston (2000) analyzed the excretion of malathion and malathion metabolites in the urine of humans who participated in the study by Gillies and Dickson (2000). About 90% of the orally administered malathion was excreted in the urine (mostly as mono- or dicarboxylic acids with lesser amounts of dimethylphosphate, dimethylthiophosphate, and dimethyldithiophosphate) by 12 hours after dosing. Virtually the entire administered dose was recovered in the urine within 24-48 hours.

The rapid oral absorption of malathion noted in the study by Reddy et al. (1989) is supported by the observation that more than 90% of the radioactivity from an oral dose of C^{14}-malathion (280 mg/kg/day) is excreted in the urine of rats over a 24-hour period (Abou Zeid et al. 1993). The kinetics of the gastrointestinal absorption of malathion were characterized in fasted mice by Ahdaya and Guthrie (1982), who determined a gastrointestinal absorption rate of 0.888 $hours^{-1}$ with absorption from the ligated stomach of 0.197 $hours^{-1}$. The gastrointestinal absorption rate of 0.888 $hours^{-1}$ is also reported in Ahdaya et al. (1981). Rapid oral absorption and excretion of malathion by rats was noted also by Garcia-Repetto et al. (1995). Conversely, in a study involving the administration of C^{14}-malathion to rats followed by whole-body autoradiographs, Saleh et al. (1997) report that malathion appears to be only poorly absorbed orally after administration in 1 mL of corn oil by gavage. This slow rate of absorption may have been due to the large quantity of corn oil used in this study relative to the size of the rats. In a PBPK model for malathion, Bouchard et al. (2003) estimate that the rate of oral absorption is about 10-fold greater than dermal absorption. The model also incorporates dermal and oral absorption fractions of 0.0705 and 0.738, respectively, which increases the mass transfer of oral relative to dermal absorption by another factor of 10.

Feldmann and Maibach (1970) assayed the dermal absorption of malathion in humans and noted that 7.84% (SD 2.71%) of the applied dose of radioactivity was recovered from the urine of volunteers over a 5-day period after the application of C^{14}-malathion to the forearm. The values reported by Feldmann and Maibach (1970) are corrected for the proportion of C^{14} found in the urine after intravenous administration. Since, as noted above, malathion was not administered intravenously to the humans, the correction involved administering the compound intravenously to guinea pigs and determining that 76% of the intravenous dose was recovered in the urine over a 5-day period.

Feldmann and Maibach (1974) and Wester et al (1996) conducted additional dermal absorption studies in humans. The study by Feldmann and Maibach (1974) is quite similar to the Feldmann and Maibach (1970) study except that the intravenous component of the study was conducted in humans. The results of this study were similar to the earlier study, with 90% of the radioactivity after the intravenous dose recovered in the urine after 5 days and 8.2%(±2.7% SD) of the dermal dose (corrected for incomplete urinary excretion) recovered in the urine after 5days.

Substantial inter-individual variability in the dermal absorption of malathion was noted in volunteers, with 1.78-15.46% of the applied C^{14}-malathion recovered in the urine over a 24-hour period after dermal exposure (Dary et al. 1994). Based on a kinetic analysis of these data, Dary et al. (1994) estimated an average first-order absorption rate of 0.015 $hour^{-1}$ with a range of 0.0043-0.026 $hour^{-1}$. These absorption rates are substantially higher than the average rate of 0.00356 $hour^{-1}$ from the study by Feldmann and Maibach (1970). This difference appears to be due to the use of a more complex kinetic model in the Dary et al. (1994). Nonetheless, the total cumulative absorption noted in the study by Dary et al. (1994, Figure 3, p. 243) was in the range of about 5% to somewhat less than 7% for neat malathion as well as 1% and 10% for aqueous solutions of malathion. These cumulative absorption rates are quite similar to the corresponding values noted by Feldmann and Maibach (1974).

In the same study, Dary et al. (1994) measured an average dermal absorption half-life in rats of 23.9 hours, corresponding to a k_a of 0.029 $hour^{-1}$. These authors also noted that nearly 80% of the dermally applied malathion was not absorbed—i.e., the compound remained on the occlusive covering or was subject to fugitive losses. Total radioactivity accounted for by urine, dose wipes, and dose site washings ranged from 55 to 93%. Substantial inter-individual variability (i.e., factors of about 7 for malaoxon) is also apparent in the activities of enzymes responsible for the detoxicification of malaoxon and malathion (Sams and Mason 1999).

In addition to inter-individual differences, there are substantial differences in the rate of malathion dermal absorption in various regions of the body, with least absorption occurring through the thick skin of the palms and the balls of the feet and most rapid absorption occurring through the dorsal surface of the hands, the armpits, and the forehead (Maibach et al. 1971). The dermal absorption of malathion may also be influenced substantially by whether or not the surface of skin is occluded/protected. Wester et al. (1983) noted a 9.2-fold increase in the amount of C^{14} excreted in the urine after exposure via non-occluded skin (6.8%), compared with occluded skin (62.8%).

Proportions of approximately 0.33-0.66 of the malathion applied to skin (scalp of the head) of volunteers was removed after washing. Only 0.2-3.2% of the applied dose was absorbed (Dennis and Lee 1999). This study, which is generally consistent with other data on malathion, is only peripherally relevant to the current risk assessment because the malathion was applied in a formulation (a shampoo not otherwise specified) used to treat hair lice.

Interspecies differences in the rate of malathion dermal absorption appear to be substantial, with greatest absorption in the rabbit (64.5%), followed by monkey (19.3%), pig (15.5%), and man (8.2%) (Wester and Noonan 1980). In guinea pigs, a dermal absorption rate of 6.8% is reported by Bucks et al. (1985). This rate is quite similar to the rate reported in humans. The use of an isolate perfused porcine flat system appears to underestimate the dermal absorption of malathion—i.e., 2.9% per day (Chang et al. 1994). Using the intact skin of anesthetized rats, time to 50% penetration of H^3-malathion (assayed as the amount remaining on intake skin) was 5.5 hours (k_a=0.126 $hour^{-1}$) (O'Brian and Dannelley 1965). In *in vivo* studies in mice, the apparent dermal absorption rate of malathion is 0.005 $hour^{-1}$, which is close to the lower range of absorption rates in humans reported by Dary et al. (1994).

Based on a comparison of AChE activities, there appears to be little difference in the dermal absorption rates of pure malathion (98%) and malathion formulated as a 50% emulsifiable concentrate. Based on C^{14}-concentrations in the urine, however, the emulsifiable concentrate appears to have been somewhat more rapidly excreted (Abou Zeid et al. 1993). These results are consistent with the results of Saleh et al. (2000) in which a 50% emulsifiable concentration of malathion was more rapidly absorbed by rats than was the neat concentration of malathion.

As with many chemical agents, the absorption of malathion may be influenced by numerous factors. The absorption of malathion from contaminated clothing was investigated by Wester et al. (1996). Absorption ranged from 8.77% for a 1% malathion solution applied directly to the skin to <1% for malathion on cotton. The dermal absorption rate of malathion may be enhanced by the ability of malathion to increase cutaneous blood flow (Boutsiouki and Clough 2004; Boutsiouki et al. 2001). Vehicles such as sunscreens and insect repellents may also increase the dermal absorption rate of malathion (Brand et al. 2003; Abdel-Rahman et al 2004). A marked vehicle effect was also observed in the study by Dary et al. (1994). As discussed above, Dary et al. (1994) noted total cumulative absorption ranging from about 5% to somewhat less than 7% for neat malathion as well as 1% and 10% for aqueous solutions of malathion. For an unspecified 50% emulsifiable concentrate, however, the total cumulative absorption of malathion was about 17%, which is about 3 times greater than neat malathion or aqueous solutions of malathion.

3.1.3.2. Kinetic Values Used in Risk Assessment

Most of the occupational exposure scenarios and many of the exposure scenarios for the general public involve the dermal route of exposure. For these exposure scenarios, dermal absorption is estimated and compared to an estimated acceptable level of oral exposure based on subchronic or chronic toxicity studies in animals. Hence, it is necessary to assess the consequences of dermal

exposure relative to oral exposure and the extent to which malathion is likely to be absorbed from the surface of the skin.

Two types of dermal exposure scenarios are considered: immersion and accidental spills. As detailed in SERA (2007a), the calculation of absorbed dose for dermal exposure scenarios involving immersion or prolonged contact with chemical solutions uses Fick's first law and requires an estimate of the permeability coefficient (K_p) expressed in cm/hour. For exposure scenarios like direct sprays or accidental spills, which involve deposition of the compound on the surface of the skin, dermal absorption rates (k_a) expressed as a proportion of the deposited dose that is absorbed per unit time are used in the exposure assessment.

In terms of the first-order dermal absorption rate, several studies are available on the dermal absorption of malathion by humans, and the results of these studies are reasonably consistent. The data from Feldmann and Maibach (1974) are probably more appropriate for a risk assessment because the estimates of dermal absorption are based on excretion rates in humans after intravenous administration of the compound rather than the estimates used from guinea pigs in the 1970 study. A re-analysis of the Feldmann and Maibach (1974) data on malathion was conducted by Thongsinthusak et al. (1999) using a lag parameter for absorption and attempting to correct for incomplete urinary excretion. This reanalysis suggests that the dermal absorption of malathion may have been somewhat less than that reported in the Feldmann and Maibach (1974) publication—i.e., 6.3-7% rather than 8.2%.

Estimates of first-order dermal absorption rates can also be derived based on quantitative structure activity relationships (SERA 2007a). These calculations are given in Worksheet B06 of the EXCEL workbooks that accompany this risk assessment. As indicated in the worksheet, the calculated first-order dermal absorption rate coefficient for malathion is 0.0019 $hour^{-1}$ with a 95% confidence interval of 0.00088 $hour^{1}$ to 0.0041$hour^{1}$.

For comparison, the data on the proportion of malathion absorbed by humans over a fixed period of exposure can be used to calculate first-order dermal absorption rates. This calculation involves a rearrangement of the basic equation for first-order absorption, $P = 1 - e^{-k \times t}$, where P is the proportion absorbed after a given time (t) and k is the first-order dermal absorption rate. Solving for k, this equation rearranges to $k = -\ln(P)/t$. As noted in Section 3.1.3.1, Feldmann and Maibach (1974) measured the proportion of malathion absorbed by humans over a 24-hour exposure period as 8.2% (2.7% SD). Taking two standard deviations to approximate 95% confidence intervals, these values correspond to a proportion of 0.082 with a range of 0.028-0.136 and to a k_a of 0.0036 $hour^{-1}$ with a range of 0.0011-0.0061 $hour^{-1}$. This estimate of the k_a, 0.0036 (0.0011-0.0061) $hour^{-1}$, is quite similar to the estimate based on structure activity considerations, 0.0019 (0.00088-0.0041) $hour^{-1}$.

For the current risk assessment, a k_a of 0.0036 (0.00110.0061) $hour^{-1}$ is used to estimate the first-order dermal absorption of malathion for neat exposures – i.e., undiluted malathion – as well as exposures to aqueous solutions. These dermal absorption rates are applied to exposures associated with mosquito control programs. As discussed in Section 2.2, the formulations of

malathion used for mosquito control, Fyfanon ULV and Atrapa VCP, are aqueous solutions of malathion. For the control insect pests on pine seed orchards, however, the Forest Service will use formulations that are emulsifiable concentrates in a petroleum base. The study by Dary et al. (1994) suggests that malathion in emulsifiable concentrate formulations may be absorbed to a greater extent than aqueous formulations by a factor of about 3. Thus, for exposure assessments associated with emulsifiable concentrate formulations, the k_a values are adjusted upward by a factor of 3—i.e., 0.0108 (0.0033-0.0183) $hour^{-1}$.

The malathion literature does not include experimental data regarding permeability coefficients (Kp) As discussed in SERA (2007a), the structure activity relationships developed by the U.S. EPA (1992) are similar to the relationships used to estimate the first-order dermal absorption rate—i.e., both algorithms are based on the molecular weight and K_{ow} of the compound. The application of the EPA algorithm to malathion is given in Worksheet B05 of the EXCEL workbooks that accompany this risk assessment. Based on the EPA algorithm, the estimated dermal permeability coefficient for malathion is 0.00153 cm/hour with a 95% confidence interval of 0.00099-0.00237 cm/hour. While no data are available on the influence of vehicles and the dermal permeability of malathion, it is reasonable to assume that the zero-order absorption rate (Kp) of malathion will be increased by the same proportion as the first-order absorption rate (k_a). Consequently, for emulsifiable concentration formulations of malathion, the Kp is adjusted upward by a factor of 3—i.e., 0.00459 (0.00297-0.00711) cm/hour.

While excretion rates are not used directly in either the dose-response assessment or risk characterization, excretion half-lives can be used to infer the effect of longer-term exposures on body burden based on the *plateau principle* (e.g., Goldstein et al. 1974). The chemical concentration in the body after a series of doses (X_{Inf}) over an infinite period of time can be estimated based on the body burden immediately after a single dose, X_0, by the relationship:

$$X_{Inf}/X_0 = 1 / (1- e^{-ke\ t^*)})$$

where t* is the interval between dosing.

The most relevant data on whole-body excretion in humans comes from the analysis by Aston (2000) in which about 90% of orally administered malathion was excreted in the urine by 12 hours after dosing. Using a first-order approximation (Goldstein et al. 1974), this measure corresponds to an elimination rate (k_e) of 0.19 $hour^{-1}$ [$ke = -\ln(1-P)/t = -\ln(1-0.9)/12 = 0.19188$ $hour^{-1}$] or about 4.6 day^{-1}. Using this k_e and a 1-day interval between doses (i.e., daily dosing), results in an increased body burden with infinite exposure, relative to the body burden after a single dose, of about 1.01. Thus, neither malathion nor its metabolites will accumulate substantially in humans over prolonged periods of exposure.

3.1.4. Acute Oral Toxicity

One type of acute toxicity information involves time-specific LD_{50} or LC_{50} values (i.e., doses or concentrations of a toxicant that result in or are estimated to result in 50% mortality of the test species during a specified exposure or observation period). These values can be viewed as an

index of acute lethal potency. Information is also available on the acute neurological effects of malathion, as detailed further in the following section (3.1.6). These acute neurotoxicity studies form the basis of the acute RfD for malathion (Section 3.3.2).

The acute toxicity of malathion is highly dependent on the purity of the compound (WHO 1998). For example, in studies of technical grade malathion submitted to the U.S. EPA as part of the registration process, the acute oral LD_{50} of technical grade malathion was 5400 mg/kg in female rats and 5700 mg/kg in male rats (Kynoch 1986a). On the other hand, highly purified recrystallized malathion has acute oral LD_{50} values as high as 12,500 mg/kg in rats, whereas a 95% pure commercial formulation has an LD_{50} of 1500 mg/kg—i.e., a difference of about a factor of 8 (Umetsu et al. 1977). Reported LD_{50} values of malathion formulations that contain high concentrations of isomalathion are less than 700 mg/kg (Hayes 1982). As discussed further in Section 3.1.9, the effect of the impurities on the toxicity of technical grade malathion involves two factors: the higher inherent toxicity of some of the impurities and the inhibition of detoxicification pathways for malathion by other impurities.

Incidents of suicidal or accidental ingestion of malathion—i.e, gross over-exposures to malathion in humans—are well-documented. Most of these incidents are of limited use in estimating toxic potency in humans because the amount of malathion ingested by the individuals cannot be estimated reliably (e.g., Asari et al. 2004; Dribben and Kirk 2001; Pannel et al. 2001). A number of cases of suicidal or accidental ingestions of malathion are summarized by Hayes (1982). Estimated lethal doses range from 56 mg/kg bw to about 1000 mg/kg bw. The lower bound of this range involved the accidental ingestion of malathion by a 75-year-old man. In humans, the consequences of gross over-exposure to malathion are highly dependant on prompt and effective medical intervention. A 42-year-old woman survived the ingestion of approximately 30,000 mg of malathion due to prompt medical treatment (Bentur et al. 2003). The body weight of the individual is not specified in the report by Bentur et al. (2003). Assuming a body weight of about 60 kg, the ingested dose would be about 500 mg/kg bw. Similar instances of survival after attempted suicides followed by medical treatment are summarized by Hayes (1982) for individuals who took malathion doses ranging from 100 to 1000 mg/kg bw.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

There are numerous studies concerning the subchronic and chronic toxicity of malathion. The published studies are reviewed in some detail by ATSDR (2003) as well as other reviews of malathion (e.g., Davis et al. 2007; *Flessel* et al. 1993; Peterson et al. 2006; Thompson 1996; Voccia et al. 1999; WHO 1998); the unpublished studies are reviewed in U.S. EPA/OPP (2006c). Some of the longer-term, repeated-dose studies focus on specific types of toxicity—e.g., neurotoxicity, reproductive effects, and immune function. These studies are discussed in the subsections below.

U.S. EPA determined that younger mammals are substantially more sensitive than older animals to malathion. Consequently, the chronic RfD for malathion is based on a short-term exposure study (i.e., 11 days) in young rats which yielded a functional NOAEL of 7.1 mg/kg/day based on

the inhibition of red blood cell cholinesterase (U.S. EPA/OPP 2006a). This study is discussed in further detail in Section 3.1.6 (Effects on Nervous System).

A previous RfD on malathion derived by the U.S. EPA was based on a 2-year bioassay in Fischer 344 rats which yielded a NOAEL of 2.4 mg/kg bw/day (Daly 1996a). In this study, malathion (97.1%) was administered in the diet at concentrations of 0, 100/50 (100 ppm for first 3 months of study, 50 ppm for duration of study), 500, 6000, or 12,000 ppm. The initial 100 ppm exposure was lowered to 50 ppm because RBC AChE inhibition was noted in female rats at 3 months. Based on measured food consumption, these dietary concentrations were equivalent to mean daily malathion intakes of 0, 2.37, 29, 359, or 739 mg/kg/day in male rats and 0, 2.95, 35, 415, or 868 mg/kg/day in female rats. At the end of the study, brain AChE inhibition was observed in males and females at dietary levels of 6000 ppm (359 and 415 mg/kg/day in males and females, respectively). At the next lower exposure concentration (500 ppm), a significant decrease in plasma ChE was observed in males (29 mg/kg/day) and a significant decrease in RBC AChE was observed in females (35 mg/kg/day). At the lowest concentration (100/50 ppm), ChE inhibition in plasma, and AChE inhibition in RBC or brain were not observed in either sex (NOAELs = of 2.37 mg/kg/day for males and 2.95 mg/kg/day for females).

In a 29- to 30-day feeding study, plasma ChE and RBC and brain AChE were not inhibited at concentrations of 500 ppm or less (corresponding to estimated daily doses of 52 mg/kg bw/day or less) (Daly 1996a). Husain et al. (1987) dosed female rats at 55 and 137.5 mg/kg/day for 32 days by gavage. At 55 mg/kg/day, no adverse effects were noted other than a slight (15%) decrease in plasma ChE activity. At 137.5 mg/kg/day, both plasma ChE and RBC AChE were inhibited.

There are two studies involving the oral toxicity of malathion to dogs, neither of which identifies a NOAEL. In a 28-day study in which malathion was administered in gel capsules, plasma ChE and RBC AChE activity were inhibited at doses as low as 125 mg/kg/day (Fischer 1988). Similarly, in a 1-year study in which malathion was also administered by capsules, RBC AChE activity was decreased (>20%) at all doses tested (62.5, 125, and 250 mg/kg bw/day) (American Cyanamid Co. 1987). Based on these data, the sensitivity of dogs to the neurological effects of malathion, relative to rats, cannot be determined because neither of the dog studies identifies a NOAEL. In addition, even if a NOAEL had been determined in dogs, this would not permit a reliable determination of the comparative sensitivities of rats and dogs to AChE inhibition because the methods of the administration of malathion in the studies on rats and dogs were distinctly different.

Mice may be somewhat less sensitive than rats to the neurological effects of malathion. In a 2-year chronic feeding study (Slauter 1994), a dietary concentration of 100 ppm (equivalent to an estimated daily dose of 17 mg/kg/day) was not associated with any significant decrease in plasma ChE or RBC and brain AChE activity.

In an early controlled human study, doses of 8 mg/day for 32 days (0.11 mg/kg/day) had no effect on cholinesterase activity, 16 mg/day (average daily doses of 0.22 mg/kg/day) over a 47-

day period was associated with decreased plasma ChE activity, and doses of 24 mg/day (average daily dose of 0.34 mg/kg/day) for 56 days were associated with both decreased plasma ChE and RBC AChE activity (Moeller and Rider 1962). As discussed in Section 3.3 (Dose-Response Assessment), this study is the basis for the U.S. EPA RfD listed on the Integrated Risk Information System (IRIS) (U.S. EPA/ORD 2002).

In the study by Lox and Davis (1983), rats exposed to malathion (99%) in drinking water for 6 months showed "...an overall hepatic degeneration taking place. This was evidenced by degenerating hepatocytes, both in the cytoplasm and nuclear areas. Likewise, leukocytic infiltration and phagocytosis were evident" (Lox and Davis 1983, p. 547 ¶6). These effects were noted only in the animals receiving malathion (n=20) and not in the control group (n=24) or in a separate group receiving diazinon (n=20). The publication, however, does not provide information on the number of animals in which these effects were observed. Although it appears that this study was well conducted, the observation of severe liver pathology at a dose of 0.15 mg/kg/day is inconsistent with other toxicity studies using much higher doses.

3.1.6. Effects on Nervous System

Malathion will inhibit AChE activity over all routes and durations of exposure. The magnitude and time of the reductions, however, will be variable, most likely depending on the rate of metabolism of malathion to malaoxon as well as the rate of recovery/ regeneration of AChE.

Neurotoxicity is the key endpoint or critical effect for malathion. Of the many available neurotoxicity studies on malathion, the study by Fulcher (2001) is designated by the U.S. EPA as the key study and is used by the U.S. EPA/OPP (2006a,c) to derive both the acute and chronic RfD values for malathion (Section 3.3). Fulcher (2001) dosed adult and neonatal rats by gavage in two phases: a single gavage administration at doses of 0, 5, 50, 150, or 450 mg/kg bw and a multiple dose study at 0, 50, or 150 mg/kg bw/day for 11 days. The adult rats consisted of pregnant dams treated from gestation day (GD) 9 through postnatal day (PND) 10. One offspring from each of these animals was then treated from PND 11 through PND 21. In addition, offspring from untreated dams were dosed on PND 11. Additional groups of adult rats, males and non-pregnant females, were treated for 11 consecutive days. The assessment endpoints in all animals included blood and brain ChE activities.

Instead of the NOAEL/LOAEL approach, the U.S. EPA used the benchmark dose method (U.S. EPA/ORD 2000) to analyze the Fulcher (2001) study. As discussed in U.S. EPA/OPP (2006c, p. 37 ff), the benchmark dose method was used to provide a more uniform and statistically robust comparison among the different groups of animals in the study. Specifically, the Agency elected to use the $BMDL_{10}$, the 95% lower limit on the dose associated with a 10% inhibition of AChE. As summarized in U.S. EPA/OPP (2006c, Table 4.1.3.1, p. 39), neonatal mice were more sensitive than adults to malathion. In acute single dose exposures, the $BMDL_{10}$ for inhibition of RBC AChE in male pups was 13.6 mg/kg bw, compared with 110 mg/kg bw in adult males. Similar, although less marked, differences were noted in the multi-dose exposures in which the $BMDL_{10}$ for inhibition of RBC AChE in male pups was 7.1 mg/kg bw/day, compared with 16.2 mg/kg bw/day in adult males. Female rats, both adults and pups, responded similarly but had

somewhat higher $BMDL_{10}$ values. As discussed further in Section 3.3 (Dose-Response Assessment), the single dose $BMDL_{10}$ value of 13.6 mg/kg bw is the basis of the acute RfD; the multiple dose $BMDL_{10}$ value of 7.1 mg/kg bw/day is the basis for the chronic RfD.

In adult animals, much higher daily doses of malathion are associated with AChE inhibition and may or may not be associated with other frank signs of toxicity. Acute single doses of 2000 mg/kg were associated with decreased plasma ChE and RBC and brain AChE, and single doses of 500 mg/kg were associated with decreases in plasma ChE and RBC AChE but not brain AChE in male and female rats (Lamb 1994a). After intraperitoneal doses of 800 mg/kg to rats, maximum plasma ChE inhibition was observed after 12 hours, while maximum inhibition of brain AChE activity occurred at 3 hours and remained substantially depressed on day 7 but not day 30 (Chauhan et al. 1973).

In a subchronic dietary study, doses of 100, 500, or 1500 ppm malathion administered to male Sprague-Dawley rats (200-500 g) for 4 weeks significantly depressed plasma ChE activity and saliva ChE activity and increased plasma antioxidant power. Although the effects were observed at all dose levels, they did not follow a dose-dependent trend (Abdhollahi et al. 2004b). Subchronic dietary exposure to 100, 316, 1000, or 1500 ppm technical malathion for 4 weeks caused increased in RBC and liver lipid peroxidation and decreased AChE and ChE activities in male Wistar rats (Akhgari et al. 2003).

The acute effects of malathion on acetylcholinesterase activity in humans were observed in a study by Gillies and Dickson (2000) in which male volunteers were given a series of single oral doses of malathion (95.8%) at 0 (lactose as a placebo), 0.5, 1.5, 5, 10, and 15 mg/kg in gelatin capsules. In other words, each male subject (n=41) received a total of five doses ranging from 0.5 to 15 mg/kg. Females volunteers (n=7) received only a single oral dose of 15 mg/kg. Three other females were treated with the placebo. For each dose, blood samples were taken for several days before dosing, at 30 minutes before dosing, and at 1, 2, 4, 8, 12, 24, and 48 hours after dosing. Oral exposure to malathion caused no statistically significant effects on plasma ChE or RBC AChE and no effects on standard hematology, clinical chemistry, urinalysis, and physical parameters. Dose-response analyses suggested a dose-related decrease in plasma ChE levels at 2 hours. When compared with placebo values, however, no dose-related decreases in acetylcholinesterase were apparent, and the plasma ChE activity in the placebo group was lower than that observed in the treated groups. The incidence of reported adverse effects was 5/14 (≈35%) in the placebo group and 13/34 (≈38%) in the treated group (Gillies and Dickson 2000, Table 6, p. 56), and these two rates are not significantly different ($p \approx 0.569$ based on the Fischer exact). No detectable concentrations of malathion (<102 µg/L) or malaoxon (<99.8 µg/L) were found in the plasma.

The longer-term dermal toxicity of malathion was assayed in a 21-day study in which malathion (94%) was applied undiluted to New Zealand rabbits at doses of 0, 50, 300 or 1000 mg/kg/day for 6 hours/day, 5 days/week for 3 weeks (Moreno 1989). A dose-related decrease in AChE activity was observed at 300 and 1000 mg/kg/day in both males and females. In male rabbits, doses of 300 mg/kg/day were associated with statistically significant decreases in plasma ChE

activity (-13%) and RBC AChE activity (-18%). At 1000 mg/kg/day, decreased AChE activity was also noted in the brain (-18% in cerebrum and -41% in cerebellum). Results were virtually identical in females for plasma ChE and RBC with decreases in plasma ChE activity (-17%) and RBC AChE activity (-26%) at 300 mg/kg/day. In females, however, there was also a decrease in brain AChE activity at 300 mg/kg/day (-19% in cerebrum), which was not seen in males. AChE activity in the cerebellum of females was only significantly inhibited (-49%) at 1000 mg/kg/day, which is similar to the inhibition observed in the male rats. The NOAEL in this study was 50 mg/kg bw/day. Using the benchmark dose analyses (U.S. EPA/ORD 2000), the U.S. EPA/OPP (2006c) calculated $BMDL_{20}$ values of 135 mg/kg bw/day for males and 143 mg/kg bw/day for females.

The inhalation toxicity of malathion was assayed in a 13-week study in which Sprague-Dawley rats (15 animals of each sex) were exposed (whole body) to malathion aerosols at concentrations of 0, 100, 450, or 2010 mg/m^3 for 5 days/week, 6 hours/day. Decreases in plasma ChE activity and RBC and brain tissue AChE activity were noted at all dose levels. For the 100, 450, or 2010 mg/m^3 exposures, clear dose-response relationships were apparent for both plasma (2, 7, 18% in males and 16, 30, 70% in females) and RBC (9, 22, 43% in males and 11, 27, 44% in females). In brain tissue, the clear dose-response relationship was also apparent in females (4, 8 and 41%); however, males had slightly greater inhibition at 100 mg/m^3 than at 450 mg/m^3 (5, 3, 17%) (Beattie 1994). In the review of this study, the U.S. EPA (2006c) identified a NOAEL of 100 mg/m^3 and a LOAEL of 450 mg/m^3 based on AChE inhibition in red blood cells.

In a controlled human study, air concentrations of 5-85 mg/m^3 were not associated with signs of acute toxicity, although plasma ChE activity was depressed (Golz 1959). During an early aerosol application of a mixture of malathion and chlorthion, no signs of toxicity and no inhibition of AChE were observed in individuals exposed to malathion in the air at typical concentrations of 0.5-4 mg/m^3 and at transient peak concentration of 56 mg/m^3 for 4-5 hours (Culver et al. 1956).

Intermediate syndrome (IMS) is distinct from either acute AChE inhibition or delayed neurotoxicity (see below) and appears to involve muscle fiber necrosis which occurs after acute AChE inhibition by organophosphorus insecticides (Karalliedde and Henry 1993). The symptoms include weakness of the head and neck, respiratory paralysis, and weakness of the proximal limb muscles (De Bleecker 1995). There are some reports of cardiac, pulmonary, neurological, and renal effects in humans during recovery from AChE inhibition; however, it is unclear whether these effects would be classified as IMS (Dive et al. 1994). IMS was diagnosed in individuals recovering from unsuccessful suicide attempts (Komori et al. 1991; Sudakin et al. 2000). Although gross overexposure to malathion (e.g., large amounts directly consumed as part of an attempted suicide) may cause IMS, this effect is not likely to result from exposure to malathion used on lands managed by the Forest Service.

Exposure to some organophosphorus insecticides and other organophosphorus compounds causes delayed neurotoxicity, often referred to as organophosphorus induced delayed neurotoxicity (OPIDN). OPIDN involves the inhibition of neuropathy target esterases (NTE)

and is a neurological effect which is totally different from AChE inhibition (Abou-Donia 1995; De Bleecker 1995; Ecobichon 1994; Jamal 1997). The animal model of choice for OPIDN is the adult hen (Ecobichon 1994; Ehrich et al. 1995).

A tentative diagnosis of delayed neurotoxicity was proposed in one incident of human poisoning (Dive et al. 1994). In a human neuroblastoma cell line, however, neither malathion nor malaoxon were found to inhibit NTE. This result is consistent with the failure of malathion (88% solution) to induce delayed neurotoxicity in adult hens after oral doses of 75, 150, or 300 mg/kg (Ehrich et al. 1995). In this study, malathion inhibited both brain NTE and brain AChE; however, brain AChE was inhibited to a greater extent than was brain NTE. In contrast, chemical agents associated with overt signs of OPIDN inhibited brain NTE to a greater extent, compared with brain AChE. Lotti and Moretto (2005) reviewed numerous case reports and toxicity studies and concluded that the available information does not demonstrate an association between malathion exposure and delayed polyneuropathy.

Four stereoisomers of isomalathion were found to inhibit neurotoxic esterase (NTE) only at concentrations 1500-150,000 times greater than concentrations that inhibit AChE in hen brains (Jianmongkol et al. 1996). This study suggests that the contaminants are not likely to be associated with delayed neurotoxic effects. Consequently, from the available information, it does not appear that malathion causes OPIDN.

Effects on the nervous system may be reflected in behavioral changes. Uppal et al. (1983) reported that malathion can impair conditioned responses in rats. Kurtz (1977) reported that malathion doses that did not reduce AChE activity substantially (50 mg/kg after intraperitoneal injection) resulted in impaired avoidance performance in rats. This effect was also noted at higher doses but was not well correlated with changes in AChE activity. Similarly, Abdel-Rahman et al. (2004) noted impaired sensory-motor performance (beam walk score, beam walk time, inclined plane and grip response) in rats after a 30-day dermal exposure to 44.4 mg/kg/day malathion in the absence of significant changes in ChE and BChE activities measured in different brain regions and in plasma.

3.1.7. Effects on Immune System

3.1.7.1. General Considerations

There is a body of literature that indicates malathion could potentially influence immune function, causing enhancement or suppression of different endpoints indicative of immune function under different exposure conditions and in different species.

Immune enhancement can lead to transient inflammatory responses like irritation to the skin or respiratory tract. Allergic or flu-like symptoms in humans were reported after aerial spraying of malathion (Brenner 1992; CDHS 1991). These reports are consistent with experimental studies in mice (e.g., Rodgers and Xiong 1997b,d; Rodgers and Ellefson 1988; Rodgers et al. 1986a) showing that oral exposures to malathion over a wide range of doses, from 0.1 to about 700 mg/kg/day, stimulate immune responses (i.e., serum histamine release and macrophage

activation). These effects, however, last for only a short period of time, usually from 2 to 4 hours after dosing.

Immune suppression can result in increased susceptibility to infections and cancer. There are no immunology studies, however, that specifically assess the immunosuppressive effects of malathion on endpoints directly related to the progression of tumors. Similarly, only two studies (Kalow and Marton 1961; Taylor et al. 1999) associate malathion exposures directly with increased susceptibility to infections which may suggest immunological impairment; however, tests for effects on humoral and cellular immune function indicators were not performed in either of these studies. Notwithstanding these limitations, concern is raised by studies that demonstrate impaired immune function based on decreased immune response indicators to foreign antigens (i.e., Banerjee et al. 1998; Casale et al. 1983; Desi et al. 1978).

3.1.7.2. Immune Enhancement

The work of Rogers and associates (Rogers 1997; Rogers and Ellefson 1988,1990,1992; Rodgers and Xiong 1996, 1997a,b,c,d) demonstrates that malathion may stimulate cell mediated immune function. While the purity of malathion is not specified in all of these publications, these investigators typically specify a purity of >99.9%, triple recrystallized malathion. In single dose studies ranging from 0.1 to 700 mg/kg, oral doses >0.1 mg/kg to mice were shown to cause an increase in serum histamine levels. In a 14-day oral study (Rodgers and Xiong 1997c), doses of 1 mg/kg/day were associated with a stimulation of macrophage and mast cell function (increased respiratory burst activity and increased mast cell degranulation) but no effect on serum histamine levels. Similar effects were noted in a 90-day gavage study in which mice were given doses of malathion (99.9%) at levels of 0.1, 1, or 10 mg/kg/day (Rogers and Xiong 1997d). As in the acute studies, a dose-related increase was noted in macrophage and mast cell function (increased respiratory burst activity, and mast cell degranulation without a detectable increase in serum histamine levels) (Rogers and Xiong 1997d). In the same study, the peritoneal macrophage phagocytic activity was increased in the 0.1 mg/kg group but decreased at the1.0 and 10 mg/kg dose levels (see immune suppression section). One other study in C57B1/6 mice showed increased respiratory burst activity in peritoneal macrophages following gavage administration of malathion (99%) at a single dose of 715 mg/kg (Rodgers and Ellefson, 1990) or at single doses of 0.05-600 mg/kg (Rodgers and Ellefson 1988). In the latter study (Rodgers and Ellefson 1988), increased degranulation of mast cells was also observed. In contrast to results in mice, serum histamine concentrations reached maximal levels in Sprague-Dawley rats 4 hours after oral (gavage) administration of malathion at single doses ranging from 0.1 to1000 mg/kg or following dermal administration of 2, 20, 200, or 2000 mg/kg (Rodgers and Xiong 1997b).

In one experiment, mice were given a single intraperitoneal dose of 200 mg/kg body weight malathion (90% purity). Four days after dosing, A/J mice were injected with mouse hepatic virus 3 (MHV3). [Note: The A/J strain of mice was used because they can usually survive exposures to MHV3.] Observations included significant increases in anti-MHV3 IgG antibody in sera in 24-hours and in splenocyte culture supernatants at 7 days post infection (Fournier et al. 1986). Increased antibody production was also noted in C57B1/6 mice exposed by intraperitoneal injection to malathion at a single dose of 200 mg/kg and immunized with sheep

red blood cells 10 days later (Fournier et al. 1986). One other study (Rodgers et al. 1986a) noted increases in anti-sheep red blood cell titers and lymphoprolifereative responses of splenocytes to nonspecific activators (mitogens) in C57B1/6 mice administered malathion (99%) at a single oral (gavage) dose of 715 mg/kg. At the same dose level there was no cholinergic toxicity, there was no change in plasma ChE, and there were no significant effects on thymus or spleen weights. Therefore, it was assumed that the observed effects were not a result of malathion-related toxicity.

Rodgers (1997) explored the effects of malathion in normal MRL +/+ mice and MRL-lpr mice. This latter strain of MRL mice has the lpr gene that increases lymphoproliferative responses. In MRL-lpr mice, 100 and 300 mg/kg doses of technical grade malathion (95%), administered by gavage once/week for 13 weeks caused signs of toxicity as evidenced by enlarged lymph nodes and elevated levels of rheumatoid factor in serum. These effects were accompanied by kidney damage manifested as increased protein in the urine and an increase in glomerular inflammation. No such effects were seen in similarly treated MRL +/+ mice (Rodgers 1997). Protein was also present in the urine of MRL-lpr mice after a dose of purified malathion (99%) (Rodgers 1997).

3.1.7.3. Immune Suppression

Several studies report effects possibly associated with immune suppression in laboratory animals exposed to malathion. In contrast to most of the single dose studies in which effects possibly associated with immune enhancement are reported, these effects are most often associated with multiple doses of malathion.

Effects of malathion exposure that may be associated with immunosuppression at doses below those associated with cholinergic toxicity are reported in three studies (Banerjee et al. 1998; Popeskovic et al. 1974; Rogers and Xiong 1997d).

In the Popeskovic et al. (1974) study, Wistar rats were gavaged with 0.61 or 1.23 mg/kg/day malathion for 15-30 days. Rats were immunized with bovine serum albumin (BSA) at different times of exposure, and the levels of anti-BSA antibodies and delayed-type hypersensitivity (DTH) responses were examined at various times after immunization. Reduced anti-BSA antibody levels and DTH responses were noted at both exposure levels.

In the Banerjee et al. (1998) study, mice and rats were given malathion (96% from M/S Hindustan Insecticides Limited, India) dietary concentrations of 20, 50, or 100 ppm, and there were no signs of overt toxicity or cholinergic effects. Mice exposed for 3-12 weeks exhibited decreased relative spleen weight, decreased macrophage migration inhibition (MMI) and leukocyte migration inhibition (LMI), decreased primary and secondary serum IgM antibody titer to SRBC, and a dose-duration related decrease in splenic PFC IgM after primary and secondary immunization with SRBC. In rats exposed for 8-22 weeks, signs of immune suppression included a significant decrease in relative spleen weight in animals immunized with ovalbumin or tetanus toxoid, decreased anti-tetanus toxoid (IgG) and anti-ovalbumin (IgG) antibody levels and decreased MMI and LMI (NOAEL = 20 ppm). In addition to the studies on mice and rats, Banerjee et al. (1998) also dosed rabbits by gavage at 0.5 or 2.5 mg/kg/day for 21

weeks and observed no adverse effects on immune function at the 0.5 mg/kg/day exposure level. At 2.5 mg/kg/day, however, adverse effects on immune function included,decreased antibody titre to ovalbumin after primary, secondary, and tertiary immunization and decreased CLMI.

In the Rogers and Xiong (1997d) 90-day gavage study, when mice were given doses of malathion (99.9%) at levels of 0.1, 1, or 10 mg/kg/day (sub-neurotoxic doses), peritoneal macrophages showed increased activity at 0.1 mg/kg/day and a dose-related decrease in activity at 1 and 10 mg/kg/day. In the study by Rodgers et al. (1986a) malathion (99%) at a dose of 143 mg/kg administered by gavage to C57B1/6 mice had no cholinergic toxicity or effects on plasma ChE, spleen and thymus weight, or thymus lymphocytes. Moreover, there was no effect on cellular or humoral immunity.

A decrement in antibody titers in rabbits was reported by Desi et al. (1978). In this study, rabbits were treated with malathion (unspecified source and purity) in gelatin capsules 5 days/week for 5-6 weeks and were given weekly intravenous injections of *Salmonella typhi* vaccine. Treatment caused significant dose- and duration-related decreases in antibody titer, which coincided with decreases in AChE activity. Similarly, Casale et al. (1983) assayed the primary IgM and IgG response to SRBC in mice dosed with malathion (95%) by gavage (5 mL corn oil/kg). At a single dose of 720 mg/kg bw, increased brain AChE and signs of cholinergic toxicity were observed along with suppressed PFC-IgM response to SRBC. A dosing regimen involving 4 doses of 240 mg/kg/day on every other day decreased plasma ChE and AChE activity in the brain, red blood cells, and liver. There were, however, no signs of cholinergic toxicity or detectable effects on the PFC-IgG response to SRBC (Casale et al. 1983).

3.1.7.4. U.S. EPA and ATSDR Evaluations of Immunotoxicity

The immunotoxicity of malathion is reviewed in U.S. EPA/OPP (2006a,c) as part of the reregistration assessment and in ATSDR (2003), the toxicological profile on malathion. The U.S. EPA review focuses explicitly on the studies by Rogers (Rodgers et al. 1986; Rodgers et al. 1996; Rodgers and Xiong, 1997), the study by Banerjee et al. (1998), and the effect of malathion on immune enhancement. The EPA concluded that malathion may induce allergic or irritative responses in humans and made the following statements in its most recent human health risk assessment for malathion:

> *Although the immunotoxicity study is identified as a data gap, it is not considered important to the quantification of risk from malathion. Rather it will be used to further characterize the hazard from malathion in terms of its effects on the immune system, and it is not expected to have an effect on the hazard values used in the risk assessment. Therefore, no additional safety factor is necessary to account for the lack of a guideline immunotoxicity study.* – U.S. EPA/OPP 2006c, pp. 56-57.

The reference to immunotoxicity as a *data gap* appears to be based on the lack of a *guideline* study for immunotoxicity. Guideline studies indicate a large group of protocols developed by the U.S. EPA's Office of Prevention, Pesticides and Toxic Substances for testing pesticides and

other toxic agents. A complete set of these guidelines is available at http://www.epa.gov/opptsfrs/home/guidelin.htm. The guidelines for immunotoxicity include the Health Effects Test Guidelines for Immunotoxicity (OPPTS 870.7800) and Biochemicals Test Guidelines for Immunotoxicity (OPPTS 880.3550). Typically, the EPA does not derive risk assessment values based on non-guideline studies, and all of the published literature on the immunotoxicity of malathion would be classified by the EPA as non-guideline.

ATSDR (2003) conducted a much broader review of the open literature on the immunotoxicity of malathion. As in the EPA review, ATSDR notes that malathion may affect the immune system at doses lower than those associated with neurotoxicity (ATSDR 2003, pp. 74-78). In terms of an impact on the quantitative assessment of risk, the viewpoint expressed in the ATSDR toxicological profile on human health (ATSDR 2003) is consistent with that of the U.S. EPA in identifying neurotoxicity rather than immunotoxicity as the endpoint of primary concern in deriving an MRL, which is the ATSDR equivalent to the RfD:

> *The physiological significance of these immunological effects is unknown and should be addressed in further studies in which the animals are challenged with pathogens. Therefore, it seems inappropriate at this time to base an acute oral MRL on subtle immunological alterations of unknown physiological significance. Worth noting also is a relatively low LOAEL of 4.4 mg/kg (the only dose level tested) for decreased hematocrit and platelet counts in rats administered the pesticide once by gavage in water (Lox 1983). It is interesting that an intermediate duration study by Lox and Davis (1983), also in rats given malathion in the drinking water, reported hematological and hepatic effects at very low doses (see below) not seen in any other gavage or feeding study. Therefore, additional studies should compare the effects of malathion on a wide range of end points given in water with those after administration mixed with food. The study design should clarify the role of the administration vehicle. The physiological significance of the LOAEL of 4.4 mg/kg from the Lox (1983) study is unknown and not appropriate for MRL derivation.* – ATSDR 2003, p. 161.

The current Forest Service risk assessment defers to the conclusions reached by the U.S. EPA and ATSDR in that neurotoxicity rather than immunotoxicity forms the basis of the dose-response assessment. The human health risk assessments conducted by the U.S. EPA/OPP (2006c) and ATSDR (2003) have been extensively peer reviewed and involved several years of effort and substantial resources. Notwithstanding this deference, there is reservation in the assessment that the effects of malathion on immune function are *not considered important to the quantification of risk*. Within the context of the available data on mammalian species, the assessments of the U.S. EPA and ATSDR on the direct relevance of immunotoxicity data to the quantitative expression of risk is reasonable. Nonetheless, in terms of immune suppression, any demonstration that malathion enhances susceptibility to pathogens would raise substantial concern about the immunotoxic effects of malathion exposure. Though it is true that mammals exposed to malathion have not shown increased susceptibility to pathogens, it is also true that the types of studies required to demonstrate that effect have not been conducted.

Residual concern for the potential of malathion to suppress immune function is enhanced by the availability of studies in fish (i.e., Beaman et al. 1999) and amphibians (i.e., Taylor et al. 1999b) indicating that exposure to malathion increases their susceptibility to pathogens. While studies on fish and amphibians are not appropriate for use quantitatively in a human health risk assessment, these studies increase concern that immune suppression by malathion could lead to clinically significant effects in mammals. Moreover, these studies in fish and amphibians are not discussed in the human health risk assessments by the U.S. EPA or ATSDR or in the ecological risk assessment by the U.S. EPA (U.S. EPA/OPP 2005m). Nonetheless, the residual concern is relatively minor. As discussed further in Sections 4.1.3.1 (Fish) and 4.1.3.2 (Amphibians), the studies that report increased susceptibility to pathogens in fish and amphibians involved exposures to malathion that are substantially higher than those associated with neurotoxicity.

3.1.8. Effects on Endocrine System

The direct effects of chemical exposure on endocrine function are most often assessed in mechanistic studies concerning estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding, or post-receptor processing). Also, changes in the structure of major endocrine glands (i.e., the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis) may be indicative of chemical effects on the endocrine system. Disruption of the endocrine system during development may give rise to effects on the reproductive system that can be expressed only after maturation (Durkin and Diamond 2002). Neurological function and endocrine function are related by the effects of neurotransmitters on the secretion of pituitary hormones, and there is some evidence in human poisoning cases that organophosphate pesticides may influence normal endocrine function (Guven et al. 1999).

Notwithstanding the above generalizations, there is little indication that malathion has a toxicologically significant impact on endocrine function (ATSDR 2003; U.S. EPA/OPP 2006c). Chen et al. (2002) noted no estrogenic potential based on *in vitro* receptor binding in human breast cancer estrogen-sensitive MCF-7 cells. Similarly, Ishihara et al. (2003) note only a very weak activity in terms of thyroid hormone binding in Japanese quail.

Based on the available *in vivo* toxicity studies, malathion is unlikely to have any significant impact on endocrine function. In a subchronic gavage study, male and female rats were dosed with 10 or 100 mg/kg/day malathion (94%) for 3.5 months. No significant effects were apparent on T3, T4, testosterone, or estradiol 17-β levels. Cortizol and aldosterone levels were significantly decreased at 10 mg/kg/day but not at 100 mg/kg/day (Ozem and Akay (1993).

High doses of malathion (800 mg/kg i.p.) caused an increase in adrenal weight and decreases in adrenal vitamin C and cholesterol accompanied by significant increases in ascorbic acid in plasma, liver, and brain. These effects are consistent with increased production of corticosteriods by the adrenals, suggesting a stress response to malathion (Chauhan et al. 1974). Similarly, increased adrenal activity (increased adrenal catecholamines and increased liver glycogen) were observed in rats after repeated intraperitoneal doses of 46 mg/kg/day over a 15-

day period (Gowda et al. 1983). No effects on adrenal glands, however, were observed in rats fed 100 or 200 ppm in the diet for 42 days (Foster 1968).

In the 24-month carcinogenicity bioassay by Daly (1996a), thyroid and parathyroid pathology was noted. These effects were reviewed by both the U.S. EPA's Office of Pesticides as well as their Science Advisory Panel and the effects were not classified as toxicologically significant or even necessarily related to malathion exposure (U.S. EPA/OPP 2006c, p. 57).

3.1.9. Reproductive and Teratogenic Effects

Malathion was tested for its ability to cause birth defects (i.e., teratogenicity) and to affect reproductive performance. Teratogenicity studies typically entail gavage administration of a compound to pregnant rats or rabbits on specific days of gestation. Reproduction studies typically involve exposing animals to a compound for more than one generation, with each generation being allowed to reproduce. As a class, organophosphate pesticides appear to be toxic but not teratogenic in developing mammals (Gupta 1995; Kitos and Suntornwat 1992; Tyl 1992), which appears to be the case with malathion. The potential reproductive effects of neurotoxic chemicals are reviewed by Andersen et al. (2000); however, this general review does not specifically address reproductive effects in mammals exposed to malathion. A general review of the epidemiology data on the reproductive effects of pesticides is provided in Arbuckle and Sever (1998). The data from this review and several other studies in humans are considered in this section.

3.1.9.1. Developmental (Teratology) Studies

Developmental studies are used to assess whether a compound has the potential to cause birth defects as well as other effects during development or immediately after birth. These studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Teratology assays as well as studies on reproductive function (Section 3.1.9.2) are generally required by the EPA for the registration of pesticides. Very specific protocols for developmental studies are established by U.S. EPA/OPPTS and are available at http://www.epa.gov/opptsfrs/publications/ OPPTS Harmonized.

While some *in vitro* studies suggest plausible biochemical mechanisms for an association between malathion exposures and congenital abnormalities (Samimi and Last 2001) or an effect on the development of oocytes *in vitro* (Ducolomb et al. 2004), the available *in vivo* studies as well as human data provide no basis for asserting that malathion is likely to cause birth defects. Two teratology studies accepted by the U.S. EPA/OPP (2006c) in the re-registration of malathion are considered in this risk assessment: an oral teratology study in rats (Lochry 1989) and an oral teratology study in rabbits (Siglin 1985b) that included a range-finding study (Singlin 1985a). In the rat study, groups of 25 pregnant rats were dosed on days 6-15 of gestation at levels of 0, 200, 400, or 800 mg/kg/day. No effects were noted in offspring, and the only effects in dams were decreases in food consumption and body weight at 800 mg/kg/day. In the range-finding study in rabbits, dams were exposed to doses of 0, 25, 50, 100, 200, or 400 mg/kg/day on days 6-18 of gestation. As with the rat study, no abnormalities were observed in any of the fetuses. Signs of neurotoxicity were apparent in dams at doses of 200 and 400 mg/kg/day (Siglin

1985a). In the full study, rabbits were dosed at 0, 25, 50, or 100 mg/kg/day on days 6-18 of gestation. At 50 mg/kg/day, the dams evidenced reduced mean body weight gains as well as increases in the incidence of resorption sites.

Other developmental toxicity studies from the open literature are reviewed by ATSDR (2003), Zimmerman (1990) and CDHS (1991). Consistent with the results of Siglin (1985b), summarized above in the discussion of the U.S. EPA risk assessment, malathion failed to cause birth defects in rabbits in a bioassay conducted at a dose level of 100 mg/kg/day on days 7-12 of gestation. Also, no skeletal abnormalities were noted in offspring of pregnant rats dosed with malathion at a rate of 500 mg/kg/day throughout gestation (Prabhakaran et al. 1993). Asmatullah et al. (1993) report a decrease in body weight and other growth parameters in fetuses taken on day 15 of gestation from pregnant mice given single gavage doses of 125, 250, or 500 mg/kg malathion on day 1 of gestation. No teratogenic effects were noted in rats at doses of up to 300 mg/kg (Khera et al. 1978). No signs of fetotoxicity or teratogenicity were observed in a standard assay in rabbits at a dose of 100 mg/kg on days 7-12 of gestation (Machin and McBride 1989a). As well, no teratogenic effects were observed in rats fed wheat contaminated with malathion or aged-malathion at concentrations in the range of 6 ppm during gestation (Bitsi et al. 1994).

3.1.9.2. Reproduction Studies

Reproduction studies involve exposing one or more generations of the test animal to the test compound. The general experimental method involves dosing the parental (P) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to mating, during mating, after mating, and through weaning of the offspring (F_1). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F_1 generation to produce another set of offspring (F_2). During these types of studies, standard observations for gross signs of toxicity are made. Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of offspring.

One 2-generation reproduction study is also included in the U.S. EPA/OPP (2006c) review of malathion (Schroeder 1990). In this study, groups (n=25) of male and female rats were fed malathion in the diet at concentrations of 0, 550, 1700, 5000, or 7500 ppm. Based on food consumption rates, these exposures are equivalent to 0, 43, 131, 394, or 612 mg/kg/day in male rats and 0, 51, 153, 451, or 703 mg/kg/day in female rats. At the highest exposure level, 7500 ppm, decreased body weights were noted in adult males and females. Decreased body weights were also noted in the offspring at dietary levels of 5000 and 7500 ppm. No signs of reproductive impairment (impaired fertility), however, were noted in any exposure groups.

The study by Schroeder (1990) is supported by a 3-generation reproduction study in rats that is published in the open literature in two papers (Ojha et al. 1991, 1992). In this study, malathion (purity and source not specified) was administered in the diet (wheat grain) at concentrations of 0, 10, 50, 100, 1000, 3000, or 5000 ppm. No signs of toxicity or changes in reproductive parameters were noted at concentrations of 1000 ppm or less. At a concentration of 3000 ppm, signs of cholinergic effects as well as decreased fetal weight gain were evident. At 5000 ppm,

cholinergic effects were more severe and all F_1 pups died within 24 hours of birth (Ojha et al. 1991, 1992). These results are similar to the earlier results of Kalow and Marton (1961) in which decreased numbers of offspring and decreased survival of offspring were noted in rats exposed to malathion in the diet at 4000 ppm (corresponding to daily doses of about 240 mg/kg bw).

The effects of malathion (97.72%) on reproductive performance was assayed also by (Kumar and Uppal 1986). In this study, female rats were given intraperitoneal doses of 46 mg/kg/day and then allowed to mate with untreated male rats. Pregnancies were allowed to progress to term and the number of live pups was recorded on days 1, 5, and 21 after birth. Compared with controls, the number of surviving pups was significantly lower on day 1 (84% of controls), day 5 (76% of controls), and day 21 (69% of controls).

3.1.9.3. Developmental Neurotoxicity

A developmental neurotoxicity study is a specialized toxicity test designed to assess the effect of direct neurotoxins on fetal development (U.S. EPA/PPTS 1998). These studies are similar to standard reproduction studies (Section 3.1.9.2) in that pregnant animals are dosed with the neurotoxin, and exposure to the offspring occurs *in utero*. Developmental neurotoxicity studies differ from standard reproduction studies in that offspring are subject to a number of specific observations and tests designed to evaluate the effect of the neurotoxin on several neurological and behavioral endpoints.

As summarized in U.S. EPA/OPP (2006c, p. 37), a developmental neurotoxicity study was conducted on rats at gavage doses of 0, 5, 50, or 150 mg/kg bw/day (MRID 44393701). In the high dose group, adverse effects were observed in both dams (increased post-dosing salivation) and offspring (delayed surface righting reflex in female pups). In the offspring, adverse effects were observed at all doses – i.e., a NOAEL was not established. At the 5 mg/kg bw/day, the pups evidenced increased auditory startle reflex peak amplitude on post-natal days 23 and 24.

3.1.9.4. Target Organ Toxicity

Male rats dosed with 44 mg/kg bw by gavage for 12 weeks showed signs of testicular damage including a decrease in testes weight, changes in seminal vesicle pH, and several other biochemical indicators of testicular damage (Balasubramanian et al. 1987a,b).

Adverse effects on sperm were observed in mammals after exposure to malathion. Giri et al. (2002) noted a dose-dependant increase in abnormal sperm morphology in mice after intraperitoneal injections of 2.5, 5, or 10 mg/kg malathion. Single gavage dosing of adult male rats with 100 mg/kg bw was associated with reduced sperm motility and alterations in sperm morphology (Akbarsha et al. 2000). Morphological changes in sperm were observed in mice exposed to intraperitoneal doses of 80 mg/kg bw (Bustos-Obregon et al. 2005). Somewhat higher intraperitoneal doses of 240 mg/kg bw administered to male rats caused decreased sperm count, damage to testicular tissue, and changes in sperm morphology (Bustos-Obregon and

Gonzalez-Hormazabal 2004). Decreased spermatogenesis was also observed in mice after dietary exposure to malathion concentrations ranging from 100 to 8000 ppm over a period of 3-4 months; however, no effects were observed at dietary concentrations of 10 ppm. The purity of the malathion used in this study (supplied by Cynamid India Limited) is not specified (Kumar and Nath 1997). An earlier study from the same laboratory specifies a purity of 97.72% malathion (Kumar and Uppal 1986).

An increase in abnormal sperm was observed in mice after a single intraperitoneal injection of 250 mg/kg malathion (96.6% from Cheminov, Denmark), in the absence of effects on other reproductive parameters (Contreras and Bustos-Obregon 1996, 1999). Dietary exposure to malathion at 270 or 1350 ppm caused no sperm abnormalities in rams over an 11-month exposure period (Jackson et al. 1975).

3.1.9.5. Human Data

In a relatively detailed study of populations in the San Francisco Bay area potentially exposed to malathion during a spray for the Mediterranean fruit fly, no statistically significant associations were found in the incidences of adverse reproductive effects including: spontaneous abortion [RR=1.20 (0.94-1.52)], fetal growth, stillbirth [RR=1.51 (0.21-11.3)], or most categories of congenital abnormalities. The relative risk for gastrointestinal anomalies, however, was marginally significant: 4.14(1.01-16.6) (Thomas et al. 1992). As discussed explicitly in an earlier publication by Thomas et al. (1990):

"... This association was only with exposures during the second trimester, for which there is no clear biologic basis. These data provide no convincing evidence that aerial spraying of malathion poses any serious risk to pregnancy." - Thomas et al. (1990), p. 795

Based on an analysis of malathion in neonatal meconium from infants born in the Philippines, Ostrea et al. (1998a,b) reported (in abstract only) marginally significant odds ratios for C-section and neonatal jaundice for newborns with detectable concentrations of malathion in meconium. No detailed publications of these data or analyses were discovered in the literature.

No association between malathion spray for the control of the Mediterranean fruit fly and low birth weights was noted in an epidemiology study conducted in California in the early 1980s (Grether et al. 1987). Similarly, no association between malathion exposure in fathers and congenital malformations were noted in an epidemiology study conducted in Spain (Garcia et al. 1998). In a Chilean town in which malathion was widely applied as a fumigant, the incidence of still births was not significantly or substantially different (16.8% vs. 17.2%) in the period before and after the malathion was used (Arevalo et al. 1987). A study by Eskenazi et al. (2004) suggests that human exposure to organophosphate pesticides may be associated with a shortened gestation period. There was no indication, however, that exposure to malathion was associated with preterm delivery in human populations.

Lindhout and Hageman (1987) report a single case in which maternal exposure to malathion was implicated in amyoplasia congenita, a congenital malformation characterized by a decrease in

skeletal muscle. Maternal exposure consisted of using a 0.5% malathion solution for the treatment of head lice.

3.1.10. Carcinogenicity and Mutagenicity

3.1.10.1. Mutagenicity

Chemically-induced mutation is related to the process of carcinogenesis, for several reasons. Many carcinogens are known to react with DNA in somatic cells and to cause mutations. It is postulated that the interaction of reactive metabolites of chemical carcinogens with DNA may induce tumors either directly by altering genetic material through a somatic mutation or indirectly by altering gene expression. Mutagenicity studies include tests with microorganisms (e.g., Ames assay), tests for genetic damage in cultured mammalian cells (e.g., unscheduled DNA repair synthesis, sister chromatid exchange, point mutations), and tests for *in vitro* transformation of rodent cell lines. The potential mutagenicity of pesticides is an area of particular concern because of reported effects in pesticide workers that are indicative of genetic damage (e.g., Yoder et al. 1973; Garaj-Vrhovac and Zeljezic 2000). Nonetheless, several pesticides, including malathion, exhibit signs of genetic toxicity but do not appear to be carcinogens in standard bioassays (Waters et al. 1988).

The U.S. EPA concluded that there is weak evidence that malathion may cause mutagenic effects in mammalian cells at high concentrations that are also cytotoxic, but that the weight of evidence does not support a concern for the mutagenic potential of malathion (U.S. EPA/OPP 2006c, p. 54). This assessment is based explicitly on three unpublished studies submitted to the U.S. EPA (U.S. EPA/OPP 2006a,c) in support of the registration of malathion: a reverse gene mutation assay with *Salmonella typhimurium* and *Escherichia coli* (Traul 1987), a chromosome aberration assay in rat bone marrow cells (Gudi 1990), and an assay for gene mutation in mouse lymphoma cells (Edwards 2001). In addition, the U.S. EPA considered two published studies (Blasiak and Kowalik 1999; Blasiak et al. 1999). Like the EPA, ATSDR acknowledges a potential for cytogenic damage but no or very little potential for mutagenicity due to malathion exposure (ATSDR 2003, p. 156).

In a detailed review of the mutagenicity studies on malathion conducted up to 1989, the California Department of Health Services (CDHS 1991) mostly agreed with the conclusion of the U.S. EPA/OPP (2000a). Several *in vivo* studies demonstrate that malathion can induce chromosomal damage in bone marrow cells at doses ranging from 120 to 240 mg/kg bw (see Table 6-8 in CDHS, 1991, p. 6-54). Nevertheless, many of the studies reporting positive results used impure malathion (i.e., as low as 30% a.i). Studies conducted with highly purified malathion (>99%) were negative (CDHS, 1991). Several *in vitro* studies demonstrate that malathion and malaoxon can induce chromosomal damage in human and other mammalian cell systems [see Table 6-9 in CDHS (1991), p. 6-55 to 6-56]. CDHS (1991) cites the study by Galloway et al. (1987) as the most convincing evidence *in vitro* that malathion may be mutagenic and notes that the positive results occurred only at highly toxic exposure levels. Although some studies demonstrate that malathion and malaoxon can induce SCE, these studies suggest the ability of malathion or malaoxon to interact with DNA but do not directly demonstrate a mutagenic effect. For example, Wong et al. (1989) found that malathion was inactive in the

standard Ames assay for mutagenicity with and without metabolic activation. Finally, CDHS (1991) reviewed the available human studies on mutagenicity of malathion *in vivo* and concluded that these studies provide no indication that malathion is mutagenic in humans.

In an *in vivo* study in mice, Abraham et al. (1997) report an increase in micronucleated cells and gross chromosomal damage after daily intraperitoneal doses of "1/15th of the LD_{50}" over a 35-day period. This effect, however, was reversible after the termination of treatment. Similarly, Giri et al. (2002) observed an increase in chromosomal aberrations in mice treated with single intraperitoneal doses 2.5, 5, or 10 mg/kg bw malathion.

In an *in vitro* assay using human T-lymphocytes, malathion (97-99%) concentrations ranging from 30 to 300 mg/L were associated with an increase in the incidence of some specific mutations (Pluth et al. 1996). This publication does not provide detailed information on dose-response relationships. The limited discussion suggests that the dose-response relationships were highly variable and that some of the more substantial responses were not reproducible [see Pluth et al. (1996), p. 2395, column 2]. In a follow-up study, Pluth et al. (1998) report that the rate of mutation (Figure 1, p. 143) appears to have a negative relationship to dose.

Malaoxon and isomalathion, but not malathion itself, were active in an assay (comet assay) for DNA damage using human lymphocytes (Blasiak et al. 1999). In an *in vivo* assay in mouse bone marrow cells, a dose-response relationship for chromosomal breaks was noted over a dose range of 0.5 to 6 mg/kg. In the same study, a dose-related increase was also noted in the dominant lethal assay using *Drosophila* over a concentration range of 2.5 to 7 ppb, with a NOAEL of 3.5 ppb. The malathion used in this assay, however, was only 50%, pure and the impurities were not characterized (Kumar et al. 1995). Using purified commercial malathion (95-99%, NOS), Osaba et al. (1999) found no indication of mutagenic activity for malathion in the *Drosophila* wing spot assay.

A clear dose-dependent increase in chromosomal aberrations and sister-chromatid exchanges was noted in human peripheral leukocytes treated *in vitro* with malathion at concentrations ranging from 0.02 to 20 ppm; however, neither the source nor the purity of the malathion is reported in this publication from India (Balaji and Sasikala 1993).

Garry et al. (1990) conducted an *in vitro* study on the induction of sister chromatid exchanges in human lymphocytes. A statistically significant and dose-related increase was noted in the incidence of SCE. The purity of the malathion used in this assay, however, is not specified in the publication. Similar results are reported by Titenko-Holland et al. (1997) in a study using 95% pure malathion—i.e., a statistically significant increase in micronucleation in isolated lymphocytes ($p<0.001$) and whole blood cultures ($p<0.03$) at malathion concentrations of 75-100 µg/L. Increases in SCE are reported also by Nicholas et al. (1979) using a 99% pure sample of malathion and Nishio and Uyeki (1981) for both malathion (99%) and malaoxon (95%).

Titenko-Holland et al. (1997) examined a group of workers involved in the application of malathion for Mediterranean fruit fly eradication. No changes were noted in lymphocyte

proliferation or micronucleus levels in these workers. A follow-up study (Windham et al. 1998) also failed to detect any evidence of genetic damage in workers involved in malathion applications in the same program. In a study of pesticide workers involved in the manufacture of malathion in India, Singaravelu et al. (1998) found a positive association between the incidence of chromosomal aberrations and the duration of pesticide handling.

3.1.10.2. Carcinogenicity

There is a large, complex, and often controversial literature on the potential carcinogenicity of malathion. IARC (1983) reviewed several early cancer bioassays and concluded that the available evidence did not support the assertion that malathion was a potential human carcinogen. In a re-review of that information, Reuber (1985) suggests that malathion is a probable human carcinogen. By far, the most complete and thorough review of the older literature on the potential carcinogenicity of malathion is that presented by the California Department of Health Services (CDHS 1991). As summarized in this review, none of the earlier studies on the carcinogenicity of malathion are sufficient to classify malathion as a carcinogen.

More recently, both the U.S. EPA/OPP (2006c) and ATSDR (2003) examined the database on the carcinogenicity of malathion. The review by U.S. EPA/OPP (2006c) also includes an evaluation by EPA's FIFRA Science Advisory Panel. None of these organizations has classified malathion or malaoxon as a carcinogen. The most recent evaluation by the U.S. EPA indicates:

> *"suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential" by all routes of exposure* (U.S. EPA/OPP 2006c, p. 55).

ATSDR (2003) does not provide a formal classification of the carcinogenic potential of malathion but does cite earlier U.S. EPA assessments that are consistent with the classification in U.S. EPA/OPP (2006c). The basic conclusion articulated in ATSDR (2003) is given below:

> *Most studies of cancer in animals have not shown evidence of carcinogenicity for malathion, or have shown evidence of cancer at doses considered excessive. Still, there is some disagreement among scientists on how to interpret the results.* ATSDR, 2003, p. 5.

The classification of malathion as presenting only suggestive evidence of carcinogenicity means that the U.S. EPA declined to conduct a quantitative dose-response assessment on the potential carcinogenicity of malathion. While the U.S. EPA considered a large number of carcinogenicity and mutagenicity studies in making this classification, the 18-month feeding study in mice (Slauter 1994) and a 2-year feeding study in rats (Daly 1996a,b) form the basis of the U.S. EPA/OPP (2003c) assessment that the information regarding the carcinogenicity of malathion does not warrant a quantitative risk assessment for this endpoint.

The basic design of the 2-year rat feeding study (Daly 1996a,b) involved dietary exposures to malathion (97.1%) at concentrations of 0, 100/50, 500, 6000, or 12,000 ppm. As noted in Section 3.1.3.5, these dietary concentrations were equivalent to mean daily malathion intakes of

0, 2.37, 29, 359, or 739 mg/kg/day in male rats and 0, 2.95, 35, 415, or 868 mg/kg/day in female rats. The most common cause of morbidity in the rats was characterized as "chronic nephropathy and mononuclear cell leukemia" (Daly 1996a, p. 5).

There is no debate that these exposures were associated with increases in the incidence of hepatocellular adenomas in female rats: 0/55 (0%) at 0 ppm, 2/55 (3.6%, p=0.24) at 100/50 ppm, 2/55 (3.6%, p=0.24) at 500 ppm, 3/55 (5.5%, p=0.12) at 6000 ppm, and 6/55 (10.9%, p=0.013) at 12,000 ppm. These increases, however, are statistically significant (using the Fisher Exact test) only in the 12,000 ppm dose group (p=0.013). Using the 500 ppm dose group as an example, there is about a 24% probability (p=0.24) that the difference in the incidence in the control group (0/55) and the incidence in the exposed group (2/55) occurred by random chance.

In the mouse bioassay (Slauter 1994), male and female mice (n=65) were exposed to dietary concentrations of 0 (control), 100, 800, 8000, or 16,000 ppm malathion. Based on food consumption measurements, these concentrations are equivalent to 0, 17.4, 143, 1476, or 2978 mg/kg/day for males and 0, 20.8, 167, 1707, or 3448 mg/kg/day for females. For both male and female mice at the two highest dose levels, there was a statistically significant increase in hepatocellular tumors (benign and malignant combined). In male mice, the incidences of hepatocellular carcinomas were 0.0, 10.9, 5.5, 10.9, and 2.0%. While an incidence of 10.9% (7/65) from the 8000 ppm dose-group represents a statistically significant difference from 0/65 incidence in the control group (p=0.00659), the response rates in the 800 and 16,000 ppm dose groups do not represent a difference that is statistically significant, compared with controls. In addition, there is no significant dose-related increase in tumor incidence in this group. For female mice, the incidence of hepatocellular carcinomas was 1.8, 0.0, 3.7, 1.9, and 3.8%. None of these incidences is statistically significant, compared with the control group. A dose-response relationship is apparent for benign tumors (hepatocellular adenomas): 1.9, 7.3, 3.6, 21.8, and 94.1% for males and 0.0, 1.8, 0.0, 17, and 80.8% for females. Moreover, when the incidence of benign and malignant tumors is combined (U.S. EPA/OPP 2000a, p. 12), some of the pooled incidences are statistically significant. For example, the combined incidence of hepatocellular adenomas (a benign lesion) and carcinomas (malignant lesions) was statistically significant by pair-wise comparison for the 100, 8000, and 16,000 ppm exposure groups, and the dose-related trend for the combined malignant and benign lesions was also statistically significant.

An epidemiology study reports elevated odds ratios for the use of malathion prior to 1965 and the development of non-Hodgkin's lymphoma in agricultural workers (Cantor et al. 1992). For use as an animal insecticide, the odds ratio was 1.8 (1.0-3.3). For use as a crop insecticide, the odds ratio was 2.9 (1.1-7.4). No significantly increased odds ratios were found for all workers combined—i.e., workers handling malathion both before and after 1965. When ranked by the number of days per year that the pesticide was used, there was no apparent relationship to the odds ratios for non-Hodgkin's lymphoma (Cantor et al. 1993). More recently, McDuffie et al. (2005) reported a significant association between malathion exposure and the development of non-Hodgkin's lymphoma (OR: 1.83%; 95% CL, 1.31-2.55). An increase in the incidence of mortality from non-Hodgkin's lymphoma occurred in a group of male lawn-care workers exposed to malathion as well as a several other pesticides (Zahm 1997). This report does not

specifically link the development of non-Hodgkin's lymphoma to malathion. No significant associations between non-Hodgkin's lymphoma and pesticide exposure was noted in a group of women exposed to agricultural pesticides while living or working on farms (Zahm et al. 1994).

There is some concern reflected in the open literature that exposure to malathion may be associated with breast cancer. In an epidemiology study of farm workers, Mills and Yang (2005) report an association between increased risk for breast cancer among female California Hispanic farm workers involved in mushroom production and exposure to malathion. The association was examined in worker groups covering periods from 1987 to 1994 as well as 1995 to 2001 based on three semi-quantitative indices of exposure—i.e., low, medium, and high, relative to a control population. The only significant increase was noted in workers with medium exposure from 1987 to 1994. Cabello et al. (2001) observed a significant increase in mammary gland tumors after either subcutaneous or intraperitoneal injection of 2.5 mg/kg bw malathion into the inguinal region of the body of 39-week-old virgin female Sprague-Dawley rats twice a day for 5 days. Mammary gland tumors formed over a 2-year period which was attributed to the inhibition of AChE, which decreased from 9.78 U/mL (±0.78 U/mL) observed in controls to 3.88 U/mL (±0.44 U/mL). The combination of atropine and malathion significantly decreased AChE activity from the control value (9.78 U/mL ±0.78 U/mL) to 2.39 U/mL (±0.29 U/mL) with no tumor formation. This study is considered by the U.S. EPA/OPP (2006c, p. 55) and is not deemed relevant in terms of altering the EPA's assessment of the carcinogenic potential of malathion. While not specifically detailed in U.S. EPA/OPP (2006c), the route of exposure used by Cabello et al. (2001)—i.e., injection—would not typically be used in a quantitative assessment. Cabello et al. (2003a,b) published additional *in vitro* studies on the effects of malathion on breast tissue cells. Again, these types of *in vitro* studies are focused on understanding mechanisms of action and are not directly useful in quantitative assessments of risk.

Given a database as large and complex as the database for the carcinogenicity of malathion, disagreements in interpretation and judgment are not surprising. Disagreements have occurred in the past and will likely continue into the future. This risk assessment defers to the judgment of the U.S. EPA and does not quantitatively consider the potential carcinogenic effects of malathion in the dose-response assessment (Section 3.3).

3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes)

Standard irritation and sensitization studies required for pesticide registration were submitted to and reviewed by the U.S. EPA/OPP (2006a,c). When applied directly and repeatedly to the skin, technical grade malathion did not cause skin sensitization in guinea pigs (Kynoch and Smith 1986). Malathion did cause slight dermal irritation (Liggett and Parcell 1985a) as well as transient eye irritation (Liggett and Parcell 1985b) in rabbits. Based on these data, the U.S. EPA/OPP (2000a), classifies malathion as non-irritating (Category IV) to the skin of rabbits and minimally irritating to the eyes of rabbits (Category III).

Some organophosphates are associated with ocular damage in workers; however there is no documented causal relationship for malathion (Boyes et al. 1994; Dementi 1994; Kamel et al. 2000). Few studies were found in the literature suggesting that malathion specifically causes any form of eye damage other than transient irritation, as discussed above (Liggett and Parcell 1985b). No ocular damage or apparent changes in the visual acuity were noted in rats treated with malathion at levels 84,000-fold above expected exposures in the use of malathion for mosquito control, where ocular exposures are expected to be much higher than those expected in boll weevil control programs (Boyes et al. 1999).

There is one early report in the literature of apparent contact dermatitis in humans exposed to technical grade malathion (Milby and Epstein 1964). According to the Centers for Disease Control (1999), cases of contact dermatitis are associated with malathion bait sprays. Also, delayed hypersensitivity was observed in human populations after the application of malathion to address Mediterranean fruit fly infestations (Schanker et al. 1992). Delayed hypersensitivity was not observed in BALB/c mice after the dermal application of technical grade malathion (Cushman and Street 1983).

3.1.12. Systemic Toxic Effects from Dermal Exposure

The dermal toxicity of technical grade malathion is very low. The U.S. EPA/OPP (2006c) lists the dermal LD_{50} for malathion in rats as >2000 mg/kg—i.e., at a dose greater than 2000 mg/kg, 50% or more of the animals may die (Kynoch 1986b). In the open literature, dermal LD_{50} values of >4400 mg/kg are reported in rat studies (NIOSH 1976) and no signs of toxicity were observed in rabbits at dermal doses of 4900 mg/kg (Hazleton and Holland 1953). As discussed in Section 3.1.3.1, this low order of dermal toxicity is probably related to the slow absorption of malathion from the surface of the skin.

3.1.13. Inhalation Exposure

Malathion also has a very low order of acute inhalation toxicity. The U.S. EPA/OPP (2003c) lists the acute 4-hour inhalation LC_{50} for malathion as >5.2 mg/L (5200 mg/m^3) from a study in which rats were exposed to a commercial formulation—i.e., Fyfanon containing 96-98% malathion (Jackson et al. 1986). Other inhalation studies suggest that the acute inhalation toxicity of malathion varies with different formulations, with concentrations as low as 2800 mg/m^3 constituting an LC_{50} for some formulations but concentrations as high as 5000 mg/m^3 causing no mortality for other formulations (CDHS 1991). Whole body exposures of mice to malathion (95%) aerosols of 6900 mg/m^3 for 5 hours caused no apparent adverse effects (Berteau and Deen 1978). Whole body exposures of rabbits to 123 mg/m^3 aerosols of malathion for 6 hours resulted in a transient decrease in plasma ChE but no effect on RBC AChE. Lower concentrations—6, 34, or 65 mg/m^3—had no effect on plasma ChE or RBC AChE (Weeks et al. 1977).

3.1.14. Inerts and Adjuvants

The U.S. EPA is responsible for regulating inerts and adjuvants in pesticide formulations. As implemented, these regulations affect only pesticide labeling and testing requirements. The term

inert has been used to designate compounds that do not have a direct toxic effect on the target species. While the term *inert* is codified in FIFRA, some inerts can be toxic, and the U.S. EPA now uses the term *Other Ingredients* rather than *inerts*.

Sometimes, the potential toxicity of inerts in pesticide formulations has an impact on the risk assessment, as in the case with herbicide formulations for which the active ingredient poses a minimal risk to humans. There is little doubt that malathion is the toxic agent of primary concern in formulated products. In addition, the formulations of malathion used in mosquito control as well as the control of some other insect pests are essentially composed of only technical grade malathion (Table 2). Other commercial products contain petroleum based solvents which are commonly used and approved by the U.S. EPA for use in pesticide formulations. Accordingly, the inerts in malathion formulations do not have an impact on the hazard identification for potential health effects in humans.

As discussed in Section 3.1.3 (Pharmacokinetics), the inerts in EC formulations appear to impact the rate of the dermal absorption of malathion. This does impact the exposure assessment for EC formulations for dermal exposure scenarios, as discussed further in Section 3.2 (Exposure Assessment).

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

In both animals (including mammals) and plants, malathion is metabolized primarily by microsomal cytochrome P-450 monooxygenase systems, glutathione S-transferase and microsomal carboxylesterases (Abou-Donia 1995; ATSDR 2003; Buratti et al. 2005; Dauterman and Main 1966; Nigg and Knaak 2000; Talcott et al. 1979b;WHO 1998). An overview of the major metabolic pathways is given in Figure 4.

Malathion itself—i.e., the malathion molecule—is relatively non-toxic and does not inhibit AChE. In mammals and other sensitive species, malathion can be metabolized to malaoxon by oxidative desulfuration by mixed function oxidases (cytochrome P-450). Malaoxon itself is the neurotoxic agent that inhibits AChE. This pattern is similar to patterns seen with many other organophosphate insecticides (Abou-Donia 1995).

The major detoxification pathway involves liver esterases, specifically carboxylesterases, which hydrolytically cleave the ethyl groups from malathion or malaoxon (e.g., Barr et al. 2005; Bhagwat and Ramachandran 1975; Mallipudi et al. 1980; Talcott et al. 1979c). Carboxylesterases are abundant in vertebrates but not insects, and this is the basis for the selective toxicity of malathion to insects, relative to humans and other mammals (Abou-Donia 1995). The resulting monocarboxylic or dicarboxylic acid metabolites are much less lipophilic than malathion or malaoxon and are much more rapidly and efficiently excreted in the urine (ATSDR; CDHS 1991; WHO 1998). At least in the rat, extrahepatic metabolism of malathion by carboxylesterases may be significant (Talcott 1979).

In the rat, greater than 80% of the urinary malathion metabolites are the diacid and monoacid metabolites (Reddy et al. 1989). Most of the metabolism of malathion occurs in the liver, with very little metabolism occurring in the blood (WHO 1998; CDHS 1991). After a single oral dose (690 mg/kg) to rats, the highest concentrations of malathion were noted in the plasma with a time to peak concentration of 6 hours. In rats, the concentration of mono-acids is about 4-5 times the concentration of diacid, except in the kidneys, where the diacid is predominant (Hayasaka et al. 1996). Relatively high concentrations of malathion and malathion metabolites in the kidney, indicative of excretion by the kidney, were noted also in goats and hens (Cannon et al. 1966).

Malathion as well as isomalathion (a contaminant in malathion discussed in the following subsection) are also conjugated with glutathione (GSH) via demethylation by a GSH-transferase (CDHS 1991; Rabovsky and Brown 1993). GSH is a naturally occurring antioxidant. Several impurities in malathion also deplete GSH and thus potentiate the toxicity of malathion (Malik and Summer 1982). Like the oxidation reaction, GSH conjugation occurs with many other organophosphate pesticides (Abou-Donia 1995; Abdel-Rahman et al. 1985). In some cases, the conjugation of malathion metabolites with GSH is sufficient to cause a depletion of GSH in the liver (Malik and Summer 1982) and lymphocytes (Banerjee et al. 1999).

Barlas (1996) directly examined the toxicity of a commercial formulation of malathion (95% purity) and a mixture of the degradation products of malathion. The degradation products were obtained by mixed culture microbial metabolism and were characterized as malathion (53%), malathion monocarboxylic acid (30%), and malaoxon (15%). The 'degraded' mixture had a 2-fold greater effect on spleen weight reduction in males than did the commercial formulation of malathion, which was essentially inactive in terms of reduced spleen weight.

3.1.15.2. Impurities

Impurities are inadvertent contaminants in the pesticide that occur as the result of the manufacturing process. Virtually no chemical, including malathion, can be synthesized without the production of at least some impurities.

Information on all of the impurities in technical grade malathion was disclosed to the U.S. EPA as part of the registration process (Cheminova 1990 for Fyfanon; Harris 1997 for Atrapa). Both of these reports on impurities (Cheminova 1990; Harris 1997) were reviewed in the process of conducting this risk assessment. Additional reports on impurities in related formulations also were reviewed (Cheminova 1999a,b; Gaskins 1993).

Much of the early literature on the toxicology of impurities in malathion was reviewed by Imamura and Gandy (1989), Zimmerman (1990), and Chambers and Dorough (1995). An overview of 16 reported impurities in malathion is given in Table 5.

As indicated in Table 5, malaoxon is an impurity in malathion as well as an *in vivo* metabolite (i.e., formed in the body during the metabolism of malathion) and environmental metabolite (i.e., formed in the environment during the degradation of malathion). The consideration of malaoxon is important in the current risk assessment because malaoxon is the primary neurotoxic agent

associated with exposures to malathion. For many pesticides, the quantitative consideration of impurities in a risk assessment is encompassed by the use of technical grade material – i.e., the pesticide as well as pesticide impurities – in toxicity studies. As detailed further in Section 3.2.3.1.1, however, this approach is not sufficient for some exposure scenarios in which the environmental formation of malaoxon needs to be considered.

Many of the impurities in malathion tend to inhibit the cleavage of the metabolism of malathion to mono- and di-acids by carboxylesterases. This cleavage enhances the excretion of malathion metabolites and hence reduces the toxic effects of malathion exposures. Thus, these impurities enhance the toxicity of malathion by inhibiting the detoxification of malathion (Fukuto 1983; Imamura and Gandy 1989; Lin et al. 1984; Pellegrini and Santi 1972; Ryan and Fukuto 1984, 1985; Talcott et al. 1979a,b; Toia et al. 1980; Verschoyle et al. 1982).

In addition to the effect on carboxylesterases, some impurities are much more acutely toxic to animals than technical grade malathion itself. For example, O,O,S-trimethyl phosphorothioate may be lethal after single oral doses as low as 15 mg/kg (Mallipudi et al. 1979; Umetsu et al. 1981). This compound also was shown to cause specific pulmonary damage (Durham and Imamura 1988; Gandy et al. 1984; Imamura and Gandy 1989; Imamura and Hasegawa 1984a; Imamura et al. 1983a; Imamura et al. 1985) and teratogenicity in the rat (Koizumi et al. 1986).

Potentiation of malathion by the impurities has been quantified in both simultaneous and sequential exposures. In simultaneous exposures (e.g., Umetsu et al. 1977), LD_{50} determinations are made for recrystallized (>99%) malathion, the impurity, and one or more mixtures of recrystallized malathion and the impurity. The observed LD_{50} for the mixture is then compared with the LD_{50} that would be expected from dose-addition (e.g., Finney 1971). In sequential exposures, the animals are pre-treated with a fixed dose of the impurity. After a period of time, the LD_{50} for purified malathion is tested in the pre-treated animals and compared with the LD_{50} for purified malathion in animals that were not pre-treated (e.g., Toia et al. 1980). In both types of studies, the greatest potentiation has been reported with O,O,O-trimethyl phosphorothioate (O,O,S-TMPT), in which the 24-hour LD_{50} of malathion to rats decreased from about 6000 to 600 mg/kg (Toia et al. 1980) and the 24-hour LD_{50} to rats of the mixture in the simultaneous exposure (1250 mg/kg for a 2% mixture) was lower than the expected LD_{50} by a factor of 10 (Umetsu et al. 1977). The joint action of malathion and malathion impurities in mice was much less, with the ratios of expected to observed LD_{50} values ranging from about 0.76 to 2.78 (Umetsu et al. 1977).

Imamura and Talcott (1985) found no mutagenic activity in the *Salmonella typhimurium* test system, with or without metabolic activation, for four of the impurities: isomalathion, O,O,S-trimethyl phosphorothioate, O,S,S-trimethyl phosphorodithioate (O,S,S-TMPD), and O,O,O-trimethyl phosphorothioate (O,O,O-TMPT).

Some malathion impurities, including O,O,S-trimethyl phosphorothioate and O,S,S-trimethyl phosphorodithioate cause an increase in blood clotting times and a decrease in β-glucuronidase activity (Keadtisuke et al. 1990).

Isomalathion is implicated in the deaths of some workers using aged malathion formulations (Aldridge et al. 1979) and other human poisonings (Dive et al. 1994). In addition, a significant correlation was reported in the isomalathion levels (0.3-3.1%) in different commercial formulations of malathion and RBC AChE activities in workers applying the formulations (Baker et al. 1978). Based on quantitative measures of carboxylesterase inhibition, isomalathion is substantially more potent than other impurities in malathion, with a Km of 0.00045 mM (Fukuto 1983; Talcott et al. 1979a). Isomalathion may increase the toxicity of malathion not only by the direct toxicity of isomalathion but also because isomalathion inhibits the detoxicification of malathion by carboxylesterases (Buratti and Testai 2005).

Four stereoisomers of isomalathion were found to be essentially ineffective in the inhibition of neurotoxic esterase (NTE) and hence not likely to be associated with OPIDN (Jianmongkol et al. 1996). Based on estimates of intraperitoneal LD_{50} values, the various diastereomeres of isomalathion are similar in their toxicities and similar in toxicity to the enantiomers of malaoxon (Polec et al. 1998). A recent study by Jianmongkol et al (1999) suggests that the (1R)- and (1S)-stereoisomers of isomalathion may inhibit AChE by differing mechanisms.

The concentration of impurities in technical grade malathion increased over a 3- to 6-month period when the malathion is stored at 40°C. For rats, the LD_{50} values for technical malathion decreased by a factor of about 25% over a 6-month holding period at 40°C but not at 20°C. There were no substantial changes in toxicity to house flies (Fukuto 1983). In the study by Gilles and Dickson (2000) (see Section 3.1.3.4.), the purity of the malathion—stored in a dark cupboard at 15-25°C—decreased from 95.8 to 95.4% over a 9-month period.

The occurrence of impurities in malathion may impact the immune activity of malathion because at least one of the impurities, O,O,S-TMPT has been associated with immune suppression. Specifically, O,O,S-TMPT causes immune suppression through an inhibition of lymphocyte proliferation. This activity, however, requires GSH, suggesting that the toxic agent may be a glutathione conjugate of O,O,S-TMPT (Thomas and Imamura 1986).

The impurities in malathion can also affect the time-course of toxicity. In a single-dose LD_{50} study using recrystallized malathion (99.7%), most rats where asymptomatic for the first 6 hours, with some dying by 20 hours, and most dying between 20 and 40 hours. With mixtures of malathion and malathion impurities (isomalathion, O,O,S-TMPD, O,S,S-TMPD, and O,O,S-TMPT), signs of toxicity were seen after 15-20 minutes and fatalities occurred between 2.5 and 48 hours. The signs of poisoning with O,S,S-TMPD and O,O,S-TMPT were consistent with AChE inhibition. O,S,S-TMPD, however, resulted in signs of general narcosis, inconsistent with AChE inhibition (Aldridge et al. 1979).

3.1.16. Toxicological Interactions

Malathion is only one of many organophosphate and carbamate insecticides that inhibit AChE activity. Because these compounds share a common mechanism of action, it is plausible that such compounds would act with malathion in a dose-additive manner. This is the basic premise

in the U.S. EPA's approach to assessing the cumulative risk of organophosphate and carbamate insecticides (U.S. EPA/OPP 2000f, 2006c).

While the assumption of additivity is in many ways a reasonable approach, it does not rule out the possibility that other AChE inhibitors may interact with and thus enhance or diminish the toxicity of malathion. Some studies suggest that greater than additive interactions may occur with some combinations of neurotoxic agents, including malathion (Moser et al. 2005, 2006; Olgun et al. 2004). For example, both EPN and parathion are AChE inhibitors and both of these compounds may enhance or synergize the toxicity of malathion. The mechanism of this enhancement involves the inhibition of carboxylesterases by EPN and parathion and is not directly related to the AChE activities of these compounds (CDHS 1991; Ramakrishna and Ramachandran 1978). A similar interaction has been observed between malathion and triorthotolyl phosphate (Cohen et al. 1972) as well as malathion and isomalathion, parathion, chlorpyrifos, and chlorpyrifos-oxon (Buratti and Testai 2005). With other organophosphates like DDVP (Cohen and Ehrich 1976), the joint action with malathion does appear to be additive.

Because the toxicity of malathion is mediated by its metabolism to malaoxon via mixed-function oxidases (MFO), numerous compounds that either induce or inhibit MFO activity could have an impact on the toxicity and/or time course of the toxicity of malathion (Ronis and Badger 1995). The protective effect of chloramphenicol for acute malathion exposures appears to be related to the inhibition of MFO (Gupta et al. 1983). Conversely, Mathews and Devi (1993, 1994) demonstrated that exogenous estrogen enhances the acute toxicity of malathion in pregnant rats, probably by the induction of liver mixed function oxidases (i.e., cytochrome P-450). As discussed in Section 3.1.7, this is the enzyme system responsible for the metabolism of malathion to malaoxon. Administration of progesterone with estrogen, however, tended to reduce the potentiating effect by the induction of hepatic glutathion S-transferase as well as carboxylesterases.

Phenobarbital and halogenated benzenes appear to protect against the acute toxic effects of malathion by the induction of liver esterases involved in the conversion of malathion to malathion mono- or di-acids (Brodeur 1967; Townsend and Carlson 1981). No apparent interactions were noted after concurrent dermal administration of malathion with hexachlorocyclohexane (Dikshith et al. 1987).

As summarized in Section 3.1.15.1, exposures to malathion may lead to the depletion of liver glutathione (GSH). Because GSH is a compound used in the detoxification of many other xenobiotics, exposures to malathion that are sufficient to cause a depletion of liver GSH may make an individual more susceptible to the toxic effects of several other compounds. Conversely, other compounds undergo conjugation with glutathione that results in an increase in toxicity—e.g., hexachlorobutadiene. For such compounds, exposures to malathion could result in a decrease in toxic effects. Although GSH depletion might lead to toxicological interactions with many compounds, generalizations cannot be made concerning the impact that such GSH depletion would have on the health of the animals. Another antioxidant, ascorbic acid, has been

shown to protect against DNA-damage by malathion in lymphocytes (Blasiak and Kowalik 1999).

Lead inhibits heme synthesis and can reduce cytochrome P-450 levels *in vivo*, which in turn could inhibit the metabolism/activation of malathion to malaoxon. In a test of this hypothesis, however, Abd-Elraof et al. (1981) found no indication that relatively high doses of lead (200 and 500 mg/kg/day) affected the metabolism of malathion in rats.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

All exposure assessments for malathion are summarized in the EXCEL workbooks that accompany this risk assessment: Attachment 1 for eight applications at a typical rate of 0.15 lb a.i./acre with a ULV formulation for mosquito control and Attachment 2 for a single application at a typical rate of 0.3 lb a.i./acre with an EC formulation for insect control in pine seed nurseries. Nursery applications may entail multiple applications as is the case with ULV applications for mosquito control. EC formulations that involve multiple applications can be readily modeled using the EXCEL workbook for ULV formulations.

In the EXCEL workbooks, Worksheet E01 summarizes exposures for workers and Worksheet E03 summarizes exposures for the general public. The consequences of using a range of application rates, as detailed in the Program Description (Section 2), is considered in the risk characterization (Section 3.4).

Three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. In scenarios involving the ULV applications of malathion (i.e., non-accidental exposure), central estimates of exposure are approximately 0.002 mg/kg/day for aerial and backpack workers and about 0.003 mg/kg/day for broadcast ground spray workers. Upper bounds of exposures are approximately 0.022 mg/kg/day for broadcast ground spray workers and 0.012 mg/kg/day for backpack and aerial workers. The exposure levels for workers involved in the application of EC formulations are about twice those for workers involved in the application of ULV formulations. The differences in exposure levels reflect the differences in the typical application rates used for mosquito control (ULV formulations) and insect control in pine seed nurseries (EC formulations).

All of the accidental exposure scenarios for workers involve dermal exposure. The accidental exposure scenarios lead to dose estimates that are substantially greater than the general exposure levels estimated for workers. The greatest estimated exposure level is approximately 23 (15-35) mg/kg bw, which is associated with wearing contaminated gloves for 1 hour while applying ULV formulations. For emulsifiable concentrate (EC) formulations, the estimated dose levels associated with accidental exposures are far less. For the contaminated gloves scenario, the doses associated with a 1-hour exposure are only about 0.2 (0.01 to 3) mg/kg bw. The reason for this difference is that ULV formulations, unlike EC formulations, are not diluted prior to application. Consequently, the malathion concentration in the ULV formulation is about 1230 mg/mL, while the malathion concentration in field solutions of EC formulations is only about 3.6 (0.36 to 36) mg/mL.

Also, the difference in malathion concentrations in field solutions of ULV and EC formulations results in substantially different exposure levels for members of the general public in both accidental spray and accidental spill scenarios. For the general public (Worksheet E03), acute levels of exposures range from minuscule (e.g., less than 0.0001 mg/kg/day) to about 105 mg/kg bw for ULV formulations and 3 mg/kg bw for EC formulation. The maximum exposure levels

for both the ULV and EC formulations are associated with the accidental spill of 200 gallons of a field solution into a small body of water. As discussed, in field solutions, the malathion concentration in the ULV formulation is much greater than that in the EC formulation. Accordingly, even though the typical application rate for an EC formulation is twice that for a ULV formulation, accidental exposure levels associated with field solutions of ULV formulations are far greater than those associated with field solutions of EC formulations.

Non-accidental acute exposure levels are much lower than accidental exposure levels for members of the general public. Estimated dose levels for EC formulations are somewhat higher than those for ULV formulations, based on the difference in typical applications rates—i.e., 0.15 lb a.i./acre for ULV and 0.3 lb a.i./acre for EC formulations. For both formulations, the highest non-accidental acute exposure levels are associated with the consumption of contaminated vegetation: 0.04 (0.009-0.3) mg/kg bw for ULV formulations and 0.05 (0.01-0.4) mg/kg bw for EC formulations. Although the application rate for EC formulations is twice that of ULV formulations, the exposure levels are comparable because the doses associated with the ULV formulations are based on residues immediately after the eighth application of malathion.

Differences in the number of applications between ULV and EC formulations also account for the similarity in longer-term exposure estimates. For both ULV and EC formulations, the highest estimated doses are associated with the consumption of contaminated vegetation: 0.007 (0.0008-0.3) mg/kg bw/day for ULV formulations and 0.004 (0.0009-0.036) mg/kg bw/day for EC formulations. All other longer-term exposure scenarios are associated with doses that are at least a factor of 10 less than the doses associated with the consumption of contaminated vegetation.

3.2.2. Workers

The malathion exposure assessments for workers are based on a standard set of exposure scenarios used for other pesticides with similar uses and application methods. While the exposure assessments vary depending on the characteristics and data relevant to a specific chemical, the organization and assumptions used in the exposure assessments are standard and consistent. For mosquito control, all of the exposure assessments for workers and members of the general public are detailed in an EXCEL workbook that accompanies this risk assessment (Attachment 1). The workbook contains a set of worksheets that details each exposure scenario discussed in the risk assessment. It also contains summary worksheets for both workers and members of the general public, which cover the range of application rates considered in this risk assessment. As discussed in Section 2 (Program Description), exposure levels associated with mosquito control are based on a total of eight applications conducted at 1-week intervals. A separate EXCEL workbook is provided for applications associated with insect control in pine seed orchards (Attachment 2). Documentation for the use of the EXCEL workbooks is provided in SERA (2005). The subsections below describe in plain language the scenarios detailed in the workbooks and discuss the malathion specific data used in the calculations.

Exposure assessments for workers are summarized in Worksheet E01 of each EXCEL workbook. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate exposures involving absorbed dose estimates based on handling a specified amount of chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific events that may occur during any type of application. The exposure assessments developed in this section as well as other similar assessments for the general public (Section 3.2.3) are based on the typical application rate (Section 2) and are detailed in Worksheet E02a of each workbook. The consequences of using different application rates in the range considered by the Forest Service are discussed further in the risk characterization (Section 3.4), and these risks are detailed in Worksheets E02b (lower bound of application rate), and E02c (upper bound of application rate).

3.2.2.1. General Exposures

As described in SERA (2007a), worker exposure rates in Forest Service risk assessments are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. Based on analyses of several different pesticides using a variety of application methods, default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. A summary of these exposure rates, taken from Table 3-3 in SERA 2007a, is given below:

Application Method	Exposure Rate (mg/kg bw per lb a.i.)
Directed foliar	0.003 (0.0003 to 0.01)
Broadcast foliar, boom spray	0.0002 (0.00001 to 0.0009)
Aerial	0.00003 (0.000001 to 0.0001)

Although there are several occupational exposure studies concerning malathion applications (Bouchard et al. 2006; Cruz Marquez et al. 2001; Machera et al. 2003; Krieger and Dinoff 2000; Tuomainen et al. 2002), only the study by Cruz Marquez et al. (2001) provides information that is useful for estimating worker exposure rates in units of mg/kg bw of absorbed dose per lb a.i. handled.

The Cruz Marquez et al. (2001) greenhouse study investigates worker exposure to semi-stationary high volume (4 L/min) spray applications of malathion to green beans, tomatoes, and cucumbers. Each of three workers applied 375 L of a solution containing 0.6 L of a 90% malathion formulation in 400 L of water. Thus, each worker applied about 0.506 kg of malathion [0.6 L formulation x 0.9 kg a.i./L formulation x 375 L/400 L = 0.506 kg a.i.], equivalent to about 1.12 lb a.i. [2.2046 lb/kg]. The absorbed dose of malathion in each worker was estimated from the total excretion of malathion monocarboxylic acid (MMA),which ranged from 133.75 to 671.24 µg per worker. The body weights of the workers are not specified in the study. Assuming a body weight of 70 kg, the absorbed doses ranged from about 0.0019 to 0.0096 mg MMA/kg bw. Based on study by Krieger and Dinoff (2000, Table 1, p. 547), the proportion of MMA excreted in urine after oral exposure to malathion is about 0.36. Correcting for this difference, the absorbed doses in terms of malathion equivalents ranged from about

0.0052 to 0.027 mg a.i./kg bw. Dividing this value by the amount of malathion applied by each worker (1.12 lb a.i.), the absorbed dose rates for the workers in the study by Cruz Marquez et al. (2001) were ranged from about 0.0046 to 0.024 mg/kg bw per lb a.i. applied [0.0052 to 0.027 mg a.i./kg bw divided by 1.12 lb a.i. applied].

The exposure rates from the study by Cruz Marquez et al. (2001) are reasonably consistent with the exposure rates used for directed foliar applications. The upper bound of 0.024 mg/kg bw per pound applied is a factor of 2.4 higher than the upper bound typically used for backpack applications. This difference is relatively modest. Exposure rates associated with an indoor application of a pesticide might be expected to be somewhat higher than those associated with outdoor applications due to decreased dispersion of the pesticide after application. Furthermore, indoor applications involve potentially greater rates of inhalation exposure, relative to outdoor applications.

While the study by Cruz Marquez et al. (2001) generally supports the worker exposure rates used in most Forest Service risk assessments, the type of application conducted in the Cruz Marquez et al. (2001) study does not correspond directly to the types of applications considered in this risk assessment. A perhaps more substantial uncertainty is associated with the specific program activities involved in either mosquito control or insect control in pine orchards. As detailed in Worksheets C01a through C01c, the estimates of absorbed doses are based on specific assumptions concerning the number of acres treated per day as well as the application rate. These assumptions are standard in all Forest Service risk assessments. Nonetheless, specific applications of malathion might involve the treatment of greater or lesser areas, and these differences would have a proportionate impact on the estimated exposure rates. These factors should be considered explicitly in assessments of specific programs.

3.2.2.2. Accidental Exposures

Typical occupational exposures may involve multiple routes of exposure (i.e., oral, dermal, and inhalation); nonetheless, dermal exposure is generally the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992). Typical multi-route exposures are encompassed by the methods used in Section 3.2.2.1 on general exposures. Accidental exposures, on the other hand, are most likely to involve splashing a solution of the pesticide into the eyes or contaminating the surface of the skin.

There are various methods for estimating absorbed doses associated with accidental dermal exposure (SERA 2007a). Two general types of exposures are modeled in this risk assessment: those involving direct contact with a solution of the pesticide and those associated with accidental spills of the pesticide onto the surface of the skin. Any number of specific exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on or in contact with the surface of the skin and by varying the surface area of the skin that is contaminated.

For this risk assessment, two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg

chemical/kg body weight. Both sets of exposure scenarios are summarized in Worksheet E01, which references other worksheets in which the specific calculations are detailed.

Exposure scenarios involving direct contact with solutions of the chemical are characterized by immersion of the hands for 1 minute in a field solution of the pesticide or wearing contaminated gloves for 1 hour. Generally, it is not reasonable to assume or postulate that the hands or any other part of a worker will be immersed in a solution of a chemical for any period of time. Nevertheless, contamination of gloves or other clothing is quite plausible. For these exposure scenarios, the key assumption is that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in a chemical solution. In both cases, the concentration of the chemical solution in contact with the skin and the resulting dermal absorption rate are basically constant.

For both scenarios (hand immersion and contaminated gloves), the assumption of zero-order absorption kinetics is appropriate. Following the general recommendations of U.S. EPA/ORD (1992), Fick's first law is used to estimate dermal exposure. As discussed in Section 3.1.3.2, an experimental dermal permeability coefficient (k_p) for malathion is not available. In the absence of experimental data, the k_p for a pesticide is typically estimated using the algorithm from U.S. EPA/ORD (1992), which is detailed in Worksheet B05. As also discussed in 3.1.3.2, however, the available data on malathion suggest that first-order dermal absorption rates for EC formulations are more rapid than rates for ULV formulation – i.e., neat malathion – by about a factor of three. Consequently, the dermal permeability coefficient (k_p) values used for EC formulations (Attachment 2) are adjusted upward by a factor of three.

Exposure scenarios involving chemical spills onto the skin are characterized by a spill on to the lower legs as well as a spill on to the hands. In these scenarios, it is assumed that a chemical solution is spilled on to a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid), the first-order absorption rate, and the duration of exposure. For both scenarios, it is assumed that the contaminated skin is effectively cleaned after 1 hour. As discussed in Section 3.1.3.2, the dermal absorption rates used in these scenarios for ULV formulations are based on experimental dermal absorption rates for neat malathion (Feldmann and Maibach 1974) and the rates for EC formulations are based on the dermal absorption rates from the study by Dary et al. (1994). As noted above and discussed in detail in Section 3.1.3.2, the first-order dermal absorption rates for EC formulations are about a factor of 3 greater than the corresponding rates for neat (i.e., ULV formulations) of malathion.

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Malaoxon Exposures

As discussed in Section 3.1.15, malaoxon is both a contaminant in and an *in vivo* metabolite of malathion, and it is malaoxon that is the active neurotoxic agent in malathion exposure scenarios. Since every toxicity study used to quantitatively assess risk in this document involves *in vivo* exposure to malathion, the occurrence of malaoxon as an *in vivo* metabolite of malathion is encompassed by the toxicity studies.

Malaoxon is also an environmental metabolite of malathion—i.e., malathion residues in natural media, such as water and vegetation, may be converted to malaoxon. As detailed in Section 3.3.4, the U.S. EPA/OPP (2006a) recommends a toxicity adjustment factor of 61 for malathion. In other words, for exposure scenarios involving both malathion (MT) and malaoxon (MO), risk is assessed by calculating the total malathion equivalents (MT_{Eq}) as the amount of malathion and the amount of malaoxon multiplied by the toxicity adjustment factor:

$$MT_{Eq} = MT + 61 \times MO.$$

As discussed in both ATSDR (2003) and U.S. EPA/OPP (2006a), malaoxon forms from the oxidation of P=S moiety in malathion to the P=O of malaoxon. There is no other pathway for the formation of malaoxon from malathion. As illustrated in Figure 4, the kinetics of malaoxon formation are complicated by the other pathways involved in the degradation of malathion – i.e., the formation phosphorothioic acids, carboxylic acids, and methylated malathion—as well as the similar degradative pathways for malaoxon.

The kinetics of these processes are not well characterized; therefore, the ability to model malaoxon concentrations in the environment is limited. As noted by the U.S. EPA/OPP (2005l, p. 15), the environmental fate parameters of malaoxon are likely to be similar to those of malathion; however, the environmental fate parameters needed to model environmental concentrations of malaoxon with any certainty are not available. Cahill and Mackay (2003) developed a model for malaoxon formation from malathion; however, the parameters used in the model are based largely on analogy to malathion and assumptions concerning the stability of malaoxon relative to malathion. While more recent data are available on the relative photolytic stability of malathion and malaoxon (Bavcon Kralj et al. 2007), information on the kinetics of the formation and degradation of malaoxon remains incomplete.

In the recent RED on malathion (U.S. EPA/OPP 2006a) and related documents prepared by the U.S. EPA/OPP in support of the RED, the exposure assessment for malaoxon is based largely on monitoring data. This approach is reasonable and is adopted in the current Forest Service risk assessment.

In terms of the current Forest Service risk assessment, the exposure scenarios of greatest concern involve the consumption of contaminated water (Section 3.2.2.4) and the consumption of

contaminated vegetation (Section 3.2.3.6). The U.S. EPA/OPP (2006e) raises substantial concern for the formation of malaoxon in drinking water because of monitoring data that suggests an essentially complete conversion of malathion to malaoxon in drinking water treatment facilities. In the drinking water exposure scenario developed by the U.S. EPA, the assumption is made that all malathion in the input water for a drinking water treatment facility is converted to malaoxon, which appears to be a reasonable worst-case assumption. Nevertheless, the use of malathion in Forest Service programs and related activities will not involve treatment of drinking water reservoirs or other bodies of water used as sources for drinking water treatment plants. Consequently, the formation of malaoxon in drinking water is not considered in the current risk assessment. Other than malaoxon formation during drinking water treatment, the risk assessments for both human health and ecological effects (U.S. EPA/OPP 2006e) conclude that malaoxon exposures in ambient water are not a substantial concern. This conclusion is supported by an assessment of extensive monitoring data from the Mediterranean Fruit Fly eradication program in California (cited by the U.S. EPA): *Malaoxon did not appear in the water until the final sampling interval (21 days after application) and the values were extremely small* (Neal et al. 1993, p. 3).

The potential significance of malaoxon residues on vegetation, however, is more difficult to assess; what is more, the EPA positions taken in the human health and ecological risk assessments differ from one another other. In the ecological risk assessment, the U.S. EPA concludes:

> *The Agency does not believe that the conditions necessary for the formation of malaoxon exist such that residues of malaoxon will be found in or on the food sources for terrestrial wildlife. Malaoxon can enter surface water via urban runoff when malathion converts to malaoxon and is washed off by rainfall. However, the Agency does not expect malaoxon to be a significant component of the ecological hazard of malathion to non-target organisms. While other degradates and impurities of malathion exist, they too are not expected to be present in the environment at concentrations high enough to contribute to the toxicity of malathion to nontarget organisms.* – U.S. EPA/OPP 2006a, p. 48

While the supporting documents provided by the U.S. EPA do not discuss the basis for this conclusion in detail, the conclusion is supported by several monitoring studies that found either no or very low residues of malaoxon on vegetation as well as the rapid dissipation of malaoxon residues on vegetation (e.g., Bradman et al. 1994; Coffin 1966; Lalah and Wandiga 1996; Neal et al. 1993; Nigg et al. 1981).

The U.S. EPA's human health risk assessment for malathion takes a somewhat more conservative approach and does quantitatively consider monitoring data on malaoxon residues on vegetation in the dietary exposure assessment (U.S. EPA/OPP 2005c). The frequencies of the detection of malaoxon on vegetation, however, are extremely low:

> *Indeed, within the more than 40,000 residue samples collected between 1992-2003, only 43 detections of malaoxon were made. Although detections of malaoxon in or on food commodities are infrequent, they are accounted for in the Agency's dietary assessment by multiplying each malaoxon detection by the TAF (61x) and adding this value to the malathion dietary residue values.* – U.S. EPA/OPP 2006a, p. 16.

While not detailed in U.S. EPA/OPP 2006a, 14 of the 45 detections of malaoxon on vegetation involved residues on cotton (U.S. EPA/OPP 2005c, Table 1, pp. 6-7), and these residues would not contribute directly to a dietary exposure assessment.

For the current Forest Service risk assessment, monitoring data from the Mediterranean fruit fly eradication program in California (Bradman et al. 1994) are used to estimate plausible exposures to malaoxon from the consumption of contaminated vegetation. Bradman et al. (1994) monitored concentrations of malathion and malaoxon on vegetation after malathion was applied at the rate of 23.8 mg/m^2 to four areas in California. This application rate corresponds to a rate of 0.238 kg/ha [10,000 m^2/hectare] or about 0.2 lb a.i./acre, which is quite similar to rates anticipated in Forest Service programs for mosquito control. After multiple applications, longer-term concentrations of malaoxon in vegetation were less than malathion concentrations by factors of 130 (based on typical concentrations) and 123 (based on upper bounds) (p. 58, Table 6). After single applications, similar ratios were noted: concentrations of malaoxon on vegetation were about 120-133 below those of malathion (p. 57, Table 5), which amounts to an extremely narrow range.

Based on the lower bound of 120—i.e., the greatest concentration of malaoxon, relative to malathion—and using the EPA's toxic equivalency factor of 61, the relative malathion equivalents on vegetation would be about 1.5 [$MT_{Eq} = 1 + 61 \times MO/120 = 1.5083\ldots$]. In other words, a monitored value of 1 ppm malathion would be associated with a co-exposure to about 0.0083 ppm malaoxon [1/120]. Using the EPA adjustment factor of 61 results in a malaoxon exposure that is equivalent to a malathion exposure of 1.5 ppm [1 ppm + (61 x 0.0083)].

The values reported by Bradman et al. (1994) are averages and do not represent the worst case scenario. Additional data on the concentrations of malathion and malaoxon on vegetation associated with the Mediterranean fruit fly eradication program are provided by Neal et al. (1993). Neal et al. (1993) monitored time-course data on the levels of malathion and malaoxon on tomatoes and lettuce over a 21-day post-application period. No malaoxon was detected on lettuce. Malaoxon was detected sporadically on tomatoes, and these data are illustrated in Figure 5. Malathion concentrations followed a relatively smooth bi-exponential decay from initial concentrations ranging from about 78 ppb to about 3 ppb on Day 21 after treatment. Malaoxon was detected on only 2 days: a concentration of about 2.2 ppb on Day 4 and a concentration of about 15 ppb on Day 21.

The data on malaoxon illustrated in Figure 5 are somewhat unusual and erratic in that there is no clear pattern in the increase of malaoxon with the steady decrease of malathion. Hernandez et al.

(2002, p. 1176) report a similarly erratic pattern in malaoxon on vegetation: *Malaoxon is detected in some samples, but there is no correlation between the diminution of the parent compound and the presence of malaoxon*.

The data from Neal et al. (1993), illustrated in Figure 5, are particularly unusual, however, because of increases in malaoxon concentrations from Day 10 to 21. On Day 10, no malaoxon was detected and the concentration for malathion was about 6 ppb. On Day 21, however, the concentration of malaoxon was about 15 ppb. If the concentration of malathion was only 6 ppb on Day 10 and if the only mechanism for malaoxon formation is via the oxidation of malathion, it is not clear how the concentration of malaoxon could reach 15 ppb on Day 21. Neal et al. (1993) do not discuss this unusual pattern of concentrations. The study by Neal et al. (1993) did involve serial sampling – i.e., different sets of samples were taken from the plant at each interval. Thus, this pattern could represent random variability in the amounts of malathion and malaoxon from different parts of the plant sampled at different times.

In any event, the data from Neal et al. (1993) appear to represent a worst case assessment, notwithstanding the questionable data from Day 21. Because of the unusual residue pattern, these data cannot be fit to a general kinetic model. As an alternative, the average of the concentrations can be used to estimate the malathion equivalent exposures. The average concentration of malathion over the 21-day period is about 24.5 ppb. Taking the two detections of malaoxon and multiplying them by the EPA toxicity adjustment factor of 61, the average concentration in terms of malaoxon equivalents over the 21-day period is about 235 ppb. Thus, over the 21-day exposure period, taking into consideration the malaoxon residues increases exposure by about a factor of 10 [235 ppb/24.5 ppb].

For the current Forest Service risk assessment, the malathion concentrations on vegetation are adjusted by a factor of 2 with a range from 1 to 10 to account for the formation of malaoxon on vegetation in the longer-term exposure scenarios. The central estimate of 2 is based on the rounding of 1.5083 to one significant place from the data on average concentrations reported by Bradman et al. (1994), as discussed above. The lower limit of 1 for the adjustment factor—i.e., no adjustment—is consistent with the preponderance of the data indicating no substantial exposure to malaoxon on vegetation. The upper bound of 10 is based on the tomato data from Neal et al. (1993). These adjustment factors are applied only to the longer-term exposure scenarios because significant concentrations of malaoxon on vegetation are not expected immediately after exposure, except to the extent that malaoxon is found as a contaminant in malathion. As discussed in Section 3.1.15.2, the impact of contaminants in malathion is implicitly considered in the dose-response assessment, because the toxicity data on malathion involves exposure to both malathion itself as well as the contaminants in technical grade malathion.

3.2.3.1.2. Likelihood and Magnitude of Exposure

The likelihood that members of the general public will be exposed to malathion in Forest Service applications is highly variable. In Forest Service programs for mosquito control, malathion may be applied in or near recreational areas like campgrounds, picnic areas, and trails. In these instances, it is plausible that members of the general public would be exposed to malathion. Malathion applications for insect pest control in pine seed orchards are less likely to involve general public exposure.

Because of the conservative exposure assumptions used in the current risk assessment, neither the probability of exposure nor the number of individuals who might be exposed has a substantial impact on the characterization of risk presented in Section 3.4. As noted in Section 1 (Introduction) and detailed in SERA (2007a, Section 1.2.2.2), the exposure assessments developed in this risk assessment are based on ***Extreme Values*** rather than a single value. Extreme value exposure assessments, as the name implies, bracket the most plausible estimate of exposure (referred to statistically as the central or maximum likelihood estimate and more generally as the typical exposure estimate) with extreme lower and upper bounds of plausible exposures.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometime referred to as the *Maximum Exposed Individual* (MEI). As this name also implies, exposure assessments that use the MEI approach are made in an attempt to characterize the extreme but still plausible upper bound on exposure. This approach is common in exposure assessments made by the U. S. EPA, other government agencies, and the International Commission on Radiological Protection (e.g., ATSDR 2002; ICRP 2005; Payne-Sturges et al. 2004). In the current risk assessment, the upper bounds on exposure are all based on the MEI.

In addition to this upper bound MEI value, the Extreme Value approach used in this risk assessment also provides a central estimate of exposure as well as a lower bound on exposure. While not germane to the assessment of upper bound risk, it is worth noting that the use of the central estimate and especially the lower bound estimate is not intended to lessen concern. To the contrary, the central and lower estimates of exposure are used to assess the feasibility of mitigation—e.g., protective measures to limit exposure. If lower bound exposure estimates exceed a level of concern (which is not the case in the current risk assessment), this is strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk.

Thus, the Extreme Value approach in the exposure assessment is part of an integrated approach designed to encompass plausible upper limits of risk for the most exposed and most sensitive individuals, regardless of the specific probabilities or number of exposures.

3.2.3.1.3. Summary of Assessments

The two types of exposure scenarios developed for the general public include acute exposure and longer-term or chronic exposure. Most of the acute exposure scenarios are accidental. They assume that an individual is exposed to the compound either during or shortly after its application. Specific scenarios are developed for direct spray, dermal contact with contaminated vegetation, as well as the consumption of contaminated fruit, water, and fish. Most of these scenarios should be regarded as extreme, some to the point of limited plausibility. The only exception is the acute exposure scenario for the consumption of contaminated ambient water. As detailed in Section 3.2.3.4.3, this acute exposure scenario is based on expected peak concentrations of malathion in surface water. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish but are based on estimated levels of exposure for longer periods after application. These scenarios all involve expected rather than accidental exposures. Nonetheless, the upper bounds of these longer-term exposure scenarios involve conservative assumptions intended to reflect exposures to the MOI (most exposed individual).

The exposure scenarios developed for the general public are summarized in Worksheet E03 of the EXCEL workbooks for ULV applications (Attachment 1) and applications of EC formulations (Attachment 2). As with the worker exposure scenarios, details of the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01–D11). The remainder of this section describes the quality of the data supporting and the rationale for its use in each of the assessments.

3.2.3.2. Direct Spray

Direct spray scenarios for members of the general public are modeled in a manner similar to accidental spills for workers (Section 3.2.2.2). In other words, it is assumed that the individual is sprayed with a field solution of the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. Two direct spray scenarios are given, one for a young child (D01a) and the other for a young woman (D01b).

For the young child, it is assumed that a naked child is sprayed directly during a ground broadcast application and that the child is completely covered (that is, 100% of the surface area of the body is exposed). This exposure scenario is intentionally extreme. As discussed in Section 3.2.3.1.1, the upper limits of this exposure scenario are intended to represent the *Extreme Value* of exposure for the *Most Exposed Individual* (MEI).

The exposure scenario involving the young woman (Worksheet D01b) is somewhat less extreme but more plausible, and assumes that the woman is accidentally sprayed over the feet and lower legs. By reason of allometric relationships between body size and dose-scaling, a young woman would typically be subject to a somewhat higher dose than the standard 70 kg man. Consequently, in an effort to ensure a conservative estimate of exposure, a young woman rather than an adult male is used in many of the exposure assessments.

For the direct spray scenarios, assumptions are made regarding the surface area of the skin and the body weight of the individual, as detailed in Worksheet A03. The rationale for and sources of the specific values used in these and other exposure scenarios are provided in the documentation for the worksheets (SERA 2005) and in the methods document for preparing Forest Service risk assessments (SERA 2007a).

Because ULV formulations involve much more concentrated solutions (i.e., undiluted formulations containing 1230 mg a.i./mL), relative to applications of emulsifiable concentrates (i.e., field solutions ranging from 0.36 to 36 mg a.i./mL), the spray scenarios for ULV formulations (Attachment 1) result in much higher exposure levels, compared with those for EC formulations (Attachment 2), even though higher dermal absorption rates are used for EC formulations (Section 3.1.3.2).

3.2.3.3. Dermal Exposure from Contaminated Vegetation

As discussed in detail in SERA (2007a), the exposure scenario involving dermal exposure from contaminated vegetation assumes that the pesticide is sprayed at a given application rate and that a young woman comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation (D02). For these exposure scenarios, there must be chemical-specific data from which to estimate dislodgeable residue (the amount of chemical released from the vegetation) and its rate of transfer from the contaminated vegetation to the skin. As detailed in Durkin et al. (1995), dermal transfer rates are reasonably consistent for a number of pesticides and the methods and rates derived in Durkin et al. (1995) are used as defined in Worksheet D02. The exposure scenario assumes a contact period of 1 hour and further assumes that the chemical is not effectively removed by washing until 24 hours after exposure. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

As noted in the previous section and discussed further in Section 3.1.3.2, this risk assessment assumes that emulsifiable concentrate (EC) formulations of malathion are generally absorbed three times more rapidly than neat (ULV) formulations. This assumption is maintained in the exposure assessment for contact with contaminated vegetation as a conservative estimate of exposure. There is, however, no certainty that the degree of dermal absorption of malathion from contaminated vegetation differs according to the formulation.

3.2.3.4. Contaminated Water

Water can become contaminated as a result of runoff, leaching from contaminated soil, a direct spill, unintentional direct spray from aerial applications, or drift from either ground or aerial applications. Estimates of malathion concentrations in ambient water are derived for scenarios involving an accidental spill (Section 3.2.3.4.1), an unintended direct spray or drift (Section 3.2.3.4.2), and for acute and longer-term exposure levels in ponds and streams associated with Forest Service applications (Section 3.2.3.4.3).

3.2.3.4.1. Accidental Spill

The accidental spill scenario assumes that a young child consumes contaminated water from a small pond (1000 m^2 in surface area and 1 meter deep) shortly after a 200-gallon spill of a field solution. The specifics of this scenario are given in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered. This scenario is dominated by arbitrary variability, and the specific assumptions used generally overestimate exposure. The actual concentration in the water would depend greatly on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed.

As with the direct spray scenario (Section 3.2.3.4), there are substantial differences in the concentrations modeled for ULV formulations, which contain 1230 mg a.i./mL malathion, as opposed to the field solutions of EC formulations, which contain from 0.36 to 35 mg a.i./mL malathion (Attachment 2, Worksheet A01). Thus, the estimated concentrations of ULV formulations in ambient surface water are greater than those for emulsifiable concentrates by factors of about 35-350 [1230 mg a.i./mL divided by 0.36 to 35 mg a.i./mL].

Another difference in this scenario between the EC and ULV formulations is that concentrations in the pond are dependant on application rate only for the EC formulations. For EC formulations, the concentrations in the pond will vary with both application rate and application volume because these two variables impact the concentration of malathion in the fields solution – i.e. the material that is spilled into the pond. For ULV formulations, the accidental spill scenario simply involves 200 gallons of the malathion formulation being spilled into the pond regardless of the application rate that is being used.

3.2.3.4.2. Accidental Direct Spray/Drift for a Pond or Stream

These scenarios are less severe but more plausible than the accidental spill scenario described above. In the application of ULV formulations for mosquito control, the Forest Service will not intentionally apply malathion to surface water. Nonetheless, direct applications may be made unintentionally to small ponds or streams unseen during aerial applications. In addition, unintentional contamination of surface water could occur due to drift.

The scenarios for the contamination of a small pond and a small stream are given in Worksheets 10a and 10b, respectively. The exposure scenarios consider both direct application as well as drift at distances from 25 to 900 feet. The resulting concentration depends on the application rate as well as the nature of the water body. For ponds, the U.S. EPA typically uses a 2-meter deep pond to develop exposure assessments (SERA 2007a), and this approach is used in Worksheet D10a. For small streams, the resulting water concentration depends on the surface area of the stream and the rate of water flow in the stream. The stream modeled using GLEAMS (see below) is about 6 feet wide (1.82 meters), and it is assumed that the pesticide is applied along a 1038 foot (316.38 meters) length of the stream with a flow rate of 710,000 L/day.

3.2.3.4.3. GLEAMS Modeling

The Forest Service developed a program, Gleams-Driver, to estimate expected peak and longer-term pesticide concentrations in surface water. Gleams-Driver serves as a preprocessor and postprocessor for GLEAMS, which is both a field scale model developed by the USDA/ARS and a program used for many years in Forest Service and other USDA risk assessments (SERA 2007b).

Gleams-Driver offers the option of conducting general exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA Agricultural Research Service (http://horizon.nserl.purdue .edu/Cligen). Gleams-Driver was used to model concentrations in a small stream and small pond.

The chemical specific values used in the GLEAMS modeling are summarized in Table 6. For the most part, the chemical specific input values used in GLEAMS modeling are similar to those used by the U.S. EPA (U.S. EPA/OPP 2006n). The EPA modeling efforts are discussed below (Section 3.2.3.4.4). The modeling input values are based on the environmental fate studies submitted to the U.S. EPA as well as standard values for GLEAMS modeling recommended by Knisel and Davis (2000). The specific sources of information used in GLEAMS modeling are given in the notes to Table 6. The water body characteristics as well as soil properties are based on a standard set of assumptions used in GLEAMS modeling for Forest Service risk assessments (SERA 2007b).

The locations selected for modeling included a total of nine sites, as illustrated in Figure 6. As detailed in SERA (2007b), these sites are standard sites for the application of Gleams-Driver in Forest Service risk assessments and are intended to represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool). For each site, Gleams-Driver was used to simulate 100 applications of malathion at a unit application rate of 1 lb/acre, and each of the simulations was followed for a period of more than 1½ years post application. For each of the nine sites, three sets of simulations were conducted with soil characteristics for clay, loam, and sand.

Because malathion may be applied on more than one occasion during a season, three simulations were conducted for each of the 27 sets of site-soil combinations modeling a single application, eight applications at 1-week intervals, and 25 applications at 1-week intervals. As discussed in Section 2, a maximum of eight applications is anticipated in Forest Service related programs. In the U.S. EPA PRZM/EXAMS modeling, a maximum of 25 applications was used (U.S. EPA/OPP 2005n). The simulations for 25 applications are included in the current risk assessment only to illustrate the consequences of exceeding the anticipated maximum of eight applications in Forest Service related programs. In addition, only summaries of these simulations are included in the current risk assessment (Table 11).

The results of the Gleams-Driver simulations are given in Table 7 (peak concentrations) and Table 8 (1-year average concentrations) for a small stream and Table 9 (peak concentrations) and Table 10 (1-year average concentrations) for a small pond. As discussed in SERA (2007b), all values are expressed as the midpoint (median) with 95% empirical confidence intervals. These tables include Gleams-Driver outputs for only a single application and eight applications at 1-week intervals, because only these simulations are used in the exposure assessments for the current risk assessment.

3.2.3.4.4. Other Modeling Efforts

The Gleams-Driver modeling discussed above and the modeling by U.S. EPA/OPP presented in U.S. EPA/OPP (2003d) are summarized in Table 11. Table 11 also summarizes the results of Gleams-Driver modeling for one and eight applications of malathion at 1-week intervals (detailed in Tables 7 through 10) and 25 applications at 1-week intervals.

In the human health risk assessment of malathion, the U.S. EPA/OPP used two water contamination models: PRZM/EXAMS (U.S. EPA/OPP 2006e) and GENEEC (U.S. EPA/OPP 2005n). As discussed in SERA (2007b), PRZM/EXAMS is a model, or more accurately a system of linked models, that the U.S. EPA uses to assess plausible concentrations of pesticides in water after agricultural applications. Different types of PRZM/EXAMS scenarios can be conducted, and the modeling summarized in Table 11 involves the use of an index reservoir (i.e., a standard reservoir) commonly used by the U.S. EPA/OPP. GENEEC is a Tier 1 screening model developed by the U.S. EPA to estimate chemical concentrations in a small pond, given the application rate, the number of applications, the interval between applications, and the standard environmental fate parameters for the chemical.

The U.S. EPA/OPP (2006e, Table 3, p. 6) modeled malathion concentrations in water over a range of labeled rates (0.8 to 6.25 lb a.i./acre), numbers of applications per year (1 to 25), and application intervals (3 to 30 days). The variations in application intervals used by the U.S. EPA somewhat complicates a direct comparison with the Gleams-Driver simulations. In Table 11 of the current risk assessment, the reported concentrations are normalized to 1 lb a.i./acre (i.e., the WCR) by dividing the concentration reported by the U.S. EPA by the application rate used in the modeling. Two sets of comparison for PRZM/EXAMS modeling are presented, one based only on 6- to 7-day application intervals (comparable to the Gleams-Driver modeling) and another set based on all simulations conducted by U.S. EPA.

The estimated peak concentration from PRZM/EXAMS is about 44.4 ppb for 6- to 7-day application intervals and 51 ppb for all simulations. These peak concentrations are comparable to and encompassed by the peak concentrations in ponds and streams based on the Gleams-Driver simulations of eight applications at 1-week intervals—i.e., 40 to 70 ppb. The lower bound for the range of concentrations modeled by the U.S. EPA is 3.7 ppb for simulations with 6- to 7-day intervals and 2.4 ppb for all simulations. These estimates are also encompassed by the Gleams-Driver simulations and are factors of about 4-12 below the central estimates from the Gleams-Driver simulations—i.e., 30 ppb for streams and 15 ppb for ponds.

As with the peak concentrations, the results of the long-term average PRZM/EXAMS modeling are comparable to the results of the Gleams-Driver modeling. The peak concentration modeled by the U.S. EPA using PRZM/EXAMS is 0.79 ppb for both 6- to 7-day application intervals and all modeling done by U.S. EPA. By comparison, the longer-term average concentrations modeled using Gleams-Driver are in the range of 1.1 ppb (streams) to 1.4 ppb (ponds).

3.2.3.4.5. Monitoring Data

There is a large body of monitoring data on malathion, much of which is reviewed by the U.S. EPA/OPP (2005n) and summarized in Table 11. All of the monitoring data involve peak concentrations. Where possible, the monitored peak values are divided by the reported application rates to normalize the peak concentrations for an application rate of 1 lb a.i./acre. These normalized values are comparable to the WCR values (i.e., water contamination rates or the expected concentration at an application rate of 1 lb a.i./acre). Some of the reported monitoring values modestly exceed the maximum peak WCR values from both the Gleams-Driver and U.S. EPA modeling. In terms of the Gleams-Driver maximum values of 70 ppb in steams, the greatest difference comes from the value of 142 ppb in grasshopper control programs, which is a factor of about 2 greater than the Gleams-Driver maximum.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

Table 12 summarizes the malathion concentrations in water used for the current risk assessment. The concentrations are given as water contamination rates, the concentrations in water expected at a normalized application rate of 1 lb a.i./acre, converted to units of ppm or mg/L per lb a.i./acre. While units of ppb or µg/L are used in Tables 1-11 as a convenience, the conversion from ppb to ppm in Table 12 is made because ppm and mg/L are the units of measure used in the EXCEL workbook for contaminated water exposure scenarios in both the human health and ecological risk assessments. The water contamination rates are entered in Worksheet B04 and are linked to the appropriate scenario specific worksheets in the EXCEL workbook.

Two sets of values are given, one for eight applications conducted at 1-week intervals and the other for a single application. The water contamination rates for eight applications are used to characterize the application of ULV formulations for mosquito control (Attachment 1), and the water contamination rates for a single application are used to characterize application of EC formulations for insect control in pine seed orchards (Attachment 2). Some Forest Service programs might involve a different number of applications, in which case, the Attachments (1 and 2) could be modified accordingly, at the project level. At this time, however, the number of malathion applications conducted in Forest Service related programs is not expected to exceed eight. As indicated in Table 11, contamination rates after 25 applications could be approximately twice as high for ponds and somewhat less than twice as high for streams, relative to rates modeled for eight applications.

For eight applications separated at 1-week intervals, the upper range of the expected peak WCR of malathion in surface water is taken as 0.07 ppm per lb a.i./acre. This estimate is based on the peak malathion concentration in streams modeled using Gleams-Driver simulations as summarized in Table 11 and detailed in Table 9 (an upper bound of 70 ppb for clay in some

regions with moderate to heavy rainfall). As discussed in Section 3.2.3.4.4, this WRC is somewhat greater than the upper bound estimate of 0.051 ppm from the PRZM/EXAMS modeling conducted by the U.S. EPA but virtually identical to the upper bound estimate of 0.0724 ppm from the more conservative GENEEC model. As also noted in Table 11, the upper bound of 0.07 ppm for the peak water contamination rate is likely to encompass accidental or incidental exposures due to spray drift and the direct spray of a small pond; however, it is somewhat less than the direct spray scenario for a small stream—i.e., 91 ppb or 0.091 ppm. In other words, while inadvertent contamination due to drift or direct spray might be considered an extreme or at least atypical exposure, these concentrations are not substantially higher than those which might be associated with normal use of malathion in some areas where eight applications are conducted at 1-week intervals.

For single applications of malathion, the upper range of the expected peak WCR in surface water is taken as 0.04 ppm per lb a.i./acre. This estimate is based on the peak malathion concentration in streams modeled using Gleams-Driver simulations as summarized in Table 11 and detailed in Table 9 (an upper bound of 40 ppb for clay in some regions with moderate to heavy rainfall). As discussed in Section 3.2.3.4.4, this WRC is somewhat less than the upper bound estimate of 0.051 ppm from the PRZM/EXAMS modeling. The upper bound of 0.04 ppm encompasses accidental or incidental exposures due to spray drift but not direct spray.

For the lower bound of the peak WCR, an argument may be made that malathion concentrations are likely to be essentially zero—i.e., applications to sites distant from open bodies of water and in areas where neither runoff nor percolation is likely to occur. For this risk assessment, the lower range of the peak water contamination rate is set at 1 ppb or 0.001 ppm per lb/acre for eight applications and 0.5 ppb or 0.0005 ppm for a single application. The selection of any non-zero values for the lower bound of the WCRs is admittedly judgmental. These values, however, are substantially less than those associated with adverse effects and do not impact the human health or ecological risk assessment (Sections 3.4 and 4.4).

The central estimate for the peak WCR is set at 0.02 ppm per lb/acre for eight applications and 0.012 for a single application. The central estimate for eight applications is based on the concentration of 19 ppb (0.019 ppm), the central modeled value in streams for areas with clay soils, cool temperatures, and average rainfall rates (Table 7). Several other sites with clay or loam soils yielded similar central estimates of WCR values. For a single application, the central estimate of 0.004 ppm (4 ppb) is based on the central estimate of the peak concentration in streams in areas with clay soil and average temperature and rainfall (Table 7). Several other simulations yield similar central estimates for streams; furthermore, 4 ppb is also the central estimate for concentrations in ponds with loam soils, cool temperatures, and greater than average rainfall (Table 9).

The water contamination rates for longer-term exposures are derived in a manner similar to that for the peak concentration. For eight applications, the upper bound of the longer-term concentration in surface water is taken as 0.0018 ppm (1.8 ppb) per lb a.i./acre. For single applications, the upper bound of the longer-term concentration in surface water is taken as

0.0005 ppm (0.5 ppb) per lb a.i./acre. As detailed in Table 10, both of these upper bound values are based on the upper bound of the longer-term concentrations modeled for ponds in areas with clay soils and average temperature and rainfall.

As with the lower bound estimates of peak concentrations, the lower bound of the longer-term concentration could be taken as zero. For the current risk assessment, the lower bound is taken as 0.00002 ppm (0.02 ppb) per lb a.i./acre for eight applications and 0.000002 ppm (0.002 ppb) for single applications. These values are admittedly somewhat arbitrary, and several much lower non-zero values are listed in Table 8 (streams) and Table 10 (ponds). As with the lower bound estimates for peak concentrations, the lower bound estimates for longer-term concentrations have no impact on the risk characterization.

The central estimates for the longer-term concentrations are taken as 0.0002 ppm (0.2 ppb) for eight applications and 0.00002 ppm (0.02 ppb) for single applications. The value of 0.2 ppb for eight applications is similar to central estimates of the longer-term concentrations modeled in streams in areas with clay soils and average rainfall (Table 8) as well as the concentrations in ponds in areas with clay soils, average temperature and greater than average rainfall(Table 10). The value of 0.02 ppb for single applications is close to the central estimates for longer-term concentrations in ponds in areas with clay soils and average to above average rainfall (Table 10).

The judgmental and to some degree arbitrary nature of the selected water contamination rates and the assumptions used to derive these rates should be apparent and appreciated. GLEAMS as well as PRZM/EXAMS are highly parameterized models intended for use in site-specific exposure assessments. The generic application of Gleams-Driver in this risk assessment is intended only to provide general estimates of plausible exposures in order to identify which exposure scenarios might present the greatest risk under a wide-ranging set of conditions and some very conservative assumptions. In the assessment of any site-specific application of malathion, these estimates may be refined by using site-specific inputs.

3.2.3.5. Oral Exposure from Contaminated Fish

Three sets of exposure scenarios for the consumption of contaminated fish are provided and each set includes separate estimates for the general population and subsistence populations. These exposure scenarios consist of one set for acute exposures following an accidental spill (Worksheets D08a and D08b), another set for acute exposures based on expected peak concentrations (Worksheets D08c and D08d), and the third set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets in each of these three sets are intended to account for different rates of wild-caught fish consumption in both general and subsistence populations. Details of exposure scenarios involving the consumption of contaminated fish are provided in Section 3.2.3.5 of SERA (2007a).

As summarized in the worksheets for an accidental spill (Worksheets D08a and D08b), the estimated water concentrations are about 3900 ppm for ULV formulations (Attachment 1) and range from about 0.27 to 27 ppm for EC formulations (Attachment 2). As noted in Section

4.1.3.1, however, many of the LC_{50} values for fish are less than 1 ppm and almost all are less than 3900 ppm. Thus, it is not clear that the exposure scenarios associated with the consumption of contaminated fish after an accidental spill are plausible or even reasonable. In other words, after the accidental spill modeled in Worksheets D08a and D08b, it is likely that many if not all fish would be in obvious distress or quite possibly dead, as discussed further in the risk characterization (Section 3.4). It seems improbable, then, that members of the general public would collect and consume the fish.

In addition to estimates of peak and longer-term term concentrations in water, this exposure scenario requires information on the bioconcentration factor (BCF). As summarized in Table 1, the U.S. EPA/OPP (2005L) uses a BCF values in edible tissue of 4.2 (acute) and 18 (longer-term). These values are used in all exposure assessments involving the consumption of contaminated fish by humans. In the ecological risk assessment, the BCF values in whole fish are used: 23 (acute) and 135 (longer-term). These values are also taken from U.S. EPA/OPP (2005L).

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Some sites maintained by the Forest Service contain surface water in which members of the general public might swim. To assess the potential risks associated with swimming in contaminated water, an exposure assessment is developed for a young woman swimming in surface water for 1 hour (Worksheet D11).

Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time. The major differences in the two scenarios involve the concentration in water and the surface area of the body that is exposed. For the worker wearing contaminated gloves, the assumption is made that both hands are exposed to the field solution—i.e., the concentration of the compound in the solution that is being applied. For the swimmer, the assumption is made that the entire body surface area is exposed to the expected peak concentrations in ambient water (Table 12). Also as with the scenario for contaminated gloves, the swimming scenario is conservative in that it assumes zero-order absorption directly from the water to the systemic circulation. While the swimmer will not be immersed for 1 hour, the entire body surface is used both as a conservative approximation (i.e., the MEI) and to consider intermittent episodes during which the whole body might be immersed or at least wet.

As with the corresponding worker exposure scenario, the 1-hour period of exposure is somewhat arbitrary, and longer periods of exposure are plausible. The 1-hour period, however, is not completely arbitrary but is intended as a unit exposure estimate. In other words, the exposure and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D11. Thus, a 2-hour exposure would lead to a hazard quotient that is twice as high as that associated with an exposure period of 1 hour. In cases in which this or other similar exposures approach a level of concern, further consideration is given to the duration of exposure in the risk characterization (Section 3.4).

3.2.3.7. Oral Exposure from Contaminated Vegetation

Although none of the Forest Service applications of malathion will involve crop treatment, Forest Service risk assessments typically include standard exposure scenarios for the acute and longer-term consumption of contaminated vegetation. Two sets of exposure scenarios are provided: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. These scenarios are detailed in Worksheets D03a and D03b for acute exposure and in Worksheets D04a and D04b for chronic exposure.

The concentration of the pesticide on contaminated fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). While the human health risk assessment conducted by the U.S. EPA/OPP (2006a,b) does not consider this exposure scenario, the use of the residue rates recommended by Fletcher et al. (1994) both here and in the ecological risk assessment (Section 4.2) is identical to the approach used by U.S. EPA/OPP in their ecological risk assessment of malathion (U.S. EPA/OPP 2005L).

For chronic exposures, both initial concentrations and a half-life on vegetation are required to estimate the time-weighted average exposure (Worksheet D04a and D04b). As in the GLEAMS modeling (Table 6), a foliar half-life of 5.5 days is used. As noted in Table 6, this value is an upper 90% confidence bound on the mean from 37 studies from which a foliar half-life could be estimated (U.S. EPA/OPP 2006n, Table 3, p. 143).

As detailed in Section 3.2.3.1.1, concurrent exposures to malathion and malaoxon are considered by using adjustment factors with a central value of 2 (range from 1 to 10) to account for the formation of malaoxon on vegetation in the longer-term exposure scenarios.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The U.S. EPA recently proposed malathion RfD values of 0.14 mg/kg bw for acute exposures and 0.070 mg/kg bw/day for longer-term exposures. Both of these RfDs are based on $BMDL_{10}$ values from studies in rat pups. Following standard practice in Forest Service risk assessments, these most recent RfD values are adopted and used in the current risk assessment to characterize risks associated with acute and longer-term exposures. Several other RfD or equivalent toxicity values have been derived previously by the U.S. EPA, The Agency for Toxic Substances and Disease Registry (ATSDR), and the World Health Organization (WHO 1998). These alternate values are considered in the current risk assessment primarily in terms of defining dose-severity relationships.

As discussed in the exposure assessment, this risk assessment considers concurrent exposure to malathion and malaoxon on contaminated vegetation, by adopting the U.S. EPA conversion factor of 61—i.e., malaoxon is considered to be 61 times more toxic than malathion. Unlike the acute and chronic RfD values, which are based on relatively short-term exposure, the conversion factor is based on data from two dietary studies involving chronic exposure of adult rats to either malathion or malaoxon.

The dose-severity relationships for acute exposure to malathion are of considerable importance because several of the acute hazard quotients discussed in the risk characterization exceed 1 by a substantial margin. The hazard quotients of greatest concern are those involving acute accidental exposure of workers or members of the general public to ULV formulations of malathion. For adults, there is minimal concern with hazard quotients of up to about 6. Based on a controlled human study, it is not clear that hazard quotients of up to about 110, corresponding to doses of 15 mg/kg bw, would be associated with overt signs of toxicity. It is not possible to clearly characterize the consequences of exposure to malathion levels greater than 15 mg/kg bw but less than about 56 mg/kg bw. Animal studies suggest that acute doses of up to 20 mg/kg bw might not be associated with severe adverse effects; however, their usefulness in characterizing human exposure is questionable. Moreover, the 20 mg/kg bw dose is quite close to the lowest reported lethal dose in humans—i.e., 56 mg/kg bw. Although individuals have survived doses of up to 1400 mg/kg bw, survival depended on prompt and effective medical intervention. Within the context of the current Forest Service risk assessment, doses greater than or equal to 56 mg/kg bw are regarded as potentially but not necessarily lethal.

3.3.2. Acute RfD

Forest Service risk assessments generally adopt oral RfD values derived by the U.S. EPA, unless there is a compelling basis for doing otherwise. Many RfD values derived by the U.S. EPA are based on an experimental NOAEL divided by an uncertainty factor. In Forest Service pesticide risk assessments, the same approach is taken for most toxicity values adopted from the U.S. EPA. For malathion, the U.S. EPA takes a different approach involving benchmark dose analysis (U.S. EPA/ORD 2000). As discussed in SERA (2007a, Section 3.3.4), benchmark dose

analysis involves fitting dose-response data to a mathematical model and estimating the lower bound of a dose associated with a fixed response rate (most often a 10% response rate that is designated as an ED_{10}). This value is abbreviated as the $BMDL_{10}$ and replaces the NOAEL. In the nomenclature of the benchmark dose method, this surrogate NOAEL is called a *point of departure*.

As discussed in Section 3.1.6 (Effects on Nervous System), the acute RfD is based on the gavage study by Fulcher (2001) in which adult and neonatal rats were given single gavage doses 0, 5, 50, 150, or 450 mg/kg bw. Based on measurements of the inhibition of red blood cell ChE, neonatal rats were more sensitive than adults to malathion. The $BMDL_{10}$ values in adult males and females were 110 and 93.7 mg/kg bw, respectively, and the corresponding values in male and female neonates were 13.6 and 14.1 mg/kg bw, respectively.

Rather than deriving separate RfD values for adults and children, the U.S. EPA elected to derive only a single acute RfD to be applied to all individuals and selected the lowest $BMDL_{10}$ value—i.e., 13.6 mg/kg bw—as the point of departure. This $BMDL_{10}$ is divided by an uncertainty factor of 100 to account for uncertainties in species-to-species extrapolation as well as sensitive individuals within the population. Because the $BMDL_{10}$ is based on responses in neonates, the FQPA (Food Quality Protection Act) uncertainty factor to account for the potentially greater sensitivity of children to pesticides is 1—i.e., no additional uncertainty factor is applied. The resulting value, 0.136 mg/kg bw, is rounded to two significant places to derive the acute RfD of 0.14 mg/kg bw (U.S. EPA/OPP 2006a,c). The acute RfD is used in this risk assessment for all acute exposure scenarios.

As discussed in Section 3.1.7.4, after considering the substantial body of literature on the immunotoxicity of malathion, including studies that demonstrate effects on the immune system at sub-neurotoxic doses, the U.S. EPA/OPP (2006a,c) and ATSDR (2003) concluded that the toxicological significance of these changes is not well understood and elected to quantify risk based on neurotoxicity. The current risk assessment defers to this position, but not without reservation.

EPA's decision to derive only one RfD for malathion rather than deriving separate acute RfDs for children and adults, which is not defended in their human health risk assessment documents (U.S. EPA/OPP 2006a,c), is considered further in the dose-severity assessment (Section 3.3.5).

3.3.3. Chronic RfD

The most recent chronic RfD derived by the U.S. EPA is 0.07 mg/kg bw/day, only a factor of 2 below the acute RfD of 0.14 mg/kg bw (U.S. EPA/OPP 2006a,c). As discussed in Section 3.1.3, since malathion is not likely to accumulate in mammals after long-term exposure, the proximity of the chronic RfD to the acute RfD is reasonable.

The chronic RfD derived by the U.S. EPA/OPP (2006a,c) is based on the same study used for the acute RfD, the Fulcher (2001). Along with the single dose series on which the acute RfD is based, Fulcher (2001) also administered gavage doses of 0, 50, or 150 mg/kg bw/day for 11 days to adult and neonatal rats. Based on measurements of the inhibition of red blood cell ChE, the

$BMDL_{10}$ values in adult males and females were 16.3 and 15.7 mg/kg bw/day, respectively, and the corresponding values in male and female neonates were 7.1 and 8.5 mg/kg bw/day, respectively (U.S. EPA/OPP 2006c, Table 4.1.3.1, p. 39). As in the single dose component of this study, neonates were more sensitive than adults—i.e., by a factor of 2.1 in males and 1.7 in females. These differences, while statistically significant, are substantially less than the 8.7 difference in sensitivity between female adults and female neonates observed in the single dose component of the Fulcher (2001)study. As with the acute RfD, the U.S. EPA took the lowest $BMDL_{10}$ —i.e., 7.1 mg/kg bw/day in males pups—and applied an uncertainty factor of 100 to derive the chronic RfD of 0.07 mg/kg bw/day.

Not surprisingly, the U.S. EPA's Integrated Risk Information System (IRIS) lists a chronic RfD of 0.02 mg/kg bw/day for malathion (U.S. EPA/ORD 2002). IRIS RfDs are derived by the U.S. EPA's National Center for Environmental Assessment (NCEA), which is part of the Agency's Offices of Research and Development. Although these RfDs are intended to represent Agency-wide values, it is not uncommon for the Office of Pesticide Programs (OPP) to derive alternative RfDs. The IRIS RfD is based on the human study by Moeller and Rider (1962). As noted in Section 3.1.5, Moeller and Rider (1962) conducted a controlled human study in which doses of 8 mg/day for 32 days (0.11 mg/kg/day) had no effect on cholinesterase activity; doses of 16 mg/day (average daily doses of 0.22 mg/kg/day) for 47days were associated with decreased plasma ChE activity; and doses of 24 mg/day (average daily dose of 0.34 mg/kg/day) for 56 days were associated with both decreased plasma ChE and RBC AChE activity. The RfD of 0.02 mg/kg bw/day is based on the NOAEL of 0.22 mg/kg/day to which is applied an uncertainty factor of 10 to address potentially sensitive subgroups.

The Agency for Toxic Substances and Disease Registry (ATSDR) derived an MRL (minimum risk level) for malathion of 0.02 mg/kg/day based on the NOAEL of 0.22 mg/kg bw/day from the Moeller and Rider (1962) study. MRLs derived by ATSDR are intended to be functionally equivalent to RfDs derived by the U.S. EPA in that the MRL is intended to represent a dose at which no adverse effects are anticipated.

An RfD of 0.02 mg/kg bw/day also was derived by the U.S. EPA/OPP in a preliminary risk assessment on malathion (2000a). This RfD, however, was based on a 2-year feeding study in rats (Daly 1996a) in which the dietary NOAEL was 100/50 ppm (100 ppm for the first 3 months and 50 ppm for the remainder of the study). Based on measured food consumption, the dietary NOAEL corresponds to an average dose of 2.37 mg/kg/day for males and 2.95 mg/kg/day for females. The U.S. EPA/OPP (2000a) selected the lower dose for males, and, as noted above, applied an uncertainty factor of 100 to derive the RfD of 0.024 mg/kg/day.

Finally, the World Health Organization (WHO 1998) derived an Acceptable Daily Intake (ADI) of 0.3 mg/kg bw/day. Like the MRL, the ADI is intended to be functionally equivalent to the RfD in that no adverse effects are anticipated at that dose level. The WHO ADI is based on a NOAEL of 29 mg/kg bw/day (500 ppm in the diet) from an early 2-year rat feeding study (NCI 1979a) using an uncertainty factor of 100. The resulting value of 0.29 mg/kg bw/day is rounded to one significant place to derive the ADI of 0.3 mg/kg bw/day. As noted by WHO (1998) this

ADI is supported by reproductive NOAEL values in the range of 25 mg/kg bw/day. In addition, the ADI of 0.3 mg/kg bw/day is quite close to the dose of 0.22 mg/kg bw/day associated only with decreased plasma ChE activity in humans (Moeller and Rider 1962).

The current Forest Service risk assessment adopts the most recent RfD of 0.07 mg/kg bw/day derived by U.S. EPA/OPP (2006a,c). Nonetheless, the other risk assessment values ranging from 0.02 to 0.3 mg/kg bw/day and the studies on which they are based, as discussed above, are considered further in the dose-severity assessment (Section 3.3.5).

3.3.4. Malaoxon Toxic Equivalency Factor

As discussed in Section 3.2.3.1.1 (Malaoxon Exposures) this Forest Service risk assessment adopts the toxicity adjustment factor of 61used by the U.S. EPA/OPP (2006a,c) for converting malaoxon exposures to equivalent malathion exposures, as it pertains to longer-term exposure scenarios involving the consumption of malathion and malaoxon on contaminated vegetation.

As detailed in U.S. EPA/OPP (2006c, pp. 52-53), the toxicity adjustment factor is based on a joint analysis by the Office of Pesticides and the EPA's National Center for Computational Toxicology (U.S. EPA/OPP 2005g) of data from two chronic feeding studies involving the inhibition of red blood cell ChE in rats exposed to malathion (Daly 1996a) and malaoxon (Daly 1996b). Initial analyses of the dose-response relationship for RBC ChE inhibition in rats yielded BMD_{10} values for malathion of 48.09 mg/kg/day (males) and 32.37 mg/kg/day (females). The corresponding values for malaoxon were 0.63 mg/kg/day and 0.52 mg/kg/day. Using the data for male rats, the EPA initially derived a toxic equivalency factor of 77 (U.S. EPA/OPP 2005g, Table 2)—i.e., 48.09 mg malathion/kg/day divided by 0.63 mg malaoxon/kg/day = 76.33 malathion/malaoxon. In other words, a unit exposure to malaoxon is equivalent to 77 unit exposures of malathion. In preparation of the final human health risk assessment in support of the EPA's RED (U.S. EPA 2006c), the data were reanalyzed and the toxicity factor was adjusted downward to 61 based on data in female rats—i.e., 47.8 mg malathion/kg/day divided by 0.78 mg malaoxon/kg/day = 61.28 (U.S. EPA 2006c, p. 53, Table 4.4.7).

There are numerous studies on malathion and malaoxon from which alternate values might be derived. For example, the California Department of Health Services recommends using an adjustment factor of 10, based on differences in acute lethality, for converting malaoxon exposure levels to equivalent concentrations of malathion (CDHS 1991, p. Table 8-2, p. 8-9). The current Forest Service risk assessment, however, defers to the most recent evaluation by the U.S. EPA/OPP (2006a,c) and uses the factor of 61 to convert anticipated exposures to malaoxon to malathion equivalents, as discussed in Section 3.2.3.1.1.

3.3.5. Dose-Severity Considerations

As detailed further in Section 3.4 (Risk Characterization), several of the exposure levels for workers and members of the general public exceed the RfD substantially. In most cases, those high exposure levels involve acute accidental exposure to ULV formulations. As discussed in Section 3.2, ULV formulations are much more concentrated than field solutions of EC formulations, and this leads to substantially higher dose estimates for accidents associated with

spills of ULV formulations on to the skin or into surface water. Consequently, dose-severity relationships for acute exposure must be elaborated. For longer-term non-accidental exposures, the excursions above the RfD are modest (i.e., about a factor of 3), and the need to elaborate on dose-severity relationships is minimal.

Table 13 summarizes studies useful for identifying plausible dose-severity relationships for humans after acute exposure to malathion. The summarized information includes the available RfDs for malathion and the studies on which they are based, the controlled human exposure study by Gillies and Dickson (2000), reports of human poisoning summarized by Hayes (1982) and Farago (1967), estimates of human LD_{50} values from Talcott et al. (1979c), as well as some acute toxicity data in rats.

Table 13 is organized into four columns: dose, corresponding hazard quotient, verbal description of the effect, and the reference. All hazard quotients are based on the acute RfD of 0.14 mg/kg bw derived by U.S. EPA/OPP (2005a,c). While this value is not a human dose in the sense that it has or can be verified experimentally, this acute RfD is interpreted as a dose at or below which no adverse effects would be expected in the most sensitive humans.

As discussed in Section 3.3.2, the U.S. EPA elected to derive a single acute RfD of 0.14 mg/kg bw based on a $BMDL_{10}$ of 13.6 mg/kg bw in rat pups from the gavage study by Fulcher (2001). While this value is and should be used for all exposures involving children, a case could be made that the $BMDL_{10}$ of 93.7 mg/kg bw in adult rats could be used to develop an acute RfD of about 0.9 mg/kg bw applicable to exposure scenarios involving workers and other adults. This RfD is bracketed by the RfD of 0.3 mg/kg bw recommended by WHO (1998) and the single dose NOAEL of 15 mg/kg bw in adults reported by Gillies and Dickson (2000). Moeller and Rider (1962) noted significant inhibition of RBC AChE activity in humans after oral doses of 0.34 mg/kg bw/day; however, the effect occurred over a 56-day period of exposure and did not involve any overt signs of toxicity. Based on these data, there would seem to be minimal concern for hazard quotients up to about 6 in adults. Moreover, based on the Gillies and Dickson (2000) study, it is not clear that hazard quotients of up to about 110—i.e., doses of 15 mg/kg bw—would be associated with overt signs of toxicity.

There is a major gap, however, in the ability to assess likely effects at doses greater than 15 mg/kg bw but less than 56 mg/kg bw, corresponding to hazard quotients of 110-400. As noted more than 40 years ago by Hayes (1982): *The dosage that would lead to mild illness* [in humans] *has not been defined.* This statement is still true.

The U.S. EPA/OPP (2006c, Table 4.1.3.2b) outlined dose-severity relationships in experimental mammals; however, most of these relationships involve repeated/longer-term dosing. In addition, the use of these data to assess likely responses in humans is highly uncertain. The U.S. EPA does cite an acute gavage LOAEL of 2000 mg/kg bw in rats associated with decreased motor activity. Using an uncertainty factor of 100, this might be associated with an equivalent human dose of 20 mg/kg bw.

While the dose of 20 mg/kg bw fits into the available dose-severity data summarized in Table 13, it is, nevertheless, very close to the lowest reported lethal dose in humans of 56 mg/kg bw (Hayes 1982). Thus, the dose of 20 mg/kg bw is included in Table 13 with reservation and is not used in Section 3.4 to elaborate on the risk characterization.

Doses at or above 56 mg/kg bw are clearly of grave concern, notwithstanding evidence that individuals have survived doses of up to 1400 mg/kg bw (Hayes 1982) and the estimated human LD_{50} value of 3655 mg/kg bw (Talcott et al. 1979c). As discussed by both Hayes (1982) and Talcott et al. (1977c), however, survival after the consumption of high doses of malathion is depended on prompt and effective medical intervention. An additional problem in interpreting much of the data summarized in reports of effects at the higher doses given in Table 13 is that most of these studies involve suicide attempts and the estimates of the ingested doses may not be precise.

Within the context of the current Forest Service risk assessment, the potential consequences of human doses that range from greater than 15 mg/kg to less than 56 mg/kg bw and correspond to hazard quotients of greater than 110 but less than 400, are regarded as indeterminate. Doses of 56 mg/kg bw and higher are regarded as potentially but not necessarily lethal.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

Although malathion is more toxic to insects than to mammals, including humans, malathion effectively inhibits enzyme activity essential to the functioning of the human nervous system—i.e., AChE activity. Consequently exposure to malathion is potentially hazardous to workers as well as members of the general public.

Virtually all accidental exposure scenarios for workers and members of the general public lead to hazard quotients that are above the level of concern. Accidental exposure scenarios for ULV formulations lead to much higher hazard quotients than corresponding scenarios for EC formulations. The difference has to do with the much higher concentration of malathion in ULV formulations—i.e., 1230 mg/mL—relative to the concentration of malathion in field solutions of EC formulations—i.e., ranging from 0.36 to 36 mg/mL. For EC formulations, the maximum hazard quotient of 22 for workers is not expected to result in overt signs of toxicity. The most severe accidental worker exposure scenario for ULV formulations (i.e., wearing contaminated gloves for 1 hour) is associated with a hazard quotient of 161 with a range from 104 to 250. The central estimate and the upper bound are both in the range in which consequences of exposure cannot be well characterized. For members of the general public, the highest hazard quotients are associated with an accidental spill into a small pond from which water is consumed by a small child. This exposure scenario leads to hazard quotients of up to 1150 for ULV formulations and 110 for EC formulations. The accidental spill of malathion into surface water should be regarded as an emergency, and vigorous actions should be taken to limit the exposure of members of the general public, particularly children.

Non-accidental exposure scenarios lead to substantially lower hazard quotients. For ULV formulations, none of the hazard quotients for workers exceeds a level of concern. For EC formulations, the highest non-accidental hazard quotients for workers is 3. Based on dose-severity considerations, there is no apparent basis for asserting that these exposure levels would cause overt signs of toxicity. For members of the general public, many of the hazard quotients associated with acute non-accidental exposures are greater in magnitude than those for workers. The greatest hazards are associated with the consumption of contaminated vegetation (HQ values up to 14). For longer-term exposures, the hazard quotients are lower, and the level of concern—i.e., an HQ greater than 1—is exceeded only for those exposures associated with the consumption of contaminated vegetation in which the upper bound of the hazard quotient is 3 for insect control in pine seed orchards and 7 for mosquito control. Hazard quotients for longer-term exposures associated with the contamination of surface water are substantially below the level of concern.

3.4.2. Workers

The quantitative risk characterization for workers exposed to malathion is summarized in Attachment 1 for ULV applications to control mosquitoes and in Attachment 2 for EC applications to control insect pests in pine seed orchards. For mosquito control (Attachment 1), risk characterization summary worksheets are provided for the range of application rates

considered in this risk assessment—i.e., 0.11 to 0.23 lb a.i./acre with a typical application rate of 0.15 lb a.i./acre. For the control of insect pests in pine seed orchards (Attachment 2), risk characterization summary worksheets are based on a typical application rate of 0.3 lb a.i./acre with a range from 0.1 lb to 1.5 lb a.i./acre. The risk characterization worksheets in Attachments 1 and 2 comprise the E02 Series: E02a (typical application rate), E02b (lowest anticipated application rate) and E02c (highest anticipated application rate).

The risk quotients associated with accidental exposures to the EC and ULV formulations of malathion—i.e., wearing contaminated gloves or spilling a malathion solution on the hands or lower legs—lead to hazard quotients that are higher, and in most cases, substantially higher than those associated with exposure levels anticipated for routine applications. The difference is particularly manifest in the exposure scenario that involves wearing contaminated gloves in the application of ULV formulations. As discussed in Section 3.2.2.2, the exposure scenarios for ULV formulations are based on the assumption of zero-order absorption of a solution—i.e., the formulation—in which the concentration of malathion is1230 mg/mL, compared with field solutions of EC formulations in which the maximum concentration of malathion is 36 mg/mL. For ULV formulations, the upper bound of the hazard quotient (HQ) for wearing contaminated gloves for 1 hour is more than 10-fold greater than the corresponding hazard quotient for wearing gloves contaminated with EC formulations – i.e., 250 compared to 22. While a greater than 30-fold difference would be expected based solely on the concentration of malathion [1230 mg/mL divided by 36 mg/mL = 34.2], the difference in concentrations is partially offset by the use of higher dermal absorption rates for EC formulations, relative to ULV formulations (Section 3.1.3.2). The worker exposure levels associated with accidental spills onto the hands or lower legs are much less than those associated with wearing contaminated gloves. The spill scenarios are based on the assumption of first-order rather than zero-order absorption and are less severe in that they do not involve exposure to essentially saturated or constant solutions of malathion. For EC formulations, the upper bound of the hazard quotient exceeds the level of concern only at the highest application rate (an upper bound HQ of 6 for a 1-hour exposure involving an accidental spill onto the lower legs). For ULV formulations, the hazard quotients for the accidental spill scenario exceed the level of concern (i.e., an HQ of 1) across the range of application rates, even at the lower bounds.

For EC formulations, the maximum hazard quotient of 22 would not necessarily result in overt signs of toxicity. As discussed in Section 3.3.5 (Dose-Severity Considerations) and summarized in Table 13, single doses of up to 15 mg/kg bw/day in humans under controlled conditions (corresponding to an HQ value of 110) are reported to inhibit plasma ChE in the absence of any overt signs of toxicity. The most severe accidental exposure scenario for ULV formulations (i.e., wearing contaminated gloves for 1 hour) is associated with a hazard quotient of 161 with a range from 104 to 250. Both the central estimate and the upper bound are in the range in which consequences of exposure cannot be well characterized.

The hazard quotients for general exposures are much lower for workers, compared with those for accidental exposures. As discussed in Section 3.2.2.1, the term *general exposures* refers to the levels of exposure during the normal application of malathion. All of these exposure scenarios

for general application are directly related to the amount of malathion handled by a worker, which is in turn directly related to the application rate and the number of acres that a worker will treat. For ULV formulations (i.e., a maximum application rate of 0.23 lb a.i./acre), none of the hazard quotients exceed a level of concern. The upper bound of the hazard quotient at the highest application rate is 0.5, below the level of concern (HQ=1) by a factor of 2. For EC formulations (i.e., a maximum application rate of 1.5 lb a.i./acre), the upper bounds of the hazard quotient for the highest application rate range from 1.7 to 3. As discussed in Section 3.3 (Dose-Response Assessment), these hazard quotients are based on the most recent chronic RfD for malathion, 0.07 mg/kg bw/day, which is based on responses in rat pups in an effort to account for the increased sensitivity of children to malathion. Since children will not be applying malathion, it is reasonable to consider the ADI (acceptable daily intake) of 0.3 mg/kg bw/day from WHO (1998) in assessing the consequences of worker exposures. A dose of 0.3 mg/kg bw/day corresponds to a hazard quotient of about 4 using the chronic RfD of 0.07 mg/kg bw/day, which is based on anticipated responses in children. Thus, while the hazard quotients ranging from 1.7 to 3 for EC formulations should be regarded with concern, there is no basis for asserting that overt signs of toxicity would be associated with these exposures.

3.4.3. General Public

The quantitative risk characterizations for members of the general public exposed to malathion are summarized in EXCEL workbooks: Attachment 1 for mosquito control and Attachment 2 for the control of insects in pine seed orchards. Like the risk characterization for workers, the risk characterization for members of the general public exposed to malathion is based on a relatively standard set of exposure scenarios used in all Forest Service risk assessments. Risk characterization summary worksheets (i.e., the E02 Series) are provided for the range of application rates, for both mosquito control (Attachment 1) and insect control in pine seed orchards (Attachment 2), considered in this risk assessment—E02a (typical application rate), E02b (lowest anticipated application rate), and E02c (highest anticipated application rate). Also as with workers, the risk quotients are based on the acute RfD of 0.14 mg/kg bw for acute exposure scenarios and the chronic RfD of 0.07 mg/kg bw/day for longer-term exposure scenarios.

As discussed in Section 3.2.3.1.2. (Likelihood and Magnitude of Exposure), all upper bound exposure assessments used for members of the general public are based on the Most Exposed Individual (MEI). This extreme value approach to risk characterization is critically important to the interpretation of hazard quotients for members of the general public. Equally important is the difference between accidental exposure levels—e.g., resulting from the accidental direct spray of a child or woman or an accidental spill of malathion into a small pond—and the exposure levels anticipated in the normal course of malathion applications in Forest Service programs—i.e., the consumption of contaminated vegetation and surface water.

3.4.3.1. Accidental Exposures

Accidental exposure scenarios involve the direct spray of an individual (a child or a woman) or an accidental spill into a small pond resulting in the consumption of contaminated water by a child or the consumption of fish by an adult. For these accidental exposure scenarios, there is a

marked difference between the risk characterization for ULV and EC formulations. As with the risk characterization for accidental exposures in workers (Section 3.4.2), these differences are related primarily to the much greater malathion concentration in ULV formulations—i.e., 1230 mg/mL – relative to malathion concentrations in field solutions of EC formulations—i.e., 0.36-36 mg/mL.

For ULV formulations, the risk characterization for accidental exposures involving members of the general public is relatively simple. Across the range of application rates used in mosquito control and across the range of assumptions used in defining the extreme value exposures, almost all accidental exposure scenarios result in hazard quotients that exceed the level of concern by a substantial margin. At the lowest application rate—i.e., 0.11 lb a.i./acre—the hazard quotients associated with the accidental spill of malathion into a pond range from about 50 to 500. At the highest application rate (0.23 lb a.i./acre), the corresponding hazard quotients range from about 100 to greater than 1000. The application rates cover a relatively narrow range, only about a factor of two. The greatest variability in the hazard quotients is driven by the differences among the exposure scenarios.

The highest hazard quotients are associated with a child's consumption of contaminated water from a small pond after an accidental spill of malathion. For ULV formulations, the lowest hazard quotient is 224 (i.e., the lower bound at the lowest application rate) and the highest hazard quotient is 1150 (i.e., the upper bound at the highest application rate). As discussed in Section 3.3.5 (Dose-Severity Considerations), there is some basis for asserting that hazard quotients for adults of up to 110 might not be associated with overt signs of toxicity. This assertion, however, cannot be made for exposures involving children. For this exposure scenario, overt signs of toxicity and perhaps very severe signs of toxicity cannot be ruled out. For EC formulations, the scenario for the accidental spill of a field solution into a small pond is less severe but still a matter of concern—i.e., the upper bound of the hazard quotient is 7 at the lowest application rate and 110 at the highest application rate.

The accidental spill scenario is intentionally extreme—i.e., 200 gallons of a field solution or undiluted ULV formulation are spilled into a small (1 acre, 1 meter deep) pond and a child consumes a day's worth of water immediately after the spill. While this scenario may be implausible, it is included in all Forest Service risk assessments as a worst-case scenario to guide individuals in responding to accidental spill events. For many pesticides that have a low order of toxicity, such as herbicides, these extreme spill scenarios lead to the highest levels of exposure but not necessarily to alarming hazard quotients. For malathion, the interpretation of the accidental spill scenarios is substantially different. The accidental spill of malathion into surface water should be regarded as an emergency, and vigorous actions should be taken to limit the exposure of members of the general public, particularly children.

The other set of accidental exposure scenarios involves the direct spray of a small child or a young woman. The direct spray scenario for a young child is particularly extreme in that the assumption is made that the entire skin surface of the child is sprayed with a field solution. Again, these exposure scenarios are intended to be extreme and are included in all Forest Service

risk assessments. For malathion, the exposure scenario for a small child leads to upper bound hazard quotients of 142-297 for ULV formulations and 6-85 for EC formulations across the range of application rates. While these hazard quotients are less than those associated with the pond spill scenario, they are nonetheless serious and would justify extreme measures to limit the absorption of malathion by the child and ensure that it receives prompt and effective medical attention.

For the exposure scenarios involving the accidental direct spray of a young woman, the upper bound hazard quotients range from 14 to 30 for ULV formulations and from 0.6 to 8 for EC formulations. All of these hazard quotients involve doses of about 4.2 mg/kg bw. Based on the studies in humans by Moeller and Rider (1962) and Gillies and Dickson (2000), the inhibition of plasma ChE is a likely effect of exposure; however, there is no basis for asserting that overt signs of toxicity would result.

3.4.3.2. Acute Non-accidental Exposures

Non-accidental acute exposure scenarios for members of the general public involve dermal contact with contaminated vegetation, the consumption of contaminated vegetation immediately after treatment, and the consumption of estimated peak concentrations of malathion in surface water. The latter could occur shortly after application or at some later time depending on rainfall patterns.

For both mosquito control and insect control in pine seed orchards, none of the non-accidental exposure scenarios involving dermal contact with contaminated vegetation or the consumption of surface water exceed the level of concern (HQ=1). The highest hazard quotient for these exposure scenarios is the upper bound hazard quotient of 0.4 for dermal contact with vegetation contaminated by EC formulations at the highest application rate (1.5 lb a.i./acre).

The consumption of contaminated vegetation, however, does lead to hazard quotients that exceed the level of concern in both applications for mosquito control and insect control in pine seed orchards. The doses associated with this scenario depend on both the number and rate of the applications. The number of applications is important because for the most exposed individual, exposure will occur on the day of the last application. Nonetheless, the maximum hazard quotient is 4 for ULV applications (mosquito control) at the highest application rate—i.e., 8 applications of 0.23 lb a.i./acre—and 14 for EC applications (insect control in pine seed orchards) — i.e., one application at a rate of 1.5 lb a.i./acre. As discussed in Section 3.2.1, insect control in pine seed orchards might involve multiple applications; however, the applications are not likely be conducted at the maximum application rate. Nonetheless, multiple applications at applications rates greater than 0.23 lb a.i./acre should be specifically addressed within the Forest Service at the project level.

As discussed in Section 3.3.5 (Dose-Severity Considerations), hazard quotients of up to about 6 may not cause adverse effects. If the U.S. EPA had elected to derive separate RfD values for adults and children, the adult RfD would be about 0.9 mg/kg bw, corresponding to a hazard quotient of 6.4, based on current acute RfD of 0.14 mg/kg bw. This range of hazard quotients

would cover all of the exposure levels from the consumption of contaminated vegetation except for the highest application rate for insect control in pine seed orchards. At this highest rate, the hazard quotient of 14 is associated with a dose of about 2 mg/kg bw, which is less than the dose of 2.4 mg/kg bw associated with decreased plasma ChE and RBC AChE but no overt signs of toxicity in the Moeller and Rider (1962) study.

3.4.3.3. Longer-term Exposures

The longer-term exposure scenarios for malathion lead to hazard quotients that are substantially lower than those associated with acute exposures. Except for the consumption of contaminated vegetation, none of the longer-term hazard quotients exceeds the level of concern (HQ=1), even at the highest anticipated application rates for mosquito control and insect control in pine seed orchards.

For the longer-term consumption of contaminated vegetation, the upper bound of the hazard quotient at the highest application rate is about 3 for insect control in pine seed orchards and 7 for mosquito control. These hazard quotients are associated with doses ranging from about 0.2 mg/kg bw/day (insect control in pine seed orchards) to 0.5 mg/kg bw/day (mosquito control). The lower end of this range is less than the ADI of 0.3 mg/kg bw/day derived by WHO (1998), and there is little basis for asserting that overt adverse effects are plausible. The consequence of longer-term exposure to the somewhat higher dose of 0.5 mg/kg bw/day is less clear. This dose is somewhat higher than the dose of 0.34 mg/kg bw/day for 54 days was associated with a decrease in plasma ChE and red blood cell AChE inhibition from the study by Moeller and Rider (1962). Whether this exposure would result in overt signs of toxicity cannot be determined.

If broadcast applications of malathion are made in areas where members of the general public might consume contaminated vegetation over a prolonged period of time, the upper bound estimates of exposure would be considered unacceptable. The contamination of ambient water is not a concern in longer-term exposures.

3.4.4. Sensitive Subgroups

Individuals with liver disease may have abnormally low levels of endogenous liver carboxylesterases (Talcott et al. 1979b). Because these esterases are involved in the metabolism of malathion to compounds that are more hydrophobic and thus more rapidly excreted than malathion, individuals with liver disease may be more sensitive than individuals with normal malathion carboxylesterase activity to malathion exposure.

Other individuals, about 3% of the population, have abnormally low levels of plasma ChE. These individuals are more sensitive than members of the general population to organophosphate insecticides. Low plasma ChE also can occur in individuals with severe liver diseases, malnutrition, alcoholism, and dermatomyositis (Abou-Donia 1995). Infants less than 6 months old also have lower AChE values, compared with adults (Maroni et al. 2000). Immature rats may be more sensitive to malathion because of a lesser rate of detoxification (Brodeur and DuBois 1967; Padilla et al. 2004; Vidair 2004; Yang et al. 2002). Mortensen et al. (1998), while investigating the potentially greater sensitivity of young animals to AChE inhibitors, found that

the affinity of AChE inhibitors (including malaoxon) for AChE is no greater in young than in old animals. As discussed in Section 3.3.3, the dose response assessment for malathion does consider the increased sensitivity of children to malathion.

In addition to the very young, the elderly may also be a sensitive subgroup. Based on studies on the toxicity of malaoxon in old and young rats, Hirvonen et al. (1993) found that older animals are more sensitive than younger animals to malaoxon. This finding is also suggested in the study by Hayes (1982) in which the fate of an elderly man is associated with the lowest lethal dose of malathion in humans.

Decreased brain AChE was noted in some patients with Alzheimer's disease (Iyo et al. 1997). It is not likely, however, that Alzheimer's victims are at increased risk from exposure to malathion or other AChE inhibitors. To the contrary, AChE inhibitors are being considered as a therapy for Alzheimer's disease because AChE inhibition increases the concentration of acetylcholine at the synapse (Shadlen and Larson 1999). Individuals with liver, kidney, or heart disease as well as individuals with cancer may have abnormally low levels of plasma ChE (Nigg and Knaak 2000).

Animals on low-protein diets tend to have a number of changes in liver function that could impact susceptibility to compounds that are either activated or detoxified in the liver. Based on acute and subacute oral exposures in rats, Bulusu and Chakravarty (1984, 1986) found some evidence that low protein diets may increase the sensitivity of mammals to malathion. In rats, the effects on dietary fat appear to be mixed, with greater sensitivity in terms of RBC AChE inhibition in rats on high (45%) and fat free diets compared with rats on normal fat (4.5%) diets (Davidson 1973).

Ghosh et al. (1999) investigated an outbreak of Reye's Syndrome that occurred in northern India in 1997. This event occurred in an area where malathion fogging had been used for mosquito control. The authors assert that:

> *Measles and varicella zoster emerged as the probable etiologies for the viral prodrome precipitating these cases of Reye's syndrome. Aspirin might have a contributory role. Malathion is another putative cofactor.* – Ghosh et al. (1999), p. 1097.

Ghosh et al. (1999) specifically detail the viral outbreaks that preceded Reye's syndrome and provide data on salicylate residues in some of the victims as well as some anecdotal information suggesting that aspirin may have been given to some of the victims. In contrast, there are no data and no discussion to support any causal association in the development of Reye's syndrome and malathion exposure. The association of Reye's syndrome with viral infections and the administration of aspirin to young children is well documented (e.g., Belay et al. 1999; Sullivan et al. 2000). Other than the assertions in Ghosh et al. (1999), no reports of associations between malathion and Reye's syndrome and no reports of associations between other organophosphates or other AChE inhibitors and Reye's syndrome were located in supplemental searches of the literature using MEDLINE. Consequently, although the assertion that malathion was ...*another*

putative cofactor... cannot be contradicted, it appears to be an unsubstantiated speculation. The hazard of such speculation is concisely articulated by Nigg and Knaak (2000):

... The real harm of attributing diseases of truly unknown cause to pesticides without adequate evidence is that the search for the true cause may be abandoned. It would have been a pity, for example, if the study of the viral origin of poliomyelitis had been abandoned because one person thought the disease was caused by DDT. – Nigg and Knaak 2000, p. 79.

3.4.5. Connected Actions

The U.S. EPA does not specifically address connected actions in their human health risk assessment of malathion (U.S. EPA/OPP 2005a,c). This is a very typical situation because pesticides are registered by the U.S. EPA under FIFRA (Federal Insecticide, Fungicide and Rodenticide Act) and considerations of connected actions are required under NEPA (National Environmental Policy Act).

The Council on Environmental Quality (CEQ), which provides the framework for implementing NEPA, defines connected actions (40 CFR 1508.25) as actions which occur in close association with the action of concern; in this case, the use of malathion as proposed in Section 2. Actions are considered to be connected if they: (i) automatically trigger other actions which may require environmental impact statements; (ii) cannot or will not proceed unless other actions are taken previously or simultaneously, and (iii) are interdependent parts of a larger action and depend on the larger action for their justification. Within the context of this assessment of malathion, "connected actions" include actions or the use of other chemicals which are necessary and occur *in close association* with use of malathion.

As discussed in Section 3.3.4, applications of malathion will involve concurrent exposure to malaoxon on contaminated vegetation, and this circumstance of exposure is considered explicitly in the exposure assessment, dose-response assessment, and risk characterization. The use of inerts and adjuvants as well as the occurrence of impurities and metabolites would be classified as connected actions under the CEQ definition. As discussed in detail in Section 3.1.14 (Inerts and Adjuvants), the malathion formulations covered in this risk assessment do not contain inerts that are classified as hazardous. However, as discussed in Section 3.1.3.1, the inerts used in emulsifiable concentrate formulations of malathion may enhance the absorption of malathion and thus increase potential risk. This enhancement in absorption is considered quantitatively in all dermal exposure assessments involving emulsifiable concentrate formulations.

3.4.6. Cumulative Effects

Cumulative effects may involve either repeated exposures to an individual agent or simultaneous exposures to the agent of concern (in this case malathion) and other agents that may cause the same effect or effects by the same or a similar mode of action.

Cumulative effects, within the context of the Food Quality Protection Act (FQPA), are addressed by the U.S. EPA (U.S. EPA/OPP 2005a):

> *Malathion is a member of the OP class of pesticides, which share a common mechanism of toxicity by affecting the nervous system via cholinesterase inhibition. A cumulative risk assessment, which evaluates exposures based on a common mechanism of toxicity, was conducted to evaluate the risk from food, drinking water, residential, and other non-occupational exposures resulting from registered uses of OP pesticides, including malathion. EPA has concluded that the cumulative risks associated with OP pesticides are below the Agency's level of concern.* (U.S. EPA/OPP 2005a, p. 62)

Within the context of Forest Service programs, the consideration of cumulative effects due to exposures to multiple chemicals should be assessed in the context of co-exposures to other carbamate insecticides and, more generally, to other insecticides that inhibit cholinesterase activity. These considerations should be should be assessed in the context of co-exposures to other organophosphate or carbamate insecticides at the program level and perhaps regional level. The general approach taken by the U.S. EPA is to assume that chemicals with common mechanisms of action will involve additive risks—i.e., the HQ values should be added for each chemical (Section 3.1.16).

In terms of repeated exposures, the current risk assessment specifically considers the effect of repeated applications of malathion and longer-term exposures to malathion for both workers and members of the general public. Consequently, the risk characterizations presented in this risk assessment for both acute and longer-term exposures specifically address and encompass the potential impact of the cumulative effects of malathion due to repeated use.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

The endpoints of concern in the ecological risk assessment are similar to those discussed in the human health risk assessment – i.e., AChE inhibition. Vertebrates including mammals, birds, reptiles, amphibians, and fish may be adversely affected by exposure to malathion because of its well-characterized neurotoxicity. Although standard toxicity studies may demonstrate other toxicological endpoints, neurotoxicity is the critical effect on which the ecological risk assessment is based.

The available information on the toxicity of malathion to experimental mammals is used to assess effects in nontarget terrestrial mammals for the ecological risk assessment. For mammals, there is no consistent relationship between body size and sensitivity to malathion. Perhaps, the variability of toxicity values within a given species (e.g., LD_{50} values for rats range from 390 to 2100 mg/kg bw) obscures any relationship between body size and sensitivity to malathion.

The toxicity of malathion to birds is characterized in acute (gavage), subacute dietary (5-day and 8-day exposures), and chronic/reproduction studies. The acute oral LD_{50} values for malathion are highly variable, generally ranging from about 167 mg/kg for ring-necked pheasants to 1485 mg/kg for mallard ducks. As with mammals, the available data do not suggest any systematic relationship between acute oral LD_{50} values and body weights in birds. Several field studies indicate that adverse effects were not detected in birds after malathion was applied at rates greater than or comparable to those anticipated in Forest Service programs. Several studies investigate the effects of injecting malathion directly into eggs containing developing bird embryos. Although the results these studies are a useful index of general toxic potency, the route of exposure is not relevant to environmental exposure and cannot be used in dose-response assessments.

There is very little data regarding the toxicity of malathion to reptiles. An approximate LD_{50} of 2324 mg/kg for the green anole, which is within the range of toxicity values determined for relatively tolerant vertebrates and birds, suggests, albeit tenuously, that the available toxicity data on birds and mammals may be representative of malathion toxicity to reptiles. A more recent study indicates that lizards exposed to 200 mg/kg bw malathion demonstrated enhanced sprint performance; yet the dose level caused 20% mortality.

The toxicity of malathion to honeybees and earthworms is relatively well characterized. Malathion is highly toxic to the honeybee with 48- to 96-hour direct spray LD_{50} values ranging from 0.2 to 0.71 µg/bee. These direct spray LD_{50} values correspond to exposure levels of 2.15-7.6 mg/kg bw, factors of about 25-100 below the LD_{50} of approximately 200 mg/kg bw in small mammals. A chronic feeding reports a the dietary NOAEL of 0.16 ppm for honeybees.

Contact LD_{50} values are reported for two species of earthworms: *Eisenia foetida* [13.5 (8.0-22.8) $\mu g/cm^2$] and *Lumbricus rubellus* [0.27 (0.14-0.50) $\mu g/cm^2$]. These studies may be used to estimate potential effects in earthworms after direct spray applications of malathion. In an extensive study investigating the effects of soil contamination on earthworms, the most sensitive species native to North America appears to be *Enchytraceus albidus*, with a 21-day NOEC of 4.74 ppm. Other data indicate that certain tropical earthworm species may be more sensitive than *Enchytraceus albidus* to the effects of malathion; however the data are based on exposure to emulsifiable concentrate formulations, and it is not clear whether the apparent increase in sensitivity is due to formulation differences or differences in species sensitivity.

The database regarding the toxicity of malathion to aquatic organisms is quite extensive. As with mammals, the toxicity values for both technical grade malathion and emulsifiable concentrate formulations are highly variable, which may reflect differences in the purity of the malathion used in the various studies. LC_{50} values in fish range from about 100 to 10,000 ppb. In studies that explicitly compare technical grade malathion and emulsifiable concentrate formulations, there is no apparent difference in toxicity when exposures are expressed as malathion equivalents. In general, larger fish appear to be somewhat less sensitive than smaller fish to malathion exposure.

Exposure to malathion inhibits AChE in aquatic animals, as it does in mammals and terrestrial invertebrates. Sublethal exposure levels may cause reproductive effects in fish, including a failure to spawn, pathological changes to the ovaries, and degenerative changes in the testis. Many of the sublethal effects, however, are reported to occur in the high ppb range—i.e., from 100 to greater than 1000 ppb. Amphibians appear to be similar to fish in their sensitivity to malathion, with 24- to 96-hour LC_{50} values ranging from about 200 to greater than 3000 ppb. Some aquatic invertebrates are far more sensitive than fish or amphibians to malathion exposure. For example, reported 48-hour LC_{50} values for daphnids range from 0.69 to 1.2 ppb. As with fish, large invertebrates appear to be less sensitive than small invertebrates to malathion exposure, at least in terms of acute LC_{50} values. While very small organisms like daphnids, scuds, and midge larvae are clearly sensitive to malathion exposure, the LC_{50} values for larger invertebrates are much higher, ranging from about 50,000 to greater than 200,000 ppb.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals

As summarized in the human health risk assessment (see Section 3.1), the database concerning the toxicity of malathion to experimental mammals is quite extensive. This information can be used in the ecological risk assessment to assess the effects of malathion exposure on nontarget terrestrial mammals. Accordingly, it is reasonable to assume that exposure to malathion will inhibit AChE and will induce neurological effects in these species (see Section 3.1.6).

A major difference between the human health and ecological risk assessment, however, concerns the way in which these data are used. In the human health risk assessment, data on several mammalian species are used to assess risk in a single species (humans) with an emphasis on

protecting the most sensitive individuals through the use of conservative methods and uncertainty factors. In the ecological risk assessment, the data on several mammalian species must be used to assess risk in numerous nontarget mammalian species. Consequently, patterns in species sensitivity are useful in determining species-to-species extrapolations. For many chemicals, systematic or allometric relationships are apparent between body weight and toxicity (e.g., Boxenbaum and D'Souza 1990); however neither the acute nor chronic oral toxicity data on malathion suggests a consistent pattern in species sensitivity.

The highly variable acute oral toxicity data on malathion within a given species may obscure any allometric relationships. For example, the LD_{50} values for rats range from 390 to 2100 mg/kg bw in the ecological risk assessment conducted by the U.S. EPA in support of the reregistration of malathion (U.S. EPA/OPP 2005m, Table 18, p. 62). This range of toxicity values encompasses or is very close to reported malathion toxicity values for other mammalian species—i.e., from about 130 to greater than 2000 mg/kg bw (e.g. NIOSH 1976, Table XV, p. 169). Undoubtedly, some of the variability is due to impurities (Section 3.1.15.2.).

Similarly, repeated exposure (subchronic or chronic) data do not suggest any clear pattern in toxicity among species. According to a study used in the U.S. EPA risk assessment on malathion (U.S. EPA/OPP 2006c), longer-term exposure to technical grade malathion results in LOAEL values for RBC ChE inhibition of 167 mg/kg bw/day for mice (MRID 43407201), 35 mg/kg bw/day for rats (MRID 43942901), and 67 mg/kg bw/day for dogs (MRID 40188501). The LOAEL for rabbits is 50 mg/kg bw/day, although this LOAEL is based on reproductive toxicity rather than ChE inhibition. Al-Qarawi and Adam (2003) report that doses of 25 mg/kg bw/day for only 6 days caused mortality in sheep. Nevertheless, because the test substance was a product formulated in China and its purity it not specified in the study, these data cannot be used to assess the relative toxicity of malathion to sheep.

There are relatively few field studies concerning the potential impact of malathion exposure on mammals. Erwin and Sharpe (1978) found no effects on populations of mice (*Peromyscus maniculatus* and *Peromyscus leucopus*), vole (*Microtus ochrogaster*), and shrew (*Blarina brevicauda*) after the aerial application of 0.585 L/ha ULV malathion (NOS) in a 42.4 km^2 area relative to population in an adjacent untreated 41.4 km^2 area.

4.1.2.2. Birds

The toxicity of malathion to birds is characterized in acute (gavage), subacute dietary (5-day and 8-day exposures), and chronic/reproduction studies. The toxicity of malathion to birds is summarized in Appendix 2 (controlled laboratory bioassays) and Appendix 3 (field studies).

The acute oral LD_{50} values for birds exposed to malathion are highly variable, generally ranging from about 167 mg/kg for ring-necked pheasants to 1485 mg/kg for mallard ducks (Tucker and Crabtree 1970, as summarized in Appendix 2). This range of acute toxicity values is similar to the one for experimental mammals—i.e., about 193-1400 mg/kg—summarized in the previous section. As with studies in mammals, bird studies show no apparent relationship between the acute lethal potency of malathion and body weight. The least sensitive species and the most

sensitive species are both relatively large birds. Much smaller birds have intermediate LD_{50} values—e.g., 500 mg/kg for the house sparrow (Mehrotra et al. 1966).

Birds may be somewhat more sensitive than mammals in terms of cholinesterase inhibition. Single gavage doses of 50 or100 mg/kg were associated with ChE inhibition in sparrows (Mehrotra et al. 1966), and oral doses of 167 mg/kg were associated with an inhibition of plasma but not brain cholinesterase activity in partridges (Walker et al. 1991). In rats, a single oral dose of 500 mg/kg (Lamb 1994a) was associated with an inhibition of plasma but not RBC or brain AChE. The possibility that birds are more sensitive than mammals to the cholinesterase inhibiting effects of malathion are further suggested by their greater sensitivity to brain AChE inhibition after exposure to malathion, compared with rats, mice, and cattle (Barber et al. 1999).

In longer-term studies, the LOAEL for plasma ChE inhibition is 160 ppm in the diet, associated with a 30% inhibition of plasma ChE, and the corresponding NOAEL was 35 ppm in a 12-week (84-day) feeding study using starlings (Dieter 1975). The LOAEL is comparable to the 90-day dietary LOAEL of 100 ppm in rats associated with a >20% inhibition of RBC AChE (Daly 1996b) (see Section 3.1.3.5). The dietary NOAEL in birds of 35 ppm is also similar to the 2-year dietary NOAEL of 50 ppm in rats (Daly 1996a). Thus, in terms of acute lethal potency and at least longer-term inhibition of cholinesterase, birds appear to be as sensitive as mammals to malathion exposure.

Based on a 21-week feeding study in bobwhite quail, dietary concentrations of 350 ppm caused no effect on reproductive parameters; however, 1200 ppm was associated with reduced shell thickness, reduced numbers of eggs laid, and reduced egg viability (Beavers 1995). A 21-week dietary study in mallards resulted in a LOAEL of 2400 ppm based on growth and viability; a NOAEL was not determined (Pederson and Fletcher 1993).

Several field studies summarized in Appendix 2 indicate that adverse effects were not observed in birds after exposure to malathion at application rates similar to or greater than those used in Forest Service programs to control insect pests (e.g., thrips) in pine seed orchards and more generally to control mosquito outbreaks. At substantially higher application rates of 2-4 lbs/acre, investigators observed decreased singing among birds, which may indicate that the birds left the treated area temporarily (Giles 1970).

Like mammals and many other animals, birds have cytochrome P-450 systems (Walker 1999), and pretreatment with inducers of mixed function oxidase—i.e., cytochrome P-450—enhances the toxicity of malathion to birds, most likely by increasing the metabolism of malathion to malaoxon (Johnston et al. 1994a,b; Walker and Johnston 1989) or inhibiting the detoxification of malathion (Johnston et al. 1994c). On the other hand, a field study conducted to investigate the effects of simultaneous exposure of birds to malathion and prochloraz (a P-450 inducer), reports that malathion toxicity was not observed in the treated birds (Johnston et al. 1996). This information is not contradictory: most inducers of cytochrome P-450 are also substrates of cytochrome P-450. Thus, simultaneous exposures to malathion and another cytochrome P-450 substrate might competitively inhibit the metabolism of malathion to malaoxon.

The rapid absorption and elimination of malathion observed in mammals is likewise observed in birds. Gupta and Paul (1977) noted a uniform distribution of ^{32}P malathion in adult (1.2-1.8 kg), female Desi poultry birds, *Gallus domesticus* given a single oral dose of 394 mg/kg. The compound was absorbed rapidly, as indicated by appreciable levels in plasma after 30 minutes and by peak plasma concentrations of 4.7 mg/mL achieved in 6 hours, after which time the levels declined rapidly and were not detectable at 48 hours. At 6 hours, the maximum concentration (100 µg/g) was present in the liver, followed by kidney, fat, spleen, heart, intestine, lung, testes, brain, muscle, and bone. At 48 hours, trace amounts of administered compound were present only in the liver, kidney, lung, and spleen. The compound appears to be excreted rapidly via urine with only a small amount detectable in feces. Fleming and Bradbury (1981) report that recovery from RBC and brain AChE inhibition (about 70 and 30%, respectively) in mallard ducklings occurred over an 18-day post-dosing period.

Several studies investigated the effects of injecting malathion directly into eggs containing developing bird embryos. Although the results of such studies—e.g., death of the embryo and other adverse effects (e.g., Dunachie and Fletcher 1969; Jackson and Gibson 1976; Wyttenbach and Thompson 1985; Greenburg and LeHam 1969; Marliac 1964)—are useful as an index of the general toxic potency of malathion, the route of exposure (direct injection) is not relevant to environmental exposure scenarios. Consequently, egg injection studies cannot be used to make dose-response assessments. Nonetheless, the findings of these studies are worth noting. As discussed by Zimmerman (1990) and U.S. EPA/OPP (2000c), the direct injection of malathion or malaoxon into bird eggs causes embryo death or other signs of toxicity, including reduced growth (Greenburg and LeHam 1969; Jackson and Gibson 1976; McLaughlin et al. 1963), increased production of insulin (Arsenault and Gibson 1974), neurological effects (McLaughlin et al. 1963), and beak defects (Greenburg and LeHam 1969).

The effects of malathion on immune function has not been examined as extensively in birds as in mammals (Section 3.1.7). After single gavage doses 92 mg/kg bw and 230 mg/kg bw, Day et al. (1995) noted an increase in cortical macrophages, necrotic lymphocytes, and pathological changes in the thymus at the high dose only. These doses, however, caused severe signs of neurotoxicity and 7 of 20 animals died in high dose group. Rishi and Garg (1993) assayed the effects of malathion in white leghorn chickens at gavage doses that did not cause signs of neurotoxicity: 22.6 (1/20 of the LD_{50}), 45.2 (1/10 of the LD_{50}), and 90.4 (1/5 of the LD_{50}) mg/kg daily for 10 or 20 days. At doses of 22.6 and 45.2 mg/kg, there were increased anti-SRBC titers and increased DTH responses, while a decrease in anti-SRBC titers was observed at the higher dose of 90.4 mg/kg with no detectable effects on DTH. No effects on immune function were noted in white leghorns after 90 days of dietary exposure to 400, 800 or 1600 ppm malathion (Varshneya et al. 1988).

There are no studies to suggest the malathion will have an adverse impact on endocrine function in birds. Ishihara et al. (2003) observed that malathion binds weakly to thyroid hormone receptors in quail; however, the binding affinity is several orders of magnitude below endogenous thyroid hormones.

4.1.2.3. Reptiles

There is very little information regarding the toxicity of malathion to reptiles. Hall and Clark (1982) examined the acute toxicity of malathion (99% purity) to the green anole, *Anolis carolinensis*. Although gavage doses of 648, 1080, or 1800 mg/kg bw caused no mortality, doses of 3000 or 5000 mg/kg caused 100% mortality in groups of five animals. Brain cholinesterase was not reduced (relative to the control group) at 648 mg/kg, but was reduced to about 50% of control activity at 1800 mg/kg. In animals that died, average brain AChE was inhibited by about 68% (3000 mg/kg) or 81% (5000 mg/kg). Based on these data, LD_{50} can be estimated crudely at about 2324 mg/kg ($[(1800 \times 3000)^{-0.5}]$).

Ozelmas and Akay (1995) assayed the toxicity of malathion in Dwarf lizards, *Lacerta parva*. In this study, groups of 50 lizards were given daily oral doses of 0, 1, 2, or 3 mg/kg/day technical malathion (purity of 96%) dissolved in sunflower oil for 16 weeks. High mortality occurred in the control group (32/50) as well as in the exposed groups: 32/50 at 1 mg/kg, 30/50 at 2 mg/kg, and 36/50 at 3 mg/kg. The difference in the mortality rate between the control and high dose group is not statistically significant using the Fisher Exact test (p= 0.260258). The authors observed histopathological changes in the kidneys and liver of all malathion-treated lizards and a dose-severity effect on the kidneys of treated lizards. At 1 mg/kg, the observed kidney effects included congestion, fatty changes, and degeneration of interstitial tissues in the cortex; at 2-3 mg/kg, the most remarkable kidney effects included heavy fatty degeneration and fibrosis. While the investigators state that fatty changes which occurred in the tissues of the fat control group might be associated with the sunflower oil, they attribute the heavy degeneration observed in the kidneys of lizards in the 2 or 3 mg/kg treatment groups to the deleterious effects of malathion. Given the high mortality in all of the animal groups, the lack of a dose-response relationship for mortality, and the very narrow dose range, the usefulness of this study for qualitative or quantitative risk assessment is highly questionable.

Holem et al. (2006) examined the effect of malathion on sprint performance in western fence lizards (*Sceloporus occidentalis*) given a single oral dose of 0.2, 2, 20, or 200 mg/kg bw. The highest dose (200 mg/kg bw) caused 20% mortality, clinical signs of organophosphate poisoning in 70% of the lizards, and increased sprint velocity (Holem et al. 2006, Fig. 1, p. 113). The reason for the enhancement of sprint velocity in the lizards was not determined in this study; however, the effect cannot be considered short term in that the enhanced performance was observed over a 13-day post-exposure period. Lower doses had no effect on sprint velocity.

4.1.2.4. Terrestrial Invertebrates

Based on the efficacy of malathion for the control of many insects, malathion applications are likely to be toxic to a host of terrestrial insects. Consistent with the approach taken by U.S. EPA (2005m), the risk assessment for terrestrial invertebrates is based primarily on toxicity to the honeybee. Additional information on the toxicity of malathion to earthworms is considered in addition to more general observations from field studies.

4.1.2.4.1. Honeybees

The honeybee is the standard toxicity test species used by the U.S. EPA to assess toxicity to nontarget terrestrial invertebrates. As summarized by U.S. EPA/OPP (2005m), malathion is highly toxic to the honeybee with 48- to 96-hour direct spray LD_{50} values ranging from 0.2 to 0.71 µg/bee (U.S. EPA/OPP 2005m, Table 19, p. 64).

Foliar contact toxicity is not as well characterized as direct spray. Nonetheless, one LD_{50} value, <1.6 µg/bee, suggests that foliar residues of malathion may be almost as toxic as a direct spray (Sweeney 1989). This study, however, used an emulsifiable concentrate formulation of malathion, and the results may not be typical of toxicity from foliar contact with ULV malathion formulations.

Published toxicity studies using bees are summarized in Appendix 3. The study by Maryland and Burkhardt (1970) appears to report much higher LD_{50} values than those used by the U.S. EPA. As indicated in Appendix 3, however, the study involved contact with treated filter paper rather than direct application to the bee. The open literature provides only one chronic feeding study of honeybees, which reports a dietary NOAEL of 0.16 ppm (Nation et al. 1986).

The toxicity of malathion to insects does not appear to be enhanced much by impurities in technical grade malathion (Pellegrini and Santi 1972). The reason for this observation is that the carboxylesterase activity in invertebrates is very low. Consequently, the inhibition of this enzyme does not have a substantial impact on the toxicity of malathion to invertebrates. Scott et al. (2000) evaluated 33 compounds, comprising five structural groups, for their ability to inhibit CYP6D1-specific monooxygenase activity in housefly microsomes. According to this study, malathion was substantially less potent than chlorpyrifos at inhibiting CYP6D1 in the housefly. The IC_{50} value for malathion – i.e., the concentration causing 50% inhibition – was 5.3×10^{-6} M (Scott et al. 2000, Figure 5, p. 68). Based on estimates of contact LD_{50} values, the toxicity to the enantiomers of malaoxon are less toxic than malathion or malaoxon to houseflies, cockroaches, granary weevils, and mites (Polec et al. 1998).

In a field study, Hester et al. (2001) investigated the effects of ground ULV malathion sprays on honey bee (*Apis melifera*) apiaries in open and forested areas downwind from the application site (wind speed ranged from 1.6 to 4.8 km/h and was always from the road toward the hives). Although this study does not specify a nominal application rate, it indicates deposition rates of about 100-700 ng/cm^2 at a distance of 7.6 meters (Hester et al. 2001, p. 4, Table 2). These deposition rates correspond to 0.1-0.7 µg/cm^2, 0.01-0.07 kg/ha, and approximately 0.0009-0.062 lbs/acre. Effects on bee colonies located 7.6, 15.2, 14.7, and 91.4 m downwind from sprays was recorded 12 and 36 hours after treatment. Bee mortality was significant in the open area at distances of 7.6 and 15.2 meters. There was only one incident of significant mortality in the forested area. In each case where bee mortality was recorded, spray deposits on filter paper were >400 ng/cm^2.

4.1.2.4.2. Earthworms

Toxicity tests on the earthworm are often used to assess the consequences of exposure to fossorial invertebrates. Contact LD_{50} values—i.e., malathion on moistened filter paper—are reported for two species of earthworms: *Eisenia foetida* [13.5 (8.0-22.8) µg/cm^2] and *Lumbricus rubellus* [0.27 (0.14-0.50) µg/cm^2] (Roberts and Dorough 1984, 1985). A somewhat more relevant assay of earthworm toxicity involves the exposure of worms in soil containing a known concentration of malathion. Based on a 14-day survival assay, the LOEC for malathion to *Eisenia fetida* was 60-75 ppm. Based on a 21-day cocoon production assay, the LOEC for *Enchytraeus albidus* was 6.64 ppm (Kuperman et al. 1999).

Kupermann et al. (1999) conducted a detailed study of malathion toxicity in two species of earthworms, *Eisenia fetida* (an earthworm species used in many standard toxicity tests) and *Enchytraeus albidus*, a species of white worm. Details of this study are summarized in Table 14 of the current risk assessment. The results indicate that *E. albidus* is a more sensitive species than *Eisenia fetida* by factors of up to about 10 for comparably sized organisms. The LOEC for all species and sizes combined was 6.64 ppm—i.e., *Enchytraeus albidus* adults with fully developed clitella and a mass of 350-450 mg. The most tolerant of the tested groups was *Eisenia fetida* (adults with fully developed clitella and a mass of 350-450 mg) with an LOEC of 75 ppm. A more recent study by Espinoza-Navarro and Bustos-Obregon (2005) reports a much higher toxicity value for *Eisenia fetida*—i.e., an LC_{50} of 880 ppm soil.

Drawida wills, an earthworm native to tropical climates, may be somewhat more sensitive than *E. albidus* to malathion exposure. Panda and Sahu (2004) noted an inhibition in AChE activity in *Drawida wills* up to 12 days after exposure to malathion from Cythion 50% EC at soil concentrations of 2.2 and 4.4 ppm. In a preliminary acute toxicity test, the calculated LC_{50} values for juvenile, immature, and adult earthworms exposed to malathion ranged from 15.07-18.81 ppm soil. Patnaik and Dash (1993) reported sublethal effects (i.e., changes in gut enzyme activities) in *Drawida wills* and two other species of tropical earthworms after exposure to aqueous solutions of a 50% EC formulation of malathion obtained in India.

Butler and Verrell (2005) studied the avoidance response of *Eisenia fetida* to a 50% emulsifiable concentrate formulation of malathion. This publication does not report nominal concentrations in soil. Instead, the results are reported as dilutions of 100 mL of the formulation added to 1 L of soil. The bulk density of the soil is not specified. Both lethal and sublethal concentrations elicited an avoidance response in *Eisenia fetida*.

Senapatie et al. (1991, 1992) studied effects on earthworms in rice fields treated with a 50% EC formulation of malathion at rates of 500 mL/acre (about 250 g/acre or about 0.5 lb a.i./acre) after one and four applications for the control of mosquitoes. While decreases in earthworm populations were noted in response to treatment, an increase in earthworm reproduction rates was also noted, suggesting a capacity for recovery.

4.1.2.4.3. Other Nontarget Invertebrates

Malathion (1.4 kg/ha or about 1.2 lb/acre) is used generally to control the population of terrestrial arthropods (Christiansen et al. 1989). Accordingly, effects on many insect species are to be expected. In a field study in which malathion was applied for mosquito control, a transient (48-hour) decrease was noted in the total number of flying insects (Jensen et al. 1999). The field study by Johansen et al. (1983) indicates that bee mortality is likely to occur for about 40-130 hours in fields treated with 0.56-0.9 kg/ha or about 0.5-0.8 lb/acre malathion.

Malathion treatments are likely to affect both ground and flying insects. A significant reduction (by 87.9%) of the dominant species of darkling beetles, *Eleodes opacus*, was apparent within 1 week after the aerial application of malathion-ULV concentrate (91%) at 0.653 kg/ha (about 0.6 lb/acre) in South Dakota (Quinn et al. 1991). Populations remained low through the rest of the summer in treated plots but increased to pre-treatment levels by 1 year after application. Populations of other less abundant darkling beetles (*E. tricostatus, E. obsoleta*, and *E. suturalis*) were not affected significantly. Another field study indicates that repeated applications of malathion bait spray for eradication of the Mediterranean fruit fly caused a substantial decrease in the populations of terrestrial midge larvae associated with galls in trees—i.e., *Rhophalomyia californica*. After a 7- to 8-year period, Ehler and Kinsey (1992) found that midge populations were comparable to those in untreated areas. This finding is somewhat consistent with the field simulation study by Hoxter and Jaber (1989) that examines the effects of malathion residues on alfalfa to honeybees. Cythion 57% EC was applied to alfalfa at a rate of 1.6 lbs a.i./acre in a spray volume of 40 gallons/acre. The alfalfa was aged 3-72 hours after application and was cut and placed in bee chambers in a laboratory that contained 25 healthy worker bees, aged 1-7 days, per chamber. Mortality was 76% in bees exposed to foliage aged for 3 hours and 66% in bees exposed to foliage aged for 8 hours. At 24 hours, residues on alfalfa decreased substantially, and no significant treatment-related mortality occurred. The reported period to decreased toxicity is somewhat less than the 40- to 130-hour period reported by Johansen et al. (1983).

Sublethal doses (concentrations ranging from 30 to 150 ng/µL of malathion) (99% a.i.) applied to the back of the thorax of 2-day-old Asian corn borer male moths (*Ostrinia frunacalis*) significantly increased the time required to take flight, compared with controls, at all dose levels in a dose-dependent manner, and adversely affected the responses of the males to pheromones (Zhou and Huang 2005). There are no reports in the literature of similar sublethal effects in nontarget species exposed to malathion.

Malathion appears to be less toxic to some beneficial insect predators than to some target species (Tillman and Mulrooney 1997). Other studies, however, suggest that beneficial insects may be affected after applications of malathion. Beneficial arthropods (male and female insidious flower bugs, *Orius insidiosus*, and male and female big-eyed bugs, *Geocoris punctipes*) were exposed to 1.0 kg a.i./ha formulated malathion (Fyfanon 9.79 ULV) via consumption of contaminated *Helicoverpa zea* (corn earworm) eggs. Treatment was highly toxic to male *O. insidious* (62% mortality). Fecundity was significantly lower, compared with controls, in *O. insidious*, and the consumption of *H. zea* eggs by *G. punctipes* was significantly lower, compared with controls (Elzen 2001). The ectoparastoid, *Catolaccus grandis*, is an effective biological

control agent against the boll weevil, *Anthonomus grandis grandis*. Exposure to cotton plants treated with formulated malathion (Fyfanon 9.79 ULV) at a rate of 1.02 kg a.i./ha was highly toxic to *C. grandis* females (97.7% mortality). At 0.24 kg a.i./ha, malathion produced 66.3% mortality in females. Furthermore, at the reduced rate of exposure to malathion, none of the pupae developed from eggs laid by *C. grandis* during the 24-hour period of exposure. Exposure had no effect on the sex ratio of the progeny from treated adults (Elzen et al. 2000).

As with many insecticides, target species may develop resistance to malathion (e.g., Arnaud and Haubruge 2002; Bajpai and Perti 1969; Diaz et al. 2000; Miyo and Oguma 2002; Mutero et al. 1994; Scoot and Georghiou 1986;). The magnitude of the resistance in resistant strains of insects can exceed a factor of 10. While it is plausible that resistance to malathion might develop in nontarget species, no such incident is reported in the literature or considered further in this risk assessment.

4.1.2.5. Terrestrial Plants (Macrophytes)

Information regarding the toxicity of malathion to terrestrial plants was not found in the available literature. Based on the available fields studies, in which no toxic effects on plants are reported, and given the mechanism of action of malathion in mammals, adverse effects on terrestrial plants are not anticipated. The uptake and metabolism of malathion by terrestrial plants are similar to that in mammals; however, the rates of uptake and metabolism by plants are much lower than those observed in mammals (Bourke et al. 1968; Getenga et al. 2000; Yoshii et al. 2000).

Product labels for some EC formulations (e.g., Malathion 5) do indicate that these formulations may cause damage to some terrestrial plants such as ferns. This precautionary language is not found on ULV formulations. While somewhat speculative, this suggests that the non-insecticidal components in these formulations (i.e., the *inerts*) may be the agents that can damage some species of terrestrial plants.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

The toxicity of malathion to fish is well documented (Appendix 4). The U.S. EPA considered numerous toxicity studies submitted in support of the registration of malathion (U.S. EPA/OPP 2005m). In addition, there are numerous published studies regarding the effects of malathion on fish. Finally, the toxicity of malathion to fish and other aquatic species was reviewed in some detail by Siepmann and Slater (1998), Mulla and Mian (1981), and Premazzi (1984).

The acute LC_{50} – i.e., the estimated concentration causing 50% mortality in a given period of time – is a common index of toxicity, similar to the LD_{50} in mammalian studies (Section 3.1.4). As discussed in SERA (2007a, Section 4.1.3.1), the U.S. EPA uses acute LC_{50} values to classify the toxicity of compounds to fish as practically nontoxic (LC_{50} > 100 mg/L), slightly toxic (>10 mg/L to 100 mg/L), moderately toxic (>1mg/L to 10 mg/L), highly toxic (>0.1 mg/L to 1 mg/L), and very highly toxic (<0.1 mg/L). While it is not uncommon for pesticides to overlap two categories, the LC_{50} values cited by the U.S. EPA/OPP (2005m) for malathion are highly

variable and span three categories, from moderately toxic to very highly toxic. Other factors that may contribute to the variability in the reported LC_{50} values include the size of the fish as well as inherent differences among various populations of the same species.

Unlike the case with mammals, there are no known associations between the acute toxicity of malathion to fish and the amount of impurities in the technical grade malathion being tested. Nonetheless, it seems plausible that such an association could contribute to the highly variable toxicity studies documented in the literature. Another important consideration regarding the acute toxicity of malathion to fish is the stability of the compound in water. As discussed by U.S. EPA/OPP, this property is particularly significant when comparing the results of static, static renewal, and flow-through bioassays (U.S. EPA/OPP 2005m). Two studies in the published literature found that smaller fish are more sensitive to malathion toxicity, compared with larger fish of the same species—i.e., the smaller fish have lower LC_{50} values (Eisler 1970; Post and Schroeder 1971). In the study by Eisler (1970) using mummichogs, a relatively small difference in body weight was associated with a difference in LC_{50} values that spanned a factor of more than 6 (i.e., 24-hour LC_{50} of 130 ppb at a body weight of 1.8 g vs. a 24-hour LC_{50} of 810 ppb at a body weight 2.5 g).

LC_{50} values for the same species of fish are available from several different investigators, and some of the differences can be substantial. For example, 48-hour LC_{50} values in mosquito fish are reported to range from 3.4 ppb (Tietze et al. 1991) to 1230 ppb (Milam et al. 2000). Because of differences in test materials and other experimental conditions, however, it is difficult to assess whether or not these differences in toxicity are attributable to inherent differences in the sensitivity of different populations of the same species of fish or other factors. Mayer and Ellersieck (1986), however, explicitly examined differences in the sensitivity of two populations of steelhead trout using the same test material and experimental conditions. The two populations were from Missouri and a location designated as Soap Lake. This work was done at the Fish and Wildlife Service laboratory in Columbia Missouri, and the Missouri population presumably refers to a local fish population. While not specified in the Mayer and Ellersieck (1986) study, Soap Lake presumably refers to the Soap Lake Washington, a lake that is noted for its very high mineral content (http://www.thelake.org/). Based on 96-hour LC_{50} values involving static exposures, the trout from Soap Lake were more sensitive than the trout from Missouri by a factor of more than 20 [94 ppb/4.1ppb = 22.9]. Details of holding and acclimation are not provided in the report by Mayer and Ellersieck (1986). Based on bioassays reported in this paper for other pesticides (see Table 11, p. 25, in Mayer and Ellersieck 1986), the trout from Soap Lake do not appear to be uniformly more sensitive to other pesticides, relative to the Missouri population. Thus, it does not seem likely that this effect is an artifact of a failure to acclimate the Soap Lake population prior to testing.

As discussed in Section 2.4, this risk assessment covers two general types of malathion formulations: ULV formulations that consist primarily of malathion with no adjuvants and emulsifiable concentrates of malathion that contain aromatic solvents and other undisclosed adjuvants (Section 3.1.14). Trim (1987) suggested that emulsifiable concentrates (EC) of malathion are more toxic than technical grade malathion to fish. This suggestion is based on a

comparison of a 96-hour LC_{50} of 22.51 ppb from his bioassay of a 57% EC formulation in mummichogs to a 96-hour LC_{50} of 80 ppb from a bioassay of technical grade malathion reported by Eisler (1970). Two studies, however, directly compared differences in the toxicity of formulations versus technical grade malathion and found no substantial differences. As summarized in Appendix 4, Haider and Inbaraj (1986) assayed technical grade malathion and a 50% EC formulation in *Channa punctatus* and noted no remarkable differences in 24-hour to 96-hour LC_{50} values. Except for the 96-hour LC_{50} values, which were virtually identical, the EC formulation appeared to be somewhat less toxic than the technical grade material. Similarly, in an unpublished study submitted to the U.S. EPA, Bowman (1989a,b) found that a 57% EC formulation was somewhat less toxic to sheepshead minnows (96-hour LC_{50} = 55 ppb), compared with technical grade malathion (96-hour LC_{50} = 33 ppb). Thus, there does not appear to be any basis for asserting that EC formulations of malathion are more toxic than technical grade malathion to fish.

A number of publications in the open literature discuss the sublethal effects of malathion on fish. While sublethal effects are a concern in this risk assessment, most of the studies reporting sublethal effects report that these effects are induced at concentrations substantially higher than LC_{50} values reported in other publications. As noted above, there is substantial variability in the toxicity data on malathion. Thus, the reports of *sublethal* effects in one study at concentrations that are above lethal exposure levels in another study do not necessarily imply that the study reporting sublethal effects in flawed. Nonetheless, most of these reports of sublethal effects at relatively high concentrations are not useful in assessing dose-response relationships in fish (Section 4.3.3.1).

Sublethal exposures to malathion caused reproductive effects in fish, including a failure in zebrafish to spawn (500 ppb) (Ansari et al 1986), pathological changes to the ovaries in catfish (190-560 ppb) (Das and Sengupta 1993), and degenerative changes in the testis of *Barbus stigma* (19.5 ppb) (Khillare and Wagh 1989). Similar to effects noted in mammalian cells (Masoud et al. 2003 as discussed in Section 3.1.2), Chen et al. (2006) report that malathion induces apoptosis via an effect on mitochondria in grass carp cells. Singh (1992) found that sublethal exposures to malathion significantly altered lipid metabolism during various phases of the annual reproductive cycle in female catfish (*Heteropneustes fossilis*), thereby decreasing breeding potential and preventing spawning. Sinha et al. (1992) report that thyroid physiology was affected to varying degrees by exposure to sublethal concentrations of malathion , depending on dose, duration, and the reproductive status of female freshwater catfish, *Clarias batrachus*. Decreased T_4 (a thyroid hormone) levels in catfish (*Heteropneustes fossilis*) exposed to malathion concentrations of 10,000 or 20,000 ppb for 4 weeks (Yadav and Singh 1986) might be attributed to the stimulation of thyroid peroxidase, which resulted in an increased rate of conversion of T_4 to T_3 (Yadav and Singh 1987). Ruiz-Leal and George (2004), however, found no indication of general oxidative stress in carp cell cultures.

Sublethal concentrations (0.73 mg/L) of malathion (NOS) caused skeletal anomalies in Indian catfish, *Heteropneustes fossilis* after 70 days of exposure. The observed anomalies included skull and fin deformities, asymmetric cranium, scoliosis, and lordosis. Moreover, signs of

toxicity, including copious secretion of mucus, dilated pupils, blanching of skin, overall body weight loss, an inability to maintain axial balance, and sporadic hyperkinesis were observed in all fish by day 10 (Srivastava and Srivastava 1990).

A sublethal (4250 ppb) exposure to malathion for 4 or 10 days caused hyperglycemia and glycogenolyisis in adult freshwater Indian catfish, *Heteropneustes fossilis*. Although there were no significant changes observed in liver DNA, RNA, blood amino acids, or hepatic protein levels after 4 days of exposure, levels of liver DNA, RNA, and hepatic protein decreased significantly and blood amino acids rose significantly after 10 days of exposure (Singh and Srivastava 1993).

Decreased brain AChE activity was found in catfish exposed to malathion water concentrations ranging from 0.19 to 0.56 ppm (Das and Sengupta 1993). Although there are substantial differences in species sensitivity to malathion, Shaonan et al. (2004) observed no substantial intrinsic differences in AChE sensitivity to malathion, oxidized to malathion *in vitro*, in purified AChE preparations from three species of freshwater fish (topmouth gudgeon, goldfish, and rainbow trout). Based on *in vitro* assays of AChE inhibition in salmon, it appears that the inhibition of AChE by metabolites of malathion and other organophosphates or carbamate insecticides is additive (Scholz et al. 2006).

Increased concentrations of ascorbic acid in the liver of *Barbus ticto*, a freshwater fish native to Asia, in response to sublethal malathion exposure (20 ppb) may be associated with the conjugation of malathion metabolites with glucuronic acid (Khillare and Wagh 1986). Furthermore, sublethal exposure to malathion (367 ppb) decreased oxygen consumption of *Tilapia mossambica*, another freshwater fish native to Mozambique (Basha et al. 1984). Finally, malathion may induce cytochrome P-450 and was shown to enhance the activation of aromatic amines in the liver of gilthead seabream (*Sparus aurata*) (Rodriguez -Ariza et al. 1995).

Decreased antibody titers in fish are associated with exposure to malathion (Beaman et al. 1999; Khalaf-Allah 1999; Plumb and Areechon 1990). Khalaf-Allah (1999) exposed *Tilapia nilotica* to 11,600 ppm malathion for 30 days and noted a decreased antibody titer for *Staphylococcus aureus* antigen in groups of vaccinated fish compared groups of non-vaccinated fish [no antigen but adjuvant] and water (no treatment) control groups. Although the investigators report that the 11,600 ppm concentration is 10% of the LC_{50} for this test species, they do not report signs of neurotoxicity. In another study, substantially lower concentrations—i.e. 0.28 and 0.98 mg a.i./L—caused a significant decrease in antibody titers to *Edwardsiella ictaluri* in catfish over a 30-day exposure period, but only at the higher concentration (Plumb and Areechon 1990). The investigators used a 56.1% emulsifiable concentrate formulation and noted no effects on immune function in fish exposed only to the organic solvent used in the formulation; thus, the effects on immune function were attributed to malathion. Beaman et al. (1999) assayed the effects of malathion on immune function in the Japanese medaka exposed to concentrations of 0.2 or 0.8 mg/L technical grade malathion for 21 days. At both concentrations, fish evidenced an increased susceptibility to the fish pathogen, *Yersinia ruckeri* on days 14 and 21 of exposure. The increased susceptibility was manifested as a dose-related increase in mortality after injection with the pathogen: about 40% in the control group, about 60% in the 0.2 mg/L exposure group,

and about 70-80% in the 0.8 mg/L exposure group. There was, however, no difference in the response at 14 or 21 days (see Figure 4, p. 537 in Beaman et al. 1999). All of these immunotoxic effects occur are concentrations that are far above LC_{50} values for the most sensitive species. Thus, immunotoxicity is not used as an endpoint in the dose-response assessment for fish.

Lockhart et al. (1985) examined the effects of aerial ULV applications of 3 oz/acre (0.210kg/ha or about 0.19 lb/acre) malathion (purity not specified) to a walleye rearing pond (surface area of 0.89 ha and maximum depth of 1.5 m) in Winnipeg, Canada. A 25% inhibition of brain cholinesterase was noted within 12 hours of the first spray. A gradual recovery of brain cholinesterase to about 80% of pre-spray values occurred over a 2-week period. A similar pattern was observed after a second spray with somewhat less inhibition of brain cholinesterase. No frank signs of insecticide poisoning were noted in any of the fish captured for analysis, and no mortality was observed in the treated pond. These results are consistent with the study by Jensen et al. (1999) in which mortality was not observed in caged mosquito fish after a ULV application of Cythion.

4.1.3.2. Amphibians

As is true for other groups of nontarget organisms, the primary mechanism of the toxicity of malathion to amphibians involves the inhibition of AChE (Bonfanti et al. 2004; Caballero De Castro et al. 1991). The sensitivity of amphibians to malathion appears to be similar to that of fish, with most 96-hour LC_{50} values ranging from 200 to greater than 3000 ppb (Appendix 5).

As detailed in Appendix 5, a notable exception is the report from India by Khangarot et al. (1985) of LC_{50} values in *Rana hexadactyla* tadpoles, a anuran species native to India, ranging from 0.59 ppb (96-hours) to 3.53 ppb (12-hour). This study involved the use of a 50% EC formulation of malathion from an Indian chemical company. In addition, the organisms appear to have been wild-caught rather than laboratory reared and the acclimation period is not specified: "*tadpoles were collected from natural a breeding ground and acclimatized to laboratory conditions prior to exposure"* (Khangarot et al. 1985, p. 391). The toxicity values given in this report are far lower than most other toxicity values given for malathion or malathion formulations. The only other reported LC_{50} value for amphibians that approaches the 96-hours LC_{50} of 0.59 ppb reported by Khangarot et al. (1985) is the 96-hour LC_{50} of 2.14 ppb for Malathion 50 (an EC formulation) (Pauli et al. 2004). This report, however, consists only of an abstract and additional details on the study are not available.

The very low LC_{50} values from the studies by Khangarot et al. (1985) and Pauli et al. (2004) are in contrast to most other toxicity studies on malathion. For example, Relyea (2004b), assayed the toxicity of a 50.5% EC formulation of malathion in several species of laboratory reared North American tadpoles and determined LC_{50} values ranging from 1250 to 3650 ppb. Similarly, in a recent risk assessment on the red-legged frog, the U.S. EPA/OPP (2007, p. 199) the discrepancy between the results reported by Khangarot et al. (1985) and most other toxicity studies on malathion in amphibians, which generally report LC50 values in the range of 200 to 9810 ppb. Nonetheless, the U.S. EPA/OPP (2007) did select the LC_{50} of 0.59 ppb from Khangarot et al. (1985) as the basis for the dose-response assessment for the red-legged frog. The use of the

study by Khangarot et al. (1985) in the current risk assessment is discussed further in Section 4.1.3.2 (dose-response assessment for amphibians).

The study by Abbasi and Soni (1991) suggests that the relationship between exposure duration and response is not pronounced in tadpoles, with 24-hour LC_{50} values of 2070 ppb and 144-hour LC_{50} values of 170 ppb. As reviewed by the U.S. EPA/OPP (2005m), exposure to malathion caused various developmental effects in amphibians. Embryotoxic effects in amphibians seem to occur only at extremely high, acutely toxic concentrations—i.e., in the range of 5000-43,000 ppb.

Baker (1985) and Giles (1970) each conducted field studies to investigate the effects of malathion on two species of salamanders: the slimy salamander (*Plethodon glutinosus*) and the red-backed salamander (*Plethodon cinereus*). Baker (1985) reports that cholinesterase inhibition was not observed in adult or juvenile *P. glutinosus* or *P. cinereus,* and no adverse effects on population densities or lipid storage patterns were observed after 10 weekly applications of malathion at a rate of 5.6 kg/ha (5 lb/acre). The malathion was applied by backpack sprayer to 10 replicate pairs of square 100 m^2 plots characterized as secondary growth trees with a sparse understory. As part of this study conducted in the laboratory, captured animals were exposed to malathion applied to the bottoms of holding cages in amounts equivalent to field applications of 2.24-8.97 kg/ha (2-8 lb/acre). Treatment caused significant inhibition (44%) of brain AChE at 5.6 kg/ha (5 lb/acre) in *P. glutinosus*; while at the same dose, brain AChE activity in *P. cinereus* was inhibited by only about 9%. At the highest dose tested (8 lb/acre), brain AChE activity in *P. cinereus* was inhibited by about 19%. The only other adverse effect observed in the laboratory study was a possible loss in digestive efficiency in *P. glutinosus* at 8 lb/acre.

Giles (1970) also monitored the effects of malathion on both *P. glutinosus* and *P. cinereus* before and after aerial application of malathion at a rate of 0.81 kg/ha (about 0.7 lb/acre) in a deciduous forested watershed. Consistent with the results of Baker (1985), no apparent differences in populations were noted.

As discussed in detail in Section 3.1.7.3, malathion exposure is associated with immunosuppression in mammals but is not shown to increase the susceptibility of mammals to infection. Studies in toads, however, document their increased susceptibility to infection after single dermal doses 1.1 or 11 mg/kg (Taylor 1998; Taylor et al. 1999a,b). As reported in the Taylor et al. (1999a) study, dermal exposure to malathion resulted in a statistically significant increase in frog mortality after injection with the pathogen *Aeromonas hydrophila*, a common bacterial pathogen in amphibians (see Taylor et al. 1999a, Table 1, p. 538). While the study involved small numbers of animals (i.e., 5 per group), the results were statistically significant ($p<0.05$). More recently, Gilbertson et al. (2003) observed immunosuppression in Northern leopard frogs (*Rana pipiens*) after a single subcutaneous injection of a sublethal dose (990 ng/g wet wt) of malathion.

As is true for mammals (see Section 3.1.15.1), glutathione and other endogenous thiols appear to be involved in the detoxicification of malathion in amphibians; moreover, exposure to malathion

decreases concentrations of glutathione and other thiols in amphibians (e.g., Anguiano et al. 2001; Venturino et al. 2001).

4.1.3.3. Aquatic Invertebrates

4.1.3.3.1. Toxicity Studies

Some aquatic invertebrates are far more sensitive than fish or amphibians to malathion exposure. As with other groups of organisms, the toxicity of malathion to aquatic invertebrates is primarily attributed to AChE inhibition (Barata et al. 2004; Printes and Callaghan 2004). While aquatic invertebrates are more sensitive than fish, the recovery period for AChE activity seems comparable for invertebrates (Barata et al. 2004) and fish (Dutta et al. 1995). The inherent sensitivity of invertebrates to AChE inhibition may be greater, however, than that of fish, based on the reported IC_{50} values for AChE inhibition in daphnids of about 10 picomoles/L or 0.0000105 µmol/L (Printes and Callaghan 2004), relative to values of about 0.50-440 µmol/L in fish (Shao-Nan and De-Fang 1996).

As summarized in Appendix 6, reported LC_{50} values for daphnids range from 0.69 to 1.2 ppb with a 48-hour LC_{50} value of 1.0 (0.7-1.4) in *Daphnia magna* reported by (Mayer and Ellersieck 1986). Similar or slightly lower LC_{50} values are reported for scuds (0.5-1.8 ppb) (Mayer and Ellersieck 1986) and 4th instar midges (Ali 1981; Stevens 1992).

Variable results are reported in the literature for daphnids. Khan et al. (1993) conducted acute and chronic bioassays with *Daphnia magna* that indicate a low degree of sensitivity to malathion, with an acute 48-hour LC_{50} value of 80 ppb (75-100 ppb) and a 21-day LC_{50} value of 63 ppb (5-100 ppb), and no changes in the number of offspring noted at concentrations of up to 50 ppb. The LOEC for reproductive effects was 100 ppb. This exposure was associated with an approximately 70% decrease in the number of offspring and an 80% mortality rate in mature daphnia. At 50 ppb, 30% of mature daphnia died; yet, there was no substantial change in reproductive performance among the survivors. On the other hand, Desi et al. (1976) report an LC_{50} for *Daphnia magna* of 3 ppb, and Maul et al. (2006) report an LC_{50} of 3.35 ppb in another daphnid, *Ceriodaphnia dubia.*

Similar to the pattern seen in fish (Section 4.1.3.1), large invertebrates appear to be less sensitive than small invertebrates to malathion exposure, at least in terms of acute LC_{50} values. While very small organisms like daphnids, scuds, and midge larvae are clearly sensitive to malathion exposure, this is not the case for all aquatic invertebrates. For example, the reported LC_{50} for the sow bug is 3000 ppb, and larger invertebrates appear to be much more tolerant, with LC_{50} values in the range of 49,170 ppb for crayfish (Holck and Meek 1987) and from 120,000 to greater than 200,000 ppb in snails (Tchounwou et al. 1992). [Details of these studies are given in Appendix 6.] Even within a species, large organisms appear to be less sensitive than small organisms to malathion exposure (Sanders and Cope 1968).

At least in daphnids, heat shock may increase tolerance to malathion (Bond and Bradley 1995). Based on very short-term bioassays in midge larvae, Kallander et al. (1997) suggest that pulse exposures appear to be less toxic than continuous exposures.

In aquatic invertebrates as in mammals, the toxicity of malathion seems to be modulated by metabolism to malaoxon via cytochrome P-450. Piperonyl butoxide, an inhibitor of cytochrome P-450 activity, inhibits the toxicity of malathion to prawn (Kobayashi et al. 1993) and daphnids (Ankley et al. 1991), probably by slowing the conversion of malathion to malaoxon. The inhibition of malathion toxicity by phenobarbital also was demonstrated in daphnids (Baldwin and LeBlanc 1994). Both DMSO and acetone are reported to antagonize the toxicity of malathion to *Daphnia magna*; however, the mechanism of this antagonism is unclear (Calleja and Persoone 1993). Many aquatic invertebrates have the cytochrome P-450 enzyme system; consequently, interactions involving cytochrome P-450 are likely to be similar to those in mammals (see Section 3.1.12). As with terrestrial invertebrates, resistance to malathion was noted in some target species such as *Culex quinquefasciatus* (Coto et al. 2000); however there seems to be no information about resistance or tolerance in nontarget species.

4.1.3.3.2. Field Studies

Consistent with the sensitivity of aquatic invertebrates to malathion in laboratory bioassays, malathion applications on watercress beds had significant effects on survival and cholinesterase activity of *Gammarus pulex* immediately below the beds and no significant detrimental effects on *Gammarus pulex* located below settling pools (Crane et al. 1995).

Kumar et al. (1994) assayed the effects of a broadcast application of 0.5 ppm Elathion (a commercial EC formulation of malathion) to the water surface of two sets of nursery ponds (0.02 ha, 1.0 m). All backswimmers (notonectids) were killed in the applications at 24 and 48 hours prior to stocking the ponds with fish. In the period ensuing after exposure, neither fish spawn nor net plankton counts were adversely effected, confirming the selective toxicity of 0.5 ppm malathion to backswimmers, *Anisops* Sp.

Jensen et al. (1999) observed no detectable decreases in the abundance or biomass of aquatic macroinvertebrates in wetlands treated with ULV applications of Cythion. Also, the survival of larval mosquitoes was high in all areas. On the other hand, Beehler et al. (1995) reports that malathion caused mortality in mosquito larvae. This study does not, however, provide malathion concentrations or sufficient information to calculate concentrations of malathion in the water. Aerial application of ULV malathion at a rate of 8 fl ounces/acre (9.7 oz ai) to a 16-square-mile area resulted in the increased drift of many species of arthropods; however, there were few individuals of any one species. Moreover, the data presented in this study suggest that almost all of the drifting insects were among those already present on the immediate banks of the irrigation canal in which the study was conducted (Urbauer and Pruess 1973).

After a malathion application that produced peak concentrations of about 10 ppb and 4 hour post-application concentrations of about 2 ppb, no adverse effects were noted on aquatic invertebrates (Kuhajda et al. 1996).

According to Werner et al. (2000), malathion is a *primary toxicant* (along with chlorpyrifos, diazinon, carbofuran, and carbaryl) to Cladocera (*Ceriiodaphnia dubia*) in water from the Sacramento-San Joaquin River Delta in California. The analytical basis for this assertion, however, is not specified. Nevertheless, this supposition is consistent with the extremely low LC_{50} values reported for other Cladocera like *Daphnia magna*.

4.1.3.4. Aquatic Plants and Microorganisms

In the ecological risk assessment conducted by the U.S. EPA/OPP (2005m), no studies on aquatic plants or microorganisms were reviewed. Nonetheless, the U.S. EPA/OPP (2005m, p. 87) did express concern for the potential effects of malathion impurities or inerts in malathion formulations on aquatic plants as well as the uptake of malathion by aquatic plants. The latter concern is supported by the study by Gao et al. (2000) demonstrating the uptake of malathion by several aquatic plants and the bioconcentration of malathion by aquatic plants (BCF values from about 1.2 to 23). In the more recent risk assessment on the California red-legged frog (U.S. EPA/OPP 2007), the U.S. EPA does cite several studies in algae from the ECOTOX database (U.S. EPA/ORD 2008). Based on the ECOTOX records, the most sensitive species is the green algae, *Pseudokirchneriella subcapitata*, with an EC_{50} for growth inhibition of 2040 ppb and a corresponding NOEC of 500 ppb from the study by Yeh and Chin (2006). The most tolerant species is the blue green algae, *Nostoc calcicola*, with an NOEC of 200,000 ppb and no reported EC50 value from the study by Piri and Ordog (1999). Only one acceptable study was identified on an aquatic macrophyte: *Spirodela polyrhiza* (large duckweed) with an NOEC of 24,065 ppb and no reported EC_{50} value (Whothley and Schott 1973).

Most other published toxicity values on aquatic plants are consistent with those reviewed by the U.S. EPA/OPP (2007). Malathion is reported to decrease cell density and decrease the growth of *Chlamydomonas reinhardtii* at concentrations of 1 mM (330 mg/L) (Netrawali et al. 1986). Based on a summary of an unpublished study by Jenkins (1993), WHO (2003) reports an NOEC of 2,300 ppb for *Selenastrum capricornutum*, a green algae that is commonly used in bioassays of pesticides. An apparent inhibition in algae growth is reported in the field trials of Francoeur et al. (1999); however the concentrations of malathion in water are not reported.

The only study that is not consistent with the studies reviewed by the U.S. EPA/OPP (2007) is the report by Torres and O'Flaherty (1976) indicating reduced chlorophyll A production and abnormal growth in *Vaucheria*, a species of filamentous algae, at a concentration, 1 ppb.

Very little information regarding the toxicity of malathion to aquatic bacteria and fungi was located in the available literature. At malathion concentrations of 5000 ppb, an increase in biological oxygen demand but no changes in bacterial populations were noted by Murry and Guthrie (1980).

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

Terrestrial animals can be exposed to pesticides after broadcast applications. The various exposure scenarios include the possibility of being sprayed directly (albeit unintentionally) with the pesticide, ingesting pesticide-contaminated media (vegetation, prey species, or water), grooming activities that result in the ingestion of the pesticide residue, or making contact with pesticide-contaminated vegetation. These scenarios are summarized in Worksheet G01 of the EXCEL workbooks that accompany this risk assessment and address exposure to malathion, based on the typical application rate used for ULV formulations in mosquito control (Attachment 1) and EC formulations in insect control in pine seed orchards (Attachment 2). The consequence of using the range of application rates for both formulations is discussed further in the risk characterization.

In acute exposure scenarios, the highest exposure for terrestrial vertebrates involves the consumption of contaminated fish by a predatory bird after an accidental spill. In that scenario, the exposure levels would be approximately 3200 mg/kg bw for ULV applications and 94 mg/kg bw for EC formulations. As discussed in the exposure scenarios for the human health risk assessment, there is substantial difference between the malathion concentration in ULV formulations (1230 mg/mL), relative to the concentrations in field solutions of EC formulations (0.36 to 36 mg/mL). This difference accounts for the discrepancies in exposure levels for nontarget species in the accidental spray and accidental spill scenarios.

The range of exposure levels for the scenario involving the consumption of contaminated vegetation by terrestrial animals is broad and varies according to the malathion formulation (ULV or EC) applied, the rates of application, and the number of applications made. For ULV formulations, central estimates range from about 0.3 mg/kg (small mammal consuming fruit) to 0.5 mg/kg (large bird consuming grasses). Upper bound estimates for the consumption of contaminated vegetation range from about 0.68 mg/kg (small mammal consuming fruit) to 19 mg/kg (large bird consuming grasses). For EC formulations, central estimates range from about 0.4 mg/kg (small mammal consuming fruit) to 8 mg/kg (large bird consuming grasses). Upper bound estimates for the consumption of contaminated vegetation range from about 0.8 mg/kg (small mammal consuming fruit) to 33 mg/kg (small bird consuming contaminated insects).

The consumption of contaminated water based on expected environmental concentrations leads to much lower levels of acute exposure with peak doses of about 0.002 mg/kg bw for both ULV and EC formulations. Longer-term exposures associated with the consumption of contaminated water are very low for both types of formulations, with maximum doses of less than 0.00005 mg/kg bw. The accidental spill scenario leads to much higher estimates of exposure with upper bound doses of about 140 mg/kg bw for ULV formulations but only 4 mg/kg bw for EC formulations. As noted above, the substantial difference between spills of ULV and EC formulations relate to the much higher concentrations of malathion in ULV formulations, compared with EC formulations.

Although ULV formulations for mosquito control will be applied at lower application rates than EC formulations for insect control in pine seed orchards, longer-term exposures to contaminated vegetation are substantially higher for ULV formulations because the typical use of these formulations is modeled as 8 applications separated at 1-week intervals. Peak exposures for ULV applications are about 11 mg/kg bw for a large mammal and 17 mg/kg bw for a large bird. For EC formulations, the corresponding exposure levels are lower by about a factor of 10—i.e., about 1.3 mg/kg bw for a large mammal and 2 mg/kg bw for a large bird. As with the acute exposures, doses associated with expected concentrations of malathion in surface water are very low—i.e., less than 0.00004 mg/kg bw for both ULV and EC formulations.

Exposure estimates for aquatic organisms are based on essentially the same information used to assess the exposure of terrestrial species to contaminated water. The estimated rates of contamination of ambient water associated with the application of ULV formulations are 0.02 (0.001-0.07) mg a.i./L per lb a.i. applied for peak exposures and 0.0002 (0.00002-0.0014) mg a.i./L per lb a.i. applied for longer-term exposures. For EC formulations, the corresponding values are 0.004 (0.0005-0.04) mg a.i./L per lb a.i. applied for peak exposures and 0.00002 (0.000002-0.0005) mg a.i./L per lb a.i. applied for longer-term exposures.

4.2.2. Terrestrial Animals

Terrestrial animals might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation.

In the exposure assessments for the ecological risk assessment, estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg for terrestrial animals. For terrestrial animals, dermal exposure is expressed in units of mg of agent per cm^2 of surface area of the organism and abbreviated as mg/cm^2. In estimating dermal dose, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal. As in the human health risk assessment, all exposure scenarios for mammals are detailed in the EXCEL workbooks for malathion (Attachment 1 for mosquito control and Attachment 2 for insect control in pine seed orchards). In each of these attachments, the exposure assessments for terrestrial animals are summarized in Worksheet G01. The computational details for each exposure assessment presented in this section are provided as scenario-specific worksheets (Worksheets F01 through F16b).

Because of the relationship of body weight to surface area as well as to the consumption of food and water, small animals will generally receive a higher dose of pesticide, in terms of mg/kg body weight, relative to large animals, for a given type of exposure. Consequently, most general exposure scenarios for mammals and birds are based on a small mammal or a small bird. For

small mammals, exposure assessments are conducted for direct spray (F01 and F02a), consumption of contaminated fruit (F03a, F04a, F04b), and consumption of contaminated water (F05, F06, F07). Generally, pesticide concentrations will be higher on grasses than on fruits and other types of vegetation (Fletcher et al. 1994). Although most small mammals do not typically consume large amounts of grass over prolonged periods of time, some small mammals, like the meadow vole (*Microtus pennsylvanicus*), may consume grasses as a substantial proportion of their diet at certain times of the year. Consequently, the acute consumption of contaminated grass by a small mammal is considered in this risk assessment (F03b). Large mammals may consume grasses over a long period of time, and these scenarios are included both for acute exposures (Worksheet F10) and longer-term exposures (Worksheets F11a and F11b). Other exposure scenarios for mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and the consumption of small mammals contaminated by direct spray by a large mammalian carnivore (Worksheet F16a). Exposure scenarios for birds involve the consumption of contaminated insects by a small bird (Worksheet F14b), the consumption of contaminated fish by a predatory bird (Worksheets F08 and F09), the consumption by a predatory bird of small mammals contaminated by direct spray (F16b), and the consumption of contaminated grasses by a large bird (F12, F13a, and F13b).

Clearly, numerous other exposure assessments could be generated. The specific exposure scenarios outlined in this section are designed to identify the groups of organisms and routes of exposure of greatest concern and to serve as guides to more detailed site-specific or region-specific assessments.

4.2.2.1. Direct Spray

The unintentional direct spray of wildlife during broadcast applications of pesticides is a plausible exposure scenario similar to the accidental exposure scenarios for the general public discussed in Section 3.2.3.2. In a scenario involving exposure to direct spray, the amount absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

For this risk assessment, three groups of direct spray or broadcast exposure assessments are conducted (Worksheets F01, F02a, and F02b). The first spray scenario, which is defined in Worksheet F01, involves a 20 g mammal that is sprayed directly over one half of the body surface as the chemical is being applied. This exposure assessment assumes first-order dermal absorption. The second exposure assessment (detailed in Worksheet F02a) assumes complete absorption over 1 day of exposure. This assessment is included in an effort to encompass the increased exposure due to grooming. The third exposure assessment is developed using the typical body weight of a honey bee, again assuming complete absorption of the compound. There are no exposure assessments for the direct spray of large mammals, principally because allometric relationships dictate that the amounts of a compound to which a large mammal will be exposed on the basis of body weight as a result of direct spray is proportionately less than the amount to which smaller mammals will be exposed on a body weight basis.

4.2.2.2. Contact with Contaminated Vegetation

As in the human health risk assessment (Section 3.2.3.3), the only approach for estimating the potential significance of dermal contact with contaminated vegetation is to assume a relationship between the application rate and dislodgeable foliar residue. Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. Wildlife species, compared with humans, are likely to spend longer periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures equilibrium may be reached regarding levels on the skin, rates of absorption, and levels on contaminated vegetation. Nonetheless, there are no data regarding the kinetics of any such process. In the absence of such data, no quantitative assessments are made for this scenario in the ecological risk assessment.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

Since malathion will be applied to or directly over vegetation, the consumption of contaminated vegetation is an obvious concern. Separate exposure assessments are developed for acute and chronic exposure scenarios involving a small mammal (Worksheets F03a, F03b, F04a and F04b), a large mammal (Worksheets F10, F11a, and F11b), and large birds (Worksheets F12, F13a, and F13b). Similarly, the consumption of contaminated insects is modeled for a small bird (Worksheet 14a) and a small mammal (Worksheet 14b). Consistent with both the assessment for residues on vegetation and the approach taken in the recent U.S. EPA ecological risk assessment of malathion (U.S. EPA/OPP 2003l, p. 26), the empirical relationships recommended by Fletcher et al. (1994) are used to estimate residues in contaminated insects (Worksheets F14a and F14b).

A similar set of scenarios is provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a) or a predatory bird (Worksheet 16a). In addition to the risks of exposure associated with the consumption of contaminated vegetation, insects, and other terrestrial prey, malathion may reach ambient water and aquatic organisms. Thus, a separate exposure scenario is developed for the consumption of contaminated fish by a predatory bird in both acute (Worksheet F08) and chronic (Worksheet F09) exposures. Details of each scenario are given in the cited worksheets.

Since multi-route exposures (e.g., the consumption of contaminated vegetation and contaminated water) are likely, numerous exposure assessments could be developed to account for the various combinations. In the current risk assessment, these considerations have no substantial impact on the assessment of risk for accidental exposures because most accidental exposure scenarios lead to hazard quotients that are substantially above a level of concern (Worksheets G02a to G02c). For non-accidental exposures, the predominant route of plausible exposure is the consumption of contaminated vegetation by herbivores or the consumption of prey by predators; therefore, explicit considerations of multiple routes of exposure would have no impact on the characterization of risk.

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating malathion concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4). The only major differences in the estimates of exposure involve the weight of the animal and the amount of water consumed. These differences are detailed and documented in the worksheets regarding the consumption of contaminated water (F05, F06, F07).

Unlike the human health risk assessment, estimates concerning the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the estimate of the ingested dose include the field dilution rates (i.e., the concentration of the chemical in the spilled solution) and the amount of solution spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons. As noted in the exposure assessment for the human health risk assessment (Section 3.2.1), ULV formulations are not diluted prior to application and contain a much greater concentration of malathion (1230 mg/mL) than do field solutions of EC formulations (0.36-36 mg/mL). Consequently, the accidental spill scenarios for ULV formulations lead to much higher exposures than do the corresponding scenarios for EC formulations.

In the exposure scenario involving ponds or streams contaminated by runoff or percolation, the factors that affect the variability in exposure estimates are the water contamination rates (Section 3.2.3.4.6) and the application rates.

4.2.3. Terrestrial Plants

In risk assessments of herbicides, a relatively standard set of exposure scenarios for terrestrial plants is typically employed in Forest Service risk assessments. These exposure scenarios are not used with malathion. As detailed in Section 4.1.2.5, there is no basis for asserting that malathion is likely to have a direct toxic effect on terrestrial plants. Consistent with the approach taken by the U.S. EPA/OPP (2005m, p. 120), quantitative values for risk characterization—i.e., RQ values in the EPA assessment and hazard quotients (HQ values) in this Forest Service risk assessment—are not derived for terrestrial plants.

4.2.4. Soil Organisms

As discussed in Section 3.2.3.4.3, estimates of malathion concentrations in soil as well as estimates from off-site movement (runoff, sediment, and percolation) are output from GLEAMS. Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 15 for the top 12 inches of soil and in Table 16 for the top 60 inches of soil. All concentration are expressed as the maximum soil concentration in units of ppm (mg a.i./kg soil) after the application of malathion at a unit rate of 1 lb a.i./acre.

As with the direct spray of vegetation or surface water, peak concentrations in soil after a single application will occur immediately after application, and the concentration will be dominated by the amount of material that is applied. Thus, differences in peak soil concentrations after a single application of malathion display little variability among locations with different weather patterns, with peak concentrations in the top 12 inches of soil ranging from 0.15 to 0.17 ppm. With multiple applications of a pesticide, peak concentrations will be higher and somewhat more variable depending on the rainfall pattern, the number of applications, and the interval between applications. For malathion, peak concentrations in the top 12 inches of soil in the course of eight applications separated by 1-week intervals range from 0.29 to 0.5 ppm.

In addition to the concentration of the pesticide in soil, risks to soil organisms may be impacted by the depth of the penetration of the pesticide into the soil column. GLEAMS does not provide this information explicitly. Nonetheless, in computing concentrations of the pesticide in soil, GLEAMS automatically partitions the soil column into various soil layers, referred to as computational soil layers and outputs the concentration of the pesticide in each computational soil layer in units of ppm, with a minimum non-zero value of 0.000001 ppm or one part per trillion. Consequently, estimates of the maximum penetration depth can be made based on the maximum depth of the computational soil layer at which a residue value of greater than zero is modeled. These estimates, for both single applications and eight applications separated by 1-week intervals, are given in Table 17. In arid regions, the GLEAMS modeling suggests that malathion will penetrate to depths ranging from 4 to 24 inches, with somewhat greater penetration in sand, relative to clay or loam soils. The penetration of malathion into the soil column is likely to be deeper—i.e., from18 to 60 inches—in regions with high rainfall rates. Because the GLEAMS modeling conducted for the current risk assessment used a maximum soil depth of 60 inches, all values in Table 17 that indicate a 60-inch penetration of malathion into soil could involve instances in which the penetration into the soil column might exceed 60 inches.

4.2.5. Aquatic Organisms

For the application of malathion, the plausibility of effects on aquatic species is assessed based on estimated concentrations of malathion in water that are identical to those used in the human health risk assessment. These values are summarized in Table 12 and discussed in Section 3.2.3.4.6.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The specific toxicity values used in this risk assessment are summarized in Table 18, and the derivation of each of these values is discussed in the various subsections of this dose-response assessment. The first column in Table 18 specifies the organism to which the toxicity value applies. The available toxicity data support separate dose-response assessments in six groups of organisms: terrestrial mammals, birds, nontarget terrestrial invertebrates, fish, amphibians, and aquatic invertebrates. Different units of exposure are used for different groups of organisms depending on how exposures are likely to occur and how the available toxicity data are expressed.

Theses toxicity values (TV) are used as the numerator in the derivation of the hazard quotients (HQ) used in the risk characterization where the hazard quotient is defined as the toxicity value divided by the exposure:

$$HQ = TV / Ex.$$

The use of these toxicity values in the ecological risk assessment is mathematically identical to the approach used in the human health risk assessment where the HQ is calculated as the acute or chronic RfD divided by the corresponding exposure. Unlike the human health risk assessment, however, the toxicity values used in the ecological risk assessment involve different endpoints for different groups of organisms and different durations of exposure. These differences are necessitated by the nature of the data that are available on the different groups of organisms.

For malathion, the different endpoints used in the dose-response assessment include doses associated with a 10% inhibition of acetylcholinesterase activity (BMD_{10} for AChE), estimated NOEC (no observed effect concentrations) for acute toxicity, developmental effects or reproductive effects, as well as doses or concentrations that are estimated to be lethal to 50% of the exposed organisms (LD_{50} or LC_{50} values). Because of the differences in the endpoints used to derive the HQ values, the interpretation of the HQ values in the risk characterization differs among the groups of organisms and durations of exposure.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

As described in the human health risk assessment (Section 3.3), the U.S. EPA/OPP (2006a,c) uses benchmark dose analyses to estimate a surrogate NOAEL values of 14 mg/kg bw for acute exposures and 7 mg/kg bw/day for longer-term exposures. Both values are based on the lower limit of doses associated with a 10% inhibition of red blood cell ChE in young rats. This method of dose-response assessment is appropriate for the human health risk assessment, which focuses on the individual; it is not appropriate, however, for the ecological risk assessment which focuses, instead, on populations.

An alternate approach that focuses on the population, yet is consistent with the dose-response assessment in the human health risk assessment, involves using central estimate of the EC_{10}. In benchmark dose analysis, this central estimate is referred to as the BMD_{10} whereas the lower limit of the EC_{10} is referred to as the $BMDL_{10}$. As described in the benchmark dose analysis (U.S. EPA/OPP 2005f), the central estimates – i.e., the BMD_{10} values – are 16.9 mg/kg bw for acute exposures and 10.8 mg/kg bw for longer-term exposures. These toxicity values, rounded to 17 and 11 mg/kg bw/day in Table 18, are used in the current risk assessment to characterize risks for acute and chronic exposures to malathion.

In its ecological risk assessment, the EPA uses a rat LD_{50} of 390 mg/kg bw to characterize risks associated with acute exposure to malathion (U.S. EPA/OPP 2005m, p. 96) and a dietary concentration of 500 ppm, associated with decreased body weight in mice, to characterize risk for longer-term exposure (U.S. EPA/OPP 2005m, p. 98). The details of these studies are not discussed in the ecological risk assessment; moreover, the studies themselves are not cited in the mammalian toxicity data summarized in the human health risk assessment (U.S. EPA/OPP 2006c).

With respect to the acute toxicity value used by the EPA to characterize risk, the Forest Service prefers not to use LD_{50} values, except in the absence of more suitable data. Furthermore, as discussed in Section 3.1.4, the LD_{50} values for malathion can be highly variable. For example, the LD_{50} of 390 mg/kg bw falls within the range of acute toxicity values generally associated with high proportions of toxic impurities in the test material. Again, the U.S. EPA/OPP (2005m) does not discuss the selection of the 390 mg/kg bw LD_{50}, relative to the more typical LD_{50} values of 5400-5700 mg/kg bw cited in the human health risk assessment (U.S. EPA/OPP 2006c, p. 26). The EPA's use of the chronic toxicity value of 500 ppm (U.S. EPA/OPP 2005m) is also not discussed in the human health risk assessment; furthermore, the NOAEL of 500 ppm is higher than concentrations in other studies associated with adverse effects—e.g., RBC AChE inhibition at a concentration of 100 ppm in the chronic study by Daly (1996a).

4.3.2.2. Birds

In its most recent ecological risk assessment, the EPA use the acute dietary LC_{50} value of 2639 ppm in ring-necked pheasants (Hill et al. 1975) and the longer-term dietary NOEC of 110 ppm in a one-generation reproduction study using bobwhite quail (Beavers et al. 1995) to assess the risk to birds from malathion exposure (U.S. EPA/OPP 2005m).

4.3.2.2.1. Acute Toxicity Value for Birds

Hill et al. (1975) is a compendium of bird toxicity studies conducted for the Fish and Wildlife Service during the early 1970s. The bioassay used by the U.S. EPA in its ecological risk assessment involves a 5-day dietary exposure of ring-necked pheasants to malathion and a corresponding LC_{50} of 2639 ppm, with a 95% confidence interval of 2220- 3098 ppm and a log dose-probit response slope of about 5.122 (Hill et al. 1975, p. 25). The bioassay included three other test species (i.e., bobwhite quail, Japanese quail, mallard ducks); however, the pheasants were the most sensitive.

Critical observations, including food consumption, are not reported in the acute dietary study conducted by Hill et al. (1975). Nonetheless, food consumption can be estimated using a body weight of about 1 kg for ring-necked pheasants, *Phasianus colchicus*, (Dunning 1993, p. 47) and the allometric relationship for food consumption in birds provided a dry diet ($F(kg/day) = 0.0582\ W(kg)^{0.651}$) (U.S. EPA/ORD 1993, p. 3-4). The result is an estimated 0.058 kg/day or a proportion of 0.058 of the body weight. Accordingly, the dietary LC_{50} of 2639 ppm corresponds to a daily dose of approximately 153 mg/kg bw (2639 ppm × 0.058) malathion.

As is the case for assessing mammalian effects of exposure, the Forest Service prefers to use NOAEL values rather than LD_{50} values to calculate hazard quotients (HQ). As described in SERA (2007a, Table 4-2), the U.S. EPA uses LD_{50} values with varying levels of concern—i.e., 0.5 for a general assessment of acute risk and 0.1 for acute risks to endangered species—to interpret risk quotients (RQ), which are equivalent to hazard quotients in the current risk assessment.

Data from the Hill et al. (1975) can be used to estimate other response rates, based on the slope of 5.122 probits/log-dose and the LD_{50} estimate of 153 mg/kg bw. Using the standard equation for probit analysis (e.g., Finney 1971, p. 25):

$$\boldsymbol{Y} = \boldsymbol{m}\ \mathrm{Log}_{10}(\mathrm{dose}) + \boldsymbol{a}$$

where $\boldsymbol{Y}$ is the probit response, $\boldsymbol{m}$ is the slope, and $\boldsymbol{a}$ is the intercept. Using the $\log_{10}$ of the LD_{50} (2.18) and substituting $\boldsymbol{Y}$ with 5 (i.e., a probit of 5 for a 50% response), the value for $\boldsymbol{a}$ is about -6.14. Taking 3.72 as the probit for a 10% response, the log of the LD_{10} is about 1.93, corresponding to an estimated LD_{10} of 85 mg/kg bw. This LD_{10}, in turn, corresponds to an HQ of 0.55 [85/153 = 0.555], which is quite close to the 0.5 EPA level of concern for general acute exposure.

Since most bird populations are likely to recover from a 10% decrease, using the toxicity value of 85 mg/kg bw, corresponding to EPA's use of the dietary LC_{50} of 2639 ppm, is not unreasonable. On the other hand, the Forest Service does not consider 10% lethality in birds a reasonable surrogate for a NOAEL. Using the 0.1 EPA level of concern for endangered species would lower the risk to about 5 probits below a 50% response, corresponding to nearly 0% lethality (i.e., about 0.0000003 or one in three million). To normalize the level of concern to 1, which is conventional in Forest Service risk assessments, the LD_{50} of 153 mg/kg bw is divided by 10 to yield a dose of 15.3 mg/kg bw, which is very close to the BMD_{10} of 17 mg/kg bw for RBC ChE inhibition in mammals. As summarized in Table 18, the toxicity value of 15.3 mg/kg bw is rounded to 15 mg/kg bw and used to calculate acute hazard quotients for birds in the risk characterization (Section 4.4.2.2).

4.3.2.2.2. Chronic Toxicity Value for Birds

For longer-term exposures, the dietary NOEC of 110 ppm in the quail reproduction study (Beavers et al. 1995), used by EPA (U.S. EPA/OPP 2005m, p. 90), is the most appropriate toxicity value available (Appendix 1). The EPA uses dietary concentrations provided in toxicity

studies with estimated pesticide concentrations in environmental media to calculate RQ values directly. As discussed in SERA (2007a), Forest Service risk assessments convert dietary toxicity values to doses expressed in units of mg/kg bw/day to account for differences in the caloric value of standard laboratory diets and the diets of birds in the wild, based on information provided in the EPA's Wildlife Exposure Factors Handbook (U.S. EPA/ORD 1993). Over the course of a quail reproduction study, food consumption was variable, averaging to about 0.08 g food/g bw (e.g., Temple et al. 2007). Using the value of 0.08 g food/g bw, the dietary concentration of 110 ppm corresponds to a dose of about 8.4 mg/kg bw/day, which is less than any gavage dose associated with signs of acute or chronic toxicity in birds (Appendix 1). As indicated in Table 18, the dose of 8.4 mg/kg bw/day, which is only modestly less than the chronic toxicity value of 11 mg/kg bw/day for mammals, is used to characterize the risk of longer-term for birds.

4.3.2.3. Reptiles

There is limited information about the toxicity of malathion to reptiles (Section 4.1.2.3). Some gavage studies indicate that doses of up to 1800 mg/kg bw were not lethal to reptiles (Hall and Clark 1982). The approximate LD_{50} from the Hall and Clark (1982) study is about 2324 mg/kg, which is within the range of toxicity values for relatively tolerant mammals and birds. The relatively similar toxicity values suggest a tenuous relationship of birds and mammals to reptiles. Although other studies associate sublethal effects in reptiles with doses as low as 1 mg/kg bw/day (Ozelmas and Akay 1995), the significance of those reports is questionable.

In its recent ecological risk assessment, the EPA does not derive separate toxicity values for reptiles (U.S. EPA/OPP 2005m). As described in the RED (U.S. EPA 2006a, p. 50), ... *acute risk to reptiles is not expected as they, like mammals, are relatively efficient at detoxifying malathion*. In terms of both acute and chronic risks, …*the Agency uses avian toxicity thresholds in the determination of hazard to reptiles* (U.S. EPA/OPP 2005m, p. 61). In light of the relatively sparse and inconsistent data on the acute toxicity of malathion to reptiles, EPA's method of evaluation seems reasonable. Accordingly, the same approach is taken in the current Forest Service risk assessment.

4.3.2.4. Terrestrial Invertebrates

As noted in Section 4.1.2.4, malathion is an effective insecticide likely to have a substantial impact on many nontarget insects. Consequently, the risk assessment for terrestrial invertebrates is based primarily on toxicity to the honeybee, despite sufficient data from which to derive toxicity values for earthworms. This approach is consistent with the EPA's (U.S. EPA 2005m),

4.3.2.4.1. Honeybees

EPA does not derive risk values for honeybees; nevertheless, their ecological risk assessment addresses the acute lethal potency of malathion, citing LD_{50} values ranging from 0.2 to 0.7 µg/bee for direct spray exposure (U.S. EPA/OPP 2005m, p. 63). Using a honeybee body weight of 0.093 g (APHIS 1993) yields LD_{50} values ranging from 2.15 to 7.6 mg/kg bw, which are substantially less (factors of about 25-100) than the lower bound LD_{50} of approximately 200 mg/kg bw for small mammals. Given that mammalian LD_{50} values in the range of 200 mg/kg bw

malathion are generally associated with high proportions of toxic impurities, this comparison of LD_{50} values probably underestimates the toxicity of malathion to insects. As noted in Section 4.3.2.1, more representative mammalian LD_{50} values range from 5400 to 5700 mg/kg bw, suggesting that malathion is more toxic to honeybees by factors of well over 2000.

Substantially higher LD_{50} values for honeybees are reported in the open literature (Appendix 3); however, these reports involve filter paper assays, which are not applicable to a quantitative assessment of risk. As summarized in Table 18, the LD_{50} value of 2.15 mg/kg bw is rounded to 2.2 mg/kg bw and is used to derive risk quotients for the direct spray of a honeybee. As discussed in Section 4.4 (Risk Characterization), the resulting risk quotients are so high to preclude the necessity of making dose-response or dose-severity assessments.

4.3.2.4.2. Earthworms

EPA's ecological risk assessment of malathion (U.S. EPA/OPP 2005m) does not quantitatively address risks to earthworms or other soil invertebrates. As summarized in Section 4.2.4, estimated peak soil concentrations in the top 12 inches of the soil horizon range from 0.15 to 0.17 ppm per lb a.i. applied per acre. As summarized in Section 4.1.2.4.2, soil bioassays contain enough information earthworm toxicity data to support a quantitative dose-response assessment.

Based on responses of earthworms native to North America (data by Kupermann et al. 1999 summarized in Table 14 of this risk assessment), the most sensitive response is the 21-day NOEC of 4.74 ppm with a corresponding LOEC of 6.64 ppm in *Enchytraeus s albidus* in sandy loam soil. The maximum malathion application rate considered in the current risk assessment is 1.5 lb a.i./acre. Using the 0.17 ppm per lb a.i./acre soil residue rate, the peak concentration in soil would be 0.255 ppm, which is lower than the NOEC of 4.74 ppm by a factor of over 18.

Because the 4.74 ppm NOEC is from a 21-day study, its application to the peak exposures summarized in Section 4.2.4 is highly conservative. As noted in Table 6, the soil half-life of malathion is about 3 days, corresponding to a decay rate of about 0.23 day^{-1} [ln(2)/3 days]. Given a peak concentration of about 0.17 ppm, the time-weighted-average (TWA) concentration over a 21-day period is approximately 0.03 ppm [0.17 (1 – exp(-0.23 $days^{-1}$x 23 days)/(0.23 $days^{-1}$x 23 days) = 0.3197 ppm]—i.e., $C_{TWA} = C_0 (1 - e^{-k\ t}) \div (k\ t)$, as described in SERA (2007a), Section 3.2.3.6. The 0.03 ppm TWA concentration is a factor greater than 150 less than the NOEC of 4.74 ppm and corresponds to an HQ of 0.006. Thus, there is no basis for asserting that malathion is likely to be hazardous to earthworms.

4.3.2.5. Terrestrial Plants (Macrophytes)

Consistent EPA's approach in their recent ecological risk assessment of malathion (U.S. EPA/OPP 2005m), quantitative toxicity values are not derived for terrestrial plants. As summarized in Section 4.1.2.5, there is no basis for asserting that exposure to malathion is likely cause adverse effects in most terrestrial plants.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

The U.S. EPA typically uses data from the most sensitive species to characterize risks to fish. Because fish sensitivity to pesticides often varies appreciably among species, as is clearly the case with malathion, most Forest Service risk assessments identify toxicity values for both sensitive and tolerant species. Generally, however, Forest Service risk assessments defer to EPA toxicity values for sensitive species, unless there is a compelling reason to do otherwise.

In the RED for malathion, the EPA selected an acute 69-hour LC_{50} of 30 ppb for bluegill sunfish (U.S. EPA/OPP 2006a, Table 20, p. 51) from a study cited as MRID 40098001,which is apparently a reference to Mayer and Ellersieck (1986). This toxicity value, however, is not cited in EPA's most recent ecological risk assessment of malathion, prepared by the Ecological Fate and Effects Division (EFED) of the Office of Pesticides (U.S. EPA/OPP 2005m). Furthermore, the discussion of the 69-hour LC_{50} [presumptive typo for the standard 96-hour study] of 30 ppb for bluegill sunfish in the EPA RED (U.S. EPA.OPP 2006a) does not appear to consider the lower LC_{50} values discussed in Section 4.1.3.1 of this risk assessment and in EPA's recent ecological risk assessment (U.S. EPA/OPP 2005m, Table 22, pp. 69-70) which indicate LC_{50} values as low as 4 ppb for sensitive trout populations (Mayer and Ellersieck 1986, Table 11, p. 25).

The current risk assessment uses the LC_{50} value of 4 ppb in trout populations (Mayer and Ellersieck 1986) to characterize risk of acute exposure for sensitive species. In Table 18, this value is converted to 0.004 mg/L to be consistent with the units of measure used in the EXCEL workbooks (Attachments 1 and 2). According to EPA's ecological risk assessment, bullheads are the most tolerant fish species, with a 96-hour LC_{50} of 11,700 ppb or 11.7 mg/L. This toxicity value is summarized in Table 18 of the current risk assessment and used in the risk characterization. As noted in EPA's ecological risk assessment, the range of toxicity values for sensitive and tolerant fish species (0.004-11.7 mg/L) encompasses the apparent sensitivities of both freshwater and estuarine marine species.

To characterize longer-term exposure to malathion, the EPA uses a 60-day NOEC of 21 ppb and corresponding LOEC of 44 ppb from a chronic toxicity study in rainbow trout (Cohle 1989). The Cohle (1989) study is cited in EPA's ecological risk assessment (U.S. EPA/OPP 2005m, Table 23, p. 71) and in the EPA RED (U.S. EPA/OPP 2006a); however, in the ecological risk assessment, the NOEC is reported as 2 ppb, which appears to be a typographical error. As summarized in Table 16 of the current risk assessment, the reproductive NOEC of 21 ppb (0.021 mg/L) is used for characterizing risks in fish associated with longer-term exposures to malathion.

The 21 ppb value would not be appropriate for characterizing longer-term risks in sensitive species of fish because this concentration is higher than the acute LC_{50} of 4 ppb in sensitive trout populations – i.e., trout from Soap Lake in the study by Mayer and Ellersieck (1986). A lower chronic NOEC of 8.6 ppb is reported in the Hermanutz (1978) reproductive study in flagfish in

which decreased growth in the first generation of fish was observed at 10.9 ppb. While the flagfish in the Hermanutz (1978) study appear to be more sensitive than the rainbow trout in the study by Cohle (1989) – i.e., an NOEC of 8.6 ppb in flagfish vs 21 ppb in trout – the longer-term NOEC of 8.6 ppb is higher than the acute LC_{50} of 4 ppb in sensitive trout populations.

In the absence of a longer-term study in fish that provides an NOEC that would appear to be protective of sensitive trout populations, the longer-term toxicity value for sensitive species of fish will be approximated based on estimates of relative potency (i.e., SERA 2007a, Section 4.3.4). As summarized in Table 18 and discussed further in Section 4.3.3.3, the most sensitive aquatic invertebrate appears to be *Daphnia magna*, with an acute LC_{50} of 1 ppb and a chronic reproductive NOEC of 0.6 ppb. Thus, the acute-to-chronic ratio for sensitive invertebrates is 0.6 [0.6 ppb / 1 ppb]. Using this ratio with the acute LC_{50} value for the most sensitive species of fish – i.e., 4 ppm from the study by Mayer and Ellersieck (1986) – the chronic NOEC for sensitive fish is estimated at 2.4 ppb [4 ppb x 0.6]. This toxicity value will be used in the current risk assessment to calculate hazard quotients for longer-term exposures to sensitive species/populations of fish and this estimated NOEC is entered into Table 18 at 0.0024 mg/L.

4.3.3.2. Amphibians

As noted in Section 4.1.3.2, most of the available toxicity studies on malathion in amphibians suggest that amphibians are no more sensitive than fish to malathion exposure. Furthermore, the weight of the evidence for malathion suggests that amphibians are not as sensitive as the most sensitive species of fish. The major exception to this generalization is the LC_{50} of 0.59 ppb for tadpoles reported in the study by Khangarot et al. (1985).

In a recent risk assessment on the California red-legged frog, the U.S. EPA uses an LC_{50} of 0.59 ppb for amphibians (U.S. EPA/OPP 2007, p. 33). Although Khangarot et al. (1985) is not directly cited in the EPA analysis, the EPA document cites ECOTOX reference number 11521 which does identify the information as coming from the Khangarot et al. (1985) study. ECOTOX is an on-line database maintained by the U.S. EPA (http://cfpub.epa.gov/ecotox) that summarizes studies that the U.S. EPA considers relevant in the conduct of ecological risk assessments.

The U.S. EPA/OPP (2007, p. 199) does note the discrepancy between the LC_{50} of 0.59 ppb and the bulk of the literature on the toxicity of malathion to amphibians:

> *One area of uncertainty with respect to the assessment of aquatic phase frogs is the selection of the acute endpoint. This endpoint (LD_{50} 0.59 µg/L) is derived from the most sensitive larval frog tested and the potential for it to be an outlier is suggested when compared to the range of similar endpoints for other tested larval frogs (200 to 9810 µg/L). Careful review of the testing protocol showed no significant problems with toxicity methods except for the use of wild caught organisms. To determine if this species was unusually sensitive or that wild caught individuals were somehow highly stressed or susceptible to pesticide intoxication, a comparison of other pesticide endpoints was made with available*

ranges for other tested amphibians with those chemicals. This comparison indicated that acute effect endpoints for this test species with other pesticides fell within the range of toxicities for other tested amphibians with those chemicals. It was concluded that there was insufficient evidence to declare the existing malathion larval frog acute toxicity endpoint an outlier.

As part of the current Forest Service risk assessment, the Khangarot et al. (1985) has been reviewed with some care and the study does appear to have been well-conducted and adequately reported, albeit not in great detail. Khangarot et al. (1985) did include several pesticides in their report, one of which is carbaryl. A Forest Service risk assessment on carbaryl has recently been completed (SERA 2008) which included a consideration of the Khangarot et al. (1985) tests on carbaryl. Consistent with the above evaluation by the U.S. EPA, the LC_{50} reported for Khangarot et al. (1985) is the highest reported LC_{50} values for carbaryl. In other words, there is no basis for asserting that the population of tadpoles used in the study by Khangarot et al. (1985) were stressed or otherwise atypically sensitive to carbaryl. Lastly, the reported LC_{50} value of 2.14 ppb from the abstract by Pauli et al. (2004), which did involve a species native to North America, provides some additional support to the use of the Khangarot et al. (1985) study in the current risk assessment.

Consistent with the approach taken by the U.S. EPA (2007), the current risk assessment also uses the LC_{50} of 0.59 ppb from Khangarot et al. (1985) to assess the acute risk of sensitive species of amphibians to malathion. Notwithstanding the above discussion, this approach is taken with some reservation because of the atypically low toxicity value reported by Khangarot et al. (1985). While there is no basis for asserting that the organisms used in the Khangarot et al. (1985) study may have been atypically sensitive to malathion or other pesticides, there is residual concern with the formulation of malathion used in the Khangarot et al. (1985) study as well as the sparse description given in Khangarot et al. (1985) on the handling of the sample and the lack of any information on the concentration of impurities in the formulation that was tested in the Khangarot et al. (1985) study. As discussed in Section 3.1.15.2 for malathion and illustrated by Eto (1974) for malathion and several many other organophosphate insecticides, impurities in and degradation products of these pesticides can have a substantial influence on the acute toxicity of these compounds. Concerns with the relevance of the malathion formulation used by Khangarot et al. (1985) to malathion applications made in Forest Service programs are only moderately diminished by the data in Pauli et al (2004) because of the lack of detail in that abstract.

The highest reported LC_{50} for malathion in amphibians is 5,900 ppb (5.9 mg/L) from the study by Relyea (2004b) and, as with the Khangarot et al. (1985) study, Relyea (2004b) used an EC formulation of malathion. The LC_{50} reported by Relyea (2004b) is not directly comparable to most other LC_{50} values because Relyea (2004b) used a 16-day period of exposure rather than the 96-hour exposure period. Nonetheless, it is reasonable to assert that a 96-hour LC_{50} would have been at least and probably greater than 5,900 ppb. Thus, the concentration of 5,900 ppb will be used as the acute toxicity value to assess risks in tolerant species of amphibians.

Except for developmental studies, there are no studies concerning the long-term exposure of amphibians to malathion. As summarized in Appendix 5, the lowest developmental NOEC for

amphibian embryos is 470 ppb from the study by de Llamas et al. (1985) using *Bufo arenarum*, and the highest developmental NOEC is 750 ppb from the study by Bonfanti et al. (2004) using *Xenopus laevis* larvae.

For the current risk assessment, the reproductive NOEC of 750 ppb reported by Bonfanti et al. (2004) is used to assess longer-term risks in tolerant species of amphibians. The lower NOEC of 470 ppb is not used because it is much higher than the 96-hour LC_{50} of 0.59 ppb reported by Khangarot et al. (1985).

This situation is similar to that in deriving a longer-term toxicity value for sensitive species of fish (Section 4.3.3.1) and, as with the dose-response assessment in fish, the relative potency method (i.e., SERA 2007a, Section 4.3.4) is used to derive a longer-term toxicity value for sensitive species of amphibians. As discussed in Section 4.3.3.3, valid acute and chronic studies are available for sensitive aquatic invertebrates – i.e., an acute LC_{50} of 1 ppb and a chronic NOEC of 0.4 ppb, both from studies in *Daphnia magna*. Taking the acute LC_{50} of 0.59 ppb reported by Khangarot et al. (1985), the acute toxicity ratio for sensitive amphibians to sensitive invertebrates is 0.59 [0.59 ppb / 1 ppb]. Using this ratio, the longer-term NOEC for sensitive species of amphibians is estimated at 0.35 ppb [0.6 ppb x 0.59] or 0.00035 mg/L.

4.3.3.3. Aquatic Invertebrates

As noted in the dose-response assessment for fish (Section 4.3.3.1), Forest Service risk assessments generally adopt toxicity values from U.S. EPA risk assessments, at least in terms of study selection for sensitive species. In addition, Forest Service risk assessments generally identify toxicity values for both sensitive and tolerant species of aquatic invertebrates.

In the U.S. EPA RED on malathion (U.S. EPA/OPP 2006a), both acute and chronic toxicity values are based on *Daphnia magna*. EPA uses as the acute toxicity value the LC_{50} of 1 ppb; and as the chronic toxicity value the reproductive NOEC of 0.06 ppb (U.S. EPA/OPP 2006a, Table 20, p. 52).

The acute LC_{50} of 1 ppb is not explicitly referenced in the EPA RED but seems to refer to the acute bioassay by Mayer and Ellersieck (1986) cited in EPA's ecological risk assessment (U.S. EPA/OPP 2005m, Table 24, p. 73).

As cited in U.S. EPA/OPP (2006a, Table 20, p. 52), the chronic daphnid NOEC of 0.06 ppb is listed with a corresponding LOEC of 0.01 ppb— i.e., a factor of 6 below the NOEC. Following this citation, the RED indicates that: *Chronic invertebrate RQs cited in the Revised EFED RED Chapter for Malathion (2000) were incorrectly calculated using the LOEC (0.1), instead of the NOEC value (0.06), which was used in this table* (U.S. EPA/OPP 2006a, p. 54). The RED does not appear to refer to the EFED assessment, U.S. EPA/OPP (2005m). In the EFED assessment, the daphnid chronic NOEC is listed as 0.006 ppb (*and not 0.06 ppb*) with an LOEC of 0.1 ppb (U.S. EPA/OPP 2005m, Table 25, p. 74). Elsewhere in the document, the EFED assessment (U.S. EPA/OPP 2005m, p. 100) mistakenly indicates that an NOEC of 0.1 ppb is to be used for

characterizing risk. Both EPA documents are referring to the study by Blakemore and Burgess (1990) in which the NOEC is 0.06 ppb and the LOEC is 0.1 ppb.

In any event, the current risk assessment defers to the EPA and for malathion uses the acute LC_{50} of 1 ppb in *Daphnia* to assess risks associated with acute exposures and the reproductive NOEC of 0.06 ppb, with a corresponding LOEC of 0.1 ppb, in daphnids to assess risks associated with longer-term exposures of sensitive species.

Notably, some acute and longer-term toxicity values are lower than those selected by the U.S. EPA. As summarized in Appendix 6 of this risk assessment and in U.S. EPA/OPP (2005m, Table 24, p. 72), Mayer and Ellersieck (1986) report LC_{50} values for other daphnids as low as 0.69 ppb; moreover, the lowest reported acute toxicity value is 0.05 ppb for the scud, *Gammarus fasciatus*, also summarized in Mayer and Ellersieck (1986). Similarly, toxicity values less than 0.06 ppb are reported for longer-term exposures. As summarized in Appendix 6, Tessier et al. (2000) observed sublethal effects in Caddisfly larvae—i.e., abnormalities in capture nets—at 0.05 ppb with an NOEC of 0.01 ppb. These lower toxicity values, however, are not remarkably different from those selected by the U.S. EPA, and, as noted in Section 4.4.3.3 (risk characterization for aquatic invertebrates), using slightly lower toxicity values would not have a substantial impact on the risk characterization.

As discussed in Section 4.1.3.3.1 (hazard identification, toxicity studies in aquatic invertebrates), toxicity values are much higher for substantially larger aquatic invertebrates, relative to daphnids and other small invertebrates—i.e., larger invertebrate species are more tolerant to malathion exposure. In larger species, acute LC_{50} values are about 3000 ppb in sow bugs (Mayer and Ellersieck 1986), 49,170 ppb in crayfish (Holck and Meek 1987), and about 200,000 ppb in adult snails (Tchounwou et al. 1992). For the current risk assessment, the intermediate LC_{50} value of 49,170 ppb in crayfish is used to characterize risk in tolerant species of invertebrates. Like the extremely low values for sensitive invertebrate species, the precise values for tolerant species have little impact on the risk characterization.

There are no life-cycle or full developmental studies involving the exposure of tolerant aquatic invertebrate species to malathion. In a study involving the toxicity of malathion to snail egg masses, Tchounwou et al. (1992) report LC_5 values – i.e., concentrations of malathion associated with mortality and failed development in 5% of the exposed eggs. This response can be taken as a reasonable analog to the egg-and-fry studies often used for chronic values in fish. For the most sensitive species of snail, *Biomphalaria havanensis*, the lower limit on the LC_5 is 1.23 mg/L or 1230 ppb (Tchounwou et al. 1992). In the absence of a standard developmental study, this lower limit is used as an approximate longer-term NOEC value for sensitive life-stages of tolerant invertebrates.

4.3.3.4. Aquatic Plants

Most studies indicate that aquatic plants are much less sensitive to malathion than aquatic animals. As summarized in Section 4.1.3.4 (hazard identification for aquatic plants), the most recent risk assessment on malathion by the U.S. EPA/OPP (2007) identifies an NOEC of 500

ppb for the most sensitive species of algae, *Pseudokirchneriella subcapitata*, from the study by Yeh and Chin (2006).

The only other study that reports effects in aquatic plants at lower concentrations is the paper by Torres and O'Flaherty (1976) indicating that 1 ppb malathion caused the inhibition of chlorophyll production and abnormal growth in *Vaucheria*, a type of filamentous freshwater algae. According to the investigators, there are no previous reports of malathion causing this type of effect in algae. As discussed by Torres and O'Flaherty (1976), this result is unusual, Over the past 30 years since Torres and O'Flaherty conducted their study, there is no further evidence in the literature that malathion affects algal growth at exposure levels in the low ppb range. While the Torres and O'Flaherty (1976) study appears to have been well conducted, this report does not seem sufficient in itself to serve as the basis for a dose-response assessment in algae. In the absence of any additional supporting information, Torres and O'Flaherty (1976) is regarded as an outlier. Consistent with the approach taken by the U.S. EPA/OPP (2007), the current Forest Service risk assessment uses the NOEC of 500 ppb (0.5 mg/L) to calculate hazard quotients in sensitive species of algae.

As will aquatic animals, there appears to be a wide-range of sensitivity to malathion in aquatic plants. The highest NOEC value summarized by U.S. EPA/OPP (2007) is 200,000 ppb (200 mg/L) for a species of blue-green algae from the study by Piri and Ordog (1999). This NOEC value will be used in the current risk assessment to characterize risks to tolerant species of algae.

There is only one study available on the toxicity of malathion to aquatic macrophyte, the NOEC of 24,065 ppb (24.065 mg/L) in *Spirodela polyrhiza* (large duckweed) from the study by Worthley and Schott (1973). This NOEC, rounded to 24 mg/L, is used to calculate hazard quotients for aquatic macrophytes. Because this is the only study that is available on macrophytes, no attempt is made to derive separate toxicity values for sensitive and tolerant species of aquatic macrophytes.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

Except for accidental exposures, most terrestrial vertebrates do not appear to be at substantial risk after applications of malathion. The risk characterization for mammals and birds are similar. The accidental spill of a large amount of malathion into a small pond leads to exposures that may exceed the level of concern for small mammals and fish-eating birds. For ULV formulations, the magnitude of the exceedance is much greater because of the higher concentration of malathion in ULV formulations, relative to concentrations in field solutions of EC formulations. Some scenarios for non-accidental acute exposures also exceed the level of concern, at least at the upper bounds of plausible exposures, for the consumption of contaminated vegetation and insects. For these scenarios, the magnitude of the exceedances at the upper bounds of exposure is substantially greater for EC formulations, relative to ULV formulations because of the higher application rates used for EC formulations. For the consumption of contaminated vegetation, the longer-term exposure scenarios for mammals and birds generally lead to hazard quotients that are below the level of concern. The only exceptions involve the upper bounds of the hazard quotients for large mammals and large birds consuming contaminated vegetation exclusively within an area treated with multiple applications of ULV formulations. Expected peak and longer-term concentrations of malathion in surface water lead to hazard quotients substantially below the level of concern.

Malathion is far more toxic to some invertebrates, particularly small insects, than it is to vertebrates. Adverse effects are expected in some terrestrial invertebrates, like insects and, perhaps, some other small arthropods. Malathion is an effective insecticide, and terrestrial insects, both target and nontarget, are likely to be adversely affected if sprayed directly with malathion at application rates used in Forest Service programs. Whether or not effects would be seen in specific populations of terrestrial insects or other arthropods could be influenced by different behavioral patterns, food sources, or habitat. Malathion is not likely to cause adverse effects in earthworms, as they appear to be much less sensitive than other invertebrates to malathion exposure. While somewhat speculative, it seems plausible that other terrestrial arthropods, such as mites and some spiders, would be adversely affected by exposure to malathion. It seems less likely that other groups of terrestrial invertebrates, such as mollusks, would be adversely affected.

Generally, the risk characterization for aquatic species is much more severe than that for terrestrial species. Within each group of organisms for which hazard quotients are derived—i.e., fish, amphibians, aquatic invertebrates, and aquatic plants—the apparent differences between sensitive and tolerant species are substantial, and these substantial differences have a major impact on the risk characterization. Three types of exposure scenarios are used to assess risks in aquatic species: an accidental spill, expected peak concentrations, and expected longer-term concentrations of malathion in surface water. As in the assessment of terrestrial organisms, the accidental spill scenario for ULV formulations is associated with much higher concentrations of malathion in water than the corresponding scenario for EC formulations. Accidental spill scenarios for ULV formulation would likely result in substantial mortality in all groups of

aquatic animals in both the sensitive and tolerant species within each group. Expected peak concentrations of malathion in surface water also exceed the levels of concern for fish, invertebrates, and amphibians at the upper bounds of the hazard quotients. Expected longer-term concentrations of malathion in surface water are below the level of concern for fish with both ULV and EC formulations. For sensitive species of amphibians, the longer-term hazard quotients modestly exceed the level of concern at the upper bounds of the application rates for both EC formulations (HQ=1.3) and ULV formulations (1.2). For sensitive species of invertebrates, the upper bound of the longer-term hazard quotient exceeds the level of concern only for EC formulations (HQ=1.3).

Some of the excursions above the level of concern for peak exposures suggest that lethality, and, perhaps, substantial lethality might be observed among some sensitive species of fish, amphibians, and invertebrates after the application of malathion. This risk characterization, however, is based on the selection of central estimates and upper bounds of water contamination rates (WCRs) that are intentionally conservative, reflecting applications in areas with clay soils and site conditions that favor high runoff. This approach is standard in general Forest Service risk assessments such as the current document. As a consequence of this conservative approach, site-specific or region-specific factors should be considered carefully in the preparation of site-specific or region-specific assessments. The application of malathion in some regions—e.g., areas with predominantly sandy or loamy soils—could lead to much lower expected peak and average concentrations in surface water than are suggested by the WCR values used in this risk assessment.

4.4.2. Terrestrial Organisms

As in the human health risk assessment, quantitative risk characterizations are expressed as hazard quotients—i.e., the level of exposure divided by the toxicity reference value. In all Forest Service risk assessments, the level of concern (LOC) is an HQ of 1. The verbal interpretation of the hazard quotient (HQ), however, depends on the endpoint on which the toxicity reference value is based.

The hazard quotients for terrestrial organisms are given in the EXCEL workbooks that accompany this risk assessment: Attachment 1 for applications of ULV formulations in mosquito control and Attachment 2 for applications of EC formulations for the control of insect pests in pine seed orchards. The risk characterization for terrestrial animals is summarized in the G02 series of worksheets: G02a (typical application rate), G02b (lowest anticipated application rate) and G02c (highest anticipated application rate).

4.4.2.1. Mammals

4.4.2.1.1. Acute HQ Values

The risk characterizations for acute exposures in terrestrial mammals are different for ULV and EC applications, primarily because of differences in application rates. As summarized in Section 2.4.1, the range of application rates for ULV formulations used to control mosquitoes is rather small (from 0.11 to 0.23 lb a.i./acre) as are the differences in the corresponding risk characterizations. Only exposure scenarios involving the accidental spill of a ULV formulation into a small pond lead to hazard quotients greater than 1. The hazard quotients for this exposure scenario is 8. Because ULV formulations are not diluted prior to use, the spill scenario for ULV formulations lead to the same concentration of malathion in the pond regardless of the application rate. As discussed in the risk characterization of the human health risk assessment (Section 3.4.3.1), the accidental spill scenario is intentionally extreme—i.e., 200 gallons of a ULV formulation (undiluted field solution) are spilled into a small pond. The extreme nature of the spill scenario involving a ULV formulation is enhanced by its high concentration of malathion (1230 mg/mL) in comparison to field solutions of EC formulations in which the malathion concentration ranges from 0.36 to 36 mg/mL.

With respect to EC formulations of malathion, the risk characterization for acute exposures in terrestrial mammals, unlike the risk characterization for ULV formulations, is contingent on the application rate. As summarized in Section 2.4.2, application rates for EC formulations of malathion to control insects in pine seed orchards range from 0.1 to 1.5 lb a.i./acre, with a typical application rate of 0.3 lb a.i./acre. At the lower bound of the application rate, none of the hazard quotients exceeds a level of concern. The highest hazard quotient for mammals is 0.4, which is the upper bound hazard quotient for the consumption of contaminated insects by a small mammal. At the typical application rate of 0.3 lb a.i./acre, the upper bound of the hazard quotient for the consumption of contaminated insects by a small mammal slightly exceeds the LOC (HQ = 1.2), and none of the other hazard quotients reaches the LOC. At the highest application rate, all of the hazard quotients for the consumption of contaminated insects exceed the LOC, ranging from 2 to 6. In addition, the upper bound of the hazard quotients for two other scenarios exceed the LOC: the consumption of contaminated grass by a large mammal (HQ=4) and the consumption of contaminated water after an accidental spill (HQ = 1.2).

4.4.2.1.2. Longer-Term HQ Values

The principal differences in the risk characterizations for ULV and EC applications involving longer-term exposures in terrestrial mammals reflect the differences in the number of applications modeled—i.e., eight applications for mosquito control and one application to control insects in pine seed orchards. For pine seed orchards, none of the longer-term hazard quotients exceeds the level of concern, even at the highest application rate. The highest hazard quotient for any mammal is 0.6 and is associated with the consumption of contaminated grasses by a large mammal. Other details pertinent to the exposure scenario include that the large mammal consumes grass entirely within the treated area after an application of 1.5 lb a.i./acre. Multiple applications of ULV formulations lead to somewhat higher concentrations on vegetation over longer-periods of time. As with the EC formulations, the greatest exposures to ULV

formulations are associated with the consumption of contaminated grasses by a large mammal consuming grass entirely within the treated area. The upper bound of the hazard quotients for this scenario includes 0.7 at the lowest application rate, 1.0 at the typical application rate, and 1.5 at the highest application rate.

For ULV and EC formulations of malathion, hazard quotients for the consumption of contaminated water are below the LOC by factors of 100,000 or greater.

The application of any effective insecticide, including malathion, is likely to alter the numbers and/or species composition of terrestrial insects and other arthropods. This alteration could lead to changes in food availability, thereby causing secondary effects of exposure on mammals. These secondary effects are likely to vary over time and among the different species of mammals.

4.4.2.2. Birds

4.4.2.2.1. Acute HQ Values

As summarized in Table 18, the toxicity values used for mammals and birds are very similar. Nonetheless, because consumption rates are different for mammals and birds and because exposure for birds is supplemented by a scenario involving the consumption of contaminated fish by a fish-eating bird, the risk characterization for birds is somewhat more severe than that for mammals.

The most severe exposure scenario for birds involves the consumption of contaminated fish after an accidental spill of malathion into a small pond. Again, spills associated with ULV formulations result in much higher levels of exposure corresponding to higher hazard quotients, relative to spills of field solutions of EC formulations. For ULV formulations, the hazard quotients for this scenario range from 71 to 214 with a central estimate of 143. These hazard quotients are associated with doses ranging from about 1000 to 3000 mg/kg bw. As summarized in Section 4.1.2.2, these doses are in the range of or greater than acute LD_{50} values for birds—i.e., ranging from less than 200 to about 1500 mg/kg. Thus, in the event of an accidental spill of a large amount of a ULV formulation into a relatively small pond, lethality in birds consuming contaminated fish could be expected. As discussed in the corresponding scenario for the human health risk assessment (Section 3.2.3.5) and detailed further in the risk characterization for fish (Section 4.4.3.1), the spill of a large amount of a ULV formulation into a small pond would produce substantial fish mortality. Substantial fish mortality could increase the exposure of mixed predatory/scavenger species of birds and could increase risks to other bird species which do not typically feed on fish.

As with other similar spill scenarios discussed in this risk assessment, the exposure scenario involving the consumption of contaminated fish after an accidental spill is much less severe with respect to field solutions of EC formulations, relative to ULV formulations. For EC formulations, the hazard quotients are much lower, ranging from 0.007 (lower bound of the HQ at the lowest application rate) to 31 (upper bound of the HQ at the highest application rate). The

upper bound hazard quotient of 31 is associated with a dose of about 141 mg/kg bw, which is only modestly below reported LD_{50} value in birds. Based on the log-dose probit-response equation developed in the dose-response assessment for birds, a dose of 141 mg/kg bw (log_{10} dose of 2.14) would be associated with a probit response rate of about 4.8 [(5.122 x 2.14) – 6.14 = 4.821], corresponding to about 42% mortality. Thus, at the highest application rate, bird mortality could be associated with the consumption of contaminated fish.

While the accidental spill scenario is more severe for ULV formulations due to the high concentration of malathion in ULV formulations, the EC formulations lead to higher acute hazard quotients for all other exposure scenarios for birds, due to their higher application rates. For the ULV formulations, the only other exposure scenarios that exceed the LOC involve the consumption of contaminated insects by a small bird (an HQ of 1.1 at the typical application rate and an HQ of 1.7 at the highest application rate) and the consumption of contaminated grass by a large bird (an HQ of 1.3 at the typical application rate and an HQ of 2 at the highest application rate). The exceedances are modest in all of these scenarios. Because the acute toxicity value is based on an approximation of an NOEC value (Section 4.3.2.2.1), it is not clear whether these exposure scenarios would result in observable adverse effects.

For applications of EC formulations, the acute exposure scenarios, other than the accidental spill (discussed above), lead to exceedances of up to 11 (the upper bound of the HQ for a small bird consuming contaminated insects) at the highest application rate. The upper bound dose associated with this scenario is about 50 mg/kg bw. This dose corresponds to a response rate of less than 1%, using the log-dose probit-response equation developed in Section 4.3.2.2.1 [(5.122 x $log_{10}(50)$) – 6.14 = 2.5 probits ≈ 0.06%]. Thus, it is not clear that any of these exposures would be associated with overt signs of toxicity in birds. By analogy to mammals, however, it is possible that depressions in AChE activity could occur. This supposition is supported by a field study (George et al. 1985) in which AChE inhibition was observed, albeit only in one bird, after malathion was applied at a rate within the range used to control insects in pine seed orchards (i.e., 0.65 kg a.i./ha or about 0.6 lb a.i./acre).

4.4.2.2.2. Longer-Term HQ Values

As with the longer-term risk characterization for mammals, the longer-term risk characterization for birds is somewhat more severe for multiple ULV applications, relative to a single EC application, even though the application rates for ULV formulations are lower. For applications of EC formulations, the longer-term hazard quotients do not exceed the level of concern, although the upper bound of the hazard quotient at the highest application rate approaches the level of concern (HQ=0.9) for the consumption of contaminated vegetation. For ULV formulations, the upper bound of the hazard quotient for this exposure assessment is exceeded modestly at the lowest application rate (HQ=1.1), typical application rate (HQ=1.6), and highest application rate (HQ=2). It is not clear that these slight exceedances of the LOC would be associated with any overt signs of toxicity. The central estimate of the hazard quotient for the consumption of contaminated vegetation for ULV formulations is below the level of concern by a factor of 20 (HQ=0.05), even at the maximum application rate. For both EC and ULV

formulations, all hazard quotients for the consumption of contaminated fish are below the LOC by a factor of at least 1000 (HQ=0.001 at the highest application rate for EC formulations).

As with mammals, secondary effects on some species of birds could occur through changes in species composition of terrestrial invertebrates, particularly arthropods. The magnitude of any secondary effects is likely to vary over time and among the different bird species. Changes in densities of bird populations after applications of malathion were reported but only in a few studies and the changes were attributed to changes in prey availability (Appendix 2).

4.4.2.3. Reptiles

The available information on reptiles (Section 4.1.2.3) does not support a dose-response assessment for this group of organisms. Following the suggestion made in the U.S. EPA's ecological risk assessment (U.S. EPA/OPP 2005m), potential risks to reptiles may be similar to those for birds.

4.4.2.4. Terrestrial Invertebrates

As noted in Section 4.1.2.4, malathion is an effective insecticide. Consequently, malathion applications that are effective for controlling pest insects are likely to have a substantial impact on many nontarget insects. Consistent with the approach taken in U.S. EPA (2005m), the risk assessment for terrestrial invertebrates is based primarily on toxicity to the honeybee. Notwithstanding that approach, there is sufficient information to quantitatively characterize risks in earthworms.

4.4.2.4.1. Honeybees

Based on acute direct spray scenarios, all hazard quotients are above unity for bees at all application rates for both ULV and EC formulations. The hazard quotients range from 7 (an application rate of 0.1 lb a.i./acre) to 109 (an application rate of 1.5 lb a.i./acre). Malathion is an effective insecticide. Consequently the direct spray of malathion at effective rates is likely to cause mortality in nontarget insects.

As summarized by the U.S. EPA/OPP (2005m, p. 66), an incident of bee mortality was reported after the application of malathion to 5000 acres of alfalfa. The U.S. EPA indicates that malathion exposure was the probable cause of the bee mortality. As discussed in Section 4.1.2.4, other field studies support the assessment that malathion is likely to be toxic not only to honeybees but to numerous other insects and terrestrial arthropods.

In assessing project-specific applications of malathion, buffers zones may be used to reduce the impact of malathion applications to honeybees and other nontarget invertebrates. The extent to which buffer zones will reduce exposure will be highly dependant on site-specific conditions. As summarized in SERA (2007, Section 4.2.3.2), drift models are available and can be used to evaluate the extent to which buffer zones could minimize effects on nontarget species. For example, in the program for the preparation of the worksheets that accompany this and other Forest Service risk assessments (SERA 2005), estimates from one of the available drift models (i.e., AgDrift) indicate that buffer zones in the range of 25 to over 900 feet can reduce deposition to fractions of about 0.1 to less than 0.00001 of the nominal application rate.

4.4.2.4.2. Earthworms

As summarized in Section 4.3.2.4.2, the most protective toxicity value for earthworms is the NOEC of 4.74 ppm with a corresponding LOEC of 6.64 ppm in *Enchytraeus s albidus* in sandy loam soil from the study by Kupermann et al. (1999).

The maximum application considered in the current risk assessment is 1.5 lb a.i./acre. Using the residue rate of 0.17 ppm in soil per lb a.i./acre (Table 15), the peak concentration in soil would be 0.255 ppm, which is lower than the NOEC of 4.74 ppm by a factor of over 18. Because the 4.74 ppm NOEC is from a 21-day study, the application of this NOEC to the peak exposures summarized in Section 4.2.4 is highly conservative.

As noted in Table 6, the soil half-life of malathion is about 3 days, corresponding to a decay rate of about 0.23 day^{-1} [ln(2)/3 days]. Given a peak concentration of about 0.17 ppm, the time-weighted-average (TWA) concentration over a 21-day period is approximately 0.03 ppm [0.17 (1 – exp(-0.23 $days^{-1}$x 23 days) / (0.23 $days^{-1}$x 23 days) = 0.3197 ppm]—i.e., $C_{TWA} = C_0 (1 - e^{-k\ t}) \div (k\ t)$, as described in SERA (2007a), Section 3.2.3.6. The 0.03 ppm TWA concentration is a factor of over 150 below the NOEC of 4.74 ppm and corresponds to an HQ of 0.006. Thus, there is no basis for asserting that malathion is likely to present a hazard to earthworms.

The extent to which this risk characterization for earthworms is applicable to other soil invertebrates is not clear. While somewhat speculative, it seems likely that soil insects and other

soil arthropods would be more sensitive (and probably much more sensitive) than earthworms to soil residues of malathion.

4.4.2.5. Other Terrestrial Organisms

There is no basis for characterizing risks to other groups of terrestrial organisms —i.e., terrestrial alga, fungi, other microorganism, and terrestrial vegetation. Very high application rates of malathion, particularly EC formulations, may damage some terrestrial plants.

4.4.3. Aquatic Organisms

As is the case for terrestrial organisms, the quantitative risk characterization for aquatic organisms is given as the hazard quotient—i.e., the level of exposure divided by the toxicity reference value—in Attachment 1 for applications of ULV formulations in mosquito control and Attachment 2 for applications of EC formulations for the control of insect pests in pine seed orchards. In each of these attachments, the risk characterization for aquatic organisms is summarized in the G03 series of worksheets: G03a (typical application rate), G03b (lowest anticipated application rate) and G03c (highest anticipated application rate). Separate sets of risk quotients are provided for fish, amphibians, aquatic invertebrates, and aquatic plants. In addition, separate hazard quotients are given for sensitive and tolerant species for each group except aquatic macrophytes. Hazard quotients are presented for the three exposure scenarios developed for aquatic organisms: the accidental spill, expected peak concentrations in surface water, and expected longer-term concentrations in surface water.

The risk characterization for aquatic species is dominated by the accidental spill scenario. As described in Section 3.2.3.4.1, this is an intentionally extreme exposure scenario included in all Forest Service risk assessments. A less obvious but very important consideration in interpreting the hazard quotients for aquatic organisms is the selection of water contamination rates (WCRs) for expected peak and longer-term concentrations of malathion in surface water. As discussed in Section 3.2.3.4.6, the central and upper bound estimates of the WCR values selected for use in the current risk assessment are based primarily on modeling of malathion concentrations in ponds and streams for locations with predominantly clay soils—i.e., a high runoff potential. The variability between the central and upper bounds of the WCR values is based primarily on differences in weather patterns for different locations. This conservative approach is taken in all Forest Service risk assessments and is central to the extreme value approach used to encompass the *Most Exposed Individual* (*MEI*), as detailed in Section 3.2.3.1.2. In the context of the ecological risk assessment, this focus is actually on the most exposed populations.

As a consequence of this conservative approach, the failure to consider site-specific or region-specific factors could lead to gross overestimates of risks to aquatic species in a project-specific analysis. The application of malathion in some regions—e.g., areas with predominantly sandy or loamy soils—would likely result in much lower expected peak and average concentrations in surface water than are suggested by the WCR values used in this risk assessment.

4.4.3.1. Fish

4.4.3.1.1. Accidental Spills

As with terrestrial organisms, the exposure scenario for the accidental spill of either the ULV formulation or a field solution of an EC formulation leads to far greater hazard quotients than the expected concentrations in ambient water as a consequence of normal use. Furthermore, water concentrations associated with an accidental spill are much higher for ULV formulations than for EC formulations.

For ULV formulations, hazard quotients for both sensitive and tolerant species exceed the level of concern by substantial margins, 80 for tolerant species of fish and over 200,000 for sensitive species of fish. Since these hazard quotients are all based on LC_{50} values, there is little need to elaborate on the risk characterization. Were 200 gallons of a ULV formulation of malathion to be spilled into a small pond, fish mortality would be substantial, if not complete, for all species.

For EC formulations, the hazard quotients are much less for the accidental spill scenario, ranging from 0.02 to 12 in tolerant species and from 23 to greater than 34,000 in sensitive species. For sensitive species of fish after an accidental spill of an EC formulation, the risk characterization is identical to that of ULV formulations: the degree of mortality is likely to be substantial. For tolerant species of fish, the risk characterization is somewhat dependent on the application rate. At the lowest application rate, the hazard quotients for tolerant species of fish range from 0.008 to 0.8, depending on the dilution of the formulation. While some degree of mortality might be apparent in tolerant fish species at the upper bound of the hazard quotient (0.8), no mortality is likely to occur in tolerant species at either the lower bound (0.008) or central estimate (0.08) of the hazard quotient. At the typical application rate, the central estimate of the hazard quotient is 0.2 with a range from 0.02 to 2. Pronounced mortality is unlikely at the lower bound; however, for tolerant species some degree of mortality is plausible at both the central estimate (0.2) and upper bound (2) of the hazard quotient. At the highest anticipated application rate, the central estimate of the hazard quotient is 1.2 with a range from 0.1 to 12. While some degree of fish mortality could occur at a hazard quotient of 0.1, it might not be pronounced or observed. Mortality would likely be observed at the central estimate of the hazard quotient (1.2) and would be pronounced at the upper bound of the hazard quotient (12).

4.4.3.1.2. Expected Peak Concentrations

The risk characterization for expected peak environmental concentrations depends largely on the application rate and the number of applications, as summarized in Table 11. The relationship between expected concentrations and the number of applications is not linear; moreover, the magnitude of the differences varies between central estimates and upper bounds of expected peak concentrations. In terms of the scenarios modeled in this risk assessment—i.e., eight applications of ULV formulations at application rates of 0.15 (0.11 to 0.23) lb a.i./acre versus one application of an EC formulation at application rates of 0.3(0.1 to 1.5) lb a.i./acre—the central estimates of peak concentrations for ULV formulations are somewhat higher than those for EC formulation; however, the upper bound estimates of peak concentrations for both types of formulations are similar.

The risk characterization for fish is also impacted substantially by the considerable difference between the toxicity values for sensitive species of fish (LC_{50} = 0.004 mg/L) and those for tolerant species of fish (LC_{50} = 11.7 mg/L). For tolerant fish species, the highest hazard quotient is 0.005 (the upper bound of expected peak concentrations in ambient water after the application of an EC formulation). This value, which is less than the LC_{50} by a factor of 200, is not likely to be associated with adverse effects in tolerant species of fish.

For sensitive species of fish, the risk characterization is much more severe. For ULV applications, the upper bounds of the hazard quotients exceed the LOC with values ranging from 1.9 to 4. Because the hazard quotients are based on LC_{50} values, fish mortality is a plausible effect of exposure. At the central estimate of plausible peak concentrations, the hazard quotients are 0.6 (lowest application rate), 0.8 (typical application rate), and 1.2 (highest application rate). Again, because the hazard quotients are based on LC_{50} values, fish mortality is a plausible effect of exposure. At the lower bounds, the hazard quotients for ULV applications range from 0.03 to 0.06. These hazard quotients are not likely to be associated with mortality of perhaps even adverse effects.

After the applications of EC formulations, which involve higher application rates but only a single application, the risk characterization for sensitive species of fish is very similar to that associated with multiple applications of ULV formulations. The upper bound of the hazard quotient is 2 at the typical application rate and ranges from1 to 15 for the spectrum of application rates. The central estimates of the hazard quotients are lower—i.e., 0.3 (0.1 to 1.5). These risk quotients substantially exceed the EPA level of concern for acute effects in endangered species (i.e., an LOC of 0.05). At the lower bounds of the hazard quotients—i.e., 0.04 (0.01 to 0.2), the EPA LOC values are exceeded only at the highest application rate.

The risk characterization for sensitive fish species is similar to the EPA's in that the range of RQ values (0.09 to 9.7) in the RED (U.S. EPA/OPP 2006a, Table 21, p. 53) corresponds well to the range of hazard quotients (0.04 to 15) presented in this risk assessment. Again, in risk characterizations, RQ values are the functional equivalent of HQ values.

4.4.3.1.3. Longer-term Concentrations

The risk characterization associated with longer-term exposures of fish to malathion differs markedly between sensitive and tolerant species not only because of the magnitude of the difference in toxicity values (i.e., 0.004 mg/L for sensitive species and 0.021 mg/L for tolerant species) but also because of the major difference in endpoints associated with each of the toxicity values (i.e., the acute LC_{50} for sensitive species and a chronic reproductive NOEC for tolerant species).

For tolerant species of fish, the highest hazard quotient is 0.04 (EC formulations at the highest application rate). This hazard quotient is less by a factor of 20 than the LOC (1.0) used by EPA and cited in the current risk assessment. Consequently, there is no plausible basis for asserting that longer-term exposures to malathion will induce adverse effects in tolerant species of fish.

The risk characterization for sensitive species of fish is much more complex. As discussed in Section 4.3.3.1, the U.S. EPA/OPP (2006a) characterizes chronic risks to fish using the 97-day reproductive NOEC of 21 ppb in rainbow trout (Cohle 1989). In the context of the EPA risk assessment, this is sensible in that the EPA uses an acute LC_{50} of 30 ppb in bluegills for assessing acute risks, and the NOEC of 21 ppb is the most conservative chronic toxicity value based on available studies.

Taking a more conservative approach, the current risk assessment uses the LC_{50} of 4 ppb in sensitive trout populations (Mayer and Ellersieck 1986) to characterize acute risks. Accordingly, it makes no sense to use the higher reproductive NOEC of 21 ppb in trout from the Cohle (1989) study.

As noted in Section 4.3.3.1, the toxicity values for fish are highly variable in studies viewed as acceptable by the U.S. EPA as well as the current risk assessment. The concern in the current risk assessment is that the chronic NOEC for sensitive species or populations of fish will clearly be lower than the reproductive NOEC of 21 ppb and lower (perhaps much lower) than the acute LC_{50} of 4 ppb in sensitive populations of trout or other salmonids. While a surrogate chronic NOEC for sensitive populations of fish could be developed using acute-to-chronic toxicity ratios, that approach is not used in current risk assessment. The application of such ratios to estimating chronic NOEC values is accompanied by a large measure of uncertainty that could distort rather than clarify risk. Thus, in the current risk assessment, the acute LC_{50} of 4 ppb is used to characterize risks associated with longer-term exposures, and its use is incorporated into the qualitative considerations of longer-term risks to sensitive species or populations of fish.

At the lower bound of the application rates as well as the typical application rates considered in this risk assessment, the maximum hazard quotient is 0.04 (the upper bound of the hazard quotient for EC formulations at an application rate of 1.5 lb a.i./acre). Even though the toxicity value used to generate these hazard quotients is an acute LC_{50}, it is not clear that adverse effects in sensitive populations of fish would result from longer-term exposures at the lower bound or typical application rates.

At the upper bounds of the application rates, however, the hazard quotients are range from 0.001 to 0.1 for ULV formulations and from 0.0008 to 0.2 for EC formulations. While the central estimates and lower bounds do not reach a level of concern, the upper bounds of the hazard quotient (from 0.1 to 0.2) exceed the LOC for endangered species (0.05). Again, because the acute LC_{50} is used to characterize risks of chronic exposure, these upper bound hazard quotients should be regarded with substantial concern because they may underestimate the risk of adverse reproductive effects.

Because the toxicity values used in the current risk assessment are different from those used in the EPA risk assessment (U.S. EPA/OPP 2006a), the risk characterization for longer-term effects in the current risk assessment is more severe than EPA's. Longer-term RQ values in the. EPA RED (2006a, Table 22, p. 52) exceed the level of concern only for malathion application rates of 2 lbs a.i./acre, which is higher than the application rates that will be used in Forest Service related programs.

4.4.3.2. Amphibians

Qualitatively, the risk characterization for amphibians is similar to that for fish. Hazard quotients associated with the accidental spill scenario are substantially above the level of concern for sensitive species for EC formulations and substantially above the level of concern for both sensitive and tolerant species for ULV formulations. Expected peak concentrations lead to exceedances of the level of concern for sensitive species of amphibians with the maximum hazard quotients reaching 27 for ULV formulations and 102 for EC formulations. Expected longer-term concentrations also exceed the level of concern for sensitive species but only at the upper bound of the HQ at the highest application rate for ULV formulations (HQ=1.2) and EC formulations (HQ=2).

4.4.3.2.1. Accidental Spills

The accidental spill of a ULV formulation into a small pond results in hazard quotients for sensitive species of amphibians of over 1 million and for tolerant species of over 150. Since these HQ values are based on LC_{50}s, there is no real difference in the qualitative risk characterization. As with fish, the accidental spill of 200 gallons of a ULV formulation into a small pond is expected to cause substantial mortality in both sensitive and tolerant species of amphibians.

Also as with fish, the risk characterization for the accidental spill of a field solution of an EC formulation is contingent on the application rate, the field dilution, and differences between sensitive and tolerant species of amphibians. Sensitive species of amphibian would likely be affected by the accidental spill of an EC formulation across the range of application rates and dilution volumes. At the lowest application rate, the hazard quotients for sensitive species are 1540 (154 to 15,397). The qualitative risk characterization is essentially identical to that for ULV formulations: mortality would be substantial.

For tolerant species of amphibians, the risk characterization is only modestly nuanced. At the lowest and typical application rates, the lower bounds of the hazard quotients are 0.02 and 0.05,

respectively. These hazard quotients are associated with the most dilute field concentration (100 gallon per acre, as described in Section 2.4.2). These hazard quotients do not exceed the EPA LOC value of 0.05 for endangered species. All other hazard quotients for tolerant species of amphibians range from 0.2 to 23. At hazard quotients that approach or exceed unity, mortality would be likely. At a hazard quotient of 23, substantial mortality would be expected.

4.4.3.2.2. Expected Peak Concentrations

The expected peak concentrations of malathion in surface water (i.e., non-accidental) are far below those associated with the accidental spill scenario for either ULV formulations (EEC values less than the spill concentrations by factors ranging from about 90,000 to more than 6 million) or EC formulations (EEC values less than the spill concentrations by factors ranging from about 1800 to 2300). Consequently, the risk characterization associated with expected peak concentrations is much less severe than that associated with the accidental spill.

As with tolerant fish species, adverse effects are not likely to be observed in tolerant species of amphibians exposed to malathion. The highest hazard quotient is 0.01 (the upper bound of the HQ for EC formulations at the highest application rate), below the LC_{50} of a factor of 100. Other hazard quotients range from 0.000008 to 0.0001 for EC formulations and from 0.00002 to 0.003 for ULV formulations. With respect to EPA's convention of taking the lowest LOC—i.e., 0.05 for endangered species—the hazard quotients are lower than the LOC for EC formulations by factors ranging from 5 to about 166 and lower than the LOC for ULV formulations by factors ranging from 16 to 2500.

For sensitive amphibian species, the risk characterization is much more severe. Hazard quotients associated with the application of ULV formulations range from 0.2 to 13 at the lowest application rate used for mosquito control – i.e., 8 applications at 0.11 lb a.i./acre separated by one-week intervals. For EC formulations, hazard quotients from 0.08 to 7 at the lowest application rate – i.e., 1 application at 0.1 lb a.i./acre.

The hazard quotients are linearly related to the application rate. For ULV formulations, the range of application rates is relatively narrow (about a factor of 2) and thus the hazard quotients at the highest application rate are only about a factor 2 higher than those at the lowest application rate. For EC formulations, however, the highest application rate is 1.5 lb a.i./acre, a factor of 15 above the lowest application rate. Thus, for sensitive species of amphibians, the hazard quotients for expected peak concentrations at the highest application rate are substantial: 10 with a range from 1.3 to 102. These hazard quotients could be associated with substantial mortality in sensitive populations of amphibians.

4.4.3.2.3. Longer-term Concentrations

Ideally, hazard quotients for longer-term exposures of aquatic organisms should be based on reproduction studies. These can be either life-cycle studies, which are commonly available for *Daphnia* and sometimes for fish or early life-stage studies that are commonly available for fish, usually trout or minnows. As discussed in Section 4.3.3.2, however, amphibian life-cycle reproduction studies are not available.

Developmental studies, however, are available, and the developmental NOEC of 0.75 mg/L from the Bonfanti et al. (2004) bioassay is used to assess longer-term effects in tolerant species of amphibians. The highest hazard quotient based on the developmental NOEC is 0.001. For chronic effects, both the Forest Service and the EPA use an LOC of 1 when the hazard quotient is based on an NOEC or equivalent value. Thus, the highest hazard quotient of 0.001 is a factor of 1000 below the level of concern.

The risk characterization for sensitive species of amphibians is much more severe, particularly for EC formulations, but is also much less certain. As discussed in Section 4.3.3.2, the longer-term toxicity value for sensitive species of amphibians is 0.35 ppb but this value is based on the relative potency method using the chronic NOEC for *Daphnia magna*. For ULV formulations – i.e., applications for mosquito control – all HQ values are below the level of concern except for the HQ of 1.2, the upper bound of the HQ at the highest application rate. For EC formulations, the risk characterization is dependant on the application rate. At the typical and lower bound of the application rates, the highest HQ is 0.4, below the level of concern by a factor of 2.5. The highest application rate, however, the HQ is 2. Because the toxicity value is based on the relative potency method rather than direct data on amphibians, the qualitative interpretation of these relatively modest excursions above the level of concern is unclear.

4.4.3.3. Aquatic Invertebrates

4.4.3.3.1. Accidental Spills

Consistent with the available information on terrestrial species, aquatic arthropods appear to include the species most sensitive to malathion. In the accidental spill scenarios, the hazard quotients for arthropods range from about 700,000 to nearly 1.5 million for ULV formulations and from about 90 to 140,000 for EC formulations. Since these hazard quotients are based an acute LC_{50}, the interpretation of risk is trivial. Sensitive aquatic invertebrates, such as small arthropods, will be killed in a spill as severe in nature as the one used in this risk assessment.

Larger arthropods and other groups of aquatic invertebrates appear to be much less sensitive to malathion. In the current risk assessment, the LC_{50} of 49 mg/L for crayfish (Holck and Meek 1987) is used to assess risks for tolerant species of invertebrates. This acute toxicity value is a factor of 49,000 higher than the daphnid LC_{50} of 0.001 mg/L used to assess risk for sensitive species of arthropods.

Despite the substantial difference in toxicity between sensitive and tolerant species, the scenario for the accidental spill of ULV formulations leads to hazard quotients ranging from 14 to 29 across the spectrum of application rates. The interpretation of risk is essentially identical to that for sensitive species: mortality is likely to be substantial.

The hazard quotients for tolerant species of invertebrates associated with spills of EC formulations are much lower because of the lower concentration of malathion in field solutions of EC formulations. At the highest rate of dilution (i.e., an application volume of 100

gallons/acre), the hazard quotients are 0.002 at the lowest application rate, 0.006 at the typical application rate, and 0.03 at the highest application rate. All of these hazard quotients are below the LOC for endangered species. Across the range of application volumes, the lowest application rate exceeds the LOC for endangered species and acute toxicity only at the upper range of the hazard quotient (i.e., 0.2 for the lowest dilution). For the typical application rate, the central and upper bound values of the hazard quotient are 0.06 and 0.6, respectively. At the highest application rate, the central and upper bound values of the hazard quotient are 0.3 and 3, respectively. All of these hazard quotients exceed the LOC for endangered species; moreover, the hazard quotients that approach or exceed 1 are likely to be associated with mortality in tolerant species of invertebrates that is at least detectable and perhaps substantial.

4.4.3.3.2. Expected Peak Concentrations

The risk characterizations for expected peak concentrations differ substantially for sensitive and tolerant species of invertebrates. By comparison, differences between ULV and EC formations are modest because of offsetting differences in the number of applications and application rates used in the exposure assessments of the two types of formulations.

For sensitive species of invertebrates, the hazard quotients range from 0.05 (the lower bound of the hazard quotient for EC formulations at the lowest application rate) to 60 (the upper bound of the hazard quotient for EC formulations at the highest application rate). The lower bound reaches the LOC for endangered species (0.05). The corresponding hazard quotient for ULV formulations is 0.1, above the LOC for endangered species by a factor of 2. The only other hazard quotient less than 1 is the central estimate of the hazard quotient for EC formulations at the lowest application rate (0.4). This hazard quotient approaches the LOC for acute toxicity (0.5). In all other cases, the hazard quotients are greater than 1 for sensitive species of invertebrates, mortality in invertebrate populations is likely. Furthermore, at the upper range of the hazard quotients, mortality is virtually certain.

The risk characterization for tolerant species of aquatic invertebrates is much less severe. The highest hazard quotient based on expected peak concentrations is 0.0003 (ULV formulations at the highest application rate). This hazard quotient is below the LOC for endangered species by a factor greater than 150 (0.05/0.0003 = 166.6). There is no basis for asserting that peak concentrations of malathion in surface water are likely to have an adverse impact on tolerant species of invertebrates—i.e., large arthropods and gastropods.

4.4.3.3.3. Longer-term Concentrations

Malathion is not persistent is water, and longer-term concentrations are much lower than the expected peak concentrations. In addition, while the chronic toxicity value for sensitive invertebrates is based on a life-cycle study in daphnids and is extremely low—i.e., 0.0006 mg/L—the acute toxicity value for malathion is only modestly higher—i.e., 0.001 mg/L. Consequently, the risk characterization for expected longer-term concentrations of malathion in surface water is much less severe than that of expected peak concentrations.

For sensitive species of invertebrates, like small arthropods, hazard quotients range from 0.004 (ULV formulations at the lowest application rate) to 1.3 (EC formulations at the highest application rate).

Because the toxicity value for deriving the hazard quotients for sensitive invertebrates is based on the NOEC of 0.06 ppb from a life-cycle study, the LOC is 1. In the study that yielded this NOEC (Blakemore and Burgess 1990), the LOEC was 0.1 ppb, only slightly higher than the NOEC of 0.06 ppb. Thus, the LOEC would correspond to a hazard quotient of about 1.7 [0.1 ppb/0.06 ppb = 1.66]. Even though the hazard quotient of 1.3 is only modestly above the LOC, concern for adverse reproductive effects cannot be dismissed. Concern for the hazard quotient of 1.3 is enhanced by the observation of Tessier et al. (2000) of sublethal effects (abnormal capture nets) in Caddisfly larvae at 0.01 ppb, a factor of 6 below the NOEC for reproductive effects in daphnids. While chronic toxicity values for invertebrates are generally and appropriately based on reproduction studies, other sublethal endpoints, such as those associated with feeding capability, are important.

Notwithstanding concern for the hazard quotient of 1.3, the central estimate of the hazard quotient for EC formulations at the highest application rate is 0.05, substantially below the LOC. For ULV formulations, the upper bound of the hazard quotient at the highest application rate is 0.7, approaching but less than the LOC based on the toxicity value of 0.06 ppb in daphnids. All other hazard quotients for sensitive invertebrates are in the range of 0.0003 to 0.3, below the LOC by factors of about 3 to over 3000.

As noted at the start of this risk characterization for aquatic organisms (Section 4.4.3), the risk characterization for all aquatic organisms is based on very conservative exposure assumptions that are not representative of all areas. Thus, while there is concern for longer-term effects in sensitive species of aquatic invertebrates, site-specific or region-specific exposure assessments should be used to refine the risk characterization presented in this generic and very conservative risk assessment.

The risk characterization for tolerant species of invertebrates is not based on a full life-cycle study. Nonetheless, the study on which it is based, Tchounwou et al. (1992), examined different life-stages in snails, and the most sensitive life-stage (eggs) is used to derive the hazard quotient for tolerant species. The highest hazard quotient for tolerant species of invertebrates is 0.0006 (the upper bound of the hazard quotient for EC formulations), which is less than the LOC by a factor greater than 1600. There is no basis for asserting that exposure to malathion in Forest Service related activities will cause adverse effects in tolerant species of invertebrates. As with the risk characterization for amphibians, confidence in this risk characterization would be enhanced by full life-cycle studies on tolerant species of invertebrates, like snails or crayfish, for example. Such studies, however, are not required by the EPA for pesticide registration. Consequently, such studies are seldom conducted.

4.4.3.4. Aquatic Plants

4.4.3.4.1. Accidental Spills

As with other groups of aquatic organisms, the hazard quotients for aquatic plants associated with accidental spills are much higher for ULV than EC formulations. For ULV formulations, accidental spills of 200 gallons of the undiluted formulation into a small pond results in HQ values of 5 for tolerant species of algae, 1,862 for sensitive species of algae, and 39 for aquatic macrophytes. As discussed in Section 4.3.3.4, the available data do not support separate dose-response assessments for tolerant and sensitive species of aquatic macrophytes.

For EC formulations at the lowest application rate, the hazard quotients exceed the level of concern only for sensitive species of algae – a central HQ value of 1.8 and a range of 0.2 to 18. At the typical application rate, the HQ values also exceed the level of concern for sensitive species of algae – a central HQ value of 5 and a range of 0.5 to 55 – and marginally exceed the LOC for macrophytes at the upper bound – a central HQ value of 0.1 and a range of 0.01 to 1.1. At the highest application rate, the HQ values are substantial for sensitive species of algae – i.e., a central HQ value of 27 and a range of 3 to 273 – but only exceed the LOC for macrophytes at the upper bound – i.e., a central HQ value of 0.6 and a range of 0.06 to 6. For tolerant species of algae, the HQ values do not exceed the level of concern even at the upper bound of the HQ at the highest application rate – i.e., an HQ value of 0.7.

4.4.3.4.2. Expected Peak Concentrations

Based on expected peak concentrations, none of the HQ values for aquatic plants exceed the level of concern. The highest HQ value is 0.1 – sensitive species of algae at the highest application rate for an EC formulation – which is below the level of concern by a factor of 10.

4.4.3.4.3. Longer-term Concentrations

Based on expected longer-term concentrations, the HQ values for aquatic plants are substantially below the level of concern. The highest HQ value is 0.002 – sensitive species of algae at the highest application rate for an EC formulation – which is below the level of concern by a factor of 500.

5. REFERENCES

NOTE: The initial entry for each reference in braces {} simply specifies how the reference are cited in the text. The final entry for each reference in brackets [] is for internal tracking of documents as well as documentation for the information sources used.

APHIS	**References from 2001 APHIS risk assessment, n=1017.**
EPA	**Studies summarized in various risk assessments by the U.S. EPA.**
SET00	**Papers from previous Forest Service risk assessments.**
SET01	**Ordered from NAL in early November, 2006.**
SET02	**Supplemental papers added in 2007.**
SET03	**Supplemental papers on the environmental fate of malaoxon added in February 2007.**
SET04	**Supplemental papers added in March to May 2008 in response to peer review.**
Std	**Standard citations used in most Forest Service risk assessments.**
Carb	**Papers brought over from carbaryl risk assessment.**
Internet	**Various reports on malathion. Most are from the U.S. EPA/OPP E-Docket No. OPP-2004-0348 available at http://www.regulations.gov. This was last checked on September 17, 2007.**

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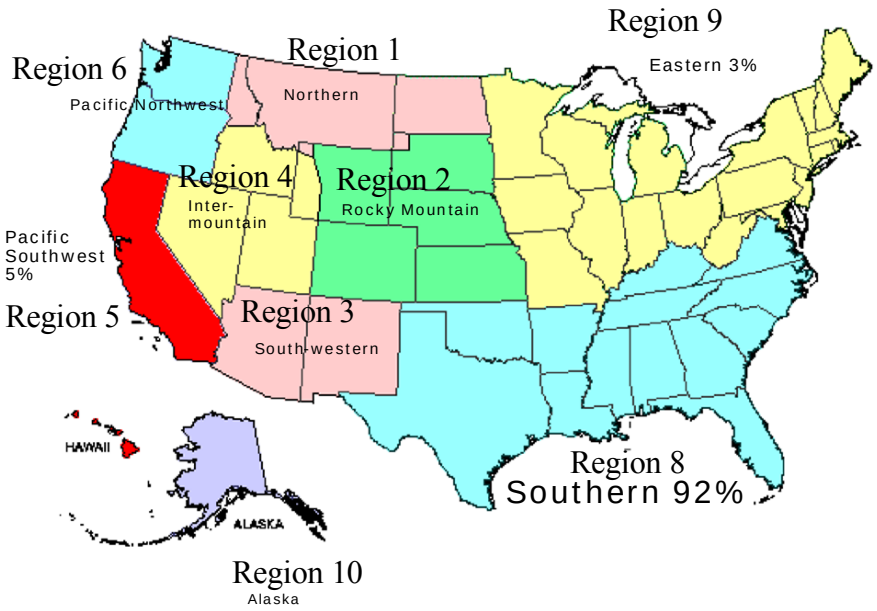
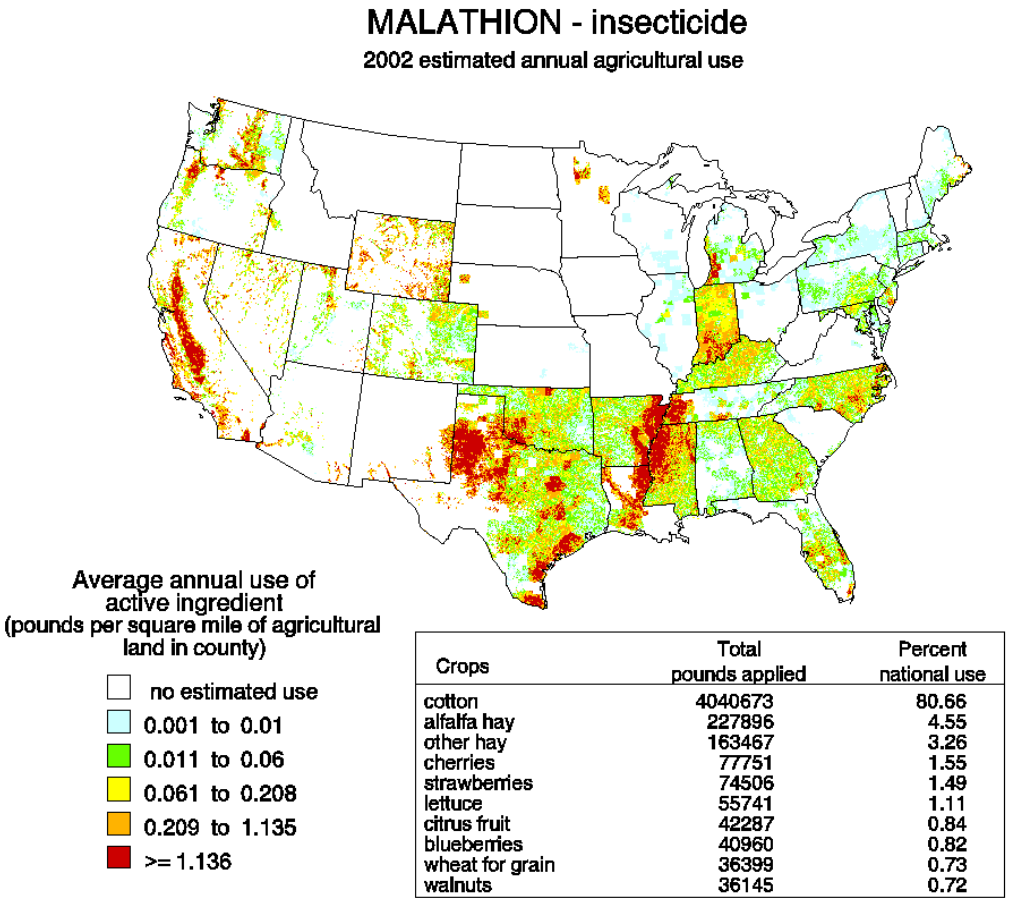


Figure 1: Uses of malathion by the Forest Service in 2004
Source: http://www.fs.fed.us/foresthealth/pesticide/reports.shtml



Crops	Total pounds applied	Percent national use
cotton	4040673	80.66
alfalfa hay	227896	4.55
other hay	163467	3.26
cherries	77751	1.55
strawberries	74506	1.49
lettuce	55741	1.11
citrus fruit	42287	0.84
blueberries	40960	0.82
wheat for grain	36399	0.73
walnuts	36145	0.72

Figure 2: Agricultural uses of malathion in the United States.
Source: U.S. Geologic Survey (USGS 2003)

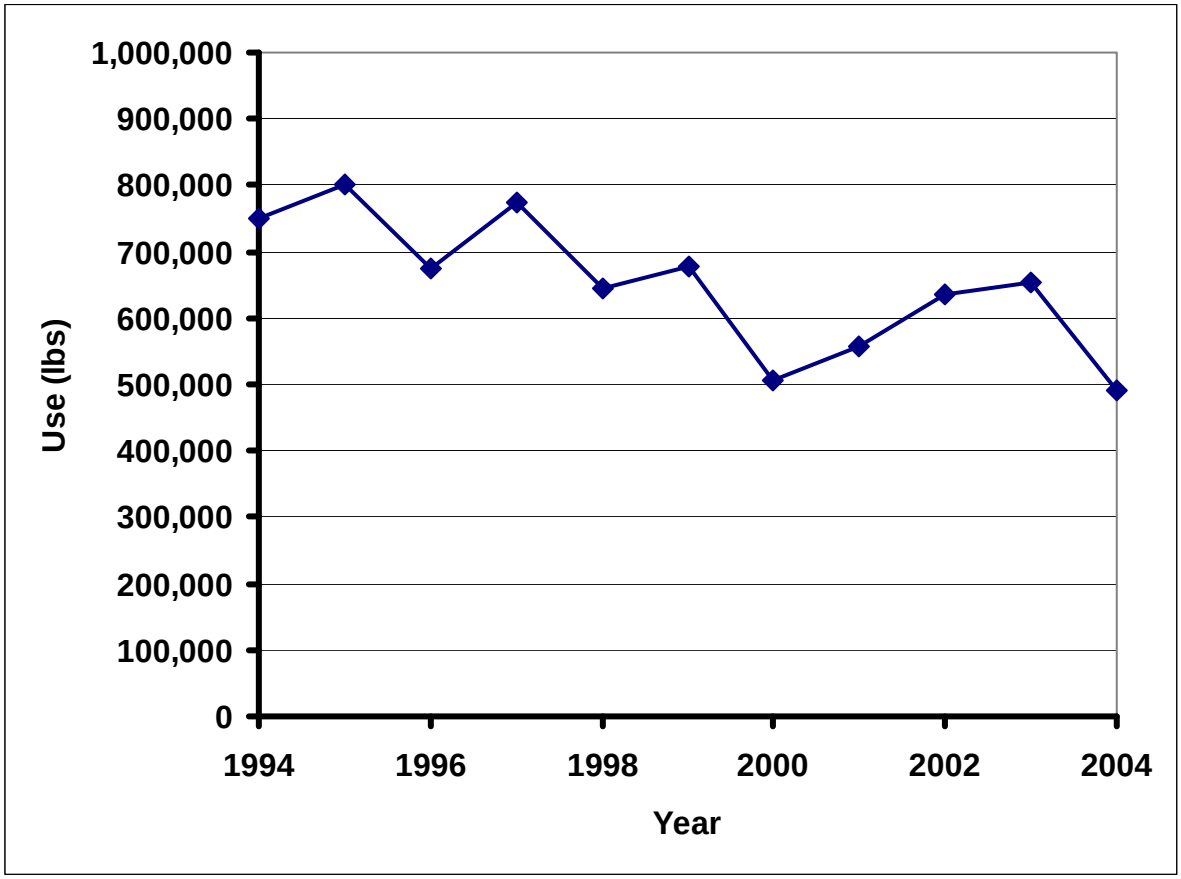


Figure 3. Use of malathion in California from 1994 to 2004
Source: California Department of Pesticide Regulation (CDPR 2006, Table 5a, p. 25)

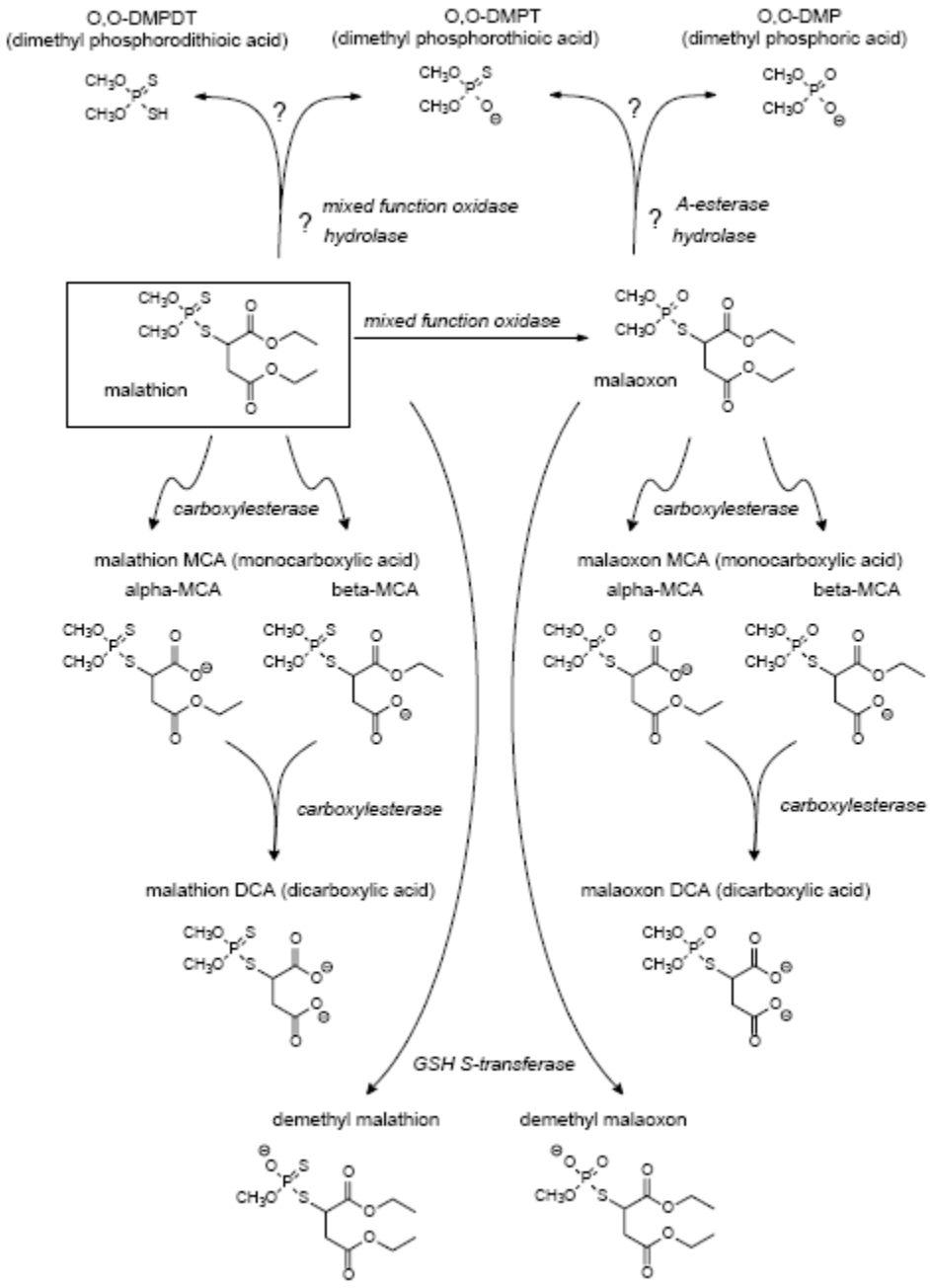


Figure 4: Metabolic Pathways for Malathion
Source: ATSDR 2003

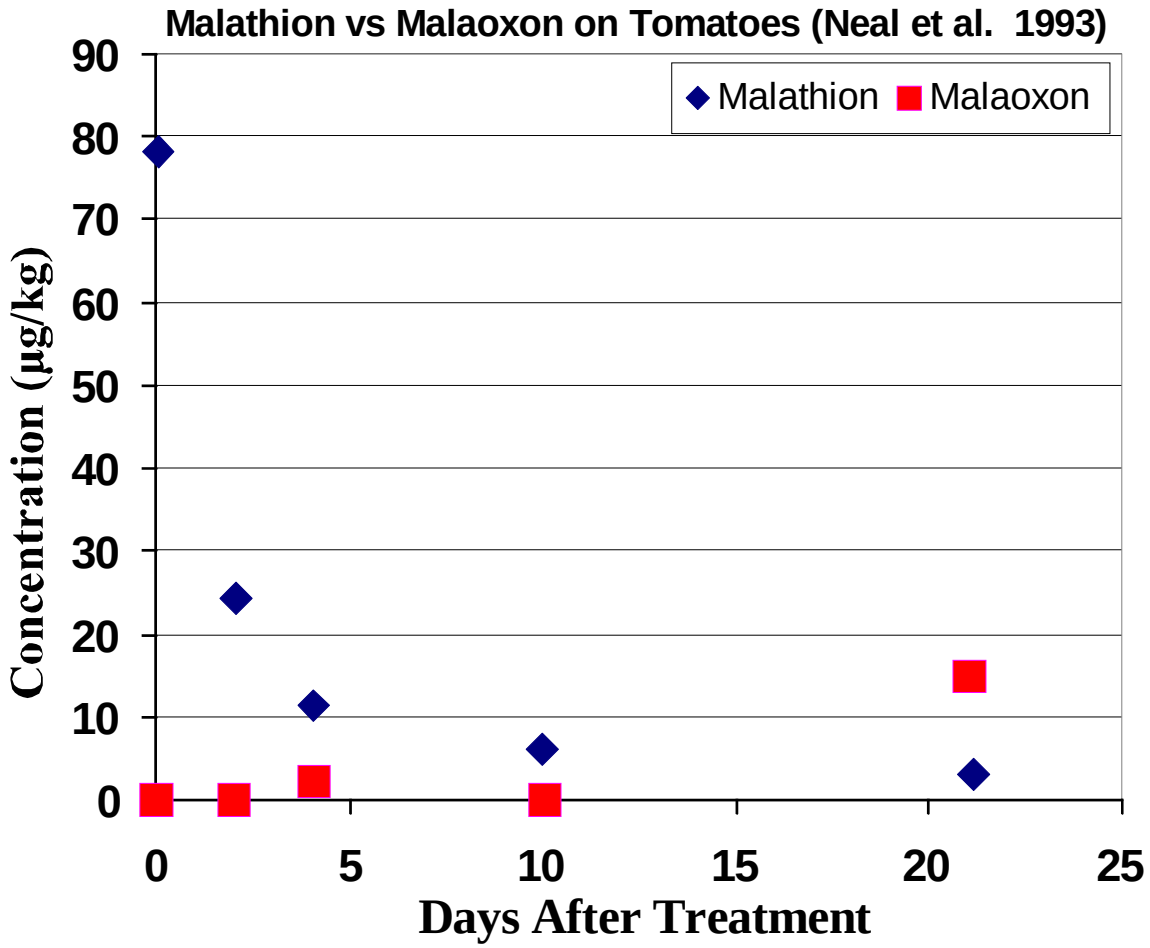


Figure 5: Residues of Malathion and Malaoxon on Tomatoes

Source: Redrawn form Neal et al. (1993). Malathion data from Figure 9 (p.47) and malaoxon data from Figure 10, p. 48. Data read using GraphRead Version 1b, available www.sera-inc.com. Data summarized below:

Day	Malathion	Malaoxon
0	78.0	
2	24.3	
4	11.3	2.2
10	6.0	
21	3.0	15.0

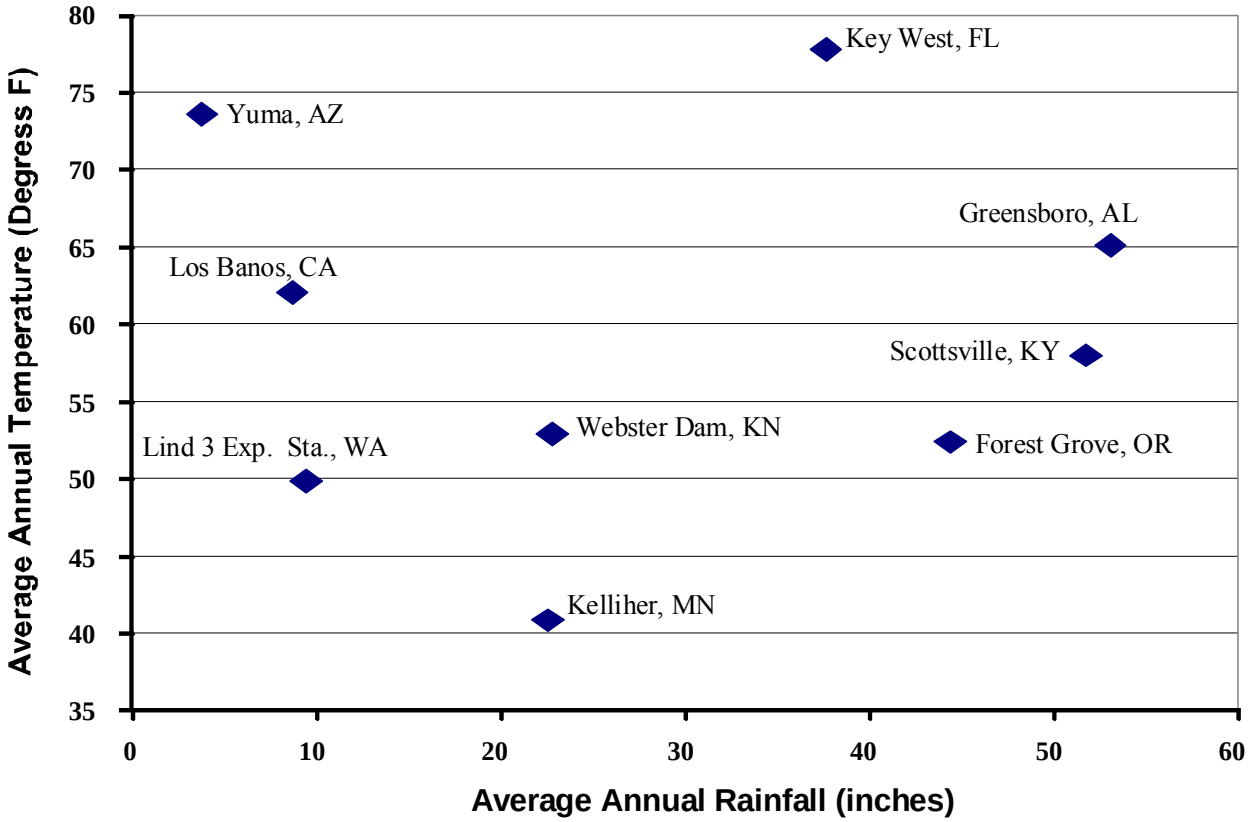


Figure 6: Specific Sites Used in Gleams-Driver Modeling

Table 1: Selected physical and chemical properties of malathion

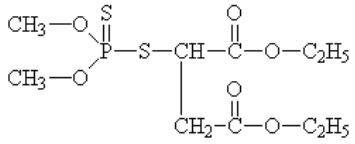
Item	Value
Structure [1]	
Aerobic soil metabolism, days	**3 (U.S. EPA/OPP 2006e)**
Aerobic aquatic metabolism, days	**3.3 (U.S. EPA/OPP 2006e)**
Anaerobic sediment (aqueous) half-time (days)	2.5 (pH 7.8) (Blumhorst1991)
Bioconcentration factor (BCF)	4.2 to 18 (Edible) (U.S. EPA/OPP 2005L) 23 to 135 (Whole fish) (U.S. EPA/OPP 2005L)
Boiling Point	156-157℃/0.7 mm Hg (Tomlin 2004) 120℃ (Freed et al.1979)
CAS number [1]	121-75-5
Density (g/ml)	1.23
Field dissipation half-time (days)	6.4 and 6.6 (field winter, Kaur et al.1998) 2.1 and 2.7 (field, summer, Kaur et al.1998) $\ln t½_{(hours)} = 5.98 + 2.84(pH) - 0.326(pH^2) - 0.202(T_C) + 0.00135(T_C{}^2)$ (Beyers and Myers 1996)
Foliar half-time (days)	3 (Knisel and Davis 2000) **5.5 [ke=0.126 d^{-1}](U.S. EPA/OPP 2006e)** 2.4 to 2.6 (Hernandez et al. 2002) 1.14 (Prieto et al. 2002)
Foliar washoff fraction	0.9 (Knisel and Davis 2000) 0.5 (U.S. EPA/OPP 2006e)
Henry's law constant	0.00114 Pa m3/mol (USDA/ARS 1995) 1.21 x 10^{-2} Pa m^3 mol^{-1} (Tomlin 2005, calc)
log K_{oc}	3.25 (Knisel and Davis 2000) 2.17-2.26 [log of 151-183] (Blumhorst 1989) 2.17 [log of 151] (U.S. EPA/OPP 2006e)
log K_{ow}	2.7 [K_{ow}=501] (USDA/ARS 1995) 2.75 [K_{ow}=562] (Tomlin 2004) 2.89 [K_{ow}=776] (Chiou et al. 1977; Freed et al.1979)
Melting Point [1]	2.85℃
Molecular weight [1]	330.4
Physical state	Technical grade: Clear amber liquid (Tomlin 2004)

Table 1: Selected physical and chemical properties of malathion *(continued)*

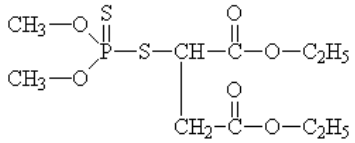
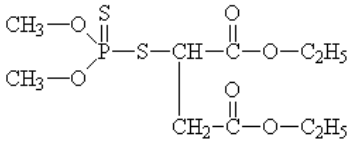
Item	Value
Structure [1]	
Odor	mercaptan (Agrimor Int'l Co. 2001) garlic-like (Guy 2001)
Odor thresholds	1 ppm in water (Fazzalari1978) 13.5 mg/m^3 in air (Ruth1986)
Soil half-time (days)	1 (Knisel and Davis 2000) <1 to 1 (Konrad et al.1969) < 1 (U.S. EPA/OPP 2000c: summary of several studies) 3.6 (sand) and 28 (loam) (Neal et al.1993) - see Section 3.2.3.9 for discussion.
Synonyms [1]	diethyl (dimethoxythiophosphorylthio)succinate [IUPAC] S-1,2-bis(ethoxycarbonyl)ethyl O,O-dimethyl phosphorodithioate [IUPAC] diethyl [(dimethoxyphosphinothioyl)thio]butanedioate [CAS]
U.S. EPA Reg. No.	1812-407 [Atrapa ULV] 67760-34 [Fyfanon ULV]
Vapor pressure [1 Pascal = 133.3 Pascals] [1 mPa=mm Hg/133,300]	5.3 mPa (30 °C) 3.38×10^{-6} mm Hg (0.45 mPa in USDA/ARS 1995) 1.25×10^{-4} mm Hg (Freed et al. 1979) 4.0×10^{-5} mm Hg (5.3 mPa Tomlin 2004) 1.3×10^{-5} mm Hg (1.7 mPa in Tsuzuki 2000)
Water half-time (hydrolysis) (days)	106 [pH 5, 25°C (ke = 0.00650/day)] (USDA/ARS 1995) 6.3 [pH 7, 25°C (ke = 0.11/day)] (USDA/ARS 1995) 0.49 [pH 9, 25°C (ke = 1.41/day)] (USDA/ARS 1995) 18.0 [pH 4.5, 25°C (ke = 0.039/day)] (Chapman and Cole 1982) 21.0 [pH 6, 20°C (ke = 0.033/day)] (Chapman and Cole 1982) 2.0 [pH 7, 20°C (ke = 0.34/day)] (Chapman and Cole 1982) 0.5 [pH 8, 20°C (ke = 1.4/day)] (Chapman and Cole 1982) 10.5 [pH 7.4, 20°C (ke=0.066/day](Freed et al.1979) 1.3 [pH 7.4, 37.5°C (ke=0.53/day](Freed et al.1979) 42 [pH 6.1, 22 °C (ke=0.017/day](Lartiges and Garrigues 1995) 19 [pH 7.3, 22°C (ke=0.036/day](Lartiges and Garrigues 1995) 6 [pH 8.1, 22°C (ke=0.12/day](Lartiges and Garrigues 1995) **6.21 (U.S. EPA/OPP 2006e)** **104 [conversion to malaoxon] (U.S. EPA/OPP 2005n)**
Water half-time (photolysis) (days)	**94 (U.S. EPA/OPP 2006e)**

Table 1: Selected physical and chemical properties of malathion *(continued)*

Item	Value
Structure [1]	
Water solubility (mg/L) [1]	130 (USDA/ARS 1995; Harman-Fetcho et al. 2000) 145 (20-25 °C)(Freed et al.1979; Tomlin 2004) 145 (20 °C)(Chiou et al. 1977) 130 (Knisel and Davis 2000) **145 (U.S. EPA/OPP 2006e)**

[1] Specific environmental fate parameters used in modeling are discussed in Section 3.2. Values used by U.S. EPA/OPP are given in bold face. Common values (e.g., molecular weight, synonyms) are given in many standard references (e.g. EXTOXNET 1996; USDA/ARS 1995). Preference is given to Tomlin (2004) and other citations are given only if values differ remarkably.

Table 2: Malathion formulations

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
*Agrisolutions Malathion 5** Agriliance, LLC (St Paul, MN) **EPA Reg. No. 9779-5** 56.8% malathion 43.2% inert ingredients (**contains 5 lbs a.i./gallon**) emulsifiable concentrate may be applied by ground sprayers or airplanes	Outdoor adult mosquito control**: use a 2% to 5% formulation area or fog spray.** For a 2% spray, dilute 1 part of formulation with 28 parts of water, for 5%, dilute 1 to 11. ***Repeat as necessary***. Mosquito larvae control: to treat mosquito larvae in standing water, intermittently flooded areas, stagnant water, and temporary rain pools, **apply 13 oz formulation/acre**. Broadcast use permitted over intermittently flooded areas. **Limitation:** *Application may not be made around bodies of water where fish or shellfish are grown and/or harvested commercially.*	contains **35.2% xylene** range aromatic solvent MSDS reports: 1.05% xylene 42.15% formulation aids
*also sold and distributed by Agriliance, LLC as: Cloverbrand malathion 5ec; Fcc mal-53; Malathion 5; Red panther malathion 5 ec; and S.f.a. mal-5e		
Fyfanon*® The Premium Grade Malathion Helena Chemical Co (Collierville TN) **EPA Reg. No. 5905-196** 56.44% malathion 43.56% inert ingredients (**contains 5 lbs a.i./gallon**) emulsifiable concentrate may be applied by air or ground equipment also sold and distributed by Helena Chemical Co. as:	Outdoor adult mosquito control: **use a 2% to 5% formulation area or fog spray.** For a 2% spray, dilute 1 part of formulation with 28 parts of water, for 5%, dilute 1 to 11. ***Repeat as necessary***. Mosquito larvae control: to treat mosquito larvae in standing water, intermittently flooded areas, stagnant water, and temporary rain pools, **apply 13 oz formulation/acre**. Broadcast use permitted over intermittently flooded areas. **Limitation:** *Application may not be made around bodies of water where fish or shellfish are grown and/or harvested commercially.*	Contains xylene range aromatic solvent (NOS) MSDS reports: 37.60% petroleum distillates 5.96% inert ingredients
*also sold and distributed by Helena Chemical Co. as Cythion The Premium Grade Malathion		

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Fyfanon®ULV* Ultra Low Volume Concentrate Insecticide Cheminova, Inc (Wayne, NJ) **EPA Reg. No. 67760-34** 96.5% malathion 3.5% inert ingredients (**contains 9.9 lbs a.i./gallon)** labeled for aerial and ground application	AERIAL APPLICATION: Adult mosquito control over cities, towns, and other areas where automobiles, trailers, trucks, and pleasure boats are present**: Apply 2.6 to 3.0 fl oz formulation/acre**. GROUND APPLICATION: Thermal aerosols or fogs for control of adult mosquitoes: **Apply 6 to 8 oz. actual/gallon (3.9-5.2 gallons formulation in 100 gallons finished solution)** by ground equipment delivering 40 gallons per hour at a vehicle speed of 5 miles per hour to treat a swath width of 300-400 feet. Nonthermal Aerosols for Adult Mosquito Control : can be obtained over a 300-foot swath with nonthermal aerosols of formulation (see label for details) Adult Mosquitoes on Rangeland, Pasture, and Other Uncultivated Non-Agricultural Areas (Wastelands, Roadsides)**:** Apply **2 to 4 fl oz/acre** by ground or air. **Repeat as necessary.** **Limitation:** *Do not apply around bodies of water where fish or shellfish are grown and/or harvested commercially.*	MSDS does not specify inerts
*also sold and distributed by Cheminova, Inc. as Agrisolutions malathion ULV; Malathion ULV; and Prentox malathion ULV		

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Fyfanon® 8 Lb. Emulsion **The Premium Grade Malathion** Helena Chemical Co. (Collierville, TN) **EPA Reg. No. 5905-250-ZA** 81.43% malathion 18.57% inert ingredients (**contains 8 lbs a.i./gallon**) labeled for aerial and ground application	Mosquito Control**: 2% to 5% fog, aerosol or space spra**y (2% solution: dilute 1 part in 45 parts of water, fuel oil or diesel oil. When using kerosene-type solvent as carrier, dilute 1 part in 45 parts of a mixture consisting of 4 parts kerosene-type solvent and 1 part aromatic hydrocarbon-type solvent; 5% solution: dilute 1 part in 18 parts of mixture using similar olvents). Mosquito Larvae In Standing Water**: 8 fl oz (approx 1/2 pint)/ acre.** ***Repeat applications as necessary***. Adult Mosquito Control: **2.4 to 4.8 fl oz/acre for adult mosquitoes and 7.2 to 9.6 fl oz/acre for adult mosquitoes and flies.** ***Repeat as necessary.*** **Limitation:** *Keep out of fish bearing waters; oil-based formulations may injure ornamental plants. Do not apply around bodies of water where fish or shellfish are grown and/or harvested commercially.*	MSDS reports: 10.57% petroleum distillates (TLV = 100 ppm for skin; Hazard = skin and eye irritant) 8.00% inert ingredients (non-hazardous).
Gordon's Malathion 50% Spray **For Flies and Garden Insects*** ***Even Gets Mosquitoes*** pbi/Gordon Corp. (Kansas City, MO) **EPA Reg. No. 33955-394** 50% malathion 50% inert ingredients (**contains 8.7 lbs a.i./gallon**) emulsifiable concentrate to be applied as fog spray for outdoor mosquito control	Mosquitoes Outdoors**: 11 tablespoons/gallon of water, fuel oil, or diesel oil (may be used as the carrier or diluents) and apply as fog or spray** to yard, patio, or other outdoor area. Repeat as necessary. **Limitations:** *highly toxic to bees, and toxic to fish, aquatic invertebrates, and aquatic life stages of amphibians. For terrestrial uses, do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Drift and runoff may be hazardous to aquatic organisms in areas near the application site. Do not contaminate water when disposing of equipment wash water.O*il *solutions may injure ornamental species.*	**MSDS reports**: 1,2,4-trimethyl benzene 12.3% cumene 0.6% ethyl benzene 0.2% petroleum solvent 24.2% Xylenes 1.2%

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
*also sold and distributed by PBI/Gordon as: 49'er malathion-50; Acme malathion 50% spray; Easy/gone concentrate malathion 50 insect spray; Easy gone concentrate multi-purpose fruit & vegetable malathion insect spray; Greenall malathion 50 insect control; Kxl malathion 50; Master nurseryman malathion 50 insect control; Proguard malathion-50		
Gowan Malathion 8 Flowable* Agricultural Insecticide Gowan Co. (Yuma, AZ) **EPA Reg. No. 10163-21** 79.5% malathion 20.5% other ingredients (**contains 8 lbs a.i./gallon**) emulsifiable concentrate product may be applied by air or ground equipment **This product is also labeled for use around the outside of buildings and small grain storage facilities.**	**Mosquito Control: 2% to 5% malathion fog, aerosol, or space spray**. (2% solution: dilute 1 part formulation in 45 parts water, fuel, or diesel oil. When using a kerosene-type solvent as a carrier, dilute 1 part formulation in 45 parts solvent consisting of 4 part kerosene-type solvent and 1 part aromatic hydrocarbon-type solvent). **Apply 0.58 to 2.86 gallons finished spray/acre.** (5% solution: dilute 1 part formulation in 18 parts solvent). **Apply 0.24 to 1.18 gallons finished spray/acre.** **Mosquito Larvae in Standing Water**: **8 fl oz/acre**. **Repeat as necessary**. **Limitations:** *Only for use in intermittently flooded areas, stagnant water, temporary rail ponds, and log ponds – KEEP OUT OF ANY FISH BEARING WATERS; broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and harvested commercially; oil-based formulations may injure ornamental s.*	**MSDS reports**: 3.1% 1-butanol only the identity of the *hazardous* ingredients are listed.
*also sold by Gowan Co. as Agro-chem brand malathion 8e; Prokil malathion 8e		

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Gowan Malathion 8 **Agricultural Insecticide** Gowan Co. (Yuma, AZ) **EPA Reg. No. 67545-AZ-1** 79.5% malathion 20.5% other ingredients (**contains 8 lbs a.i./gallon**) product may be applied by air or ground equipment **This product is also labeled for use around the outside of buildings and small grain storage facilities.**	**Mosquito Control: 2% to 5% malathion fog, aerosol, or space spray**. (2% solution: 1 part formulation to 45 parts water, fuel, or diesel oil. When using a kerosene-type solvent as a carrier, dilute 1 part formulation in 45 parts solvent consisting of 4 part kerosene-type solvent and 1 part aromatic hydrocarbon-type solvent). **Apply 0.58 to 2.86 gallons finished spray/acre.** (5% solution: 1 part formulation to 18 parts solvent). **Apply 0.24 to 1.18 gallons finished spray/acre.** **Mosquito Larvae in Standing Water**: **8 fl oz/acre**. **Repeat as necessary**. **Limitation:** U*se only in intermittently flooded areas, stagnant water, temporary rail ponds, and log ponds – KEEP OUT OF ANY FISH BEARING WATERS; broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and harvested commercially; oil-based formulations may injure ornamental s.*	**MSDS reports**: 1.3% 1-butanol only the identity of the *hazardous* ingredients are listed.
Hi-Yield 55% Malathion Insect Spray **EPA Reg. No. 7401-10-34911** 55% malathion (Density = 1.05 g/mL, 0.525 g a.i./mL, 0.525 kg/L, 1.157 lb a.i./0.2642 gal, 4.38 lb a.i./gal, 0.034 lb/oz)	Label Directions for control of thrips: 2 teaspoons per gallon of water and spray thoroughly.	MSDS specifies the inerts only as petroleum distillates. The product label specifies the distillates as "Aromatic Petroleum Derivatives Solvents".

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
ATRAPA VCP Insecticide: **A Premium Grade Malathion for Ultra Low Volume Application*** Griffin, LLC (Valdosta, GA) **EPA Reg. No. 1812-407** 96.5% malathion 3.5% inert ingredients (**contains 9.9 lbs a.i./gallon**) labeled for aerial (fixed-wing aircraft and helicopter) and ground (thermal aerosols or fogs) applications **This product is not labeled for control of mosquito larvae**	Adult mosquito control in populated and rural areas: Aerial: **2.6 to 3.0 fl oz formulation/acre** **Limitations**: undiluted droplets of formulation will permanently damage vehicle paint finishes unless aircraft meets all of label specifications; broadcast use only over intermittently flooded areas; do not apply to water bodies in which fish or shellfish are grown or harvested commercially. Ground (thermal aerosols or fogs): **6 to 8 oz actual/gallon (3.9 to 5.2 gallons formulation in 100 gallons finished solution)** Non-thermal aerosols: see label	MSDS does not specify inerts
*also sold and distributed by Griffin, LLC as **Atrapa ULV**		

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Malathion 8 Aquamul Loveland Products, Inc. (Greeley, CO) **EPA Reg. No. 34704-474** 81.8% malathion 18.2% inert ingredients (**contains 8 lbs a.i./gallon**) product may be applied by air or ground equipment **This product is also labeled for use around the outside of buildings and small grain storage facilities.**	**Mosquito Control: 2% to 5% malathion fog, aerosol, or space spray**. (2% solution: dilute 1 part formulation in 45 parts water, fuel, or diesel oil. When using a kerosene-type solvent as a carrier, dilute 1 part formulation in 45 parts solvent consisting of 4 part kerosene-type solvent and 1 part aromatic hydrocarbon-type solvent). **Apply 0.58 to 2.86 gallons finished spray/acre.** (5% solution: dilute 1 part formulation in 18 parts solvent). **Apply 0.24 to 1.18 gallons finished spray/acre.** **Mosquito Larvae in Standing Water**: **8 fl oz/acre**. **Repeat as necessary**. Limitations: **NOT REGISTERED FOR AQUATIC USE IN NEW YORK STATE.** *Only for use in intermittently flooded areas, stagnant water, temporary rail ponds, and log ponds – KEEP OUT OF ANY FISH BEARING WATERS; broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and harvested commercially; oil-based formulations may injure ornamental s*	MSDS does not specify inerts

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Malathion 8-E Insecticide* Loveland Products, Inc. (Greeley, CO) **EPA Reg. No. 34704-452** 79.5% malathion 20.5% inert ingredients (**contains 8 lbs a.i./gallon**) emulsifiable concentrate product may be applied by air or ground equipment Formulation can be applied to agricultural (see label for details) and non-agricultural lands.	**Adult Mosquito Control**: 7.2 to 9.6 fl oz formulation/acre by air or ground equipment. ***Repeat as necessary***. **Limitations**: Shrubbery and vegetation around stagnant pools, marshy areas, ponds and shorelines may be treated, but not by broadcast application. **Fog or Spray**: **2% to 5% malathion fog, aerosol, or space spray**. (2% solution: dilute 1 part formulation in 45 parts water, fuel, or diesel oil. When using a kerosene-type solvent as a carrier, dilute 1 part formulation in 45 parts solvent consisting of 4 part kerosene-type solvent and 1 part aromatic hydrocarbon-type solvent). **Apply 0.58 to 2.86 gallons finished spray/acre.** (5% solution: dilute 1 part formulation in 18 parts solvent). **Apply 0.24 to 1.18 gallons finished spray/acre.** **Limitations**: Avoid application when winds exceed 5 mi/hr; do not apply oil-based spray mixtures to ornamentals; avoid spray contact with automobiles. **Mosquito Larva in Standing Water**: 8 fl oz (approx. ½ lb actual malathion)/acre. ***Repeat applications as necessary***. **Limitations**: Broadcast use only over intermittently flooded areas. Do not apply around bodies of water where fish and shellfish are grown and/or harvested commercially.	**MSDS reports**: 20.50% inert ingredients including aromatic hydrocarbons, contains naphthalene (NOS)
*also sold and distributed by Loveland Products, Inc as **Clean crop malathion 8e insecticide**		

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Malathion 8EC Micro Flo Co, LLC (Memphis, TN) **EPA Reg. No. 51036-214** 80.75% malathion 19.25% inert ingredients (**contains 8 lbs a.i./gallon**) product may be applied by air or ground equipment emulsifiable concentrate **This product is also labeled for use around the outside of buildings and small grain storage facilities.**	**Mosquito Control**: : **2% to 5% malathion fog, aerosol, or space spray**. (2% solution: dilute 1 part formulation in 45 parts water, fuel, or diesel oil. When using a kerosene-type solvent as a carrier, dilute 1 part formulation in 45 parts solvent consisting of 4 part kerosene-type solvent and 1 part aromatic hydrocarbon-type solvent). **Apply 0.58 to 2.86 gallons finished spray/acre.** (5% solution: dilute 1 part formulation in 18 parts solvent). **Apply 0.24 to 1.18 gallons finished spray/acre.** **Mosquito Larvae in Standing Water**: **8 fl oz/acre**. **Repeat as necessary**. **Limitations:** *Only for use in intermittently flooded areas, stagnant water, temporary rail ponds, and log ponds – KEEP OUT OF ANY FISH BEARING WATERS; broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and harvested commercially; oil-based formulations may injure ornamentals.*	**MSDS reports**: 15.0 % aromatic hydrocarbon(s), including 1-2% naphthalene

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Martin's 57% Malathion Premium Grade Control Solutions, Inc (Pasadena, TX) **EPA Reg. No. 769-620-53883** 57.0% malathion 43.0% inert ingredients* *contains petroleum distillate (**contains 5 lbs a.i./gallon**) emulsifiable concentrate product may be applied by air or ground equipment	**Adult Mosquitoes**: 1 part formulation to 28 parts water, fuel oil, or diesel oil: spray bldg foundations, shrubs, low trees and lawns. **Limitations**: oil mixes may cause injury to shrubs, trees, and grass; do not allow oil- or water-based sprays to contact automobile paint surfaces. **Mosquito Larvae**: 13 fl oz formulation/acre: use in standing water (intermittently flooded areas, irrigation systems and sewage systems). **Limitations**: Broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and/or harvested commercially.	MSDS does not specify inerts
Prentox 5 LB. Malathon Spray* Prentiss , Inc (Floral Park, NY) **EPA Reg. No. 655-777** 57.0% malathion 43.0% inert ingredients emulsifiable concentrate product may be applied by air or ground equipment	**Adult Mosquitoes**: 1 part formulation to 28 parts water, fuel oil, or diesel oil: spray bldg foundations, shrubs, low trees and lawns. **Limitations**: oil mixes may cause injury to shrubs, trees, and grass; do not allow oil- or water-based sprays to contact automobile paint surfaces. **Mosquito Larvae**: 13 fl oz formulation/acre: use in standing water (intermittently flooded areas, irrigation systems and sewage systems). **Limitations**: Broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and/or harvested commercially.	**MSDS reports**: Xylene range aromatic solvent 34% (see below): 1,2,4-trimethyl benzene 32% mixed xylenes 3.0% cumene 1.5% ethyl benzene 0.5%
*also sold and distributed by Prentiss, Inc as Agway malathion 5e; B&G malathion 57-e; Blue ribbon malathion 5e; Chemsan 5 lb malathion spray; Malathion 57% concentrate insecticide; Octagon malathion 57%; and PCO malathion e-5 insecticide		

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Prentox 50% Emulsifiable Insecticide* Prentiss, Inc (Floral Park, NY) **EPA Reg. No. 655-598** 50% malathion 50% inert ingredients emulsifiable concentrate	**Mosquitoes**: 3 tsp/gallon of water or 50 fl oz/100 gallons of water. (**Note: 6 tsp = 1 fl oz; 2 tbsp = 1 fl oz; 16 fl ozs = 1 pt; 32 fl ozs = 1 qt**)	**MSDS reports**: Xylene range aromatic solvent 34% (see below): 1,2,4-trimethyl benzene 32% mixed xylenes 3.0% cumene 1.5% ethyl benzene 0.5%
*also sold and distributed by Prentiss, Inc as **50% malathion emulsifiable concentrate premium grade; B&G malathion 50e**		
Spectracide Malathion Insect Spray Spectrum Group Division of United Industries Corp (St Louis, MO) **EPA Reg. No. 46515-19-8845** 50% malathion 50% other ingredients This is a household product	**Mosquito Control**: mix 9 tbs/gallon of water. Spray foundation of houses and lawn areas. ***Repeat as necessary*** **Limitations**: product should not be used in or on electrical equipment because it is a possible shock hazard.	No MSDS Contains xylene range aromatic solvent

Table 2: Formulations of Malathion *(continued)*

Brand Name Company/Composition	Application Rate (Specified by Label)	Inerts (Specified)
Malathion 57 EC* Loveland Products, Inc. (Greeley, CO) **EPA Reg. No. 34704-108** 57% malathion 43% inert ingredients (**contains 5 lbs a.i./gallon**) emulsifiable concentrate	**Mosquitoes**: Mix 1 pint formulation as directed to treat 1 ¼ to 2 acres (2 oz/6000/sq ft for smaller areas): **2% to 5% spray or fog on lawns and patios**. (2% solution: dilute 1 part (1 pint) formulation in 28 parts [3 ½ gallons] water or kerosene type solvent such as fuel oil or diesel oil). (5% solution: dilute 1 part [1 pint] formulation in 11 parts [1 3/8 gallons]water or similar oil solvents. **Limitations**: do not apply near food crops; may cause spotting on automobile paint; highly toxic to bees; toxic to fish, aquatic invertebrates, and aquatic life stages of amphibians; do not apply directly to water or to areas where surface water is present; **recommended application rates may kill shrimp and crabs**.	**MSDS reports**: 43% inert ingredients (contains naphthalene) NOS
*also sold and distributed by Loveland Products, Inc. as Clean crop malathion 57 EC and Big 57 malathion grain and bin treatment		
Malathion 57%* Athea Laboratories, Inc. (Milwaukee, WI) **EPA Reg. No. 10088-56** 57% malathion 43% inert ingredients emulsifiable concentrate	**Adult Mosquitoes**: Water solution**: 1 part concentrate to 28 parts water** Oil solution: **1 part concentrate to 28 parts mixture consisting of 4 parts kerosene to 1 part toluene.** **Limitation**: avoid application to ornamentals **Mosquito Larva in standing water**: (intermittently flooded areas, stagnant water, temporary rain pools) **13 fl oz concentrate/acre** **Limitations**: broadcast use only over intermittently flooded areas; do not apply around bodies of water where fish or shellfish are grown and/or harvested commercially.	**MSDS reports:** 20-30% light aromatic naphtha 10-15% 1,2,4-trimethyl benzene <2% xylene

Table 3: Use of Malathion by Forest Service Region in 2004

Region [a]	Pounds	Acres	Average Application Rate (lbs/acre)	Proportion (based on total pounds used)
5: Pacific Southwest [b]	1.27	0.17	7.47	0.05
8: Southern	24.15	170.36	0.41	0.92
9: Eastern	0.72	7.36	0.098	0.03
Total/Average [c]	26.14	177.89	0.15	

[a] Information take from Forest Service 2004 pesticide use report, available at: http://www.fs.fed.us/foresthealth/pesticide/reports.shtml.
[b] Application expressed as 1.27 lbs applied to 7392 ft^2 for nursery insect control.
[c] Pounds and acres are totals. The application rate is an average across all regions.

Table 4: Applications of Malathion in Forest Service Region 8 from 1995 to 2005

Year	Pounds Applied	Acres Treated	lb a.i./acre	Formulation [EPA Registration No.] Ground Application Method [a]
1995	22	58	0.38	Malathion 5 EC [1386-124 [c]] Mist Blower Application
1996	36	63	0.57	Malathion 5 EC [1386-124 [c]] Hydraulic Sprayer
1998	5	20	0.25	Malathion 5 EC [1386-124 [c]] Not specified
1999	40	40	1.00	Malathion 5 EC [1386-124] [c] Air Blast Sprayer
2001	0.93	10	0.09	Fyfanon ULV [4787-8] Grizzly Fogger
2004 [b]	0.527	0.36	1.46	Hi-Yield® 55% [7401-10-34911] Hand sprayer (not a backpack)
2004	24.15	170.36	0.14	Malathion 5 EC [9779-5 [c]] Air blast sprayer
2005	0.25	0.397	0.63	Hi-Yield® 55% [7401-10-34911] Hand sprayer (not a backpack)
2005	28	175	0.16	Malathion 5 EC [9779-5 [c]] Air blast sprayer
Totals And Average	156.707	536.757	Ave: 0.29	Totals for pounds applied and acres treated and the overall average application rate.

[a] Applications only to lands managed by the Forest Service for the control of insect pests in pine seed orchards (Mistretta 2007).
[b] This is reported as an application of Hi-Yield® 55% [7401-10-34911] at a rate of 15.5 oz to 0.36 acres. This corresponds to an application of 0.527 lb a.i. (0.034 lb/oz as indicated in Table 2) per 0.36 acres or
[c] EPA registration number 9779-5 is assigned to Malathion 5 EC from Agrisolutions. EPA registration number 1386-124 is assigned to Malathion 5 EC from Universal Crop Protection Alliance, LLC

Table 5: Impurities in technical grade malathion

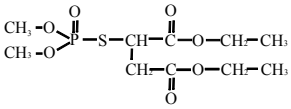
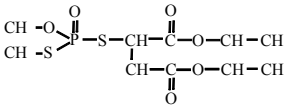
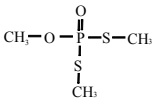
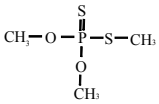
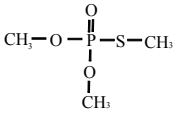
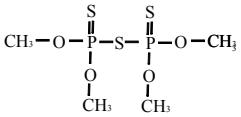
Identity	Structure	Comment(s)
Malaoxon Cmpd #12 in Fukuto 1983		Primary neurotoxic agent. Also a metabolite. ≤0.17% (Aldridge et al. 1979) Trace (Fukuto 1983) 0.1% (ATSDR 2003)
Isomalathion Cmpd #7 in Fukuto 1983 Cmpd J in Umetsu et al. 1977		Concentrations in malathion formulations correlated with toxicity to rats (Aldridge et al. 1979). Potentiates malathion. (Aldridge et al.1979; Fukuto 1983; Ryan and Fukuto 1985). Potent inhibitor carboxyesterase (Talcott et al. 1979a) and AChE (Thompson et al. 1989). 0.2% (Umetsu et al. 1977; ATSDR 2003)
O,S,S-TMPD [O,S,S-Trimethyl phosphorodithioate] (Zimmerman 1990) Cmpd #8 in Fukuto 1983 Cmpd L in Umetsu et al. 1977		Signs consistent with AChE inhibition (Aldridge et al. 1979). Potentiates malathion (Aldridge et al.1979; Fukuto 1983; Ryan and Fukuto 1985). Inhibits carboxyesterases (Talcott et al. 1979a). 0.003% (Umetsu et al. 1977). Antagonizes the toxicity of O,O,S-TMPT (Hammond et al. 1982a)
O,O,S-TMPD [O,O,S-Trimethylphosphorodithioate] (Zimmerman 1990) Cmpd #1 in Fukuto 1983		Signs inconsistent with AChE inhibition. Potentiates malathion (Aldridge et al. 1979; Fukuto 1983). Inhibits carboxyesterases (Talcott et al. 1979a) 1.1% (Umetsu et al.1977)
O,O,S-TMPT [O,O,S-Trimethylphosphorothioate] (Zimmerman 1990; Imamura and Gandy 1989) Cmpd #11 in Fukuto 1983 Cmpd O in Umetsu et al. 1977		Effects inconsistent with AChE inhibition (Fukuto (1983). Primary toxic effect is weight loss. Death occurs at 2-44 days after dosing without other signs of toxicity (Fukuto 1983; Mallipudi et al. 1979; Umetsu et al. 1981). 0.04% (Umetsu et al. 1977). 0.1-0.2% (Thomas and Imamura 1986)
Cmpd #2 in Fukuto 1983		No apparent interaction with malathion (Fukuto 1983). 0.5% (Umetsu et al. 1977)
Cmpd #3 in Fukuto 1983	HSCH(COOCH2CH3)CH2-(COOCH2CH3)	Trace (Fukuto 1983)
Cmpds #4 in Fukuto 1983 Cmpds F in Umetsu et al. 1977	(CH3O)2P(S)S-CH(COOCH2CH3)CH2COOCH3 and (CH3O)2P(S)S-CH(COOCH3)CH2COOCH3	>0.1% (Umetsu et al. 1977)
Cmpd #5 in Fukuto 1983 Cmpd G in Umetsu et al. 1977	[CH(COOCH2CH3)CH2-COOCH2CH3]2	>0.3% (Umetsu et al. 1977)
Cmpd #6 in Fukuto 1983 Cmpd H in Umetsu et al. 1977	S[CH(COOCH2CH3)CH2-COOCH2CH3]2	>0.5% (Umetsu et al. 1977)

Table 5: Impurities in technical grade malathion

Identity	Structure	Comment(s)
Cmpd #9 in Fukuto 1983 Cmpd M in Umetsu et al. 1977	(CH3O)2P(S)S-CH(COOCH2CH3)CH2COOH	0.6-0.8% (Umetsu et al. 1977)
Cmpd #10 in Fukuto 1983 Cmpd N in Umetsu et al. 1977	(CH3O)2P(S)SCH(COOH)CH2-COOCH2CH3	0.1-0.15% (Fukuto 1983)
Cmpd #13 in Fukuto 1983	(CH3O)3P=0	0.3% (Fukuto 1983)
O,O,O-trimethyl phosphothionate	(CH3O)3P=S	Weak potentiation of malathion (Toia et al. 1980). 0.09% (Fukuto 1983)
Cmpd #14 in Fukuto 1983		0.05% (U.S. EPA/OPP 2000c)
diethylfumarate	CH3CH2OC(O)CHCHC(O)O-CH2CH3	Antagonizes the toxicity of O,O,S-TMPT (Hammond et al. 1982a; Umetsu et al. 1981) Milby and Esptein 1964 0.9% (U.S. EPA/OPP 2000c)
sulfuric acid		0.05% (ATSDR 2003)

Table 6: Chemical input parameters used in GLEAMS modeling for malathion

Parameter	Clay	Loam	Sand	Note/ Reference
Halftimes (days)				
Aquatic Sediment		3.3		Note 1
Foliar		5.5		Note 2
Soil		3		Note 3
Water		6.21		Note 4
Soil $K_{o/c}$, mL/g		151		Note 5
Sediment K_d, mL/g	3.2	2.53	1.0	Note 5
Water Solubility, mg/L		145		Note 3
Foliar wash-off fraction		0.9		Note 6
Fraction applied to foliage		0.5		Note 7

Note 1 Value for aerobic aquatic metabolism used by U.S. EPA/OPP 2006e (Table 2, p. 5) in PRZM/EXAMS modeling. A somewhat shorter half life (2.5 days) is available for anaerobic metabolism.

Note 2 Value used by U.S. EPA/OPP 2006n (Table 3, p. 143) in PRZM/EXAMS modeling based on a foliar decay rate of 0.126 day^{-1} (ln(2)/0.126 day^{-1}). Represents an upper 90% confidence bound on the mean from 37 studies from which foliar halftimes could be estimated (U.S. EPA/OPP 2006e, Attachment 2, p. 16).

Note 3 Value used by U.S. EPA/OPP 2006e in PRZM/EXAMS modeling. Somewhat shorter and longer soil halftimes are reported in the literature. The water solubility used is identical to that recommended by Tomlin (2004). See Table 1.

Note 4 Value used by U.S. EPA/OPP 2006e for hydrolysis in PRZM/EXAMS modeling (Table 2, p. 5). No adjustment made for photolysis, which has a halftime of about 94 days.

Note 5 The Koc of 151 is the value used by U.S. EPA/OPP (2006e) in PRZM/EXAMS modeling. All Kd estimates are based on the Ko/c: Kd = Koc x OC. Soil organic matter (OM) of 1.2% (sand), 2.9% (loam), and 3.7% (clay) from Table 2 in SERA (2007b). Organic carbon as a proportion is estimated as OC = OM/1.724 from Knisel and Davis (2002): 0.0069 (sand), 0.0168 (loam), and 0.0215 (clay).

Note 6 The value of 0.9 is recommended by Knisel and Davis (2000). Foliar washoff of 0.5 cm^{-1} is the value used by U.S. EPA/OPP 2006e in PRZM/EXAMS modeling.

Note 7 The fractional application of 0.5 to foliage is a default for broadcast applications to foliage.

Table 7: Peak concentrations in a small stream based on Gleams-Driver simulations

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**0 (0 - 3.1)**	**0 (0 - 0.06)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.026)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 0.4)**	**0 (0 - 0.008)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**7 (0.21 - 40)**	**2 (0.00009 - 19)**	**0 (0 - 0.3)**
Average Rainfall and Temperate Location	**4 (0.11 - 30)**	**0.8 (0.000008 - 20)**	**0 (0 - 0.4)**
Average Rainfall and Cool Location	**2.8 (0.005 - 16)**	**0.16 (0 - 7)**	**0 (0 - 0.00015)**
Wet and Warm Location	**3 (0.15 - 22)**	**0.4 (0.0007 - 8)**	**0 (0 - 0.08)**
Wet and Temperate Location	**1.7 (0.00022 - 14)**	**0.07 (0 - 7)**	**0 (0 - 0.016)**
Wet and Cool Location	**25 (12 - 40)**	**12 (4 - 23)**	**0.014 (0.00012 - 0.5)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**0.0016 (0 - 27)**	**0 (0 - 6)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.14)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 13)**	**0 (0 - 0.6)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**30 (11 - 70)**	**16 (1.3 - 40)**	**0.0005 (0 - 0.6)**
Average Rainfall and Temperate Location	**31 (8 - 70)**	**15 (0.6 - 40)**	**0.0008 (0 - 0.9)**
Average Rainfall and Cool Location	**19 (1.7 - 50)**	**6 (0 - 27)**	**0 (0 - 0.29)**
Wet and Warm Location	**30 (13 - 70)**	**16 (3 - 40)**	**0.07 (0 - 0.9)**
Wet and Temperate Location	**18 (0.8 - 60)**	**4 (0.0016 - 30)**	**0 (0 - 0.6)**
Wet and Cool Location	**40 (29 - 70)**	**22 (13 - 40)**	**0.3 (0.0011 - 1)**

Table 8: Average concentrations in a small stream based on Gleams-Driver simulations

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**0 (0 - 0.009)**	**0 (0 - 0.0002)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.00007)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 0.0011)**	**0 (0 - 0.000021)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**0.028 (0.0006 - 0.13)**	**0.007 (2.4E-07 - 0.07)**	**0 (0 - 0.0008)**
Average Rainfall and Temperate Location	**0.015 (0.0003 - 0.12)**	**0.0023 (2.2E-08 - 0.06)**	**0 (0 - 0.001)**
Average Rainfall and Cool Location	**0.009 (0.000015 - 0.07)**	**0.0004 (0 - 0.025)**	**0 (0 - 4.0E-07)**
Wet and Warm Location	**0.014 (0.0008 - 0.06)**	**0.0013 (2.4E-06 - 0.022)**	**0 (0 - 0.00021)**
Wet and Temperate Location	**0.006 (7.0E-07 - 0.06)**	**0.00021 (0 - 0.022)**	**0 (0 - 0.00004)**
Wet and Cool Location	**0.13 (0.07 - 0.18)**	**0.05 (0.014 - 0.09)**	**0.00005 (6.0E-07 - 0.0015)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**0.000004 (0 - 0.08)**	**0 (0 - 0.018)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.0004)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 0.04)**	**0 (0 - 0.0016)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**0.22 (0.06 - 0.4)**	**0.07 (0.005 - 0.17)**	**1.3E-06 (0 - 0.0019)**
Average Rainfall and Temperate Location	**0.21 (0.03 - 0.4)**	**0.07 (0.0017 - 0.22)**	**2.2E-06 (0 - 0.0026)**
Average Rainfall and Cool Location	**0.1 (0.007 - 0.3)**	**0.02 (0 - 0.13)**	**0 (0 - 0.0008)**
Wet and Warm	**0.26**	**0.08**	**0.00024**

Location	**(0.09 - 0.5)**	**(0.012 - 0.26)**	**(0 - 0.0029)**
Wet and Temperate Location	**0.09 (0.003 - 0.28)**	**0.015 (0.000006 - 0.12)**	**0 (0 - 0.0018)**
Wet and Cool Location	**0.7 (0.5 - 1.1)**	**0.27 (0.13 - 0.5)**	**0.001 (0.000005 - 0.005)**

Table 9: Peak concentrations in a small pond based on Gleams-Driver simulations

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**0 (0 - 0.8)**	**0 (0 - 0.027)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.005)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 0.13)**	**0 (0 - 0.002)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**3 (0.05 - 16)**	**1 (0.00002 - 9)**	**0 (0 - 0.15)**
Average Rainfall and Temperate Location	**1.8 (0.03 - 17)**	**0.3 (2.6E-06 - 11)**	**0 (0 - 0.21)**
Average Rainfall and Cool Location	**1 (0.0014 - 8)**	**0.06 (0 - 4)**	**0 (0 - 0.00009)**
Wet and Warm Location	**0.8 (0.05 - 7)**	**0.1 (0.00027 - 2.5)**	**0 (0 - 0.03)**
Wet and Temperate Location	**0.5 (0.00005 - 6)**	**0.029 (0 - 3)**	**0 (0 - 0.009)**
Wet and Cool Location	**8 (3.1 - 13)**	**4 (0.8 - 7)**	**0.004 (0.00004 - 0.16)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**0.0004 (0 - 13)**	**0 (0 - 2.5)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.03)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 4)**	**0 (0 - 0.22)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**17 (4 - 40)**	**8 (0.4 - 21)**	**0.0003 (0 - 0.4)**
Average Rainfall and Temperate Location	**17 (2.6 - 40)**	**8 (0.25 - 25)**	**0.0004 (0 - 0.6)**
Average Rainfall and Cool Location	**9 (0.5 - 30)**	**2.8 (0 - 15)**	**0 (0 - 0.17)**
Wet and Warm Location	**14 (4 - 40)**	**7 (1.2 - 24)**	**0.03 (0 - 0.4)**
Wet and	**7**	**1.4**	**0**

Temperate Location	**(0.19 - 30)**	**(0.0006 - 18)**	**(0 - 0.29)**
Wet and Cool Location	**15 (9 - 27)**	**8 (4 - 16)**	**0.09 (0.0004 - 0.4)**

Table 10: Average concentrations in a small pond based on Gleams-Driver simulations

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**0 (0 - 0.014)**	**0 (0 - 0.0005)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.00009)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 0.0025)**	**0 (0 - 0.00004)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**0.08 (0.001 - 0.4)**	**0.023 (4.0E-07 - 0.23)**	**0 (0 - 0.004)**
Average Rainfall and Temperate Location	**0.04 (0.001 - 0.5)**	**0.007 (5.0E-08 - 0.29)**	**0 (0 - 0.006)**
Average Rainfall and Cool Location	**0.024 (0.00004 - 0.17)**	**0.0014 (0 - 0.09)**	**0 (0 - 2.7E-06)**
Wet and Warm Location	**0.021 (0.0016 - 0.14)**	**0.0027 (0.000005 - 0.06)**	**0 (0 - 0.0009)**
Wet and Temperate Location	**0.014 (1.2E-06 - 0.16)**	**0.0006 (0 - 0.07)**	**0 (0 - 0.00013)**
Wet and Cool Location	**0.15 (0.07 - 0.24)**	**0.06 (0.017 - 0.14)**	**0.00008 (9.0E-07 - 0.0025)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**0.000007 (0 - 0.23)**	**0 (0 - 0.05)**	**0 (0 - 0)**
Dry and Temperate Location	**0 (0 - 0.0006)**	**0 (0 - 0)**	**0 (0 - 0)**
Dry and Cold Location	**0 (0 - 0.07)**	**0 (0 - 0.004)**	**0 (0 - 0)**
Average Rainfall and Warm Location	**0.7 (0.13 - 1.4)**	**0.28 (0.012 - 0.7)**	**0.000009 (0 - 0.013)**
Average Rainfall and Temperate Location	**0.6 (0.08 - 1.8)**	**0.27 (0.005 - 1)**	**0.000011 (0 - 0.018)**
Average Rainfall and Cool Location	**0.29 (0.014 - 1.2)**	**0.07 (0 - 0.5)**	**0 (0 - 0.005)**
Wet and Warm	**0.6**	**0.26**	**0.0009**

Location	**(0.21 - 1.4)**	**(0.04 - 0.7)**	**(0 - 0.012)**
Wet and Temperate Location	**0.21 (0.005 - 0.9)**	**0.04 (0.000014 - 0.5)**	**0 (0 - 0.006)**
Wet and Cool Location	**0.9 (0.5 - 1.4)**	**0.4 (0.16 - 0.7)**	**0.002 (0.000011 - 0.01)**

Table 11: Estimated water contamination rates (WCR) based on modeling and monitoring
(all concentrations are in µg/L or ppb per lb/acre applied)

Scenario	Peak	Long-Term Average
MODELING FOR THIS RISK ASSESSMENT (1 lb a.i./acre)		
Direct Spray of Pond (Section 3.2.3.4.2) [a]	56	N/A
Pond, drift at 25 feet (Section 3.2.3.4.2) [a]	8.0	N/A
Direct Spray of Stream (Section 3.2.3.4.2) [a]	91	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) [a]	13.1	N/A
Gleams-Driver, Stream, Section 3.2.3.4.4	4 (0 – 40) [1 application] 30 (0 – 70) [8 applications] 40 (0 – 90) [25 applications]	0.02 (0 – 0.13) [1 application] 0.2 (0 – 1.1) [8 applications] 0.4 (0 – 1.6) [25 applications]
Gleams-Driver, Pond, Section 3.2.3.4.4	1 (0 – 17) [1 application] 15 (0 – 40) [8 applications] 25 (0 – 80) [25 applications]	0.02 (0 – 0.5) [1 application] 0.2 (0 – 1.8) [8 applications] 1.4 (0 – 2.9) [25 applications]
OTHER MODELING		
U.S. EPA		
PRZM/EXAMS, Index Reservoir [b]	3.7 – 44.4 [6 to 7 day intervals] 2.4 – 51 [all]	0.36 – 0.79 [6 to 7 day intervals] 0.04 – 0.79 [all]
GENEEC [c]	22.8 – 72.4	N/A
MONITORING		
Ground water, various [d]	0.007 – 6.17	N/A
APHIS, Florida Medfly Program [e]	0.2 - 51	N/A
Grasshopper control [e]	0.18 – 142	N/A
Boll weevil control [e]	0.11 – 54	N/A
Mosquito control, streams [f]	0.2 – 82.6	N/A
Mosquito control, other [f]	5.2 – 69	N/A

[a] Section 3.2.3.4.2 discusses expected concentrations in terms of the nominal application rate of 1 lb a.i./acre. The values for direct spray and drift are taken from Worksheet 10a (direct spray and drift as 25 feet for a pond) and Worksheet 10b (direct spray and drift as 25 feet for a stream) adjusted to WRC values based on the application rate of 0.75 lbs/acre.

[b] From U.S. EPA/OPP 2006e, Table 3, p. 6. Values adjusted to WCR values by dividing the estimated concentration by the application rate used in the modeling.

[c] From U.S. EPA/OPP 2005n, Table 2, p. 140. Values adjusted to WCR values by dividing by the modeled concentration by the application rate used in the modeling.

[d] From U.S. EPA/OPP 2005n, p. 141 - 145 . Values not associated with application rate.

[e] From U.S. EPA/OPP 2005n, Appendix 4, p. 146. Medfly values not explicitly associated with application rate. Grasshopper values adjusted for application rate of 8 oz/acre (0.6 lb/acre at formulation of 9.9 lb/gallon). Boll weevil values adjusted for application rate of 12 oz/acre (0.9 lb/acre at formulation of 9.9 lb/gallon).

[f] From U.S. EPA/OPP 2005n, Appendix 4, p. 148 ff. Various application rates. Values above not adjusted.

Table 12: Concentrations of malathion in surface water used in this risk assessment
(see Section 3.2.3.4.6 for discussion)

	Water contamination rate in mg/L per lb/acre applied [a]	
8 applications at 1 week intervals	**Peak**	**Longer-term**
Central	0.02	0.0002
Lower	0.001	0.00002
Upper	0.07	0.0014
1 application	**Peak**	**Longer-term**
Central	0.004	0.00002
Lower	0.0005	0.000002
Upper	0.04	0.0005

[a] Water contamination rates – concentrations in units of mg a.i./L expected at an application rate of 1 lb a.i./acre. Units of mg a.i./L are used in the EXCEL workbook that accompanies this risk assessment.

Table 13: Estimates of Dose-Severity Relationships for Acute Exposures to Malathion

NOTE: The dose-severity relationships detailed in this table and discussed in Section 3.3.5 should not be interpreted as suggesting that exposures above the acute or chronic RfD values are acceptable.

Dose (mg/kg bw)	Corresponding Hazard Quotient	Organism (number of individuals): Effect	Reference
0.14	**1**	**Human Equivalent Dose: Based on a $BMDL_{10}$ of 13.6 mg/kg bw rat pups after gavage exposure with an uncertainty factor of 100. No adverse effects anticipated in any individuals.**	**U.S. EPA/OPP 2006a,c**
0.3	**2.1**	**Human Equivalent Dose: WHO RfD based on animal NOAEL of 29 mg/kg bw/day.**	**WHO 1998**
0.34	**2.4**	**Human Dose: Decreased plasma ChE and RBC AChE activity after 56 days of dosing**	**Moeller and Rider 1962**
0.9	**6.4**	**Human Equivalent Dose: Based on a $BMDL_{10}$ of 93.7 mg/kg bw in adult rats after gavage exposure with an uncertainty factor of 100. No adverse effects anticipated in adults.**	**U.S. EPA/OPP 2006a,c**
15	**110**	**Human Dose: Inhibition of plasma ChE but no signs of toxicity.**	**Gillies and Dickson 2000**
20?	***140?***	**Human Equivalent Dose: Rats LOAEL of 2000 mg/kg, *This value is not recommended for application to the risk characterization for humans. See text for discussion.***	**U.S. EPA/OPP 2006c, MRID 45646401**
Not Defined		**Human Equivalent Dose for Mild signs of toxicity.**	**Hayes 1982**

56	400	Human Dose: Lethal dose in accidental poisoning of an elderly man	Hayes 1982
100	700	Human Dose: Survival after accidental poisoning	Hayes 1982
190	1400	Human Dose: Survival after accidental ingestion by a 34 month old boy.	Hayes 1982
350 to 1000	2500 to 7100	Human Dose: Fatal suicidal ingestion.	Farago 1967
3,655 (2,992 - 4,319)	26,800 (22,000 to 32,000)	Estimated human LD50 with 95% confidence interval.	Talcott et al. 1979c
5400	36,000	LD_{50} in rats	U.S. EPA/OPP 2006c

Table 14: Toxicity of malathion to various species of earthworm

Source: Kupermann et al. 1999

Animal	Dose	Response
Standard Acute Toxicity Bioassay		
Eisenia fetida, adults with fully developed clitella and a mass of 350-450 mg, 5 worms/dose group	6, 12, 25, 50, 75, or 100 ppm malathion (95%) in standard artificial soil (10% organic matter) for 14 days	LOEC = 75.0 ppm EC_{50} = 70 ppm
Eisenia fetida, adults with fully developed clitella and a mass of 350-450 mg, 5 worms/dose group	20, 40, 60 80, 100, or 120 ppm (95%) in sandy loam soil (4.3% organic matter) for 14 days	LOEC = 75.0 ppm EC_{50} = 95 ppm
Eisenia fetida, adults with fully developed clitella and a mass of 350-450 mg, 5 worms/dose group	25, 50, 75, 100, 125, or 150 ppm (95%) in Sassafras sandy loam soil (2.3% organic matter) for 14 days	LOEC = 60.0 ppm EC_{50} = 42 ppm
Enchytraeus albidus, adults with fully developed clitella and a mass of 350-450 mg, 10 worms/dose group	5.38, 7.75, 13.40, 23.15, or 40.0 ppm (95%) in standard artificial soil (10% organic matter) for 21 days	LOEC = 23.15 ppm EC_{50} = not determined
Enchytraeus s albidus, adults with fully developed clitella and a mass of 350-450 mg, 10 worms/dose group	4.74, 6.64, 13.02, 35.71, or 50.0 ppm (95%) in sandy loam soil (4.3% organic matter) for 21 days	LOEC = 6.64 ppm EC_{50} = not determined
Enchytraeus albidus, adults with fully developed clitella and a mass of 350-450 mg, 10 worms/dose group	5.38, 7.75, 13.40, 23.15, or 40.0 ppm (95%) in sandy loam soil (4.3% organic matter) for 21 days	LOEC = 23.15 ppm EC_{50} = not determined
Chronic Toxicity-Reproduction		
Eisenia fetida, juveniles	2.93, 5.85, 11.7, 17.55, 23.4, or 28.0 ppm (95%) in standard artificial soil (10% organic matter) for 21 days	LOEC = 18.0 ppm EC_{50} = 16 ppm
Eisenia fetida, juveniles	7, 14, 21, 28, or 35 ppm (95%) in sandy loam soil (4.3% organic matter) for 21 days	LOEC = 14.0 ppm EC_{50} = 37 ppm
Eisenia fetida, juveniles	7, 14, 28, 35, or 42 ppm (95%) in Sassafras sandy loam soil (2.3% organic matter) for 21 days	LOEC = 21.0 ppm EC_{50} = 20 ppm
Enchytraeus albidus, juveniles	5.38, 7.75, 13.40, 23.15, or 40.0 ppm (95%) in standard artificial soil (10% organic matter) for 21 days	LOEC = 7.75 ppm EC_{50} = 9.8 ppm

Table 15: Maximum Soil Concentrations in Top 12 Inches of Soil Column

(All values expressed as ppm or mg/kg soil at an application rate of 1 lb a.i./acre)

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**0.17 (0.17 - 0.17)**	**0.16 (0.16 - 0.16)**	**0.16 (0.16 - 0.16)**
Dry and Temperate Location	**0.17 (0.17 - 0.17)**	**0.16 (0.16 - 0.16)**	**0.16 (0.16 - 0.16)**
Dry and Cold Location	**0.17 (0.16 - 0.17)**	**0.16 (0.15 - 0.16)**	**0.16 (0.15 - 0.16)**
Average Rainfall and Warm Location	**0.17 (0.16 - 0.17)**	**0.16 (0.15 - 0.16)**	**0.16 (0.15 - 0.16)**
Average Rainfall and Temperate Location	**0.17 (0.16 - 0.17)**	**0.16 (0.15 - 0.16)**	**0.16 (0.15 - 0.16)**
Average Rainfall and Cool Location	**0.17 (0.16 - 0.17)**	**0.16 (0.15 - 0.16)**	**0.16 (0.15 - 0.16)**
Wet and Warm Location	**0.16 (0.16 - 0.17)**	**0.15 (0.15 - 0.16)**	**0.15 (0.15 - 0.16)**
Wet and Temperate Location	**0.17 (0.16 - 0.17)**	**0.16 (0.15 - 0.16)**	**0.16 (0.15 - 0.16)**
Wet and Cool Location	**0.16 (0.15 - 0.17)**	**0.15 (0.14 - 0.16)**	**0.15 (0.15 - 0.16)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**0.3 (0.3 - 0.5)**	**0.3 (0.3 - 0.5)**	**0.3 (0.3 - 0.5)**
Dry and Temperate Location	**0.3 (0.3 - 0.5)**	**0.3 (0.3 - 0.5)**	**0.3 (0.3 - 0.5)**
Dry and Cold Location	**0.3 (0.31 - 0.6)**	**0.3 (0.29 - 0.5)**	**0.3 (0.29 - 0.5)**
Average Rainfall and Warm Location	**0.3 (0.3 - 0.4)**	**0.3 (0.28 - 0.4)**	**0.3 (0.28 - 0.4)**
Average Rainfall and Temperate Location	**0.3 (0.31 - 0.5)**	**0.3 (0.29 - 0.5)**	**0.32 (0.28 - 0.4)**
Average Rainfall and Cool Location	**0.3 (0.31 - 0.4)**	**0.31 (0.29 - 0.4)**	**0.31 (0.28 - 0.4)**
Wet and Warm Location	**0.29 (0.27 - 0.4)**	**0.27 (0.26 - 0.4)**	**0.26 (0.25 - 0.4)**
Wet and Temperate Location	**0.3 (0.31 - 0.5)**	**0.3 (0.29 - 0.5)**	**0.3 (0.29 - 0.5)**

Wet and Cool Location	**0.29 (0.28 - 0.4)**	**0.27 (0.26 - 0.4)**	**0.27 (0.26 - 0.4)**

Table 16: Maximum Soil Concentrations in Top 60 Inches of Soil Column
(All values expressed as ppm or mg/kg soil at an application rate of 1 lb a.i./acre)

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**0.03 (0.03 - 0.03)**	**0.031 (0.031 - 0.031)**	**0.031 (0.031 - 0.031)**
Dry and Temperate Location	**0.03 (0.03 - 0.03)**	**0.031 (0.031 - 0.031)**	**0.031 (0.031 - 0.031)**
Dry and Cold Location	**0.03 (0.03 - 0.03)**	**0.031 (0.029 - 0.031)**	**0.031 (0.029 - 0.031)**
Average Rainfall and Warm Location	**0.03 (0.03 - 0.03)**	**0.031 (0.03 - 0.031)**	**0.031 (0.03 - 0.031)**
Average Rainfall and Temperate Location	**0.03 (0.03 - 0.03)**	**0.031 (0.03 - 0.031)**	**0.031 (0.03 - 0.031)**
Average Rainfall and Cool Location	**0.03 (0.03 - 0.03)**	**0.031 (0.03 - 0.031)**	**0.031 (0.03 - 0.031)**
Wet and Warm Location	**0.03 (0.03 - 0.03)**	**0.03 (0.03 - 0.031)**	**0.03 (0.03 - 0.031)**
Wet and Temperate Location	**0.03 (0.03 - 0.03)**	**0.031 (0.03 - 0.031)**	**0.031 (0.03 - 0.031)**
Wet and Cool Location	**0.03 (0.03 - 0.03)**	**0.03 (0.029 - 0.031)**	**0.03 (0.03 - 0.031)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**0.07 (0.07 - 0.1)**	**0.07 (0.06 - 0.1)**	**0.07 (0.06 - 0.1)**
Dry and Temperate Location	**0.07 (0.07 - 0.1)**	**0.07 (0.06 - 0.1)**	**0.07 (0.06 - 0.1)**
Dry and Cold Location	**0.07 (0.06 - 0.11)**	**0.06 (0.06 - 0.11)**	**0.06 (0.06 - 0.11)**
Average Rainfall and Warm Location	**0.07 (0.06 - 0.09)**	**0.06 (0.06 - 0.08)**	**0.06 (0.06 - 0.08)**
Average Rainfall and Temperate Location	**0.07 (0.06 - 0.09)**	**0.06 (0.06 - 0.09)**	**0.06 (0.06 - 0.09)**
Average Rainfall and Cool Location	**0.07 (0.06 - 0.09)**	**0.06 (0.06 - 0.08)**	**0.06 (0.06 - 0.08)**
Wet and Warm Location	**0.06 (0.05 - 0.08)**	**0.05 (0.05 - 0.07)**	**0.05 (0.05 - 0.07)**

Wet and Temperate Location	**0.07 (0.06 - 0.11)**	**0.06 (0.06 - 0.1)**	**0.06 (0.06 - 0.1)**
Wet and Cool Location	**0.06 (0.06 - 0.08)**	**0.05 (0.05 - 0.08)**	**0.05 (0.05 - 0.08)**

Table 17: Estimated Maximum Penetration into the Soil Column

(All values expressed in inches)

SINGLE APPLICATION			
Site	Clay	Loam	Sand
Dry and Warm Location	**8 (4 - 18)**	**4 (4 - 18)**	**8 (4 - 24)**
Dry and Temperate Location	**4 (4 - 12)**	**4 (4 - 8)**	**4 (4 - 12)**
Dry and Cold Location	**12 (4 - 18)**	**12 (4 - 18)**	**12 (4 - 24)**
Average Rainfall and Warm Location	**18 (12 - 24)**	**24 (12 - 30)**	**36 (18 - 54)**
Average Rainfall and Temperate Location	**18 (12 - 24)**	**18 (12 - 30)**	**30 (18 - 54)**
Average Rainfall and Cool Location	**18 (12 - 24)**	**18 (12 - 24)**	**30 (18 - 42)**
Wet and Warm Location	**18 (18 - 24)**	**24 (18 - 30)**	**30 (24 - 48)**
Wet and Temperate Location	**18 (12 - 24)**	**18 (12 - 30)**	**24 (12 - 42)**
Wet and Cool Location	**30 (30 - 30)**	**36 (30 - 36)**	**60 (54 - 60)**
8 APPLICATIONS, 7 DAY INTERVAL			
Dry and Warm Location	**12 (4 - 24)**	**8 (4 - 24)**	**12 (4 - 36)**
Dry and Temperate Location	**4 (4 - 12)**	**4 (4 - 8)**	**4 (4 - 12)**
Dry and Cold Location	**18 (8 - 18)**	**18 (8 - 18)**	**18 (8 - 30)**
Average Rainfall and Warm Location	**24 (18 - 30)**	**30 (18 - 36)**	**42 (30 - 60)**
Average Rainfall and Temperate Location	**24 (18 - 30)**	**30 (18 - 36)**	**42 (30 - 60)**
Average Rainfall and Cool Location	**24 (18 - 24)**	**24 (18 - 30)**	**36 (24 - 60)**
Wet and Warm	**24**	**30**	**54**

Location	(24 - 30)	(24 - 36)	(36 - 60)
Wet and Temperate Location	24 (18 - 30)	24 (18 - 30)	36 (24 - 54)
Wet and Cool Location	30 (30 - 36)	36 (36 - 42)	60 (54 - 60)

Table 18: Summary of Toxicity Values Used in the Ecological Risk Assessment

(all amounts expressed as a.i.).

Organism Group/Duration	Endpoint	Toxicity Value	Reference
Acute	**Terrestrial Organisms**		
Mammals	BMD_{10} for AChE	17 mg/kg bw	Section 4.3.2.1
Birds	Estimated NOEC	15 mg/kg bw	Section 4.3.2.2
Honey Bee	LD_{50}	2.2 mg/kg bw	Section 4.3.2.3.
Longer-term			
Mammals	BMD_{10} for AChE	11 mg/kg bw/day	Section 4.3.2.1
Birds	NOEC for reproductive effects	11 mg/kg bw/day	Section 4.3.2.2
Acute	**Aquatic Organisms**		
Amphibians			
Sensitive (*Rana hexadactyla*)	96-hour LC_{50} value	0.00059 mg/L (tadpoles)	Section 4.3.3.2.
Tolerant (*Bufo americanus*)	16-day LC_{50} value	5.9 mg/L (tadpoles)	Section 4.3.3.2.
Fish Sensitive (Trout)	LC_{50}	0.004 mg/L	Section 4.3.3.1
Tolerant (Bullhead)	LC_{50}	11.7 mg/L	Section 4.3.3.1
Invertebrates			
Sensitive (*Daphnia magna*)	LC_{50}	0.001 mg/L	Section 4.3.3.3
Tolerant (Crayfish)	LC_{50}	49 mg/L	Section 4.3.3.3
Algae Sensitive (*Pseudokirchneriella subcapitata*)	NOEC	0.5 mg/L	Section 4.3.3.4
Tolerant (*Nostoc clacicola*)	NOEC	200 mg/L	Section 4.3.3.4
Macrophytes (*Spirodela polyrhiza*)	NOEC	24 mg/L	Section 4.3.3.4
Longer-term			
Amphibians			
Sensitive (*Rana tigrina*)	Reproductive NOEC based on relative potency method	0.00035 mg/L	Section 4.3.3.2.
Tolerant (*Xenopus laevis*)	Developmental NOEC	0.75 mg/L (larvae)	Section 4.3.3.2.
Fish Sensitive (Trout)	Reproductive NOEC based on relative potency method	0.0024 mg/L	Section 4.3.3.1
Tolerant (Trout)	Reproductive NOEC	0.021 mg/L	Section 4.3.3.1
Invertebrates			
Sensitive (*Daphnia magna*)	Reproductive NOEC	0.0006 mg/L	Section 4.3.3.3
Tolerant (Snail eggs)	Developmental NOEC	1.23 mg/L	Section 4.3.3.3

List of Appendices

Appendix 1: Toxicity Studies in Birds

Three separate tables are included: Acute Toxicity, Longer-term studies, and Egg Injection. Each table is sorted by Reference and then by Organism.

Acute Toxicity

Organism	Dose	Response	Reference
Sharp tailed grouse	Malathion (technical, NOS)	14-day LD_{50} = 220 mg/kg (95% CI = 171-240 mg/kg)	Hudson et al. 1984
Mallard ducklings, *Anas platyrhynchos*, 14-days old, 36 treated ducklings and 36 controls	single oral dose of 650 mg/kg malathion (purity 95%) in corn oil; sacrifices at 1,2,4, 7, 11, and 17 days after exposure	Mean ChE activity in brain was 67% of controls; the projected number of days required to recover to 80 % and 100% of control activity levels were 4 and 26, respectively. At 20 hours after exposure, ChE brain activity in 6 surviving ducklings was significantly ($P \leq 0.05$, *t* test) greater (mean = 67.0%) than in 7 ducklings that died (mean = 36.5%).	Fleming and Bradbury 1981

Notes on Fleming and Bradbury 1981: This study investigates the recovery of cholinesterase activity in mallard duckling exposed to one of several organophosphorus pesticides, including malathion. In all cases, the in vivo recovery of brain ChE activity to within 2 standard deviations of the mean activity of control ducklings occurred within 8 days after exposure. In the case of malathion, recovery took only 4 days. Plasma ChE recovery was also rapid, but showed an erratic pattern of recovery and no statistical comparison with brain ChE recovery could be made.

Mallard ducklings, *Anas platyrhynchos*, 2-weeks old, 6/dose group	single oral dose of 0, 112.5, 225, 450, 700, or 900 mg/kg malathion (purity 95%) in corn oil; sacrifice at 16 hours after exposure	No morality at ≤450 mg/kg; survival was 3/4 at 700 mg/kg and 2/6 at 900 mg/kg. Inhibition of brain AChE and blood ChE activity expressed as percentage of activity in controls: **brain:** 112.5 mg/kg: mean = 104 (94-123) 225 mg/kg: mean = 104 (86-120) 450 mg/kg: mean = 78 (38-103) **700 mg/kg: mean = 48 (30-61) LOAEL** 900 mg/kg: mean = 49 (38-61) **plasma:** 112.5 mg/kg: mean = 97 (72-167) **225 mg/kg: mean = 73 (59-91) LOAEL** 450 mg/kg: mean = 68 (36-86) 700 mg/kg: mean = 28 (24-36) 900 mg/kg: mean = 65 (61-69)	Fleming and Bradbury 1981

Acute Toxicity

Organism	Dose	Response	Reference
House sparrow (*Passer domestticus* L)	50 or 100 mg/kg/day malathion (NOS) for 8 days	At 50 mg/kg/day, first death occurred after 3 doses and brain ChE was inhibited 31% in this bird; at 100 mg/kg/day, first death occurred afer 2 doses and brain ChE was inhibited 52% in this bird. Birds in both groups that died after the first death was observed had increasing levels of brain ChE inhibition; birds surviving 8 doses for 50 mg/kg/day had normal ChE activity.	Habig 1995 MRID 43860801
Sharp-tailed grouse, *Pediocetes phasianellus*, live-trapped on their breeding ground	single oral dose (by capsule) of 171-300 mg/kg	Depression and inactivity were observed within a few hours of dosing; death or full recovery in survivors occurred within 72 hours. Mortality rates: 1/6 at 171-200 mg/kg; **3/6 at 201-220 mg/kg**; 1/6 at 221-240 mg/kg; 1/1 at 300 mg/kg	Habig 1995 MRID 43860801
Bobwhite quail, 14 days old	malathion (95% a.i.)	5-day LC_{50} = 3497 ppm (95% CI = 2959-4011 ppm)	Heath et al. 1972 Hill et al. 1975 MRID 00022923
Japanese quail, 14 days old	malathion (95% a.i.)	5-day LC_{50} = 2962 ppm (95% CI = 2453-3656 ppm)	Heath et al. 1972 Hill et al. 1975 MRID 00022923
Mallard duck, 16 days old	malathion (95% a.i.)	5-day LC_{50} >5000 ppm	Heath et al. 1972 Hill et al. 1975 MRID 00022923
Ring-necked pheasant, 10 days old	malathion (95% a.i.)	5-day LC_{50} = 2639 ppm (95% CI = 2220-3098 ppm)	Heath et al. 1972 Hill et al. 1975 MRID 00022923
Japanese quail, *Coturnix japonica*,10/ dose group	dietary concentration of 1320-4000 ppm malathion (95% a.i.) in corn oil, observation period 5 days	LC_{50} = 2968 ppm (95% CI = 2240-3932 ppm)	Hill and Camardese 1986

Acute Toxicity

Organism	Dose	Response	Reference
Sharp-tailed grouse	oral doses malathion (NOS)	Lethal dose = 200-240 mg/kg; death or full recovery within 72 hours. Sublethal signs of toxicity included depression, slow reactions, blinking, head nodding, and eventual heart or respiratory failure.	McEwen and Brown 1966 MRID 113233
House sparrow (*Passer domesticus*)	Malathion in seed diet at 998 ppm	75% decrease in food consumption relative to controls.	Mehrotra et al. 1966
House sparrow (*Passer domesticus*)	50, 100, 250, and 500 mg/kg bw by gavage in acetone.	AChE inhibition within 5 minutes of ingestion: 25% (50 mg/kg bw), 50% (100 mg/kg bw), 75% (250 mg/kg bw), 83% (500 mg/kg bw). Sublethal effects at 250 and 500 mg/kg bw included increased respiration, head droop, ejection of white fluid from mouth, chronic and tonic convulsions. At 50 and 100 mg/kg, birds recovered within 24 hours Mortality = 18% at 250 mg/kg and 57% at 500 mg/kg. **Note on Mehrotra et al. 1966:** As noted in the bibliography, this study is summarized in U.S. EPA/OPP (2000c). The summary in U.S. EPA appears to have mixed doses reported as mg/bird with doses reported as mg/kg bw (see U.S. EPA/OPP 2000c, pp. 58 to 59). The Mehrotra study does not appear to have been published and is not in a listing (provided by U.S. EPA for the current risk assessment) of studies submitted for registration.	Mehrotra et al. 1966
Red-winged blackbird		LD_{50}: 400 mg/kg	Schafer et al. 1983
Horned lark, males and females, adults, 9	Malathion (95% a.i.)	14-day LD_{50} = 403 mg/kg (95% CI = 247-658 mg/kg)	Hudson et al. 1984
Mallard duck, females, 3 months old, 24	Malathion (95% a.i.)	14-day LD_{50} = 1485 mg/kg (95% CI = 1020-2150 mg/kg) Sublethal signs of toxicity included ataxia, walking high on toes, wing drop, falling stiffly with spread wings, tenesmus, foamy salivation, tremors. Mortalities occurred 100 minutes to overnight after treatment.	Hudson et al. 1984
Ring-necked pheasant, females, 3 months old, 12	Malathion (95% a.i.)	14-day LD_{50} = 167 mg/kg (95% CI = 120-231 mg/kg)	Hudson et al. 1984

Acute Toxicity			
Organism	**Dose**	**Response**	**Reference**
Red-legged partridges, *Alectoris rufia*	167 mg/kg malathion (NOS)	55% inhibition of blood cholinesterase after 1 hour; no measurable inhibition of brain cholinesterase after 4 hours	Walker et al. 1991

Longer-term			
Organism	**Dose**	**Response**	**Reference**
Northern bobwhite quail, *Colinus virginianus*, 18 weeks old, 16 pairs/dose group	continuous dietary concentra-tions of 0, 110, 350 or 1200 ppm malathion (96.4%) for 21 weeks	NOEL = 110 ppm NOEL (**for reproductive effects**) =350 ppm LOEL = 350 ppm–regressed ovaries (4/15), abnormally enlarged/flaccid gizzards, and decreased numbers of eggs hatched 1200 ppm – abnormally enlarged/flaccid gizzards, decreased egg production, decreased egg viability, increased number of cracked eggs due to possible weakening of shell, and decreased embryo survival. Maternal toxicity manifested as weight loss, decreased food consumption, some mortality, and clinical signs of toxicity.	Beavers et al. 1995 MRID 43501501
Starling (*Sturnus vulgaris*), wild trapped	8, 35, or 160 ppm malathion (NOS) in diet for 12 weeks	No mortality At 160 ppm, 30% decrease in ChE ($P<0.05$) and 50% increase in LDH activites ($P<0.05$). No significant increase in circulating levels of cratine kinase or aspartate aminotransferase.	Dieter 1975

Longer-term			
Organism	**Dose**	**Response**	**Reference**
Bobwhite quail, 21 weeks old, 5 males and 5 females per dose group, body weight range 150-250 g	0, 250, 500, 1500, 2000, or 2500 ppm technical grade malathion (purity 94.0%) in the diet for 28 days	At 250 ppm, one bird was lethargic and lost an excessive amount of weight; however, total remission of all signs was achieved by day 23 At 500 ppm, signs of toxicity included lethargy, white chalky droppings, notably excessive weight loss and death (1/10), with the first signs of toxicity noted on day 7; however, total remission of all signs was achieved by day 26 At 1500 ppm, signs of toxicity included lethargy, white, chalky diarrhea, anorexia, notably excessive weight loss, inability to stand, extreme weakness, and death (7/10), with the first signs of toxicity noted on day 6 At 2000 and 2500 ppm, signs of toxicity included lethargy, white, chalky diarrhea, anorexia, notably excessive weight loss, inability to walk, and death (10/10), with the first signs of toxicity noted at day 5	Fletcher and Pedersen 1989 MRID 41999801
Coturnix quail, *Coturnix coturnix japonica*, 3 days old, 30 birds/dose group	0, 20, 40, or 75 mg commercial malathion (56.5% a.i.) in corn oil injected into crop for 21 days	Brain AChE activity decreased to 75.3% at 20 mg; 55.8% at 40 mg; and 31.7% at 75 mg. Normal levels of brain AChE were observed in all treated birds 20 days after treatment was discontinued. There was a corresponding alteration in the physical ability of the birds as demonstrated by the "flap" test. The investigators report a definite linear correlation between brain AChE and impaired physical ability in quail exposed to sublethal doses of malathion for 21 days.	Meydani and Post 1979

Longer-term			
Organism	**Dose**	**Response**	**Reference**
Bobwhite quail, 48 males and 96 females, 26-27 weeks old	0, 30, 100, or 300 ppm technical malathion (94.0% purity) in diet for 28 dayss	At 6 weeks, females given 30 ppm a.i. had significantly (P≤0.05) increased body weight gain; no other effects on body weight were observed at any dose level in the course of the study. Ingestion of technical grade malathion by the parental generation did not appear to adversely affect the F_0 or the F_1 generations. NOEL = 300 ppm a.i..	Pedersen 1989 MRID 41367801
Mallard duck, *Anas platyrhynchos*, 23 weeks old, 16/sex/dose group	0, 240, 1200, or 2400 ppm technical malathion (94.0%) in diet for 20 consecutive weeks	Signs of toxicity included statistically significant lower body weights in males (2400 ppm) at termination, statistically significant (P≤0.05) decrease in eggshell thickness at 2400 ppm, which may be correlated with the slightly higherpercentage of cracked or broken eggs in this dose group, and a statistically significant (P≤0.01)increased incidence of infertile eggs, only at 2400 ppm. Based on study parameters (body weights, food consumption, egg production, hatchability, viability, etc.), the NOEL = 1200 ppm LOEL = 2400 ppm for effects on growth and viability	Pedersen and Fletcher 1993 MRID 42782101
White leghorn cockerels, 4 weeks old, 18 birds/dose group	0, 400, 800, or 1600 ppm malathion (NOS) in diet for 90 days	Significant decrease in body weight at 800 and 1600 ppm; significant increases in liver/body weight ratios at all dose levels; significant inhibition of aniline hydroxylation and demethylation of p-chloro-N-methyl aniline by liver microsomes at all dose levels; significant increases in plasma half-lives of antipyrine at 800 and 1600 ppm; and markedly incrased pentobarbital sleeping in all treated birds.	Varshney et al. 1986

Egg Injection Studies			
Organism	**Dose**	**Response**	**Reference**
Hen eggs	injection of 25, 100, 200, 300, 400, or 500 ppm malathion (NOS) dissolved in acetone	Higher doses (NOS) significantly decreased hatchability: 25 ppm (85%), 100 ppm (87%), 200 ppm (62%), 300 ppm (71%), 400 ppm (42%), and 500 ppm (6%).	Dunachie and Fletcher 1969
Leghorn chicken, fertile eggs	daily injection of 0.1 mL 95% technical malathion in corn oil on days 4-12 of incubation	Concentration of malathion that caused 50% mortality is age dependent (4- to 5-day old embryos were most sensitive). 50% of survivors of day 8-12 injections were featherless or had sparse feathers only in the abdominal region. 95% of the survivors of day 6-7 injections were smaller than controls. 98% of the survivors of day 4-5 injections had a combination of plumage, hind limb, beak, and size defects, characterized as *malathion syndrome* (see detailed note below)..	Greenburg and LeHam 1969

Further Notes on Greenburg and LeHam (1969): These investigators define *malathion syndrome* in terms of effects on the legs, beak, plumage, and body size. **Legs**: hind limbs reduced to about one half of the normal size and there was permanent curled toe paralysis in all affected chicks; in 10% of the affected chicks the joint between the tarsometatarsus bone projected dorsally; 1/50 chicks bilaterally lacked the tarsometatarsus bone and phalanges. **Beak**: The mandible length was reduced; 50% of the chicks had parrot beak (distal end of the maxilla was curved downwards over the mandible). **Plumage**: 25% of chicks lacked feathers, especially in the abdominal area; 4% of chicks were featherless; and all hatched chicks had coarse and hair-like down (clubbed down). **Body Size:** Overall sizes of the dosed chicks were about two-thirds that of normal. Six percent of the dosed chicks were dwarfs (about one-quarter of the normal size).

Egg Injection Studies			
Organism	**Dose**	**Response**	**Reference**
White leghorn chicken, fertile eggs	0.1 mL 2% malathion (96% technical grade) in corn oil on day 5 of incubation	In malathion treated embryos (after an 8- to 20-day incubation period), adverse effects included the retarded growth of the tibiotarsus and a weakening of the cartilage model that resulted in the bending of the tibiotarsus and invasion of the proliferative zone by fibrous connective tissue and bone..	Jackson and Gibson 1976
Chicken (NOS), eggs	50 mg/egg malathion (NOS) by injection	effects included shortening of legs and bleaching of feathers	Marliac 1964
White leghorn chicken eggs 24, 48, or 72 hours old at time of injection, 10 eggs/dose group	0, 0.125, 0.25, 0.5, or 1.0 mg at 24 and 48 hours; 0, 1.0, 2.0, or 4.0 mg at 72 hours.	All doses as 96% pure malathion diluted in corn oil. No apparent NOEL; the overall incidence of total defects to wing level notochord and spinal chord, caudal spinal cord, eyes (lens and optic cup), diencephalon (epiphysis and other), cardiovascular system (heart, dorsal aorta, and cardinal veins), and the tailbud was both dose and age-related, doubling for each doubling of dose and tripling for each 24 hours (less age) of exposure.	Wyttenbach and Thompson 1985

Appendix 2: Terrestrial Field Studies

Terrestrial Field Studies		
Application	**Observations**	**Reference**
Ultra-low volume aerial application of 0.4-0.6 lbs /acre technical, undiluted malathion to 115 square miles (38 square miles sprayed only in early May; 39 square miles sprayed only in late May; and 38 square miles sprayed both in early and late May) of grain fields in Michigan.	No detrimental effects to bird life. No mortality. The proportion of successful early bluebird nests was high in sprayed (9/11 nests) and unsprayed (26/34 nests) areas.	Black and Zorb 1966
Application of 6.8 fluid ounces/acre malathion (NOS)	No direct effects on wildlife, as monitored by population censuses, carcass counts, and residue analysis.	Dobroski et al. 1984
Application of 8 fluid ounces/acre malathion (NOS) to approximately 4300 acres of meadows and rolling grasslands in Utah national forest.	No adverse effects on abundant species of birds and no adverse effects or behavioral responses in any wildlife species.	Dobroski et al. 1984
Ultra-low volume applications at 1 and 10 times normal application rated	No neurotoxicity to bobwhite quail. No inhibition of cholinesterase activity. Food consumption was normal.	Dobroski et al. 1984
Malathion (NOS) applied at 0.65 kg/ha (9.6 oz/ac) in ULV formulation in western rangelands. Three other treatments, including sevin-4-oil, carbaryl bait, and *Nosema locustae* bait, were used in this field study. None of the treatments exceeded 15,000 ha.	No significant differences noted in total bird density and species richness, diversity, or balance of distribution of the 5 most abundant bird species between pretreatment and post -treatment samples. Densities of western meadowlarks (*Sturnella neglecta*), were, however, significantly lower on treated fields 10 and 21 days post-treatment. Investigators noted little evidence of depressed acetylcholinesterase activity in birds collected from treated sites. One horned lark collected on a site treated with malathion showed evidence of AChE inhibition. Study concludes that declines in bird density on treated sites is most likely the result of reduced food (in this case grasshoppers) availability for insectivorous birds.	George et al. 1995

Terrestrial Field Studies		
Application	**Observations**	**Reference**
Aerial application of 0.81 kg/ha malathion labeled with sulfur 35 to deciduous-forested 8-ha watershed	No evidence of adverse effects on survival or behavior on populations of ruffed grouse, *Bonasa umbellus*. No effects were observed from single-swath application; however, the second application, 10 days later, caused notable silence among birds in the treated area, compared with controls. Silence lasted for 2 days. Within 4 days after application, there were no noticeable differences between bird populations in treated and untreated areas. **Notes on Giles 1970 study:** Investigator speculates that the reason for the observed silence may have been due to emigration, behavioral responses associated with food loss, or the sublethal effect of the malathion. Only a few birds (usually no more than 10) were seen alive during a day on the treated area.	Giles 1970
Aerial application of malathion ULV to stop epidemic transmission of malaria in Haiti. Malathion (NOS) was applied at a rate of 6 ounces/acre for the first treatment and 4.5 ounces/acre for all subsequent cycles (NOS).	Except that sparrows stopped foraging for 1 hour post treatment, there were no adverse effects on avian behavior, no adverse effect on brain ChE, no evidence of moribund or dead birds. The avian species monitored included village weavers, migrating warblers, and cattle egrets.	Habig 1995 MRID 43860801
Aerial application of ULV malathion (95%) over Hale County, Texas towns. Malathion was sprayed nine times at a rate of 214 g/ha (3 fluid ounces/acre).	No decline in the population of house sparrows, which represented 93%of the avifauna in the study area); no significant inhibition of brain ChE levels, no indication of matting anomaly, nestling aggressiveness, or changes in feeding behavior	Habig 1995 MRID 43860801
Aerial thermal fog of malathion under natural conditions in areas in Collier County, Florida, exposed to normal mosquito control operations. The three study areas selected included canals, ponds, and cypress heads. Six plots (three treated and three untreated) of each area type were monitored for one full year.	The results indicated no significant differences between bird counts in the treated and untreated plots. Resident bird species included green heron, red-shouldered hawk, bobwhite, mourning dove, ground dove, kingfisher, pileated woodpecker, red-bellied woodpecker, carolina wren, mocking bird, catbird, white-eyed vireo, yellow throat, eastern meadowlark, and cardinal.	Habig 1995 MRID 43860801
Ground application (aerosol fog generator) at a label rate of 1.5 ounces/minute (1X; used for mosquito control) and also 10X label rate malathion (ULV concentrate) weekly (5 weeks) or daily (20 exposures over 34 days). Actual levels of malathion sprayed were 0.038 lbs a.i./acre (1X) and 0.38 lbs/acre (10X)	All bobwhite quail, *Colinus virginianus*, were caged 50 feet from the foggers during spraying. Exposure did not cause detectable neurotoxic signs in the birds; all birds remained alert, active, and coordinated, food consumption was normal and no diarrhea was detected, there were no incidence of treatment related mortality, and no indication of red cell ChE inhibition.	Habig 1995 MRID 43860801

Terrestrial Field Studies

Application	Observations	Reference
Aerial application of 900g/ha to four separate plots in the Grib Forest outside of Copenhagen (two plots treated in 1965 and two plots treated in 1967). The applications were timed to occur when the eggs of three bird species had just hatched. The three bird species included the great tit, *Parus major*, the coal tit, *Parus alter*, and the pied flycatcher, *Fecediela hypoleuca*.	There were no treatment related effects on breeding success (number of young flying); no significant difference in the loss of nestlings from treated plots, compared with untreated plots; brain ChE activity was inhibited in nestlings from one brood of coal tits and two broods of pied flycatchers and each of the these broods had nestling deaths attributed to treatment.	Habig 1995 MRID 43860801
Malathion-ULV (NOS) aerial application to 520 ha treatment area at a rate of 585 g/ha (8 fluid oz/acre) under conditions minimizing drift (winds <10 km/h). The two treated areas are located in the shrub-steppe habitat of sourthern Idaho. Treatments took place at different treatment sites in June 1989 and 1990.	No adult mortality to sage thrashers (*Oreoscoptes montanus*) or nestling Brewer's sparrow (*Spizella breweri*). Nestling mortality could not be attributed to malathion. There were no treatment-related effects either year on the percentage of eggs hatched or the percentage of nestlings fledged for either species. In addition there were no detectable differences in estimates of nest survivorship for either species. In 1989, the mean number of sage thrashers fledged per nest attempt was lower on the treated site, compared with control plot, but this effect was not observed in 1990. The investigators conclude that under the conditions of this study, exposure to malathion had no observable direct effects and only marginal indirect effect through food-base reduction on Brewer's sparrow and sage thrasher nestling growth and survival.	Howe et al. 1996
Cythion Ultra Low Volume (95% malathion) applied at a rate of 210 mL/ha over entire city of Winnipeg (Manitoba, Canada) to control mosquito carriers of Western Equine Encephalitis virus. The actual spray deposition rate on the site where the cage was located was 140 mL/ ha over 3 hours.	The cage was left *in situ* during and for 3 hours following the spray operation. There were no signs of toxicity or effects on behavior of the caged sparrows during or after the spraying. Furthermore, ChE levels were not significantly suppressed in post-spray specimens, compared with pre-spray specimens.	Kucera 1987
Reduced agent-area treatment with 0.3 L (ULV without carrier) malathion (Fyfanon) with 342 g a.i./ha treated to 4/5 of a 243-ha plot (termed 342-80 treatment, effectively 272 g a.i. ha^{-1} *protected*) to control grasshoppers on two rangeland sites in Wyoming during an outbreak.	**Population density of birds:** bird densities did not reflect the changes in the grasshopper populations after treatment; there were no signs of direct intoxication of the birds due to treatment; suppression of bird population density observed in this study varied significantly among plots in each of the treated sites. **Notes on Norelius and Lockwood 1999:** Authors assert that "the changes in bird density were almost certainly a function the alterations in the prey base, rather than the result of direct or indirect (via consumption of dead or dying grasshoppers) intoxication."	Norelius and Lockwood 1999

Terrestrial Field Studies		
Application	**Observations**	**Reference**
Up to 7 annual aerial applications of 12 or 16 oz (≈1.2 lbs a.i./acre) technical malathion at 5-22 day intervals for 5 years to various cotton fields adjacent to quail habitats. Planes were flown at an altitude of approximately 25 feet, covering a 100-foot swath.	Despite minor fluctuations in wild quail and bird populations on the study sites, no dead birds were found after spray operations and there were no pronounced population changes other than those attributed to normal turnover or migration dynamics.	Parsons and Davis 1971
Standard ULV aerial application of malathion (Malagrex-ULV) against green moth larvae (*Tortrix viridana*) in Spain at an application rate of 1160 g a.i./ha in spring 1988.	No effect on breeding success of the blue tit (*Parus caeruleus*) including nest abadnoment, nest success, hatching success, nestling mortality, daily survival rate, and nestling weight). Malathion caused nearly 100% mortality of the target pest.	Pascual 1994

Appendix 3: Toxicity Studies in Bees

Organism	Exposure	Response	Reference
Alfalfa leafcutter bees, *Megachile rotundata*, average weight 22 mg (females) and 26 mg (males)	1.0 lbs/acre malathion (5 lb EC); 6 hour residue	24-hour mortality = 100%	Johansen 1972
Alkali bees, *Nomi melanderi*, average weight 74 mg (females) and 87 mg (males)	1.0 lbs/acre malathion (5 lb EC); 6 hour residue	24-hour mortality = 47%	Johansen 1972
Honey bees, *Apis mellifera*, average weight 128 mg (workers)	1.0 lbs/acre malathion (5 lb EC); 6 hour residue	24-hour mortality = 100%	Johansen 1972

Notes on Johansen 1972: The author reports that the typical pattern of susceptibility of bees to insecticides appears to be alfalfa leafcutter bee>alkali bee>honey bee>bumble bee. And notes that the sequence appears to be related to size. Honey bees were not tested for susceptibility to malathion in this study.

Alfalfa leafcutter bees, *Megachile rotundata*, 20-40 bees, surface to volume ratio = 94/33 mm^2/λ (females)	malathion, 0.9 kg ai/ha	toxicity of field weathered residues assessed by treating 0.004-ha plots of second-growth alfalfa RT25 = 57 hours (indicates residual time required to bring bee mortality down to 25% in cage test exposures to field-weathered exposures)	Johansen et al. 1983
Alfalfa leafcutter bees, *Megachile rotundata*, 20-40 bees, surface to volume ratio = 94/33 mm^2/λ (females)	malathion ULV, 0.56 kg ai/ha	toxicity of field weathered residues assessed by treating 0.004-ha plots of second-growth alfalfa RT25 = 158 hours (indicates residual time required to bring bee mortality down to 25% in cage test exposures to field-weathered exposures)	Johansen et al. 1983
Alkali bees, *Nomi melanderi*, 12-18 bees, surface to volume ratio = 165/87 mm^2/λ (females)	malathion, 0.9 kg ai/ha	toxicity of field weathered residues assessed by treating 0.004-ha plots of second-growth alfalfa RT25 = not determined (indicates residual time required to bring bee mortality down to 25% in cage test exposures to field-weathered exposures)	Johansen et al. 1983
Alkali bees, *Nomi melanderi*, 12-18 bees, surface to volume ratio = 165/87 mm^2/λ (females)	malathion ULV, 0.56 kg ai/ha	toxicity of field weathered residues assessed by treating 0.004-ha plots of second-growth alfalfa RT25 = not determined (indicates residual time required to bring bee mortality down to 25% in cage test exposures to field-weathered exposures)	Johansen et al. 1983

Organism	Exposure	Response	Reference
Honey bees, *Apis mellifera*, 60-100 workers, surface to volume ratio = 186/128 mm^2/λ (workers)	malathion, 0.9 kg ai/ha	toxicity of field weathered residues assessed by treating 0.004-ha plots of second-growth alfalfa RT25 = 40 hours (indicates residual time required to bring bee mortality down to 25% in cage test exposures to field-weathered exposures)	Johansen et al. 1983
Honey bees, *Apis mellifera*, 60-100 workers, surface to volume ratio = 186/128 mm^2/λ (workers)	malathion ULV, 0.56 kg ai/ha	toxicity of field weathered residues assessed by treating 0.004-ha plots of second-growth alfalfa RT25 = 131 hours (indicates residual time required to bring bee mortality down to 25% in cage test exposures to field-weathered exposures) Notes on Johansen et al. 1983: Although this study investigates residue exposure, nectar contamination and leaf piece contamination, acute oral exposure, and field studies involving pesticides and bees, only the residue exposure study involves the use of malathion.	Johansen et al. 1983
Honey bees	1 oz application of malathion (55% EC) directed into ventilation saw cuts in the frame of the bee hives	Malathion killed all adult bees within 6 hours.	Keener and Pless 1974 MRID 5009244
Italian honey bees, *Apis mellifera* L., **1 week old**	0, 48, or 60 µg/100 mm filter paper malathion (NOS) for 24, 48, or 72 hours	**at 48 µg**: 24-hr mortality =0% (controls =3%) 48-hr mortality =17% (controls =3%) 72-hr mortality =60% (controls = 3%) **at 60 µg**: 24-hr mortality =5% (controls = 3%) 48-hr mortality =38% (controls = 3%) 72-hr mortality =40% (controls = 3%)	Maryland and Burkhardt 1970
Italian honey bees, *Apis mellifera* L., **2 weeks old**	0, 48, or 60 µg/100 mm filter paper malathion (NOS) for 24, 48, or 72 hours	**at 48 µg**: 24-hr mortality =2% (controls = 0%) 48-hr mortality =38% (controls = 0%) 72-hr mortality =68% (controls = 0%) **at 60 µg**: 24-hr mortality =0% (controls = 0%) 48-hr mortality =20% (controls = 0%) 72-hr mortality =100% (controls = 0%)	Maryland and Burkhardt 1970

Organism	Exposure	Response	Reference
Italian honey bees, *Apis mellifera* L., **3 weeks old**	0, 48, or 60 µg/100 mm filter paper malathion (NOS) for 24, 48, or 72 hours	**at 48 µg**: 24-hr mortality =0% (controls = 2%) 48-hr mortality =3% (controls = 3%) 72-hr mortality =33% (controls = 3%) **at 60 µg**: 24-hr mortality =0% (controls = 2%) 48-hr mortality =22% (controls = 3%) 72-hr mortality =83% (controls = 3%)	Maryland and Burkhardt 1970
Italian honey bees, *Apis mellifera* L., 3 weeks old, 6 replications, 10 bees/replicate	0 or 57 µg/100 mm petri dish malathion (NOS) for 24 hours on various surfaces	**% mortality after 24-hour dermal exposure to various surfaces**: filter paper = 2%(controls = 1%) plastic = 100% (controls = 2%) glass = 100% (controls = 0%) rhubarb leaves = 97%(controls = 0%) alfalfa leaves = 67%(controls = 1%) silty clay loam = 58%(controls =40%) loam = 83%(controls = 50%) sandy loam = 67%(controls = 38%) sand = 46%(controls = 16%)	Maryland and Burkhardt 1970
Notes on Maryland and Burkhardt 1970: The investigators report that bee mortality in this study was generally high on all treated soils, even among controls. The investigators speculate that the continued fanning of the bee's wings caused small soil particles to become airborne and taken into the respiratory system, suffocating the bees. In addition, they speculate that malathion toxicity could also might have been aggravated by the soil surfaces when soil particles become dusted on the bodies of the bees, thereby increasing insect-malathion contact. Due to it's large particle size, sand surface seems to be an exception.			
Italian honey bees, *Apis mellifera* L., 3 weeks old, 6 replications, 10 bees/replicate	57 µg/100 mm petri dish malathion (NOS) for 24 hours on various surfaces	volatilization of malathion concentration was essentially unaffected by the type of absorbing surface.	Maryland and Burkhardt 1970
Italian honey bees, *Apis mellifera* L., **newly emerged**	0, 48, or 60 µg/100 mm filter paper malathion (NOS) for 24, 48, or 72 hours	**at 48 µg**: 24-hr mortality =17% (controls = 0%) 48-hr mortality =20% (controls = 0%) 72-hr mortality =23% (controls = 0%) **at 60 µg**: 24-hr mortality =52% (controls = 0%) 48-hr mortality =58% (controls = 0%) 72-hr mortality =67% (controls = 0%)	Maryland and Burkhardt 1970
Italian honey bees, *Apis mellifera* L., **random ages**	0, 48, or 60 µg/100 mm filter paper malathion (NOS) for 24, 48, or 72 hours	**at 48 µg**: 24-hr mortality =12% (controls = 8%) 48-hr mortality =47% (controls = 22%) 72-hr mortality =53% (controls = 35%) **at 60 µg**: 24-hr mortality =5% (controls = 8%) 48-hr mortality =75% (controls = 22%) 72-hr mortality =88% (controls = 35%)	Maryland and Burkhardt 1970

Appendix 4: Toxicity Studies on Fish

Three separate tables are included: Freshwater Acute, Estuarine/Saltwater Acute, and Chronic. Each table is sorted by Reference and then by Organism.

FRESHWATER ACUTE

Organism	Exposure	Response	Reference
Hill trout *Barilius vagra*	96-hours, static 57% EC formulation, NOS	96-hours LC50: 7.93 and 7.66 ppm in duplicate bioassays.	Alam and Maughan 1992
Zebrafish, *Brachydanio rerio*, 6 groups of two females and six males	0.5 mg/L malathion (NOS) for 4 months	Number of mature follicles decreased dramatically and the number of atretic (degenerating) follicles increased dramatically; fish had decreased body weight and failed to spawn; recovery after two months in freshwater included an increase in the number of all stages of oocytes, but gravidity and spawning did not return to normal.	Ansari et al. 1986
Zebrafish, *Brachydanio rerio*, females	0.9 mg/L malathion (NOS) for 7 days	Histopathological changes in the ovary included atretic follicles and loss of characteristic spherical shape; number of mature follicles increased nominally after 7 days of recovery in fresh water, but atretic follicles remained unaltered	Ansari et al. 1986
Channel catfish (*Ictalurus punctatus*), fingerlings, av. length of 16.5 cm, av. weight of 26.8 g, 5 replicates of 10 treated fish, 5 replicates of 10 control fish in under static test conditions	4.5 mg/L commercial grade malathion (56.1% a.i., 35.2% organic solvent, 8.7% inert solvent) for 96 hours	Treated fish were lethargic, yet sensitive to disturbances, showed loss of equilibrium and direction of movement, and about 80% developed vertebral deformities clearly visible in radiographs. Significant ($P<0.05$) increases in erythrocytes and decreases in leukocytes were observed in treated fish at 48, 72, and 96 hours, with correspondingly significant increases in hematocrit and hemoglobin at 72 and 96 hours. Plasma glucose was significantly higher in treated fish throughout the sampling period. Other adverse effects included necrosis of the gills and vacuolation and focal necrosis of the liver.	Areechon and Plumb 1990
Tilapia mossambica	malathion (NOS)	48-hour LC_{50}: 0.367 (0.303-0.431) ppm	Basha et al. 1983
Tilapia mossambica	malathion (commercial grade, NOS)	0.1 mg/L for 48 hours (sublethal): modest decrease on O_2 consumption significant at 36 and 48 hours. Decrease in liver glycogen.	Basha et al. 1983

FRESHWATER ACUTE			
Organism	**Exposure**	**Response**	**Reference**
Rainbow trout, *Oncorhynchus mykiss*, larvae, 40-days old, 0.24 ± 0.08 g, 30.8 ± 2.9 mm, 30/dose group	technical grade malathion (99.5%) at nominal concentrations of 20 or 40 µg/L for 24-96 hours under static renewal conditions	Mortality <12% per treatment observed at 24 and 48 hours at both test concentrations. Cholinesterase activity decreased significantly with increasing concentrations (2-way ANOVA P=0.0008), with the greatest decrease observed at 48 hours of exposure. Adverse effects on physiological parameters (swimming speed and distance and rate of turning) were significantly correlated with changes in ChE activity.	Beauvais et al. 2000
Colorado squawfish (*Ptychocheiilus lucius*), mean weight = 8.0 g, mean length = 74 mm	technical grade malathion (93%) for 24 hours	Threshold and effect concentrations for AChE inhibition: threshold: 150 µg/L (95% CI = 83.8-270) NOEC = 371 µg/L LOEC = 707 µg/L	Beyers and Sikoski 1994
Colorado squawfish (*Ptychocheiilus lucius*), 26- and 6-day-old larvae, mean weight = 4 mg, mean length = 9.4 mm	technical malathion (93%)	4-day renewal LC_{50} = 9.14 mg/L (95% confidence limit = 8.36, 10.0) NOEC for growth = 1680 µg/L	Beyers et al. 1994a
Colorado bonytail (*Gila elegans*), 26- and 6-day-old larvae, mean weight = 2 mg, mean length = 6.8 mm	technical malathion (93% pure)	4-day renewal LC_{50} = 15.3 mg/L (95% confidence limit = 14.4, 16.4) NOEC for growth = 990 µg/L	Beyers et al. 1994b
Walking catfish, *Clarias batrachus*	96-hours, static 33% EC formulation, NOS	24-hour TLM = 0.063 mg/L 48-hour TLM = 0.052 mg/L 72-hour TLM = 0.049 mg/L 96-hour TLM = 0.047 mg/L	Bhatnagar et al. 1988
Rainbow trout (*Oncorynchus mykiss*)	technical malathion (>98% pure) 24 and 48 hours at 20 and 40 µg/L.	Only moderate lethality (<12% per treatment). Sublethal effects due to exposure included dramatic decreases in swimming speed and distance as well as marked changes in the complexity of swimming paths after 24-hours. At 96-hours, decreases in swimming speed and distance were still observed. Fish recovered fully after 48 hours in clean water.	Brewer et al. 2001
Zebrafish *Brachydanio rerio*, embryos	0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mg/L malathion (99% purity) for up to 120 hours	Dose-dependent adverse effects including a significant reduction in body length and eye diameter and an increase in abdominal cavity. Significant effect on hatching at and on survival at 72 and 96 hours but only at the two highest concentrations (2.5 and 3.0 mg/L).	Cook et al. 2005

FRESHWATER ACUTE

Organism	Exposure	Response	Reference
Rainbow trout (*Oncorynchus mykiss*)	Malathion (NOS)	Effect of temperature on toxicity in µg/L: 24 h / 48 h / 96 h 45 °F: 100 / 79 / 77 55 °F: 85 / 70 / 68 65 °F: 130 / 120 / 110	Cope 1965
Catfish, *Clarias batrachus* (Linnaeus), 80-90 g, 170-205 mm, 10/dose group	0, 0.19, 0.28, or 0.56 ppm technical grade malathion for 120 days	Dose-dependent inhibition of brain AChE activity was significant (P<0.001) as follows: 53.78 ± 2.9 at 0.19 ppm 41.82 ± 2.2 at 0.28 ppm 23.35 ± 2.6 at 0.56 ppm Ovarian effects included los of stage II and III oocytes and inhibition of steroidogenesis at all test concentrations.	Das and Sengupta 1993
Guppies, *Lebistes reticulatus*, males, 4/dose group	0, 0.01, 1, 10, or 100 mg/L Cythion (formulation containing 95% malathion) for 1 week	NOEC = 0.1 mg/L ≥1 mg/L caused 100% mortality LC_{50} = 0.819 mg/L	Desi et al. 1976
Carp (*Cyprinus carpio*)	Malathion (commercial grade NOS), daily static renewal	96-hour LC_{50} = 0.002 mg/L Kidney pathology including necrosis at 15 day exposures to 0.002 mg/L.	Dhanapakiam and Premlatha 1994
Trout (*Salmo gairdneri*)	Malathion (technical grade NOS) daily renewal	Two 96-h LC50 determinations. Test 1 = 0.161 (0.137-0.201) mg/L Test 1 = 0.115 (0.094-0.146) mg/L	Douglas et al. 1986
Catfish, *Heteropneustes fossilis*, air breathing fish	0, 6, 8, 10, 12, 14, 16, 18, 20, 22 mg/L commercial grade malathion (50% a.i.)	24-hour LC_{50} = 16.28 mg/L 48-hour LC_{50} = 14.53 mg/L 96-hour LC_{50} = 11.80 mg/L	Dutta et al. 1992
Catfish, *Heteropneustes fossillis* (Bloch), females, 20 g, average length 15 cm (air breathing fish)	sublethal concentration (NOS) of malathion (50% a.i., 33% organic solvent, 17% inerts) for up to 96 hours	Histopathological liver changes after 24 hours included highly significant decrease in hepatic cell diameter; after 48 hours, further decrease in hepatic cell diameter, some degeneration of the cell membranes, vacuolation in the cytoplasm, and pyknotic (deep staining) and eccentric nuclei; after 72 hours, cell diameter began to increase but remained significantly decreased from control, and some cell membranes continued to disintegrate; at 96 hours, greater damage to cellular organization was observed, cell membranes were ruptured and fused together, some cells were necrotic with complete extrusion of nuclei apparent. There was no difference in the hepatic diameter of cells, compared with controls, at 96 hours.	Dutta et al. 1994b

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Organism	**Exposure**	**Response**	**Reference**
Catfish, *Heteropneustes fossillis* (Bloch), females, 28.0-32.0 g (air breathing fish)	sublethal concentration (1.2 mg/L) malathion (50% a.i.,) for up to 96 hours	After 24 hours, cytoplasm clumping was observed, after 48 hours, the clumping intensified and degeneration of the follicular cells was observed; after 72 hours, an increased number of nucleoli, shrinking of nuclear materials, and adherence of oocytes was observed; and at 96 hours the nuclear material of the oocytes shrunk to a smaller clump, oocytes fused together, and follicular epithelium became loose and ruptured. Estrogen levels decreased after 72 hours of exposure.	Dutta et al. 1994b
Catfish, *Heteropneustes fossillis* (Bloch), 8.0-15.0 and 25-40 g, five fish/weight group (air breathing fish)	sublethal concentration (1.2 mg/L) malathion (50% a.i.) for up to 96 hours	In juveniles, mean acetylcholinesterase activity is decreased at all exposure duration and is significantly different from controls. In adults, mean acetylcholinesterase activity is decreased only after 24 hours of exposure. In the higher weight group acetylcholinesterase activity recovers at 96 hours of exposure, indicating that detoxification capacity of fish increases with age.	Dutta et al. 1995
Catfish, *Heteropneustes fossillis* (Bloch), 28-32 g (air breathing fish)	sublethal concentration (4 mg/L) of malathion (50% EC) 96 hours	Ultrastructural damage to the gills observed at 24 hours, with most severe damage observed at 72 hours. By 96 hours of exposure, signs of gill structure regeneration were apparent.	Dutta et al. 1996
Notopterus notopterus (Mor), 8.6-11.0 cm, 14.4-19.0 g	technical grade malathion	96-hour LC_{50} = 0.077 mg/L (95% CI = 0.061-0.103)	Gupta et al. 1994
Zebrafish, *Dania rerio*, eggs and larvae	Malathion (NOS), concentrations up to 6 µM (1.8 mg/L)	Increases in malformations of embryos at 3µM (0.9 mg/L) and 6 µM (1.8 mg/L).	Fraysse et al. 2006
Green snakehead (*Channa punctatus*)	96-hours, static 50% EC formulation and technical grade	LC_{50} (mg/L) Duration / Technical grade / Formulation 24-hour 9.16 9.93 48-hour 6.59 8.21 72-hour 5.10 5.94 96-hour 4.51 4.38 Differences not statistically significant based on 95% confidence intervals. See Table 1 of publication.	Haider and Inbaraj 1986
Flagfish, *Jordanella floridae*, 33-days old, 40 fish/group in flow-through system	0, 116, 170, 294, 374, or 516 µg/L (mean measured concentrations) of 95% pure malathion for 216 hours in a flow-through system	96-hour LC_{50} = 349µg/L	Hermanutz 1978

FRESHWATER ACUTE			
Organism	**Exposure**	**Response**	**Reference**
Carp, *Cyprinus cario carpio* L, fingerlings, 7-8 g, 8 cm	malathion (NOS) in static bioassay	LC_0 = 0.01 ppm LC_{10} = 0.034 ppm LC_{25} = 0.061 ppm LC_{50} = 0.138 ppm LC_{75} = 0.281 ppm	Jagan et al. 1989
Barbus ticto (HAM)	0.020 ppm malathion (NOS) for 96 hours	Ascorbic acid levels increased in liver (187.5 ± 2.29 mg/g wet wt) and muscle (63.23 ± 1.19 mg/g wet wt), with higher concentrations in the liver.	Khillare and Wagh 1986
Barbus stigma (HAM)	0.01950 ppm malathion (NOS) for 96 hours	Pathological changes included rupture of the seminiferous tubules, degeneration of the interstitial cells, and swelling in portions of the epithelial cells. Spermatocytes were not greatly affected.	Khillare and Wagh 1989
Black bullhead catfish	95% a.i.	96-hour LC50 = 11,700 ppb (confidence limit = 9600-14,100 ppb)	Mayer and Ellersieck 1986
Bluegill sunfish	95% a.i.	96-hour LC50 = 20 ppb (confidence limit = 16-25 ppb)	Mayer and Ellersieck 1986
Bluegill sunfish	95% a.i.	96-hour LC50 = 30 ppb (confidence limit = 10-88 ppb)	Mayer and Ellersieck 1986
Brown trout	95% a.i.	96-hour LC50 = 101 ppb (confidence limit = 84-115 ppb)	Mayer and Ellersieck 1986
Carp	95% a.i.	96-hour LC50 = 6590 ppb (confidence limit = 4920-8820 ppb)	Mayer and Ellersieck 1986
Channel catfish	95% a.i.	96-hour LC50 = 7620 ppb (confidence limit = 5820-9970 ppb)	Mayer and Ellersieck 1986
Coho salmon	95% a.i.	96-hour LC50 = 170 ppb (confidence limit = 160-180 ppb)	Mayer and Ellersieck 1986
Cutthroat trout	95% a.i.	96-hour LC50 = 174 ppb (confidence limit = 112-269 ppb)	Mayer and Ellersieck 1986
Fathead minnow	95% a.i.	96-hour LC50 = 8650 ppb (confidence limit = 6450-11,500 ppb)	Mayer and Ellersieck 1986
Goldfish	95% a.i.	96-hour LC50 = 10,700 ppb (confidence limit = 8340-13,800 ppb)	Mayer and Ellersieck 1986
Green sunfish	95% a.i.	96-hour LC50 = 1460 ppb (confidence limit = 900-2340 ppb)	Mayer and Ellersieck 1986
Lake trout	95% a.i.	96-hour LC50 = 76 ppb (confidence limit = 47-123 ppb)	Mayer and Ellersieck 1986
Largemouth bass	95% a.i.	96-hour LC50 = 250 ppb (confidence limit = 229-310 ppb)	Mayer and Ellersieck 1986
Redear sunfish	95% a.i.	96-hour LC50 = 62 ppb (confidence limit = 58-67 ppb)	Mayer and Ellersieck 1986
Steelhead trout	95% a.i.	Differences between populations: Missouri: 24-h LC_{50} = 160 ppb 96-h LC_{50} = 94 ppb Missouri: 24-h LC_{50} = 39 ppb 96-h LC_{50} = 4.1 ppb	Mayer and Ellersieck 1986
Tilapia	95% a.i.	96-hour LC50 = 2000 ppb (confidence limit = NR)	Mayer and Ellersieck 1986

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Organism	Exposure	Response	Reference
Walleye	95% a.i.	96-hour LC50 = 64 ppb (confidence limit = 59-70 ppb)	Mayer and Ellersieck 1986
Yellow perch	95% a.i.	96-hour LC50 = 263 ppb (confidence limit = 205-338 ppb)	Mayer and Ellersieck 1986
Mosquito fish, Gambusia affinis	Technical grade	48-hour LC50 = 1.23 ppm	Milam et al. 2000
African catfish (*Clarias gariepinus*) larvae	0, 0.3, 0.63, 1.25, 2.5, or 5.0 mg/L malathion (98% analytical standard) for 5 days	Survival decreased from 97.4% (controls) to 71.8% (5.0 mg/L); growth was adversely affected at ≥2.5 mg/L; abnormality (deformed notochord and pericardial edema) of the larvae was dose dependent, with 43.2% and 65.1% abnormal larvae observed in the two highest dose groups. There was a significant increase in the number of larvae with pericardial edema in the 5.0 mg/L exposure group.	Nguyen et al. 1997
African catfish (*Clarias gariepinus*), embryo-larva	technical grade malathion (98% pure), 5-day exposures to 0, 0.3, 0.63, 1.25. 2.5, or 5 mg/L	LC_{50}: 3.42 (2.91-4.01) mg/L NOEC: 0.63 mg/L LOEC: 1.25 mg/L Deformation of notochord at LOEC and higher.	Nguyen and Janssen 2001 and 2002
Zebra fish (*Danio rerio*), embryo-larva	technical grade malathion (98% pure), 12-day exposures	LC_{50}: 1.80 (1.50-2.08) mg/L NOEC: 1 mg/L LOEC: 3 mg/L Deformations at sublethal concentrations.	Nguyen and Janssen 2001
Green snakehead (*Channa punctatus*)	Technical grade (Indian, purity not specified)	96-hour LC50 = 6.61 ppm	Pandey et al. 2005
Nile tilapia, *Oreochromis niloticus*m fingerlings	technical grade malathion (98% pure)	96-hour LC_{50} = 2.2 ppm (95% CI = 2.1-2.3 ppm)	Pathiratne and George 1999
Brook trout (*Salvelinus fontinalis*)	technical grade malathion (95% pure), static renewal daily	Effects of body weight on LC_{50}. Concentration in ppb Body weight: 72-h LC_{50} / 96-h LC_{50} 1.15 g: 160 (144-182) / 130 (110-154) 2.13 g: 150 (104-216) / 120 (96-153)	Post and Schroeder 1971
Cutthroat trout (*Oncorhynchus clarki*)	technical grade malathion (95% pure), static renewal daily	Effects of body weight on LC_{50}. Concentration in ppb Body weight: 72-h LC_{50} / 96-h LC_{50} 0.33 g: 200 (163-245) / 150 (133-170) 1.25 g: / 201 (175-231)	Post and Schroeder 1971
Rainbow trout, *Slamo gairdneri,* 0.41 g	technical grade malathion (95% pure), static renewal daily	24-hour LC_{50} = 240 (198-291) ppb 48-hour LC_{50} = 196 (165-223) ppb 72-hour LC_{50} = 175 (146-209) ppb 96-hour LC_{50} = 122 (98-153) ppb	Post and Schroeder 1971
Coho salmon, *Oncorhynchus kisutch,* 1.7 g	technical grade malathion (95% pure), static renewal daily	24-hour LC_{50} = 300 (211-346) ppb 96-hour LC_{50} = 265 (208-388) ppb	Post and Schroeder 1971
Striped bass, *Marone saxat1is,* wild caught	Malathion (Analabs, Inc. NOS)	24-hour TLM: 0.091 mg/L 48-hour TLM: 0.070 mg/L 96-hour TLM: 0.039 mg/L	Rehwoldt et al. 1977

FRESHWATER ACUTE			
Organism	**Exposure**	**Response**	**Reference**
Banded killyfish, *Fundulus diaphanous,* wild caught	Malathion (Analabs, Inc. NOS)	24-hour TLM: 0.38 mg/L 48-hour TLM: 0.29 mg/L 96-hour TLM: 0.24 mg/L	Rehwoldt et al. 1977
Pumpkinseed, *Lepomis gibbosus,* wild caught	Malathion (Analabs, Inc. NOS)	24-hour TLM: 0.92 mg/L 48-hour TLM: 0.60 mg/L 96-hour TLM: 0.48 mg/L	Rehwoldt et al. 1977
White perch, *Roccus americanus,* wild caught	Malathion (Analabs, Inc. NOS)	24-hour TLM: 2.1 mg/L 48-hour TLM: 1.9 mg/L 96-hour TLM: 1.1 mg/L	Rehwoldt et al. 1977
American eel, *Anguilla rostrata,* wild caught	Malathion (Analabs, Inc. NOS)	24-hour TLM: 1.6 mg/L 48-hour TLM: 0.71 mg/L 96-hour TLM: 0.50 mg/L	Rehwoldt et al. 1977
Carp, *Cyprinus carpio*, wild caught	Malathion (Analabs, Inc. NOS)	24-hour TLM: 2.6 mg/L 48-hour TLM: 2.1 mg/L 96-hour TLM: 1.9 mg/L	Rehwoldt et al. 1977
Guppy, *Libistes reticulatus,* pet store	Malathion (Analabs, Inc. NOS)	24-hour TLM: 2.2 mg/L 48-hour TLM: 1.8 mg/L 96-hour TLM: 1.2 mg/L	Rehwoldt et al. 1977
Chinook salmon, *Oncorhynchus tshawytscha*	**Malaoxon**	Inhibition of olfactory AChE. IC_{50}: 4.1 µg/L (SE 0.3) Additive effect with several OPs and carbamates	Scholz et al. 2006
Goldfish, *Carassius auratus*, 5.4-7.2 g	technical grade malathion (98%) under static condition without aeration	96-hour LC_{50} = 11.3 ppm (95% CI = 10.6-11.9 ppm)	Shao-Nan and De-Fang 1996
Goldfish, *Carassius auratus*, 5.4-7.2 g	technical grade malathion (98%), *in vitro*	IC_{50} = 3.23 ± 0.44 mmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Goldfish, *Carassius auratus*, 5.4-7.2 g	**malaoxon**, *in vitro*	IC_{50} = 0.35 ± 0.07 µmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Mosquitofish, *Gambusia affinis*, 0.20-0.26 g	technical grade malathion (98%) under static condition without aeration	96-hour LC_{50} = 0.70 ppm (95% CI = 0.65-0.76 ppm)	Shao-Nan and De-Fang 1996
Mosquitofish, *Gambusia affinis*, 0.20-0.26 g	technical grade malathion (98%) , *in vitro*	IC_{50} = not determined (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Mosquitofish, *Gambusia affinis*, 0.20-0.26 g	malaoxon, *in vitro*	IC_{50} = 0.50 ± 0.15 µmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Nile tilapia, *Tilapia noilotica*, 6.9-7.5 g	technical grade malathion (98%) under static condition without aeration	96-hour LC_{50} = 4.6 ppm (95% CI = 4.5-4.8 ppm)	Shao-Nan and De-Fang 1996
Nile tilapia, *Tilapia noilotica*, 6.9-7.5 g	technical grade malathion (98%) , *in vitro*	IC_{50} = 1.85 ± 0.77 mmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996

FRESHWATER ACUTE			
Organism	**Exposure**	**Response**	**Reference**
Nile tilapia, *Tilapia noilotica*, 6.9-7.5 g	Malaoxon, *in vitro*	IC_{50} = 0.33 ± 0.13 µmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Rainbow trout, *Slamo gairdneri*, 8.5-9.3 g	technical grade malathion (98%) under static condition without aeration	96-hour LC_{50} = 0.25 ppm (95% CI = 0.21-0.30 ppm)	Shao-Nan and De-Fang 1996
Rainbow trout, *Slamo gairdneri*, 8.5-9.3 g	technical grade malathion (98%), *in vitro*	IC_{50} = 1.00 ± 0.09 mmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Rainbow trout, *Slamo gairdneri*, 8.5-9.3 g	**malaoxon**, *in vitro*	IC_{50} = 0.26 ± 0.12 µmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Topmouth gudgeon, *Pseudorasbora parva*, 0.6-1.0 g	technical grade malathion (98%) under static condition without aeration	96-hour LC_{50} = 14.5 ppm (95% CI = 10.8-19.6 ppm)	Shao-Nan and De-Fang 1996
Topmouth gudgeon, *Pseudorasbora parva*, 0.6-1.0 g	technical grade malathion (98%), *in vitro*	IC_{50} = not determined (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Topmouth gudgeon, *Pseudorasbora parva*, 0.6-1.0 g	**malaoxon**, *in vitro*	IC_{50} = 0.92 ± 0.02 µmol/L (inhibition of brain AChE activity)	Shao-Nan and De-Fang 1996
Green snakehead (*Channa punctatus*)	Malathion, NOS	24-hour LC_{50} = 4.12-4.25 mg/L 48-hour LC_{50} = 3.66-3.75 mg/L 72-hour LC_{50} = 3.27-3.36 mg/L 96-hour LC_{50} = 2.87-2.94 mg/L	Singh et al. 1984
Catfish, *Heteropneustes fossilis*	Malathion, NOS	24-hour LC_{50} = 5.70-5.92 mg/L 48-hour LC_{50} = 3.66-3.75 mg/L 72-hour LC_{50} = 5.25-5.50 mg/L 96-hour LC_{50} = 4.80-5.10 mg/L	Singh et al. 1984
Banded gourami (*Colisa fasciatus*)	Technical grade (94%)	24-hour LC_{50} = 3.15 (2.93-3.49) mg/L 48-hour LC_{50} = 2.85 (2.67-3.07) mg/L 72-hour LC_{50} = 2.43 (2.27-2.58) mg/L 96-hour LC_{50} = 2.12 (1.94-2.25) mg/L Sublethal effects included significant changes in glycogen, pyruvate, lactate, and total protein levels in the treated fish.	Singh et al. 2004
Red tilapia, 24 g, 12 cm	malathion (84% w/w purity) for 96 hours	96-hour LC_{50} = 5.88 ppm Effects at sublethal concentrations which became more apparent at higher concentrations and longer durations of exposure included hypersensitivity to external stimuli, excitability and erratic swimming, violent contractions, and gulping at the surface film and air.	Sulaiman et al. 1989

FRESHWATER ACUTE			
Organism	**Exposure**	**Response**	**Reference**
Red tilapia, 24 g, 12 cm	5.88 ppm malathion (84% w/w purity) for 96 hours	Morphological alterations of the gill, liver, and gut were observed in treated fish. No differences in the general architecture of the heart, stomach, or muscle were observed.	Sulaiman et al. 1989
Red tilapia, 24 g, 12 cm	5.88 ppm malathion (84% w/w purity) for 96 hours	AChE activity decreased significantly in the muscle (6.2% of control), brain (8.2% of control), gut (32.4% of control), and liver (35.4% of control) tissues of moribund fish after 24 hours of exposure; increased duration of exposure resulted in corresponding increase of in AChE activity to maximum of 75% in the gut, indicating a recovery phase; at 96 hours of exposure, the maximum AChE activity was 20.3% in muscle 70.6% in liver. By day 6 of recovery in malathion-free water, liver AChE recovered to 88% of normal values and brain AChE recovered to only 50% of normal values.	Sulaiman et al. 1989
Green snakehead, *Channa punctatus*	Malathion, NOS	96-hour LC_{50}: 7 mg/L	Thakur and Sahai 1994
Snakehead, *Channa striatus*	Malathion, NOS	96-hour LC_{50}: 8 mg/L	Thakur and Sahai 1994
Sucker head, *Garra gotyla gotyla*	Malathion, NOS	96-hour LC_{50}: 3.5 mg/L	Thakur and Sahai 1994
Mosquitofish, *Gambusi affinis*, 3-5 days old	Cythion (NOS) under static conditions for 24 and 48 hours	24-hour LC_{50} = 12.68 µg a.i./mL (95% CI = 12.11-13.20 µg a.i./mL) 48-hour LC_{50} = 3.44 µg a.i./mL (95% CI = 2.72-4.37 µg a.i./mL)	Tietze et al. 1991
Carp, *Cyprinus carpio*, larvae	Malathion, commercial grade, NOS, static	96-h TL_{50}: 84 µg/L	Verma et al. 1981
Asian stinging catfish, *Saccobranchus fossilis*	Malathion (Malatox), 50EC	24-hour LC_{50} = 18.49 mg/L 48-hour LC_{50} = 17.18 mg/L 72-hour LC_{50} = 16.18 mg/L 96-hour LC_{50} = 15.00 mg/L	Verma et al. 1982

ESTUARINE/SALTWATER ACUTE			
Organism	**Exposure**	**Response**	**Reference**
Sheepshead minnow, *Cyprinodon variegatus*	95% a.i.; flow through test	96-hour LC_{50} = 33.0 ppb (confidence limit = 14-63)	Bowman 1989a MRID 41174301
Sheepshead minnow, *Cyprinodon variegatus*	96-hour, static **57% EC**	96-hour LC_{50} = 55 ppb (confidence limit = NR)	Bowman 1989b MRID 41252101
American eel, *Angullia rostrata*	static, technical grade (NOS)	24-hour to 96-hour LC_{50} = 82 ppb	Eisler 1970
Atlantic silverside, *Menidia menidia*	static, technical grade (NOS)	24-hour LC_{50} = 315 ppb 48-hour LC_{50} = 315 ppb 96-hour LC_{50} = 125 ppb	Eisler 1970
Bluehead, *Thalassoma bifasciatum*	static, technical grade (NOS)	24-hour LC_{50} = 33 ppb 48-hour LC_{50} = 27 ppb 96-hour LC_{50} = 27 ppb	Eisler 1970
Northern puffer, *Sphaeroides maculatus*	static, technical grade (NOS)	24-hour LC_{50} = 9,000 ppb 48-hour LC_{50} = 6,000 ppb 96-hour LC_{50} = 3,250 ppb	Eisler 1970
Striped killifish, *Fundulus majalis*	static, technical grade (NOS)	24-hour LC_{50} = 280 ppb 48-hour LC_{50} = 250 ppb 96-hour LC_{50} = 250 ppb	Eisler 1970
Striped mullet, *Mugil cephalus*	static, technical grade (NOS)	24-hour LC_{50} = >960 ppb 48-hour LC_{50} = 330 ppb 96-hour LC_{50} = 330 ppb	Eisler 1970; Also cited in Mayer and Ellersieck 1986
Longnose killifish, *Fundulus similis*	95% a.i.; flow through test	48-hour LC_{50} = 150 ppb (confidence limit = NR)	Mayer and Ellersieck 1986
Spot, *Leiostomus xanthurus*	95% a.i.; flow through test	48-hour LC_{50} = 320 ppb (confidence limit = NR)	Mayer and Ellersieck 1986
Mummichog, *Fundulus heteroclitus*	96-hour, static	Concentration in ppb Body weight / 24-h LC_{50} / 48-h LC_{50} / 96-h LC_{50} 1.8 g / 130 / 80 / 80 2.5 g / 810 / 440 / 440	Eisler 1970
Mummichog, *Fundulus heteroclitus*	96-hour, static 57% EC formulation, NOS	96-hour LC_{50} = 22.51 (16.01-31.24) µg/L	Trim 1987
Striped bass	95% a.i.	96-hour LC_{50} = 60 ppb (confidence limit = NR)	Wellborn 1971 MRID 156311
Gilthead seabream (*Sparus aurata* L)	96.7% a.i., 0.4 mg/L for up to 96 hours followed by examination of gills	A variety of alterations in gill enzymes indicative of oxidative stress. Hyperplasia of gill epithelium. No mortality.	Rosety et al. 2005

CHRONIC

Organism	Exposure	Response	Reference
Mosquitofish (*Gambusia affinis*)	technical grade malathion (Malathion 20 EM). Sublethal concentrations of 0, 0.01 or 0.02 mg/L for 10, 20, or 30 days.	Dose-dependent histopathological changes in the gills.	Cengiz and Unlu 2003
Rainbow trout, *Oncorhynchus mykiss*, newly fertilized eggs, 8 hours post fertilization	mean measured concentrations of 5.1, 9.9, 21, 44, or 85 µg/L Cythion technical malathion (purity 94%) for 60 days post hatch under flow-through conditions mean measured concentrations ranged from 99-110% of nominal test concentrations (5.0, 10, 20, 40, or 80 µg/L)	Fry survival was significantly reduced in the 44 and 84 µg/L concentrations at days 37 and 60 post hatch, but not at lower concentrations; a growth effect was detected at the 44 µg /L concentration on day 37 post hatch, but by day 60 post hatch analysis indicated no growth effects at any of the test levels still containing fish. NOEC = 21 µg/L LOEC = 44 µg/L	Cohle 1989 MRID 41422401
Flagfish, *Jordanella floridae*, 33-days old, 40 fish/group in flow-through system	0, 116, 170, 294, 374, or 516 µg/L (mean measured concentrations) of 95% pure malathion for 216 hours in a flow-through system	96-hour LC_{50} = 349µg/L	Hermanutz 1978
Flagfish, *Jordanella floridae*,	0, 5.8, 8.6, 10.9, 15.0, 19.3, 24.7, or 31.5 µg/L (mean measured concentrations) of 95% pure malathion for two generations (30- to 65- and 65- to 110-day intervals) in flow-through system.	Significant (P=0.05) reduction in growth of first generation at ≥10.9 µg/L Significant (P=0.05) reduction in survival of first generation at 31.5 and 24.7 µg/L. No effect on the mean number of eggs produced per female in either generation.. No adverse effects on survival through hatching and subsequent survival of second generation at any test concentration	Hermanutz 1978

Channa punctatus (Bloch), 36±6 g	0, 0.19, 0.28, and 0.56 ppm technical grade malathion for 120 days (resting of ovaries to spawning period)	Treated fish had stage I oocytes only and not stage II and III oocytes at all concentrations tested. Malathion treated fish had an absence of Δ5, 3β-HSD and G-6-PD activity in the follicular layer of oocytes at all concentrations (described as an inhibition of ovarian steroidogenesis). In addition, there was a dose-dependent significant decrease in brain AChE activity.	Inbaraj and Haider 1988
Banded killyfish, Striped bass, White perch, American eel, pumpkinseed, and Carp	Exposures to 0.01 ppm for "several month". Renewal is not specified	16% to 35% inhibition of brain AChE with no overt signs of toxicity.	Rehwoldt et al. 1977
Green snakehead (*Channa punctatus*)	0, 0.05, 0.10, 0.15., 0.20, or 0.25 mg/L malathion (EC 50%) for 30 days. 24-hour renewal, 50% EC formulation	Changes in mineral composition of inner ear.	Sawhney and Johal 1999
Channa punctatus (Bloch), 8 fish/dose group	0, 0.05, 0.10, 0.15., 0.20, or 0.25 mg/L malathion (EC 50%) for 30 days	alterations of erythrocytes were observed in fish exposed to 0.05 mg/L for 5 days and the number of altered erythrocytes increased significantly at 15 and 30 day in a dose-dependent manner.	Sawhney and Johal 2000
Fathead minnow	technical grade for 158 days	LOEC = 350 ppb ***NOTE:*** This study was not found in a search of the OPP submissions database.	U.S. EPA/OPP 2000c, referring to ABC Labs 1997 MRID D234663

Appendix 5: Toxicity Studies on Amphibians

Organism	Exposure	Observations	Reference
Frogs, *Rana tigrina*, tadpoles	≥0.01 ppm malathion (NOS)	adverse effects included stress manifested as sluggish and imbalanced behavior 24- hour LC_{50} = 2.07 ppm 48- hour LC_{50} = 1.99 ppm 72- hour LC_{50} = 1.64 ppm 96- hour LC_{50} = 1.41 ppm 144- hour LC_{50} = 0.17 ppm	Abbasi and Soni 1991
Hensel toads, *Bufo arenarum*,	Malathion (99% purity), 2 or 20 mg/L for 96-hours	At 20 ppm malathion, recently fertilized embryos had a decreased rate of gastrula formation; however, at 96 hours of exposure, there was no evidence of severe malformation and development was not arrested. In larvae, which were more sensitive than embryos to exposure, 20.00 ppm malathion caused spinal curvature, tail folding, circle swimming movement, frequent dropsy, and edema. GSH depletion.	Anguiano et al. 2001
African Clawed Frog (*Xenopus laevis*), up to stage 47 of free swimming larva	Malathion (99% purity), 375, 750, 1500, 3000, and 6000 µg/L.	FETAX Assay Teratogenic effects were clearly dose-dependent with significant differences, compared with controls, expressed at ≥1,500 µg/L (1.5 mg/L). EC_{50} for teratogenic effects: 2394 µg/L (2.4 mg/L). NOEC of 750 µg/L for malformations (see Table 2, p. 193). Clear dose-response effect on AChE inhibition that was associated with muscular damage (manifested primarily as abnormal tail flexure) in the embryos.	Bonfanti et al. 2004
Hensel toads, *Bufo arenarum*, newly fertilized embryos	44 mg/L malathion (94%) in amphibian Ringer's solution with 2.8 acetone for 72-120 hours	Continuous exposure inhibited acetylcholinesterase, butyrylcholinesterase, and carboxylesterase activities. These enzyme recovered after 24 hours in embryos treated for 72 hours, but showed different rates of recovery in embryos treated for 120 hours. All esterase activity was abolished within 48 hours of continuous exposure, but if exposure continues new bands of esterase activity were apparent at 120 hours. Embryos treated from 72 or 120 hours and transferred to uncontaminated medium for 120 hours had zymograms similar to controls.	Caballero De Castro et al. 1991
Hensel toads, *Bufo arenarum*, newly fertilized embryos	0.0047. 0.47. or 47.3 mg/L malathion (NOS) with 0.5% ethanol in Ringer's solution for 5 days	0.0047 and 0.47 mg/L had no effect on larval development or metamorphosis; however, there was a substantial inhibition of AChE with a slight recovery in complete operculum larvae at 0.0047. 47.3 mg/L produced 100% mortality within 5 days. Behavioral effects were not observed in surviving larvae.	de Llamas et al. 1985

Organism	Exposure	Observations	Reference
Bullfrog (*Rana catesbeiana*), tadpoles	Malathion (96%), 28-day static renewal daily.	Concentrations ≥2500 µg/L significantly decreased survival; exposure caused a dose-related delay in tadpole development over time and the effect was significant in tadpoles exposed to ≥1000 µg/L, compared with controls; equilibrium posture, the most sensitive effect observed in the study, was significantly impaired at 500-3000 µg/L.	Fordham et al. 2001
Indian green frog (*Rana hexadactyla*) tadpoles	Malathion, 50% EC formulation from Bharat Petroleum, India	12- hour LC_{50} = 3.54 (2.91-4.03) ppb 24- hour LC_{50} = 0.846 (0.798-0.94) ppb 48- hour LC_{50} = 0.613(0.55 – 0.69) ppb 72- hour LC_{50} = 0.613 (0.55 – 0.69) ppb 96- hour LC_{50} = 0.59 (0.43 – 0.78) ppb	Khangarot et al. 1985
Fowlers toad, *Bufo woodhousei*	Technical grade	96-hour EC50 = 420 ppb	Mayer and Ellersieck 1986; cited in U.S. EPA/OPP 2005m
Chorus frog, *Pseudacris triseriata*	Technical grade	96-hour EC50 = 200 ppb	Mayer and Ellersieck 1986; cited in U.S. EPA/OPP 2005m
Leopard frog (*Rana pipiens*) tadpoles	Malathion 50 (50% EC formulaton.	96-hour LC50 = 2.14 ppb EC formulation reportedly more toxic than Fyfanon but no details provided. Abstract only.	Pauli et al. 2004
Tadpoles: Leopard frog (*Rana pipiens*), Green frog (*Rana clamitans*), Bullfrog (*Rana catesbeiana*), Gray tree frog (*Hyla versicolor*), American toad (*Bufo americanus*)	0, 1, and 2 mg/L a.i. for 16 days. Malathion characterized only as a 50.6% formulation.	American toads: reduced growth at both concentrations. Survival reduced only at 2 mg/L. Leopard frogs, bullfrogs and green frogs: reduced growth at both concentrations. Tree frog: no affect on growth. Note: Formulation is not specified.	Relyea 2004a

Organism	Exposure	Observations	Reference
Leopard frog (*Rana pipiens*), Green frog (*Rana clamitans*), Bullfrog (*Rana catesbeiana*), Gray tree frog (*Hyla versicolor*), American toad (*Bufo americanus*); tadpoles	Malathion characterized only as a 50.6% formulation. See above note on formulation. Concentrations of 0.1, 1, 5, 10, and 20 mg/L. Static renewal every 4th day. Duration of all bioassays was 16 day. With and without predator cues (caged newts, *Notophthalmus viridescens*)	All values are 16-day LC_{50}s. Green frog: LC_{50} – 3.65 mg/L, no predator influence. American Toads: LC_{50} – 5.9 mg/L, no predator influence. Leopard frog: LC_{50} – 2.4 mg/L, no predator influence. Wood frog: LC_{50} – 1.25 mg/L, no predator influence. Tree frog: LC_{50} – 4.13 mg/L without predator and 2.00 mg/L with predator.	Relyea 2004b
Foothill yellow-legged frog (*Rana boylii*)	Malathion, technical grade, 99% pure Malaoxon, 99% pure	Malahtion 96-h LC_{50}: 2.137 mg/L. Inversions in the concentration-response relathionship prevented the calculation of confidence intervals. Malaoxon 96-h LC_{50}: 0.025 (0.014 to 0.18) mg/L	Sparling and Fellers 2007

Appendix 6: Toxicity Studies on Aquatic Invertebrates

Three separate tables are included: Freshwater Acute, Estuarine/Saltwater Acute, and Chronic. Each table is sorted by Reference and then by Organism.

Freshwater Acute

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Chironomid midges, *Chironomus crassicaudatus* Malloch, 4th instars	malathion (NOS)	24-hour LC_{50} = 0.056 ppm 24-hour LC_{50} = 0.16 ppm	Ali 1981
Chironomid midges, *Chironomus decorus* Johannsen, 4th instars	malathion (NOS)	24-hour LC_{50} = 0.032 ppm 24-hour LC_{50} = 0.12 ppm	Ali 1981
Chironomid midges, *Glyptotendipes paripes* Edwards, 4th instars	malathion (NOS)	24-hour LC_{50} = 0.004 ppm 24-hour LC_{50} = 0.0079 ppm	Ali 1981
Crayfish (*Procambarus clarkii*)	malathion (NOS), 0, 0.4, 0.8 and 1.6 mg/L	No mortality.	Andreu-Moliner et al. 1986
Ceriodaphnia dubia, <48 hrs old,	95-99% pure malathion	48-hour LC_{50} = 2.12 µg/L	Ankley et al. 1991
Daphnia magna, 4th instar	95% pure malathion,	48-hour LC_{50} = 12.38 (7.34-15.74) nM [Corresponds to 4.1 (2.4-5.2 µg/L)] In time-course experiments, recovery of AChE levels took 24 (50% recovery) and 96 hours (almost 100% recovery).	Barata et al. 2004
Field crab, *Oziotelphusa senex senex*, males, 15±2 g	0.2 or 6 ppm commercial grade (EC 50) malathion for 1 or 7 days	Significant alterations in hepatic glycogen and blood glucose	Bashamo-hideen et al. 1989
Midge larvae (*Chironomus* tentans	Malathion (NOS)	96-hour EC_{50} of 15 µg/L (1.2-1.9 µg/L)	Belden and Lydy 2001
Water flea, *Daphnia magna*	57% EC	48-hour EC50 = 2.2 ppb (confidence limit = 1.9-2.5)	Blakemore and Burgess 1990 MRID 41718401

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Mussel larvae, *Glochidium*	0, 0.0001, 0.001, 0.01, or 0.1 mg/L Cythion (formulation containing 95% malathion) for 48 hours	At ≥0.001, significant changes were observed, compared with controls. At 0.0001, no differences were observed, compared with controls and the concentration was considered harmless.	Desi et al. 1976
Mussels, *Anodonta cygnea*	0, 0.1, 1, 10, or 100 mg/L Cythion (formulation containing 95% malathion) for 48 hours	At 10 or 100 mg/L, periodical activity of mussels was significantly reduced ($p<0.05$). At 0.1 or 1.0 mg/L, no significant change in activity	Desi et al. 1976
Water flea, *Daphnia magna*, 30/dose group	0, 0.001, 0.01, 0.1, 1, 10, or 10 mg/L Cythion (formulation containing 95% malathion)	≥0.01 mg/L caused 100% mortality NOEC = 0.001 mg/L	Desi et al. 1976
Daphnia magna	Malathion (NOS)	0.00027 (0.00015-0.00049) mg/L	Gaaboub et al. 1975
Mosquito larvae, *Culex pipiens*, 4th instar	Malathion (NOS)	0.0015 (0.0012-0.0018) mg/L	Gaaboub et al. 1975
Mosquito larvae, *Anopheles quadrimaculatus*, 4th instar	Cythion (oil concentrate formulation containing 95% malathion)	24-hour LC_{50} = 0.069 ppm (95% fiducial limits = 0.060-0.080 ppm)	Holck and Meek 1987
Mosquito larvae, *Culex salinarius*, 4th instar	Cythion (oil concentrate formulation containing 95% malathion)	24-hour LC_{50} = 0.053 ppm (95% fiducial limits = 0.047-0.061 ppm)	Holck and Meek 1987
Mosquito larvae, *Psorophora columbiae*, 4th instar	Cythion (oil concentrate formulation containing 95% malathion)	24-hour LC_{50} = 0.011 ppm (95% fiducial limits = 0.10-0.012 ppm)	Holck and Meek 1987
Red swamp crawfish, *Procambarus clarkii*,	Cythion (oil concentrate formulation containing 95% malathion)	96-hour LC_{50} = 49.17 ppm (95% fiducial limits = 43.26-54.14 ppm)	Holck and Meek 1987

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Crayfish (*Procambaraus clarkii*)	Malathion, 50% a.i., NOS	96-hour LC50 (malathion 50% a.i.) = 1.75 mg/L	Jimenez et al. 2003
Grass shrimp (*Palaemonetes pugio*)	Malathion, NOS	***Newly hatched larvae***: EC_{50} =7.33(6.07-8.85) µg/L ***18-day-old larvae***: EC_{50} =22.04 (16.67-29.11) µg/L ***Adult***: EC_{50} = 596.45 (227.69-1560.87) µg/L	Key 1995
Grass shrimp (*Palaemonetes pugio*)	Malathion, NOS	newly hatched larvae: 96-hour LC50 = 8.94 (7.53-10.63) µg/L; LOEC = 3.75 µg/L; NOEC = 1.88 µg/L 18-day-old larvae: 96-hour LC50 = 13.26 (9.67-15.98) µg/L; LOEC = 12.50 µg/L; NOEC = <12.50 µg/L postlarvae (juvenile shrimp): 96-hour LC50 = 39.92 (32.49-50.1) µg/L; LOEC = 25.00 µg/L; NOEC =12.50 µg/L	Key and Fulton 2006
Daphnia magna, young	0.01, 0.025 ,0.050, 0.075, 0.100, 0.125, 0.150, or 0.200 mg/L malathion (NOS) for 48 hours	NOEC - 0.01 mg/L 48-hour LC_{50} = 0.08 ppm (95%CL = 0.075-0.100 ppm)	Khan et al. 1993
Backswimmers, *Anisops* sp., 5-15 mm	0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 ppm malathion (Elathion 50 EC, 50% a.i.)	>0.3 ppm caused erratic movements in insects within 2-4 hours ≤0.5 ppm resulted in 24-hour mortality rates of 20-96% >0.5 ppm resulted in 100% mortality	Kumar et al. 1994
Backswimmer, *Amosps sardeis*	malathion (NOS) under static conditions of exposure	LC_{50} = 8.61 µg/L (hours not specified)	Lahr 1999
Fairy shrimp, *Streptocephalus sudanicus*	malathion (NOS), under static conditions of exposure	EC_{50} = 1230 µg/L (hours not specified)	Lahr 1999
mussels (*Mytilus edulis*) and clams (*Macoma balthica*)	0.02 and 0.1 mg/L malathion (NOS) for 7 days	No inhibition of AChE activity in gill tissue (mussels) or foot tissue (clams).	Lehtonen and Leinio 2003

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Mediterranean mussel (*Mytilus galloprovincialis*)	Malathion (NOS)	24-hour EC50 = 2.2 (2.0-2.4) mg/L	Losso et al. 2004
Grass shrimp (*Palaemonetes pugio*)	Malathion (MicroFlo)	Stage VI embryo: EC50 =55.53 (22.08-80.73) µg/L Stage VII embryo: EC50 =29.93 (25.22-44.22) µg/L	Lund et al. 2000
Daphnid, *Ceriodaphnia dubia*	malathion (99.2% purity)	48-hour LC50 = 3.35µg/L. Increase in toxicity with predator stress.	Maul et al. 2006
Crayfish, *Orconectes nais*	95% a.i.	96-hour LC50 = 180 ppb (confidence limit = 130-230)	Mayer and Ellersieck 1986
Daphnid, *Simocephalus serrulatus*	95% a.i.	48-hour LC50 = 0.69 ppb (confidence limit = 0.4-0.79)	Mayer and Ellersieck 1986
Glass shrimp, *Palaemonetes kadiakensis*	95% a.i.	96-hour LC50 = 12 ppb (confidence limit = NR)	Mayer and Ellersieck 1986
Scud, *Gammarus fasciatus*	95% a.i.	96-hour LC50 = 0.5 ppb (confidence limit = NR)	Mayer and Ellersieck 1986
Seed shrimp, *Cypridopsis vidua*	95% a.i.	49-hour LC50 = 47 ppb (confidence limit = 32-69)	Mayer and Ellersieck 1986
Sow bug, *Asellus brevicaudus*	95% a.i.	96-hour LC50 = 3000 ppb (confidence limit = 1500-8500)	Mayer and Ellersieck 1986
Water flea, *Daphnia magna*	95% a.i.	48-hour EC50 = 1.0 ppb (confidence limit = 0.7-1.4)	Mayer and Ellersieck 1986
Water flea, Daphnia pulex	95% a.i.	48-hour EC50 = 1.8 ppb (confidence limit = 1.4-2.4)	Mayer and Ellersieck 1986
Mosquito larvae, *Anopheles quadrimaculatus*	Malathion (NOS)	48-hour LC50 = 1 ppb	Milam et al. 2000
Giant prawn, *Macrobrachium rosenbergii*, 20±2 mm, 0.25±0.1 g	liquid malathion (NOS)	24- hour LC_{50} = 0.241 ppm (95% confidence limits = 0.013-4.638) 48- hour LC_{50} = 0.016 ppm (95% confidence limits = 0.0007-0.391) 96- hour LC_{50} = 0.009 mg/L (95% confidence limits = 0.0004-0.210)	Natarajan et al. 1992
Rotifer, *Brachionus calyciflorus*, 10 test group	malathion (obtained from Cheminova, NOS)	24-hour EC_{50} = 80840 µg/L (ppb) (71550-91330) sensitivity rank = 100	Nelson and Roline 1998

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Ceriodaphnia dubia, 4 days old	malathion (obtained from Cheminova, NOS)	24-hour LC_{50} = 3.18 µg/L (2.36-4.27) sensitivity rank = 1.0	Nelson and Roline 1998
Ceriodaphnia dubia, 4 days old	malathion (obtained from Cheminova, NOS)	48-hour LC_{50} = 1.14 µg/L (1.04-1.25) sensitivity rank = 1.0	Nelson and Roline 1998
Simocephalus vetulus (Cladocera: Daphniidae)	malathion (NOS)	Water: 48-hour LC_{50} = 2.9 µg/L (2.4 to 3.6 µg/L) Sediment: 48-hour LC_{50} = 3.8 µg/L (2.1 to 4.4 µg/L) Decrease in AChE activity to 12 h followed by partial recovery. Probably associated with decrease in malathion concentrations.	Olvera-Hernandez et al. 2004
Black fly larvae (*Simulium vittatum*)	malathion (analytical grade, NOS)	48-hour LC50 = 54.20 µg/L	Overmyer et al. 2003
Daphnia magna	malathion (98.6%)	48-hour EC_{50} = 10.56 (9.99-11.47) pM [Corresponds to 3.5 (3.3-3.8) µg/L] 48-hour IC50 (estimated 50% AChE inhibition) 9.48 ± 1.30 pM [Corresponds to 3.1 ± 4.3 µg/L] Note the very close relationship for immobility and AChE inhibition.	Printes and Callaghan 2004
Daphnia magna	malathion (NOS)	EC_{50}: 0.0107 µM (3.5 µg/L)	Rider and LeBlanc 2005
Rice bloodworm, *Chironomus terrperi*, larvae, 4th instar	malathion (emulsifiable concentrate) for 24 hours	24-hour LC_{50} = 8.4 ppb (95% fiducial limits = 8.1-8.7 ppb) 24-hour LC90 = 12.9 ppb (95% fiducial limits = 11.8-14.1 ppb)	Stevens 1992
Snails, *Biomphalaria havanensis*, adults (5-6 mm)	malathion (91% a.i. or 9.33 lbs/gallon of solution)	24- hour LC_5 = 70.64 mg/L (95% confidence limits = 33.97-102.02) 24- hour LC_{50} = 202.93 mg/L (95% confidence limits =158.91-244.16) 24- hour LC_{95} = 582.96 mg/L (95% confidence limits = 442.71-244.16) SLOPE = 3.59 mg/L (95% confidence limits =2.31-4.86)	Tchounwou et al. 1992

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Snails, *Biomphalaria havanensis*, adults (5-6 mm)	malathion (91% a.i. or 9.33 lbs/gallon of solution)	48- hour LC_5 = 51.57 mg/L (95% confidence limits =30.84-68.69) 48- hour LC_{50} = 126.27 mg/L (95% confidence limits =104.50-146.88) 48- hour LC_{95} = 309.18 mg/L (95% confidence limits = 249.11-446.43) SLOPE = 4.23 mg/L (95% confidence limits =2.92-5.54)	Tchounwou et al. 1992
Snails, *Biomphalaria havanensis*, eggs	malathion (91% a.i. or 9.33 lbs/gallon of solution)	24- hour LC_5 = 42.63 mg/L (95% confidence limits =1.23-71-72) 24- hour LC_{50} = 94.78 mg/L (95% confidence limits =35-49-143.97) 24- hour LC_{95} = 210.73 mg/L (95% confidence limits = 139.99-2119.52) SLOPE = 4.74 mg/L (95% confidence limits = 1.05-8.43)	Tchounwou et al. 1992
Snails, *Biomphalaria havanensis*, juveniles (2-3 mm)	malathion (91% a.i. or 9.33 lbs/gallon of solution)	24- hour LC_5 =88.88 mg/L (95% confidence limits = 64.76-105.93) 24- hour LC_{50} = 149.10 mg/L (95% confidence limits = 131.37-165.43) 24- hour LC_{95} = 250.12 mg/L (95% confidence limits = 217.99-428.32) SLOPE = 7.32 mg/L (95% confidence limits = 4.94-9.67)	Tchounwou et al. 1992
Snails, *Helisoma trivolvus*, adults (8-10 mm)	malathion (91% a.i. or 9.33 lbs/gallon of solution)	24- hour LC_5 =225.71 mg/L (95% confidence limits =161.44-279.14) 24- hour LC_{50} = 478.65 mg/L (95% confidence limits = 416.75-536.25) 24- hour LC_{95} = 1015.04 mg/L (95% confidence limits = 872.77-1269.90) SLOPE = 5.04 mg/L (95% confidence limits = 3.79-6.28)	Tchounwou et al. 1992

Freshwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Snails, *Helisoma trivolvus*, adults (8-10 mm)	malathion (91% a.i. or 9.33 lbs/gallon of solution)	48- hour LC_5 = 121.28 mg/L (95% confidence limits = 79.10-152.13) 48- hour LC_{50} = 228.84 mg/L (95% confidence limits = 111.47-261.04) 48- hour LC_{95} = 432.13 mg/L (95% confidence limits = 374-581.43) SLOPE = 5.96 mg/L (95% confidence limits = 3.95-7.96)	Tchounwou et al. 1992
Snails, *Helisoma trivolvus*, eggs	malathion (91% a.i. or 9.33 lbs/gallon of solution)	24- hour LC_5 = 92.57 mg/L (95% confidence limits = 75.49-107.56) 24- hour LC_{50} = 187.65 mg/L (95% confidence limits = 170.95-203.73) 24- hour LC_{95} = 380.40 mg/L (95% confidence limits = 341.54-437.41) SLOPE = 5.36 mg/L (95% confidence limits = 4.44-6.28)	Tchounwou et al. 1992
Snails, *Helisoma trivolvus*, juveniles (3-5 mm)	malathion (91% a.i. or 9.33 lbs/gallon of solution)	24- hour LC_5 = 138.91 mg/L (95% confidence limits = 102.76-167.63) 24- hour LC_{50} = 268.11 mg/L (95% confidence limits = 237.21-296.78) 24- hour LC_{95} = 517.47 mg/L (95% confidence limits = 450.49-638.68) SLOPE = 5.76 mg/L (95% confidence limits = 4.28-7.24)	Tchounwou et al. 1992
Scud, *Gammarus lacustris*	technical grade	48-hour LC50 = 1.8 ppb (confidence limit = 1.3-2.4) NOTE: This study is not otherwise referenced in U.S. EPA/OPP 2000c as was not found in a search of the OPP submissions database.	U.S. EPA/OPP 2000c, referring to FWS Labs 1969 MRID 05009242

Estuarine/Saltwater Acute

Estuarine/Saltwater Acute

Organism	Exposure	Response	Reference
Mysid (*Neomysis mercedis*)	technical malathion (94.2%)	96-hour LC_{50} = 2.2 µg/L (95% confidence limit = 2.0-2.5)	Brandt et al. 1993
Rotifer, *Brachionus calyciflorus*	malathion (95%)	24-hour LC_{50} = 33.72 mg/L (95% confidence limits = 28.79-38.65)	Fernandez-Casalderry et al. 1992
Copepods, *Tigriopus brevicornis* (Müller), naupliu, copepodid, ovigerous female	malathion, technical grade	Nauplius: 96-hour LC_{50} = 7.2 µg/L (95% confidence limit = 5.2-9.2) Copepodid: 96-hour LC_{50} = 20.5 µg/L (95% confidence limit = 18.5-22.5) Ovigerous female: 96-hour LC_{50} = 24.3 µg/L (95% confidence limit = 22.3-26.3)	Forget et al. 1998
Brine shrimp, *Artemia* Sp., neonates	high purity standard malathion (min 95%)	24-hour EC_{50} >140 mg/L 24-hour EC_{10} >140 mg/L	Guzzella et al. 1997
Rotifer, *Brachionus plicatilis*, neonates	high purity standard malathion (min 95%)	mean 24-hour EC_{50} = 74 mg/L mean 24-hour EC_{10} = 22 mg/L	Guzzella et al. 1997
Grass shrimp, *Palaemonetes pugio*, 18-day old larvae	malathion (NOS) for 24 hours	24-hour EC_{50} = 22.04 µg/L (95% CI = 16.67-29.11 µg/L)	Key 1995
Grass shrimp, *Palaemonetes pugio*, adult	malathion (NOS) for 24 hours	24-hour EC_{50} = 596.45 µg/L (95% CI = 227.69-1560.87 µg/L) Key 1995 is a dissertation. Lund et al. 2000 cite the data on new hatched larvae, 18-day old larvae, and adult grass shrimp.	Key 1995
Grass shrimp, *Palaemonetes pugio*, newly hatched larvae	malathion (NOS) for 24 hours	24-hour EC_{50} = 7.33 µg/L (95% CI = 6.07-8.85 µg/L)	Key 1995
Grass shrimp, *Palaemonetes pugio*, 18-day old larvae	nominal concentrations of 0, 12.5, 25.0, 50.0, 100.0, or 200.00 µg/L technical grade malathion for 96 hours in static renewal bioassay	96-hour EC50 = 13.24 µg/L (95% CI = 9.91-17.70 µg/L)	Key et al. 1998

Estuarine/Saltwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Grass shrimp, *Palaemonetes pugio*, adults	nominal concentrations of 0, 12.5, 25.0, 50.0, 100.0, or 200.00 µg/L technical grade malathion for 96 hours in static renewal bioassay	96-hour EC50 = 38.19 µg/L (95% CI =31.91- 45.69 µg/L)	Key et al. 1998
Notes on Key et al. 1998: These investigators also conducted a pulse exposure bioassay at larval life stage to simulate field conditions. To simulate the length of a tidal cycle, the larvae were exposed to malathion 6 hours/day every 5 days. After 4 pulse doses, mortality was greatest in the two highest concentrations (15.0 and 30.0 µg/L) and the number of instars to post larvae was significantly lower in the highest concentration, compared with controls. AChE activity, measured on day 0 and day 15 was not significantly different from controls. The investigators conclude that exposure to malathion may not have a direct, measurable impact on growth but may alter natural metamorphic rhythms at the highest concentrations.			
Grass shrimp, Palaemonetes pugio, newly hatched larvae, 1-2 days old, 30/dose group	nominal concentrations of 0, 1.88, 3.75, 7.50, 15.0, or 30 µg/L technical grade malathion for 96 hours in static renewal bioassay	96-hour EC50 = 9.06 µg/L (95% CI = 7.65-10.73 µg/L)	Key et al. 1998
Grass shrimp, *Palaemonetes pugio*, Stage VI embryo	nominal concentrations of 7.50, 15.00, 30.00, 60.00, or 120.00 µg/L technical grade malathion for 24 hours	Decrease in AChE activity 24-hour EC_{50} = 55.53 µg/L (95% CI = 22.08-80.73 µg/L)	Lund et al. 2000
Grass shrimp, *Palaemonetes pugio*, Stage VII embryo	nominal concentrations of 7.50, 15.00, 30.00, 60.00, or 120.00 µg/L technical grade malathion for 24 hours	Significant decrease in AChE activity 24- hour EC_{50} = 29.93 µg/L (95% CI = 25.22-44.22 µg/L)	Lund et al. 2000
Blue crab, *Callinectes sapidus*	95% a.i.	48-hour LC_{50} >1000 ppb	Mayer and Ellersieck 1986
Eastern oyster, *Crassostrea virginica*	95% a.i.	96-hour LC_{50} > 1000 ppb	Mayer and Ellersieck 1986
Pink shrimp, *Penaeus duorarum*	95% a.i.	48-hour LC_{50} = 280 ppb (confidence limit = NR)	Mayer and Ellersieck 1986

Estuarine/Saltwater Acute			
Organism	**Exposure**	**Response**	**Reference**
Penaeid prawn, *Metapenaeus monoceros*	Malathion (95% purity)	96-hour LC_{50}: 1.93 (1.31-1.65) mg/L	Reddy and Rao 1992
Eastern oyster, *Crassostrea virginica*	57% EC	96-hour EC_{50} = 2960 ppb (confidence limit = NR)	Wade and Wisk 1992 MRID 42249901

Chronic

Chronic			
Organism	**Exposure**	**Response**	**Reference**
Indian rice field crab, *Oziotelphusa* senex senex, avg weight = 30 g, 40/exposure duration	2 mg/L technical grade malathion (95% w/v) for 10, 20, or 30 days	No mortality at any exposure duration; decreased food consumption at 15 days, total lack of food consumption at 25 days; hyperglycemia was observed after all exposure durations; also observed were alterations in the activity levels of certain biologically important enzymes. The investigators speculate that the observed alterations in enzyme activity may be attributed to the stress condition of the crab.	Reddy et al. 1986
Caddisfly larvae (*Hydropsyche slossonae*)	0.01, 0.05, 0.1, 0.5, or 1.0 µg/L malathion (96.7% a.i.), 20 days, dynamic flow-through	All concentrations ≥0.05 µg/L caused significant abnormalities in capture nets. NOEC: 0.01 µg/L LOAEL: 0.05 µg/L Note: There is a clear time-dependence. See Figure 4 of publication. Although abnormal nets were not significantly increased from controls at 0.01 µg/L, an increase in the rate of abnormal nets is apparent. See Figure 4 of publication. Significant inhibition in AChE activity only at 0.1 µg/L and greater. After 10 days of exposure, there was a significant increase of the midline anomaly frequencies at ≥0.1 µg/L (40-100% of midline anomalies occurred on the capture nets), which corresponded to the significant decrease of AChE activity at the same concentrations. Exposure to 0.5 and 1.0 µg/L resulted in decreased symmetry of the nets. The occurrence of net asymmetry was also correlated with percent inhibition of AChE at 0.5 and 1.0 µg/L.	Tessier et al. 2000