APPENDIX J

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

DATE: July 31, 2006

MEMORANDUM

SUBJECT: **Malathion**: Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). PC Code: 057701. Case No. 0248. DP Barcode: D330680

Regulatory Action: Phase 6 Reregistration Action
Risk Assessment Type: Single Chemical Aggregate

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Attached is HED's updated, revised human health risk assessment for the organophosphate insecticide, Malathion for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This document presents HED's safety finding in accordance with tolerance reassessment based on aggregate exposure to malathion from food, water, and non-occupational (residential) sources. It also includes an assessment of the risks from occupational exposure to malation.

This revised risk assessment reflects changes resulting from public comments submitted in response to the Federal Register/Volume 70, No.184 Notice; September 23, 2005. A new chronic dietary hazard value was derived from the repeat dose comparative (young and adult rats) cholinesterase malathion study and thus the FQPA factor of 10x was not required. Also, in the absence of dermal and inhalation studies with malaoxon, the toxicity adjustment factor (TAF) calculated from oral studies (61x – changed from 77x based on comments received) is applicable to residues of malaoxon for risk assessment reflecting all exposure durations, routes, and scenarios. The assessments for acute and chronic dietary exposure (food and water) and residential exposures have been revised to incorporate the recent endpoint selection, FQPA Safety Factor decisions, and new TAF. The supporting documentations are as follows:

- *Malathion: Revised Acute, Probabilistic and Chronic Dietary (Food + Drinking Water) Exposure and Risk Assessments for the Malathion Reregistration Eligibility Decision. PC Code: 057701. DP Barcode: D330636. Sheila Piper, July 13, 2006.*
- *Malathion: Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. (DP Barcode: D330678; Chemical Number: 057701; EPA MRID No.: 43945001). Jack Arthur, July 6, 2006.*
- *Malathion: Occupational Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. (DP Barcode: D330675; Chemical Number: 057701; EPA MRID Nos.: 45005910, 45491901, 45138202, 45491902, 45138201 and 45469501). Jack Arthur, July 6, 2006.*
- *Drinking Water Exposure Modeling Evaluating the Effect of Varying Crop Scenarios, Application Rate, Application Interval, Spray Drift Levels, Soil Half Life. PC Code: 057701; DP Barcode: D327331. Norman Birchfield, June 15, 2006.*

In accordance with the Public Participation Pilot Process developed by the Tolerance Reassessment Advisory Committee (TRAC), the Agency held a Technical Briefing on November 9, 2000 where the results of HED's Human Health Risk Assessment (22-September-2000; D269070) were presented to the general public. This Technical Briefing concluded Phase 4 of the TRAC Public Participation Pilot Process and initiated Phase 5 of that process. During Phase 5, all interested parties were invited to participate and provide comments and suggestions on ways the Agency might mitigate the estimated risks presented in the revised risk assessment. The mitigation proposals and new toxicity data received during Phase 5 have been incorporated into this updated, revised assessment. This risk assessment includes toxicology reviews from Louis Scarano and Anna Lowit, a summary of the residue chemistry review from William Smith, dietary exposure assessment from Sheila Piper, occupational/residential exposures and risk assessment from Jack Arthur, a summary of the incident reports from Jerry Blondell,

environmental fate and drinking water exposures from Norman Birchfield [Environmental Fate and Effects Division (EFED)], as well as risk assessment and characterization from Sheila Piper.

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1.0 Executive Summary

Malathion is a non-systemic, wide spectrum organophosphorus (OP) insecticide. It is used in the agricultural production of a wide variety of food/feed crops to control insects such as aphids, leafhoppers, and Japanese beetles. Malathion is also used in the Cotton Boll Weevil Eradication Program, Fruit Fly (Medfly) Control Program, and mosquito-borne disease control. It is also available to the home gardener for outdoor residential uses which include vegetable gardens, home orchards and ornamentals. The Agency has been informed by the basic producer (Cheminova A/S letters dated March 10, 1998 and March 18, 2002) that certain formulations and use sites will not be supported for reregistration. As a consequence, this risk assessment does not address any existing product labels permitting indoor uses, direct animal (pet and livestock) treatments, among other uses in the market place. When end-use product DCIs are developed, the Agency will require that all end-use product labels be amended such that they are consistent with the basic producer labels.

Malathion is formulated as a technical, a dust, an emulsifiable concentrate (EC), a ready-to-use (RTU), a pressurized liquid, and a wettable powder (WP). Several of the 95% liquids are intended for ultra-low-volume (ULV) applications. Malathion can be applied using ground or aerial equipment, thermal and non-thermal fogger, groundboom, airblast sprayer, chemigation, and a variety of hand-held equipment such as backpack sprayers, low pressure handwands, hose-end sprayers, and power dusters. Multiple foliar applications may be made as needed depending on pest presence.

There is a non-FIFRA pharmaceutical use of malathion as a pediculicide for the treatment of head lice and their ova. The Food and Drug Administration (FDA) approves uses of pesticide containing pharmaceutical products under FFDCA. This analysis is not included in this document but will be incorporated into the Agency's RED as a supplementary assessment.

Malathion, like other members of the OP common mechanism group, inhibits cholinesterase (ChE) as a mode of toxic action. Malathion is metabolically activated to its ChE inhibiting oxon metabolite, malaoxon (oxidation of the P=S moiety to P=O), in insects and mammals. Both malathion and malaoxon are detoxified by carboxyesterases leading to polar, water-soluble, compounds that are excreted. Mammalian systems show greater carboxyesterase activity, as compared with insects, so that the toxic agent malaoxon builds up more in insects than in mammals. This accounts for the increased toxicity of malathion in insects.

In a rat metabolism study, malathion is excreted in the urine (80-90%) in the first 24 hours of exposure. Unchanged malathion was typically found to be the major residue in rats. Dicarboxylic acid and monocarboxylic acid metabolites account for the majority of the radioactivity. In the rat study, radioactivity did not bioaccumulate in any of the organ/tissues analyzed.

The toxicology database for malathion is substantially complete and of acceptable quality to assess the potential hazard to humans, including special sensitivity of infants and children. Malathion exhibits low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). The findings in acute subchronic, chronic and developmental neurotoxicity studies indicate that the major adverse effects of chemical is the inhibition of plasma, red blood cell (RBC) and brain ChE activity. Cholinesterase inhibition (ChEI) in the nervous system as measured in various compartments has been observed in multiple species (rat, mouse, rabbit, and dog) following oral, dermal and inhalation routes of administration. ChE inhibition provides the critical effect for the acute and chronic reference doses and for the short and intermediate term oral and dermal risk

assessments. Other treatment related effects of malathion via the inhalation route were histopathologically evident lesions of the nasal cavity and larynx.

Malaoxon, a degradate of malathion, can be formed in the environment under some conditions. Following direct exposure, malaoxon is a more potent ChE inhibitor than the parent, malathion. Benchmark dose (BMD) modeling was used to evaluate relative potency for malathion and malaoxon. Male, red blood cell (RBC) ChEI in adult rats provide the endpoint for calculating the toxicity adjustment factor (TAF). No studies evaluating acute ChEI due to malaoxon are available. EPA has published a Data Call In Notice (DCI) for special acute and repeated dose comparative ChE studies in juveniles dosed with malaoxon and malathion. This study will provide data for RBC and brain ChE for acute and multiple exposures to malaoxon. There is, however, an adequate chronic toxicity study in malaoxon which provides ChE data for estimating a TAF. In the absence of dermal and inhalation studies with malaoxon, the TAF calculated from oral studies (61x) is applicable to residues of malaoxon for risk assessment reflecting all exposure durations, routes, and scenarios.

The mutagenicity database indicates that there is weak evidence of a mutagenic effect in mammalian cells at high and cytotoxic concentrations. Following long-term oral exposures, increased incidences of liver and nasal/oral tumors were observed in rats and increased incidence of liver tumors were observed in mice. Malathion has been classified as "suggestive evidence of carcinogenicity" in accordance with the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (July 1999). A quantitative cancer dose-response assessment is not indicated for pesticides in the "suggestive" category. Malaoxon, the active ChE inhibiting metabolite of malathion, is not carcinogenic in rats.

In standard guideline prenatal developmental toxicity studies, no developmental toxicity was observed in rats. In rabbits, increased incidences of mean resorption sites were considered evidence of qualitative differences in susceptibility between adult and developing animals. In a two-generation reproduction study in rats, effects on pre-weaning pup growth at doses lower than those causing parental body weight decreases was considered evidence of quantitative differences in susceptibility between adult and young animals. From the full complement of neurotoxicity studies in adult and juvenile test animals, there was evidence of quantitative differences in susceptibility between adults and young in the developmental neurotoxicity study and its companion comparative ChEI study in the rat.

The potential for increased susceptibility of infants and children from exposure to malathion was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. HED has determined that there is evidence that following acute or repeated dose exposures to malathion, young animals exhibit adverse effects more readily than adults. HED has oral data for this most sensitive subpopulation and is using it to determine the appropriate point of departure (PoD) for use in assessing risk for acute and chronic dietary and incidental oral scenarios. In those instances where the HED is using a PoD derived from pup data, the FQPA SF is reduced to 1x. HED recommends retention of the FQPA SF of 10x for those scenarios where risk assessment endpoints are derived from studies in adult animals. Consequently, for dermal exposure scenarios, where the PoD is derived from adult animals and children are expected to be exposed, the FQPA SF of 10x has been retained. Similarly, for inhalation exposure scenarios where the endpoint selected is ChE inhibition (in order to aggregate non-occupational exposures) and the PoD is based on adult animals, the FQPA SF of 10x has also been retained. Finally, the FQPA SF of 10x is retained for the bystander inhalation scenario in order to account for the lack of a NOAEL, severity of effect, as well as any differential in susceptibility in the young.

The acute RfD was based on a BMD analysis of RBC ChEI data to arrive at a $BMDL_{10}$ as a point of departure (PoD) value. The $BMDL_{10}$ is the lower 95% confidence limit on the estimated mean RBC ChEI 10% effect level. For the acute RfD, data from the acute dose portion of a comparative cholinesterase study in rat pups was used. An uncertainty factor of 100x was applied to account for interspecies extrapolation (10x) and for intraspecies variation (10x). An FQPA factor of 10x is not required because the value used is from studies with very young rats (11-days old). The chronic RfD and short- and incidental-oral endpoints were based on RBC ChEI in rat offspring from a multiple dose comparative cholinesterase study. Again, an uncertainty factor of 100x was applied to account for interspecies extrapolation (10x) and for intraspecies variation (10x). An FQPA factor of 10x is not required because the value used is from studies with very young rats (11-day old rats exposed daily for 11 days).

For endpoint selections applicable to short-term durations, the endpoint is based on a $BMDL_{20}$ estimate for RBC ChEI in male and female rabbits from combining two separate 21-day dermal toxicity studies. For the short-term dermal endpoint, the UFs differ for adults and children. The UF for adults of 100x was applied to account for interspecies extrapolation (10x) and intraspecies variation (10x). For children, an UF of 1000x was applied to account for interspecies extrapolation (10x), intraspecies variation (10x), and for the susceptibility of the young (FQPA of 10x).

The short-term inhalation endpoint was based on histopathological lesions of the nasal cavity and the larynx (the lowest dose) from a 90-day inhalation study in rats. The short-term inhalation endpoint was selected because the lesions were noted at a dose lower than that which resulted in ChEI and the lesions were observed in both short- and long-term studies. An UF of 1000x was applied to the short-term inhalation endpoint to account for interspecies extrapolation (10x), intraspecies variation (10x), and for an FQPA safety factor (10x) to account for the lack of a NOAEL as well as to address potential sensitivities in children.

The potential sources for malathion residues in the environment include: 1) agricultural use on a wide variety of food/feed crops; 2) outdoor residential uses in home vegetable and ornamental gardens; 3) public health uses over wide areas for mosquito control (for both nuisance mosquito control and vector disease control); 4) use in the Cotton Boll Weevil Eradication Program; and 5) use in the Fruit Fly (Medfly) Control Program. The pathways by which the general population is likely to be exposed to malathion residues are through ingestion of food and drinking water, and in residential settings (e.g., homeowner use on garden plants, public health mosquito control, and off-target drift from agricultural use).

Malathion is relatively mobile and shows little persistence in soil and water. Limited environmental fate data are available for the degradate malaoxon; however, malaoxon is expected to have similar chemical properties, environmental persistence, and mobility to malathion. Numerous monitoring studies confirm malathion and malaoxon can reach surface drinking water treatment facility intakes, but insufficient targeted monitoring studies are available to adequately define acute malathion and malaoxon concentrations in drinking water; thus, surface water concentrations associated with a range of malathion uses were conservatively modeled by the Environmental Fate and Effects Division (EFED) using several crops and the Index Reservoir scenario (PRZM/EXAMS) and a less-refined interim rice paddy model. Ground water monitoring studies are available

and have detected malathion. EFED has recommended use of the monitoring studies for the malathion/malaoxon EEC as they are more conservative than the SCI-GROW modeling results.

Revised acute and chronic dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed as part of the registrant, Cheminova's response to EPA's revised risk assessment (S. Kinard, D321543, 9/13/2005) for malathion and include the following reregistration action; (1) new chronic toxicological endpoint; (2) new toxicity adjustment factor (TAF) of 61x for malaoxon; and (3) new drinking water estimates provided by the Environmental Fate and Effects Division (EFED).

The acute dietary risk estimates from food alone are below HED's level of concern (<100 % aPAD) at the 99.9th percentile of exposure. Malathion dietary exposure at the 99.9th percentile from food alone is 5% of the aPAD for the U.S. population and 11% of the aPAD for all infants (<1 yr old), the most highly exposed population subgroup. The chronic dietary risk from malathion exposure from food alone is well below HED's level of concern for all population subgroups (<1% of the cPAD).

Non-occupational (residential) exposure to malathion and malaoxon residues via dermal and inhalation routes can occur during mixing, loading, and application activities. Postapplication exposure potentials also exist. There is potential dermal exposure to persons entering treated sites following application of malathion-containing products. There is also potential for dermal and inhalation exposure to individuals (bystanders) contacting lawns at home or in public areas from aerial or ground applications for mosquito control and pest eradication programs. Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for the residential handler and postapplication dermal, inhalation (mosquito, boll weevil, and fruit fly control), and inadvertent oral ingestion exposure to adults and/or children. The duration of exposure is expected to be short-term for the residential handler and for postapplication events.

Results for residential handler exposure assessments, combining dermal and inhalation exposures, indicate that the total risks do not exceed HED's level of concern for any scenario. Transfer coefficients for low contact activities (e.g., scouting, weeding) were used in calculating combined risks because an unrealistic overestimation of risks would result from compounding the conservative assumptions regarding exposure to handlers with exposure from high contact activities on the same day; therefore, the combined risks following residential application and postapplication activities resulted in risks that do not exceed HED's level of concern.

As a consequence of public health use of malathion for mosquito control, separate assessments of dermal, inhalation, and incidental oral exposures resulted in risks that are not of concern. Likewise, when exposure from dermal, inhalation, and incidental oral routes were combined, the resulting MOEs do not exceed HED's level of concern.

Results of the residential postapplication risk assessment for short-term exposure from boll weevil treatment demonstrate that risks via the dermal, inhalation and incidental oral are not of concern for adults and toddlers from the use of malathion. Combined risks to adults and toddlers are also not of concern for postapplication residential exposure in areas near fields being treated for the boll weevil.

Risks resulting from adult postapplication exposures following aerial fruit fly application do not exceed HED's level of concern, either from route-specific or combined dermal, inhalation, and incidental oral (toddlers only) exposures.

Exposures to residues of deposited malathion that remain untransformed on solid surfaces must also be combined with malaoxon (the more toxic, environmental degrade of malathion) exposures. Toddler risks from deposited residues of malathion and transformed malaoxon on decks and playground equipment are believed to represent the worst case for all residential populations engaged in any activity on outdoor hard surfaces. Therefore, adult exposures and risks were not assessed, nor were risks from contact with driveways, sidewalks, etc. Postapplication risks to toddlers from contacting malathion and malaoxon residues deposited on surfaces following public health mosquitocide, boll weevil, and fruit fly treatments do not exceed HED's level of concern. Risks were driven by dermal exposure and assumed malathion-to-malaoxon transformation rates.

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. Aggregate exposure risk assessments were performed for acute and chronic dietary (food and drinking water) exposures; and for short-term exposures (food, water and residential). HED's level of concern was not exceeded for any of these aggregate assessments.

The aggregate chronic dietary risk estimates include average exposures to combined residues of malathion and malaoxon in food and water. A new chronic RfD (0.07 mg/kg/day) was based on a BMD analysis of RBC ChEI in the multiple dose portion of a comparative cholinesterase study in rat pups. The estimated surface water concentration was based on data from the highest one-in-ten year annual concentration from aerial application to California lettuce using the maximum label rate and assuming a 3-day half-life in soil. Each value was adjusted for the malaoxon toxicity adjustment factor of 61x.

Chronic dietary exposure risks from food alone did not exceed HED's level of concern for the U.S. general population and all population subgroups (<1% of the cPAD). The chronic dietary exposure risk from food and drinking water using the worst-case 1-in-10 year annual concentration is below HED's level of concern (<100% cPAD) for the U.S. population and all population subgroups. Malathion dietary exposure from food and drinking water was <1% of the cPAD for the U.S. population and all infants <1 yr, the most highly exposed population subgroup.

Occupational exposure may result from malathion agricultural uses (i.e., multiple food-use crops) and non-agricultural uses (e.g., outdoor residential vegetable gardens, home orchards, ornamentals and perimeter house treatments, and wide-area mosquito treatment). Exposure may occur to both handlers and postapplication workers who enter and conduct activities in treated use sites.

Most mixer/loader scenarios exceed HED's level of concern assuming that baseline clothing is worn (i.e., long pants, long sleeved shirt, shoes & socks). With the addition of gloves, most mixer/loader scenarios no longer exceed HED's level of concern, except for those that involve high application rates, large areas of treatment, or wettable powder formulations. For these latter exceptions, additional clothing, a respirator, or engineering controls such as a closed mixing/loading system are required in order to reduce exposure such that risks no longer exceed HED's level of concern.

Most applicator scenarios do not result in exposures that exceed HED's level of concern with handlers wearing baseline clothing. For most of the scenarios that do exceed HED's level of concern at baseline, gloves, additional clothing, or headgear provide effective protection. No flagger scenarios reflecting various formulation/crop combinations are of concern assuming flaggers wear baseline clothing.

All crops and application rates were also assessed for postapplication activities ranging from very low to very high contact. Resulting "days after treatment" at which an MOE of 100 was reached varied from 0 to 4 days. Most activities reach an MOE ≥100 on 0 - 2 days. An interim REI of 12 hours is established for malathion under the Worker Protection Standard (WPS).

2.0 Ingredient Profile

Product Chemistry Chapter for the Malathion Reregistration Eligibility Decision (RED) Document. William O. Smith. DP Barcode D256522. June 2, 1999.

Residue Chemistry Chapter for the Malathion Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D239453. William O. Smith. April 14, 1999.

Malathion is a non-systemic, wide spectrum organophosphorus (OP) insecticide. It is used in the agricultural production of a wide variety of food/feed crops to control insects such as aphids, leafhoppers, and Japanese beetles. Malathion is also used in the cotton boll weevil, fruit fly, and mormon cricket eradication programs and as a general wide-area treatment for mosquito-borne disease control (adulticide). It is also available to the home gardener for outdoor residential uses which include vegetable gardens, home orchards, ornamentals and lawns. The Agency has been informed by the basic producer (Cheminova A/S letters dated March 10, 1998 and March 18, 2002) that certain formulations and use sites will not be supported for reregistration. As a consequence, this risk assessment does not address any existing product labels permitting indoor uses, direct animal (pet and livestock) treatments, among other uses in the market place. When end-use product DCIs are developed, the Agency will require that all end-use product labels be amended such that they are consistent with the basic producer labels.

Malathion is formulated as a technical (91-95% ai), a dust (1-10% ai), an emulsifiable concentrate (3-82% ai), a ready-to-use (1.5-95% ai), a pressurized liquid (0.5-3% ai), and a wettable powder (6-50% ai). Several of the 95% liquids are intended for ultra-low-volume (ULV) applications. Malathion can be applied using ground or aerial equipment, thermal and non-thermal fogger, ground boom, airblast sprayer, chemigation, and a variety of hand-held equipment such as backpack sprayers, low pressure handwands, hose-end sprayers, and power dusters. Multiple foliar applications may be made as needed depending on pest presence at application rates ranging from 0.1 to 8.7 lb ai/A.

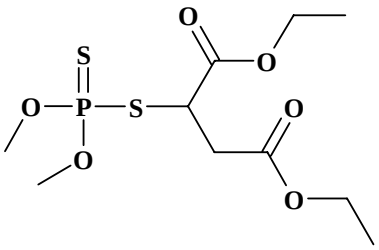
2.1 Summary of Registered/Proposed Uses

Cheminova summarized malathion usage in four major market areas and provided the following market share information: USDA Boll Weevil and other special program uses (59-61%), general agriculture uses (16-20%), public health uses (8-15%), and home and garden uses (10%). Based on available pesticide survey information from EPA's Biological and Economics Assessment Division reflecting total lb ai used per year for the period 1988 to 2000, the most predominant agricultural use of malathion is on cotton (33%; excluding the cotton usage as part of the USDA's Boll Weevil Eradication Program), followed by cereal grains (11%), alfalfa (15%), small fruits and berries (about 5%), pome and stone fruits (5%), and tree nuts (3%). Of the postharvest usage of malathion on corn, wheat and oats, an average of 34% of the bushels of wheat are treated with malathion.

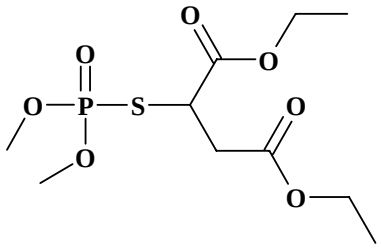
There is a non-FIFRA pharmaceutical use of malathion as a pediculicide for the treatment of head lice and their ova. The Food and Drug Administration (FDA) approves uses of pesticidal-containing pharmaceutical products under FFDCA. HED is currently working with FDA to derive appropriate exposure assessment methodology to determine how the pharmaceutical use of malathion should be considered in EPA's aggregate risk assessment. A supplementary risk assessment for this use will be incorporated into the Agency's IRED.

2.2 Structure and Nomenclature

With regard to the product chemistry database supporting reregistration of malathion, registrants are required to either certify that the suppliers of beginning materials and the manufacturing processes for the malathion manufacturing-use products have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages. Data requirements for specific manufacturing-use product registrations are detailed in the malathion Product Chemistry Chapter (DP Barcode D256522, W. Smith, June 2, 1999).

TABLE 2.2.1 Malathion Test Compound Nomenclature		
Chemical Structure		
Empirical Formula	$C_{10}H_{19}O_6PS_2$	
Common name	Malathion	
IUPAC name	O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate	
CAS Registry Number	121-75-5	
End-use product/EP	Technical (91-95% ai), dust (1-10% ai), emulsifiable concentrate (3-82% ai), ready-to-use (1.5-95% ai), pressurized liquid (0.5-3% ai), and wettable powder (6-50% ai).	
Chemical Class	Organophosphate	
Known Impurities of Concern	Empirical Formula:	$C_{10}H_{19}O_6PS_2$

	Common Name:	Isomalathion
	IUPAC Name:	Butanedioic acid, [[methoxy(methylthio)phosphinyl]thio]-, diethylester
	CAS Registry Number:	3344-12-5

TABLE 2.2.2 Malaoxon Test Compound Nomenclature	
Chemical Structure	
Empirical Formula	$C_{10}H_{19}O_7PS$
Common name	Malaoxon (the active ChE inhibiting metabolite of malathion)
IUPAC name	O,O-dimethyl thiophosphate of diethyl mercaptosuccinate
CAS Registry Number	1634-78-2
End-use product/EP	Not Registered
Chemical Class	Organophosphate

A number of impurities have been reported to be present in representative technical formulations of malathion. Currently available data in support of reregistration, indicate that potential impurities and degradates are found either to be less toxic than the parent or the malaoxon, or are present at levels which do not pose a residue concern. Isomalathion is an impurity known to be present at very low levels in both technical grade and end-use product samples of malathion. These low levels of isomalathion may be formed during the process of manufacturing malathion, and low levels of isomalathion may also be formed if malathion undergoes chemical

rearrangement (isomerization) during product storage. Data provided by the registrant indicate that Fyfanon® Technical (EPA Reg. No. 4787-5) is stable for 1 year when stored under warehouse conditions (20-23^{o}C) although a small amount of isomalathion accumulated (increase from <0.01% to about 0.1%). Storage of malathion at 54^{o}C for 2 weeks resulted in an increase of isomalathion from about 0.05% to 0.2%.

2.3 Physical and Chemical Properties

TABLE 2.3.2 Malathion Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	330.4	Product Chemistry Chapter (W. Smith, June 2, 1999)
Boiling point/range	156-157^{o}C	Product Chemistry Chapter (W. Smith, June 2, 1999)
Melting point	2.8^{o}C	SRC PhysProp Database
Density (25^{o}C)	1.2	SRC PhysProp Database
Water solubility (25^{o}C)	145 ppm	Product Chemistry Chapter (W. Smith, June 2, 1999)
Solvent solubility (temperature not specified)	readily soluble in most alcohols, esters, aromatic solvents, and ketones, and is only slightly soluble in aliphatic hydrocarbons	Product Chemistry Chapter (W. Smith, June 2, 1999)
Vapor pressure (30^{o}C)	0.00004 mmHg	Product Chemistry Chapter (W. Smith, June 2, 1999)
Octanol/water partition coefficient, logP_{OW} (25^{o}C)	2.36	SRC PhysProp Database
Half Life	Aerobic soil T½ = 3 days (used for EEC modeling)	
TABLE 2.3.2 Malaoxon Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	314.29	Chemical Abstracts
Boiling Point	114^{o}C	Chemical Abstracts
Melting point/range	<20^{o}C	Chemical Abstracts
Water solubility (22^{o}C)	0.5-1.0 g/100 mL	Chemical Abstracts
Vapor pressure (10-50^{o}C)	2.45E-06 to 3.2E-04 torr	Chemical Abstracts
Half Life	Aerobic soil T½ = 21 days (used for EEC modeling)	Chemical Abstracts

3.0 Metabolism Assessment

The nature of the residue in plants and livestock is adequately understood. Based on available plant metabolism data, the HED Metabolism Committee has determined that the malathion residues of concern in plants consists of malathion and its metabolite malaoxon. The residues of malathion in livestock commodities represent a Category 3 situation under 40 CFR §180.6(a), i.e., there is no reasonable expectation of malathion residues being transferred from treated feed items to livestock commodities.

3.1 Comparative Metabolic Profile

The metabolic pathway for malathion in plants is similar to that in rat: oxidation of malathion to malaoxon and de-esterification to form mono- and dicarboxylic acids and succinate derivatives. Unchanged malathion was typically found to be the major residue in both plants and rats. Malaoxon, when present, comprised a small portion of the total radioactivity. Rat metabolism studies also showed that when orally administered, malathion is excreted primarily in the urine in the first 24 hours following exposure, with lesser amounts excreted in the feces. Radioactivity did not bioaccumulate in any of the organs/tissues analyzed.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

Metabolism studies with alfalfa, lettuce, cotton, and wheat adequately depict the qualitative nature of the residue in plants. The metabolic pathway for malathion in these plants is similar: oxidation of malathion to malaoxon and de-esterification to form mono- and dicarboxylic acids and succinate derivatives. Residues were predominantly found in edible vegetative portions and were also present in cotton seed and wheat grain following foliar application. Unchanged malathion was typically found to be the major residue; malaoxon, when present, comprised a very small portion ($\leq$1%) of the total radioactivity.

3.2.2 Description of Livestock Metabolism

Ruminant and poultry metabolism studies have been submitted, evaluated, and found acceptable to fulfill livestock metabolism reregistration requirements. Neither malathion nor malaoxon was observed in eggs, milk, or tissues following oral administration of [^{14}C] malathion at exaggerated rates. The residues of malathion in animal commodities represent a Category 3 situation under 40 CFR §180.6(a): i.e., situations in which it is not possible to establish with certainty whether finite residues will be incurred, but there is no reasonable expectation of finite residues in animal commodities. Therefore, there is no need for tolerances in these commodities based on livestock dietary exposure to malathion.

3.2.3 Description of Rotational Crop Metabolism

The nature of the residue in rotational crops is understood, and no additional confined rotational crop data are required for the purpose of reregistration. Malaoxon was not detected in/on any fractions or extracts collected from samples representing 30-day plant-back interval (PBI). Malathion was identified in the organosoluble fractions of immature lettuce, immature turnips, and wheat forage from the same PBI. Because malathion was identified in 30-PBI rotational crops and quantified at levels greater than 0.01 ppm, the registrant(s) was required to conduct limited field rotational crop studies. Rotational crop restrictions are needed on malathion end-use product labels. The appropriate PBIs will be determined pending submission of the required field rotational crop studies.

3.3 Environmental Degradation

The Environmental Fate and Effects Division (EFED) has provided an analysis of available monitoring data and a drinking water assessment using PRZM/EXAMS to estimate the potential concentration of malathion and its degradate malaoxon in ground and surface water. In addition, EFED's analysis of available drinking water facility monitoring data indicates that all malathion entering a drinking water treatment facility is expected to be converted to malaoxon. Based on environmental fate characteristics, model predictions and actual monitoring studies, the Agency predicts that malathion will reach drinking water sources. Numerous monitoring studies confirm that malathion/malaoxon can reach surface drinking water treatment facility intakes but insufficient targeted monitoring studies are available to adequately define acute malathion/malaoxon concentrations in drinking water; thus, surface water concentrations associated with a range of malathion use scenarios were modeled.

The environmental fate data on malathion indicate that it is relatively mobile and shows little persistence in soil and water. The primary route of dissipation of malathion in surface soils appears to be aerobic metabolism. Limited fate data are available for the degradate malaoxon. However, based on its chemical similarity to malathion, the parent and its degradate are expected to have similar chemical properties. Malaoxon is also expected to have similar environmental persistence and mobility to malathion and when observed, it was a minor degradate (<10%) in most studies reviewed, malaoxon peak concentrations are unlikely to exceed malathion's peak concentration.

3.4 Tabular Summary of Metabolites and Degradates

Table 3.4 Tabular Summary of Metabolites and Degradates

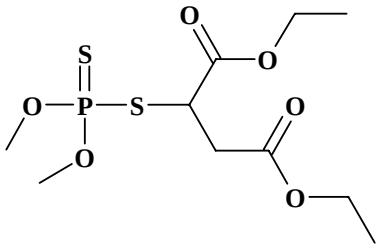
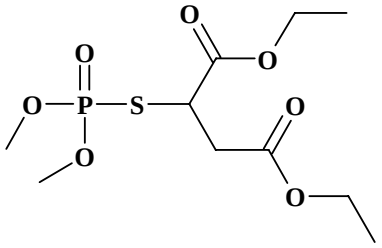
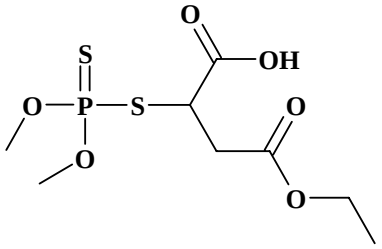
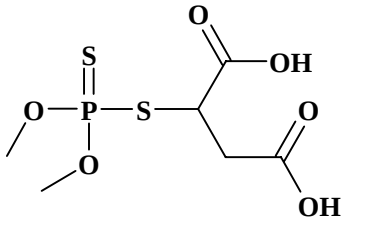
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM) [1]		Structure
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
Malathion	Alfalfa Forage	46.7		
	Alfalfa Hay	19.6		
	Wheat Grain	30.5		
	Wheat Straw	11.8		
	Wheat Forage		9.0	
	Cottonseed	34.5		
	Leaf Lettuce	29.9		
	Livestock		180.6(a)(3)	
Malaoxon	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		<0.1	
	Wheat Forage		0.4	
	Cottonseed		0.4	
	Leaf Lettuce		0.1	
	Livestock		180.6(a)(3)	
Monocarboxylic acid of malathion (monoacid or MCA)	Alfalfa Forage	10.6		
	Alfalfa Hay		Not Reported	
	Wheat Grain		3.3[2]	
	Wheat Straw		7.6[2]	
	Wheat Forage		9.4[2]	
	Cottonseed		1.7[2]	
	Leaf Lettuce	11.7		
	Livestock		180.6(a)(3)	
Dicarboxylic acid of malathion (diacid or DCA)	Alfalfa Forage		0.2	
	Alfalfa Hay		Not Reported	
	Wheat Grain		1.2	
	Wheat Straw		0.7	
	Wheat Forage		1.8	
	Cottonseed		ND	
	Leaf Lettuce		4.9	
	Livestock		180.6(a)(3)	
Monoethyl Maleate	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	

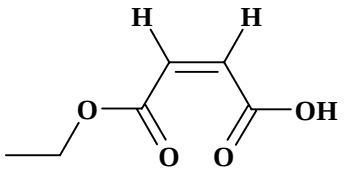
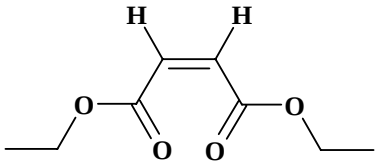
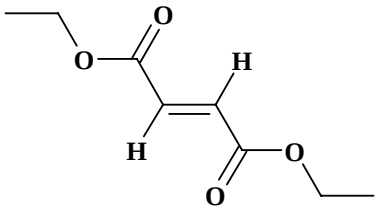
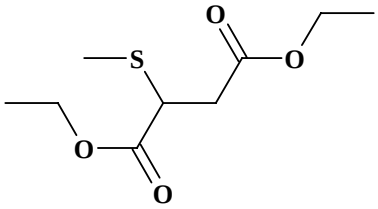
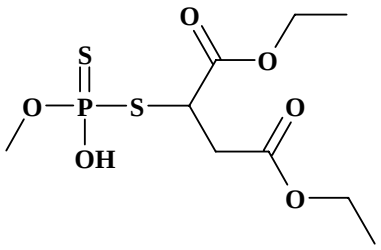
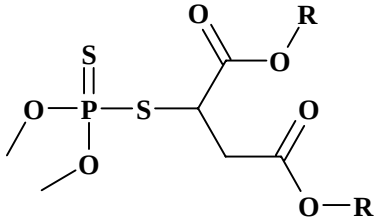
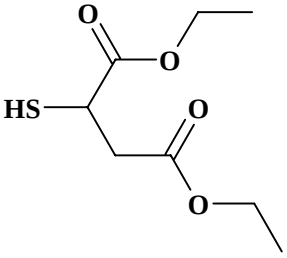
Table 3.4 Tabular Summary of Metabolites and Degradates				
	Wheat Straw		ND	
	Wheat Forage		ND	
	Cottonseed		0.1	
	Leaf Lettuce		ND	
	Livestock		180.6(a)(3)	
Diethyl Maleate	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		0.1	
	Wheat Forage		2.2	
	Cottonseed		ND	
	Leaf Lettuce		ND	
	Livestock		180.6(a)(3)	
Diethyl fumarate	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		0.2	
	Wheat Forage		ND	
	Cottonseed		0.3	
	Leaf Lettuce		0.8	
	Livestock		180.6(a)(3)	
Diethyl methylthio succinate	Alfalfa Forage		2.5	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		ND	
	Wheat Forage		ND	
	Cottonseed		ND	
	Leaf Lettuce		ND	
	Livestock		180.6(a)(3)	
DesMe Malathion[3]	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		ND	
	Wheat Forage		ND	

Table 3.4 Tabular Summary of Metabolites and Degradates				
	Cottonseed		ND	
	Leaf Lettuce		0.4	
	Livestock		180.6(a)(3)	
CL 78,872[4]	Alfalfa Forage		1.2	
	Alfalfa Hay		1.2	
	Wheat Grain		ND	
	Wheat Straw		0.3	
	Wheat Forage		8.6	
	Cottonseed		0.2	
	Leaf Lettuce		6.8	
	Livestock		180.6(a)(3)	
CL 26,782[5]	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		0.1	
	Wheat Forage		ND	
	Cottonseed		0.1	
	Leaf Lettuce		0.1	
	Livestock		180.6(a)(3)	

1. ND = Not detected.
2. Coeluted with diethyl methylthiosuccinate; activity attributed to malathion monocarboxylic acid.
3. S-(1,2-dicarboethoxy)ethyl)-O-methyl hydrogen phosphorodithioate.
4. Impurity in Technical Malathion. Mixed Esters. R = either CH_3 or C_2H_5.
5. Impurity in Technical Malathion.

3.5 Toxicity Profile of Major Metabolites and Degradates

A rat metabolism study showed that orally administered malathion is excreted primarily in the urine (80-90%) in the first 24 hours following exposure, with lesser amounts excreted in the feces. Radioactivity did not bioaccumulate in any of the organ/tissues analyzed. Although eight radiolabeled metabolites were observed in urine, greater than 80% of the radioactivity in urine was represented by the diacid (DCA) and monoacid (MCA) metabolites. The remaining radiolabeled metabolites were identified as components of "peak A" and "peak B." It was determined that between 4 and 6% of the administered dose was converted to malaoxon, the more active ChE inhibiting metabolite of malathion.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

Tolerances have been established for residues of malathion *per se* in/on food/feed commodities [40 CFR §180.111, §185.3850, §185.7000, and §186.3850] and meat, milk poultry and eggs [40 CFR §180.111]. *Because animal metabolism data indicate that there is little likelihood of residue transfer to meat, milk, poultry and eggs, tolerances for malathion residues in these commodities may be revoked.* Based on available plant metabolism data, the HED Metabolism Committee has determined that the malathion residues of concern in plants consists of malathion and its metabolite malaoxon. The tolerance expression (currently expressed in terms of malathion *per se*) should be revised to include malathion and malaoxon.

3.6.1 Tabular Summary

Table 3.6 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	malathion and malaoxon	malathion and malaoxon
	Rotational Crop	malathion and malaoxon	malathion and malaoxon
Livestock	Ruminant	180.6(a)(3)	180.6(a)(3)
	Poultry	180.6(a)(3)	180.6(a)(3)
Drinking Water		malathion and malaoxon	Not Applicable

3.6.2 Rationale for Inclusion of Metabolites and Degradates

In vivo, malaoxon is the active ChE-inhibiting, oxon metabolite of malathion. Under some conditions, malaoxon can be formed as an environmental breakdown product of malathion. Monitoring data indicate malaoxon's presence in food; therefore, this metabolite is included in this tolerance expression.

4.0 Hazard Characterization/Assessment

A number of documents were relied on heavily in developing the current hazard assessment (TXR0051549, TXR0052951, TXR0053521, TXR005967, and US EPA, 2002 [NOTE: All TXR references are listed in the reference section of this document]). In some cases, previous decisions or opinions expressed in historical documents have been changed to reflect the best and most current scientific information and methods available at this time. The current risk assessment is consistent with OPP's current risk assessment and science policies. In the last few years, OPP has increased its understanding and implementation of benchmark dose (BMD) techniques. BMD methods provide a more robust approach for developing points of departure (PoD) for risk extrapolation, for evaluating relative potency, and evaluating life-stage sensitivity. The Agency has relied heavily on BMD in the malathion human health risk assessment. The methods and computer code used here have been previously reviewed by the FIFRA Scientific Advisory Panel and are publicly available on the internet. The Agency has also received a new dermal toxicity study with malathion that further characterizes the dose-response relationship for ChE inhibition. This risk assessment also reflects incorporation of comments made by the public on the revised malathion risk assessment. For responses to all comments, see TXR 0054040.

4.1 Hazard Characterization

Malathion (O,O-dimethyl thiophosphate of diethyl mercaptosuccinate) is an OP insecticide. Similar to other members of this class, the mode of toxic action is the inhibition of cholinesterase (ChE). Malathion is metabolically activated to its ChE inhibiting oxon metabolite, malaoxon (oxidation of the P=S moiety to P=O), in insects and mammals. Both malathion and malaoxon are detoxified by carboxylesterases and other metabolic processes, leading to polar, water-soluble, compounds that are excreted. Mammalian systems show greater carboxylesterase activity, as compared with insects, so that the toxic agent malaoxon builds up more in insects than in mammals. This accounts for the selective toxicity of malathion towards insects.

4.1.1 Database Summary

Studies Available and Considered

The toxicology database for malathion is substantially complete and of acceptable quality to assess the potential hazard to humans, including special sensitivity of infants and children. The database includes prenatal developmental toxicity studies in rats and rabbits, a two-generation reproductive toxicity study in rats, an acute delayed neurotoxicity study in hens, an acute neurotoxicity study in rats, a subchronic neurotoxicity study in rats, a developmental neurotoxicity study in rats (with a supplemental range-finding study), and a comparative ChE study in adult and immature rats. In addition to these studies, the registrant has submitted an extensive database of guideline toxicology studies, as required in 40 CFR Part 158.340 (i.e., acute, subchronic, chronic, carcinogenicity, and metabolism studies). The test substance used in these studies was typically the technical grade of the active ingredient (TGAI) malathion, and the strength, purity, composition, and stability of each test material was adequately documented. The presence of impurities in the technical material (specifically isomalathion) and the possible formation of the active oxon (malaoxon) under certain environmental conditions that would result in direct environmental exposure to the oxon are special considerations that are discussed below.

The toxicity profile provides generally well-characterized developmental, reproductive, endocrine, carcinogenic, mutagenic, and neurotoxic effects. The only data gaps are for an acute and repeated special comparative cholinesterase assay in juvenile animals with malaoxon and malathion (Data Call In Notice sent in October, 2004) and an immunotoxicity study. An acute comparative ChE study with malaoxon has been conducted by the registrant, however it has been deemed unacceptable and must be repeated to fulfill the DCI (MRIDs 46756701, 46756702, 46756703, 46756704, and 46756705 and TXR0053748). An immunotoxicity study is required to further characterize suggestive evidence of immune responses reported in literature studies with malathion.

Mode of Action, Metabolism, Toxicokinetic Data

Malathion belongs to a class of insecticides (organophosphorous compounds) which act as ChE inhibitors through phosphorylation of the active site of acetylcholinesterase (AChE). Malathion is metabolized to its oxon (malaoxon) in both insects and mammals. The oxon is the active ChE inhibiting metabolite of malathion. AChE is an enzyme found in cholinergic neurons whose function is to break down acetylcholine and thus terminate acetylcholine's ability to properly bind at the receptor sites. Inhibition of this enzyme leads to an accumulation of free, unbound acetylcholine at nerve endings which leads to the symptoms and associated functional deficits known for AChE inhibitors: peripherally - smooth muscle contractions (e.g., abdominal cramps; glandular secretions (e.g,. sweating); skeletal muscle twitching; and, at higher concentrations, paralysis); centrally - possible effects on learning, memory and other behavioral parameters. Measurement of cholinesterase inhibition (ChEI) to properly assess cholinergic pathways of the peripheral nervous system is typically not submitted to EPA as part of pesticide registration. As a surrogate, ChE activities in circulating blood are used as an indicator of possible neuronal ChE activity. ChE activity in the brain is a reasonable measure of effects on the central nervous system; such data are typically provided to EPA in animal studies.
When administered to animals directly, malaoxon is a more potent ChE inhibitor than malathion.

In the rat, malathion is excreted primarily in the urine (80-90%) in the first 24 hours following exposure, with lesser amounts excreted in the feces. At 72 hours, the highest concentration of radioactivity was observed in the liver (< 0.3% of the administered radioactivity). Radioactivity did not bioaccumulate in any of the organs/tissues analyzed. Although eight radiolabeled metabolites were observed in urine, greater than 80% of the radioactivity in urine was represented by the dicarboxylic acid (DCA)-malathion and monocarboxylic acid (MCA)-malathion metabolites. It is estimated that between 4 and 6% of the administered malathion dose in this rat metabolism study is converted to malaoxon, the active ChE-inhibiting metabolite of malathion (TX007791).

Sufficiency of Studies

The available animal data are considered sufficient information to assess human hazard in the context of dose, duration, timing and route of exposure. Results of impending studies (immunotoxicity study with malathion and acute and repeated comparative ChE study in juvenile rats with malaoxon and malathion) will provide additional information on specific aspects of the hazard of malathion and its oxon metabolite. Section 4.4.7 provides a description of the currently available information regarding relative potency of malaoxon and the parent compound, malathion.

4.1.2 Toxicological Effects

As a member of the organophosphorous insecticide family of chemicals, malathion is a well-known neurotoxic agent due to its ability to inhibit ChE resulting in an accumulation of acetylcholine at various synapses and neuromuscular junctions of an exposed organism. Table 4.1.2b provides a summary of the subchronic, chronic, and other information relevant to the malathion toxicity profile. Malathion exhibits low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). It exhibits only slight eye and dermal irritation and is not dermally sensitizing (Table 4.1.2a).

Table 4.1.2a Acute Toxicity Profile - Malathion

Guideline	Type of Study - Species	MRID (Date)	Results	Toxicity Category
§81-1 870.1100	Acute Oral - Rat	00159876 (1986)	LD_{50}= 5400(M)/5700(F) mg/kg	IV
§81-2 870.1200	Acute Dermal - Rat	00159877 (1986)	LD_{50} >2000 mg/kg (M)(F)	III
§81-3 870.1300	Acute Inhalation - Rat	00159878 (1986)	LC_{50}> 5.2 mg/L (M)(F)	IV
§81-4 870.2400	Eye Irritation - Rabbit	00159880 (1985)	Slight conjunctival irritation; Clear by 7 days	III
§81-5 870.2500	Skin Irritation - Rabbit	00159879 (1985)	Slight dermal irritation (PIS=1.1)	IV
§81-6 870.2600	Dermal Sensitization - Guinea pig	00159881 (1986)	Not a skin sensitizer	N/A

General Toxicity, Developmental and Reproductive Toxicity, and Neurotoxicity

The findings in a variety of studies following acute, subchronic, and chronic exposure indicate that the major target for this chemical is the nervous system. The inhibition of ChE - particularly in blood - provides a measure of exposure/effect and is the critical endpoint for risk assessment. ChEI in various compartments has been observed in multiple species (rat, mouse, and dog) following oral routes of administration and in rabbits and rats following dermal and inhalation exposures, respectively.

A full complement of neurotoxicity studies has been submitted to the Agency for malathion, including an acute delayed neurotoxicity study in hens, acute and subchronic toxicity studies in adult rats, a developmental neurotoxicity study (with range-finding study) in rats, and a comparative ChE study that examined the response in adults and juvenile rats following acute or repeated gavage doses of malathion. No evidence of organophosphate-induced delayed neurotoxicity was found in hens following a single 1008 mg/kg dose of malathion.

The comparative ChE study established adult ChE NOAELs for acute exposure at 150 mg/kg/day, and for repeated exposures at 5 mg/kg/day. For offspring dosed acutely on PND 11 or repeatedly from PND 11-21, RBC ChEI (16-72% following acute exposure and 15-68% following repeated exposures) was noted at all doses tested, including the lowest dose of 5 mg/kg/day. For this risk assessment, benchmark dose (BMD) estimates for RBC ChEI were estimated (see Section 4.1.3.1). In the developmental neurotoxicity study in rats, effects were noted in offspring at all doses tested (details in Section 4.1.3).

In available subchronic dermal and inhalation studies with malathion, plasma and RBC ChEI were exhibited in both rabbits (at approximately 100 mg/kg/day) and rats (0.45 mg/L) following dermal (two 21-day studies) and inhalation (90-day study) exposure, respectively, and brain ChEI in female rabbits following dermal exposure. Brain ChEI occurred at higher doses in both species. No clinical signs or other treatment-related effects were observed in dermally treated rabbits. Both clinical signs and treatment-related microscopic lesions of the nasal cavity and larynx were observed in rats following inhalation exposure in whole body exposure chambers.

Standard guideline prenatal developmental toxicity studies in rats and rabbits were conducted with malathion. No developmental toxicity was observed in rats up to maternal doses of 800 mg/kg/day. In rabbits, increased incidence of mean resorption sites was noted at doses that resulted in decreased maternal body weight gains (50 mg/kg/day and greater); this was considered evidence of qualitative susceptibility to the developing fetuses. In a two-generation reproduction study in rats, effects on pre-weaning pup growth were observed at doses that resulted in no parental toxicity (394-451 mg/kg/d). Minimal parental toxicity (decreased body weights in F0 dams during gestation and lactation and in F1 offspring during the second generation pre-mating period) was observed at higher dose levels (612-703 mg/kg/d) than the dose at which pup body weights were affected (394-451 mg/kg/d), indicating increased susceptibility to the pups. It is notable that the doses causing body weight decrement in the reproductive toxicity study are much higher than those used to establish oral PoDs for the risk assessment. There were no effects of malathion on reproductive function; however, ChE activity was not measured.

There was evidence of quantitative susceptibility in the developmental neurotoxicity study and its companion comparative ChE studies in that the ChEI occurs in juveniles at lower doses than in adults.

Chronic Toxicity

Chronic studies have been performed in rats and dogs. In the rat study - in addition to the expected ChEI - changes in various organ weights and both neoplastic and non-neoplastic microscopic changes were observed in different organs following daily exposures (approximately 30 mg/kg/d) for 24 months (see Section 4.4.3 for executive summary of combined chronic/carcinogenicity study in rats). In the chronic dog study, there was no mortality or clinical signs from daily dosing of up to 250 mg/kg/d via capsule. Plasma and RBC ChEI (~20% and ~30% decrease, respectively, from pre-test values) were observed in both males and females at the lowest tested dose (62.5 mg/kg/d).

Mutagenicity and Carcinogenicity

The mutagenicity database for malathion indicates that there is weak evidence of a mutagenic effect in mammalian cells at high and cytotoxic concentrations. Negative mutagenic responses were noted for the guideline *in vitro* mammalian cell gene mutation test, the *in vivo* bone marrow cytogenetic assay, and the *in vitro* primary rat hepatocytes unscheduled DNA synthesis (UDS) assay. In an acceptable guideline mouse lymphoma forward gene mutation assay, malathion was mutagenic over a very narrow range of concentrations that were cytotoxic. A large body of published literature (over 30 studies) has also been evaluated for their contribution to the weight of evidence concerns for the mutagenicity of malathion. The weight of evidence from both guideline studies and the open literature do not support a mutagenic concern for malathion. The FIFRA SAP agreed with this conclusion (FIFRA SAP, 2000).

The relevant data on the carcinogenic potential of malathion was evaluated by the Cancer Assessment Review Committee (CARC) (2-Feb-2000 and 28-April-2000) and a FIFRA SAP review (report dated December 14, 2000). The CARC considered the SAP recommendations and concluded that the cancer classification should remain as “suggestive.” Additionally, the CARC recently evaluated a publication by Cabello et al.(2001) and concluded that the paper provided insufficient basis for revising the cancer classification for malathion. A cancer dose-response assessment, e.g., a low dose linear extrapolation model, is not indicated for pesticides in the “suggestive” category.

Immunotoxicity

Published literature studies have shown that malathion can affect immune function depending on route, magnitude, and frequency of administration. This information has prompted the requirement for a guideline immunotoxicity study to better characterize the potential effects of malathion on the immune system.

Possible human allergic or irritative response reported by the Toxics Epidemiology Program of Los Angeles County after aerial spraying with malathion-bait for eradication of the Mediterranean fruit fly in the late 1980's prompted a series of animal studies to assess possible immunotoxicity concerns (Rodgers and Xiong, 1997; California Dept. of Health Services, 1991). Literature reports conclude that acute administration of malathion enhanced the humoral immune response in mice (Rodgers et al., 1986, 1996).

Additional repeat dose studies by the same investigators have shown that malathion enhances the respiratory burst activity in mice at all doses tested in a dose-dependent manner following daily oral exposures of from 0.1 to 10 mg/kg/d for 90 days (Rodgers and Xiong, 1997)[1].

In another subchronic study, mice, rats and rabbits were exposed to malathion at dose levels of 20, 50, or 100 ppm (approximately 1-30 mg/kg/d depending on species) in the diet for 12, 22 or 13 weeks, respectively (Banerjee, et al., 1998). Significant suppression of humoral response (PFC and antibody titers) in a dose-time dependent relationship after both primary and secondary immunization was observed in the mice and rats from six to eight weeks after exposure began until study termination. The study authors stated that the effects of malathion on immune responses are more dependent on time than on dose, suggesting a threshold susceptibility to exposure.

In conclusion, although there was suggestive evidence to show that malathion induces a human allergic or irritative response, a guideline hypersensitivity study in guinea pigs showed that malathion is a non-sensitizer. Reports are inconclusive for the effects of malathion on humoral immunity. An immunotoxicity study is required by the Agency and is considered a data gap.

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion

Guideline No./ Study Type	MRID No. (year)/ Classification/ Doses	Results
870.3200 - 21-Day dermal toxicity (NZ rabbit) (Malathion tech. 94% a.i.)	MRID 41054201 (1989) Doses: 0, 50, 300, 1000 mg/kg/day Acceptable/guideline	$BMDL_{20}$ of 135 mg/kg/d (males) and 143 mg/kg/d (females). This benchmark dose (BMD) is the lower 95% confidence interval for the estimated mean dose at which 20% RBC ChEI is observed.
870.3200 – 21-Day dermal toxicity (NZ rabbit) (Malathion tech. 96% a.i.)	MRID 46790501 (2006) Doses: 0, 75, 100, 150, 500 mg/kg/day Acceptable/guideline	$BMDL_{20}$ of 143 mg/kg/d (males) and 119 mg/kg/d (females). This benchmark dose (BMD) is the lower 95% confidence interval for the estimated mean dose at which 20% RBC ChEI is observed. Dermal irritation noted at all doses.

[1] The lowest dose in this study that caused effects [0.1 mg/kg/d] was not used in the risk assessment for the following reasons: (1) the mode of action for malathion is believed to be neurotoxicity via ChEI; (2) the experiment was exploratory in nature; and (3) the experiment was not a guideline study following Good laboratory Practices (GLP). Therefore, requesting a guideline immunotoxicity study to better characterize this potential effect is a prudent step that should be followed before this endpoint could be chosen for risk assessment purposes.

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.3465 - 90-day Inhalation- Rat (Malathion tech. 96.4% a.i.)	MRID 43266601 (1994) Whole-body inhalation exposures of: 0, 0.1, 0.45, 2.01 mg/L Acceptable/non-guideline	Systemic NOAEL: not established Systemic LOAEL: 0.1 mg/L (LDT), based on histopathologic lesions of the nasal cavity and larnyx in males and females. ChEI NOAEL: 0.1 mg/L ChEI LOAEL: 0.45 mg/L, based on plasma and RBC ChEI in females
870.3465 - 2-week (range-finding) Inhalation-Rat (Malathion tech. 96.4%a.i.)	MRID 44554301 (1993) Dose level: 0, 0.5, 1.5, 4.5 mg/L Acceptable/non-guideline	Systemic NOAEL: not established Systemic LOAEL: 0.5 mg/L, based on nasal and laryngeal epithelial effects ChEI NOAEL: not established ChEI LOAEL: 0.5 mg/L, based on RBC ChEI
870.3700a - Developmental-Rat (Malathion tech. 94% a.i.)	MRID 41160901 (1989) Doses: 0, 200, 400, 800 mg/kg/d (Days 6-15 of gestation) Acceptable/guideline	Maternal NOAEL: 400 mg/kg/day Maternal LOAEL: 800 mg/kg/day, based on reduced mean body weight gains and reduced mean food consumption. Developmental NOAEL: 800 mg/kg/day Developmental LOAEL: >800 mg/kg/day; no adverse developmental effects were observed at the highest tested dose.

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.3700b - Developmental-Rabbit (Malathion tech. 92.4% a.i.)	MRID 00152569 (1985) and Supplemental Report MRID 40812001 (1985) Doses: 0, 25, 50, 100 mg/kg/d (Days 6-18 of gestation) Acceptable/guideline	Maternal NOAEL: 25 mg/kg/day Maternal LOAEL: 50 mg/kg/day, based on reduced mean body weight gains during period of malathion exposure (Days 6-18 of gestation). Developmental NOAEL: 25 mg/kg/day Developmental LOAEL: 50 mg/kg/day; increased mean number of resorption sites/dose. (NOTE: Cholinergic signs and mortality seen in range-finding study at 200 and 400 mg/kg/d).
870.3800 - Two-generation Reproduction-Rat (Malathion tech. 94% a.i.)	MRID 41583401 (1997) Doses: 0, 550, 1700, 5000, 7500 ppm in feed (equivalent to 0, 43, 131, 394, and 612 mg/kg/d in males and 0, 51, 153, 451, and 703 mg/kg/d in females) Acceptable/guideline	Parental NOAEL: 394%/451& mg/kg/day Parental LOAEL: 612% /703& mg/kg/day, based on decreased F0 generation body weights during gestation and lactation (females) and decreased F1 pre-mating body weights (males and females). Offspring NOAEL: 131% /153& mg/kg/day Offspring LOAEL: 394% /451& mg/kg/day, based on decreased pup body weights during the late lactation period in F1 and F2 pups.
870.4100 - Chronic toxicity-dogs	MRID 40188501 (1987) Dose level:0,62.5,125,250 mg/kg/day (gelatin capsule) Unacceptable/guideline	Systemic NOAEL: >250 mg/kg/day (HDT) ChEI NOAEL: Not established. ChEI LOAEL: <62.5 mg/kg/day based on plasma and RBC ChEI

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.4200 - Combined chronic toxicity/ carcinogenicity-F344 rats (Malathion tech. 97.1% a.i.)	MRID 43942901 (1996) Dose levels: 0, 100/50 ppm (4%/5& mg/kg/d), 500 ppm (29%/35& mg/kg/d), 6,000 ppm (359%/415& mg/kg/d), 12,000 ppm (739%/868& mg/kg/d) Acceptable/guideline	ChEI NOAEL: 3 mg/kg/day (see note below) ChEI LOAEL: 35 mg/kg/day, based on significant RBC ChEI in females. Increased incidence of liver tumors in female rats only at excessive doses. NOTE: The low dose level was 100 ppm in the diet for three months which was dropped to 50 ppm for the remainder of the study (21 more months). The calculated dose for the three-month exposure was 7 (M) and 8 (F). The calculated dose from the 21 month exposure was 2 (M) and 3 (F) mg/kg/d. Assuming that a LOAEL for ChEI could be 8 mg/kg/d for three months [based on effects observed in females at that time), then a reasonable NOAEL would be 3 mg/kg/day for the 24 month study (the 21-month exposure value for females).
870.4200 - Combined chronic toxicity/ carcinogenicity-F344 rats (Malaoxon tech. 96.4% a.i.)	MRID 43975201 (1996) Dose levels: 0, 20, 1000, 2000 ppm in feed (equivalent to 0, 1, 57, 114 mg/kg/d in males and 0, 1, 68, 141 mg/kg/d in females). Acceptable/guideline	ChEI NOAEL: not determined ChEI LOAEL: 1 mg/kg/day based on 19-21% RBC ChEI males at 6 months. Systemic NOAEL: 1 mg/kg/d Systemic LOAEL: 57 mg/kg/d (males - mineral deposits in stomach muscularis) and 68 mg/kg/d (females - mortality, histological changes in nasoturbinates, lung interstitium, and tympanic cavity. Increased incidence of leukemia in male rats at highest dose only.

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.4300 - Carcinogenicity- B6C3F1 mice (Malathion tech. 96.4% a.i.)	MRID 43407201 (1994) Dose levels: 0, 100 ppm (17.4%/20.8 mg/kg/d), 800 ppm (143%/167 mg/kg/d), 8,000 ppm (1476%/1707 mg/kg/d),16,000 ppm (2978%/3448& mg/kg/d). Acceptable/guideline	Systemic NOAEL: 143%/167 mg/kg/day Systemic LOAEL: 1,476%/1,707 mg/kg/day, based on decreased body weights and food consumption, increased liver weight, and increased hepatocellular hypertrophy in males and females. ChEI NOAEL: 17.4%/20.8 mg/kg/day CHEI LOAEL: 143%/167 mg/kg/day, based on plasma and RBC ChEI in males and females. Increased incidence of liver tumors in male and female mice only at excessive doses.
870.5100 - Bacterial Reverse Gene Mutation Assay Malathion (95.2%)	MRID 40939302 (1987) Acceptable/guideline	**Negative** in *Salmonella typhimurium* and in *Escherichia coli* up to the limit dose (5,000 :g/plate +/-S9) in independent tests.
870.5300 - Mouse Lymphoma Forward Gene Mutation Assay	MRID 45554501 (2001) Doses: up to $\geq$ 1000 ug/mL Guideline/Acceptable	In a cell forward gene mutation assay at the TK $^{+/-}$ locus, independent tests were **negative** up to cytotoxic doses without S9 activation ($\geq$1000 :g/mL) and **weakly positive** with S9 activation over a narrow range of cytotoxic concentrations (2000 and 2200 :g/mL).
870.5385 - Mammalian Bone Marrow Chromosome Aberration Test In vivo (rats) Malathion (94%)	MRID 41451201 (1990) Doses: 500 to 2000 mg/kg (single oral dose) Guideline/Acceptable	**Negative**. A dose-related reduction in mitotic indices (MI) was seen in treated females at 24 hours. Reduced MIs were also seen in high-dose males and females at 48 hours.

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.5550 - Unscheduled DNA Synthesis in Mammalian Cells (rat) in Culture Malathion (94%)	MRID 41389301 (1990) Guideline/Acceptable	**Negative** up to cytotoxic concentrations (≥0.12 µL/mL; ~150 µg/mL).
Alkaline Single Cell Gel Electrophoresis (Comet Assay) Human Lymphocytes Malathion, malaoxon, and isomalathion (all at 99,8%)	MRID 45686902 (1999) Non-Guideline/Acceptable	In a comet assay, malathion was **negative** in peripheral blood lymphocytes exposed to 25, 75, or 200 µM (the highest concentration tested). By contrast, 200 µM malaoxon or 200 µM isomalathion induced dose-related significant increases in DNA damage.
870.6100 - Acute Oral Delayed Neurotoxicity in the Hen (Malathion tech. 93.6%)	MRID 40939301 (1988) Doses: 0, 10007.5 mg/kg followed by 852.5 mg/kg/d 21 days later (all hens pre-treated with atropine before each dose) Acceptable/guideline	Neither gross necropsies nor histopathological examination revealed any treatment-related effects in treated hens. Negative for any evidence of acute delayed neurotoxicity.
870.6200a Acute neurotoxicity-Rat (Malathion tech. 96.4%)	MRID 43146701 (1994) Doses: 0, 500, 1000, 2000 mg/kg/d Acceptable/guideline	NOAEL = 1000 mg/kg LOAEL = 2000 mg/kg (limit dose), based on decreased motor activity and clinical signs at the peak time of effect on day 1 (15 min post dosing) and plasma and RBC ChEI at day 7.

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.6200b Subchronic neurotoxicity- Rat (Malathion tech. 96.4%)	MRID 43269501 (1994) Doses: 0, 50, 5000, 20,000 ppm in diet (equivalent to 0, 4, 352, 1486 mg/kg/d in males and 0, 4, 395, 1575 mg/kg/d in females). Acceptable/guideline	NOAEL (M/F): 4 mg/kg/day LOAEL (M/F): 352/395 mg/kg/day, based on plasma, RBC ChEI in males and females and brain ChEI in females. No neurotoxicity noted at high-dose.
870.6300 Developmental neurotoxicity - rat (Malathion tech. 96.0%)	MRID 45646401 (2002) Doses: 0, 5, 50, 150 mg/kg/d Acceptable/guideline	Maternal NOAEL:50 mg/kg/day Maternal LOAEL: 150 mg/kg/day, based on increased incidence of post-dosing salivation Offspring NOAEL: Not determined (<5 mg/kg/day) Offspring LOAEL: 5 mg/kg/day, based on increased auditory startle reflex peak amplitude in PND 23/24 males and females.
(870.6300) Comparative ChE study - rat (Malathion tech. 96.0%)	MRID 45566201 (2002) Acute exposures (adults and pups) - 0, 5, 50, 150, 450 mg/kg/d. Repeat exposures (11 days to both adults and pups): 0, 5, 50, 150 mg/kg/d. Acceptable/guideline	Acute exposures $BMDL_{10}$ of 13.6 mg/kg (offspring, males) and 93.7 mg/kg (adult, females). This benchmark dose (BMD) is the lower 95% confidence interval for the estimated mean dose at which 10% RBC ChEI is observed. Repeated exposures (11 days) $BMDL_{10}$ of 7.1 mg/kg/d (offspring, males) and 15.7 mg/kg (adult, females). This benchmark dose (BMD) is the lower 95% confidence interval for the estimated mean dose at which 10% RBC ChEI is observed

Table 4.1.2b Subchronic, Chronic, and Other Information Relevant to the Toxicity of Malathion		
Guideline No./ Study Type	**MRID No. (year)/ Classification/ Doses**	**Results**
870.7485 41367701 (1989)	Metabolism-Rat Acceptable/guideline	Malathion and its metabolites are excreted primarily in the urine (80-90%) in the first 24 hours following exposure, with lesser amounts excreted in the feces. At 72 hours, the highest concentration of radioactivity was observed in the liver, but less than 0.3% of the administered radioactivity was present in that organ. Radioactivity did not bioaccumulate in any of the organ/tissues analyzed. Although eight radiolabeled metabolites were observed in urine, greater than 80% of the radioactivity in urine was represented by the diacid (DCA) and monoacid (MCA) metabolites. The remaining radiolabeled metabolites were identified as components of "peak A" and "peak B." It was estimated that between 4 and 6% of the administered dose was converted to malaoxon, the active ChE inhibiting metabolite of malathion.

4.1.3 Dose-Response

With the exception of the residential/occupational short- and intermediate-term inhalation exposure scenarios, all other doses and endpoints selected for the malathion risk assessment are based on RBC ChEI. For these inhalation exposure scenarios, the appropriate animal toxicology study (90-day inhalation study) showed effects on the respiratory epithelium at a dose lower than that which caused ChEI (see Section 4.6.6 for more information). Therefore, this section will discuss neurotoxicity and neurotoxicity biomarkers of exposure/effect only.

A number of neurotoxicity studies have been evaluated: an acute neurotoxicity study, a subchronic neurotoxicity study, a developmental neurotoxicity (DNT) study, and a comparative malathion ChE study in juvenile and adult rats. The executive summaries of all studies are in Appendix 2.0 unless otherwise noted.

In the acute neurotoxicity study (MRID 43146701), adult rats were given single oral doses of 0, 500, 1000, or 2000 mg/kg malathion in corn oil. Treatment-related effects on behavioral parameters were minimal at even the highest dose tested (2000 mg/kg), and plasma and RBC ChEI results were highly variable. In the subchronic neurotoxicity study (MRID 43269501), rats were fed malathion in the diet at doses of 0, 50, 5000, or 20,000 ppm (equivalent to 0, 4, 352, 1486 mg/kg/d for males and 0, 4, 395, 1575 mg/kg/d for females) for 90 days.

There were no effects on neurobehavioral parameters up to the highest dose tested (1486-1575 mg/kg/day); the ChEI NOAEL was 4 mg/kg/day, based on effects in all compartments at 352-395 mg/kg/day. The large dose spread between the low dose (4 mg/kg/d) and the mid-dose (~350 mg/kg/d) makes interpretation of this study difficult.

In a DNT study (MRID 45646401), malathion was administered to pregnant female rats via gavage at dose levels of 0, 5, 50, or 150 mg/kg/d from gestation day 6 to postnatal day (PND) 10. Offspring were gavaged with the same dose levels for 11 days (from PND 11 - PND 21). Findings at all dose levels included increased auditory startle reflex peak amplitude in both male and female weanlings (PND 23/24). At the mid- and high-dose levels, there was an increased incidence of slightly flattened gait in PND 60 males, and motor activity counts were decreased in female pups at PND 17 and 22. At the high-dose, additional treatment-related findings included post-dosing clinical observations on PND 17 and 18, and delayed surface righting reflex in PND 11 female pups. The neuropathological findings were not investigated for the low- and mid- dose groups. The maternal NOAEL for this study was based upon post-dosing salivation at the highest dose tested (150 mg/kg/day).

4.1.3.1 Comparative ChE Study

The comparative ChE study (MRID 45566201) is the critical study for endpoint selection of the acute and chronic reference doses and the incidental oral risk assessments. As such, a detailed discussion of this study is provided here.

In a comparative ChE study (MRID 45566201), malathion was administered to rats by gavage at dose levels of 0, 5, 50, 150, or 450 mg/kg bw/day for acute exposures and 0, 5, 50, and 150 mg/kg/day for repeated exposures. Treatment groups consisted of 9 pregnant dams treated from GD 6 through GD 20 and terminated; 10 pregnant dams treated from GD 6 through PND 10 followed by treatment of 1 male and 1 female offspring/litter on PND 11 through PND 21; and groups of 8 untreated dams whose offspring were treated on PND 11. In addition, groups of 16 adult male and female rats were given either a single dose or 11 consecutive days of dosing with malathion. The primary purpose of this study was to determine the effect of malathion on blood and brain ChE activities in adult male and female rats, pregnant dams, fetuses, and juvenile rats following both acute and repeated exposures. Overall, acute or repeated exposure to malathion resulted in statistically and biologically significant decreases in ChE activity in the blood and/or brain in dams, fetuses, weanling pups, and adult male and female rats. Fetuses exhibited less ChE inhibition compared to the dams. Offspring were more susceptible to ChEI following direct dosing in weanling pups. However, by PND 60 (39 days after the last dose), ChE activity levels in offspring were similar between control and treated groups.

NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response. A more robust approach for evaluating comparative sensitivity is the use of benchmark dose modeling. In order to provide a more robust estimate of the relative sensitivity of juvenile and adult animals exposed to malathion, a benchmark dose (BMD) analysis of the comparative ChE study was performed on RBC and brain ChE data from adult and juvenile animals (TXR0053251, 2005). The estimated dose at which 10% ChEI is observed (BMD_{10}) and the lower 95%

confidence intervals ($BMDL_{10}$) were estimated by fitting the ChE activity data to an exponential dose-response model using generalized nonlinear least squares. The exponential model was used in the Preliminary OP Cumulative Risk Assessment (USEPA, 2001) to determine relative potency factors and points of departure. The exponential model and statistical methods used to calculate the BMD_{10}s and $BMDL_{10}$s have been supported by the FIFRA Science Advisory Panel (FIFRA, 2002). Technical description of the statistical methods can be found in the cumulative hazard assessment of the OP Cumulative Risk Assessment 2006 Update (USEPA, 2006). Model fits and model parameters specific to this analysis can be found in TXR0053251 (2005). The exponential model used here can be downloaded at http://www.epa.gov/pesticides/cumulative/EPA_approach_methods.htm.

When considering the appropriate benchmark response level, the Agency considers statistical and biological considerations. The 10% response level used by OPP for brain ChE inhibition is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity and is a response level close to the background ChE. As part of EPA's Revised Cumulative Risk Assessment for the OPs, EPA performed a power analysis of brain ChE data available for more than 30 OPs (USEPA, 2002b). The results of the analysis indicated that most studies can reliably detect 10% brain ChE inhibition. Furthermore, in studies submitted to EPA for pesticide registration, clinical signs and behavioral effects have not been shown in studies with near and/or below 10% brain ChE inhibition. The registrant, Cheminova, submitted a statistical analysis which suggested that a 20% response level is statistically supportable due the variability associated with measurements of RBC ChE inhibition. However, the Agency notes that the estimated $BMDL_{20}$ of 29 mg/kg/day for RBC ChEI in young animals is between the doses of 5 and 50 mg/kg/d. At 50 mg/kg/day, motor activity and gait were affected. Thus, there is uncertainty that a PoD derived from the estimated $BMDL_{20}$ may not be protective of functional and behavioral effects in the young. As such, the Agency believes that based on the currently available information that a **$BMDL_{10}$** provides the most appropriate benchmark response level for the acute and chronic RfDs and the incidental oral risk assessments.

The results of the BMD analysis of the malathion comparative ChE data are provided in Table 4.1.3.1. Overall, the RBC ChE activity data from the adults and pups (PND11, PND21) fit the exponential equation well (see TXR00535251). The brain data from the PND21 pups fits the basic model well. Adult rat brain data are shallow (i.e., flat) and provide BMD estimates outside the tested dose range. RBC ChE inhibition in pups is a critical endpoint for malathion and the current analysis is sufficiently robust for developing PoDs and for evaluating relative sensitivity between juvenile and adult rats. For acute exposures, male PND 11 RBC ChE data provided the most sensitive endpoint: BMD_{10} =16.9 mg/kg and $BMDL_{10}$ = 13.6 mg/kg. For multiple exposures (11 consecutive days) exposures, male PND 21 RBC ChE data provided the most sensitive endpoint: BMD_{10} =10.8 mg/kg and $BMDL_{10}$ = 7.1 mg/kg. In addition to the estimates, the last two columns in Table 4.1.3.1 show the ratio of adult/pup BMD_{10} values - which is a direct estimate of the sensitivity of the young versus adult rats. The rat pups appear approximately eight times more sensitive than adults under the acute exposure conditions and approximately two times more sensitive under repeated dose exposure conditions.

Table 4.1.3.1 Benchmark Dose Analysis of Malathion Comparative ChE Data

Exposure Condition, Age, and ChE Compartment			BMD_{10} (mg/kg/d)		$BMDL_{10}$ (mg/kg/d)		Ratio Between Adults and Pups (Using BMD_{10} s)		
			Males	Females	Males	Females	ChE	Males	Females
Acute	Adult	RBC	491[1]	158	110	93.7	**RBC**	**ND[2]**	**8.7**
		Brain	315[1]	NA	170	NA			
	Pup	RBC	16.9	18.1	13.6	14.1	**Brain**	**ND**	**NA**
		Brain	24.6	23.6	22.7	17.8			
Repeated Dose	Adult	RBC	22.7	23.0	16.3	15.7	**RBC**	**2.1**	**1.7**
		Brain	889[1]	349[1]	311	160			
	Pup	RBC	10.8	13.8	7.1	8.5	**Brain**	**ND**	**ND**
		Brain	91.2	85.7	72.7	67.5			

[1]Results of BMD analysis are outside the dose range used in the study.

[2] ND = Not determined (one or more values are outside the range of doses used in the study).

4.1.3.2 21-Day Dermal Studies

Two dermal toxicity studies in rabbits provide the critical studies for extrapolation of dermal risk from occupational and non-occupational risk assessments. A BMD approach was also used to arrive at PoDs for dermal exposure scenarios in this risk assessment. In this case, adult rabbits were used in two separate studies (a 1989 study [MRID 41054201] and a 2006 study [MRID 46790501]). The dose levels in the 1989 study were 0, 50, 300, and 1000 mg/kg/d and in the 2006 study they were 0, 75, 100, 150, and 500 mg/kg/d. The data were

combined in a BMD analysis submitted by Cheminova (MRIDs 46755601 and MRID 46821701). EPA has evaluated the submitted analysis and considers it to be well-conducted and reasonable for use for PoD derivation. Table 4.1.3.2a presents the BMD and BMDL values for RBC ChEI at various response levels.

Table 4.1.3.2a: Summary of Red Blood Cell (RBC) Benchmark Dose Values from Malathion 21-Day Dermal Studies in Rabbits[1]

BMD	Sex	RBC BMDs for Each Parameter (all in mg/kg/day)		
		2006 Study	1989 Study	Combined
BMD_{10} (lower limit)	Males	104 (90.4)	79.3 (63.8)	121 (83.5)
	Females	80.7 (71.6)	84.1 (67.5)	102 (70.1)
BMD_{20} (lower limit)	Males	167 (143)	168 (135)	211 (149)
	Females	135 (119)	178 (143)	179 **(127)**

[1] Taken from Table 5.1 in MRID 46821701 (2006)

As noted above (Section 4.1.3.1), OPP has recognized a 10% response level for developing PoDs in cases where brain ChE inhibition is the critical toxic effect. This benchmark response level is based on extensive work done by OPP for the OP and *N*-methyl carbamate cumulative risk assessments. The Agency has not established a typical benchmark response level for RBC ChE inhibition but considers the 10% response level as a reasonable starting point. The Agency notes that RBC ChEI does not represent the target tissue for OPs but instead RBC ChE inhibition data is considered a surrogate for peripheral ChE inhibition when peripheral data are not available. As such, the Agency may consider alternative benchmark response levels on a chemical by chemical basis and only for those chemicals where sufficient information is available to ensure that a different response level is protective to functional and behavioral effects. The registrant, Cheminova, submitted a statistical analysis which suggested that a 20% response level is statistically supportable due the variability associated with measurements of RBC ChE inhibition. In determining whether a 20% RBC ChEI would be sufficiently protective of any possible neurotoxic effects (identified as clinical signs) an analysis was done by OPP on a number of malathion and malaoxon studies (see Table 4.1.3.2b).

Based on the information provided in Table 4.1.3.2b, the following conclusions have been made:

- For malaoxon, the lowest dose at which adults experienced clinical signs was 114 mg/kg/d (yellow anogenital staining – chronic rat oral study with malaoxon). RBC ChEI ranged from 44-65% over the 24 month period and brain ChEI ranged from 11-74%.
- For malathion, the lowest dose at which adults experienced clinical signs was 150 mg/kg/d. Cholinergic effects (salivation) were seen in two separate studies (the developmental neurotoxicity [DNT] and comparative cholinesterase studies with malathion) in treated dams only (exposure duration of ~30 days). RBC ChEI at that dose was 51% and there was no brain ChEI.
- For malathion, there were no clinical signs in either of the two 21-day dermal toxicity studies in rabbits (dosing up to 1000 mg/kg/d). However, statistically significant RBC and brain ChEI was observed at 75 mg/kg/d (17%) and 500 mg/kg/d (22%), respectively.

Table 4.1.3.2b: Clinical Signs and ChEI: Malathion and Malaoxon Studies					
Study	**Duration**	**Dosing (mg/kg/d)**	**Clinical Signs[1]**	**RBC ChEI[1,2]**	**Brain ChEI[1,2]**
MRID 45566201 (Comparative ChE study with malathion)	Acute	0,5,50,150, 450	P – tremors (450) A – None	P = *61 to* ***72*** A = *17 to 25*	P = ***84*** A - None
	Repeated (11 days)	0,5,50,150	P – None D – salivation (150) A - None	Fe= *19* P = *67 to 68* D= ***51*** A = *43 to 48*	Fe= None P= *16* D= None A = None
MRID 45646401 (Dev. Neurotox Study)	Repeated (~30 days in dams; pups directly for 11 days)	0, 5, 50, 150	P –tremors, prostration, hypoactivity (150) D = salivation (150)	Not measured directly – measurements made with another group of animals in comparative ChE study (MRID 45566201)	
MRID 45646401 (Neurotox.)	Acute	0, 500, 1000, 2000 (gavage)	A = decrease in motor activity (2000)	F = ***39*** M = **40**	A = None
MRID 43269501 (Neurotox)	Repeated (90 days)	M = 0, 4, 352, 1486 F = 0, 4, 395, 1575 (diet)	A = yellow anogenital staining (1486/1575)	A = ***53 to 68***	A = **11 to *50***
MRID 41054201 (Dermal toxicity in rabbits)	Repeated (21-days)	0, 50, 300, 1000	None	A = *73 to 75*	A= *41 to 66*
MRID 46790501 (Dermal toxicity in rabbits)	Repeated (21-days)	0, 75, 100, 150, 500	None	M = *61* F = *69*	M = *22* F = *23*
MRID 43942901 (Chronic study in rats – malathion)	Repeated (24 months)	M = 0, 4, 29, 359, 739 F = 0, 5, 35, 415, 868 (diet)	A = yellow anogenital staining throughout the study (high dose only)	A[3] = 52-66	A= 15 to 67
MRID 43975201 (Chronic study in rats – malaoxon)	Repeated (24 months)	M = 0, 1, 57, 114 F = 0, 1, 68, 141 (diet)	A = yellow anogenital staining throughout the study (high dose only)	A[3] = 44 to 65,	A = 11 to 78

[1] P = pups; A = adults; Fe = fetus; D = dams, F = females; M = males.

[2] Values listed are % ChEI by compartment (either RBC or brain). Only the highest values are presented at the highest dose. When ranges are given, they represent male and females; in other cases male and female values are reported separately. Bolded values represent inhibition at which listed clinical signs were observed. Italicized values represent inhibition that was statistically significant.

[3] In this case, ranges represent percent inhibition both for males and females and across all time points measured (3, 6, 12, and 24 months).

Thus, the Agency has concluded that a 20% response level for RBC ChEI in the *malathion adult animal data set* is protective of obvious clinical signs/symptoms in adult animals following both oral (acute and repeated

dose) and dermal (repeated dose) exposures. Moreover, the Agency prefers route specific studies for extrapolating risk. Pharmacokinetic profiles from different exposure routes can vary. Two well-conducted dermal toxicity studies are available for malathion and are the most appropriate studies for extrapolating dermal risk. The Agency has further concluded that for dermal risk assessments, a $BMDL_{20}$ of 127 mg/kg/day scenarios is an appropriate PoD.

4.2 FQPA Hazard Consideration

4.2.1 Adequacy of the Toxicity Database

The toxicology database for malathion is adequate to assess potential risk to infants and children, although it is acknowledged that some residual uncertainties remain. The database that address potential differences between the young and the old are: prenatal developmental toxicity studies in rats and rabbits, a two-generation reproductive toxicity study in rats, an acute neurotoxicity study in rats, a subchronic neurotoxicity study in rats, a developmental neurotoxicity study in rats (with a supplemental range-finding study), and a comparative ChE study in adult and immature rats. Executive summaries of these studies are provided in Appendix 2.0. (NOTE: Cheminova recently submitted an acute rat comparative ChE study with malaoxon; however, it is unacceptable and must be repeated to comply with the DCI [TXR 0053748]. This study is expected to further inform susceptibility of the young).

A full complement of neurotoxicity studies has been submitted to the Agency for malathion. There was no evidence of organophosphate-induced delayed neurotoxicity in hens following a single 1008 mg/kg dose of malathion (MRID 40939302). A number of studies in the peer-reviewed literature have also addressed various aspects of the neurotoxic potential of malathion (MRID 45642901 [Desi, et al., 1976]; MRID 45642902 [Kurtz, 1977]; MRID 45045001 [Ehrich, et al., 1993]; and MRID 45046301 [Mendoza, 1976]). The results of these studies are consistent with the results of the comparative ChE study and the developmental neurotoxicity study with malathion, in that they demonstrate evidence of behavioral effects at low doses and increased susceptibility of the immature individual.

Based on the available data, there is evidence that following acute or repeated dose exposure conditions to malathion young animals are more susceptible compared to adult animals. For some exposure scenarios, data from pups is used directly for PoD determination and thus the FQPA factor is removed. For those scenarios where data from adult animals is used for PoD determination, the FQPA factor is retained to account for potential sensitivity to the young (see Table 4.7).

- **No susceptibility** was observed in the **prenatal developmental toxicity study in rats**. In that study, the maternal NOAEL (400 mg/kg/day) was based upon reduced mean body weight gains and reduced mean food consumption during the period of treatment at the maternal LOAEL of 800 mg/kg/day. No developmental abnormalities were observed up to the highest dose tested (800 mg/kg/day). ChE activity was not measured in dams or fetuses in this study (MRID 41160901).

- In the **prenatal developmental toxicity study in rabbits**, the maternal NOAEL was 25 mg/kg/day, based on reduced mean body weight gains during the treatment period (gestation days 6-18) at the LOAEL of 50 mg/kg/day. The developmental NOAEL was also 25 mg/kg/day, based upon a biologically significant increase in the incidence of resorptions at 50 mg/kg/day. The fetal finding (increased fetal death) is considered evidence of increased **qualitative susceptibility**. ChE activity was not measured in the doses or fetuses in this study (MRID 00152569).

- In the **two-generation reproduction study in rats**, the parental toxicity NOAEL was 5000 ppm (394 mg/kg/day in males and 451 mg/kg/day in females) and the parental toxicity LOAEL was 7500 ppm (612 mg/kg/day in males and 703 mg/kg/day in females) based on decreased body weights in F0 females during gestation and lactation and on decreased body weights in F1 males and females during the pre-mating period. The developmental offspring NOAEL was 1700 ppm (131 mg/kg/day in males and 153 mg/kg/day in females) and the developmental toxicity LOAEL is 5000 ppm (394 mg/kg/day in males and 451 mg/kg/day in females) based on decreased pup body weights during the lactation period in F1A and F2B pups. This profile is evidence of **quantitative susceptibility** in the offspring (MRID 41583401). [NOTE: However, it is noted that these doses are large because they represent dietary exposures as opposed to gavage doses in other studies]

- In the **developmental neurotoxicity study in rats**, the maternal NOAEL was 50 mg/kg/day, based on increased incidences of post-dosing salivation (and RBC ChEI, which was observed in the companion ChE study) at the LOAEL of 150 mg/kg/day. The offspring NOAEL for this study was not identified. The offspring LOAEL was identified at the lowest dose tested (5 mg/kg/day), based upon increased auditory startle reflex peak amplitude in PND 23/24 males and females. This auditory startle effect was not corroborated by other (DNT parameter) effects at this dose and thus its relevance and importance to the risk assessment are questionable. However, it is an important part of the hazard characterization. OPP has identified RBC ChEI as measured in the companion comparative ChE study as the PoD for risk assessment purposes. These findings are considered evidence of increased **quantitative susceptibility** (MRID 45446401).

- In the **range-finding developmental neurotoxicity study in rats**, although NOAELs were not established (due to the disparity of dosing regimens within the study), it was noted that RBC ChEI was observed at the lowest dose tested (7.5 mg/kg/day) for PND 21 offspring that had been directly dosed from PND 11-21, while for dams that had been dosed from GD6-20, RBC ChE was not inhibited at a dose level of 150 mg/kg/day. These findings are evidence of increased **quantitative susceptibility** and support the findings observed in other more rigorous studies (MRID 45642901).

- In the **comparative ChE study**, ChE activity measures following acute or repeated gavage doses of malathion, demonstrated that juvenile rats are more susceptible than adults following direct dosing (MRID 45566201). **Quantitative susceptibility** was therefore observed.

- Also in the **comparative ChE study, no susceptibility** was demonstrated for RBC ChEI in fetuses (inhibited at 750 mg/kg/d) examined at birth (GD 20) when compared to dams (inhibited at 75 mg/kg/d) exposed from GD6-20 (see executive summary in Appendix 2.0 for preliminary dose-range finding DNT study results [MRID 456270010]).

Using NOAELs/LOAELs from the developmental, two-generation and DNT studies, the range in pup-to-adult sensitivity is 0.5 - 30 fold. The only case where the adults were more sensitive than pups was in the rat developmental study (ChE activity was not measured). In the rabbit developmental study, there was no apparent quantitative susceptibility difference. However, in using a benchmark dose (BMD) approach - which utilizes the complete dose-response curve on a given effect in a study - the range in pup-to-adult sensitivity is 2.1 - 8.7 fold using the comparative ChE study. This approach is more appropriate because the NOAELs/LOAELs are reflective of dose selection. Because the BMD analysis allows for the use of all the data points, it is a more appropriate approach to determining the enhanced susceptibility of pups versus adults where the two groups were studied. Table 4.2.1 below summarizes this analysis.

Table 4.2.1 Determination of Pre and/or Post-Natal Susceptibility

Study	Adult	Pup	Ratio of Adult/Pup Hazard Value
Comparative ChE (rat) - acute exposure scenario (MRID 45566201)	BMD_{10} = 158 mg/kg/d (RBC ChEI)	BMD_{10} = 18.1 mg/kg/d (RBC ChEI)	**8.7**
Comparative ChE (rat) - chronic exposure scenario (MRID 45566201)	BMD_{10} = 23 mg/kg/d (RBC ChEI)	BMD_{10} = 13.8 mg/kg/d (RBC ChEI)	**2.1**

4.2.2 Degree of Concern Analysis and Residual Uncertainties for Pre-and/or Post-natal Susceptibility

Since there is evidence of increased susceptibility of the young following exposure to malathion in the developmental rabbit study, the rat reproductive study, the range-finding and main developmental neurotoxicity studies, and the companion comparative ChE study in rats, HED performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HED determines whether these residual concerns can be addressed by a FQPA safety factor and, if so, the size of the factor needed.

Prenatal developmental toxicity study in rabbits (MRID 00152569): This prenatal developmental toxicity study in rabbits was considered to be adequate for the assessment of effects of *in utero* exposure to rabbit fetuses. The NOAEL was well-characterized; the incidences of fetal resorptions were similar at the mid- and

high-doses in this study, suggesting a plateau. At higher doses, maternal toxicity prevented evaluation of fetal effects. This study did not measure ChE activity. There was **no residual uncertainty** identified for this study.

Two-generation reproduction study in rats (MRID 41583401): The reproduction study was well-conducted and adequately assessed hazard to adults and offspring within the limitations of the protocol; the dose response was well-characterized. The study demonstrated the wide differences in gross toxicological response between offspring and adults to dietary malathion exposure. The NOAELs for offspring response in this reproduction study (131/153 mg/kg/day for M/F) were much higher than the BMDL for offspring from the comparative ChE study (7.1 mg/kg/day for the repeated dose exposures) and the NOAEL from the chronic carcinogenicity study in rats (3 mg/kg/day), which were used to select endpoints and doses for risk assessment for malathion (see Table 4.7). **No residual uncertainty** was identified for this study.

The **developmental neurotoxicity study** (MRID 45646401) and the companion **comparative ChE study** (MRID 45566201) were found to be both well-conducted and acceptable. Appropriate and sensitive endpoints were evaluated in the study (e.g., ChEI in 3 compartments, and guideline-specified neurobehavioral and neuropathological evaluations), and a definitive dose-response was established. BMDLs of 13.6 mg/kg/d for acute exposure and 7.1 mg/kg/d for repeated-dose exposure were estimated in the comparative ChE study. A NOAEL was not established for neurobehavioral effects in the DNT study (LOAEL of 5 mg/kg/d [lowest dose tested] for increase in auditory startle reflex peak amplitude). There are several reasons why there is **a low concern for residual uncertainty** for this effect: (1) the auditory startle effect appears to be possibly treatment-related, but not dose-related; (2) other DNT parameters (motor activity, learning and memory, and neuropathology effects) were not observed at this low dose to corroborate developmental neurotoxicity; and (3) using the BMDL of 7.1 for the well-characterized RBC ChEI effect is a reasonable risk assessment approach. Thus, the endpoints and doses selected for acute, short-term, intermediate-term, and chronic risk assessment for malathion, and the uncertainty factors applied to those endpoints/doses, are expected to adequately address the lack of a NOAEL in the DNT study.

- **Concerns for possible latent neurobehavioral effects observed in the DNT study.** Although the last day of dosing was PND 21 in the DNT study, neurobehavioral effects were seen at study termination (i.e., at least 39 days post-treatment) in adult offspring. These included slightly flattened gait in PND 60 males at 50 and 150 mg/kg/day (number of animals with flattened gait were 0, 1, 3, and 6 for the control, 5, 50, and 150 mg/kg/d dose groups, respectively). At the time of these observations, ChE activity had fully recovered. Overall, there is a low degree of residual concern.

Thus, overall, there is a low degree of residual concern.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

There is no increased susceptibility expected to females of child-bearing age. Effects observed in the rat and rabbit developmental studies showed reduced body weight gains with NOAELs of 400 and 25 mg/kg/d, respectively. The aRfD for the general population is lower and thus would be protective of this population group.

4.4.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Comparative ChE study in rats

MRID No: 45566201

Executive Summary: In a comparative ChE study (MRID 45566201), malathion (96.0% a.i., batch/lot # 9010501) was administered to groups of Crl:CD® (SD) IGS BR rats by gavage at dose levels of 0, 5, 50, 150, or 450 mg/kg bw/day for acute exposures and 0, 5, 50, and 150 mg/kg/day for repeated exposures. Treatment groups consisted of 9 pregnant dams treated from GD 6 through GD 20 and terminated; 10 pregnant dams treated from GD 6 through PND 10 followed by treatment of 1 male and 1 female offspring/litter on PND 11 through PND 21; and groups of 8 untreated dams whose offspring were treated on PND 11. In addition, groups of 16 adult male and female rats were given either a single dose or 11 consecutive days of dosing with malathion. The primary purpose of this study was to determine the effect of malathion on blood and brain ChE activities in adult male and female rats, pregnant dams, fetuses, and juvenile rats following both acute and repeated exposures.

An acute 450 mg/kg dose of malathion resulted in tremors in 5 of 16 PND 11 pups at 1-2 hours post-treatment, as well as moribundity in one pup; no clinical observations were noted in young adults at this dose. Repeated doses of malathion resulted in post-dose salivation at 150 mg/kg/day in dams during gestation and/or lactation, but did not adversely affect survival, clinical observations, body weight, body weight gain, brain weight, or gross pathology in adult male and female rats, juveniles, or fetuses. Additionally, reproductive performance, gestation length, sex ratio, pre- and postnatal viability were unaffected.

Acute or repeated exposure to malathion resulted in statistically and biologically significant decreases in ChE activity in the blood and/or brain in dams, fetuses, weanling pups, and adult male and female rats. In pups, RBC effects were noted at 5 mg/kg in males and 50 mg/kg in females following single dose acute exposures, and at 5 mg/kg/day in both sexes after repeated exposures. Following a single dose to young adults, effects were observed at 450 mg/kg, while after 11 or 14 doses, effects were observed at 50 mg/kg/day in young adults and pregnant dams. By PND 60 (39 days after the last dose), ChE activity levels in offspring were similar between control and treated groups.

This description is the executive summary for this study. This study is classified **Acceptable/Non-guideline** for the determination of plasma, RBC, and brain ChE activities following treatment with malathion in adult, fetal, and juvenile rats.

Dose and Endpoint for Establishing aRfD: Using the acute-dose portion of this study, a benchmark dose value was estimated. The BMDL to be used is based on RBC ChEI in male pups and is **13.6 mg/kg**. The BMDL is the lower 95% confidence limit on the estimated mean RBC ChEI 10% effect level.

Uncertainty Factor (UF): An UF of 100 will be used (10x for interspecies extrapolation and 10x for intraspecies variation). Susceptibility of the young is already accounted for because they were part of the experimental group and it is what the dose and endpoint are based on.

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for this exposure scenario.

Acute RfD for General Population = $\frac{13.6 \text{ mg/kg } (BMDL_{10})}{100 \text{ (UF)}} = 0.14 \text{ mg/kg}$

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Comparative ChE study in rats (repeated dose portion)

MRID No: 45566201

Executive Summary: In a comparative ChE study (MRID 45566201), malathion (96.0% a.i., batch/lot # 9010501) was administered to groups of Crl:CD® (SD) IGS BR rats by gavage at dose levels of 0, 5, 50, 150, or 450 mg/kg bw/day for acute exposures and 0, 5, 50, and 150 mg/kg/day for repeated exposures. Treatment groups consisted of 9 pregnant dams treated from GD 6 through GD 20 and terminated; 10 pregnant dams treated from GD 6 through PND 10 followed by treatment of 1 male and 1 female offspring/litter on PND 11 through PND 21; and groups of 8 untreated dams whose offspring were treated on PND 11. In addition, groups of 16 adult male and female rats were given either a single dose or 11 consecutive days of dosing with malathion. The primary purpose of this study was to determine the effect of malathion on blood and brain ChE activities in adult male and female rats, pregnant dams, fetuses, and juvenile rats following both acute and repeated exposures.

An acute 450 mg/kg dose of malathion resulted in tremors in 5 of 16 PND 11 pups at 1-2 hours post-treatment, as well as moribundity in one pup; no clinical observations were noted in young adults at this dose. Repeated doses of malathion resulted in post-dose salivation at 150 mg/kg/day in dams during gestation and/or lactation, but did not adversely affect survival, clinical observations, body weight, body weight gain, brain weight, or gross pathology in adult male and female rats, juveniles, or fetuses. Additionally, reproductive performance, gestation length, sex ratio, pre- and postnatal viability were unaffected.

Acute or repeated exposure to malathion resulted in statistically and biologically significant decreases in ChE activity in the blood and/or brain in dams, fetuses, weanling pups, and adult male and female rats. In pups, RBC effects were noted at 5 mg/kg in males and 50 mg/kg in females following single dose acute exposures, and at 5 mg/kg/day in both sexes after repeated exposures. Following a single dose to young adults, effects were observed at 450 mg/kg, while after 11 or 14 doses, effects were observed at

50 mg/kg/day in young adults and pregnant dams. By PND 60 (39 days after the last dose), ChE activity levels in offspring were similar between control and treated groups.

This description is the executive summary for this study. This study is classified **Acceptible/Non-guideline** for the determination of plasma, RBC, and brain ChE activities following treatment with malathion in adult, fetal, and juvenile rats.

Dose and Endpoint for Risk Assessment: Using the repeated-dose portion of this study, a benchmark dose value was estimated. The BMDL to be used is based on RBC ChEI in male pups and is **7.1 mg/kg/d**. The BMDL is the lower 95% confidence limit on the estimated mean RBC ChEI 10% effect level.

Uncertainty Factor (UF): An UF of 100 will be used (10x for interspecies extrapolation and 10x for intraspecies variation). Susceptibility of the young is already accounted for because they were part of the experimental group and it is what the dose and endpoint are based on.

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for this exposure scenario.

$$\textbf{Chronic RfD} = \frac{7.1 \text{ mg/kg/d } (BMDL_{10})}{100 \text{ (UF)}} = 0.07 \text{ mg/kg}$$

4.4.4 Incidental Oral Exposure (Short [1-30 days] and Intermediate [1-6 months] Term)

Study Selected: Comparative ChE study in rats

MRID No: 45566201

Executive Summary: See above under Chronic Reference Dose (Section 4.4.3) for executive summary

Dose and Endpoint for Risk Assessment: Using the repeated-dose portion of this study, a benchmark dose value was estimated. The BMDL to be used is based on RBC ChEI in male pups and is **7.1 mg/kg/d**. The BMDL is the lower 95% confidence limit on the estimated mean RBC ChEI 10% effect level.

Uncertainty Factor (UF): An UF of 100 will be used (10x for interspecies extrapolation and 10x for intraspecies variation). Susceptibility of the young is already accounted for because they were part of the experimental group and it is what the dose and endpoint are based on.

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for this exposure scenario.

4.4.5 Dermal Exposure (Short [1-30 days], Intermediate [1-6 months], and Long-Term [>6 months])

Study Selected: Benchmark Dose Meta-Analysis of Two 21-Day Dermal Study in Rabbits

MRID No: 41054201 (1989)

Executive Summary: In a 21-day dermal toxicity study in rabbits groups of 6 male and 6 female New Zealand rabbits were treated dermally with undiluted technical malathion (94% a.i.) at dose levels of 0, 50, 300 or 1000 mg/kg/day for 6 hours/day, 5 days/week for 3 weeks. Assessments included clinical signs and mortality, dermal effects, food consumption, body weight, hematology and clinical chemistry (including ChE activity of plasma, erythrocytes and brain). Gross necropsy was performed on all animals. The weight of the liver, kidneys, gonads and adrenals were recorded. Histopathology was performed on the following tissues for the high dose and control groups: adrenals, kidneys, liver, ovaries, skin (treated area), skin (mammary area), testes/epididymis and gross lesions.

With the exception of a dose-related decreased ChE activity in both males and females at 1000 and 300 mg/kg/day, no treatment-related toxic effects (other than one possible mortality in the 1000 mg/kg/day group attributable to acute mucoid gastroenteritis) were observed in the study. No clinical signs were noted and there were no treatment-related changes in body weights, food consumption, hematology, clinical chemistries, gross necropsies, organ weights or histopathology. Dermal reactions at the application site were not observed. For males, the NOAEL and LOAEL, respectively, for ChEI were considered to be the following: for plasma inhibition, 50 and 300 mg/kg/day (-13%); for RBC inhibition, 50 and 300 mg/kg/day (-18%); for brain (cerebrum) inhibition, 300 and 1000 mg/kg/day (-65%); and for brain (cerebellum) inhibition, 300 and 1000 mg/kg/day (-41%). For females, the comparable NOAELs and LOAELs were the following: for plasma inhibition, 50 and 300 mg/kg/day (-17%); for RBC inhibition, 50 and 300 mg/kg/day (-26%); for brain (cerebrum) inhibition, 50 and 300 mg/kg/day (-19%); and for brain (cerebellum) inhibition, 300 and 1000 mg/kg/day (-49%).

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a 21-day dermal study **(870.3200)** in the rabbit.

MRID No: 46790501 (2006)

Executive Summary: In a 21-day dermal toxicity study, malathion (96%a.i.) was applied to the shaved skin of 10 New Zealand White rabbits per sex per dose at the following dose levels (daily exposures for six hours/day over a 21-day period): 0, 75, 100, 150, and 500 mg/kg/day. All rabbits survived until scheduled sacrifice with the exception of one female rabbit in the 150 mg/kg/day dose group which was sacrificed on Day 11 which showed the following clinical signs before sacrifice: erythema, flaking, red perivaginal substance and swollen vagina. At necropsy the only finding was a dark red uterus. The death was not considered treatment-related.

There were no treatment-related clinical observations or effects on body weight, food consumption, hematology, clinical chemistry, organ weight or pathology. Dermal irritancy was observed in all dosed groups (except control) and the severity increased with dose.

Red blood cell (RBC) cholinesterase activity (ChE) was significantly reduced in males at all dose levels (17.5%, 18.4%, 19.4%, and 60.9% at 75, 100, 150, and 500 mg/kg/d, respectively). The females had significant decreases in RBC ChE at the top two dose levels (24.2% and 71.2% at 150 and 500 mg/kg/d, respectively). Plasma (32-37%) and brain (22-23%) ChE were significantly reduced in both males and females at the highest dose only (500 mg/kg/d).

There was no dermal irritation NOAEL, effects were observed at all doses tested and severity increased with increasing dose.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a 21-day dermal study **(870.3200)** in the rabbit.

Dose and Endpoint for Risk Assessment: Using data from both 21-day dermal studies, a benchmark dose value was estimated. The $BMDL_{20}$ to be used is based on RBC ChEI in and is **127 mg/kg/d**. The BMDL is the lower 95% confidence limit on the RBC ChEI 20% effect level.

Uncertainty Factor (UF): The UFs will be different for adults and children. A UF of 100 will be used for adults (10X for interspecies variation and 10x for intraspecies variation). For children, a UF of 1000 will be used (10X for interspecies variation, 10x for intraspecies variation, and $10X_{FQPA}$).

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for this exposure scenario. Use of 21day studies for the long-term exposure scenario is reasonable given the evidence that RBC ChEI reaches a steady-state in organophosphate-treated animals after approximately 21 days (U.S. EPA, 2002). There are no malathion – or malaoxon - developmental studies using either the dermal route of exposure. Thus, unlike the oral route of exposure, a comparison between pregnant and non-pregnant animals for the dermal route cannot be done. However, there is no concern for women of child-bearing age following dermal exposure given the following:

- The observed susceptibility differences between young and old are a result of postnatal exposures and ChEI data from gestational only exposures indicate that fetuses are less sensitive than the mother at birth.
- The animal species on which the PoD is based is the rabbit. The oral developmental studies suggest that the rabbit is more sensitive than the rat and so using the rabbit for this endpoint is conservative and probably protective of any possible sensitivity.
- In the dermal studies with malathion, there were no gender differences in response to exposures. (If females were more sensitive, then there might be some concern for women of child-bearing age).
- Finally, the oral exposure route data suggest there is no enhanced sensitivity in pregnant animals versus non-pregnant animals and there is no reason to believe that this would be route-specific.

4.4.6 Inhalation Exposure (Short and Intermediate-Term)

Study Selected: 90-Day Inhalation Study in Rats

MRID No: 43266601

Executive Summary: In a subchronic (13-week) inhalation study, groups of Sprague-Dawley rats (15/sex/concentration) were exposed in whole body inhalation chambers to malathion (96.4%) at aerosol concentrations of 0, 0.1, 0.45, or 2.01 mg/L for 6 hours/day, 5 days/week for 13 weeks. Assessments included those of clinical signs, body weight, food consumption, ophthalmoscopic examinations, hematology, clinical chemistry (including ChE activity of plasma, erythrocytes and brain), urinalysis and gross and histopathology of Guideline required tissues. Treatment had no effects on survival, body weights or food consumption. Cholinergic signs observed at 2.01 mg/L and sporadically in a few animals at the lower doses included red staining of the urogenital areas, excess salivation and ungroomed oily fur.

Treatment-related histopathological lesions were seen in the nasal cavity and the larynx of both sexes of rats at all concentrations tested. The lesions in the nasal cavity were characterized as slight to moderate degeneration and/or hyperplasia of the olfactory epithelium which was locally extensive. The lesions of the larynx were characterized as epithelial hyperplasia, with squamous keratinization occurring in some rats. In addition, the olfactory/respiratory epithelial junction was severely affected in most animals.

For systemic toxicity, a NOAEL was not established and the LOAEL was 0.1 mg/kg/day based on histopathologic lesions of the nasal cavity and larynx. Inhibition of plasma and red blood cell ChE activity was observed in female rats at 0.45 mg/L and above. In male rats, inhibition of ChE activity was observed in plasma at 2.01 mg/L and in red blood cells at $\geq$ 0.45 mg/L. Inhibition of brain ChE activity was seen only at the highest concentration. **For ChEI, a NOAEL was established for plasma and red blood cells at 0.1 mg/L with a LOAEL of 0.45 mg/L**.

This subchronic inhalation toxicity study in the rat is classified **Acceptable/guideline** for a subchronic inhalation toxicity study in the rodent **(870.3465)**.

Dose and Endpoint for Risk Assessment: There was no NOAEL observed in this study. The lowest dose (0.1 mg/L) is a LOAEL based on histopathological lesions of the nasal cavity and the larynx. This endpoint was selected because the lesions were noted at a dose lower than that which resulted in ChEI and the lesions were observed in both short- and long-term studies

Uncertainty Factor (UF): A UF of 1000 will be used (10X for interspecies variation, 10x for intraspecies variation, and a 10X FQPA factor for the lack of a NOAEL and for the severity of the effect seen at the LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: The effect of concern in this study is a portal-of-entry effect that is not likely to be age-dependent or age-sensitive. There are no malathion – or malaoxon - developmental studies using the inhalation route of exposure. Thus, unlike the oral route of exposure, a comparison between pregnant and non-pregnant animals for the inhalation route cannot be done. However, there is no concern for women of child-bearing age following inhalation exposure given the following:

- The observed susceptibility differences between young and old are a result of postnatal exposures and ChEI data from gestational only exposures indicate that fetuses are less sensitive than the mother at birth.
- In the inhalation studies with malathion, there were no gender differences in response to exposures. (If females were more sensitive, then there might be some concern for women of child-bearing age).
- Finally, the oral exposure route data suggest there is no enhanced sensitivity in pregnant animals versus non-pregnant animals and there is no reason to believe that this would be route-specific.

4.4.7 Toxicity Adjustment Factor for Malaoxon

As described in 6.1.2 and 6.3.4 exposure sections below, under certain environmental conditions, humans may be directly exposed to malaoxon following applications of malathion. As the oxon metabolite of malathion, malaoxon is a more potent ChE inhibitor. EPA has performed BMD modeling to evaluate relative potency for malathion and malaoxon and to estimate a toxicity adjustment factor (TAF) to account for the increased potency of malaoxon in estimates of risk.

Ideally, TAFs are needed for acute/short-term and 'steady state' (chronic, intermediate- and long-term) exposure durations. As shown in the OP cumulative risk assessment, for most OPs, cholinesterase inhibition reaches steady state following approximately 21 days of oral exposure (USEPA, 2002). Once steady state is reached BMD values are generally consistent and do not change with longer exposures. At the present time, two malaoxon studies are available which provide blood and brain cholinesterase data—14-day rat study (MRID no. 46080001) and 2-year chronic rat study (MRID no. 43975201); no acceptable studies evaluating acute ChE inhibition of malaoxon are currently available. Thus, no appropriate data are available to calculate an acute TAF. EPA has published a data call-in notice for a comparative cholinesterase study in juvenile rats in malaoxon and malathion. This study will include measurements of brain and RBC ChE following acute and multiple exposures to malaoxon and malathion.

As described in the guidance document for cumulative risk assessment (USEPA, 2002), comparisons of toxic potency should be made using a uniform basis of comparison, by using to the extent possible a common response derived from a comparable measurement methodology, species, and sex for all the exposure routes of interest. Dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no or low observed adverse effect levels) for determining relative toxic potency and calculating TAFs. NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response across different chemicals. In the present analysis, OPP has collaborated with Dr. Woodrow Setzer of EPA's National Center for Computational Toxicology (NCCT) to perform BMD modeling in the evaluation of the relative potency of malathion and malaoxon. The modeling procedure used in this analysis is very similar to the exponential model and statistical procedures being used to estimate cumulative risk to the OPs which has been supported by the FIFRA Scientific Advisory Panel (FIFRA SAP; 2002). A technical description of the methods used here along with dose-response curves and information regarding fit can be found in TXR no. 0052951 (Lowit and Setzer, 2005). (Revisions involved corrections to the dose levels used in the 2-year studies.) The revised analyses can be found in HED's Response to Comments (TXR0054040) document.

The steady state TAF for male RBC cholinesterase is **61** with upper and lower confidence limits of 170and 22, respectively (Table 4.4.7 below). The TAF calculated for the male data is similar to the value estimated for the female rats. In the absence of acute oral studies in addition to dermal and inhalation studies with malaoxon, the TAF of **61x** calculated from oral studies is applicable to residues of malaoxon for risk assessment reflecting all exposure durations, routes, and scenarios.

Table 4.4.7 Benchmark dose calculations (BMD_{10}) for RBC cholinesterase inhibition in adult rats with malathion and malaoxon.

	MALE	FEMALE
Malathion	36.5	47.8
Malaoxon	0.83	0.78
'Steady State' Toxicity Adjustment Factor	**61**	44

4.4.8 Margins of Exposure

The target Margins of Exposure (MOEs) for residential and occupational exposure and risk assessment are as follows:

Table 4.4.8 Target Margins of Exposure for Residential and Occupational Exposure and Risk

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (>6 Months)
Occupational Exposure			
Dermal	100		
Inhalation	1000		NR
Residential Exposure			
Incidental Oral	100	NR	NR
Dermal	1000 (children) 100 (adults)		NR
Inhalation	1000		NR

NR-not required.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, an aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. For the toxicity endpoints used the aggregate risk assessment see Table 4.7.

4.4.10 Classification of Carcinogenic Potential

The database for mutagenicity is considered adequate and no further testing is required at this time. A weak positive effect was reported in a recently submitted mouse lymphoma study for compliance with PR Notice 86-5 mammalian cell gene mutation assay (MRID 45554501). Findings from this acceptable guideline study indicated that increases in the mutation frequency were observed over a narrow range of high concentrations (2200-2000 µg/mL +S9) that were cytotoxic [(11-36%) relative total growth (RTG)]. Other guideline studies for malathion were acceptable and negative. The weak positive effect in this study could be due to the metabolite, malaoxon which was positive in this test system only in the absence of S9 activation and only at cytotoxic concentrations (150 nL/mL–Trial 1 and 200 nL/mL –Trial 2) that caused 15-20% RTG. Although more electrophilic than malathion, malaoxon is not carcinogenic in rats. However, it is equally likely that the response observed in the above mentioned mouse lymphoma assay may be due to malathion. Nevertheless, the response is weak and is typical of the effect induced by weak or equivocal mutagens in this test system.

Although there have been reports of positive genotoxicity in the literature, the Cancer Assessment Review Committee (CARC, 28-April-2000) cautioned that data from the open literature should be interpreted with care because positive clastogenic results were found in studies that were compromised by a lack of purity information on the test article, testing with commercial or 50% malathion formulations or finding positive responses at precipitating concentrations or at cytotoxic concentrations. Still others had technical shortcomings that precluded drawing meaningful conclusions from the data. In addition, studies showing induction of chromosome aberrations at cytotoxic levels (60% reduced cell confluence) in conjunction with the increased occurrence of unstable chromosome aberrations (e.g., chromatid and chromosome breaks), which generally lead to cell death, were not considered to be adequate evidence of a positive response or supportive of a direct DNA reactive mutagenic capability of the agent.

In August 2000, an external scientific peer review meeting of the FIFRA Scientific Advisory Panel (SAP) met to review a set of scientific issues, including mutagencity, being considered by the Agency on malathion. SAP agreed with the Agency's interpretation of the mutagenicity data, concluding that "There was no evidence for mutagenic concern" (SAP, 2000). At this meeting, two published comet assays (MRID 45686901 and 45686902) were submitted to the SAP for comment.

HED has concluded that there is weak evidence of a mutagenic effect in mammalian cells at high and cytotoxic concentrations. However, the weight of the evidence from both the guideline studies and the open literature do not support a mutagenic concern for malathion. Similarly, there is no convincing correlation to support the use of SAR to predict the possible mutagenicity and carcinogenicity of this group of compounds.

The database for carcinogenicity is considered complete. The relevant data on the carcinogenic potential of malathion was evaluated by the Cancer Assessment Review Committee (CARC) (2-Feb-2000 and 28-April-2000). In accordance with the EPA *Proposed Guidelines for Carcinogen Risk*

Assessment (July 1999), the Committee classified malathion as **"suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential"** by all routes of exposure. This classification was based on the following factors: (i) occurrence of liver tumors in male and female B6C3F1 mice and in female Fischer 344 rats only at excessive doses; (ii) the presence of a few rare tumors (oral palate mucosa - female, and nasal respiratory epithelium - male and female) in Fischer 344 rats. With the exception of one nasal and one oral tumor in female rats, all other tumor types were determined to occur at excessive doses or were unrelated to treatment with malathion. These tumors cannot be distinguished as either treatment related or due to random occurrence; (iii) the evidence for mutagenicity is not supportive of a mutagenic concern in carcinogenicity; and (iv) malaoxon, a structurally related chemical, is not carcinogenic in male or female Fischer 344 rats. There was a subsequent review of the carcinogenic potential of malathion by a FIFRA Scientific Advisory Panel (SAP) on August 17-18, 2000. The Panel report, "A Consultation on the EPA Health Effects Division's Proposed Classification of the Human Carcinogenic Potential of Malathion," dated December 14, 2000, offers an overall equivocal recommendation on the proposed HED CARC classification of malathion as "suggestive." About half of the Panel members agreed with the "suggestive" classification and an almost equal number of Panel members concluded that a category of "not likely to be carcinogenic to humans" best fits the weight-of-evidence evaluation of the animal carcinogenicity data on malathion. One Panel member indicated that the classification should be "likely." The CARC considered the SAP recommendations and concluded that the cancer classification should remain as "suggestive." However, the Agency believes the chronic risk assessment will be protective of any potential carcinogenic effects. Additionally, the CARC recently evaluated a publication by Cabello et al. (2001) and concluded that the paper provided insufficient basis for revising the cancer classification for malathion. Consistent with the recent (2005) EPA Guidelines for Carcinogenic Risk Assessment (available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283) a cancer dose-response assessment, e.g., a low dose linear extrapolation model, is not normally performed for substances in the "suggestive" category. Six other non-guideline carcinogenicity studies have been reviewed by HED (see HED memorandum dated December 9, 1997 [TXR 012433]). One study, a malaoxon study on B6C3F1 mice, was considered to be acceptable and negative for carcinogenicity. The remaining five studies were determined to be inadequate to make a definitive determination of the carcinogenicity of malathion or malaoxon. Please see Appendix 2.0 for a short description of each study.

The Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, directs the Agency to use an additional tenfold (10x) safety factor (SF) to account for potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. FFDCA authorizes the Agency to reduce the 10x FQPA SF only if reliable data demonstrate that the resulting margin of exposure is adequate to protect infants and children. The toxicology database for malathion is adequate although data gaps remain: a guideline immunotoxicity study and a special comparative ChEI study for acute and repeated exposures in juvenile animals with malaoxon and malathion.

The data the Agency used to address potential differences between young and adult animals are the following guideline studies: pre-natal developmental toxicity in rats and rabbits; a two-generation reproductive toxicity study in rats; an acute neurotoxicity study in rats ; a sub-chronic neurotoxicity study in rats; and a developmental neurotoxicity study in rats (with a supplemental range-finding study). Additionally, a comparative ChE study with malathion in adult and immature rats for acute and repeated exposures is also available. Consistent with its mode of action, ChE inhibition provides the critical effect for determining the point of departure for the oral, dermal and inhalation (aggregate only) routes of exposure. The comparative ChE in the young demonstrate that juvenile animals are more sensitive than adults.

In order to account for the increased toxicity due to exposure from malaoxon, the Agency is applying a Toxicity Adjustment Factor (TAF) of 61x to malaoxon exposures. The Agency has data on malaoxon (including a 14-day and 2-year feeding study in rats) for repeated exposures which shows malaoxon to be 61x more toxic to adults than malathion. This TAF is, in the absence of data, assumed to be health protective in assessing single (acute) exposures to malaoxon in adults as well as both acute and repeated exposures to the young. The Agency will be receiving confirmatory acute and repeated dose toxicity data for the young in the near future, as discussed earlier.

The Agency has determined that there is evidence that following acute or repeated dose exposures to malathion, young animals exhibit adverse effects more readily than adults. The Agency has oral data for this most sensitive subpopulation and is using it to determine the appropriate point of departure (PoD) for use in assessing risk for acute and chronic dietary and incidental oral scenarios. In those instances where the Agency is using a PoD derived on pup data, the FQPA SF is reduced to 1x. The Agency has decided to retain the FQPA SF (10x) for those scenarios where the PoD does not already reflect the most sensitive population (i.e., the PoD is derived from adult animal studies). Consequently, for dermal exposure scenarios, where the PoD is derived from adult animals and children are expected to be exposed, the FQPA SF of 10x has been retained. Similarly, for inhalation exposure scenarios where the endpoint selected is ChE inhibition (in order to aggregate non-occupational exposures) and the PoD is based on adult animals, the FQPA SF of 10x has also been retained. Finally, the Agency has retained the FQPA SF of 10x for the bystander inhalation scenario in order to account for the lack of a NOAEL, severity of effect, as well as any differential in susceptibility in the young.

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.

FQPA also requires that the completeness of the exposure data base be considered in deciding whether to retain, reduce or remove the FQPA SF. The Agency is confident that the risk assessment for each potential exposure scenario will not underestimate dietary or non-occupational exposures to infants and children.

4.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on malathion, there was no estrogen or androgen mediated toxicity. Thyroid effects were observed in the combined chronic/carcingenicity study in rats. These effects included an increase in parathyroid hyperplasia in male and a significant trend in thyroid follicular cell adenomas and/or carcinomas and thyroid c-cell carcinomas (all in males). However, the FIFRA SAP did not consider the thyroid effects of concern or necessarily related to malathion exposure (SAP, 2000). When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, malathion may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.7 Summary of Toxicological Doses and Endpoints

Table 4.7 Summary of Toxicological Doses and Endpoints for Malathion for Use in Human Risk Assessment			
Exposure Scenario	**Dose Used in Risk Assessment (mg/kg/day) UF/MOE**	**FQPA Safety Factor and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dietary Risk Assessments			
Acute Dietary (Females 13-49)	There is no increased susceptibility expected to females of child-bearing age. Effects observed in the rat and rabbit developmental studies showed reduced body weight gains with NOAELs of 400 and 25 mg/kg/d, respectively. The aRfD for the general population is lower and thus would be protective of this population group.		
Acute Dietary (General population including infants and children)	Oral $BMDL_{10}$ = 13.6 mg/kg UF = 100[1] **Acute RfD** = 0.14 mg/kg	FQPA SF 1X[2] aPAD = acute RfD/FQPA SF =0.14 mg/kg/day	$BMDL_{10}$[3] = 13.6 mg/kg/day based on RBC ChEI in male pups. Comparative ChE acute oral study in the rat.
Chronic Dietary (All populations)	Oral $BMDL_{10}$ = 7.1 mg/kg/d[4] UF = 100 **Chronic RfD** = 0.07 mg/kg/day	FQPA SF 1X cPAD = chronic RfD/FQPA SF =0.071 mg/kg/day	$BMDL_{10}$ = 7.1 mg/kg/d based on RBC ChEI in offspring. Comparative ChE multiple dose oral study in the rat
Non-Dietary Risk Assessments			
Short- (1-30 days) and Intermediate- Term (1 - 6 Months) Incidental Oral	Oral $BMDL_{10}$[4] = 7.1 mg/kg/d	**Residential** (Short-term only) LOC for MOE = 100[5] **Occupational** = N/A	$BMDL_{10}$ = 7.1 mg/kg/d based on RBC ChEI in offspring. Comparative ChE multiple dose oral study in the rat
Short- (1-30 days) and Intermediate- Term (1 - 6 Months) Dermal (children)	Dermal $BMDL_{20}$[6] = 127 mg/kg/d	**Residential** (Short-term only) LOC for MOE = 1000[7] **Occupational** = N/A	$BMDL_{20}$[6] = 127 mg/kg/d based on RBC ChEI (%) in two separate 21-day dermal studies in rabbits
Short- (1-30 days) and Intermediate- Term (1 - 6 Months) Dermal (adults)[10]	Dermal $BMDL_{20}$[6] = 127 mg/kg/d	**Residential** (Short-term only) LOC for MOE = 100 **Occupational** LOC for MOE = 100	$BMDL_{20}$[6] = 127 mg/kg/d based on RBC ChEI (%) in two separate 21-day dermal studies in rabbits
Long-term (>6 mo) Dermal (adults)	Dermal $BMDL_{20}$[6] = 127 mg/kg/d	**Residential** = N/A **Occupational** LOC for MOE = 100	$BMDL_{20}$[6] = 127 mg/kg/d based on RBC ChEI (%) in two separate 21-day dermal studies in rabbits
Short- (1-30 days) and Intermediate-term (1 - 6 Months) Inhalation (all populations)[10]	Inhalation LOAEL= 0.1 mg/L (25.8 mg/kg/day)	**Residential** (Short-term only) LOC for MOE = 1000[7] **FQPA SF 10X**	LOAEL= 0.1 mg/L (25.8 mg/kg/d) based on histopathology in respiratory epithelium 90-day inhalation study in rats
	Inhalation LOAEL= 0.1 mg/L (25.8 mg/kg/day)	**Occupational** LOC for MOE = 1000[8]	LOAEL= 0.1 mg/L (25.8 mg/kg/d) based on histopathology in respiratory epithelium 90-day inhalation study in rats

Table 4.7 Summary of Toxicological Doses and Endpoints for Malathion for Use in Human Risk Assessment			
Exposure Scenario	**Dose Used in Risk Assessment (mg/kg/day) UF/MOE**	**FQPA Safety Factor and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Short-term (1-30 days) and Intermediate-term (1-6 mo) Inhalation **(children) Aggregate Only**	Inhalation NOAEL= 0.1 mg/L (25.8 mg/kg/day) **MOE** = 100 (ChEI)	**Residential** (Short-term only) LOC for MOE = 1000[9] **Occupational** = N/A	LOAEL = 0.45 mg/L (115 mg/kg/day) based on plasma and RBC ChEI 90-day inhalation study in rats
Short-term (1-30 days) and Intermediate-term (1-6 mo) Inhalation **(adults) Aggregate Only**	Inhalation NOAEL= 0.1 mg/L (25.8 mg/kg/day) **MOE** = 100 (ChEI)	**Residential** (Short-term only) LOC for MOE = 100 **Occupational** LOC for MOE = 100	LOAEL = 0.45 mg/L (115 mg/kg/day) based on plasma and RBC ChEI 90-day inhalation study in rats
Cancer	**Classification:** Suggestive evidence of carcinogenicity		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* Refer to Section 4.5

[1] UF = 100 [10x for interspecies extrapolation and a 10x for intraspecies variations was used].

[2] FQPA factor of 1 used because susceptibility of the young already accounted for because they were part of the experimental group.

[3] Benchmark Dose Lower Limit (BMDL), lower 95% confidence limit on the RBC CheI 10% effect level. Doses used in the study were: 0, 5, 50, 150, and 450 mg/kg/d.

[4] Benchmark Dose Lower Limit (BMDL), lower 95% confidence limit on the RBC CheI 10% effect level. Doses used in the study were: 0, 5, 50, and 150 mg/kg/d.

[5] MOE = 100 [10x for interspecies extrapolation, 10x for intraspecies variations]. Susceptibility of the young already accounted for because they were part of the experimental group.

[6] Benchmark Dose Lower Limit (BMDL), lower 95% confidence limit on the RBC CheI 20% effect level. BMD estimate based on combining two dermal toxicity studies (see text).

[7] MOE = 1000 [10x for interspecies extrapolation, 10x for intraspecies variations, and an FQPA 10x for a LOAEL to NOAEL extrapolation, for the severity of the effect, as well as any differential susceptibility in the young.] This endpoint is for the bystander inhalation exposure scenario.

[8] MOE = 1000 [10x for interspecies extrapolation, 10x for intraspecies variations, and an uncertainty factor for a LOAEL to NOAEL extrapolation and for the severity of the effect.]

[9] MOE = 1000 [10x for interspecies extrapolation, 10x for intraspecies variations, and 10x for known susceptibility of the young based on the comparative ChE study].

[10] There is also no concern for women of child-bearing age following dermal and/or inhalation exposure given the following: (i) the observed susceptibility differences between young and old are a result of postnatal exposures and ChEI data from gestational only exposures indicate that fetuses are less sensitive than the mother at birth.; (ii) the dermal toxicity endpoint is based on the more sensitive species (rabbit); (iii) in dermal and inhalation studies, females were neither more sensitive nor responded differently than males; and, (iv) oral studies indicate that there is no enhanced sensitivity of pregnant animals versus non-pregnant animals to malathion, and there is no reason to believe that this is route-specific.

5.0 Public Health Data

a) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other Federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992.

b) Poison Control Centers (PCC) - as the result of Data-Call-Ins issued in 1993, OPP received Poison Control Center data covering the years 1985 through 1992 for 28 organophosphate pesticides, including malathion. This source includes information gathered from about 70 centers at hospitals and universities. In addition, OPP purchased Poison Control Center data on all pesticides for the years 1993-1998. This information was summarized in the earlier reviews (September 11, 2000 review D268749 and the August 18, 1998 Review D247492). The current review summarizes data from 1999 through 2003 and compares it to the earlier findings.

c) California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. The earlier review covered data from 1982 through 1998. This review adds data from 1999 through 2003 and compares it to earlier findings. By law, physicians are required to report all occurrences of illness suspected of being related to pesticide exposure.

d) National Pesticide Telecommunications Network (NPTN) - a toll -free information service supported by OPP receives and organizes information from the top 200 active ingredients for which telephone calls were received. Information is tabulated for categories of human incidents, animal incidents, calls for information, etc.

5.1 Incident Reports and Trends

The number of malathion exposures and poisonings have declined in recent years; however, most of this decline has occurred in the residential setting and there is no usage surveys to determine whether all or most of this decline is due to less use or safer handling. Likely some of the decline is due to less widespread use of malathion due to medfly outbreaks and as a choice for use against carriers of West Nile Virus. Agricultural use has declined slightly in California in recent years but that does not explain most of the decline in poisoning reported from that State.

Organophosphates are responsible for disproportionately more serious poisonings in comparison with other pesticides. In the 1990 survey of home and garden use (Whitmore et al. 1992, page 55 and Table G) 19% of the containers in U.S. homes were organophosphates. In the 1993 survey of non-agricultural pesticide use by certified and commercial applicators, 21% of the pounds active ingredient applied were organophosphates (Lucas et al. 1994, Table 13). Similarly, for Poison Control Centers, 15% of all unintentional pesticide exposures are due to organophosphates, but 18% of the symptomatic cases, 27% of the hospitalized cases, and 28% of the life-threatening or fatal cases were due to organophosphates (based on 1993-1996 data provided by AAPCC). National death statistics report that 40% of the accidental deaths from pesticides (where the type of pesticide is known) were due to organophosphates during the 1980s (Blondell 1997).

Symptoms commonly reported for malathion exposure from the above sources cover the spectrum normally associated with organophosphate exposure, and include headache, nausea, dizziness, muscle weakness, drowsiness, difficult breathing, diarrhea, excess secretions, agitation, confusion, blurred vision and, death from accidental or intentional ingestions (i.e., suicides). The most recent five years of data (1999-2003) from California show a marked decline of 59% (from 27.5 to 11.2) in total illnesses attributed to malathion from the 1982-1998 time span. There were 79 cases reported from 1999-2003 and, of these, malathion was determined to be the primary cause of illness in 55 cases. As before, cases were included if malathion was considered a possible, probable, or definite cause of the reported illness. Only 5 of the 55 cases were related to use in agriculture and 4 of the 5 were systemic poisonings. On average, there were 14,846 agriculturally-related applications of malathion from 1999 through 2003 in California. Thus, there were 0.27 systemic poisonings per 1,000 applications from 1999-2003 which compares favorably with much older data from 1982 through 1989 which found a median of 0.41 poisonings per 1,000 applications. However, the earlier data did not have a requirement that all agricultural applications be reported, just commercial and applications by a licensed pesticide applicator. Therefore, it is not clear whether the current rate of poisoning per thousand applications is due to a real decline or an artifact of use reporting. Still, the decline in systemic poisonings from 1990-96 (20.4 per year) to 1999-2003 (8.2 per year) demonstrates a 60% decline in all systemic poisonings whether related to agriculture or not and this decline appears to be real and not an artifact of a great decline in malathion use.

The pattern of incidents was similar to previous years. There were three suicides (ingestions of concentrate: 6-8 ounces, over a cup, and an unknown quantity) and 3 attempted suicides (one case ingested about 8 ounces of 0.125% malathion). Interestingly, as reported earlier, a number of rescue personnel attending the suicide victims were also poisoned by the strong odor and from contact with contamination. There were four such individuals in one case and nine persons sick from attending another suicide victim. Fourteen of the cases became sick from applications that occurred nearby (e.g., from drift). Some of these were due to highly concentrated applications that had not been diluted properly. Five cases involved the applicators themselves and there was mention of a leaking or broken bottle in six cases.

Much of the information presented above has inherent limitations, including inadequate documentation of exposure and effects, reporting biases and absence of denominator information on the population at risk. However, certain consistent patterns of risk factors can be identified. The large majority of malathion incidents appear to involve minor symptoms which in many cases may be a reaction to the odor rather than cholinergic poisoning. Nonetheless, symptoms brought on by odor effects are poisonings by definition. Broken bottles and other inadequate packaging accounted for over a quarter of the cases in California from 1982 through 1995. Drift and exposure to odors was another common cause of incidents in California. These latter typically resulted in mild and transient symptoms. In many cases it appears that symptoms are brought on by the offensive odor of the compound alone (i.e., ChE depression need not be present). More serious malathion cases typically involve application by hand or backpack sprayer and direct exposure to concentrate. Often, serious exposures result from equipment

failure such as hose breaks or failure to exercise minimal precautions during maintenance or clean-up. Though less hazardous than other organophosphates and carbamates on most measures, malathion has a higher incidence of life-threatening cases in Poison Control Center data. Extensive exposure to concentrates appears to be a likely risk factor in these cases.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

Potential exposure to residues of malathion and its malaoxon metabolite in the diet occurs through food and water sources. Malathion is typically applied to crops multiple times during the growing season. It is also applied postharvest directly to cereal grains in storage silos. The field trial residue data supporting reassessed tolerances indicate there are quantifiable residues of malathion on edible crops; however, there is little (if any) likelihood of residue transfer to meat and milk. Field trial and metabolism data indicate that malaoxon is usually a minor metabolite in plants, if detected at all. Laboratory studies indicate that malathion is not likely to persist in surface water and it is not expected to leach to ground water; however, based on fate characteristics, model predictions and actual monitoring studies, the Agency predicts malathion will reach drinking water sources and has conducted conservative modeling assessments to estimate drinking water concentrations.

6.1.1 Residue Profile

Residue Chemistry Chapter for the Malathion Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D239453. William O. Smith. April 14, 1999.

Tolerances have been established for residues of malathion *per se* in/on food/feed commodities [40 CFR §180.111, §185.3850, §185.7000, and §186.3850] and meat, milk poultry and eggs [40 CFR §180.111]. *Because animal metabolism data indicate that there is little likelihood of residue transfer to meat, milk, poultry and eggs, tolerances for malathion residues in these commodities may be revoked.* Based on available plant metabolism data, the HED Metabolism Committee has determined that the malathion residues of concern in plants consists of malathion and its metabolite malaoxon; see Tables 2.2.1 and 2.2.2 for chemical structures and full chemical names. The tolerance expression (currently expressed in terms of malathion *per se*) should be revised to include malathion and malaoxon.

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for residues of malathion in/on various raw agricultural and processed commodities. The Codex MRLs are expressed in terms of malathion *per se*. The Codex MRLs and the U.S. tolerances will be incompatible when the U.S. tolerance expression for plant commodities is revised to include both residues of malathion and the metabolite malaoxon.
For the determination of malathion and malaoxon residues in plant commodities, the registrant has proposed flame photometric detection (FPD) method M-1866 as an enforcement method.

The limit of quantification (LOQ) of each compound is 0.05 ppm. Method M-1866 has undergone a successful independent laboratory validation, and acceptable radiovalidation data using samples from an alfalfa metabolism study have also been submitted and evaluated. Pending a successful tolerance method validation to be conducted by EPA's Analytical Chemistry Laboratory, Method M-1866 will be approved for enforcement purposes. For the determination of residues of malathion *per se* in animal commodities, the Pesticide Analytical Manual (PAM, Vol. II, §180.111) lists GLC Methods A and B for enforcement of malathion tolerances.

The reregistration requirements for multiresidue method testing for residues of malathion and malaoxon are satisfied. The 2/97 FDA PESTDATA database (PAM Volume I, Appendix I) indicates that malathion is completely recovered (>80%) using multiresidue methods PAM Volume I Sections 302 (Luke method; Protocol D), 303 (Mills, Onley, and Gaither method; Protocol E), and 304 (Mills method for fatty food). Malaoxon is completely recovered (>80%) using multiresidue method PAM Volume I Sections 302 (Luke method; Protocol D) but is not recovered using method Sections 303 (Mills, Onley, and Gaither method; Protocol E), and 304 (Mills method for fatty food).

The current malathion tolerances for animal commodities were established based on use patterns involving direct animal treatments which would, in all probability, result in significant malathion residues of concern in eggs, milk, and animal tissues. Therefore, if the direct animal treatment uses of malathion to poultry and livestock animals are canceled, then the established tolerances for residues of malathion *per se* in eggs, milk, and animal tissues may be revoked (Greybeard Committee decision on Malathion, 10/19/94). Note: The registrant has indicated they do not intend to support direct livestock treatment for reregistration. If another party wished to do so, then appropriate dermal metabolism and magnitude of the residue studies are required.

The submitted residue data from field trials and processing studies depict combined residues of malathion and its malaoxon metabolite. Combined residues of malathion and its malaoxon metabolite are likely to be found at detectable levels in samples of raw and processed commodities following preharvest and postharvest applications; however, malaoxon is usually a minor metabolite, if detected at all. In general, field trials met the criteria for the required number of samples and were conducted in locations representative of the major growing regions specific to the crop tested. The test systems utilized representative product formulations, applied at maximum rates using application equipment in accordance with label specifications. These data were obtained using analytical methods adequately validated for data collection. Storage stability data support the integrity of the residue data for malathion and malaoxon.

Malathion uses in food/feed handling establishments are not being supported by the registrant. If no interested party wishes to support these uses then all related indoor uses must be deleted from malathion end-use products. Otherwise studies must be conducted to determine residues in food or feed resulting from treatment of food/feed handling establishments with malathion.

In the nature of the residue in confined rotational crops study, malathion was identified in the

organosoluble fractions of immature lettuce, immature turnips, and wheat forage from the same plant back interval (PBI). Because malathion was identified in 30-PBI rotational crops and quantified at levels greater than 0.01 ppm, the registrant(s) was required to conduct limited field rotational crop studies. Rotational crop restrictions are needed on malathion end-use product labels. The appropriate PBIs will be determined pending submission of the required field rotational crop studies.

Residue data from crop field trials, processing studies, and livestock feeding studies have been reviewed for the purpose of tolerance reassessment. HED has high confidence in the available, geographically representative, field trial data. HED is recommending revocation of tolerances for certain commodities for one or more of the following reasons: established tolerances for animal commodities for direct animal treatment uses have been canceled; and there are no longer significant livestock feed items for the commodity. A summary of reassessed tolerances is provided in Appendix 3.0 of this document.

6.1.2 Acute and Chronic Dietary Exposure and Risk

Malathion. *Revised Acute, Probabilistic and Chronic Dietary (Food + Water) Exposure and Risk Assessments for the Malathion Reregistration Eligibility Decision. PC Code: 057701. DP Barcode: D330636. Sheila Piper. July 13, 2006.*

Revised acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which use food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed as part of the registrant, Cheminova's response to EPA's revised risk assessment (S. Kinard, D321543, 9/13/2005) for malathion and include the following reregistration action: (1) new chronic toxicological endpoint; (2) new toxicity adjustment factor (TAF) for malaoxon; and (3) new drinking water estimates provided by the Environmental Fate and Effects Division (EFED).

Highly refined probabilistic acute and chronic dietary exposure assessment was conducted for all supported food uses. Malathion residue estimates used in this assessment include malathion and the oxygen analog metabolite malaoxon. Malaoxon is considered to be more toxic than malathion. To account for this, HED has performed benchmark dose modeling to evaluate relative potency for malathion and malaoxon. An acute and chronic toxicity adjustment factor (TAF) of 61x calculated from oral studies is applicable to residues of malaoxon (see toxicology section). Pesticide residues were included from 1999-2003 USDA-PDP monitoring data and FDA & FOODCONTAM data which analyzed for malathion and malaoxon, and revised chronic Population Adjusted Doses (PADs). Anticipated residues were further refined using percent crop treated (%CT) data and processing factors where appropriate.

The acute dietary risk estimates from food alone are below HED's level of concern (5% of the aPAD for the U.S. population and 11% of the aPAD for all infants (<1 yr old), the most highly exposed population subgroup).

Acute dietary (food and drinking water) risk estimates based on various default input parameters were above HED's level of concern (>100% aPAD) at the 99.9th percentile of exposure. The CA lettuce maximum aerial scenario results in the highest drinking water concentrations, and consequently the highest dietary (food + water) exposure. When refinements (proposed application rates and regional PCAs) were made to the estimated drinking water concentrations, the acute dietary risk estimates for food and drinking water were below HED's level of concern (<100% aPAD) at the 99.9th percentile of exposure. See section 7.1 Acute Aggregate Risk and Table 7.1.1 which provides a summary of default (upper bound) and refined (lower bound) acute dietary risk estimates from food and water.

The chronic dietary risk from malathion exposure from food alone is well below HED's level of concern for the U.S. general population and all population subgroups (<1% of the cPAD).

Table 6.1 Summary of Dietary Exposure and Risk for Malathion to Food Only.

Population Subgroup [a]	Acute Dietary (99.9th Percentile)			Chronic Dietary			Cancer Dietary	
	aPAD, mg/kg	Exposure, mg/kg/day	% aPAD	cPAD, mg/kg/day	Exposure, mg/kg/day	% cPAD	Exposure mg/kg/day	Risk
General U.S. Population	0.14	0.006975	5	0.003	0.000148	<1	Suggestive evidence of carcinogenicity	
All Infants < 1 yr	0.14	0.015734	11	0.003	0.000219	<1	NA	
Children 1-2 yrs	0.14	0.013100	9	0.003	0.000343	<1		
Children 3-5 yrs	0.14	0.012432	9	0.003	0.000334	<1		
Children 6-12 yrs	0.14	0.009531	7	0.003	0.000241	<1		
Youth 13-19 yrs	0.14	0.007372	5	0.003	0.000155	<1		
Adults 20-49 yrs	0.14	0.005487	4	0.003	0.000130	<1		
Adults 50+ yrs	0.14	0.004227	3	0.003	0.000007	<1		
Females 13-49 yrs	0.14	0.005473	4	0.003	0.000113	<1		

6.2 Water Exposure and Risk

Drinking Water Exposure Modeling Evaluating the Effect of Varying Crop Scenarios, Application Rate, Application Interval, Spray Drift Levels, Soil Half Life. PC Code: 057701. DP Barcode: D327331. Norman Birchfield. June 15, 2006.

The Environmental Fate and Effects Division (EFED) provided an analysis of available monitoring data and a screening-level assessment using PRZM/EXAMS to estimate the potential concentration of malathion and its degradate malaoxon in ground and surface water. In addition, EFED's analysis of available drinking water facility monitoring data, indicates that all malathion entering a drinking water treatment facility is expected to be converted to malaoxon. Based on fate characteristics, model predictions and actual monitoring studies, the Agency predicts malathion will reach drinking water sources. Numerous monitoring studies confirm malathion/malaoxon can reach surface drinking water treatment facility intakes but insufficient

targeted monitoring studies are available to adequately define acute malathion/malaoxon concentrations in drinking water; thus, surface water concentrations associated with a range of malathion uses were conservatively modeled.

6.2.1 Estimated Drinking Water Concentrations

As with previous malathion drinking water assessments, modeled scenarios were chosen to represent a range of major malathion uses and the geographic area encompassed. Sixteen separate crop scenarios were selected for to model potential malation drinking water residues in surface water drinking sources. Inputs for application rate, application intervals, and crops were provided by SRRD and the Biological and Economic Analysis Division (BEAD) to represent proposed maximum and typical application rates. In the absence of information on the time of year when malathion is used, the rainiest season for a site was chosen to reflect high-end runoff and exposure values. Scenarios expected to yield the highest drinking water concentrations; based on BEAD usage data, application rate, and runoff potential; were selected for this assessment in order to provide high-end estimates for all currently labeled malathion uses (see Table 6.2). Base inputs for the persistence, physical properties, and mobility of malathion in this assessment are consistent with values used in previous assessments (except for modeling additional soil half lives) and input parameter guidance.

Table 6.2. Selected Input Parameters for Drinking Water Modeling

	Soil Half-life	**Percent Crop Area**	**Application Method**	**Application Date**	**Application Rate**
Default	3 day	National default (87%)	Ground and Aerial	Rainiest part of the year, depending upon scenario modeled[3]	Maximum supported
Refined	1 day[1]	Regional PCAs[2]	Ground and Aerial	Typical first application date[4]	Proposed (reduced) application values

[1] EPA notes that under certain soil conditions, malathion aerobic half-life may be 24 hours.
[2] Regional PCAs used include the following Southeast (0.38); Central (0.80); Western (0.56); and, North West (0.63).
[3] Default *first application date* is intended to reflect month with heaviest rainfall in the modeled area: southeast (May 1); central (Jan. 1); northwest (Jan. 1).
[4] First application data was needed only to refine model scenario for strawberry grown in CA (May 1).

The drinking water models used in this analysis require the input of a single aerobic soil metabolism half-life for the entire modeled period. A 1-day aerobic soil metabolism half-life was tested along with the 3-day half-life used in previous assessments to evaluate the effect of a shorter soil half-life. Malathion on moist, microbially active soils would be expected to degrade faster than dryer, less active soils. Regional percent cropped area factors (PCAs) were used in this assessment. PCAs are fractions that represent the largest fraction of a watershed that is expected to be planted in a crop or combination of crops. In previous assessments the more conservative national-level PCA, representing the most heavily cropped watershed in the country, was used while in the current assessment more refined regional PCAs are used. Also,

the drinking water concentrations have been adjusted to account for 100% conversion to malaoxon, which is expected during chlorination, addressing the difference in molecular weight between malathion and malaoxon (a factor of 0.951) and the estimated concentrations are adjusted for malaoxon's increased toxicity adjustment factor (TAF) of 61x.

The PRZM-EXAMs surface water modeling data from the highest 1-in-10 year annual concentration for the 3-day half-life aerial CA lettuce scenario with the maximum rate of 3.621 ppb (4.1677 * 0.87 PCA) was used in the chronic dietary exposure assessment.

6.3 Residential (Non-Occupational) Exposure and Risk

Malathion: *Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D330678. Jack Arthur. July 6, 2006.*

In addition to exposure to malathion from food and drinking water, exposure may also result from outdoor residential uses of malathion, including on vegetable gardens, home orchards, ornamentals, treatment for flying insect pests, wide-area treatments for mosquito vector control, and spray drift from agricultural uses.

6.3.1 Residential Recreational Use Pattern

Malathion is formulated as a dust (1-10% ai), an emulsifiable concentrate (3-82% ai), a ready-to-use liquid (1.5-95% ai), a pressurized liquid (0.5-3% ai), and a wettable powder (6-50% ai). Several of the 95% ai liquids are intended for Ultra-Low-Volume (ULV) applications in state and local mosquito abatement programs. Several malathion-containing end-use products also contain other active ingredients such as captan and methoxychlor. The risk potential for exposure to other active ingredients has been addressed in the risk assessments for those compounds.

Malathion is currently registered for outdoor use in residential and recreational settings for control of bagworms, red spider mites, aphids, mosquitoes, flies, fleas and other outdoor household pests. Potential use sites may include herbaceous and woody ornamentals, vegetables and small fruits, fruit trees, citrus trees, and building perimeters. In addition, residential exposure may occur from malathion's use in wide-area treatments for mosquito-borne disease control and spray drift from agricultural uses (e.g., aerial application to cotton). The non-occupational use sites are listed in Table 6.3.1.

According to the National Home and Garden Pesticide Use Survey Final Report, Volume 1 (March, 1992), the major use of malathion in the home garden is on roses and other ornamentals (about 42%), followed by edible food crops (about 25%), and lawns (about 18%). [Note: The registrant has indicated that turf (lawn) uses will no longer be supported on the technical label.]

Table 6.3.1 Malathion Non-occupational (Residential/Recreational) Use Sites				
Use Site	**Target Crops or Pests**	**Maximum Rates**	**Timing and Frequency**	**Application Equipment**
Homeowner Fruit Trees	Includes apples, cherries, grapes, peaches, plums, oranges and tangerines	0.034 lb ai/gallon	Typical applications are made when new spring growth for flowering begins. Repeat at 7-10 day intervals. A maximum number of applications or seasonal use rate has not been established.	Low pressure handwand, hose end sprayer, and backpack sprayer.
Homeowner Ornamentals	Includes shade trees, evergreens, and roses	0.034 lb ai/gallon	Apply when insects are present and repeat as necessary.	Low pressure handwand, hose end sprayer and backpack sprayer.
Homeowner Vegetables/Small Fruits	Includes beans, beets, broccoli, cabbage, collards, cucumbers, melons, tomatoes, peas, peppers and strawberries	0.023 lb ai/gal	Apply one or more full coverage spray as needed.	Low pressure handwand, hose end sprayer and backpack sprayer.

Table 6.3.1 Malathion Non-occupational (Residential/Recreational) Use Sites				
Use Site	**Target Crops or Pests**	**Maximum Rates**	**Timing and Frequency**	**Application Equipment**
Homeowner Outdoor Building Perimeter Treatments	Treatment for outdoor household pests (i.e., roaches, ants, clover mites, spiders, silverfish, crickets, earwigs)	0.1547 lb ai/gal (0.011 lb ai/gal for hose end sprayer)	For residual adult mosquito control, apply as a course spray to lower foundation of house and firewood piles. Repeat as necessary. If only clover mites, treat building perimeters in a 10 ft. wide strip along side of house. Repeat as necessary.	Low pressure handwand, hose end sprayer and backpack sprayer.
Outdoor Yard	Mosquito and flying insect pests	0.1 lb ai/Acre	Apply for mosquito and fly control. Fogger machines are recommended to be used at dusk, with repeat applications as necessary.	Hand-held fogger unit

The residential exposure risk assessment presented here is based, for the most part, on the sites and use patterns on representative product labels registered to, or proposed by the basic producer, Cheminova. When end-use product DCIs are developed (e.g., at issuance of the IRED), the Registration Division should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the basic producer labels.

6.3.2 Home Uses

At this time, there are outdoor residential uses of malathion which include vegetable gardens, home orchards, ornamentals, yard foggers and perimeter house treatments; however, postapplication exposure following building perimeter treatment is considered to be negligible, and has not been assessed. Residential exposure may also occur from malathion's use in wide-area treatments for mosquito vector control, and spray drift from agricultural uses (e.g., boll weevil eradication and fruit fly control). Due to the unique circumstances regarding the special uses of malathion in public health mosquito abatement control, the USDA's Boll Weevil Eradication Program, and fruit fly (Medfly) control, potential residential bystander exposures from these uses are assessed separately in sections 6.3.3.1, 6.3.3.2, and 6.3.3.3, below.

6.3.2.1 Residential Handler Exposure Scenarios

EPA has determined that residential handlers are likely to be exposed during malathion use. Residential handler exposure to malathion residues via dermal and inhalation routes can occur during handling, mixing, loading, and applying activities. The exposure duration of these activities is classified as short-term (1-30 days) based on label directions for multiple applications which may be made every seven days “as necessary.” Based on the frequency of use by residential handlers and the relatively short environmental half-life, use of malathion is not expected to result in continuous exposure durations of one to several months or longer, such that intermediate- or long-term residential exposure assessments would be needed.

The anticipated use patterns and current labeling indicate several major exposure scenarios, based on the types of equipment that potentially can be used to make malathion applications. These scenarios include:

- mixing/loading/applying liquids with a low pressure handwand;
- mixing/loading/applying wettable powders with a low pressure handwand;
- loading/applying liquids with a hose end sprayer;
- mixing/loading/applying liquids with a backpack sprayer; and
- mixing/loading/applying liquids for hand-held fogger applications.

6.3.2.2 Residential Handler Exposure Data Sources and Assumptions

Several handler assessments were completed using PHED data due to the lack of a more refined dataset. However, HED has overall confidence that the calculated homeowner handler risks are not underestimated, since a number of maximum or upper range input variables were used in the calculations (e.g., maximum application rates).

The following assumptions and factors were used in order to complete this exposure assessment:

- Calculations were completed at the maximum application rates recommended by the available malathion labels to cover the range of maximum risk levels associated with various use patterns. No use data were provided by the registrant concerning the actual application rates that are commonly used for malathion.

- The duration of exposure is expected to be short-term (1-30 days) based on label directions for multiple applications of malathion to fruits, vegetables, ornamentals and outdoor building perimeters which may be made every 7 days "as necessary." The frequency of homeowner applications is not expected to result in a continuous exposure duration of several months. None of the currently registered residential or other non-occupational uses would result in long-term exposures.

- Generally, the use of PPE and engineering controls are not considered acceptable options for products sold for use by homeowners.

- For the low pressure handwand and the backpack sprayer, the Agency's standard value of 5 gallons of spray per day was used for fruit trees, ornamentals and vegetable/small fruit gardens. A value of 4 gallons per day was used for building perimeter treatments. This latter deviation from the standard value is based on published information from the U.S. Census Bureau and the National Association of Home Builders on typical home sizes to estimate the square foot range of house perimeters for which homeowner building perimeter treatment might be expected (200 linear feet, 2-foot wide swath). The registrant submits that one gallon of malathion product spray solution will cover 400 ft^2 at the labeled rate of 0.1547 lb ai/gallon. The estimate of 4 gallons per day is an upper range value based on the assumption that other residential outbuildings (e.g. detached garages, kennels) and wood piles will be treated, as well. (*Cheminova, Inc., MRID 454573-01; Memo from J. Arthur, HED, DP Barcode D276978, October 2001*).

- For the backpack sprayers, an estimate of 5 gallons of spray per day for fruit trees, ornamentals, vegetable/small fruit gardens, and building perimeter treatment was used for the homeowner scenario.

- For hose-end sprayers, a value of 96 gallons was used for building perimeter treatment. The HED standard value for hose-end sprayer daily use rate is 100 gallons, but the product label indicates that one unit of product will make up to 96 gallons of diluted spray.

- Because there are no PHED data for handheld foggers, the assessment was based on the unit exposure values for applying aerosols from the Draft Residential SOPs. These unit exposure values represent a conservative surrogate for residential handlers who mix, load and apply liquid malathion with a handheld fogger.

- For hose-end sprayers, the unit exposure is the geometric mean value for "Residential Application: Hose-end Sprayer: Ready-to-Use (no mixing)," taken from EPA memo, "Summary of HED's Reviews of Outdoor Residential Exposure Task Force (ORETF) Chemical Handler Exposure Studies" (MRID 44972201. ORETF Study OAM004), from G. Bangs (HED) to D. Fuller (SRRD), dated April 30, 2001. The ORETF recently submitted proprietary data to the Agency on hose-end sprayers, push-type granular spreaders, and handgun sprayers (MRID # 44972201). The ORETF data were used in this assessment in place of PHED data for the garden hose-end sprayer scenario. The ORETF data were designed to replace the present PHED data with higher-confidence, higher quality data that contain more replicates than the PHED data for those scenarios.

- For low-pressure hand wand sprayers, the unit exposure is the geometric mean value from study of hand-held pump sprayer exposure (Merrick, 1998, MRID 44518501), as submitted by Cheminova A/S in, "Estimation of Potential Exposures and Risks to Residents Applying Malathion for Residential Mosquito Control," MRID 45457301, July 2001.

- All other unit exposure values in this assessment are taken from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments, May 1997, unless otherwise indicated.

6.3.2.3 Residential Handler Risk Characterization

Risks were determined using the Margin of Exposure (MOE) approach, where a ratio of the route appropriate toxicological endpoint to estimated exposure is calculated (MOE = endpoint/exposure). Cholinesterase inhibition (ChEI) was selected as the toxicity endpoint for combined short-term dermal and inhalation exposure. Because ChEI was observed in both dermal and inhalation toxicity studies, it is appropriate to consider the total risk contribution from both exposure routes. In addition, for the inhalation route alone, histopathological lesions of the respiratory epithelium were chosen as the toxicity endpoint of concern.

As presented in Table 6.3.2.3, calculations based on combined dermal and inhalation risks, using the cholinesterase endpoint, indicate that the total risks for all scenarios and do not exceed HED's level of concern (i.e., MOE $\geq$ 100). The MOEs for inhalation alone, using the histopathological lesions of the respiratory epithelium endpoint, do not exceed HED's level of concern (LOC of 1000).

Table 6.3.2.3 Residential Handler Short-term Risks to Malathion at Baseline

Exposure Scenario (Scen. #)	Crop Type or Target	Baseline Dermal Dose (mg/kg/day)[a]	Baseline Inhalation Dose (mg/kg/day)[b]	Baseline Dermal MOE[c]	Baseline Inhalation MOE[d]	Baseline Total MOE[e]
Mixer/Loader/Applicator Exposure						
Mixing/Loading/Applying Liquid with a Low Pressure Handwand (1a)	Fruit Trees	0.14	0.00001	900	2,600,000	900
	Ornamentals	0.14	0.00001	900	2,600,000	900
	Vegetable/Small Fruit Garden	0.09	0.00001	1400	2,600,000	1400
	Building Perimeter	0.50	0.00006	250	430,000	250
Mixing/Loading/Applying Wettable Powder with a Low Pressure Handwand (1b)	Fruit Trees	0.18	0.00079	700	33,000	690
	Ornamentals	0.27	0.0012	470	22,000	470
	Vegetable/Small Fruit Garden	0.32	0.0014	400	18,000	380
Mixing/Loading/Applying Liquids with a Hose End Sprayer (2)	Fruit Trees	0.126	0.00053	1000	49,000	1000
	Ornamentals	0.126	0.00053	1000	49,000	1000
	Vegetable/Small Fruit Garden	0.085	0.00036	1200	72,000	1200
	Building Perimeter	0.04	0.0002	3200	150,000	3200
Mixing/Loading/Applying Liquids with a Backpack Sprayer (3)	Fruit Tree	0.01	0.00007	13,000	350,000	13,000
	Ornamentals	0.01	0.00007	13,000	350,000	13,000
	Vegetable/Small Fruit Garden	0.01	0.00004	13,000	650,000	13,000
	Building Perimeter	0.06	0.00033	2100	530,000	2100
Mixing/Loading/Applying Liquids with a Handheld Fogger (4)	Mosquitoes	0.16	0.0017	790	15,000	770

Footnotes:

a Baseline Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day) / Body Weight (70 kg).

b Baseline Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day) / Body Weight (70 kg).

c Baseline Dermal MOE = NOAEL (127 mg/kg/day) / Baseline Dermal Dose (mg/kg/day). LOC = 100 (for cholinesterase effects)

d Baseline Inhalation MOE = NOAEL (25.8 mg/kg/day) / Baseline Inhalation Dose (mg/kg/day). LOC = 100 (for cholinesterase effects); and, 1000 (for histopathologic lesions)

e Total MOE = 1 / ((1/Calculated Dermal MOE) + (1/Calculated Inhalation MOE)). LOC = 100 (for cholinesterase effects)

6.3.2.4 Residential Noncancer Postapplication Exposure Scenarios

HED has determined that there is potential for non-occupational postapplication exposures to malathion residues from the following sources: 1) contact with malathion-treated home gardens and orchards; 2) contact with malathion-treated commercial “pick-your-own” strawberries or other orchards; 3) public health use of malathion for wide area mosquito control; and 4) off-target spray drift from agricultural Boll Weevil Eradication Program and Fruit fly (Medfly) control. Sources 3) and 4) are covered later in Section 6.3.3.

HED considers the potential for contact with malathion residues while working in treated vegetable gardens, harvesting from fruit and nut trees, harvesting strawberries in commercial "pick-your-own" fields, and activities in the yard following outdoor fogger use to be the most likely postapplication risks from home uses of malathion. With the exception of the fogger use, the inhalation component of postapplication exposure in these scenarios is believed to be negligible and is therefore not included in the determination of postapplication risk for home and garden residential exposure sources. Also, postapplication exposure from the use of malathion for perimeter house treatment is considered to be negligible.

The scenarios likely to result in exposures are as follows:

- Dermal exposure from residues on vegetable/small fruit gardens (adult);
- Dermal exposure from residues on fruit trees (adult);
- Dermal exposure from "pick your own" strawberries (adult); and
- Dermal and inhalation (adults and toddlers) and incidental oral (toddlers only) exposure following handheld fogger use at residential, park and school sites.

6.3.2.5 Residential Noncancer Postapplication Data Sources and Assumptions

Residential noncancer postapplication exposures were assessed for both adults and toddlers based on guidance provided in the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment (5/11/97 Version) and HED Exposure SAC Policy 12 modifications (2/22/2001).*

The following additional general assumptions were made:

- Postapplication was assessed on the same day the pesticide is applied because it was assumed that the homeowner could be exposed to gardens, fruits and nuts, ornamental shrubs, flowers, trees, and turf immediately after application. Therefore, postapplication exposures were based on day 0.

- Adults were assumed to weigh 70 kg. Toddlers (3 years old), used to represent the 1 to 6 year old age group, were assumed to weigh 15 kg.

- Dislodgeable foliar residues were estimated assuming that 20% of the application rate is initially retained on plant surfaces.

Additional parameters that effect residue transfers from vegetative surfaces to skin, skin-to-mouth, and object-to-mouth activities for adults and/or children are included as footnotes to Table 6.3.2.6 and more fully described in the Revised Residential Exposure and Risk Assessment (J. Arthur, D330678).

6.3.2.6 Residential Noncancer Postapplication Risk Characterization

The detailed results of the residential postapplication exposure assessment are presented in Table 6.3.2.6:

- The calculations of short-term risks indicate that **for all residential postapplication scenarios, the MOEs for both the cholinesterase inhibition and histopathological lesions endpoints do not exceed HED's level of concern**.

NOTE: For postapplication (dermal) exposure of adults and (dermal and incidental oral) exposure of toddlers following use of a handheld fogger, refer to the determination of the postapplication risks following public health mosquito control using a ground-based truck fogger (Sections 3.3 and 6.3). The profile of surface residues following use of a handheld fogger is assumed to be the same as that following the ground-based fogger due to similar methods and rate of application. As seen in the referenced sections, **postapplication dermal and incidental oral risks following** truck fogger applications (and, by comparison, **handheld foggers**) **do not exceed HED's level of concern for individual or combined routes of exposure**.

Transfer coefficients used are believed to be the best currently available for the assessment of malathion postapplication exposure potential.

As stated previously, postapplication exposure to residues following perimeter house treatment is considered by HED to be negligible, and is not assessed. However, existing label language (e.g., EPA Reg. 239-739) for outdoor household pest control gives a range of directions for perimeter house applications that include treatment of just building foundations and wood piles, to treatment of the ground surrounding the perimeter of the house in a swath up to 10 feet wide. Treatment of a 10-foot wide swath around most residential structures is believed to be tantamount to a broadcast turf treatment, a use for which the registrant of the technical product has formally withdrawn support. In a submission by the registrant (Cheminova A/S, "Estimation of Potential Exposures and Risks to Residents Applying Malathion for Residential Mosquito Control," p. 8., MRID 4547301, July 2001), perimeter treatment by low-pressure handwand was described: "For residential mosquito control, malathion is applied around the perimeter of the house, outbuildings, wood piles, etc. Malathion may be phytotoxic to some ornamental species at the application concentration necessary fo residual mosquito control (0.1547 lb ai/gallon).

Therefore, malathion mixed at the concentration for residual mosquito control is applied only to the perimeter of buildings and not to foliage. Mosquitos are controlled by landing on the treated area and contacting the active ingredient. One gallon of spray treats 200 linear feet, assuming a 2-foot wide band of spray." Final label directions for perimeter house treatment should specifically require such treatment to only include structural foundations and wood piles, and the 2-foot wide path surrounding the same. This language would avoid the problem of phytotoxicity, as well as eliminating the possibility of an unintended broadcast turf exposure.

NOTE: In Table 6.3.2.6, only the inhalation risk estimates are presented for postapplication exposure following the use of the outdoor fogger. For postapplication dermal exposure of adults and dermal and incidental oral exposure of toddlers following use of an outdoor handheld fogger, refer to the determination of the postapplication risks following public health mosquito control using a ground-based truck fogger (Sections 3.3 and 6.3). The profile of surface residues following use of a handheld fogger is essentially the same as that following the ground-based fogger due to similar methods and rate of application. **Postapplication dermal and incidental oral risks following** truck fogger applications (and, by comparison, **handheld foggers**) **do not exceed HED's level of concern for individual or combined routes of exposure**.

Table 6.3.2.6 Short-Term Postapplication Scenarios and Estimated Risks for Malathion Residential Uses

Scenario	Crop or Target	Receptor	Application Rate (AR)	DFR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	Absorption Rate (%)	Freq. (FQ) (events/ hr) or Inhal rate (IR) (m^3/hr)	BW (kg)	ADD (mg/kg/day)[c]	MOE[d]
Dermal exposure	Vegetable/Small Fruit Gardens	Adult	0.000115 (lbs ai/sq ft)[a]	11	500	0.67	100	-	70	0.053	2400
	"Pick-your-own" strawberries	Adult	0.000115 (lbs ai/sq ft)[a]	11	1,500	2	100	-	70	0.47	270
					400					0.126	1000
	Fruit Trees	Adult	0.00017 (lbs ai/sq ft)[a]	16	1000	0.67	100	-	70	0.153	830
Inhalation	Outdoor Fogger	Adult	0.046 mg/m^3	-	-	5	100	1 m^3/hr Inhal. rate	70	0.0033	7800
		Toddler				3		0.7 m^3/hr Inhal. rate	15	0.0064	4000

a Application rates are estimated as follows: vegetable/small fruit gardens- (0.023 lb ai/gal * 5 gallons)/1000 ft^2; fruit trees and ornamentals-(0.034 lb ai/gal * 5 gal)/1000 ft^2.

b Dislodgeable foliar residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on foliage (20%) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day) Dermal exposure: [DFR (ug/cm^2) * Tc (cm^2/hr) * mg/1000 ug * ET (hrs/day) * absorption factor (%)] / [BW (kg)];
Inhalation exposure: [AR (mg/m^3) * IR (m^3/hr) * ET (hrs/day) * absorption factor (%)] / [BW (kg)];

d MOE = NOAEL or BMDL/ADD, where

BMDL (adult dermal) = 127 mg/kg/day, with an LOC of 100;
NOAEL (adult and toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000 (for adult and toddler histopathologic lesions), and an LOC of 100 (for adult cholinesterase effects).
NOAEL (toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000 (for cholinesterase effects).

6.3.2.7 Combined Residential Handler and Postapplication Risk Characterization

Risks from different activities are combined when the toxicity endpoint is the same for all routes of exposure, and when it is reasonable to assume that the activities might occur on the same day. Such is the case when considering the cholinesterase inhibition toxicity endpoint for adults who are exposed through handling (dermal and inhalation) and from postapplication activities (dermal) on the same day.

Transfer coefficient's for low contact activities (e.g., scouting, weeding) were used in calculating combined risks because an unrealistic overestimation of risks would result from compounding the conservative assumptions regarding exposure to handlers with exposure from high contact activities (e.g., harvesting) on the same day. **Table 6.3.2.7 below, presents some combinations of residential applicator and postapplication activities that resulted in the highest exposure potential but, where exposure estimates for each separate activity were not of concern. These combinations result in MOEs of >100, and are not of concern to HED.**

Table 6.3.2.7 Combined Handling and Postapplication Risks from Residential Malathion Uses (Adults)

Scenario	Total Dermal Daily Dose (mg/kg/day)	Total Dermal MOE[1]	Total Inhal. Daily Dose (mg/kg/day)	Total Inhal. MOE[1]	Total Combined MOE[2]
Mixing, loading and applying **wettable powder** with low-pressure handwand **on vegetable gardens** plus Postapplication activities **with home fruit trees.**	0.47	270	0.0014	18,000	260
Mixing, loading and applying **wettable powder** with low-pressure handwand **on vegetable gardens** plus Postapplication activities **with vegetable gardens.**	0.37	340	0.0014	18,000	330
Mixing, loading and applying **liquids** with low-pressure handwand **on fruit trees** plus Postapplication activities **with home fruit trees**.	0.29	440	0.00001	2,600,000	440
Mixing, loading and applying **liquids** with low-pressure handwand **on vegetable gardens** plus Postapplication activities **with fruit trees**.	0.24	530	0.00001	2,600,000	530
Mixing, loading and applying **liquids** with low-pressure handwand **on fruit trees** plus postapplication activities **with vegetable gardens**.	0.19	670	0.00001	2,600,000	670

1. Total MOE = NOAEL/Total Daily Dose, where:
BMDL = 127 mg/kg/day, for dermal, with an LOC of 100 for cholinesterase effects
NOAEL = 25.8 mg/kg/day, for inhalation, with an LOC of 100 for cholinesterase effects; Note: LOAEL = 25.8 mg/kg/day, for inhalation, with an LOC of 1000 for histopathological lesion effects (not used for combined risk determination)

2 Total Combined MOE = 1/[(1/MOEdermal) + (1/MOEinhalation)]

6.3.3 Other (Public Health, Spray Drift, etc.)

HED has determined that there is potential for postapplication exposures to adults and children contacting residues on turf resulting from public health mosquito control, boll weevil uses, and fruit fly (Medfly) uses. Inhalation exposure usually does not factor significantly into postapplication risk for home and garden uses. However, due to the use of malathion in ULV aerial and truck fogger applications to control mosquitoes (adulticide), its wide use in USDA's Boll Weevil Eradication Program, and Fruit Fly (Medfly) control, risk assessments have been developed for residential inhalation exposure from aerial ULV and ground-based applications. In addition, potential dermal and non-dietary exposures have been estimated because of the concern for the residues that may be deposited during the ultra low volume (ULV) aerial and ground-based fogger applications in the vicinity of residential dwellings and other recreational areas (e.g., school playgrounds, parks, athletic fields). The dermal, inhalation, and hand-to-mouth components of postapplication exposure have been included for public health mosquito control, Boll Weevil and Fruit Fly (Medfly) uses and are fully described below in sections 6.3.3.1, 6.3.3.2, and 6.3.3.3.

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for malathion. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift to specific products with significant risks associated with drift.

6.3.3.1 Public Health ULV Mosquito Control Uses

HED has determined that there are potential postapplication exposures to adults and children from the ultra low volume (ULV) aerial and ground-based fogger applications for public health mosquito control uses in the vicinity of residential dwellings. The assessment has been developed to ensure that the potential exposures are not underestimated and to represent a conservative model that encompasses potential exposures received in other recreational areas (e.g., school playgrounds, parks, athletic fields). The scenarios likely to result in postapplication exposures are as follows:

- Dermal exposure from residues deposited on turf at residential, park, and school sites (adult and toddler);
- Incidental nondietary ingestion of residues deposited on turf at residential, park, and school sites from hand-to-mouth transfer (toddler);
- Incidental nondietary ingestion of residues deposited on turf at residential, park, and school sites from object-to-mouth transfer (toddler); and
- Incidental nondietary ingestion of soil from treated areas (toddler); and Inhalation (adult and toddler).

Residential risks were assessed for both adults and toddlers. The equations and assumptions used for each of the scenarios were taken from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments guidance document. Interim changes to these SOPs have been adopted by the HED Exposure Science Advisory Council regarding standard values for turf transferrable residues, turf transfer coefficient and hand-to-mouth activities and are included in this assessment. For calculation formulas relevant to exposure on treated turf, refer to the Revised Residential Exposure and Risk Assessment (J. Arthur, D330678). Additionally, the open literature and the Spray Drift Task Force (SDTF) *Ag*DRIFT model were used to assess air concentrations and deposition to residential turf after aerial applications of ULV liquids.

No proprietary data from the Spray Drift Task Force were used in this assessment. Additionally, AgDRIFT was recently presented before the FIFRA Science Advisory Panel. Modifications to the model are possible as a result of the SAP comments. These modifications, however, are anticipated by HED to not significantly alter the results of this assessment. Any significant modifications to the model may require further refinement of this assessment. Even given the potential for modification of the model, the assessment is much more refined than assuming 100 percent of the application rate is deposited on the turf in residential areas where aerial ULV applications occur. The latter approach (i.e., 100% deposition) is recognized by HED as completely unrealistic given what is known concerning the engineering aspects of malaria vector control and other aerial ULV applications.

The following general assumptions were made for all scenarios:

- Postapplication was assessed on the same day the pesticide is applied because it was assumed that the homeowner could be exposed to turfgrass immediately after application. Therefore, postapplication exposures were based on day 0.

- Adults were assumed to weigh 70 kg. Toddlers (3 years old), used to represent the 1 to 6 year old age group, were assumed to weigh 15 kg.

- The maximum labeled application rate (ULV) for aerial mosquito control is 0.23 lb ai/acre. The maximum labeled application rate (ULV) for ground-based fogger mosquito control is 0.11 lb ai/acre. (based on FYFANON® ULV label; EPA Reg. No. 4787-8).

For additional information regarding specific scenario assumptions, please refer to the Revised Residential Exposure and Risk Assessment (J. Arthur, D330678).

An assessment of **dermal, inhalation and incidental oral exposure from this malathion use resulted in MOEs for individual routes of exposure that did not exceed HED's level of concern (adult dermal LOC of 100; children dermal LOC of 1000; inhalation LOC of 1000; and oral LOC of 100). Likewise, when exposure from dermal, inhalation and incidental oral routes were combined, the resulting MOEs do not exceed HED's level of concern**. The combined inhalation and dermal short-term risk estimates for adults, and combined dermal, inhalation and incidental oral risk estimates for toddlers from postapplication exposure following public health mosquito treatment are presented below in Table 6.3.3.1. Adult combined risks were calculated using the Total MOE approach. For toddlers, however, combined risk was estimated by calculating an aggregate risk index (ARI) because, while dermal and inhalation endpoint effects are the same, they occur at different dose levels and have different associated levels of concern for the MOE (i.e., for dermal and inhalation, the LOC = 1000; for incidental oral, the LOC = 100). Calculated ARIs of > 1 are not of concern. For additional information on the formula and methods used to calculate ARI for toddlers, please refer to the Revised Residential Exposure and Risk Assessment (J. Arthur, D330678).

It is also important to note that these estimated risks are based on conservative assumptions regarding the circumstances of exposure:

- Maximum label rates were used;
- For truck-foggers, individuals were assumed to be standing for 20 minutes in an air concentration that is based on the entire application rate (with a 1% dilution factor);
- No dissipation (breakdown) of malathion in the breathing zone concentration was assumed;
- The dermal transfer coefficient used for the toddler calculation, based on a Jazzercise activity, represents a bounding estimate of dermal exposure; and
- The duration in which exposed populations are assumed to be in contact with treated turf (i.e., 2 hours/day for adults and toddlers) is an upper percentile estimate based on data available in the *EPA Exposure Factors Handbook.*

Under the Food Quality Protection Act (FQPA), various exposure scenarios that could result in multiple non-occupational exposures to a particular pesticide must be aggregated. A realistic exposure assessment under this FQPA requirement would aggregate exposure only from activities that would reasonably be expected to occur on the same day. The assessment is done separately for adults and toddlers.

Table 6.3.3.1 Combined Dermal, Inhalation and Incidental Oral Short-term Risks from Public Health Mosquito Control									
Scenario	Application Rate	Dermal Daily Dose (mg/kg/day)	Dermal MOE[1]	Inhalation Daily Dose (mg/kg/day)	Inhal. MOE[1]	Total Incid. Oral Dose[2] (mg/kg/day)	Total Incid. Oral MOE[1]	Total MOE[3]	Total ARI[3]
Adult									
(1) Postapplication following **Ground ULV** truck fogger application	0.0000025 (lb ai/sq ft)	0.00033	380,000	0.00028	92,000	N/A	N/A	74,000	N/A
(2) Postapplication following **Aerial ULV** application.	0.0000053 (lb ai/sq ft)	0.005	25,000	0.00013 (helicopter)	200,000	N/A	N/A	22,000	N/A
				0.000052 (fixed-wing)	500,000			24,000	N/A
Toddler									
(1) Postapplication following **Ground ULV** application	0.0000025 (lb ai/sq ft)	0.00055	230,000	0.0011	23,000	0.000084	85,000	N/A	20
(2) Postapplication following **Aerial ULV** application	0.0000053 (lb ai/sq ft)	0.0083	15,000	0.00057 (helicopter)	40,000	0.0012	6000	N/A	9
				0.00022 (fixed-wing)	120,000			N/A	10

1. MOE = NOAEL or BMDL/ADD, where

$BMDL_{20}$ (adult dermal) = 127 mg/kg/day, with an LOC of 100.
NOAEL (adult inhalation) = 25.8 mg/kg/day, with an LOC of 100 (for cholinesterase endpoint);
Note: LOAEL = 25.8 mg/kg/day, for inhalation, with an LOC of 1000 for histopathological lesion effects (not used for combined risk determination)
$BMDL_{20}$ (toddler dermal) = 127 mg/kg/day, with an LOC of 1000.
NOAEL (toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000.
$BMDL_{10}$ (toddler incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

2. Total Incidental oral dose = combined dose from hand-to-mouth, object-to-mouth, and soil ingestion.
3. Total MOEs greater than or equal to 100 for adults, or Total ARIs greater than or equal to 1 for toddlers, are not of concern to HED.
N/A = Not applicable.

6.3.3.2 Boll Weevil Eradication Use

The Boll Weevil Eradication Program (BWEP) is a special project under the direction of the United States Department of Agriculture. This program is unique in that it attempts to systematically eradicate the boll weevil pest in cotton-growing regions of the US. This comprehensive and systematic approach was considered to be sufficiently different from normal agricultural use of malathion, that it was decided to address the exposure and risk from the BWEP, separately in the sections to follow.

The BWEP utilizes malathion formulated as a 95% a.i. ultra low volume (ULV) concentrate, applied primarily by fixed-wing aircraft (98%), with the remaining acres treated by high-cycle ground equipment, mist blowers, and helicopters. Label application rates range from 0.3 to 1.5 lb ai/acre. Typical application rates are reported to be 10 to 12 fluid ounces per acre (or 0.7 to 0.9 lb ai/A using Fyfanon® ULV). Malathion applications begin at the pinhead square crop phenology and end at the defoliation stage, or if a killing freeze occurs. Typical length of the program is four years. The number of applications is 6-10 in the first year; 4-6 in the second year; 1-2 in the third year; and minimal in the fourth year. Applications are made at intervals of 7 - 10 days.

HED has determined that there is potential for non-occupational postapplication exposures to malathion residues from spray drift associated with the use of malathion on cotton in the USDA BWEP. These potential exposures are estimated because of the concern for residues that may be deposited during the ultra low volume (ULV) aerial applications in the vicinity of residential dwellings. The assessment has been developed to ensure that the potential exposures are not underestimated and to represent a conservative model that encompasses potential exposures received in other recreational areas (e.g., school playgrounds, parks, athletic fields).

This assessment considers the potential for inhalation (adults and children), dermal contact with residues on residential turf (adults and children), and incidental ingestion (children only) of malathion residues on residential turf and soil, following application of malathion to nearby cotton fields. HED believes it is reasonable to expect dermal, inhalation, and incidental oral exposure from this application to occur in a single day.

The scenarios likely to result in dermal and inhalation (adult and child), and incidental non-dietary (child) postapplication exposures resulting from boll weevil control uses are identical to those used for assessment of bystander exposures resulting from mosquito control uses.

The same data sources, equations and assumptions used for assessment of bystander exposures resulting from mosquito control have been used for assessment of spray drift from Boll Weevil control uses, with the following exceptions:

- The typical maximum application rate (ULV) for aerial boll weevil control is 1.2 lb ai/acre.
- From the edge of the treatment area to 75 feet downwind, approximately 57 percent of the theoretical application is deposited. Thus, the amount of residue on turf resulting from aerial ULV application and available for dermal transfer is estimated as follows:
- amount available for transfer = amount deposited x amount dislodgeable (1.3%), where, amount deposited = application rate x deposition rate (57%).

For additional information regarding specific scenario assumptions, please refer to the Revised Residential Exposure and Risk Assessment (J. Arthur, D330678).

Results of the residential postapplication risk assessment for short-term exposure from boll weevil treatment are presented in Table 6.3.3.2. Risks were estimated by comparing potential exposures against appropriate toxicity endpoints for the routes and durations of anticipated exposure. An assessment of **dermal, inhalation and incidental oral exposure from this malathion use resulted in MOEs for individual routes of exposure that did not exceed HED's level of concern (adult dermal LOC of 100; children dermal LOC of 1000; inhalation LOC of 1000; and oral LOC of 100). Likewise, when exposure from dermal, inhalation and incidental oral routes were combined, the resulting MOEs do not exceed HED's level of concern**. Results demonstrate that risks are not of concern for adults and toddlers from the use of malathion in the BWEP. Combined Risks to adults and toddlers are also not of concern for postapplication residential (bystander) exposure in areas nearby fields being treated for boll weevil.

Table 6.3.3.2 Combined Dermal, Inhalation and Incidental Oral Short-term Risks from Boll Weevil Treatment									
Scenario	Application Rate	Dermal Daily Dose (mg/kg/day)	Dermal MOE[1]	Inhalation Daily Dose (mg/kg/day)	Inhal. MOE[1]	Total Incidental Oral Dose[2] (mg/kg/day)	Total Incidental Oral MOE[1]	Total MOE[3]	Total ARI[3]
Adult									
Postapplication Following Aerial ULV Boll Weevil Treatment	0.000028 (lb ai/sq ft)	0.041	3100	0.00026	99,000	N/A	N/A	3000	N/A
Toddler									
Postapplication Following Aerial ULV Boll Weevil Treatment	0.000028 (lb ai/sq ft)	0.069	1800	0.0013	20,000	0.012	590	N/A	1.3

1. MOE = NOAEL or BMDL/ADD, where

$BMDL_{20}$ (adult dermal) = 127 mg/kg/day, with an LOC of 100.
NOAEL (adult inhalation) = 25.8 mg/kg/day, with an LOC of 100;
Note: LOAEL = 25.8 mg/kg/day, for inhalation, with an LOC of 1000 for histopathological lesion effects (not used for combined risk determination)
$BMDL_{20}$ (toddler dermal) = 127 mg/kg/day, with an LOC of 1000.
NOAEL (toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000.
$BMDL_{10}$ (toddler incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

2. Total Incidental oral dose = combined dose from hand-to-mouth, object-to-mouth, and soil ingestion.
3. Total MOEs greater than or equal to 100 for adults, or Total ARIs greater than or equal to 1 for toddlers, are not of concern to HED.
N/A = Not applicable

Monitoring data collected by the USDA Animal and Plant Health Inspection Service (APHIS) also show levels of exposure to be relatively low in sites adjacent to spraying in accordance with the USDA BWEP. For example, in the USDA Environmental Monitoring Report - 1995 Southeast BWEP, all personal breathing zone samples were < 0.001 mg/m^3 . This, when compared to the air concentration predicted by the HED assessment (1.32 mg/m^3), indicates that the HED assessment includes assumptions that lead to estimates of exposure that are higher than are being found in some actual boll weevil treatment sites. For a complete discussion of monitoring data see the Revised Residential Exposure and Risk Assessment (J. Arthur, D330678).

6.3.3.3 Fruit Fly (Medfly) Control

A manual search for specific pests in the OPP's REF's database identified a total of five 24(c) registrations to control fruitflies (the most notorious being the Mediterranean fruit fly, or "medfly"), in CA, FL, and TX. In order for the 24(c) registration uses to be considered in a reregistration eligibility decision, they have been included in this exposure/risk assessment.

Treatment programs to control fruit fly pests have been undertaken in the states of California, Florida and Texas. Applications are usually made by helicopters flying at 200 to 300 feet altitude, or fixed-wing aircraft flying at 500 feet altitude. Sensitive areas, such as bodies of water are usually given a 200-foot, no-spray buffer zone. Malathion end-use products are mixed with a protein hydrolase bait which is sprayed aerially or by ground sprayers, settles on target surfaces, and is eaten by the target fruit fly pests.

HED has determined that there is a potential for non-occupational postapplication exposures to malathion from its use to control various fruit fly pests. These potential exposures result from direct deposition of residues in residential areas during the area-wide treatment of fruit flies and from spraydrift to residential areas nearby to treated agricultural fields. The assessment has been developed to ensure that the potential exposures are not underestimated and to represent a conservative model that encompasses potential exposures received in residential and public places such as recreational areas (e.g., school playgrounds, parks, athletic fields).

This assessment considers the potential for inhalation (adults and children), dermal contact with residues on residential turf (adults and children), and incidental ingestion (children only) of malathion residues on residential turf and soil, following application of malathion to control fruit flies. HED believes it is reasonable to expect dermal, inhalation, and incidental oral exposure from this application to occur in a single day.

The scenarios likely to result in dermal and inhalation (adult and child), and incidental non-dietary ingestion (child) exposures resulting from fruit fly control uses are as follows:

- Dermal exposure from residues deposited on turf at residential, park, and school sites (adult and toddler);

- Incidental nondietary ingestion of residues deposited on turf at residential, park, and school sites from hand-to-mouth transfer (toddler);
- Incidental nondietary ingestion of residues deposited on turf at residential, park, and school sites from object-to-mouth transfer (toddler);
- Incidental nondietary ingestion of residues deposited on soil at residential, park, and school sites from ingestion of soil (toddler); and
- Inhalation from airborne spray (adult and toddler).

Residential exposures were assessed for both adults and toddlers based on guidance provided in the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment (12/11/97 Version)* and subsequent revisions (HED Science Advisory Council on Exposure, Policy 11, February 2001). Surface residue and air concentration monitoring data are available from the state of California and from the United States Department of Agriculture's (USDA) Cooperative Medfly Project in the state of Florida. While the sources of data show similar results when adjusted for sampling times and application rates, the data from the 1991 California Department of Health Services (CDHS) were used because they are based on the most thorough analysis of the data, and because the data are used in the California's Health Risk Assessment. Also, these data were used as a basis for HED's Section 18 assessment of malathion for use in controlling the Med fly in Florida (January 12, 1999; DP Barcodes D250394, D249865 & D251682).

The following general assumptions were made for all scenarios:

- Exposure to residues on turfgrass following aerial treatment of fruit flies is considered to be the worst-case scenario for use in assessing residential dermal postapplication risk.

- Postapplication was assessed on the same day the pesticide is applied because it was assumed that the homeowner could be exposed to turfgrass immediately after application. Therefore, postapplication exposures were based on day 0.

Adult postapplication exposures following aerial fruit fly application are not of concern. The results of the residential postapplication exposure assessment resulting from the fruit fly control use are presented in Table 6.3.3.3. Toddler risk is driven by dermal exposure to residues on turf from spraydrift residues resulting from fruit fly treatment.

Table 6.3.3.3 Combined Dermal, Inhalation and Incidental Oral Short-term Risks From Fruit Fly Treatment								
Scenario	Application Rate	Dermal Daily Dose (mg/kg/day)	Dermal MOE[1]	Inhalation Daily Dose (mg/kg/day)	Inhal. MOE[1]	Total Incidental Oral Dose[2] (mg/kg/day)	Total Incidental Oral MOE[1]	Total Risk
Adult								
Postapplication Following Aerial Fruit Fly Treatment	0.09 (lb ai/A)	0.023	5500	1.5E-7	1.7E+8	Not Applicable	Not Applicable	5500 (Total MOE[3])
Toddler								
Postapplication Following Aerial Fruit Fly Treatment	0.09 (lb ai/A)	0.038	3300	5.7E-7	4.5E+7	0.0019	3700	1.7 (Total ARI[4])

1. MOE = NOAEL or BMDL/ADD, where

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$BMDL_{20}$ (adult dermal) = 127 mg/kg/day, with an LOC of 100;
$BMDL_{20}$ (toddler dermal) = 127 mg/kg/day, with an LOC of 1000;
$BMDL_{10}$ (toddler incidental oral) = 7.1 mg/kg/day, with an LOC of 100.
LOAEL (adult and toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000 (histopathologic lesions)
NOAEL (adult inhalation) = 25.8 mg/kg/day, with an LOC of 100 (for cholinesterase effects).
NOAEL (toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000 (for cholinesterase effects).

2. Total Incidental oral dose = combined dose from hand-to-mouth, object-to-mouth, and soil ingestion.

3. Total MOEs equal to, or greater than 100, do not exceed HED=s level of concern.

4. Total ARIs equal to, or greater than 1, do not exceed HED=s level of concern.

6.3.4 Malaoxon Residential Exposure

In vivo, malaoxon is the active ChEI, oxon metabolite of malathion. Under some conditions, malaoxon can be formed as an environmental breakdown product of malathion. Monitoring data indicate malaoxon's presence in air, soil, sand and hard surfaces; with minimal to no presence on foliage, following aerial spraying. Further, these data indicate that the greatest potential for malaoxon formation occurs when malathion residues deposit on hard, dry surfaces. For these reasons, HED believes that residential contact with outdoor hard surfaces following aerial application of malathion presents the most relevant and worst case scenario for assessing the risk from malaoxon exposure. Specifically, HED has estimated toddler exposures from potential contact with malaoxon residues on wood decks and playground equipment following aerial ULV public health mosquito treatment, boll weevil eradication, and fruit fly treatment. The full risk from this scenario must also include exposures to untransformed malathion residues. Therefore, screening level and refined risks were estimated for toddler exposure to combined residues of malaoxon and untransformed malathion deposited on decks and playground equipment. Because toddler risks from this scenario are believed to represent the worst case for all residential populations engaged in any activity on outdoor hard surfaces, adult exposures and risks were not assessed, nor were risks from contact with driveways, sidewalks, etc.

6.3.4.1 Malaoxon Residential Exposure Scenarios

Malaoxon residues on decks and playground equipment result from the transformation of malathion residues that have deposited following area-wide aerial or ground-fogging treatments. Because both chemicals present the same toxic effect (i.e., cholesterase inhibition), exposure to both malaoxon and untransformed malathion residues must be accounted for in the estimate of risk from contacting decks and playground equipment.

6.3.4.2 Malaoxon Residential Exposure Data Sources and Assumptions

Malaoxon residues are determined by starting with the malathion residues estimated in previous sections of this document to deposit on hard surfaces as a result of aerial ULV public health mosquito treatment, boll weevil eradication, and fruit fly treatment. These malathion residues are adjusted by the malathion-to-malaoxon transformation factor (1%, 5%, or 10%), and by a toxicity adjustment factor of 61x. **Untransformed malathion residues** are determined simply by adjusting the malathion residues estimated in previous sections of this document to deposit on hard surfaces as a result of aerial ULV public health mosquito treatment, boll weevil eradication, and fruit fly treatment by dissipation adjustment factors of 99%, 40% or 6% (corresponding to the timeframe in which malaoxon transformation is estimated to reach 1%, 5% and 10%, respectively), but no TAF is applied.

Exposure is expressed as average daily doses (ADD) mg/kg/day and are determined separately for malaoxon and malathion residues on hard surfaces for various routes of exposure (i.e., dermal contact (for adults and toddlers) and incidental oral (for toddlers only)). The individual ADD's are then added together and compared to the appropriate common toxicity endpoint to determine the combined malathion and malaoxon risk.

6.3.4.3 Malaoxon Residential Risk Characterization

The calculated exposures in this assessment are not considered to underestimate risk because they include maximum application rates and conservative deposition estimates. The following is a discussion of the input variables and assumptions used in this assessment. The detailed results of the residential postapplication exposure assessment for malaoxon, are presented below in Tables 6.3.4.3a-3j.

Table 6.3.4.3a Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Public Health Mosquito Control (with 1% malaoxon formation on outdoor hard surfaces)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.0000053	0.09 (malathion 99%) 0.07 (malaoxon 1%)	393	1	0.0024 0.0018	0.0042	30,000
Dermal (grnd ULV)	0.0000025	0.0061 (malathion 99%) 0.0037 (malaoxon 1%)	393	1	0.00016 0.000097	0.00026	490,000
Hand-to-Mouth (air ULV)	0.0000053	0.045 (malathion 99%) 0.035 (malaoxon 1%)	-	1	0.0006 0.00047	0.0011	6,500
Hand-to-Mouth (grnd ULV)	0.0000025	0.0030 (malathion 99%) 0.0019 (malaoxon 1%)	-	1	0.00004 0.000025	0.000065	110,000

A Application rates are estimated as follows: AR air ULV = (0.23 lb ai/A)/43,560 sq. ft. per A; AR ground ULV = (0.11 lb ai/A)/43,560 sq. ft. per A.

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition [0.35 for air ULV, or 0.05 for ground ULV]) * (1% for malaoxon transformation; 99% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3b Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Public Health Mosquito Control (with 5% malaoxon formation on outdoor hard surfaces)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.0000053	0.036 (malathion 40%) 0.28 (malaoxon 5%)	393	1	0.0002 0.0073	0.0075	17,000
Dermal (grnd ULV)	0.0000025	0.0025 (malathion 40%) 0.019 (malaoxon 5%)	393	1	0.000066 0.0005	0.00057	220,000
Hand-to-Mouth (air ULV)	0.0000053	0.018 (malathion 40%) 0.14 (malaoxon 5%)	-	1	0.00024 0.0019	0.002	3600
Hand-to-Mouth (grnd ULV)	0.0000025	0.0012 (malathion 40%) 0.0093 (malaoxon 5%)	-	1	0.000016 0.00012	0.00014	51,000

a Application rates are estimated as follows: AR air ULV = (0.23 lb ai/A)/43,560 sq. ft. per A; AR ground ULV = (0.11 lb ai/A)/43,560 sq. ft. per A

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition [0.35 for air ULV, or 0.05 for ground ULV]) * (5% for malaoxon transformation; 40% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3c Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Public Health Mosquito Control (with 10% malaoxon formation on outdoor hard surfaces)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.0000053	0.0055 (malathion 6%) 0.55 (malaoxon 10%)	393	1	0.00014 0.014	0.014	9100
Dermal (grnd ULV)	0.0000025	0.00037 (malathion 6%) 0.037 (malaoxon 10%)	393	1	0.0000097 0.00097	0.00098	130,000
Hand-to-Mouth (air ULV)	0.0000053	0.0027 (malathion 6%) 0.28 (malaoxon 10%)	-	1	0.000036 0.0037	0.0037	1900
Hand-to-Mouth (grnd ULV)	0.0000025	0.00018 (malathion 6%) 0.019 (malaoxon 10%)	-	1	0.0000024 0.00025	0.00025	28,000

a Application rates are estimated as follows: AR air ULV = (0.23 lb ai/A)/43,560 sq. ft. per A; AR ground ULV = (0.11 lb ai/A)/43,560 sq. ft. per A.

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition [0.35 for air ULV, or 0.05 for ground ULV]) * (10% for malaoxon transformation; 6% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

BMDL20 (dermal) = 127 mg/kg/day, with an LOC of 1000;
BMDL10 (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3d Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Boll Weevil Control (with 1% malaoxon formation on outdoor hard surfaces)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.000028	0.77 (malathion 99%) 0.48 (malaoxon 1%)	393	1	0.02 0.013	0.033	3800
Hand-to-Mouth (air ULV)	0.000028	0.39 (malathion 99%) 0.24 (malaoxon 1%)	-	1	0.0052 0.0032	0.0084	850

a Application rates are estimated as follows: AR air ULV = (1.2 lb ai/A)/43,560 sq. ft. per A.

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition (0.57 for air ULV) * (1% for malaoxon transformation; 99% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3e Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Boll Weevil Control (with 5% malaoxon formation on outdoor hard surfaces)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.000028	0.31 (malathion 40%) 2.4 (malaoxon 5%)	393	1	0.0081 0.063	0.071	1800
Hand-to-Mouth (air ULV)	0.000028	0.16 (malathion 40%) 1.19 (malaoxon 5%)	-	1	0.0021 0.016	0.018	390

a Application rates are estimated as follows: AR air ULV = (1.2 lb ai/A)/43,560 sq. ft. per A

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition (0.57 for air ULV) * (5% for malaoxon transformation; 40% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3f Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Boll Weevil Control (with 10% malaoxon formation on outdoor hard surfaces, calculated with the application rate typically used in the BWEP)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.000021	0.035 (malathion 6%) 3.58 (malaoxon 10%)	393	1	0.0009 0.09	0.09	1400
Hand-to-Mouth (air ULV)	0.000021	0.0176 (malathion 6%) 1.79 (malaoxon 10%)	-	1	0.000235 0.0239	0.02	360

a Application rates are estimated as follows: AR air ULV = (0.9 lb ai/A)/43,560 sq. ft. per A

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition (0.57 for air ULV) * (10% for malaoxon transformation; 6% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3g Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Boll Weevil Control (with 10% malaoxon formation on outdoor hard surfaces)

Scenario	Application Rate (AR) Per Treatment (lbs ai/sq ft)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.000028	0.047 (malathion 6%) 4.77 (malaoxon 10%)	393	1	0.0012 0.12	0.12	1100
Hand-to-Mouth (air ULV)	0.000028	0.023 (malathion 6%) 2.39 (malaoxon 10%)	-	1	0.0003 0.03	0.03	240

a Application rates are estimated as follows: AR air ULV = (1.2 lb ai/A)/43,560 sq. ft. per A

b Surface transferrable residue (ug/cm^2) = [AR (lbs ai/ft^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * deposition (0.57 for air ULV) * (10% for malaoxon transformation; 6% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 4.54E+8 ug/lb * 1.08E-3 ft^2/cm^2].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3h Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Fruit Fly Treatment (with 1% malaoxon formation on outdoor hard surfaces

Scenario	Deposition (mg/cm^2)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.0011	0.11 (malathion 99%) 0.067 (malaoxon 1%)	393	1	0.0029 0.0018	0.0047	27,000
Hand-to-Mouth (air ULV)	0.0011	0.054 (malathion 99%) 0.034 (malaoxon 1%)	-	1	0.00072 0.0045	0.0012	6000

a Deposition from California monitoring data.

b Surface transferrable residue (ug/cm^2) = [monitored deposition (mg/cm^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * (1% for malaoxon transformation; 99% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 1000 ug/mg].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;

$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3i Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Fruit Fly Treatment (with 5% malaoxon formation on outdoor hard surfaces)

Scenario	Deposition (mg/cm^2)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[d]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[e]
Dermal (air ULV)	0.0011	0.044 (malathion 40%) 0.34 (malaoxon 5%)	393	1	0.0012 0.0089	0.01	13,000
Hand-to-Mouth (air ULV)	0.0011	0.022 (malathion 40%) 0.17 (malaoxon 5%)	-	1	0.00029 0.0023	0.0026	2700

a Deposition from California monitoring data.

b Surface transferrable residue (ug/cm^2) = [monitored deposition (mg/cm^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * (5% for malaoxon transformation; 40% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 1000 ug/mg].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];

Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;
$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

Table 6.3.4.3j Malathion/Malaoxon Toddler Short-Term Postapplication Risks from Fruit Fly Treatment (with 10% malaoxon formation on outdoor hard surfaces)

Scenario	Deposition (mg/cm^2)[a]	STR (ug/cm^2)[b]	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	ADD (mg/kg/day)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.0011	0.0066 (malathion 6%) 0.67 (malaoxon 10%)	393	1	0.00017 0.018	0.018	7100
Hand-to-Mouth (air ULV)	0.0011	0.0033 (malathion 6%) 0.34 (malaoxon 10%)	-	1	0.000044 0.0045	0.0045	1600

a Deposition from California monitoring data.

b Surface transferrable residue (ug/cm^2) = [monitored deposition (mg/cm^2) * fraction ai retained on hard surface (10% for dermal, and 5% for hand-to-mouth) * (10% for malaoxon transformation; 6% for untransformed malathion) * (61x Toxicity Adjustment Factor for malaoxon residues only) * 1000 ug/mg].

c Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [STR (ug/cm^2) * Tc (cm^2/hr) * mg/1,000 ug * ET (hrs/day)] / [BW (15 kg)];
Hand-to-mouth: = [STR (ug/cm^2) * SA (20 cm^2/event) * FQ (20 events/hr) * mg/1,000 ug * Saliva extraction (50%) * ET (hrs/day)] / [BW (15 kg)];

d MOE = BMDL/ADD, where

$BMDL_{20}$ (dermal) = 127 mg/kg/day, with an LOC of 1000;
$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

The following sections summarize the postapplication risks to toddlers from contacting malathion/malaoxon residues on decks and playground equipment following area wide public health mosquitocide, boll weevil, and fruit fly treatments. HED's LOC is not exceeded if dermal MOEs are greater than or equal to 1000, incidental oral MOEs are greater than or equal to100, and total ARIs (combined dermal and incidental oral exposures) are greater than or equal to 1.

Risks from Public Health Mosquitocide Treatments

All individual dermal and incidental oral risks (MOEs) to toddlers from malathion/malaoxon residues following public health mosquitocide use do not exceed HED's level of concern for both aerial and ground application, and for malathion-to-malaoxon transformation rates of 1%, 5% and 10%. The following are ARIs resulting from combined dermal and incidental oral exposures:

Total ARIs at the 1% rate, are:

- **20** for aerial and
- **340** for ground applications.

Total ARIs at the 5% rate are:

- **12** for aerial and
- **150** for ground applications.

Total ARIs at the 10% rate are:

- **6** for aerial and
- **90** for ground applications.

These ARIs do not exceed HED's level of concern.

Risks from Boll Weevil Eradication Treatments

None of the individual dermal or incidental oral risks (MOEs) to toddlers from malathion/malaoxon residues following boll weevil eradication cause concern to HED for any of the malathion-to-malaoxon transformation rates assessed. The following are Total ARIs resulting from combined dermal and incidental oral exposures at various malathion-to-malaoxon transformation rates:

Total ARI at the 1% rate is **2.6**.

Total ARI at the 5% rate is **1.2**.

Total ARI at the 10% rate is **0.8**.

The total ARIs for the 1% and 5% transformation rates do not exceed HED's level of concern. While the **total ARI for the 10% transformation rate is not greater than or equal to 1 (thus exceeding HED's level of concern), it should be noted that many conservative values were used in the risk calculation, including the maximum supported application rate**.

If the typical application rate of 0.9 lb ai/acre is used for the 10% conversion rate scenario, the total MOE for dermal risk is 1400, for incidental oral risk is 360, and **the total ARI = 1, which is not of concern to HED**. For the 5% conversion rate, the total ARI = 1.6, and for the 1% conversion rate, the ARI = 3.6.

Further, if the typical application rate of 0.9 lb ai/acre and an alternative nozzle orientation (45% backwards or less, with a resulting deposition rate of 50%) is used for the 10% conversion rate scenario, the total ARI = 1.1.

It should be noted that postapplication risks from the use of malathion in the USDA-APHIS Rangeland Grasshopper and Mormon Cricket Suppression Program are not of concern to HED. This program applies malathion in a manner similar to the BWEP, only at approximately one half of the application rate (maximum of 0.62 lb ai/acre). While the BWEP results in a marginal risk concern at the 10% malaoxon transformation rate when using the highest application rate, the much lower rate for grasshopper/cricket suppression would mitigate even that marginal concern.

Risks from Fruit Fly Treatments

All individual and combined dermal and incidental oral risks (MOEs) to toddlers from malathion/malaoxon residues following fruit fly treatment use **do not exceed HED's level of concern** for malathion-to-malaoxon transformation rates of 1%, 5% and 10%. The following are ARIs resulting from combined dermal and incidental oral exposures:

Total ARI at the 1% rate is **12**.

Total ARI at the 5% rate is **8.7**

Total ARI at the 10% rate is **4.9**.

The total ARIs for all transformation rates (1%, 5% and 10%) do not exceed HED's level of concern.

Major uncertainties in the analysis stem from extrapolating malaoxon formation in the residues from dense acid-hydrolyzed corn gluten bait spray formulation used on medflies to formation in the residues from the ultra low volume (fine droplet size) formulations used on mosquitoes and cotton. In addition, the potential rate of malaoxon formation ranges by, at least, an order of magnitude in the available monitoring data (i.e., less than 1% to greater than 10%) depending upon substrate and conditions. Residue studies that looked at the formation and dissipation of malaoxon in airborne spray and, particularly, in deposited residues of ULV malathion over a 10- to 30-day period would eliminate much of the uncertainty. Alternatively, a chamber test to elucidate the conditions for malaoxon formation on a hard surface, with concurrent measurement of off-gas, and radiolabeled mass balance measurements could be performed.

There is also some uncertainty associated with using a single TAF for all durations and exposure scenarios. As noted, acute ChE data are not available at this time for malaoxon; however, these data are considered a data gap that will likely be filled. The degree to which the TAF calculated from steady state measurements of RBC ChE is predictive of acute exposures is unknown.

Although the TAF calculated for malaoxon and malathion is estimated from oral studies, this value approximates the relative potency of the compounds *inside* the body and can therefore be applied to dermal exposures without the need to correct for dermal absorption. There is some uncertainty regarding risk estimates for dermal exposures, it is considered a reasonable approach at this time. The degree to which the pharmacokinetic characteristics of malaoxon (i.e., absorption, distribution, metabolism) are similar to malathion following dermal and inhalation exposure is unknown. At this time, a dermal toxicity study and/or dermal absorption study specific to malaoxon are not available. However, based on the structural similarities between malathion and malaoxon, it is assumed that the toxicokinetic properties regarding dermal absorption are similar between the two chemicals. Also, two dermal studies performed in rats showed RBC ChEI - evidence that malathion is activated to malaoxon following dermal exposure.

7.0 Aggregate Risk Assessments and Risk Characterization

Malathion. Revised *Acute, Probabilistic and Chronic Dietary (Food + Water) Exposure and Risk Assessments for the Malathion Reregistration Eligibility Decision. PC Code: 057701. DP Barcode: D330636. Sheila Piper. July 13, 2006.*

Malathion: *Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D330678. Jack Arthur. July 6, 2006.*

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Aggregate exposure risk assessments were performed for acute and chronic dietary (food + drinking water) exposures using Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03). Exposures to malathion from dietary (food and water) sources alone exceed HED's level of concern. As mentioned earlier in the residential exposure discussion, the potential risks for exposures from residential uses, are also of concern for some scenarios. Any aggregation of residential exposures with dietary levels of exposure would only serve to increase the reported risks. A cancer aggregate risk assessment was not performed. A quantified dose-response cancer assessment is not indicated for malathion as the chemical is classified as "suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential."

7.1 Acute Aggregate Risk

Highly refined probabilistic acute dietary exposure and risk assessment was conducted for all supported food uses and drinking water. Malathion residue estimates used in this assessment include malathion and the oxygen analog metabolite malaoxon. Malaoxon is considered more toxic than malathion. To account for this, HED has performed benchmark dose modeling to evaluate relative potency for malathion and malaoxon. A toxicity adjustment factor (TAF) of 61x calculated from oral studies is applicable to residues of malaoxon (see toxicology section). Pesticide residues were included from 1999-2003 USDA-PDP monitoring data and FDA & FOODCONTAM data which analyzed for malathion and malaoxon, and new chronic Population Adjusted Doses (PADs). Anticipated residues were further refined using percent crop treated (%CT) data and processing factors, where appropriate.

Estimated residues in drinking water were provided by EFED and incorporated directly into the acute assessment. The assessment was conducted using the full distribution of estimated residues in surface water generated by the PRZM-EXAMS model and each residue was multiplied by 61 to account for the malaoxon TAF (see drinking water section) and 100% conversion of malathion to malaoxon was assumed during drinking water treatment. Sixteen separate crop scenarios were selected to model potential malation drinking water residues in surface water drinking sources. The surrogate scenarios were selected and based on geographic location, usage information, percent crop treated, and crop type. Drinking water modeling input parameters included, among other parameters, the following: aerobic soil metabolism half-life; Percent Crop Area (PCA); application method; application date; and application rate.

Acute dietary risk estimates based on various default input parameters from food and drinking water were above HED's level of concern (>100% aPAD) at the 99.9th percentile of exposure. The CA lettuce maximum aerial scenario results in the highest drinking water concentrations, and consequently the highest dietary (food + water) exposure. Dietary exposure to malathion for CA lettuce maximum aerial application at the 99.9th percentile from food and drinking water are 144% of the aPAD for the U.S. population and 520% of the aPAD for all infants (<1 yr old), the most highly exposed population subgroup.

When refinements (proposed application rates and regional PCAs) were made to the estimated

drinking water concentrations, the acute dietary risk estimates from food and drinking water were below HED's level of concern (<100% aPAD) at the 99.9th percentile of exposure. Table 7.1.1 provides a summary of default (upper bound) and refined (lower bound) acute dietary risk estimates from food and water.

Table 7.1.1 Summary of Malathion Acute Dietary Risk Estimates from Food and Drinking Water Scenarios				
Site	**Population**	**% aPAD Estimate based on Default Inputs**	**% aPAD Estimate based on Refined Inputs**	**Comments**
Acute Dietary Estimate at the 99.9th Percentile				
Lettuce, CA max rate aerial app	U.S Population	144	19	Default estimates were refined with: - proposed application values - regional PCA - 1 day half-life
	All Infants (< 1 yr)	**520**	63	
	Children 1-2 yrs	218	29	
	Children 3-5 yrs	200	27	
Peach, TX	U.S Population	146	22	Used GA Peach as surrogate model Default estimate was refined with: - proposed application values - regional PCA[1]
	All Infants (< 1 yr)	485	73	
	Children 1–2 yrs	222	34	
	Children 3-5 yrs	201	30	
Citrus, FL max rate aerial app	U.S Population	123	11	Default estimate was refined with: - proposed application values
	All Infants (< 1 yr)	430	37	
	Children 1–2 yrs	184	20	
	Children 3-5 yrs	166	17	
Tomato, FL max rate aerial app	U.S Population	115	-	Default exposure estimates refined with: - proposed revised application rates - regional PCA All population subgroups have lower estimated exposure than *all infants, therefore* other populations were not modeled
	All Infants (< 1 yr)	410	72	
	Children 1–2 yrs	177	-	
	Children 3-5 yrs	162	-	
Strawberry, CA max rate aerial app	U.S Population	102	20	Default estimate was refined with: - first application date - regional PCA
	All Infants (< 1 yr)	370	59	
	Children 1–2 yrs	153	30	
	Children 3-5 yrs	140	28	
Cotton, MS max rate aerial app	U.S Population	73	7	Default estimates refined with - proposed revised application rates
	All Infants (< 1 yr)	262	19	
	Children 1–2 yrs	111	13	
	Children 3-5 yrs	101	11	
Cherry, WA	U.S Population	62	29	Default estimate was refined with: - proposed application values - regional PCA
	All Infants (< 1 yr)	207	94	
	Children 1–2 yrs	91	43	

Table 7.1.1 Summary of Malathion Acute Dietary Risk Estimates from Food and Drinking Water Scenarios				
Site	**Population**	**% aPAD Estimate based on Default Inputs**	**% aPAD Estimate based on Refined Inputs**	**Comments**
Acute Dietary Estimate at the 99.9th Percentile				
	Children 3-5 yrs	81	39	
Cabbage, FL max rate aerial app	U.S Population	57	13	Default estimates refined with: - proposed revised application rates
	All Infants (< 1 yr)	195	46	
	Children 1–2 yrs	83	22	
	Children 3-5 yrs	76	20	
Sorghum, TX max rate aerial app	U.S Population	39	5	Default estimates refined with: - proposed revised application rates
	All Infants (< 1 yr)	128	12	
	Children 1–2 yrs	58	9	
	Children 3-5 yrs	53	9	
Asparagus, WA	U.S Population	38	-	Default estimate was refined with: - proposed application values - regional PCA All population subgroups have lower estimated exposure than *all infants*, therefore, other populations were not modeled
	All Infants (< 1 yr)	123	94	
	Children 1–2 yrs	55	-	
	Children 3-5 yrs	51	-	
Apple, OR max rate aerial app	U.S Population	21	10	Default estimates were refined with: - - proposed revised application values
	All Infants (< 1 yr)	67	32	
	Children 1–2 yrs	31	16	
	Children 3-5 yrs	28	15	
Alfalfa, MN Max rate Aerial app	U.S Population	15	12	Alfalfa, MN groung application also modeled

[1] An adequate Peach, TX modeling scenario was unavailable; therefore, EPA combined south central PCA with GA peach modeling scenario
-- Not analyzed

The chronic risk from malathion exposure from food alone and food and drinking water is well below HED's level of concern for the U.S. general population and all population subgroups (<1% of the cPAD). The chronic dietary risk estimates from food and drinking water using the worst-case aerial CA lettuce maximum application 1-in-10 year annual concentration are all below HED's level of concern (<100% cPAD) for the U.S. population and all population subgroups. Malathion dietary risk estimates from food and drinking water are <1% of the cPAD for the U.S. population and for all infants <1 yr, the most highly exposed population subgroup (Table 7.1.2).

Table 7.1.2 Malathion Results of Chronic Dietary Risk Analysis For Food Only and Food + Drinking Water-CA Lettuce Maximum Aerial Application					
Population Subgroup	**cPAD** (mg/kg/day)	**Food Only**		**Food + Drinking Water CA Lettuce Max Aerial**	
		Exposure (mg/kg/day)	**% cPAD**	**Exposure** (mg/kg/day)	**% cPAD**
General U.S. Population	0.07	0.000148	<1	0.000224	<1
All Infants (<1 yr old)	0.07	0.000219	<1	0.000469	<1
Children 1-2 yrs old	0.07	0.000343	<1	0.000456	<1
Children 3-5 yrs old	0.07	0.000334	<1	0.000441	<1
Children 6-12 yrs old	0.07	0.000241	<1	0.000315	<1
Youth 13-19 yrs old	0.07	0.000155	<1	0.000210	<1
Adults 20-49 yrs old	0.07	0.000130	<1	0.000201	<1
Adults 50+ yrs old	0.07	0.000077	<1	0.000152	<1
Females 13-49 yrs old	0.07	0.000113	<1	0.000184	<1

7.2 Short-Term Aggregate Risk

Aggregate short-term risk estimates include the contribution of risk from chronic dietary sources (food + water) and short-term residential sources

In aggregating short-term risk, HED considers background chronic dietary exposure (food + drinking water) and short-term non-occupational exposures (dermal + inhalation + incidental oral). Malathion is currently registered for uses that could result in short-term residential handler exposure as well as short-term postapplication exposure to adults and children. HED has determined that, based on the short-term, non-dietary toxicity profile, it is appropriate to aggregate food, water, and residential pathways of exposure for assessment of short-term risks (Table 7.2.1).

HED believes area wide aerial application of malathion for public health uses, boll weevil eradication program (BWEP) and fruit fly eradication represents the worst-case exposure pathways for use in the aggregate assessment. Of these, the BWEP results in highest potential risk. However, because the BWEP and fruit fly eradication programs are limited in scope and duration, the public health use of malathion was chosen for the aggregate assessment. The bowll-weevil assessment was only included for comparative purposes (see table 7.2.1 below).

The aerial application of malathion for public health mosquito control represents the most likely and wide-spread co-occurring exposure pathway for the general U.S. population.

Table 7.2.1 Short-term Aggregate Risk

Population	ARI Food + water[1]	ARI oral[1]	ARI dermal[1]	Aggregate ARI[2]
Public Health Mosquito Control (with 10% malaoxon formation on outdoor hard surface)				
Children 1-2 yrs old	16,000/100* 160	1,900/100* 19	9,100/1000* 9.1	6.0
Boll Weevil Control (with 10% malaoxon formation on outdoor hard surfaces)[3]				
Children 1-2 yrs old	16,000/100 160	360/100 3.6	1,400/1000 1.4	1.0
Boll Weevil Control (with 10% malaoxon formation on outdoor hard surfaces)[4]				
Children 1-2 yrs old	16,000/100 160	360/100 3.6	1,600/1000 1.6	1.1

[1] $ARI = [MOE_{CALCULATED} \div MOE_{ACCEPTABLE}]$ (Note: Target ARI = 1); *MOE/UF

[2] Aggregate $ARI = \dfrac{1}{\frac{1}{ARI_{FOOD+WATER}} + \frac{1}{ARI_{ORAL}} + \frac{1}{ARI_{DERMAL}}}$

[3] Using the typical application rate (0.9 lbs ai/A) and alternative nozzle configuration

[4] Using the typical application rate (0.9 lbs ai/A)=

7.3 Intemediate-Term and Long-Term Aggregate Risk

Intermediate and long term residential exposure scenarios are not considered likely and therefore, aggregate risks for these scenarios were not assessed. Even if intermediate term exposures were possible, because the toxicity endpoint doses are the same for both short and intermediate term exposure the risks will be similar.

7.4 Cancer Risk

A cancer aggregate risk assessment was not performed. A quantified dose-response dietary cancer assessment is not indicated for malathion as the chemical is classified as "suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential."

8.0 Cumulative Risk Characterization/Assessment

The Food Quality Protection Act of 1996 requires EPA to consider potential human health risks from all pathways of dietary and non-dietary exposures to more than one pesticide acting through a common mechanism of toxicity. The Agency has determined that the organophosphate pesticides share a common mechanism of toxicity: inhibition of acetylcholinesterase through phosphorylation of the active site. Malathion is an organophosphate pesticide and is included in the Agency's cumulative risk assessment for this class of pesticides. However, the current document provides risk estimates for malathion and its oxon metabolite, malaoxon. The revised organophosphate (OP) cumulative risk assessment was released to the public for comment in the Federal Register on June 20, 2002 (67 FR 41993). Information about organophosphate pesticides, the OP cumulative risk assessment, and related documents may be found at: http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposures and Risks

Malathion: *Occupational Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D330675. Jach Arthur. July 6, 2006.*

Occupational exposure may result from malathion agricultural uses (i.e., multiple food-use crops) and non-agricultural uses (e.g., outdoor residential vegetable gardens, home orchards, ornamentals and perimeter house treatments, and wide-area mosquito treatment). Exposure may occur to both handlers and postapplication workers who enter and conduct activities in treated use sites.

9.1 Occupational Use Pattern

Based on a July 2002 review of OPP Reference Files System (REFS), there are active

registrations for 213 products containing malathion. Malathion, [S-1,2-bis (ethoxycarbonyl)ethyl O,O-dimethyl phosphorodithioate] is an organophosphate insecticide, formulated as a technical (91-95% ai), a dust (1-10% ai), an emulsifiable concentrate (3-82% ai), a ready-to-use (1.5-95% ai), a pressurized liquid (0.5-3% ai), and a wettable powder (6-50% ai). Several of the 95% liquids are intended for Ultra-Low-Volume (ULV) applications.

At this time, malathion is registered for occupational use on terrestrial food and feed crops, indoor food crops, aquatic food crops, terrestrial non-food crops, forestry, indoor non-food, and indoor and outdoor residential. A summary of occupational use sites is listed below in Tables 9.1.1a and 9.1.1b.

Table 9.1.1a Summary of Agricultural Crop Use Sites

Crop Group	Formulation	Use Site	Application Rates (lb ai/acre, unless otherwise stated)			Application Equipment
			Label	SRRD Proposed	Growers Proposed	
BERRY: LOW	EC, WP	Strawberry	2	NA	NA	Chemigation, Groundboom
	WP	Blueberries (lowbush)	1.25	NA	NA	Aerial, Chemigation, Groundboom
	WP - ULV		0.76	NA	NA	
BUNCH/ BUNDLE	EC	Hops	0.63	NA	NA	Chemigation, Groundboom, Airblast
FIELD & ROW CROPS: LOW to MEDIUM (Nongrass Animal Feeds)	EC	Alfalfa, Clover, Lespedeza, Lupine, Vetch	1.25	NA	NA	Aerial, Chemigation, Groundboom
	EC - ULV		0.62	NA	NA	
FIELD & ROW CROPS: LOW to MEDIUM (Cereal Grains)	EC	Barley, Oats, Rice, Rye, Wild Rice	1.25	NA	NA	Aerial, Chemigation, Groundboom
		Wheat	1.25	1.0	NA	
	EC - ULV	Barley, Oats, Rice, Rye, Wheat, Wild Rice	0.61	NA	NA	
FIELD & ROW CROPS: LOW to MEDIUM (Fiber)	EC	Cotton	2.5	NA	NA	Aerial, Chemigation, Groundboom
	EC - ULV		1.22	NA	NA	
	EC	Flax	0.5	NA	NA	
FIELD & ROW CROPS: LOW to MEDIUM (Forage Grass)	EC	Grass	1.25	NA	NA	Aerial
	EC - ULV		0.92	NA	NA	

Table 9.1.1a Summary of Agricultural Crop Use Sites						
Crop Group	Formulation	Use Site	Application Rates (lb ai/acre, unless otherwise stated)			Application Equipment
			Label	SRRD Proposed	Growers Proposed	
FIELD & ROW CROPS: LOW to MEDIUM (Sugarbeets)	EC	Sugarbeets	1.25	NA	NA	Aerial, Chemigation, Groundboom
FIELD & ROW CROPS: LOW to MEDIUM (Peanuts)	EC	Peanuts	2.5	NA	NA	Aerial, Chemigation, Groundboom
FIELD & ROW CROPS: LOW to MEDIUM (Herbs & Spices)	EC	Mint	0.94	NA	NA	Chemigation, Groundboom
FIELD & ROW CROPS: LOW to MEDIUM (Legume Vegetable)	EC	Peas	2.5	1.0	NA	Aerial, Chemigation, Groundboom
FIELD & ROW CROPS: TALL	EC	Corn, Sorghum	1.25	1.0	NA	Aerial, Chemigation, Groundboom
	EC - ULV		0.61	NA	NA	
CUT FLOWERS	EC	Flowers and Foliage Grown for Cuttings	2.5	NA	NA	Chemigation, Groundboom, Handgun, Low-Pressure Handwand, Backpack Sprayer
TREE FRUIT: DECIDUOUS (Pome Fruits)	EC	Apples, Pears, Quince	1.25	NA	NA	Aerial, Chemigation, Airblast
TREE FRUIT: DECIDUOUS (Stone Fruits)	EC	Apricots	3.75	1.5	NA	Aerial, Chemigation, Airblast
		Nectarine, Peach	3.75	3.0	NA	
		Figs	2.5	2.0	NA	
		Cherries (sweet and tart)	3.75	1.75	NA	
	EC - ULV		1.22	NA	NA	
TREE FRUIT: EVERGREEN	EC	Grapefruit, Lemon,	6.25	0.75	7.5 (single application)	Aerial, Chemigation,

Table 9.1.1a Summary of Agricultural Crop Use Sites						
Crop Group	Formulation	Use Site	Application Rates (lb ai/acre, unless otherwise stated)			Application Equipment
			Label	SRRD Proposed	Growers Proposed	
	EC - ULV		0.175	NA	NA	
	EC	Lime	NA	1.4	NA	
TREE FRUIT: EVERGREEN (Tropical Fruit)	EC	Avocado	4.7	NA	NA	Aerial, Chemigation, Airblast
		Guava, Papaya	1.25	NA	NA	
		Mango	1.25	NA	4.5	
		Kumquat	6.25	0.75	NA	
	EC - ULV		1.4	NA	NA	
	Dust	Dates	4.25	2.75	NA	Power duster
TREE FRUIT: EVERGREEN (Pine trees)	EC	Pine Seed Orchards, Christmas Tree Plantations, Slash Pine Plantations, & Forest Trees	2.5	NA	NA	Aerial, Chemigation, Airblast, Handgun
TREE NUTS	EC	Chestnuts	5	2.5	NA	Aerial, Chemigation, Airblast
		Macadamia Nuts	0.94	NA	NA	
		Pecans	2.5	NA	8.0	
		Walnuts	2.5	NA	NA	
UNASSIGNED (Ornamentals)	EC	Shrubs, Woody Plants, Shade Trees	2.5	NA	NA	Groundboom, Low-Pressure Handwand, Backpack Sprayer, Handgun
		Flowers, Flowering Plants, Nursery Stock,				
UNASSIGNED (Trees)	EC	Forest Trees	2.5	NA	NA	Aerial, Airblast, Handgun

Table 9.1.1a Summary of Agricultural Crop Use Sites						
Crop Group	Formulation	Use Site	Application Rates (lb ai/acre, unless otherwise stated)			Application Equipment
			Label	SRRD Proposed	Growers Proposed	
VEGETABLE: ROOT & TUBER	EC	Garden Beets, Carrot, Horseradish, Parsnip, Radish, Rutabaga, Salsify, Turnip	1.25	NA	NA	Aerial, Chemigation, Groundboom
		Potatoes, Sweet Potatoes, Chayote Root, & Yams	1.56	NA	NA	
		Garlic, Leeks, Onion, Shallots	1.56	NA	NA	Chemigation, Groundboom
VEGETABLE: CUCURBIT	EC	Cantaloupe, Melon, Pumpkin, Winter Squash, Watermelon	1	NA	NA	Aerial, Chemigation, Groundboom
		Chayote Fruit, Cucumber, Summer Squash	1.88	1.75	NA	
VEGETABLE: FRUITING	EC	Eggplant	3.43	1.56	NA	Aerial, Chemigation, Groundboom
		Tomato, Tomatillo	3.43	1.56	NA	
		Pepper	1.56	NA	NA	
		Okra	1.5	1.2	NA	
VEGETABLE: HEAD & STEM BRASSICA	EC	Broccoli, Broccoli Raab, Brussels Sprouts, Cabbage, Cauliflower, Chinese Broccoli	1.25	NA	NA	Aerial, Chemigation, Groundboom

Table 9.1.1a Summary of Agricultural Crop Use Sites						
Crop Group	Formulation	Use Site	Application Rates (lb ai/acre, unless otherwise stated)			Application Equipment
			Label	SRRD Proposed	Growers Proposed	
VEGETABLE: LEAFY	EC	Celery, Collard, Kale, Kohlrabi Mustard Green, Chinese Greens	1.25	NA	NA	Aerial, Chemigation, Groundboom
		Dandelion	2	1.25	NA	
		Parsley	2	1.5	NA	
		Spinach, Swiss Chard	2	NA	NA	
		Endive & Escarole	1.88	1.24	NA	
		Lettuce	1.88	NA	NA	
		Chives	1.56	NA	NA	
		Watercress	1.25	NA	NA	
STALK & STEM VEGETABLE	EC	Asparagus	1.25	NA	NA	Aerial, Chemigation, Groundboom
		Pineapples	5	NA	NA	
VINE/ TRELLIS	EC	Grape	1.88	NA	NA	Aerial, Chemigation, Groundboom, Airblast
		Passion Fruit	1.25	NA	NA	
	WP	Blackberry, Raspberry, Boysenberry, Dewberry, Loganberry	2	NA	NA	
		Blueberries (highbush)	1.25	NA	NA	
	WP - ULV		0.76	NA	NA	
EDIBLE FUNGI	EC	Mushroom	1.7	NA	NA	Low-Pressure Handwand Sprayer, Backpack Sprayer, Handgun Sprayer

Table 9.1.1b Summary of Non-Agricultural Crop Use Sites				
Use Site	Formulation	Target	Maximum Application Rate	Application Method
Grape root	EC	Grape root	0.019 lb ai per gallon	Hand dipping or basket dipping
Storage grain facility	EC	Stored Commodities Such As Corn, Wheat, Barley, Oats,& Rye	0.25 lb ai per gallon	Low-pressure handwand, backpack sprayer
	Dust		0.0003 lbs ai per square foot	Power duster
Agricultural premises	EC	Outside Barns, Applied as Bait Only	0.27 lbs ai per gallon	Low-pressure handwand, backpack sprayer
Wide Area Outdoors	EC - ULV	Mosquitoes	0.23 lb ai per acre	Aerial
	EC		9.9 lb ai per gallon	Non-Thermal fogger
			0.51 lb ai per gallon	Thermal truck fogger
Windows, Doorways, Other openings	EC		0.1 lb ai per gallon	Paint Brush

9.2 Occupational Handler Exposures and Risks

EPA has determined that there are potential short- and intermediate-term occupational handler exposures to individuals that mix, load, and apply malathion. There is also a potential short- and intermediate-term occupational exposure to individuals that do flagging for aerial applications.

9.2.1 Occupational Handler Exposure Scenarios

The anticipated use patterns indicate a number of exposure scenarios, based on the types of equipment and activities used to make malathion applications. These scenarios include:

- mixing/loading liquids for groundboom application;

- mixing/loading liquids for aerial and chemigation application;
- mixing/loading liquids for airblast sprayer;
- mixing/loading liquids for dipping;
- mixing/loading liquids for a fogger;
- loading dusts for power duster;
- mixing/loading wettable powders for groundboom application;
- mixing/loading wettable powders for aerial and chemigation application;
- applying sprays with an airblast sprayer;
- applying sprays with a groundboom sprayer;
- applying sprays with a fixed-wing aircraft (also covers use of helicopter application);
- applying sprays with a truck-mounted fogger;
- applying dusts with a power duster;
- dipping plants;
- mixing/loading/applying liquid with a low pressure handwand;
- mixing/ loading/applying with a backpack sprayer;
- mixing/ loading/applying with a low-pressure handgun;
- mixing/loading/applying with a paintbrush; and
- flagging for aerial spray application.

9.2.2 Occupational Handler Exposure Data Sources and Assumptions

No chemical-specific handler exposure data were submitted in support of the reregistration of malathion. Therefore, an exposure assessment for each scenario was developed, where appropriate data are available, using the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED was designed by a task force consisting of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association.

The following assumptions and factors, including were used to complete this exposure assessment:

- Average body weight of an adult handler is 70 kg. This body weight is used in both the short- and intermediate-term assessment, since the endpoint of concern is not sex-specific (i.e., the cholinesterase inhibition could be assumed to occur in males or females).

- Average work day interval represents an 8 hour workday (e.g., the acres treated or volume of spray solution prepared in a typical day).

- For fogging mosquitoes with a truck-mounted fogger, no PHED data were available; thus, as a surrogate, the PHED baseline unit exposure data for an airblast sprayer (0.36 mg/lb ai for dermal and 4.5 :g/lb for inhalation) were used to calculate dermal and inhalation exposure. In addition, the gallons handled were taken from information provided on the label (EPA Reg. 4787-8) which indicated that a thermal fogger sprays at a rate of 40 gal/hr and a non-thermal fogger sprays at a rate of 4 gal/hr. EPA assumed the fogger was used 4 hrs per day.

- For loading dusts for a power duster, no PHED data were available; thus, as a surrogate, the PHED baseline unit exposure data for wettable powders (3.7 mg/lb ai for dermal and 43 :g/lb for inhalation) were used to calculate dermal and inhalation exposure. Applicator exposure from using power dusters is a data gap.

- It is assumed that mushroom houses are treated with malathion to control flies as often as twice per week during an approximately 9-month period when pest pressure is at its greatest (April - December). The average area treated per day is assumed to be 16,000 ft^2 (Personal communication with Dr. Clifford Keil, Associate Professor, Univ. of Delaware, Oct. 16, 2002).

- For agricultural uses, exposure calculations were based on the maximum application rates used in residue field trial studies in support of food tolerances and supported by the primary producer, Cheminova. For non-agricultural uses, maximum application rates were identified, as listed on the available malathion labels and LUIS reports.

- When scenario-specific data are not available, HED calculates unit exposure values using generic protection factors that are applied to represent the use of personal protective equipment (PPE) and engineering controls.

- Unit exposure values from a recent Agricultural Handler Exposure Task Force study were included for airblast application scenarios. These unit exposure values apply to airblast applicators wearing chemical resistant headgear.

9.2.3 Occupational Handler Risk Characterization

Most mixer/loader scenarios exceed HED's level of concern at baseline clothing (i.e., long pants, long sleeved shirt, shoes & socks). With the addition of gloves, most mixer/loader scenarios do not exceed HED's level of concern, except for those that involve high application rates, large area of treatment, or wettable powder formulations. For these latter exceptions, most require additional clothing, a respirator, or engineering controls such as a closed mixing/loading system, in order to not exceed HED's level of concern.

Most applicator scenarios do not exceed HED's level of concern with handlers wearing baseline clothing. For most of those scenarios that exceed HED's level of concern at baseline, gloves, additional clothing, or headgear provide effective protection.

All flagger scenarios for all formulations and crops do not exceed HED's level of concern with handlers wearing baseline clothing.

For a summary of occupational handler risks and mitigation, for those scenarios where mitigation is necessary see Table 9.2.3. For additional information regarding specific scenario assumptions and risk estimates, please refer to the Occupational Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. (J. Arthur; D330675).

Table 9.2.3**. Summary of Malathion Non-Cancer Handler Risk Estimates Requiring PPE greater than Baseline and Gloves**

Exposure Scenario	Crop or Use	Max. Application Rate	Max. Area Treated Daily	Base-line	PPE-G-NR	PPE-G-80%R	PPE-G-DL-80%R	EC
Mixer/Loader (M/L)								
M/L Liquids for ULV Aerial Application	Field & Row Crop (Rice, Barely , Oats, Rye, and Wild Rice)	0.61 lb ai/A	7500 A	1	67	NA	110	
	Field & Row Crops (Cotton)	1.22 lb ai/A	7500 A	0	34	NA	53	110
M/L Wettable Powders for Aerial Application	Blueberries (Low)	1.25 lb aiA	350 A	5	53	96	120	
		0.76 lb ai/A	350 A	9	88	160		
	Blueberries (Vine/Trellis)	1.25 lb ai/A	350 A	5	53	96	120	
		0.76 lb aiA	350 A	9	88	160		
	Blackberry, Boysenberry, Dewberry, Loganberry, and Raspberry	2 lb ai/A	350 A	3	33	60	74	1,200
M/L Wettable Powder for Chemigation	Blueberries (Low)	1.25 lb aiA	350 A	5	53	96	120	
		0.76 lb ai/A	350 A	9	88	160		
	Blueberries (Vine/Trellis)	1.25 lb ai/A	350 A	5	53	96	120	
		0.76 lb aiA	350 A	9	88	160		
	Strawberries	2 lb ai/A	350 A	3	33	60	74	1,200
	Blackberry, Boysenberry, Dewberry, Loganberry, and Raspberry	2 lb ai/A	350 A	3	33	60	74	1,200
Application Only								
Liquids via Aerial Application	All 77 crop scenarios assessed	0.175 to 8 Lb ai/A	350 to 7500 A	ND	ND	NA	ND	180 to 27,000
Dust Via Mechanical Duster	Tree Fruit:Evergreens (Tropical)	4.25 lb ai/A	5 A	ND	ND	ND	ND	ND
		2.75 lb ai/A	5 A	ND	ND	ND	ND	ND

ND= No Data
NA= Not Assessed
NF= Not Feasible

9.3 Occupational Noncancer Postapplication Exposures and Risks

EPA has determined that there are potential short- and intermediate-term occupational postapplication exposures to individuals entering treated fields and contacting malathion residues on plant surfaces. Chronic exposure is not expected for handlers, and therefore is not assessed. Only postapplication dermal exposure has been assessed because postapplication inhalation exposure is expected to be negligible. Workers are expected, generally, to be performing activities (harvesting or non-harvesting) in malathion-treated fields for more than 30 consecutive workdays in a growing season (i.e., short- and intermediate-term exposure potential), with some fields receiving repeat malathion applications at 7-10 day intervals. Because of the seasonal nature of malathion use, a long-term exposure scenario is not expected for field workers.

9.3.1 Occupational Noncancer Postapplication Exposure Scenarios

Occupational exposure may result from malathion agricultural uses (i.e., multiple food-use crops). Exposure may occur to postapplication workers who enter and conduct activities in treated use sites.

9.3.2 Occupational Noncancer Postapplication Exposure Data Sources and Assumptions

Postapplication exposure scenarios assessed for malathion were developed from the revised HED Exposure Science Advisory Council Policy (Policy 003 - revised August 7, 2000) on Agricultural Transfer Coefficients. Transfer coefficients are based primarily on data submitted by the Agricultural Reentry Task Force (ARTF) to the Agency or from published literature studies. Data from these studies are proprietary and compensation issues with ARTF may need to be addressed. The crop groupings and activities were based in large part on the ARTF Scoping Survey.

9.3.3 Occupational Noncancer Postapplication Risk Characterization

All crops and application rates were assessed for postapplication activities ranging from very low to very high contact. Resulting "days after treatment" at which an MOE of 100 was reached varied from 0 to 4 days. Most activities reach an MOE ≥100 on days 0 -2. An interim REI of 12 hours is established for malathion under the Worker Protection Standard (WPS).

For a summary of occupational noncancer postapplication risks and mitigation, see Table 9.3.3. For additional information regarding specific scenario assumptions and risk estimates, please refer to the Occupational Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. (J. Arthur; D330675)

Table 9.3.3: REI Summary for Malathion Agricultural Crops

Crop Group	Use Site	Application Rate (lb ai/A)	Application Rate Source	REI (in hours unless otherwise indicated)
Berry: low	Strawberry	2	EC/WP label	12
	Blueberry (low bush)	1.2	EC/WP label	12
		0.77	ULV label	12
Bunch/Bundle	hops	0.63	EC/WP label	12
Field and Row Crops: low – medium (nongrass, animal feeds)	Alfalfa, clover, lespedeza, lupine, vetch	1.25	EC/WP label	12
		0.61	ULV label	12
Field and Row Crops: low – medium (cereal grains)	Barley, oats, rice, tye, wild rice	1.25	Label	12
		0.61	ULV	12
	wheat	1.25	Label	12
		1.0	Proposed revised for EC/WP	12
		0.61	ULV	12
Field and Row Crops: low – medium (fiber)	Cotton	2.5	Label	2 day
		1.22	ULV label	1 day
	Flax	0.5	Label	12
Field and Row Crops: low – medium (forage grass)	Grass	1.25	Label	12
		0.92	ULV label	12
Field and Row Crops: low – medium (sugarbeets)	sugarbeets	1.25	label	12 hr
Field and Row Crops: low – medium (peanuts)	Peanuts	2.5	label	24
Field and Row Crops: low – medium (herbs and spices)	Mint	0.94	label	12
Field and Row Crops: low – medium (legume vegetable)	Peas	2.5	Label	2 day
		1.0	Proposed revised for EC/WP	2 day for hand harvesting, 12 hr for all other activities
Field and Row Crops: Tall	Corn	1.25	Label	12
		1.0	Proposed revised for EC/WP	4 days for detasseling 12 hr for all other activities
		0.61	ULV	3 days for detasseling 12 hr for all other activities
	Sorghum	0.61	ULV	12

Cut Flowers	Flowers	2.5	Label	12
Tree Fruit Deciduous (pome fruits)	Apples, pears, quince	1.25	label	12
Tree Fruit Deciduous (stone fruits)	Apricots	3.75	label	12 hr for med expos 2 day for high expos
		1.5	Proposed revised for EC/WP	12
	Nectarine[2], peach	3.75	label	2 day
		3.0	Proposed revised for EC/WP	24hr
	Figs	2.5	label	12
		2.0	EPA Proposed revised for EC/WP	24
	Cherries (sweet and tart)	3.75	Label	2
		1.75	Proposed revised for EC/WP	12
		1.22	ULV	12
Tree Fruit: Evergreen (citrus fruits)	Grapefruit, Lemon, lime, orange, tangelo, tangerine,	6.25	Label	3 day
		CA: 7.5	Grower proposed revised	3
		FL: 4.5	Grower proposed revised	2
		0.175	ULV	12
Tree Fruit: Evergreen (tropical fruits)	Avocado	4.70	Label	3
		4.7	EC/WP Final	2
	Guava, papaya	1.25	Label	12
	Mango	1.25	Label	12
	Kumquat	6.25	label	3 day
		4.5	proposed revised	2 day
		0.92	ULV label	12 hrs
	Dates	4.25	Label	2 day
Tree Fruit: Evergreen (pine nuts)	Pine seed orchards, Christmas tree plantations, slash pine plantations, forest trees	2.5	label	24
Tree Nuts	Chestnuts	5	label	2
		2.5	proposed revised	24
	Macadamia nuts	0.94	label	12
	Pecans	2.5	Label	24
		8.0	proposed revised	3
	walnuts	2.5	label	24
Un-assigned (ornamentals)	Shrubs, woody plants, shade trees	2.5	Label	12
	Flowers, flowering plants, nursery stock	2.5	label	12
Un-assigned (trees)	Forest trees	2.5	label	24

Vegetable: root and tuber	Garden beets, carrot, horseradish, parsnip, radish, rutabaga, salsify, turnip	1.25	label	24
	Potatoes, sweet potatoes	1.56	Label	12
	Chayote root, yams	1.56	Label	24
	Garlic, leeks, green onion, shallots	1.56	Label	24
	Dry onion	1.56	Label	12
Vegetable: cucurbit	Cantabllupe, melon, pumpkin, winter squash, watermelon	1.0	Label	12
	Chayote fruit, cucumber	1.88	Label	24
	Summer squash	1.88	Label	24
		1.75	proposed revised	24
Vegetable: fruiting	eggplant	3.43	Label	24
		1.56	Proposed revised	12
	Fresh tomato, tomatillo	3.43	Label	24
		1.56	Proposed revised	12
	Processed tomato	3.43	Label	24
		1.56	Proposed revised	12
	pepper	1.56	Label	12
	okra	1.5	Label	12
		1.2	Proposed revised	12
	Broccoli, broccoli raab, Brussels sprouts, cabbage, cauliflower, Chinese broccoli	1.25	label	2 day
Vegtable: leafy	Celery, kohlrabi	1.25	Label	24
	Collard, kale, mustard green, Chinese greens	1.25	Label	24
	dandelion	2	Label	2 day
		1.25	Proposed revised	24
	parsley	2	Label	2 day
		1.5	Proposed revised	24
	spinach	2	Label	2 day
	Swiss chard	2	Label	2 day
	Endive and escarole	1.88	Label	24
		1.24	Proposed revised	12
	lettuce	1.88	Label	24
	chives	1.56	Label	24
	watercress	1.25	label	24
Stalk & Stem Vegetables	asparagus	1.25	label	12
	pineapples	5	Label	2 day
Vine/Trellis	grape	1.88	Label	24
	Passion fruit	1.25	Label	12
	Blackberry, raspberry, boysenberry, dewberry, loganberry	2	Label	12
	Blueberry (highbush)	1.25	label	12
Edible Fungi	mushroom	1.7	label	12

10.0 Data Needs and Label Requirements

Additional data requirements have been identified in the referenced Science Chapters and are summarized here.

10.1 Toxicology

OPPTS 870.7800: A guideline immunotoxicity study (870.7800) should be required for the characterization of suggestive evidence of effects on immune response that has been observed in literature studies with malathion.

10.2 Residue Chemistry

OPPTS 860.1200: The registrant must comply with OPPTS 860.1500 regarding the use of ground or aerial equipment. Unless adequate field trial data reflecting aerial application of malathion in <2 gal of water/A (<10 gal of water/A for tree or orchard crops) are available, malathion product labels must specify that aerial applications are to be made in a minimum of 2 gallons water per acre (or 10 gallons per acre in the case of tree or orchard crops).

OPPTS 860.1400: The data requirements imposed in the Malathion Reregistration Standard for these guideline topics remain outstanding. In lieu of the required residue data, the registrant(s) may modify malathion use to allow broadcast use only over intermittently flooded areas, and that applications may not be made around bodies of water where fish or shellfish are grown and/or harvested commercially.

OPPTS 860.1500: The reregistration requirements for magnitude of the residue in/on the following RACs resulting from preharvest uses have not been fulfilled: apple; barley hay; celery; corn (sweet) stover; cotton gin byproducts; date (data under review); oat hay, quince (will rely on apple data); sorghum forage and stover; and wheat hay.

OPPTS 860.1520: The reregistration data requirements for magnitude of the residue in the processed commodities of the following crops are required: flax; and wheat (reflecting postharvest treatment). Additionally, processing data for peanut, plum, rice (reflecting postharvest treatment), safflower, sugar beet, soybean, and sunflower are required should any registrant elect to support uses of malathion on these crops.

OPPTS 860.1900: Rotational crop restrictions are needed on malathion end-use product labels. The appropriate PBIs will be determined pending submission of the required field rotational crop studies.

10.3 Occupational and Residential Exposure

Data Gaps: Residue studies that measure the formation and dissipation of malaoxon in airborne spray and, particularly, in deposited residues of ULV malathion on hard surfaces over a 10- to 30-day period would eliminate much of the uncertainty surrounding estimates of malathion residues on decks and outdoor playground equipment. Alternatively, a chamber test to elucidate the conditions for malaoxon formation on a hard surface, with concurrent measurement of off-gas, and radiolabeled mass balance measurements could be performed.

Label Changes: Label directions for perimeter house treatment should specify such treatment to only include structural foundations and wood piles, and the 2-foot wide path surrounding the same.

References.

Malathion: Revised Acute, Probabilistic and Chronic Dietary (Food + Drinking Water) Exposure and Risk Assessments for the Malathion Reregistration Eligibility Decision. PC Code: 057701. DP Barcode: D330636. Sheila Piper, July 13, 2006.

Malathion: Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. (DP Barcode: D330678; Chemical Number: 057701; EPA MRID No.: 43945001). Jack Arthur, July 6, 2006.

Malathion: Occupational Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. (DP Barcode: D330675; Chemical Number: 057701; EPA MRID Nos.: 45005910, 45491901, 45138202, 45491902, 45138201 and 45469501). Jack Arthur, July 6, 2006.

Drinking Water Exposure Modeling Evaluating the Effect of Varying Crop Scenarios, Application Rate, Application Interval, Spray Drift Levels, Soil Half Life. PC Code: 057701; DP Barcode: D327331. Norman Birchfield, June 15, 2006.

Malathion: Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D321547. Jack Arthur. September 12, 2005.

Malathion: Acute, Probabilistic and Chronic Dietary (Food + Water) Exposure Assessments for the Reregistration Eligibility Decision. PC Code: 057701. DP Barcode: D320923. Sheila Piper. August 26, 2005.

Malathion: Occupational Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D315898. Jach Arthur. June 2, 2005.

Second Update Review of Malathion Incident Reports. PC Code: 057701. DP Barcode D315907. Jerome Blondell. May, 2005.

Benchmark Dose Analysis of Brain and Rbc Data from the Malathion Comparative Cholinesterase Study in Juvenile and Adult Rats. PC Code: 057701. DP Barcode: D315405. Anna Lowit. April 11, 2005.

Malathion and Malaoxon: Comparative Toxicity and Estimation of Toxicity Adjustment Factor. PC Codes: 057701, 657701. DP Barcodes: D293912, D295144, D310501, D310800. Anna Lowit. April 11, 2005.

Estimated Chronic Drinking Water Exposure Values for Malaoxon. PC Code: 057701. DP Barcode: D315267. Norman Birchfield. March 24, 2005.

Transmittal of Estimated Daily Drinking Water Concentrations of Malaoxon Resulting from Malathion use on Multiple Crops at Typical and Maximum Intensity. PC Code: 057701. DP Barcode: D292663. Norman Birchfield. June 30, 2004.

Estimates of Malathion Concentrations in Drinking Water as a Result of Terrestrial Uses and Rice Use. PC Code: 057701. DP Barcode: D285199. Norman Birchfield. September 16, 2002.

Residue Chemistry Chapter for the Malathion Reregistration Eligibility Decision (RED) Document. PC Code: 057701. DP Barcode: D239453. William O. Smith. April 14, 1999.

Toxicology MRID References

00152569 Siglin, J. (1985) A Teratology Study with AC 6,601 in Rabbits: FDRL Study No. 8171. Unpublished study prepared by Food and Drug Research Laboratories. (Incorporates a range-finding study)

00159876 Kynoch, S. (1986) Acute Oral Toxicity to Rats of Malathion (Fyfanon) Technical: 851341D/CHV 33/AC. Unpublished study prepared by Huntingdon Research Centre Ltd.

00159877 Kynoch, S. (1986) Acute Dermal Toxicity to Rats of Malathion (Fyfanon) Technical: 85133OD/CHV 34/AC. Unpublished study prepared by Huntingdon Research Centre Ltd.

00159878 Jackson, G.; Hardy, C.; Gopinath, G.; et al. (1986) Fyfanon (Malathion) 96/98% Technical: Acute Inhalation Toxicity Study in Rats, 4-hour Exposure: CHV 28/8640. Unpublished study prepared by Huntingdon Research Centre Ltd.

00159879 Liggett, M.; Parcell, B. (1985) Irritant Effects on Rabbit Skin of Malathion (Fyfanon) Technical: 851221D/CHV 35/SE. Unpublished study prepared by Huntingdon Research Centre Ltd.

00159880 Liggett, M.; Parcell, B. (1985) Irritant Effects on the Rabbit Eye of Malathion (Fyfanon) Technical: 851214D/CHV 36/SE. Unpublished study prepared by Huntingdon Research Centre Ltd.

00159881 Kynoch, S.; Smith, P. (1986) Delayed Contact Hypersensitivity in the Guinea-pig with Malathion (Fyfanon) Technical: 8666D/CHV 37/SS. Unpublished study prepared by Huntingdon Research Centre Ltd.

40188501 Tegeris Laboratories, Inc. (1987) One-year Oral Toxicity Study in Purebred Beagle Dogs with AC6,601:Lab Number: 85010. Unpublished study.

40812001 Singlin, J. (1985) A Resubmission of Rabbit Teratology Study, FDRL Study No. 8171 (MRID 152569), with Appendix III included.

40939301 Fletcher, D. (1988) 42-Day Neurotoxicity Study with AC 6,601 Technical in Mature White Leghorn Hens: Report No. BLAL 87 DN 109. Unpublished study prepared by Bio-Life Associates, Ltd.

40939302 Traul, K. (1987) Evaluation of CL 6601 in the Bacterial/Microsome Mutagenicity Test: Study No. 114. Unpublished study prepared by American Cyanamid Co.

41054201 Moreno, O. (1989) 21-Day Dermal Toxicity Study with AC 6,601 in Rabbits: Laboratory Report No. MB 88-9191. Unpublished study prepared by MB Research Laboratories, Inc.

41160901 Lochry, E. (1989) A Development Toxicity Study with AC 6,601 in Rats: Argus Research Laboratories Protocol 101-005. Unpublished study prepared by Argus Research Laboratories, Inc.

41367701 Reddy, V. Freeman, T. and Cannon, M. (1989) Disposition and Metabolism of 14C-Labeled Malathion in Rats (Preliminary and Definitive Study). Midwest Research Institute. Study No. MRI 9354-B. Unpublished

41389301 Pant, K. (1990) Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures by Autoradiography with AC 6,601: Lab Project Number: 0125-5100. Unpublished study prepared by Sitek Research Laboratories.

41451201 Gudi, R. (1990) Acute Test for Chemical Induction of Chromosome Aberration in Rat Bone Marrow Cells in vivo with AC 6,601: Lab Report Number: 0125-1531. Unpublished study prepared by Sitek Research Laboratories.

41583401 Schroeder, R. (1990) A Two-Generation (two litters) Reproduction Study with AC 6,601 to Rats. Study No. 87-3243. Unpublished Study prepared by Bio/Dynamics, Inc.

41842401 Seely, J. (1991) Histopathologic Evaluation: "The Evaluation of the Chronic Effects of AC 6,601 Administered in the Diet to Sprague-Dawley Rats for 24 Consecutive Months": Lab Project Number: 90-78. Unpublished study prepared by Pathco, Inc.

43146701 Lamb, I. (1994) An Acute Neurotoxicity Study of Malathion in Rats: Final

Report: Lab Project Number: WIL/206005. Unpublished study prepared by WIL Research Labs, Inc.

43269501 Lamb, I. (1994) A Subchronic (13-Week) Neurotoxicity study of Malathion in Rats: Final Report: Lab Project Number: WIL-206006. Unpublished study prepared by WIL Research Labs. 1729 p.

43266601 Beattie, G. (1994) A 13-Week Toxicity Study of Aerosolized Malathion Administered by Whole Body Inhalation Exposure to the Albino Rat: Lab Project Number: 90729. Unpublished study prepared by Product Safety Assessment, Bio-Research Labs, Ltd.

43407201 Slauter, R. (1994) 18-Month Oral (Dietary) Oncogenicity Study in Mice: Malathion: Lab Project Number: 668-001. Unpublished study prepared by International Research and Development Corp.

43942901 Daly, I. (1996) A 24-Month Oral Toxicity/Oncogenicity Study of Malathion in the Rat via Dietary Administration: Final Report: Lab Project Number: 90-3641: J-11 90-3641. Unpublished study prepared by Huntingdon Life Sciences.

43975201 Daly, I. (1996) A 24-Month Oral Toxicity/Oncogenicity Study of Malaoxon in the Rat via Dietary Administration: Final Report: Lab Project Number: 93-2234. Unpublished study prepared by Huntingdon Life Sciences. Relates to L0000076 and 43469901.

44479301 Auletta, C.S. (1997) Report on Additional Statistical Analyses on Combined Chronic Toxicity/Carcinogenicity Study of Malaoxon in Rats, Huntingdon Life Sciences Study No. 92-2234.

44554301 Beattie, G. (1993) "A 2-Week Toxicity Study of Aerosolized Malathion Administered by Whole-body Inhalation Exposure to the Albino Rat." Product Safety Assessment, Bio-Research Laboratories Ltd., 87 Senneville Road, Senneville, Quebec H9X 3R3 Canada and Product Stability and Characterization, Cheminova Agro A/S, DK-7620 Lemvig, Denmark. Laboratory Project ID 90557. Study completed July 20, 1993.

45045001 Ehrich, M., Shell, L., Rozum, M., and Jortner, B.S. (1993) Short-term clinical and neuropathologic effects of ChE inhibitors in rats. *J. Am. Coll. Toxicol*. 12(1), 55-68

45046301 Mendoza, C.E. (1976) Toxicity and effects of malathion on esterases of suckling albino rats. *Toxicol. and Applied Pharmacol*. 35, 229-238.

45554501 Edwards, C. Nicholas (2001) Malathion Technical *In Vitro* Mammalian Cell

Gene Mutation Test Performed with Mouse Lymphoma Cells (L5178Y). Unpublished study prepared by Scantox, Lille Skensved, Denmark. Laboratory Project ID 40413. October 12, 2001.

45566201 Fulcher, S.M.. (2001) Malathion: Effects on ChE in the CD rat (adult and juvenile) by oral gavage administration. Unpublished study prepared by Huntingdon Life Sciences, Ltd., Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England. Doc. No. CHV067/012452. November 30, 2001.

45626801 Robinson, K. (2002) Evaluation of the embryo-lethal potential of malathion in the rabbit. Unpublished report prepared by ClinTrials BioResearch, Ltd., Senneville, Quebec, Canada. January 6, 2002.

45627001 Fulcher, S.M. (2002) Malathion dose finding study in CD rats by oral gavage administration preliminary to developmental neurotoxicity study. Unpublished study prepared by Huntingdon Life Sciences, Ltd., Cambridgeshire PE28 4HS, England. Laboratory Project No. CHV/062, February 27, 2002.

45642901 Desi, I., et al (1976) Toxicity of Malathion to mammals, aquatic organisms and tissue culture cells. Arch. Environ. Contam. Toxicol. 3, 410-425.

45642902 Kurtz, P.S. (1977) Dissociated Behavioral and ChE Decrements following Malathion Exposure. Tox. App. Pharm. 42, 589-594.

45646401 Fulcher, S. M. (2002) Malathion. Developmental neurotoxicity study in the CD rat by oral gavage administration. Unpublished study prepared by Huntington Life Sciences, Ltd., Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England. Laboratory report number CHV/066; 013331, March 21, 2002.

45686901 Blasiak, J. and Kowalik, J. (1999) Protective action of sodium ascorbate against the DNA-damaging effects of malathion. *Pest. Biochem. Physiol.* 65:110-118.

45686902 Blasiak, J. Jalosgynski, P., Trzeciak, A. and Szyfter, K. (1999) *In vitro* studies on the genotoxicity of the organophosphorus insecticide malathion and its two analogues. *Mutat. Res.* 445:275-283.

46755601 Reiss, R. (2006). Estimation of Benchmark Doses for Red Blood Cell Cholinesterase for Dermal Exposures to Malathion. Report submitted by Sciences International, Inc., Alexandria, VA on behalf of Cheminova. February 2, 2006.

46790501 Reiss, R. (2006). Amended Report for MRID 46755601: Estimation of Benchmark Doses for Red Blood Cell Cholinesterase for Dermal Exposures to

Malathion. Report submitted by Sciences International, Inc., Alexandria, VA on behalf of Cheminova. April 26, 2006.

46821701 Barnett, J. (2006). Percutaneous Repeated Dose 21-Day Toxicity Study of Malathion in Rabbits. Charles River Laboratories Preclinical Services, 905 Sheehy Drive, Building A, Horsham, PA 19044. Laboratory Project Number: TQC00016, March 21, 2006. MRID 46790501. Unpublished.

TXR0051549 Malathion - Report of the Hazard Identification Assessment Review Committee. Memo dated January 28, 2003 from S. Makris and B. Dementi.

TXR005967 Malathion: Revised Toxicology Chapter for the RED. Memo dated September 13, 2002 from S.Makris.

TXR0052951 Malathion and malaoxon: Comparative toxicity and estimation of toxicity adjustment factor. Memo dated 4/11/05 from A. Lowit and R.W. Setzer.

TXR0053251 Benchmark dose analysis of brain and RBC data from the malathion comparative ChE study in juvenile and adult rats (MRID 45566201). Memo dated 4/11/05 from A. Lowit.

TXR0053748 Review of malathion and malaoxon acute comparative cholinesterase study and related range finding and time to peak effect studies (MRID nos. 46756701, 46756702, 46756703, 46756704, 46756705).

FIFRA SAP Scientific Advisory Panel (2000) SAP Report No. 2000-04, December 14, 2000. Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: A Consultation on the EPA Health Effect Division's Proposed Classification of the Human Carcinogenic Potential of Malathion. FIFRA Scientfic Advisory Panel Meeting, August 17-18, 2000, Arlington, VA.

U.S.EPA Malathion, EPA Technical Report, Protocol for Dermal Exposure Assessment, Part 6. Percutaneous Skin Absorption Study in Humans. Memorandum from Robert Zendzian to Joanne Edwards dated November 6, 1994. HED Doc. 011314. "Review of protocol for dermal exposure assessment: a technical report, Castles, M. and Reddy, V. Midwest Research Institute, Kansas City, MO, Contract 68-DO-0137, Jan 1993, for Environmental Monitoring Systems Laboratory, ORD, USEPA, Las Vegas, Nevada.." Office of Pesticides Program, Health Effects Division, U.S.EPA, Washington, DC.

U.S.EPA Malathion. New Executive Summaries for Selected Toxicology Studies on Malathion and Malaoxon. Memorandum from Edwin Budd to Diana Locke, dated December 9, 1997. HED Doc. 012433. Office of Pesticides Program, Health Effects Division, U.S.EPA, Washington, DC.

U.S.EPA Malathion: Report of the Hazard Identification Assessment Review Committee. December 17, 1997. HED Doc. 012440. Office of Pesticides Program, Health Effects Division, U.S.EPA, Washington, DC.

U.S.EPA Lateulere, D. Memorandum: Malathion Uses Subject to Reregistration Risk Assessments. Prepared by the Malathion Reregistration Eligibility Decision (RED) Team. U.S.EPA, Office of Pesticide Programs, Special Review Branch. February 17, 1998.

U.S.EPA Malathion: Re-evaluation - A report of the Hazard Identification Assessment Review Committee. December 22, 1998. HED Doc. 013032. Office of Pesticide Programs, Health Effects Division, U.S. EPA, Washington, DC.

U.S.EPA Malathion: Revised NOAEL for Derivation of the Chronic Reference Dose-Report of the Hazard Identification Assessment Review Committee. November 1, 1999. HED Doc. 013820. Office of Pesticide Programs, Health Effects Division, U.S. EPA, Washington, DC.

U.S.EPA Malathion: Re-evaluation - A report of the Hazard Identification Assessment Review Committee. August 31, 2000. HED Doc. 014310. Office of Pesticide Programs, Health Effects Division, U.S. EPA, Washington, DC.

U.S.EPA Malathion - Report of the Hazard Identification Assessment Review Committee. June 13, 2002. TXR 0050804. Office of Pesticide Programs, Health Effects Division, U.S.EPA, Washington, DC.

U.S.EPA Malathion - Reassessment Report of the FQPA Safety Factor Committee. August 06, 2002. TXR 0051034 Office of Pesticide Programs, Health Effects Division, U.S.EPA, Washington, DC.

U.S. EPA Cancer Assessment Document #1: Evaluation of the Carcinogenic Potential of Malathion. February 2, 2000. Office of Pesticide Programs, Health Effects Division, U.S. EPA, Washington, DC.

U.S. EPA Cancer Assessment Document #2: Evaluation of the Carcinogenic Potential of Malathion. April 28, 2000. TXR 013991. Office of Pesticide Programs, Health Effects Division, U.S. EPA, Washington, DC.

U.S. EPA Revised Organophosphorous Pesticide Cumulative Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, DC. June 10, 2002. http://www.epa.gov/pesticides/cumulative/rra-op/

NON-MRID References

Banerjee, B. D., Pasha, S. T., Hussain, Q. Z., Koner, B. C. and Ray, A. (1998) A comparative evaluation of immunotoxicity of malathion after subchronic exposure in experimental animals. *Indian J. Experimental Biology*, 36, 273-282.

Cabello, G., et al. (2001) A Rat Mammary Tumor Model Induced by the Organophosphorous Pesticides Parathion and Malathion, Possibly through Acetylcholinesterase Inhibition. *Environmental Health Perspectives*, 109(5):471-479.

California Department of Health Services, 1991. *Health Risk Assessment of Aerial Application of Malathion Bait: Summary Report.* February 1991. Available at http://www.oehha.org/pesticides/reports/index.html .

Chanda, SM, TL Lassiter, VC Moser, S Barone, Jr., and S Padilla. 2002. *Tissue carboxylesterases and chlorpyrifos toxicity in the developing rat.* Human and Ecological Risk Assessment (8)(1): 75-90.

Dauterman, W. C. and Main, A. R. (1966). Relationship Between Acute Toxicity and *In Vitro* Inhibition and Hydrolysis of a Series of Carboxy Homologs of Malathion. *Toxicol. Appl. Pharmacol*. 9:408-418.

Rodgers, K. and Xiong, S. (1997) Effect of administration of malathion for 90 days on macrophage function and mast cell degranulation. *Toxicology Letters* 93, 73-82.

Rodgers, K., Amand, K. St., and Xiong, S. (1996) Effects of malathion on humoral immunity and macrophage function in mast cell-deficient mice. *Fundam. Appl. Toxicol*. 31, 252-258.

Rodgers, K. E., Leung, N., Ware, C. F., Devens, B. H., and Imamura, T. (1986) Lack of immunosuppressive effects of acute and subacute administration of malathion on murine cellular and humoral immune responses. *Pestic. Biochem. Physiol*., 25, 358-365.

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for Food Use for malathion are summarized in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Data Requirements

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	no[1]	---
870.3150 Oral Subchronic (nonrodent)	no[1]	---
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	---
870.3465 90-Day Inhalation	yes[1]	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes[2]
870.5550 Mutagenicity—Other Genotoxic Effects		
870.6100a Acute Delayed Neurotox. (hen)	yes	yes
870.6100b 90-Day Neurotoxicity (hen)	yes	yes
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity	yes	yes[3]

Table 1. Data Requirements		
Test	**Technical**	
	Required	**Satisfied**
870.7485 General Metabolism.....	yes	yes
870.7600 Dermal Penetration	no	yes
870.7800 Immunotoxicity.....	yes[4]	no

[1] The requirements for subchronic feeding studies in the rodent and non-rodent (dog) were waived in the 1988 Malathion Registration Standard since chronic studies were imposed. A new subchronic inhalation study in rats is required based on the results of the two-week range-finding study (MRID 44554301) and the lack of a NOAEL for ChEI in the 90-day study (MRID 43266601).

[2] Mutagenicity - Other Genotoxc Effects satisfied by Unscheduled DNA Synthesis in Mammalian Cells in Culture (OPPTS 870.5550) and two alkaline single cell gel electrophoresis (comet cell) assays (no guideline number).

[3] Developmental neurotoxicity testing includes a companion study that evaluated ChEI in adult and immature rats following either acute or repeated gavage doses.

[4] A guideline immunototoxicity study is required by the Agency to characterize suggestive evidence of effects on immune response that have been observed in literature studies.

2.0 SOME CRITICAL AND NON-CRITICAL TOXICOLOGY STUDIES

SUBCHRONIC/CHRONIC STUDIES (Three)

1. A 2-week range-finding study (MRID 44554301) was conducted in pursuit of dose (concentration) selection for the required guideline subchronic inhalation study in the rat. The concentrations of malathion technical (96.4% a.i.) in air employed in the study were 0 (air), 0.5, 1.5, and 4.5 mg/L (128, 384, and 1151 mg/kg/day for males and 134, 403, and 1208 mg/kg/day for females). In this brief study, there is evidence of considerable attention to GLP principles and FIFRA testing requirements. The parameters evaluated - clinical signs, body weight, food consumption, complete clinical chemistry including ChEI (plasma, erythrocyte, brain), hematology, urinalysis, organ weights, macro- and microscopic pathology - attest to an exceptional and well-performed study for a range-finding study. It satisfies many guideline testing requirements, a chief drawback with respect to which being the few animals (5/sex/group) employed as compared to the minimum (10/sex/group) in guideline testing.

Principal findings include nasal and laryngeal effects at all doses. In the nasal cavity, “loss of goblet cells and/or cilia, respiratory epithelium” was reported for all male and female rats in all dose groups. “Hyperplasia of the respiratory epithelium” was identified in 4/5 males and 3/5 females in Group 2 and in all animals of both sexes in Groups 3 and 4. In the larynx, 3/5, 4/5, and 5/5 male rats, respectively, in Groups 2, 3, and 4, and all female rats in all dose groups exhibited epithelial hyperplasia. The nasal and laryngeal effects were not observed in controls.

There were no other remarkable histopathological findings. It should be noted that in the two animals sacrificed early, i.e., one Group 4 male and one Group 3 female, sacrificed on days 10 and 9, respectively, the nasal and laryngeal effects were evident. Male rats exhibited a slight, dosing related decrease in body weight gain at all doses, an effect seen in females only at the highest dose level. Males consumed less food, in a dosing-related manner across all doses, while in females there was a slight reduction only in the high dose group.

Evidence of ChEI was seen in all doses in both sexes for erythrocyte ChE. Plasma ChE was inhibited in females at all doses and in males at the mid and high dose levels. Brain ChE was clearly inhibited at the highest dose in both sexes and possibly so in females at all doses. It was clear that the enzyme in at least one of its forms was inhibited at all doses in both sexes. There were some cholinergic clinical signs of toxicity in males at all dose levels and in females at the mid and high dose levels.

Based on organ weights changes, possible target organs were liver (both sexes) at the top two doses and kidney (males) at possibly all doses. More data would be needed to confirm these and certain other findings, notably those of spleen and thymus among females.

The principle findings in this study were the early onset of nasal and laryngeal epithelial effects that signal the need to determine the time course and dose relatedness of these effects. There was no NOAEL for the effects after only 2 weeks of treatment. There was also no NOAEL for ChEI. The question of the NOAELs was not settled in the subchronic study that followed this study.

This 2-week inhalation study in rats is classified as **Acceptable/non-guideline**. It does not satisfy the guideline requirement for a subchronic inhalation study (§82-4) because it was conducted as a range-finding study for purposes of dose selection for the conduct of the full subchronic inhalation guideline study.

2. <u>In a combined chronic toxicity/carcinogenicity study (MRID 43975201),</u> malaoxon (96.4% a.i.), the ChE inhibiting metabolite of malathion, was administered to F344 rats via the diet for up to 104-105 weeks at dose levels of 0, 20, 1000 or 2000 ppm (equivalent to 0, 1, 57 and 114 mg/kg/day in males and 0, 1, 68 and 141 mg/kg/day in females).

Ten animals/sex/group were sacrificed at 3, 6 and 12 months for interim evaluations and ChE activity determinations. Standard parameters were examined. Full histopathological examinations were performed on control and high dose animals at 12 and 24 months and on all animals that died or were sacrificed during the study. Additional tissues, as appropriate, also were examined from other dose groups.

Mortality was significantly increased in high dose males (control, 29%; high dose, 53%) and in mid and high dose females (control, 13%; mid dose, 44% high dose, 49%). Body weights were decreased in the high dose males and females throughout most of the study. The mean terminal body weight of high dose males was statistically significantly decreased by 14% compared to the control group. The mean terminal body weight of high dose females was decreased by 11% but

did not reach statistical significance. Food intake was consistently greater in both sexes at the high dose and increased sporadically at the mid dose throughout the study. Treatment-related yellow anogenital staining was observed in high dose males and females. Increased incidences of emaciated rats were seen especially among the early decedent females.

Foreign material (food, hair) and cellular debris were found in the nasal cavity of high dose males and mid and high dose females. Nasal lumen inflammation was seen in high dose males and in mid and high dose females. Nasal lumen epithelial hyperplasia was increased in mid and high dose females. Lung interstitium inflammation was increased in mid and high dose females, and tympanic cavity inflammation was seen in mid and high dose early female decedents. Increased incidences of mineral deposits in the stomach muscularis were seen in mid and high dose males and females. The mean liver and kidney weights were increased in high dose males at 12 months, and the mean adrenal weight was increased in high dose males at 24 months. The mean spleen weight was decreased in high dose females at 24 months.

The plasma ChE activity was decreased in males by 74%-91% and in females by 82%-96% compared to the controls after 3, 6, 12 and 24 months of malaoxon treatment at the mid and high doses. The erythrocyte ChE activity was decreased 54-66% in males and 45%-65% in females at the mid and high doses. The erythrocyte ChE activity was also decreased by 21% in males and 19 % in females at 6 months of treatment at 20 ppm. Brain ChE activity was decreased 11-18% during months 3-12 and 74% at 24 months compared to controls in high dose males and at the mid dose by 30% at 24 months. It was decreased by 61%-78% in high dose females at all time points and by 5%-14% at the mid dose ater 3, 6, and 12 months of treatment in females.

A NOAEL was not determined for ChE activity inhibition in this study. The LOAEL is 20 ppm (1 mg/kg/day) for males and females based on the 19-21% inhibition of erythrocyte ChE activity after 6 months of treatment. A NOAEL of 20 ppm (1 mg/kg/day) and a LOAEL of 1000 ppm (57 mg/kg/day for males, 68 mg/kg/day for females) for systemic toxicity were defined. In females, the systemic LOAEL was based on increased mortality, and microscopic changes in the nasoturbinal tissues, lung interstitium, and tympanic cavity. In males, the systemic LOAEL was based on mineral deposits in the stomach muscularis.

The only statistically significant tumorigenic response was that of leukemia in male rats at the 2000 ppm dose level, accompanied by a positive dose-trend analysis.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a combined chronic toxicity/carcinogenicity study **(870.4300)** in the rat.

3. In an one-year chronic oral toxicity study in dogs (MRID 40188501), malathion (95%) was administered daily in gelatin capsules to groups of 6 male and 6 female beagle dogs at dose levels of 0, 62.5, 125 or 250 mg/kg/day. There were no mortalities or treatment-related clinical signs of toxicity observed. No overall ChE NOAEL was demonstrated in this study (<62.5 mg/kg/day). The overall ChE LOAEL was 62.5 mg/kg/day (LDT) based on inhibition of plasma and erythrocyte ChE activity in both males and females. The NOAEL was 250 mg/kg/day for

brain ChE. The systemic NOAEL in this study for both males and females was 250 mg/kg/day (HDT) and that no systemic LOAEL was demonstrated (>250 mg/kg/day).

This study was classified **Unacceptable/guideline** because NOAELs were not established for inhibition of ChE activity for plasma and erythrocytes in either males or females, and it does not satisfy Guideline 83-1 for a chronic toxicity study **(870.4100b)** in a non-rodent species.

NEUROTOXICITY STUDIES (Ten)

1. In an acute delayed neurotoxicity study in hens (MRID 40939301), technical grade malathion (93.6% purity) was administered in a single oral dose by gavage to 60 mature White Leghorn hens at a dose level of 1007.5 mg/kg (1.3 x the oral LD50 of 775 mg/kg). The hens were atropinized previously with 10 mg/kg of atropine sulfate IM and ½, 1, 3 and 5 hours post-dosing with 30 mg/kg IM. Twenty-one days later, survivors were again given malathion at a dose level of 852.5 mg/kg (1.1 x the LD50). The birds were atropinized as before. Twenty-one days later (42 days after the first dose), the surviving hens were sacrificed. Fifteen negative control hens were treated similarly but were given tap water, rather than malathion, on days 0 and 21. In this study, hens treated with malathion did not exhibit any evidence of acute delayed neurotoxicity.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for an acute delayed neurotoxicity study **(870.6100)** in the hen.

2. In an acute neurotoxicity in rats (MRID 43146701), malathion was evaluated for acute neurotoxicity, including ChEI, using Sprague-Dawley rats in groups of 27 rats/sex following single oral gavage dosages of 0, 500, 1000 or 2000 mg/kg in corn oil. FOB, locomotor activity, histopathology and ChE assays were performed at pretest, peak effect (15 minutes post-dosing), day 7 and day 14. Treatment-related clinical signs were observed at all doses, being most definitive at the 2000 mg/kg dose level. Among FOB parameters (home cage, handling, open field, sensory, neuromuscular and physiological observations) and locomotor activity, there were no remarkable treatment-related effects except a possible decreased motor activity among rats at the 2000 mg/kg level.

For rats of both sexes, the brain ChE NOAEL was the highest dose tested, 2000 mg/kg. Among females, plasma ChE was possibly inhibited (ranging 11-48%) at all doses on days 0, 7 and 15, being statistically significant only at 500 mg/kg on day 7. A dose response was not evident. High variability in assay results, coupled with small numbers of animals (5/sex/group) at given time points render a conclusion as to NOAEL/LOAEL difficult. In males, no effect was observed on plasma ChE. Concerning erythrocyte ChE, among females, statistically significant inhibition of 39% and non-significant inhibition of 34%, respectively, at 2000 and 1000 mg/kg on day 7 support an effect in females, where LOAEL/NOAEL = 2000/1000 mg/kg and possibly 1000/500 mg/kg. In males there were no statistically significant inhibitions of this enzyme, though there was a 40% non-significant inhibition at day 7 at 2000 mg/kg.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for an acute neurotoxicity screening battery **(870.6200)** in rats.

3. A preliminary dose range-finding developmental neurotoxicity study (MRID 45627001) with malathion (96% a.i., batch/lot 9010501) was conducted in two phases. In Phase 1, malathion was administered by gavage to 15 female Crl:CD® BR rats per dose at dose levels of 0, 7.5, 750 or 1250 mg/kg bw/day. Ten maternal animals/group were administered the test substance from gestation day (GD) 6 through postnatal day (PND) 10; an additional five dams/group were dosed on GD 6-20. Following mortalities at 1250 mg/kg/day during the first four days of treatment, the dose for this group was reduced to 1000 mg/kg/day. In Phase 2, 10 maternal animals/group were administered the test substance from GD 6 through PND 10; an additional five dams/group were dosed on GD 6-20, at doses of 0, 7.5, 35, 75, or 150 mg/kg/day. In both phases, two male and two female pups/litter were treated from PND 11 to 21. For Phase 1, an additional 2 male and 2 female pups/litter (from dams treated at 0 or 7.5 mg/kg/day) were also dosed from PND 11 to 21 at 200 or 450 mg/kg/day. The females treated up to GD 20 were killed three hours after dosing on that day; litter data were assessed and ChE activity determined in maternal and fetal plasma, RBC, and brain. Treated offspring were killed two hours after dosing on postnatal day 21 and ChE activities determined.

Under the conditions of this study, no adverse effects of treatment were observed in maternal animals at 7.5 or 35 mg/kg/day. Transient post-dosing salivation was seen in the majority of dams at 75 and 150 mg/kg/day. Signs of severe toxicity were observed at 750 and 1250/1000 mg/kg/day, and included tremors, prostrate posture, abnormal gait, decreased body weight and food consumption, moribundity, and mortality; dosing was stopped for these groups and survivors were sacrificed on GD 20. At GD 20, RBC ChEI was observed in dams at 75 mg/kg/day and above; plasma and brain cholineserase inhibition were observed at 750 mg/kg/day and above.

In offspring that were dosed directly, overt clinical signs of toxicity (body tremors and moribundity) were observed at doses of 200 and 450 mg/kg/day; due to the excessive toxicity, dosing was terminated and pups sacrificed before reaching weaning. RBC ChEI was observed at all doses tested (i.e., 7.5 mg/kg/day and above) in PND 21 pups. Brain ChEI was seen at 75 mg/kg/day and above, and plasma ChE was inhibited at 150 mg/kg/day and above. For GD 20 fetuses, RBC ChE was inhibited at 750 mg/kg/day and above.

The results from this study were used to select the doses used in the definitive developmental neurotoxicity study (MRID 45646401). The highest dose tested in that study was set at 150 mg/kg/day, based upon the severity of clinical signs noted at 200 mg/kg/day in directly dosed pups on this dose range-finding study.

This study is classified **Acceptible/Non-guideline** as a dose range-finding study and does not satisfy the guideline requirement for a developmental neurotoxicity study **(870.6300)** in rats, but provides information critical to the interpretation of the main study.

4. In a subchronic neurotoxicity study (MRID 43269501), technical malathion (96.4% a.i.) was administered continuously in the diet for 90 days to groups of 25 male and female Sprague-Dawley rats at dose levels of 0, 50, 5000 or 20,000 ppm (equivalent to 0, 4, 352 and 1486 mg/kg/day for males and 0, 4, 395 or 1575 mg/kg/day for females). The rats were subjected to neurotoxicity assessment at pretest, weeks 3, 7 and 12. Plasma, erythrocyte and brain region ChE determinations were performed on 5 rats/sex/group one week prior to study initiation and during weeks 3, 7 and 13. Definite effects were noted in the high dose group only, which included cholinergic signs and decreased body weight gain. Among neurotoxicity parameters (FOB and motor activity) there were no effects. Hence, LOAEL is 1486 (males), 1575 (females) mg/kg/day. The NOAEL is 352 (males) 395 (females) mg/kg/day. For ChEI, plasma ChE (males 12-20%, females 15-30%, erythrocyte ChE (males 49-61% and females 49-53%) and brain (i.e., cortex 12-20% in females) were inhibited at 352 or 395 mg/kg/day, respectively. Higher levels of ChEI were noted for the high dose group and male brain (i.e., mid-brain 24%). The LOAEL is 352 (males), 395 (females) mg/kg/day based on plasma and erythrocyte ChE, and 395 (females) mg/kg/day based on brain ChE. The NOAEL is 4 mg/kg/day based on plasma and erythrocyte ChE in both sexes and brain ChE in females.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a subchronic neurotoxicity screening battery **(870.6200)** in rats.

5. In a developmental neurotoxicity study (MRID 45646401), malathion (96% a.i., batch # 9010501) was administered to 24 parental female Crl:CD®BR rats per dose by gavage at dose levels of 0, 5.0, 50, or 150 mg/kg bw/day in corn oil from gestation day 6 through postnatal day 10, and to the offspring from postnatal day 11 to postnatal day 21 inclusive. A Functional Observational Battery was performed on 10 dams/dose on gestation days 12 and 18 and lactation days 4 and 10. Offspring were evaluated as follows: age-appropriate functional observation battery on days 4, 11, 21, 35, 45, and 60, automated motor activity on days 13, 17, 22, and 60; assessment of auditory startle response on days 23/24 and 60/61, assessment of learning and memory (Morris Water Maze) at postnatal days 23/24, and at postnatal day 61/62 (separate groups), brain weights on days 11, 21, and 65, and brain histopathology and morphometrics on days 21 and 65. Pup physical development was assessed by body weight. Sexual maturation of females was assessed by age of vaginal opening, and sexual maturation of males was assessed by age at completion of balano-preputial separation.

There were no treatment-related maternal deaths before scheduled termination. Clinical signs were limited to transient post-dosing salivation (5/24 control, 4/24 at 5 mg/kg/day, 3/24 at 50 mg/kg/day, and 20/24 at 150 mg/kg/day). There were no other treatment-related effects on cholinergic signs, and there were no effects on maternal body weight, food consumption, or reproductive indices. **The maternal LOAEL for malathion in rats is 150 mg/kg/day based on an increased incidence of post-dosing salivation. The maternal NOAEL is 50 mg/kg/day.**

The **offspring NOAEL is <5 mg/kg/day** (the lowest dose tested). The **offspring LOAEL is 5 mg/kg/day, based upon increased auditory startle reflex peak amplitude in PND 23/24 male and female offspring**. At 50 mg/kg/day, there was an increased incidence of slightly flattened

gait in PND 60 males, and motor activity counts (rearing and ambulatory) were decreased in female pups at PND 17 and 22. At 150 mg/kg/day, additional treatment-related findings included post-dosing clinical observations on PND 17 and 18 (whole body tremors, hypoactivity, prostrate posture, partially closed eyelids, and/or abnormal gait), delayed surface righting reflex in PND 11 female pups, and increased incidences of slightly flattened gait in PND 60 males.

6. In a companion ChEI study (MRID 45566201), acute or repeated exposure to malathion resulted in statistically and biologically significant decreases in ChE activity in the blood and/or brain in dams, fetuses, weanling pups, and adult male and female rats. In pups, effects on RBC ChE were noted at 5 mg/kg in males and 50 mg/kg in females following single dose acute exposures on PND 11, and at 5 mg/kg/day in both sexes on PND 21 after 11 repeated exposures. Following a single dose to young adults, effects on RBC ChE were observed at 450 mg/kg, while after 11 or 14 doses, effects were observed at 50 mg/kg/day in young adults and pregnant dams. In pups, brain ChE was inhibited at 150 mg/kg/day following an acute dose (44-48%) in PND 11 pups or after 11 repeated doses (16% in PND 21 pups). Based upon the results of the ChE study, it is evident that all behavioral and neuropathological effects of treatment observed in the dams and offspring in the developmental neurotoxicity study occurred at doses at which ChE was, or had been, inhibited. For acute and repeated exposures the overall LOAEL for ChEI was 5 mg/kg/day, based on RBC ChEI in PND 11 and 21 pups. The NOAEL was not determined.

This study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental neurotoxicity study **(870.6300)** in rats.

Other Non-guideline Information on Neurotoxicity

There are a number of published peer-reviewed studies that address various aspects of the neurotoxic potential of malathion. The following studies have been highlighted because they provide additional information and support to 1) the evaluation of the neurotoxic profile of malathion (i.e., evidence for behavioral effects at low doses of malathion) and for 2) the evaluation of potential effects of malathion on infants and children (i.e., increased susceptibility of the immature individual).

7. Desi, I., Gonczi, L., Kneffel, A., Strohmayer, A., and Szabo, Z. (1976) Toxicity of malathion to mammals, aquatic organisms and tissue culture cells. *Arch. Environ. Contam. Toxicol.* 3, 410-425 (MRID 45642901).

Abstract: The effect of malathion on rats (75 and 38 mg/kg bwt), aquatic organisms (100 to 0.001 mg/L), and cells in tissue culture (1000 to 1 ppm) was studied. The conventional toxicological tests conducted for 90 days on rats yielded negative results. ChE activity was determined in plasma, liver, brain and erythrocyte samples. It was significantly reduced in the erythrocytes of animals treated with the larger dose for 21 days and in the cerebral cortex of rats fed either of the doses. ChE activity of rats consuming malathion for 90 days did not differ significantly from that of the control. In contrast, the psychophysiological examinations utilized in the experiments indicated abnormalities within 21 days. Alterations were observed in the EEG and EMG records after 90 days of feeding. Malathion had a definitely harmful

effect on phylogenetically and ontogenetically young aquatic organisms, as well as on the cells of monkey kidney culture. The latter finding suggests that the preparation has a destructive effects on cells. Although it is not suggested that malathion should be regarded a toxic agent thus requiring limitation of application, attention is directed to the fact that inconsiderate use of the preparation may involve potential dangers for man and his environment.

8. Kurtz, P.J. (1977) Dissociated behavioral and ChE decrements following malathion exposure. *Toxicol. and Applied Pharm.* 42, 589-594 (MRID 45642902).

This was a journal publication of research conducted by the U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD. As stated in the 1976 Army report, "*The purpose of this study was to acquire further information concerning the toxic effects of low dosages of malathion (technical name) on animal behavior and to compare activity following treatment. This information will facilitate the evaluation of the potential toxic hazard resulting from exposure to* ***low*** (emphasis added) *levels of the compound."* Elsewhere the report indicates that: "*The present study examined some of the behavioral and biochemical effects of the organophosphate insecticide, malathion, a compound employed extensively in both military and civilian pesticide applications. The principal area of interest was the relationship between the behavioral and anticholinesterase effects of malathion.*" The report asserts that behavioral effects occurred at doses even below those for which ChEI was identified.

Abstract: Rat conditioned avoidance performance and erythrocyte, plasma, and brain ChE activity were examined after a single intraperitoneal injection of 25, 50, 100, or 150 mg/kg of malathion. Avoidance performance was significantly impaired 1 hr after injection with 50 mg/kg, although blood and brain ChE remained at greater than 90% of control values. The higher dosages (100) and 150 mg/kg) produced significant decreases in blood and brain ChE activity as well as avoidance performance, but the behavioral and biochemical decrements did not necessarily coincide. The results suggest that low dosages of malathion may disrupt behavior without significantly reducing ChE activity.

9. Ehrich, M., Shell, L., Rozum, M., and Jortner, B.S. (1993) Short-term clinical and neuropathologic effects of ChE inhibitors in rats. *J. Am. Coll. Toxicol*. 12(1), 55-68 (MRID 45045001).

Abstract: Adult male Long Evans rats were given a single administration of 3 dosage levels of the organophosphorus compounds tri-ortho-tolyl phosphate (TOTP), diisopropyl fluorophosphate (DFP), phenyl saligenin phosphate (PSP), mipafox, malathion, and dichlorvos or the carbamate carbaryl. Acetylcholinesterase and neurotoxic esterase activities were inhibited in a dose-dependant manner, with the highest dosages of all of these compounds inhibiting activities of these enzymes in brain by at least 37% and 64%, respectively, at 4 and 48 hours after administration. Rats given the high doses of TOTP (1000 mg/kg), DFP (3 mg/kg), malathion (2000 mg/kg), and carbaryl (160 mg/kg) weighed significantly less than control rats 14 days after administration. A functional observational battery (FOB) was used to screen for neurotoxic effects 1, 2, and 3 weeks after exposure. All 7 test compounds were

capable of causing changes in parameters indicative of behavioral and central nervous system excitability. In addition, dose-related alterations in response to approach were seen in rats given DFP, malathion, dichlorvos and carbaryl. Mild to moderate myelinated fiber degeneration was seen in the rostral levels of the fasciculus gracilis in rats given TOTP, DFP, PSP and mipafox, but no significant neuropathologic lesions were noted in rats given dichlorvos, malathion, or carbaryl.

10. Mendoza, C.E. (1976) Toxicity and effects of malathion on esterases of suckling albino rats. *Toxicol. and Applied Pharmacol*. 35, 229-238 (MRID 45046301).

Abstract: Malathion toxicity in suckling Wistar rats and its effects on cholinesterases and carboxylesterases were studied. The 1-day old pups *[LD50 209 mg/kg]* were found to be nine times more susceptible to malathion than the 17-day-old pups *[1806 mg/kg]*. Based on the hydrolysis of indophenyl acetate, liver esterases were markedly inhibited by malathion from 0.5 to 24 hr after dosing. Brain cholinesterases were also inhibited within 0.5 hr but showed a sign of recovery 3 hr after malathion dosing. The development of ChE and carboxylesterases in different organs was followed in rats 1-84 days old.

DEVELOPMENTAL STUDIES (Three)

1. In a developmental toxicity study in rats (MRID 41160901), Malathion (94%) was administered by daily oral gavage to groups of 25 pregnant Sprague-Dawley dams on days 6 through 15 of gestation at dose levels of 0, 200, 400 or 800 mg/kg/day. No treatment-related mortalities occurred during the study. Clinical signs of toxicity were observed only at 800 mg/kg/day, consisting of urine stained abnormal fur in 5/25 dams and chromodacryorrhea and chromorhinorrhea in one dam. The maternal NOAEL is 400 mg/kg/day and the maternal LOAEL is 800 mg/kg/day based on reduced mean body weight gains and reduced mean food consumption during the period of treatment. The developmental toxicity NOAEL is $\geq$ 800 mg/kg/day, the highest dose level tested since no adverse developmental effects were observed at any dose level in this study.

This developmental toxicity study in the rat is classified **Acceptable/guideline** and satisfies the guideline requirement for a prenatal developmental toxicity study in the rodent **(870.3700a)**.

2. In a developmental toxicity study in rabbits (MRID 00152569, 40812001, 45626801), Malathion (92.4%) was administered by daily oral gavage to groups of 20 pregnant New Zealand white does on days 6 through 18 of gestation at dose levels of 0, 25, 50 or 100 mg/kg/day. Anorexia and soft stools may have occurred at slightly higher incidence in the 100 mg/kg/day animals. The maternal NOAEL is 25 mg/kg/day and the maternal LOAEL is 50 mg/kg/day based on reduced mean body weight gains during days 6-18 of gestation (period of treatment with malathion). The developmental toxicity NOAEL is 25 mg/kg/day and the developmental toxicity LOAEL is 50 mg/kg/day based on an increased incidence of mean resorption sites per doe.

This developmental toxicity study in the rabbit is classified **Acceptable/guideline** and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits **(OPPTS 870.3700b)**.

3. In a range-finding study in rabbits (MRID 00152569), pregnant New Zealand white rabbits (5/group) received oral administration of Malathion (92.4%) in corn oil at doses of 0, 25, 50, 100, 200, or 400 mg/kg/day on Gestation Days (GD) 6-18. No mortalities or clinical signs were observed at 25, 50 or 100 mg/kg/day. At 200 mg/kg/day, 2 does died, 1 on GD 11 (5 days after dosing) and another on GD 17 (11 days after dosing). At 400 mg/kg/day, 4 does died, 1 on GD 7, 1 on GD 8 and 2 on GD 9. Cholinergic signs of toxicity seen at 200 and 400 mg/kg/day included tremors, decreased activity and salivation. External examinations of the fetuses did not indicate any gross abnormalities. For Maternal Toxicity, the NOAEL was 100 mg/kg/day and the LOAEL was 200 mg/kg/day based on mortality and clinical signs.

This range-finding prenatal developmental toxicity study in the rabbit is classified **Acceptable/nonguideline** and does not satisfy the guideline requirement for a prenatal developmental toxicity study in rabbits **(OPPTS 870.3700b)**, but provides information critical to the interpretation of the main study.

REPRODUCTIVE TOXICITY (One)

In a two-generation reproduction study in rats (MRID 41583401), malathion (94.0% purity) was administered continuously in the diet for two successive generations to groups of 25 male and 25 female Sprague-Dawley rats at dose levels of 0, 550, 1700, 5000 or 7500 ppm (equivalent to 0, 43, 131, 394 or 612 mg/kg/day in males and 0, 51, 153, 451 or 703 mg/kg/day in females). Following 63 days of treatment (at about 105 days of age), males and females were mated (1:1) to produce the F1A litters. Two weeks after weaning, F0 males and females were again mated to produce the F1B litters. One male and one female F1B pup/litter were randomly selected to be F1 parents. Following 79 days of treatment, F1 males and females were mated, as before, to produce F2 and F2B litters. No treatment-related mortality or clinical signs of toxicity were observed in the F0 or F1 parental animals at any dose level.

The parental toxicity NOAEL is 5000 ppm (394 mg/kg/day in males and 451 mg/kg/day in females) and the parental toxicity LOAEL is 7500 ppm (612 mg/kg/day in males and 703 mg/kg/day in females) based on decreased body weights in F0 females during gestation and lactation and on decreased body weights in F1 males and females during the pre-mating period. The developmental toxicity NOAEL is 1700 ppm (131 mg/kg/day in males and 153 mg/kg/day in females) and the developmental toxicity LOAEL is 5000 ppm (394 mg/kg/day in males and 451 mg/kg/day in females) based on decreased pup body weights during the lactation period in F1A and F2B pups. The reproductive toxicity NOAEL is $\geq$ 7500 ppm (>612 mg/kg/day in males and >703 mg/kg/day in females). The reproductive toxicity LOAEL is >7500 (>612 mg/kg/day in males and >703 mg/kg/day in females). No reproductive toxicity was observed in this study.

This two-generation reproduction study in the rat is classified **Acceptable/guideline** and satisfies the guideline requirement for a reproduction and fertility effects study in rats **(OPPTS 870.3800).**

CARCINOGENICITY STUDIES (Two)

1. In a combined chronic toxicity/carcinogenicity study in rats (MRID 4394201), malathion (97.1% a.i.) was administered to 90 Fischer 344 rats/sex/dose via the diet for up to 24 months at dose levels of 0, 100/50 (100 ppm for first 3 months of study, 50 ppm for duration of study in both sexes due to finding of erythrocyte ChEI in females only at 3 month assay) 500, 6,000 or 12,000 ppm [equivalent to respective mean values of 0, 4, 29, 359 and 739 mg/kg/day (males) and 0, 5, 35, 415 and 868 mg/kg/day (females)].

The only clinical sign observed was yellow anogenital staining among females at 12000 ppm (highest dose). Increased mortality was seen in females at 12000 ppm and in males at 500, 6000 and 12000 ppm. All 12000 ppm males died or were sacrificed moribund by about 94 weeks. Treatment related decrements in body weight gain were observed at 6000 and 12000 ppm in both sexes. Food consumption was increased at 100 ppm in males for the first 3 months (prior to lowering of dose to 50 ppm). At subsequent time points for males, and across all time points for females food consumption was increased in the 6000 and 12000 ppm groups.

Plasma ChEI was significantly inhibited in males (all doses above 50 ppm) and females (all doses above 500 ppm). Significant brain and RBC ChEI was observed in both males and female at all doses above 500 ppm. In addition, females exposed to malathion at 100 ppm in feed for three months showed significant RBC ChEI and thus prompted lower the dose from 100 ppm to 50 ppm.

Other effects were seen at similar or higher doses. Hematological parameters were affects at all doses above 500 ppm (erythrocyte count was reduced in males at 12000 ppm, and the following were observed in rats of both sexes at 6000 and 12000 ppm: increased platelet count, decreased mean corpuscular volume and mean corpuscular hemoglobin). Decreased aspartate aminotransferase, females, 12000 ppm; decreased alkaline phosphatase, males and females, 6000 and 12000 ppm; elevated blood urea nitrogen, males, 12000 ppm; elevated cholesterol, males and females, 6000 and 12000 ppm; elevated gamma-glutamyl transpeptidase, males and females, 6000 and 12000 ppm.

The following organ weights were affected: increased kidney and liver weights, males and females, 6000 and 12000 ppm; thyroid/parathyroid weight increased (males), decreased (females) 6000 and 12000 ppm; increased spleen weight, males, 6000 and 12000 ppm; increased heart weight, males, 6000 ppm (term). Non-neoplastic microscopic findings included the following: nasal mucosa and nasopharynx (several pathologies), males and females, 6000 and 12000 ppm; bilateral subacute-chronic inflammation/chronic nephropathy (high incidence in all study groups including controls), increased severity, males, 6000 and 12000 ppm, females, 500, 6000 and 12000 ppm; stomach (several pathologies), males and females, 6000 and 12000 ppm;

increased incidence parathyroid hyperplasia, males and females, all doses; other findings in various tissues (thyroid, lymph nodes, lungs, liver, spleen, adrenal gland, eyes) as summarized in the DER, being more remarkable in males, and often extending across the top three doses in males and top two doses in females.

Neoplastic microscopic findings included the following: treatment-related increased combined hepatocellular adenomas/carcinomas, females at all doses, incidences: 0/55 (0%), 2/55 (3.6%), 2/55 (3.6%), 3/55 (5.5%) and 6/55 (10.9%) for the 0, 100/50, 500, 6000 and 12000 ppm groups, respectively; rare tumors (one in each of four dose groups) on nasoturbinal slide preparations considered compound related effects: males, carcinoma 12000 ppm, adenoma 6000 ppm; females, squamous cell carcinoma 100/50 and 12000 ppm. Other tumor types observed included testes interstitial cell tumors significant at all doses with possibly decreased latency; significant trend in thyroid follicular cell adenomas and/or carcinomas, males; significant trend and positive pairwise comparison at 500 ppm for thyroid c-cell carcinoma, males; significant difference in pair-wise comparison, mononuclear cell leukemia, 100/50 ppm, females; significant difference in pair-wise comparisons, pituitary pars distalis carcinomas, 500 and 6000 ppm, females; significant difference in pair-wise comparison, pituitary pars distalis adenomas and/or carcinomas combined, 500 ppm, females. Tumorigenic responses may have been compromised by high mortality in males at 6000 and 12000 ppm and in females at 12000 ppm.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a combined chronic toxicity/carcinogenicity study **(870.4300)** in the rat.

2. In an 18-month carcinogenicity study in mice (MRID 43407201), technical grade malathion (96.4% a.i.) was administered in the diet to groups of 65 male and 65 female B6C3F1 BR strain mice at dose levels of 0 (control), 100 ppm, 800 ppm, 8000 ppm or 16000 ppm (equivalent to 0, 17.4, 143, 1476 or 2978 mg/kg/day in males and to 0, 20.8, 167, 1707 or 3448 mg/kg/day in females). ChE (plasma, erythrocyte and brain) activity was assayed at 9 (erythrocyte ChE only), 12 and 18 months.

At 8000 ppm and 16000 ppm in both males and females, treatment related effects included decreased absolute body weights ranging from 14.3 to 20.0% in males and 9.7 to 16.1% in females throughout the entire duration of the study. Decreased food consumption was noted at 16000 ppm for mice of both sexes during the first 3 weeks and 13 weeks. After 26 weeks and for the remainder of the study, dose-related decreases in food consumption were observed at 8000 ppm and 16000 ppm, both sexes. Statistically significant inhibition of plasma and erythrocyte ChE activity was observed in males at 8000 and 16000 ppm and in females at 800, 8000 and 16000 ppm, while inhibition of brain ChE activity was seen in males and females only at 16000 ppm. Mortality rates, clinical signs of toxicity and hematological parameters were not affected by treatment with malathion at any dose.

A treatment-related increased incidence of hepatocellular tumors was observed in both male and female mice in this study at 8000 ppm and 16000 ppm. The percent incidences of hepatocellular

adenomas for males were 1.9%, 7.3%, 3.6%, 21.8% and 94.1%; of hepatocellular carcinomas were 0.0%, 10.9%, 5.5%,%, 10.9% and 2.0%; and of combined hepatocellular adenomas/carcinomas were 1.9%, 18.2%, 9.1%, 32.7% and 96.1% for the 0 (control), 100, 800, 8000 and 16000 ppm groups, respectively. For male mice, combined incidences at 16000, 8000 and 100 ppm were statistically significant by pair-wise comparison and the dose trend was positive. For female mice, the percent incidences of hepatocellular adenomas were 0.0%, 1.8%, 0.0%, 17.0% and 80.8%; of hepatocellular carcinomas were 1.8%, 0.0%, 3.7%, 1.9% and 3.8%; and of combined hepatocellular adenomas/carcinomas were 1.8%, 1.8%, 3.7%, 18.9% and 84.6% for the 0 (control), 100, 800, 8000 and 16000 ppm groups, respectively. Combined incidences at 16000 and 8000 ppm were statistically significant by pair-wise comparison and the dose trend test was positive.

The increased tumor incidences in the livers of both males and females at 8000 ppm and 16000 ppm were accompanied by concurrent observations of masses, nodules and foci in the livers of these animals at the terminal sacrifice and also by increased liver weights and highly increased incidences of hepatocellular hypertrophy in the livers at 12 and 18 months. The data for hepatocyte hypertrophy was quite remarkable in that an extremely steep dose-response curve was observed for both males and females in this study. Thus, in the control, 100 ppm and 800 ppm groups, no case of hepatocellular hypertrophy was observed in any animal at any time during the entire duration of this study whereas at 8000 ppm and 16000 ppm, a >50% incidence was observed at 12 months and a 100% incidence at 18 months.

Other findings were observed in this study that appeared to be related to treatment, but their biological significance was uncertain. These findings included the following: decreased vacuolation in the convoluted tubules of the kidneys in males; increased mineralization of the kidneys in females; decreased fibrous osteodystrophy of the femur and sternum in females; and early disappearance of the "x zone" in the adrenal cortex of females.

The NOAEL for ChEI for both sexes was estimated to be 100 ppm (17.4 mg/kg/day in males and 20.8 mg/kg/day in females) for plasma and erythrocyte cholinesterases and 8000 ppm (1476 mg/kg/day in males and 1707 mg/kg/day in females) for brain ChE. Although there was some decrease in ChE activity at these doses, the decreases were not statistically significant and the data were considered to be too variable to conclude that the inhibition seen was really related to treatment. The LOAEL for ChEI for both sexes was estimated to be 800 ppm (143 mg/kg/day in males and 167 mg/kg/day in females) for plasma and erythrocyte ChE and 16000 ppm (2978 mg/kg/day in males and 3448 mg/kg/day in females) for brain ChE. The NOAEL for systemic effects was 800 ppm (143 mg/kg/day in males and 167 mg/kg/day in females). The LOAEL was 8000 ppm (1476 mg/kg/day in males and 1707 mg/kg/day in females), based on decreased body weights and food consumption in males and females, increased liver weight in males and females and increased hepatocellular hypertrophy in males and females.

This study is classified **Acceptable-guideline** and satisfies the guideline requirement for an oncogenicity feeding study **(870.4200b)** in the mouse.

METABOLISM STUDIES (One)

In a metabolism study in rats (MRID 41367701), single doses of radiolabeled ^{14}C-malathion (98% purity) were administered by oral gavage to groups of 5 male and 5 female Sprague-Dawley rats at dose levels of 40 mg/kg, 800 mg/kg and 40 mg/kg following 15 days of daily oral gavage of non-radio labeled malathion (94.6%) at a dose level of 40 mg/kg/day. The rats were then placed in metabolism cages and urine and feces were collected for 72 hours for determination of excretion of radioactivity and analysis of biotransformation products. At 72 hours, the animals were sacrificed and major organs/tissues were collected, weighed and analyzed for radioactivity.

More than 90% of the radioactivity in the 40 mg/kg dose was excreted within 72 hours, with most excretion occurring in the first 24 hours. Approximately 80-90% of the administered radioactivity was excreted in the urine. Only minor differences in urine/fecal excretion ratios were observed between animals given 40 mg/kg, 800 mg/kg and 40 mg/kg after 15 previous daily doses of malathion. At 72 hours, the highest concentration of radioactivity was observed in the liver, but less than 0.3% of the administered radioactivity was present in that organ. Radioactivity did not bioaccumulate in any of the organs/tissue analyzed. Although 8 radiolabeled metabolites were observed in urine, greater than 80% of the radioactivity in urine was represented by the diacid and monoacid metabolites. It was determined that between 4 and 6% of the administered dose was converted to malaoxon.

This study is classified **Acceptable-guideline** and satisfies the guideline requirement for a metabolism study **(870.7485)** in the rat.

3.0 TOLERANCE REASSESSMENT TABLE

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Tolerance Listed Under 40 CFR §180.111			
Alfalfa (PRE-H)	135	125	[*Alfalfa, forage*]
		185	[*Alfalfa, hay*]
Almond hulls (PRE-H)	50	Revoke	Not supported under reregistration
Almonds (PRE- and POST-H)	8	Revoke	Not supported under reregistration
Almonds, shells	50	Revoke	Not supported under reregistration
Apples (PRE-H)	8	TBD [3]	[*Apple*] Additional apple field trial data are required.
Apricots (PRE-H)	8	1	[*Apricot*]
Asparagus (PRE-H)	8	2	[*Asparagus*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Avocados (PRE-H)	8	0.2	[*Avocado*]
Barley, grain (PRE- and POST-H)	8	8	[*Barley, grain (PRE- and POST-H)*] Translated from wheat data.
Beans (PRE-H)	8	2	[*Bean, dry*]
		2	[*Bean, succulent*]
Beets (including tops)(PRE-H)	8	4	[*Beet, garden, tops*] translated from turnip tops data.
		0.5	[*Beet, garden, roots*] Translated from turnip root data.
Beets, sugar, roots (PRE-H)	1	Revoke	Not supported under reregistration
Beets, sugar, tops (PRE-H)	8	Revoke	Not supported under reregistration
Birdsfoot trefoil, forage (PRE-H)	135	125	*[trefoil, forage]* Translate alfalfa and clover data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Birdsfoot trefoil, hay (PRE-H)	135	185	*[trefoil, hay]* Translate alfalfa and clover data.
Blackberries (PRE-H)	8	6	[*Blackberry*]
Blueberries (PRE-H)	8	8	[*Blueberry*]
Boysenberries (PRE-H)	8	6	[*Boysenberry*] Translated from blackberry and raspberry data.
Carrots (PRE-H)	8	1	[*Carrot*]
Cattle, fat (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Cattle, mbyp [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Cattle, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Chayote fruit	8	0.2	Translated cucumber data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Chayote roots	8	0.1	Translated potato data.
Cherries (PRE-H)	8	3	[*Cherry*]
Chestnuts (PRE-H)	1	1	[Chestnut]
Clover (PRE-H)	135	125	[*Clover, forage*]
		125	[*Clover, hay*]
Corn, forage (PRE-H)	8	5	[*Corn, field, forage*]
		45	[*Corn, sweet, forage*]
Corn, fresh (including sweet K + CWHR) (PRE-H)	2	0.1	[*Corn, sweet (K + CWHR)*]
Corn, grain (POST-H)	8	8	[*Corn, field, grain (PRE- and POST-H)*]
Cottonseed (PRE-H)	2	20	[*Cotton, undelinted seed*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Cowpea, forage (PRE-H)	135	Revoke	Not supported under reregistration
Cowpea, hay (PRE-H)	135	Revoke	Not supported under reregistration
Cranberries (PRE-H)	8	Revoke	Not supported under reregistration
Cucumbers (PRE-H)	8	0.2	[*Cucumber*]
Currants (PRE-H)	8	8	[*Currant*] Translated from blueberry data.
Dates (PRE-H)	8	TBD	Further data required (data under review)
Dewberries (PRE-H)	8	6	[*Dewberry*] Translated from blackberry data.
Eggplants (PRE-H)	8	2	[*Eggplant*] Translated from tomato data.
Eggs (from application to poultry)	0.1	Revoke	Contingent upon cancellation of direct animal treatment uses.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Figs (PRE-H)	8	1	[*Fig*]
Filberts (PRE-H)	1	Revoke	Not supported under reregistration
Flax seed	0.1	0.1	[*Flax, seed*]
Flax straw	1	Revoke	Not a significant RAC of flax.
Garlic (PRE-H)	8	1	[*Garlic*] Translated from onion bulb data.
Goats, fat (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Goats, mbyp [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Goats, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Gooseberries (PRE-H)	8	6	[*Gooseberry*] Translated from blackberry and raspberry data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Grapefruit (PRE-H)	8	4	[*Grapefruit*] Translated from orange data.
Grapes (PRE-H)	8	4	[*Grape*]
Grass, (PRE-H)	135	200	[*Grass, forage*]
Grass, hay (PRE-H)	135	270	[*Grass, hay*]
Guavas (PRE-H)	8	1	[*Guava*]
Hogs, fat (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Hogs, mbyp [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Hogs, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Hops (PRE-H)	1	1	[*Hops, dried*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Horseradish (PRE-H)	8	0.5	[*Horseradish*] Translated from turnip root data.
Horses, fat (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Horses, mbyp [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Horses, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Kumquats (PRE-H)	8	4	[*Kumquat*] Translated from orange data.
Leeks (PRE-H)	8	6	[*Leek*] Translated from green onion data.
Lemons (PRE-H)	8	4	[*Lemon*] Translated from orange data.
Lentils (PRE-H)	8	Revoke	Not supported under reregistration
Lespedeza, hay (PRE-H)	135	185	Translated from alfalfa hay data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Lespedeza, seed (PRE-H)	8	Revoke	Not a significant RAC of lespedeza
Lespedeza, straw (PRE-H)	135	Revoke	Not a significant RAC of lespedeza
Limes (PRE-H)	8	4	[*Lime*] Translated from orange data.
Loganberries (PRE-H)	8	6	[*Loganberry*] Translated from blackberry and raspberry data.
Lupine, hay (PRE-H)	135	Revoke	Not a significant RAC of lupine
Lupine, seed (PRE-H)	8	2	Translated from dry beans data
Lupine, straw (PRE-H)	135	Revoke	Not a significant RAC of lupine
Macadamia nuts (PRE-H)	1	0.2	[*Macadamia nut*]
Mangos (PRE-H)	8	0.2	[*Mango*]
Melons (PRE-H)	8	1	[*Melon*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Milk, fat (from application to dairy cows)	0.5	Revoke	Contingent upon cancellation of direct animal treatment uses.
Mushrooms (PRE-H)	8	0.2	[*Mushroom*]
Nectarines (PRE-H)	8	1	[*Nectarine*] Translated from apricot data.
Oats, grain (PRE- and POST-H)	8	8	[*Oats, grain (PRE- and POST-H)*] Translated from wheat grain data.
Okra (PRE-H)	8	3	[*Okra*]
Onions (including green onions) (PRE-H)	8	1	[*Onion, bulb*]
		6	[*Onion, green*]
Oranges (PRE-H)	8	4	[*Orange*]
Papayas (PRE-H)	1	1	[*Papaya*]
Parsnips (PRE-H)	8	0.5	[*Parsnip*] Translated from turnip root data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Passion fruit (PRE-H)	8	0.2	[*Passion fruit*]
Peaches (PRE-H)	8	6	[*Peach*]
Peanut, forage (PRE-H)	135	Revoke	Not supported under reregistration
Peanut, hay (PRE-H)	135	Revoke	Not supported under reregistration
Peanuts (PRE- and POST-H)	8	Revoke	Not supported under reregistration
Pears (PRE-H)	8	3	[Pear]
Peas (PRE-H)	8	2	[*Pea, succulent*] Dry peas not being supported under reregistration.
Peavine, hay (PRE-H)	8	Revoke	Not supported under reregistration
Peavines (PRE-H)	8	Revoke	Not supported under reregistration
Pecans (PRE-H)	8	0.2	[*Pecan*] Translated from walnut data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Peppermint (PRE-H)	8	2	[*Peppermint*]
Peppers (PRE-H)	8	0.5	[*Pepper*]
Pineapples (PRE-H)	8	0.2	[*Pineapple*]
Plums (PRE-H)	8	Revoke	Not supported under reregistration
Potatoes (PRE-H)	8	0.1	[*Potato*]
Poultry, fat (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Poultry, mbyp [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Poultry, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Prunes (PRE-H)	8	Revoke	Not supported under reregistration.
Pumpkins (PRE-H)	8	1	[*Pumpkin*]Translated from melon data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Quinces (PRE-H)	8	TBD	[*Quince*] Translate from apple data. Further apple data required.
Radishes (PRE-H)	8	0.5	[*Radish*] Translated from turnip root data.
Raspberries (PRE-H)	8	6	[*Raspberry*]
Rice, grain (PRE- and POST-H)	8	30	[*Rice, grain (PRE-H)*] Postharvest use on rice not supported under reregistration.
Rice, wild	8	30	[*Rice, wild*] Translated from rice grain data.
Rutabagas (PRE-H)	8	0.5	[*Rutabaga*] Translated from turnip root data.
Rye, grain (PRE- and POST-H)	8	8	[*Rye, grain (PRE- and POST-H)*] Translated from wheat grain data.
Safflower, seed (PRE-H)	0.2	Revoke	Not supported under reregistration
Salsify (including tops) (PRE-H)	8	4	*[Salsify, tops (leaves)]* Translated from turnip tops data.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
		0.5	*[Salsify, root]* Translated from turnip root data.
Shallots (PRE-H)	8	6	[*Shallot*]Translated from green onion data.
Sheep, fat (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Sheep, mbyp [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Sheep, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Sorghum, forage (PRE-H)	8	TBD	[*Sorghum, forage*] Additional data are required.
Sorghum, grain (PRE- and POST-H)	8	8	[*Sorghum, grain (PRE- and POST-H)*] Postharvest data translated from field corn grain data.
Soybeans (dry and succulent) (PRE-H)	8	Revoke	Not supported under reregistration

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Soybeans, forage (PRE-H)	135	Revoke	Not supported under reregistration
Soybeans, hay (PRE-H)	135	Revoke	Not supported under reregistration
Spearmint (PRE-H)	8	2	[*Spearmint*]
Squash, summer and winter (PRE-H)	8	0.2	[*Squash, summer*] Translated from cucumber data.
		1	[*Squash, winter*] Translated from winter squash data.
Strawberries (PRE-H)	8	1	[*Strawberry*]
Sunflower seeds (POST-H)	8	Revoke	Not supported under reregistration
Sweet potatoes (PRE-H)	1	0.1	[*Sweet potato*] Translated from potato data.
Tangerines (PRE-H)	8	4	[*Tangerine*] Translated from orange data.
Tomatoes (PRE-H)	8	2	[*Tomato*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Turnips (including tops) (PRE-H)	8	4	[*Turnip, tops*]
		0.5	[*Turnip, roots*]
Vegetables, leafy, *Brassica* (cole)	8	8	[*Brassica (cole) leafy vegetables group*]
Vegetables, leafy (except *Brassica*)	8	TBD	[*Leafy vegetables (except Brassica vegetables) group*] Further data required on representative commodity, celery.
Vetch, hay (PRE-H)	135	185	Based on alfalfa data
Vetch, seed (PRE-H)	8	Revoke	Not a RAC of vetch
Vetch, straw (PRE-H)	135	Revoke	Not a RAC of vetch
Walnuts (PRE-H)	8	0.2	[*Walnut*]
Wheat, grain (PRE- and POST-H)	8	8	[*Wheat, grain (PRE- and POST-H)*]

Tolerance To Be Proposed Under 40 CFR §180.111			
Apple, pomace, wet	None	TBD	Level will be determined when RAC tolerance reassessed. Further data are required on RAC.
Aspirated grain fractions	None	700	Based on postharvest treated corn grain; the highest value measured in aspirated grain fractions.
Barley, hay	None	TBD	Translate from wheat hay data when adequate data have been reviewed.
Barley, straw	None	50	Translated from wheat straw data.
Citrus, pulp, dried	None	20	
Citrus, oil	None	400	
Corn, field, stover	None	30	
Corn, sweet, stover	None	TBD	Sweet corn stover data are required.
Corn, flour	None	14	
Corn, meal	None	14	

Tolerance To Be Proposed Under 40 CFR §180.111			
Cotton, gin byproducts	None	TBD	Cotton gin byproducts data required.
Fig, dried	None	2	
Lespedeza, forage	None	125	Translated from alfalfa and clover data.
Oats, forage	None	4	Translated from wheat forage data.
Oats, hay	None	TBD	Translate from wheat hay data when adequate data reviewed.
Oats, straw	None	50	Translated from wheat straw data.
Pineapple, process residue	None	0.4	
Peppermint, oil	None	15	
Radish, tops	None	4	Translated from turnip tops data
Rice, hulls	None	150	

Tolerance To Be Proposed Under 40 CFR §180.111			
Rice, straw	None	60	
Rye, forage	None	4	Translated from wheat forage data.
Rye, straw	None	50	Translated from wheat straw data.
Sorghum, stover	None	TBD	
Spearmint, oil	None	15	
Vetch, forage	None	125	Translated from alfalfa and clover data
Watercress	None	0.2	
Wheat, forage	None	4	
Wheat, hay	None	TBD	Field trial data are required for wheat hay.
Wheat, straw	None	50	
Tolerances Listed Under 40 CFR §185.3850			

Tolerance To Be Proposed Under 40 CFR §180.111			
Raisins	12	Revoke	Not supported under reregistration
Safflower, refined oil	0.6	Revoke	Not supported under reregistration
Tolerances Listed Under 40 CFR §185.7000			
Raisins	12	Revoke	Not supported under reregistration
Tolerances Listed Under 40 CFR §186. 3850			
Dehydrated citrus pulp [post-H]	50	Revoke	Not supported under reregistration
Non-medicated cattle feed concentrate blocks.	10	Revoke	Not supported under reregistration

[1] Maximum residue of treated RAC sample(s) following application of malathion formulation according to the maximum use patterns the registrant(s) wishes to support for reregistration.
[2] The reassessed tolerances are contingent upon the recommended label revisions outlined in Table B.
[3] TBD = To be determined. Reassessment of tolerance(s) cannot be made at this time because additional data are required.
[4] The tolerance level shall not be exceeded in any cut of meat or in any meat byproduct from cattle, goats, hogs, horse, poultry, or sheep.