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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: September 13, 2005

MEMORANDUM

SUBJECT: **Malathion**: Updated Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). PC Code: 057701. Case No. 0248. DP Barcode: D321543.

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.

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. Dissenting opinions by Brian Dementi are presented in Appendix 4.0. This risk assessment includes toxicology reviews from Louis Scarano, Anna Lowit, and Brian Dementi, a summary of the residue chemistry review from William Smith, dietary exposure and risk assessment from Sheila Piper, occupational exposure 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 Sherrie Kinard.

RDI: BRSrSci: A. Nielsen
RARC Review May 17, 2005

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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, 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.

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. This analysis is not included in this document but will be incorporated into the Agency's IRED as a supplementary assessment.

Malathion, like all members of the OP class, inhibits cholinesterase (ChE) as a mode of toxic action. Malathion is metabolically converted to its structurally similar 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.

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 target organ for this chemical is the inhibition of plasma, red blood cell (RBC) and brain ChE activity. Cholinesterase inhibition (ChEI) in the nervous system as measured by various compartments has been observed in multiple species (rat, mouse, and dog) following oral, dermal and inhalation routes of administration. Other treatment related effects of malathion via the inhalation route were histopathologic lesions of the nasal cavity and larnyx.

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 ChE study in the rat. HED notes that there are two human oral toxicity studies (one acute study and one repeated dose study); however, these studies are not being utilized for this assessment.

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.

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. Dicarboxilic acid and monocarboxilic acid metabolites account for the majority of the radioactivity. In the rat study, radioactivity did not bioaccumulate in any of the organ/tissues analyzed.

Malaoxon, the active ChE inhibiting metabolite of malathion, is not carcinogenic in rats. Malaoxon following oral direct exposure is a more potent ChEI than the parent, malathion. To account for this, benchmark dose (BMD) modeling was used to evaluate relative potency for malathion and malaoxon. Male, red blood cell (RBC) ChEI in adult rat provides 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 a comparative ChEI study in juvenile and adult rats dosed with malaoxon. 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. Following the receipt of the comparative ChE study using malaoxon, HED will reconsider the relative potency of malaoxon and malathion. In the absence of dermal and inhalation studies with malaoxon, the TAF calculated from oral studies (77x) is applicable to residues of malaoxon for risk assessment reflecting all exposure durations, routes, and scenarios.

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 recommends retention of a **hazard-based special FQPA factor of 10x**. This factor is meant to provide a measure of additional safety for the developing individual. Use of an FQPA factor of

10x is reasonable given the susceptibility ratio seen between adults and young using the BMD analysis of the comparative ChE assay in rats. It is believed that if the residual toxicological issues were fully characterized, the magnitude of difference from the current conservative assessment would likely be less than 10x.

For acute and chronic reference dose (RfD) endpoint selection, the acute RfD was based on a BMD analysis of RBC ChEI data from the acute dose portion of a comparative cholinesterase study in rat pups. An uncertainty factor of 100x was applied to account for interspecies variation (10x) and for intraspecies variation (10x). The special FQPA factor of 10x is not required because the value used is from studies with very young rats (11-days old). The chronic RfD was based on RBC ChEI in female rats observed during the first three months of the 24 month study. The dose was then dropped for the remaining 21 months and this value is being used as a NOAEL. The uncertainty factor of 1000X was applied to account for interspecies variation (10x), intraspecies variation (10x), and for the susceptibility of young (FQPA of 10x).

The selection of the residential incidental oral endpoint was based on the repeated-dose portion of a comparative cholinesterase study and a benchmark dose value was estimated. The benchmark dose level (BMDL) used is based on RBC ChEI in male pups. The BMDL is the lower 95% confidence limit on the RBC ChEI 10% effect level. An UF of 100x was applied to account for interspecies variation (10x) and intraspecies variation (10x). Susceptibility of the young is already accounted for because they were part of the experimental group and it is the basis of the dose and endpoint.

For endpoint selections applicable to short-term durations, the short-term dermal endpoint is based on RBC ChEI in male and female rabbits and brain ChEI in female rabbits from a 21-day dermal toxicity study, and 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. 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 variation (10x) and intraspecies variation (10x). For children, an UF of 1000x was applied to account for interspecies variation (10x), intraspecies variation (10x), and for the susceptibility of the young (FQPA of 10x). 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 account for interspecies variation (10x), intraspecies variation (10x), and for the susceptibility of the young (FQPA of 10x).

The potential for malathion residues in the environment results from: 1) agricultural use on a wide variety of food/feed crops; 2) public health uses over wide areas for mosquito-borne disease control; 3) outdoor residential uses in home vegetable and ornamental gardens; 4) outdoor commercial uses at residential sites or public access areas such as parks, recreational areas, and playgrounds; 5) use in the Cotton Boll Weevil Eradication Program; and 6) use in the Fruit Fly (Medfly) Control Program. The pathways by which the general population are likely to be exposed to malathion residues are through ingestion of food and drinking water, and in residential settings (lawns, 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 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.

Tier 3, probabilistic acute and refined chronic dietary risk assessments were conducted using the Lifeline Model Version 2.0 and Dietary Exposure Evaluation Model (DEEM-FCID J, Version 2.02) using food consumption data from the U.S. Department of Agriculture=s Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Malathion residue estimates reflected use of monitoring data, processing factors, and percent crop treated (%CT) data and include malathion and the oxygen analog metabolite malaoxon. An acute and chronic toxicity adjustment factor (TAF) of 77x calculated from oral studies was used to adjust residues of malaoxon.

The acute dietary exposure to malathion from food alone is not of concern for the U.S. general population and all population subgroups at the 99.9th percentile using DEEM-FCID. The chronic dietary exposure to malathion from food alone is also not of concern for the U.S. population and all population subgroups using DEEM-FCID. Children 1-2 yrs. of age is the highest exposed population subgroup for both acute and chronic dietary food assessments.

Non-occupational (residential) exposure to malathion and malaoxon residues via dermal and inhalation routes can occur during handling, 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. 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 for do not exceed HED's level of concern for any scenario. The postapplication exposure assessment indicates that toddler short-term inhalation exposure following use of a fogger unit to control outdoor flying insect pests exceed HED's level of concern. 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 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 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 exposure in areas nearby fields being treated for boll weevil.

Risks resulting from adult postapplication exposures following aerial fruit fly application do not exceed HED's level of concern; however, toddler exposures from residues on turf following aerial fruit fly treatment are of concern. Toddler risks are driven by dermal exposure to residues on turf resulting from spray drift during fruit fly treatment.

Malaoxon exposures must also be combined with exposures to residues of deposited malathion that remain untransformed (90% of total deposited malathion 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. Postapplication risks to toddlers from contacting malathion and malaoxon residues following public health mosquitocide, boll weevil and fruit fly treatments exceeded HED's level of concern in a preliminary screening-level assessment when using a number of upper percentile input variables in the risk calculation (e.g., 95th percentile transfer coefficient; 2-hour exposure duration). Risks were driven by dermal exposure and the assumed malathion-to-malaoxon transformation rate. When certain alternative, less conservative, input variables are chosen from available ranges of values, risks do not exceed HED's level of concern, except for those resulting from boll weevil eradication when using a 5% or 10% malathion-to-malaoxon transformation rate, and fruit fly using 10%. The calculated exposures in this assessment include maximum application rates and conservative deposition estimates.

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 using the Lifeline Model Version 2.0 and Dietary Exposure Evaluation Model (DEEM-FCID **J** , Version 2.02). 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 resulting from some residential uses are also of concern. 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".

The aggregate acute dietary risk estimates include exposure to combined residues of malathion and malaoxon residues in food and water and does not include non-dietary (dermal, inhalation, and incidental oral) exposures. Acute dietary exposure from food alone does not exceed HED's level of concern. However, for 9 of the 26 water scenarios (from PRZM/EXAMs), aggregate acute dietary risks exceeded HED's level of concern; for the FL citrus scenario, about 90% of the aggregate acute dietary risk is attributable to potential residues in drinking water.

The aggregate chronic dietary risk estimates include average exposures to combined residues of malathion and malaoxon in food and water. No chronic residential use scenarios were identified. 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; however, aggregate chronic risks from food and water for the U.S. general population and all population subgroups are of concern. For the FL citrus scenario, about 95% of the aggregate chronic dietary risk is attributable to potential residues in drinking water.

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 are 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 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 $\geq$100 on day 0. 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 Eradication Program 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

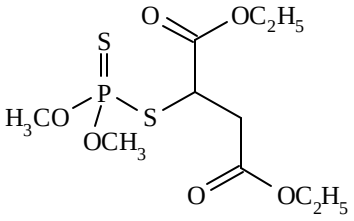
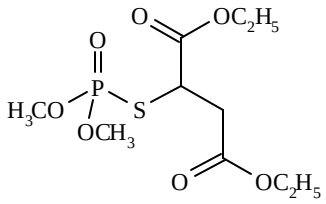
Chemical Structure		
Empirical Formula	$C_{10}H_{19}O_6PS_2$	
Common name	Malathion	
IUPAC name	O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate	
CAS Registry Number	121-75-5	
End-use product/EP	Technical (91-95% ai), dust (1-10% ai), emulsifiable concentrate (3-82% ai), ready-to-use (1.5-95% 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°C) although a small amount of isomalathion accumulated (increase from <0.01% to about 0.1%). Storage of malathion at 54°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°C	Product Chemistry Chapter (W. Smith, June 2, 1999)
Melting point	2.8°C	SRC PhysProp Database
Density (25°C)	1.2	SRC PhysProp Database
Water solubility (25°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°C)	0.00004 mmHg	Product Chemistry Chapter (W. Smith, June 2, 1999)
Octanol/water partition coefficient, $\log P_{OW}$ (25°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°C	Chemical Abstracts
Melting point/range	<20°C	Chemical Abstracts
Water solubility (22°C)	0.5-1.0 g/100 mL	Chemical Abstracts
Vapor pressure (10-50°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 plant and animal 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 animal

commodities represent a Category 3 situation under 40 CFR §180.6(a).

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 organ/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 predominately 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 animal metabolism reregistration requirements. Neither malathion nor malaoxon were observed in eggs, milk, or animal 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 under reasonable worst case exposure scenarios, but there is no reasonable expectation of the occurrence 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 confined 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 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 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 concentration is unlikely to exceed malathion's peak concentration.

3.4 Tabular Summary of Metabolites and Degradates

Table 3.4 Tabular Summary of Metabolites and Degradates

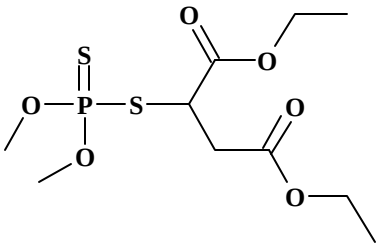
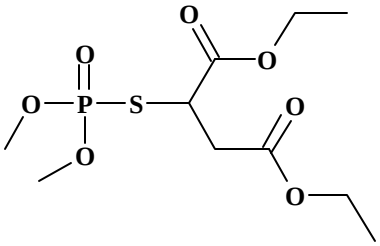
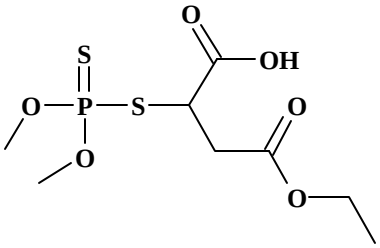
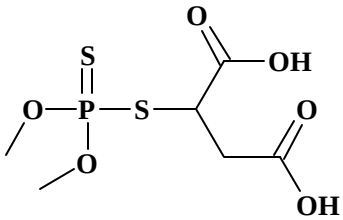
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
Malathion	Alfalfa Forage	46.7		
	Alfalfa Hay	19.6		
	Wheat Grain	30.5		
	Wheat Straw	11.8		
	Wheat Forage		9.0	
	Cottonseed	34.5		
	Leaf Lettuce	29.9		
	Livestock		180.6(a)(3)	
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	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	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)	

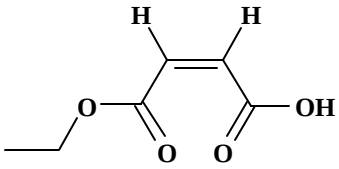
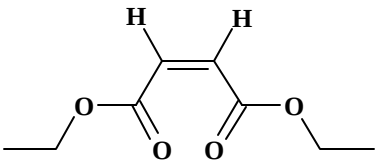
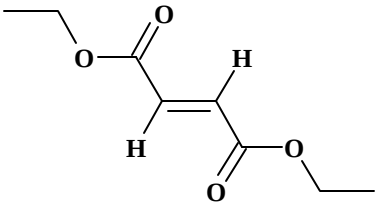
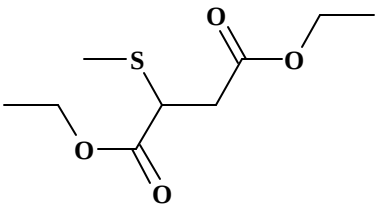
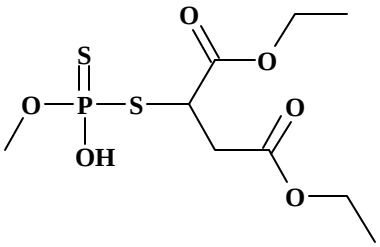
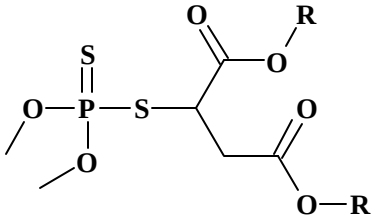
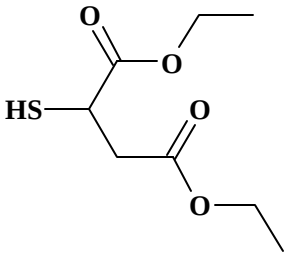
Table 3.4 Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
Monoethyl Maleate	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		ND	
	Wheat Forage		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)	

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)	
DesMe Malathion[3]	Alfalfa Forage		ND	
	Alfalfa Hay		ND	
	Wheat Grain		ND	
	Wheat Straw		ND	
	Wheat Forage		ND	
	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)ehtyl)-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

The documents listed below were relied on heavily in developing the current hazard assessment. In some cases, decisions or opinions expressed in historical documents have been changed. This assessment is consistent with OPP's current risk assessment and science policies.

TXR0051549	*Malathion - Report of the Hazard Identification Assessment Review Committee. Memo dated January 28, 2003 from S. Makris and B. Dementi.*
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 cholinesterase study in juvenile and adult rats (MRID 45566201). Memo dated 4/11/05 from A. Lowit.*
TXR005967	*Malathion: Revised Toxicology Chapter for the RED. Memo dated September 13, 2002 from S. Makris.*
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/

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.

4.1 Hazard Characterization

Malathion (O,O-dimethyl thiophosphate of diethyl mercaptosuccinate) is an organophosphorus insecticide, and like all members of this class, the mode of toxic action is the inhibition of cholinesterase (ChE). Malathion is metabolically converted to its 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 (specifically isomalathion) and the possible formation of the active oxon (malaoxon) under certain conditions that would result in direct 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. An immunotoxicity study is required to further characterize suggestive evidence of immune responses reported in literature studies with malathion. A comparative ChE study with malaoxon is being conducted by the registrant (protocol reviewed by EPA in January, 2005).

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 the acetylcholinesterase (AChE). 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.

Malathion is metabolized to its oxon (malaoxon) in both insects and mammals. The oxon is the active ChE inhibiting metabolite of malathion. 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 organ/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 comparative ChE study with malaoxon) will provide additional information on specific aspects of the hazard of 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. 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 4.1a). Malaoxon is the oxon and active ChE inhibiting metabolite of malathion. As described further below in exposure sections 6.1.2 and 6.3.4, humans may be directly exposed to malaoxon. Section 4.4.7 provides a description of the relative potency of malaoxon and the parent compound, malathion.

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

Table 4.1.2b provides a summary of the subchronic, chronic, and other information relevant to the malathion toxicity profile.

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 have been observed in multiple species (rat, mouse, rabbit, and dog) following oral routes of administration and in rabbits and rats following dermal and inhalation exposures, respectively.

In available subchronic studies with malathion, plasma and RBC ChEI were exhibited at the LOAEL in both rabbits and rats following dermal and inhalation exposure 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 larnyx 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 incidences of mean resorption sites were 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, indicating increased susceptibility to the pups. There were no effects of malathion on reproductive function and ChE activity was not measured.

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 findings of the adult neurotoxicity studies were somewhat inconsistent with effects observed in the developmental neurotoxicity and comparative ChE studies(details provided in Section 4.1.3).

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. In the developmental neurotoxicity study in rats, effects were noted in offspring at all doses tested (details in Section 4.1.3).

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 for adults and/or the magnitude of the inhibition at the same dose level was substantially greater for pups than for young 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 for 24 months (see Section 4.4.3 for executive summary of combined chronic/carcinogenicity study in rats). In the chronic dog study, there were 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) was 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 Angles 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 report 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 a 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.

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[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.

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 in rats has not been submitted but is required by the Agency. This requirement 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 (1988) Doses: 0, 50, 300, 1000 mg/kg/day Acceptable/guideline	ChEI NOAEL: 50 mg/kg/day ChEI LOAEL: 300 mg/kg/day, based on plasma and RBC ChEI in males; and plasma, RBC, and brain ChEI in females.
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/doe. (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
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).

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 (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.
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 µg/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 (1000 µg/mL) and **weakly positive** with S9 activation over a narrow range of cytotoxic concentrations (2000 and 2200 µg/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.
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.

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**
(870.6300) 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[1] Adult NOAEL: 150 mg/kg/day Adult LOAEL: 450 mg/kg/day, based on P and RBC ChEI Offspring NOAEL was not determined (<5 mg/kg/day) Offspring LOAEL: 5 mg/kg/day, based on RBC ChEI Repeated exposures (11 days)[1] Adult NOAEL: 5 mg/kg/day Adult LOAEL: 50 mg/kg/day, based on RBC ChEI Offspring NOAEL was not determined (<5 mg/kg/day) Offspring LOAEL: 5 mg/kg/day, based on RBC ChEI
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.

[1] Observed values are presented here for completeness. Actual values used in the risk assessment are estimates using a Benchmark Dose (BMD) approach - see text at Section 4.1.3.1 for discussion and BMD values.

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 ChE study in 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.

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, delayed surface righting reflex in PND 11 female pups, increased incidence of slightly flattened gait in PND 60 male offspring, and increased thickness of the corpus callosum in PND 63-67 offspring. 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).

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.

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.

4.1.3.1 Benchmark Dose Analysis of Comparative ChE Study

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; USEPA, 2000)[2]. 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 BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the blood and brain compartments and is a response level close to the background ChE activity. 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 calculated 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 Preliminary OP Cumulative Risk Assessment (USEPA, 2001). Model fits and model parameters specific to this analysis can be found in TXR0053251 (2005). The exponential model used here can be downloaded by the public at http://www.epa.gov/pesticides/cumulative/EPA_approach_methods.htm.

[2] The BMD analysis was discussed at the December, 2002 HIARC meeting. At that time, it was determined that the BMD approach was not appropriate (see 1/28/03 HIARC report-TXR 0057549). Since that time, understanding of the BMD methods and use have matured and discussions with experts have resulted in reinstating the BMD analysis.

The results of the BMD analysis of the malathion comparative ChE data are provided in Table 4.1.3.1a. Overall, the RBC ChE activity data from the adults and pups (PND11, PND21) fit the exponential equation well. 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 4.1.3.1a 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 4.1.3.1a Benchmark Dose Analysis of Malathion Comparative ChE Data

Exposure Condition, Age, and ChE Compartment			BMD_{10} (mg/kg/d)		BMDL (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).

Therefore, rat pups were more susceptible than adults to ChEI following a single oral dose of malathion. This susceptibility was observed in terms of the dose level at which effects were observed (i.e., the ChEI occurred at lower doses in juveniles than for adults), the compartments in which a response was elicited (e.g., brain ChE was inhibited in offspring but was not observed in adults up to the highest dose tested), and the magnitude of the response (i.e., when inhibition was noted for both age groups at the same dose level, the percent inhibition was substantially greater for pups than for young adults).

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.

Table 4.1.3.1c below summarizes the appropriate potential regulatory hazard values for RBC ChEI for the malathion risk assesssment:

Table 4.1.3.1c Summary of RBC ChEI NOAELs by Species and Study Duration[1]

Species	Acute Exposure	Short-Term Exposure	Long-Term Exposure
Animal (rat - adult)	93.7 mg/kg (BMDL)[2]	15.7 mg/kg/d (BMDL)[2]	3 mg/kg/d (NOAEL)[3]
Animal (rat - pup)	13.6 mg/kg (BMDL)[2]	7.1 mg/kg/d (BMDL)[2]	Not available[4]

[1] For risk assessment purposes, the lowest values have been identified and reported.
[2] From comparative ChE study (MRID 45566201).
[3] From combined chronic/carcinogenicity study in rats (executive summary in Section 4.4.3).
[4] There are no long-term studies available with young animals.

4.1.4 FQPA

Based on the available data, there is evidence that following acute or repeated dose exposure conditions to malathion young animals are more susceptible to various toxic or other (i.e., ChEI and auditory startle response) effects as compared to adult animals. Therefore, a $10X_{FQPA}$ factor will be applied to certain exposure scenarios in the risk assessment (see Table 4.7).

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

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 specific studies in 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. The registrant is currently conducting a rat comparative ChE study with malaoxon.

4.2.2 Evidence of Neurotoxicity

As noted above (Sections 4.1.2 and 4.1.3), 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). Acute exposures to adult rats resulted in ChEI in one or more compartments (plasma, RBC, brain) in several different studies, although some inconsistencies were observed (NOAELs ranging from 150 mg/kg to 1000 mg/kg) [MRID 43146701]. Developmental neurotoxicity studies showed a variety of neurobehavioral and neuropathological effects in young rats at doses which showed no effects in the dams from the same study (MRID 45646401). Acute exposure to rat pups in the comparative ChE study showed ChEI at all dose levels, although no clinical signs were observed (lowest dose 5 mg/kg) [MRID 45566201]. These last two studies provided evidence of quantitative susceptibility between adult and young animals.

Executive summaries of acute neurotoxicity, subchronic neurotoxicity, and developmental neurotoxicity studies are in Appendix 2.0.

4.2.3 Developmental Toxicity Studies

Adequate data are available for malathion for evaluation of developmental toxicity in rats and rabbits. In rabbits, developmental effects (slightly increased incidence of mean resorption sites per dam) were noted at 50 mg/kg/day where maternal toxicity was also observed (MRIDs 00152569 and 40812001). No developmental effects were noted in rats at the highest dose tested (800 mg/kg/day) while maternal toxicity (cholinergic signs and reduced mean body weights) were observed in both species at this dose (MRID 41160901). Executive summaries for both of these studies are in Appendix 2.0.

4.2.4 Reproductive Toxicity Study

Malathion did not induce reproductive toxicity in rats at the highest dose tested in a two-generation reproduction and fertility study (MRID 41583401). The offspring NOAEL was lower than the parental systemic NOAEL in this study, and the effects in the parental animals were minimal in nature, indicating an increased susceptibility to the offspring. An executive summary for this study is in Appendix 2.0.

4.2.5 Pre-and/or Postnatal Toxicity

4.2.5.1 Determination of Susceptibility

There is a concern for pre- and/or postnatal toxicity resulting from exposure to malathion. Susceptibility was noted in several studies. The susceptibility profile for each study that included immature animals follows.

- **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 does 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).

- 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. 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 (MRID 45566201). **Quantitative susceptibility** was observed as shown in Table 4.1c. This same susceptibility difference was not 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]).

Table 4.2.5.1 below summarizes this analysis. 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 susceptibility difference.

The last four rows in Table 4.2.5.1 describe studies in which pups appear to be more susceptible than adults given the toxicity measure, dose, and duration of exposure. The ratio for the two-generation study compared to the rat DNT ratio is likely a result of the two-generation study being a more crude measure of pup effect (thus under-estimating pup sensitivity) and the subtle effects seen in the DNT study may overestimate pup sensitivity because the effects may be transient. 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 4.2.5.1 Determination of Pre and/or Post-Natal Susceptibility			
Study	**Adult**	**Pup**	**Ratio of Adult/Pup Hazard Value**
Rabbit Developmental (MRID 00152569)	25 mg/kg/d (NOAEL - dec. body wt. gain)	25 mg/kg/d (NOAEL - fetal death)	1 (No evidence of susceptibility)
Rat Developmental (MRID 41160901)	400 mg/kg/d (NOAEL - dec. body wt. gain)	800 mg/kg/d - HDT (NOAEL)	0.5 (Adults more sensitive)
2-Generation Rat (MRID 41583401)	394-451 mg/kg/d (M/F - NOAEL based on dec. body wt.)	131-153 mg/kg/d (M/F - NOAEL based on dec. body wt.)	**2.9 -3.0** (Pups more sensitive)
Rat DNT (MRID 45646401)	150 mg/kg/d (LOAEL - based on post-dosing salivation)	5 mg/kg/d (LOAEL; lowest dose tested - based on inc. aud. startle reflex ampl.)	**30**
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**

4.2.5.2 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 special 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 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). 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.

4.3 Recommendation for a Developmental Neurotoxicity Study

A DNT study was conducted and submitted and is part of this analysis (executive summaries of the main study and range-finding study are in Appendix 2.0). A comparative ChE study with malaoxon is being conducted.

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 **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 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 RBC ChEI 10% effect level. The doses used in the study were 0, 5, 50, and 150 mg/kg/d.

Uncertainty Factor (UF). An UF of 100 will be used (10x for interspecies variation 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 = $\frac{13.6 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.14 \text{ mg/kg}$

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Combined chronic toxicity/carcinogenicity study in rats

MRID No. 43942901

Executive Summary: In a combined chronic toxicity/carcinogenicity study in rats, 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.

Dose and Endpoint for Establishing cRfD: RBC ChEI in females observed at 8 mg/kg/day during the first three months of the 24 month study. The dose was then dropped to approximately 3 mg/kg/day for the remaining 21 months; 3 mg/kg/d is the NOAEL.

Uncertainty Factor (UF): 1000x (10x for interspecies variation and 10x for intraspecies variation and 10x UF_{FQPA}).

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for this exposure scenario. It should be noted, however, that the application of the 10x UF_{FQPA} for a chronic exposure scenario is conservative in terms of that portion of the factor which is based on the demonstrated susceptibility in young animals compared to adults for ChEI. This is due to the likelihood that the susceptibility in young animals noted in several malathion studies will diminish as the animals reach adulthood. Based on experiments exposing rats of various ages to chlorpyrifos, Chanda et al. (2002) show that the susceptibility difference is likely due to carboxylesterase levels which are low at birth and gradually increase as the animal reaches adulthood.

$$\textbf{Chronic RfD} = \frac{\text{3 mg/kg/d (NOAEL)}}{\text{1000 (UF)}} = 0.003 \text{ mg/kg}$$

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: 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 RBC ChEI 10% effect level. The doses used in the study were 0, 5, 50, and 150 mg/kg/d.

Uncertainty Factor (UF). An UF of 100 will be used (10x for interspecies variation 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: 21-Day Dermal Study in Rabbits

MRID No. 41054201

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%).

The NOAEL was 50 mg/kg/day and the LOAEL was 300 mg/kg/day based on inhibition of plasma and RBC ChE activity in males and females and on inhibition of brain (cerebrum) ChE activity in females. The overall systemic NOAEL was 300 mg/kg/day and the overall systemic LOAEL was 1000 mg/kg/day based on possible mortality (1 male).

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: The NOAEL of 50 mg/kg/d is based on RBC ChEI in male and female rabbits and brain ChEI in female rabbits; both at 300 mg/kg/day.

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 a 21 day study 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). A concern might be raised that use of a rabbit dermal study could underestimate risk for OP pesticides that require the in vivo formation of the oxon to become toxic. This is because of two reasons: (1) the dermal route initially bypasses the liver (site of oxon formation) and (2) rabbits appear to have a higher level of circulating arylesterases (which detoxify sulfur-containing OP pesticides before they reach the liver and form oxons) than do rats. In this case, however, the evidence shows that the RBC ChEI at relatively low levels (NOAEL of 50 mg/kg/d and LOAEL of 300 mg/kg/d via the dermal route) in the rabbit is in reasonable agreement with the oral developmental toxicity rabbit data (NOAEL and LOAEL of 25 and 50 mg/kg/d, respectively for decrease in body weight gain) and is *more* protective than the oral developmental toxicity rat data (NOAEL and LOAEL of 400 and 800 mg/kg/d, respectively, for decrease in body weight gain).

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 ≥ 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 for the lack of a NOAEL and for the severity of the effect seen at the LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: It was concluded that the hazard-based special FQPA factor should not be applied to the nasal histopathology LOAEL, since there are no indications of age-related susceptibility and/or residual concerns for this endpoint.

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. To account for this, 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, only two malaoxon studies are available which provide relevant blood and brain cholinesterase data—14-day rat study (MRID no. 46080001) and 2-year chronic rat study (MRID no. 43975201); no 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 and adult rats in malaoxon. This study will include measurements of brain and RBC ChE following acute and multiple exposures. Following the receipt of this study, EPA will re-consider the TAF(s).

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 Health and Environmental Effects Research Laboratory to perform BMD modeling (USEPA, 2000) in the evaluation of the relative toxicity 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).

The steady state TAF for male RBC cholinesterase is **77** with upper and lower confidence limits of 127and 46, 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 **77x** 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	48.09	32.37
Malaoxon	0.63	0.52
'Steady State' Toxicity Adjustment Factor	**77**	62

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. The two exposure scenarios deemed necessary for an aggregate assessment are the short (1-30 days) and intermediate-term (1-6 months) inhalation scenarios for children and adults. For aggregate risk assessment, the NOAEL for ChEI in the 90-day inhalation study is selected and the hazard-based special FQPA factor is applied (see Table 4.7).

4.4.10 Classification of Carcinogenic Potential

The data base 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 data base 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." 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.

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.

4.5 Special FQPA Safety Factor

HED recommends retention of a **hazard-based special FQPA factor of 10x**. This factor is meant to provide a measure of additional safety for the developing individual. Use of an FQPA factor of 10 is reasonable given the susceptibility ratio seen between adults/young using the BMD analysis (~8.7)- which use all the data available in an experiment to estimate effect levels as opposed to being constrained by the dose levels used (see Section 4.2.5.1 and Table 4.2). It is believed that if the residual toxicological issues were fully characterized, the magnitude of difference from the current conservative assessment would likely be less than 10-fold.

The proposed endpoints and doses for risk assessment are already based on, or consider, the most sensitive population (i.e., the developing individual). Although there is some residual concern for the presence of latent effects on neurological function in the DNT study, it is noted that this endpoint has already been handled conservatively in the risk assessment by virtue of endpoint selection and application of traditional uncertainty factors; therefore, the 10-fold special FQPA factor is believed to be sufficient to address this issue and should be applied only in instances where the pup data are not being used (see discussion in Section 4.2.5.2 and Tables 4.4 and 4.5).

Finally, although there is uncertainty in the toxicity database due to the absence of a guideline immunotoxicity study and a comparative cholinesterase study with malaoxon, an additional uncertainty factor to account for these data gaps is not necessary because the existing 10X UF_{FQPA} is sufficiently protective.

Table 4.5 Summary of Uncertainty Factors Used in the Malathion Risk Assessment

Exposure Scenario	Hazard Study Chosen	Intersp. (10)	Intrasp. (10)	FQPA (10)		Comments
				Special FQPA Concerns	LOAEL to NOAEL	
Acute Dietary[1]	Comparative ChE (BMDL for young rats)	X	X			FQPA factor not needed because data with young rats used.
Chronic Dietary[1]	Chronic rat	X	X	X		FQPA factor needed because only adults used in study.
Incidental Oral[2] (Residential)	Comparative ChE (BMDL for young rats)	X	X			FQPA factor not needed because data with young rats used.

Table 4.5 Summary of Uncertainty Factors Used in the Malathion Risk Assessment						
Exposure Scenario	**Hazard Study Chosen**	**Intersp. (10)**	**Intrasp. (10)**	**FQPA (10)**		**Comments**
				Special FQPA Concerns	**LOAEL to NOAEL**	
Dermal[3] (Res. - Children)	Dermal study in rabbits	X	X	X		FQPA factor needed because animal data with adults only.
Dermal[3] (Res. - Adults)		X	X			FQPA factor not needed because adult animal data used and human population of interest is adults.
Dermal[2] (Occup. - Adults)		X	X			
Dermal[4] (Occup. - Adults)		X	X			
Inhalation[1,2] (Res. and Occup. - Adults)	Inhalation Study (90-day)	X	X		X	LOAEL to NOAEL factor needed because lowest tested dose resulted in effects on respiratory epithelium.
Inhalation[2] (Aggregate; Res. - Children)		X	X	X		For aggregate assessment, ChEI is endpoint of concern. FQPA factor needed for children risk assessment because only adult rats used in inhalation study.
Inhalation[2] (Aggregate; Res. and Occup. - Adults)		X	X			

[1] All populations.
[2] Short (1-30 days) and Intermediate (1-6 months) term scenarios.
[3] Short (1-30 days) term only.
[4] Long (>6 months) term only.

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 female rats (all doses) and a significant trend in thyroid follicular cell adenomas and/or carcinomas and thyroid c-cell carcinomas (all in males). 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	Special 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)	NOAEL = 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	$BMDL_{10}$[5] = 0.14 mg/kg/day based on RBC ChEI in male pups. Comparative ChE acute oral study in the rat.
Chronic Dietary (All populations)	NOAEL = 3 mg/kg/d[4] UF = 100 **Chronic RfD** = 0.03 mg/kg/day	FQPA SF 10X[3] cPAD = chronic RfD/FQPA SF =0.003 mg/kg/day	NOAEL =3 mg/kg/day based on RBC ChEI in females in chronic/ carcinogenicity oral study in the rat (LOAEL = 35 mg/kg/d)
Non-Dietary Risk Assessments			
Short- (1-30 days) and Intermediate- Term (1 - 6 Months) Incidental Oral	Oral $BMDL_{10}$[5] = 7.1 mg/kg/d	**Residential** (Short-term only) LOC for MOE = 100[6] **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)[2]	Dermal NOAEL = 50 mg/kg/day	**Residential** (Short-term only) LOC for MOE = 1000[7] **Occupational** = N/A	LOAEL = 300 mg/kg/day based on plasma and RBC ChEI (♂, ♀) and brain ChEI (♀) in 21-day dermal study in rabbits
Short- (1-30 days) and Intermediate- Term (1 - 6 Months) Dermal (adults)	Dermal NOAEL = 50 mg/kg/day	**Residential** (Short-term only) LOC for MOE = 100 **Occupational** LOC for MOE = 100	LOAEL = 300 mg/kg/day based on plasma and RBC ChEI (♂, ♀) and brain ChEI (♀) in 21-day dermal study in rabbits
Long-term (>6 mo) Dermal (adults)	Dermal NOAEL = 50 mg/kg/day	**Residential** = N/A **Occupational** LOC for MOE = 100	LOAEL = 300 mg/kg/day based on plasma and RBC ChEI (♂, ♀) and brain ChEI (♀) in 21-day dermal study in rabbits
Short- (1-30 days) and Intermediate-term (1 - 6 Months) Inhalation (all populations)[8]	Inhalation LOAEL= 0.1 mg/L (25.8 mg/kg/day)	**Residential** (Short-term only) LOC for MOE = 1000[9] **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**	**Special 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[7] **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 = Special 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 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] A 10x FQPA Safety Factor was used to account for differences in susceptibility observed in the comparative ChE study.

[4] The combined chronic/onco study in rats low dose level was 100 ppm in the diet for 3 months which was dropped to 50 ppm in the diet for the remainder of the study (21 months). The calculated dose for the 3-month exposure was 8-9 mg/kg/d. The calculated dose from the 21 month exposure was 2-3 mg/kg/d. Assuming that a LOAEL for ChEI effects could be 8 mg/kg/d (effects that prompted a lowering of the dose to 2-3 mg/kg/d), then an appropriate NOAEL would be 3 mg/kg/d.

[5] 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.

[6] 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.

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

[8] Absorption via the inhalation route is assumed to be equivalent to oral absorption.

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

5.0 Public Health Data

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

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 Figure A 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 for reregistration. 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: (1) established tolerances for animal commodities may be revoked if direct animal treatment uses are canceled; (2) there are no longer significant livestock feed items for the commodity; and (3) currently there are no registered uses. A summary of reassessed tolerances is provided in Appendix 5.0 of this document.

6.1.2 Acute and Chronic Dietary Exposure and Risk

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.*

Acute and chronic dietary risk assessments were conducted using the Lifeline Model Version 2.0 and Dietary Exposure Evaluation Model (DEEM-FCID**J**, Version 2.02), 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 to support malathion food uses and were performed to support the reregistration eligibility decision.

A Tier 3, acute probabilistic and a refined 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 77x 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 acute and chronic Population Adjusted Doses (PADs). Anticipated residues were further refined using percent crop treated (%CT) data and processing factors where appropriate.

The acute dietary exposure to malathion from food alone is below HED=s level of concern for all population subgroups (20% aPAD for the U.S. population and 46% aPAD for children 1-2 yrs) at the 99.9th percentile using DEEM-FCID. The chronic dietary exposure to malathion from food alone is also below HED=s level of concern for all population subgroups (8% cPAD for the U.S. population and 24% cPAD for children 1-2 yrs using DEEM-FCID.

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	0.027721	20	0.003	0.000312	10	Suggestive evidence of carcinogenicity	
All Infants < 1 yr	0.14	0.027917	20	0.003	0.000498	17	NA	
Children 1-2 yrs	**0.14**	0.063762	**46**	**0.003**	**0.000817**	**27**		
Children 3-5 yrs	0.14	0.055906	40	0.003	0.000639	21		
Children 6-12 yrs	0.14	0.030488	22	0.003	0.000473	16		
Youth 13-19 yrs	0.14	0.018155	13	0.003	0.000256	9		
Adults 20-49 yrs	0.14	0.021022	15	0.003	0.000300	10		
Adults 50+ yrs	0.14	0.018455	13	0.003	0.000157	5		
Females 13-49 yrs	0.14	0.018455	13	0.003	0.000254	9		

[a] The values for the population with the highest risk for each type of risk assessment are bolded.

6.2 Water Exposure and Risk

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.

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

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

The estimated water concentrations provided are for both malathion and malaoxon. Since malaoxon is 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 concentration is unlikely to exceed malathion's peak concentration. In a limited sampling of water entering and leaving a water treatment plant, both malathion and malaoxon levels generally decreased after treatment, however one sample showed an increase in malaoxon (USDA, 1997). In the USGS/EPA Pilot Reservoir Monitoring Project (USGS 2001), malathion detections occur only in drinking water facility intake water and malaoxon detections only occur in treated water. EFED recognizes that conversion of malathion to malaoxon appears to be more efficient during water treatment than under conditions in the field, thus all malathion entering a drinking water treatment facility is expected to be converted to malaoxon during drinking water treatment. The drinking water concentrations in this assessment 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.

Twenty-six different crop/location scenarios were analyzed using PRZM-EXAMS in order to represent the wide range of locations where malathion is used in the U.S. (See Table 7.1.3). The estimated drinking water concentrations from surface water sources were calculated using Tier II PRZM (Pesticide Root Zone Model) and EXAMS (Exposure Analysis Modeling System). Based on the modeling results for surface water derived drinking water, the Florida citrus aerial maximum application is the highest one in ten year peak concentration and the Oregon apple air-blast typical application rate gives the lowest one in ten year peak concentration (see Table 6.2 for results). Table 6.2 also shows the highest one in ten year annual mean for chronic drinking water concentration of 2.61 ppb from Florida citrus aerial maximum application rate and 0.042 ppb from Oregon apple airblast typical application rate gives the lowest one in ten year annual mean.

Table 6.2 Summary of Estimated Surface and Ground Water Concentrations for Malathion.

Exposure Duration	Malathion			
	Florida Citrus Max Arial Rate (ppm)	**Florida Citrus Adjusted for TAF-77X (ppm)**	**Oregon Apple Typical Rate (ppm)**	**Oregon Apple Adjusted for TAF-77X (ppm)**
Acute	1.69E-01	**1.30E+01**	4.67E-03	**3.60E-01**
	2.19-01	**1.69E+01**	5.05E-03	**3.89E-01**
	2.39-01	**1.84E+01**	5.92E-03	**4.56E-01**
Chronic (non-cancer)	0.00261	**0.20097**	0.000042	**0.00323**

* USDA Boll Weevil Eradication Programs report typical ULV applications (6-10 per year) at 0.7 to 0.9 lb ai/A/application.

****** TAF= Residue value (ppm) x 77 (TAF). The bold values were used in the dietary assessment.
Bolded values are the values used for risk assessment purposes.

First tier ground water concentrations were derived from monitoring data because they were higher than results predicted using the SCI-GROW model. The highest detected malathion concentration in ground water was 3 ppb. Malaoxon was not examined in this study. Therefore, EFED recommended conservative ground water estimates of 3 ppb for malathion and 3 ppb for malaoxon based on the assumption that the concentration of malaoxon will not exceed malathion.

6.3 Residential (Non-Occupational) Exposure and Risk

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

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, perimeter 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.
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	0.15 lb ai/gal	Apply for mosquito and fly control. Fogger machines are recommended to be used at dusk, with repeat applications as necessary.	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 liquids for 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, upper range durations of exposure).

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.

- For foggers, the unit exposure value for mixing and loading liquids from the Draft Residential SOPs was used. Residential handlers mix and load fogger units with liquid malathion product, turn on the unit, and then leave the area, such that no exposure from actual application activity is expected.

- 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.

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 indicate that the total risks for all scenarios and do not exceed HED’s level of concern. The MOEs for inhalation alone do not exceed HED's level of concern (LOC of 1000).

Table 6.3.2.3 Residential Handler Short-term Risks to Malathion.

Exposure Scenario (Scen. #)	Crop Type or Target	Maximum Application Rates[a]	Amount Handled per Day[b]	Baseline Dermal Dose (mg/kg/day)[c]	Baseline Inhalation Dose (mg/kg/day)[d]	Baseline Dermal MOE[e]	Baseline Inhalation MOE[f]	Baseline Total MOE[g]
Mixer/Loader/Applicator Exposure								
Mixing/Loading/Applying Liquid with a Low Pressure Handwand (1a)	Fruit Trees	0.034 lb ai/gal	5 gal	0.14	0.00001	360	2,600,000	360
	Ornamentals	0.034 lb ai/gal	5 gal	0.14	0.00001	360	2,600,000	360
	Vegetable/Small Fruit Garden	0.023 lb ai/gal	5 gal	0.09	0.00001	560	2,600,000	560
	Building Perimeter	0.1547 lb ai/gal	4 gal	0.50	0.00006	101	430,000	100
Mixing/Loading/Applying Wettable Powder with a Low Pressure Handwand (1b)	Fruit Trees	0.010 lb ai/gal	5 gal	0.18	0.00079	280	33,000	280
	Ornamentals	0.015 lb ai/gal	5 gal	0.27	0.0012	190	22,000	190
	Vegetable/Small Fruit Garden	0.018 lb ai/gal	5 gal	0.32	0.0014	160	18,000	160
Mixing/Loading/Applying Liquids with a Hose End Sprayer (2)	Fruit Trees	0.034 lb ai/gal	5 gal	0.07	0.00002	690	110,000	690
	Ornamentals	0.034 lb ai/gal	5 gal	0.07	0.00002	690	110,000	690
	Vegetable/Small Fruit Garden	0.023 lb ai/gal	5 gal	0.05	0.00002	1000	220,000	1000
	Building Perimeter	0.0114 lb ai/gal	96 gal	0.04	0.0002	1300	150,000	1300

Table 6.3.2.3 Residential Handler Short-term Risks to Malathion.

Exposure Scenario (Scen. #)	Crop Type or Target	Maximum Application Rates[a]	Amount Handled per Day[b]	Baseline Dermal Dose (mg/kg/day)[c]	Baseline Inhalation Dose (mg/kg/day)[d]	Baseline Dermal MOE[e]	Baseline Inhalation MOE[f]	Baseline Total MOE[g]
Mixer/Loader/Applicator Exposure								
Mixing/Loading/Applying Liquids with a Backpack Sprayer (3)	Fruit Tree	0.034 lb ai/gal	5 gal	0.01	0.00007	5000	350,000	5000
	Ornamentals	0.034 lb ai/gal	5 gal	0.01	0.00007	5000	350,000	5000
	Vegetable/Small Fruit Garden	0.023 lb ai/gal	5 gal	0.01	0.00004	5000	650,000	5000
	Building Perimeter	0.1 lb ai/acre ***	5 gal	0.06	0.00033	890	530,000	890
Mixing/Loading/Applying Liquids with a Fogger (4)	Mosquitoes		0.018 acres (0.0092 A/unit x 2 units)	0.00007	0.00000003	700000	860 M	700,000

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);
- Inhalation exposure from airborne malathion following fogger use at residential, park and school sites (adult and toddler);

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, D321547).

6.3.2.6 Residential Noncancer Postapplication Risk Characterization

The postapplication exposure assessment indicates that certain scenarios exceed HED's level of concern. The detailed results of the residential postapplication exposure assessment are presented in Table 6.3.2.6 and scenarios of concern are summarized here as follows:

- Toddler (MOE of 90, with a LOC of 1000) inhalation following use of fogger unit to control outdoor flying insect pests.

The outdoor fogger risk is based on inhalation exposure, and, therefore assumes that the fogger will be used just prior (day 0) to residential activity in the treated area. Some label instructions for fogger use indicate that treatment should occur at dusk, but this does not preclude potential exposure from outdoor residential evening activities.

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. An informal assessment of potential dermal and incidental oral exposures to residues on turf following a

wide-swath residential building perimeter treatment resulted in risks that exceed HED's level of concern.

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

Scenario	Crop or Target	Receptor	Application Rate (AR) Per Treatment	DFR/TTR (ug/cm^2)[b]	Grt (ug/cm^2)	Srt (ug/g)	Transfer Coefficient (Tc) (cm^2/hr)	Exposure Time (ET) (hrs/day)	Absorption Rate (%)	Surface Area (SA) (cm^2/ event)	Freq. (FQ) (events/ hr)	IgR (cm^2/day) or (mg/day)	BW (kg)	ADD (mg/kg/day)	MOE[c]
Dermal exposure	Vegetable/Small Fruit	Adult	0.000115	11	-	-	500	0.67	100	-	-	-	70	0.053	940
	"Pick-your-own" strawberries	Adult	0.000115 (lbs ai/sq ft)[a]	11	-	-	1,500	2	100	-	-	-	70	0.47	106
							400							0.126	400
	Fruit Trees &	Adult	0.00017	16	-	-	1000	0.67	100	-	-	-	70	0.153	330
Inhalation	Outdoor Fogger	Adult	2 mg/m^3	-	-	-	-	5	100	-	-	-	70	0.143	1800
		Toddler						3					15	0.28	90

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 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)];

c MOE = NOAEL or BMDL/ADD, where

NOAEL (adult dermal) = 50 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 ChE effects).
NOAEL (toddler inhalation) = 25.8 mg/kg/day, with an LOC of 1000 (for ChE effects).

6.3.2.7 Combined Residential Handler and Postapplication Risk Characterization

Risks from different activities and routes of exposure are combined when the toxicity endpoint is the same, and when it is reasonable to assume that the activities might occur on the same day or same time period. This occurs for ChEI when adults are exposed through handling (dermal and inhalation) and from postapplication activities (dermal) on the same day. However, since toddler postapplication inhalation risks from fogger use are already of concern to HED, exposures from these uses are not combined with other scenarios here. This leaves only certain adult residential use scenarios to be combined.

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 (i.e., it is unlikely that a homeowner would routinely apply malathion to home fruit trees and harvest the fruit that 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. It can be seen that these combinations result in MOEs of >100, and are not of concern to HED.

Table6.3.2.7 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	106	0.0014	18,000	105
Mixing, loading and applying **wettable powder** with low-pressure handwand **on vegetable gardens** plus Postapplication activities **with vegetable gardens.**	0.37	134	0.0014	18,000	133
Mixing, loading and applying **liquids** with low-pressure handwand **on fruit trees** plus Postapplication activities **with home fruit trees**.	0.29	172	0.00001	2,600,000	172
Mixing, loading and applying **liquids** with low-pressure handwand **on vegetable gardens** plus Postapplication activities **with fruit trees**.	0.24	208	0.00001	2,600,000	208
Mixing, loading and applying **liquids** with low-pressure handwand **on fruit trees** plus Postapplication activities **with vegetable gardens**.	0.19	263	0.00001	2,600,000	263

1. Total MOE = NOAEL/Total Daily Dose, where:
   NOAEL = 50 mg/kg/day, for dermal, with an LOC of 100 (ChE effects)
   NOAEL = 25.8 mg/kg/day, for inhalation, with an LOC of 100 (ChE effects)
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);
- 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, D321547). 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 assessments. 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[7] 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, D321547).

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 $\geq$ 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, D321547).

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;
- 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	150,000	0.00094	27,000	N/A	N/A	23,000	N/A
(2) Postapplication following **Aerial ULV** application.	0.0000053 (lb ai/sq ft)	0.005	10,000	0.00013 (helicopter)	200,000	N/A	N/A	9500	N/A
				0.000052 (fixed-wing)	500,000			9800	N/A
Toddler									
(1) Postapplication following **Ground ULV** application	0.0000025 (lb ai/sq ft)	0.00055	91,000	0.0035	7400	0.000084	85,000	N/A	6.8
(2) Postapplication following **Aerial ULV** application	0.0000053 (lb ai/sq ft)	0.0083	6000	0.00057 (helicopter)	40,000	0.0012	6000	N/A	2.8
				0.00022 (fixed-wing)	120,000			N/A	2.9

1. MOE = NOAEL or BMDL/ADD, where

NOAEL (adult dermal) = 50 mg/kg/day, with an LOC of 100.
NOAEL (adult inhalation) = 25.8 mg/kg/day, with an LOC of 100.
NOAEL (toddler dermal) = 50 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 ≥100 for adults, or Total ARIs ≥1 for toddlers, do not exceed HED's level of concern.
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 on cotton, specifically, or in agriculture, in general, 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 application rate (ULV) for aerial boll weevil control is 0.9 lb ai/acre.
- From the edge of the treatment area to 75 feet downwind, approximately 40 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 (40%).

For additional information regarding specific scenario assumptions, please refer to the Revised

Residential Exposure and Risk Assessment (J. Arthur, D321547).

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. 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 Eradication Program Use

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									
Postapplication Following Aerial ULV Boll Weevil Treatment	0.000021 (lb ai/sq ft)	0.022	2,300	0.000068	380,000	N/A	N/A	2,300	N/A
Toddler									
Postapplication Following Aerial ULV Boll Weevil Treatment	0.000021 (lb ai/sq ft)	0.036	1,400	0.00033	78,000	0.0055	1300	N/A	1.3

1. MOE = NOAEL or BMDL/ADD, where

NOAEL (adult dermal) = 50 mg/kg/day, with an LOC of 100.
NOAEL (adult inhalation) = 25.8 mg/kg/day, with an LOC of 100.
NOAEL (toddler dermal) = 50 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 ≥100 for adults, or Total ARIs ≥1 for toddlers, do not exceed HED=s level of concern.
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, D321547).

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. It is HED's understanding that spinosad is the compound of choice for medfly control, and therefore, that malathion use in medfly programs is not likely to be significant. However, it also is presumed that stakeholders are interested in keeping malathion as an available tool for medfly programs. In order for these 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; however, toddler exposure from residues on turf following aerial fruit fly treatment result in risks of concern (i.e., MOE of 700 for dermal contact with an LOC of 1000). Toddler combined exposures from dermal, inhalation and incidental oral routes results in an ARI = 0.66, where an ARI $\geq$ 1 is needed. The results of the residential postapplication exposure assessment resulting from the fruit fly control use are presented in Table 6.3.3.2. 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 Incid. Oral Dose[2] (mg/kg/day)	Total Incid. Oral MOE[1]	Total MOE[3]	Total ARI[4]
Adult									
Postapplication Following Aerial Fruit Fly Treatment	0.18 (lb ai/A)	0.046	1,100	3.10E-07	8.30E+06	N/A	N/A	1,100	N/A
Toddler									
Postapplication Following Aerial Fruit Fly Treatment	0.18 (lb ai/A)	0.076	700	1.00E-06	5.00E+06	0.004	1,300	N/A	0.66

1. MOE = NOAEL or BMDL/ADD, where

NOAEL (adult dermal) = 50 mg/kg/day, with an LOC of 100;
NOAEL (toddler dermal) = 50 mg/kg/day, with an LOC of 1000;
$BMDL_{10}$ (toddler incidental oral) = 7.1 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)

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 77x. 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 an adjustment factor of 99%, 95% or 90%.

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

Postapplication risks to toddlers from contacting malathion and malaoxon residues following public health mosquitocide, boll weevil and fruit fly treatments exceeded HED's level of concern in a preliminary screening-level assessment when using a number of upper percentile input variables in the risk calculation (e.g., 95th percentile transfer coefficient; 2-hour exposure duration). Risks were driven by dermal exposure and the assumed malathion-to-malaoxon transformation rate. When certain alternative, less conservative, input variables are chosen from available ranges of values, risks do not exceed HED's level of concern, except for those resulting from boll weevil eradication when using a 5% or 10% malathion-to-malaoxon transformation rate, and fruit fly using 10%. The calculated exposures include maximum application rates and conservative deposition estimates. The detailed results of the residential postapplication exposure assessment for malaoxon, are presented below in Table 6.3.4.3a, 6.3.4.3b, 6.3.4.3c, 6.3.4.3d, 6.3.4.3e, 6.3.4.3f, 6.3.4.3g, 6.3.4.3h, and 6.3.4.3i.

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	12,000
Dermal (grnd ULV)	0.0000025	0.0061 (malathion 99%) 0.0047 (malaoxon 1%)	393	1	0.00016 0.0001	0.00026	190,000
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%) 0.0024 (malaoxon 1%)	-	1	0.00004 0.000032	0.000072	99,000

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) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 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	0.086 (malathion 95%) 0.35 (malaoxon 5%)	393	1	0.0023 0.0092	0.0120	4,200
Dermal (grnd ULV)	0.0000025	0.0058 (malathion 95%) 0.024 (malaoxon 5%)	3	1	0.00015 0.00063	0.00078	64,000
Hand-to-Mouth (air ULV)	0.0000053	0.043 (malathion 95%) 0.18 (malaoxon 5%)	-	1	0.00057 0.0024	0.003	2,400
Hand-to-Mouth (grnd ULV)	0.0000025	0.0029 (malathion 95%) 0.012 (malaoxon 5%)	-	1	0.000039 0.00016	0.0002	36,000

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; 95% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 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	0.082 (malathion 90%)	393	1	0.0021	0.0200	2,500
		0.7 (malaoxon 10%)			0.0180		
Dermal (grnd ULV)	0.0000025	0.0055 (malathion 90%)	393	1	0.00014	0.0013	38,000
		0.047 (malaoxon 10%)			0.0012		
Hand-to-Mouth (air ULV)	0.0000053	0.041 (malathion 90%)	-	1	0.00055	0.0053	1,300
		0.35 (malaoxon 10%)			0.0047		
Hand-to-Mouth (grnd ULV)	0.0000025	0.0028 (malathion 90%)	-	1	0.000037	0.00036	20,000
		0.024 (malaoxon 10%)			0.00032		

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; 90% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 mg/kg/day , with an LOC of 1000;

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

Table 6.3.4.3d 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)	0.000021	0.41 (malathion 99%) 0.32 (malaoxon 1%)	393	1	0.0120 0.0084	0.0200	2,500
Hand-to-Mouth (air ULV)	.000021	0.20 (malathion 99%) 0.16 (malaoxon 1%)	-	1	0.0027 0.0021	0.0048	1,500

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 (0.40 for air ULV) * (1% for malaoxon transformation; 99% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 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)	0.000021	0.39 (malathion 95%) 1.6 (malaoxon 5%)	393	1	0.0100 0.0420	0.0520	960
Hand-to-Mouth (air ULV)	0.000021	0.20 (malathion 95%) 0.79 (malaoxon 5%)	-	1	0.0027 0.011	0.014	500

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 (0.40 for air ULV) * (5% for malaoxon transformation; 95% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 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)

fScenario	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	0.37 (malathion 90%)	393	1	0.0097	0.0940	530
		3.2 (malaoxon 10%)			0.0840		
Hand-to-Mouth (air ULV)	0.000021	0.19 (malathion 90%)	-	1	0.0025	0.024	300
		1.6 (malaoxon 10%)			0.021		

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 (0.40 for air ULV) * (10% for malaoxon transformation; 90% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 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 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)	0.0021	0.21 (malathion 99%)	393	1	0.0055	0.0097	5,200
		0.16 (malaoxon 1%)			0.0042		
Hand-to-Mouth (air ULV)	0.0021	0.10 (malathion 99%)	-	1	0.0013	0.0024	3,000
		0.081 (malaoxon 1%)			0.0011		

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) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where
NOAEL (dermal) = 50 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 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)[c]	Total ADD for Malathion and Malaoxon (mg/kg/day)	Total MOE[d]
Dermal (air ULV)	0.0021	0.20 (malathion 95%) 0.81 (malaoxon 5%)	393	1	0.0052 0.0210	0.0260	1,900
Hand-to-Mouth (air ULV)	0.0021	0.10 (malathion 95%) 0.40 (malaoxon 5%)	-	1	0.0013 0.0053	0.0066	1,100

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; 95% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where

NOAEL (dermal) = 50 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 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)	0.0021	0.19 (malathion 90%) 1.6 (malaoxon 10%)	393	1	0.0050 0.0420	0.0470	1,100
Hand-to-Mouth (air ULV)	0.0021	0.09 (malathion 90%) 0.81 (malaoxon 10%)	-	1	0.0012 0.011	0.012	590

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; 90% for untransformed malathion) * (77x 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 = NOAEL or $BMDL_{10}$/ADD, where
NOAEL (dermal) = 50 mg/kg/day , with an LOC of 1000;
$BMDL_{10}$ (incidental oral) = 7.1 mg/kg/day, with an LOC of 100.

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. The degree to which the TAF calculated from steady state measurements of RBC ChE is predictive of acute exposures is unknown. It is notable that the acute TAF calculated by EPA for dimethoate and its oxon metabolite, omethoate is larger than the steady TAF for these chemicals (12x for acute vs. 3x for steady state). In addition, 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. 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. Although this analysis provides uncertainty regarding risk estimates for dermal exposures, it is considered a reasonable approach at this time.

7.0 Aggregate Risk Assessments and Risk Characterization

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

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 the Lifeline Model Version 2.0 and Dietary Exposure Evaluation Model (DEEM-FCID **J**, Version 2.02). 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

A Tier 3, acute probabilistic dietary exposure 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 77x 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 acute and 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 77 to account for the malaoxon TAF (see drinking water section) and 100% conversion of malathion to malaoxon was assumed during drinking water treatment. The PRZM-EXAMS distributions used in this dietary assessment represent two scenarios: Florida citrus maximum aerial application rate which has the highest 1-in-10 year peak concentration and Oregon apple air-blast at typical application rate which has the lowest 1-in-10 year peak concentration for drinking water.

The acute dietary exposure estimates for food and drinking water using the worst-case FL citrus crop scenario for drinking water are at the 99.9th percentile of exposure and are of concern (> 100% aPAD). Malathion dietary exposure at the 99.9th percentile for food and drinking water for U.S. population was 155% aPAD using DEEM-FCID and 540% aPAD for all infants less than 1 year of age, the most highly exposed population subgroup.

Table 7.1.1 Result of Acute Dietary + Water Exposure and Risk Estimates for Malathion Using the Florida Citrus Crop Water Scenario.			
Population Subgroup	**PAD, mg/kg/day**	**DEEM-FCID**	
		Exposure, mg/kg/day	**% PAD**
Acute Dietary Estimates (99.9th Percentile of Exposure)			
U.S. Population	0.14	0.217679	155
All infants (< 1 yr)	**0.14**	**0.756401**	**540**
Children 1-2 yrs	0.14	0.331551	237
Children 3-5 yrs	0.14	0.299780	214
Children 6-12 yrs	0.14	0.207194	148
Youth 13-19 yrs	0.14	0.164443	117
Females 13-49 yrs	0.14	0.189449	135
Adults 20-49 yrs	0.14	0.196217	140
Adults 50+ yrs	0.14	0.189449	135

The acute dietary exposure estimates for food and drinking water using the Oregon apple crop scenario for drinking water are also at the 99.9th percentile of exposure, but are not of concern (< 100% aPAD). Malathion dietary exposure at the 99.9th percentile for food and drinking water for the U.S. population was 19% aPAD using DEEM-FCID and 43% aPAD for children 1-2 yrs, the most highly exposed population subgroup.

Table 7.1.2 Result of Acute Dietary + Water Exposure and Risk Estimates for Malathion Using the Oregon Apple Crop Water Scenario.			
Population Subgroup	**PAD, mg/kg/day**	**DEEM-FCID**	
		Exposure, mg/kg/day	**% PAD**
Acute Dietary Estimates (99.9th Percentile of Exposure)			
U.S. Population	0.14	0.030304	22
All infants (< 1 yr)	0.14	0.060646	43
Children 1-2 yrs	0.14	**0.064102**	**46**
Children 3-5 yrs	0.14	0.058861	42
Children 6-12 yrs	0.14	0.032267	23
Youth 13-19 yrs	0.14	0.021005	15
Females 13-49 yrs	0.14	0.020980	15
Adults 20-49 yrs	0.14	0.023958	17
Adults 50+ yrs	0.14	0.020305	15

Twenty-six different crop/location scenarios were analyzed using PRZM-EXAMS in order to represent the wide range of locations where malathion is used in the U.S. (See Table 7.1.3). Table 7.1.3

demonstrates the acute food plus water aggregate assessments for all 26 scenarios.

Table 7.1.3 Malathion Results of Acute Dietary Exposure Analysis Food + Drinking Water From a Variety of Crop Scenarios Using DEEM-FCID

Rank	State/crop/intensity/ app method	30-year peak Malaoxon conc. (ppm)	U.S. Population %aPAD	All Infants* %aPAD	Children 1-2 yrs* %aPAD	Children 35 yrs* %aPAD
Acute Dietary Estimates 99.9th Percentile						
1	FLcitrusMAXaerial	0.239	155	540	236	214
2	FLcitrusMAXairblast	0.219	124	450	190	175
3	MScottonMAXground	0.137	91	327	139	127
4	MScottonMAXaerial	0.135	93	333	142	129
5	TXsorghumMAXground	0.134	48	156	68	72
6	TXsorghumMAXaerial	0.131	51	167	73	74
7	FLcabbageMAXground	0.075	63	221	97	91
8	FLcabbageMAXaerial	0.075	73	246	108	100
9	MNalfalfaMAXaerial	0.024	26	69	51	47
10	MNalfalfaMAXground	0.023	23	44	46	43
11	MNalfalfaTYPaerial	0.023	23	53	47	43
12	MNalfalfaTYPground	0.022	23	50	46	43
13	TXsorghumTYPaerial	0.019	23	50	46	43
14	FLcitrusTYPaerial	0.018	22	48	46	43
15	TXsorghumTYPground	0.018	22	43	46	43
16	MScottonTYPaerialBWEP	0.016	21	36	46	42
17	MScottonTYPgroundBWEP	0.016	20	20	46	40
18	FLcitrusTYPairblast	0.016	21	36	46	42
19	FLcabbageTYPaerial	0.016	24	60	48	43
20	MScottonTYPground	0.015	20	26	46	41
21	MScottonTYPaerial	0.015	20	27	46	41
22	FLcabbageTYPground	0.013	22	40	46	42
23	ORappleMAXaerial	0.011	22	41	46	42
24	ORappleTYPaerial	0.01	22	43	46	42
25	ORappleMAXairblast	0.007	22	39	46	42
26	ORappleTYPairblast	0.006	20	24	46	40

* Use only sub-population that were significant contributors to malathion dietary risk assessment

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. 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.

7.3 Long-Term Aggregate Risk

A refined chronic dietary exposure assessment was also conducted for the supported food uses of malathion and drinking water using a single point estimate of malathion residues for food and drinking water. The estimated surface water concentration was based on data from the highest one in ten year annual mean from Florida citrus aerial maximum application rate and the lowest one in ten year annual mean from Oregon apple airblast at typical application rate. Each value was adjusted for the malaoxon toxicity adjusted factor of 77x.

The chronic dietary exposure estimates for food and drinking water using the worst-case FL citrus crop scenario for drinking water for the U.S. population and all population subgroups are of concern (>100% cPAD). Malathion dietary exposure for food and drinking water for the U.S. population was 149% cPAD using DEEM-FCID and 104% cPAD using Lifeline; and 472% cPAD with DEEM-FCID and 385% cPAD with Lifeline for infants, the most highly exposed population subgroup.

Table 7.3.1 Result of Chronic Dietary + Water Exposure and Risk Estimates for Malathion Using the Florida Citrus Crop Water Scenario.

Population Subgroup	PAD, mg/kg/day	DEEM-FCID		Lifeline	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Chronic Dietary Estimates					
U.S. Population	0.003	0.0048	149	0.003119	104
All infants (< 1 yr)	**0.003**	**0.014162**	**472**	**0.011554**	**385**
Children 1-2 yrs	0.003	0.007006	234	0.006845	228
Children 3-5 yrs	0.003	0.006433	214	0.005904	197
Children 6-12 yrs	0.003	0.00447	149	0.003424	114
Youth 13-19 yrs	0.003	0.003268	109	0.002362	79
Adults 20-49 yrs	0.003	0.004191	140	0.002744	92
Adults 50+ yrs	0.003	0.004251	142	0.002846	95
Females 13-49 yrs	0.003	0.00413	138	0.003109	101

The chronic dietary exposure estimates for food and drinking water using the Oregon apple scenario for drinking water are below HED's level of concern (<100% cPAD) for the U.S. population and all population subgroups. Malathion dietary exposure for food and water for the U.S. population was 10% cPAD using DEEM-FCID and Lifeline; and 27% cPAD with DEEM-FCID and 22% cPAD with Lifeline for children 1-2 years, the most highly exposed population subgroup.

Table 7.3.2 Malathion Results of Chronic Dietary Exposure Analysis Food + Drinking Water From a Variety of Crop Scenarios Using DEEM-FCID

Population Subgroup	PAD, mg/kg/day	DEEM-FCID		Lifeline	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Chronic Dietary Estimates					
U.S. Population	0.003	0.000312	10	0.000311	10
All infants (< 1 yr)	0.003	0.000498	17	0.000394	13
Children 1-2 yrs	**0.003**	**0.000817**	**27**	**0.000664**	**22**
Children 3-5 yrs	0.003	0.000639	21	0.000627	21
Children 6-12 yrs	0.003	0.000473	16	0.000407	14
Youth 13-19 yrs	0.003	0.000256	9	0.000291	10
Adults 20-49 yrs	0.003	0.0003	10	0.00027	9
Adults 50+ yrs	0.003	0.000157	5	0.000281	9
Females 13-49 yrs	0.003	0.000254	9	0.000309	10

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 Interim Reregistration Eligibility Decision (IRED) Document. PC Code: 057701. DP Barcode: D315898. Jach Arthur. June 2, 2005.*

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.

HED has determined that there are potential occupational exposures to handlers (i.e., mixers, loaders, applicators), as well as to postapplication workers from the use of malathion.
In subsequent sections of this document, occupational exposure and risks are presented in summary tables in two groupings according to formulation; with emulsifiable concentrate (EC), wettable powder (WP) and ready-to-use (RTU) formulations in one group, and ultra-low volume (ULV) formulation in another. Application rates, and consequent risks for ULV formulations are sufficiently lower than EC, WP and RTU formulations, to be presented separately.

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 Table 9.1.

Table 9.1 Summary of Occupational Use Sites

Crop Group	Formulation	Use Site	Rate (lb ai/acre, unless otherwise stated)	Application Equipment
Non-grass animal feed	EC	alfalfa, clover, lespedeza, lupin, vetch	1.25	Groundboom, Aerial, Chemigation
	ULV	alfalfa, clover, lespedeza, lupin, vetch	0.61	
Pome fruits	EC	apples, pear, quince	1.25	Airblast, Aerial
Stone fruits	EC	apricots, cherries (sweet and tart),nectarine, peach	3.75	Airblast, Aerial
	ULV	cherries (sweet and tart)	1.22	
Stalk and stem vegetables	EC	asparagus	1.25	Groundboom, Aerial
Tropical and subtropical fruits	EC	avocado,	4.7	Groundboom, Airblast, Aerial
		figs	2.5	
		guava, mango, papaya, passionfruit	1.25	
		pineapples	5	
Cereal grains	EC	barley, corn, oats, rice, rye, sorghum, wheat, wild rice	1.25	Groundboom, Aerial, Chemigation
	ULV	barley, corn, oats, rice, rye, sorghum, wheat, wild rice	0.61	
Root and tuber vegetables	EC	garden beets, carrot, horseradish, parsnip, radish, rutabaga, salsify, turnip	1.25	Groundboom, Aerial
		potatoes, sweet potatoes,chayote root and yams	1.56	
Berries	WP	blackberry, boysenberry, dewberry, loganberry, raspberry	2	Groundboom, Aerial

		blueberries	1.25	
	ULV	blueberries	0.76	
Brassica leafy vegetables	EC	broccoli, broccoli raab, brussels sprouts, cabbage, cauliflower, collard, kale, kohlrabi, mustard green	1.25	Groundboom, Aerial
Cucurbit vegetables	EC	cantaloupe, melon, pumpkin, winter squash, watermelon	1	Groundboom, Aerial
		cucumber and summer squash, Chayote fruit	1.88	
Leafy vegetables	EC	celery	1.25	Groundboom, Aerial
		dandelion, parsley, spinach, Swiss chard,	2	
		endive and lettuce	1.88	
		watercress	1.25	
Tree nuts	EC	chestnuts	5	Airblast, Aerial
		macadamia nuts	0.94	
		pecans, walnuts	2.5	
Oilseed	EC	cotton	2.5	Groundboom, Aerial
	ULV	cotton	1.22	
	EC	flax	0.5	
Fruiting vegetables	EC	eggplant, tomato	3.43	Groundboom
		okra	1.5	
Bulb vegetables	EC	garlic, leeks, onion, shallots,	1.56	Groundboom
Citrus fruits	EC	grapefruits, kumquat, lemon, lime, orange, tangelo, tangerines	6.25	Airblast, Aerial
	ULV	grapefruits, lemon, lime, orange, tangelo, tangerines	0.175	
	ULV	kumquat	0.92	
Small fruits	EC	grape	1.88	Airblast

	EC, WP	strawberry	2	Groundboom, Chemigation
Forage grass	EC	grass	1.25	Aerial
	ULV	hay grass	0.92	

Herbs and spices	EC	mint	0.94	Groundboom, Chemigation (Airblast for hops)
		hops	0.63	
		pepper	1.56	
Edible fungi	EC	mushroom	1.7	Low-Pressure Handgun
Legume vegetable	EC	peas	2.5	Groundboom, Aerial, Chemigation
Ornamentals	EC	flowers, shrubs, flowering plants, nursery stock, and woody plants	2.5	Groundboom, Low-Pressure Handwand, Backpack Sprayer
Pine Trees	EC	pine seed orchards, Christmas tree plantations, slash pine plantations, shrubs, shade trees, and forest trees	2.5	Aerial, Chemigation
Grape Root	EC	grape roots	1.9 lb ai per 100 gallons.	Hand or Basket Dipping
Storage Grain Facility	EC	stored commodities such as corn, wheat, barley, oats, and rye	5 lb ai per 20 gallons.	Low-Pressure Handwand, Backpack Sprayer
	Dust		0.3 lbs ai per 1,000 square feet	Power Duster
Agricultural Premises	EC	outside barns, applied as a bait only	0.27 lbai per gal	Low-Pressure Handwand, Backpack Sprayer
Dates	Dust	dates	4.25	Power Duster
Mosquitoes	ULV	mosquitoes	0.23	Aerial
	EC		9.9 lb ai per gal	Non-thermal Truck Fogger
			0.51 lb ai per gal	Thermal Truck Fogger
	EC		0.1 lb ai per gal	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 exposures 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 μg/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 μg/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). Unit exposure values for a low-pressure handgun (mixer/loader/applicator, liquid flowable) from a study conducted by the Outdoor Residential Exposure Taskforce (ORETF) were used as the closest surrogate for the application equipment employed in mushroom houses.

- 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.

- A 90% protection factor has been applied to the "head and neck" unit exposure value from the PHED Surrogate Table, for certain airblast applicator scenarios. This value comes from a recent Agricultural Handler Exposure Task Force study (MRIID 46448201, Dec. 30, 2004) for which an official HED secondary review has yet to be completed. This protection factor was applied for certain airblast scenrios where headgear would provide an alternative to more stringent mitigation approaches such as respirators, double layer of clothing or enclosed cabs. It is used pending an official secondary review and acceptance of the study by the Agency.

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 (*except airblast application of EC to apricots, cherries, nectarines, peaches, avocados, figs, chestnuts, pecans, walnuts, citrus fruits and ornamentals, and applying sprays for mosquitoes with a non-thermal fogger),* 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, 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 Interim Reregistration Eligibility Decision (IRED) Document. (J. Arthur; D315898).

Table 9.2.3 Summary of Occupational Handler Risks and Mitigation

Scenario	# Scenarios where Total MOE < 100 with baseline PPE	# Scenarios where Total MOE < 100 with PPE1	# Scenarios where Total MOE < 100 with PPE2	# Scenarios where Total MOE < 100 with PPE3	# Scenarios where Total MOE < 100 with PPE4	# Scenarios where Total MOE < 100 with PPE5	# Scenarios where Total MOE < 100 with PPE6	# Scenarios where Total MOE < 100 with Eng. Control
Agricultural Crops Treated with Emulsifiable Concentrate, Wettable Powder and Ready-to-Use Formulations								
Mixer/Loader liquids for all application equipment (ie., groundboom, airblast, aerial/chemigation) Total Scenarios = 78	67	11	8	7	6	4	4	0
Applicator liquids for groundboom Total Scenarios = 26	0	-	-	-	-	-	-	-
Applicator liquids for airblast Total Scenarios = 11	3*	0*	-	-	-	-	-	-
Applicator liquids for aerial Total Scenarios = 30	ND	ND	ND	ND	ND	ND	ND	0
Flagging (for aerial) Total Scenarios = 26	0	-	-	-	-	-	-	-
Agricultural Crops Treated with Ultra Low Volume Foumulations								
Mixer/Loader liquids for all application equipment (ie., groundboom, airblast, aerial/chemigation) Total Scenarios = 17	16	1	0	-	-	-	-	-
Applicator liquids for groundboom Total Scenarios = 6	0	-	-	-	-	-	-	-
Applicator liquids for airblast Total Scenarios = 3	0	-	-	-	-	-	-	-
Applicator liquids for aerial Total Scenarios = 7	ND	ND	ND	ND	ND	ND	ND	0
Flagging (for Aerial) Total Scenarios = 6	0	-	-	-	-	-	-	-

Scenario	# Scenarios where Total MOE < 100 with baseline PPE	# Scenarios where Total MOE < 100 with PPE1	# Scenarios where Total MOE < 100 with PPE2	# Scenarios where Total MOE < 100 with PPE3	# Scenarios where Total MOE < 100 with PPE4	# Scenarios where Total MOE < 100 with PPE5	# Scenarios where Total MOE < 100 with PPE6	# Scenarios where Total MOE < 100 with Eng. Control
Unique or Non-Food Uses								
Mixer/Loader liquids for groundboom, airblast, aerial/chemigation, fogger, plant dipping. Total Scenarios = 9	7	2	2	2	1	0	-	-
Mixer/Loader dust for power duster. Total Scenarios = 1 (plus 1 with ND)	1	0	-	-	-	-	-	-
Mixer/Loader/Applicator for low-pressure handwand, backpack sprayer, paint brush. Total Scenarios = 8	8	0	-	-	-	-	-	-
Applicator for dipping plants Total Scenarios = 1	ND	ND	ND	ND	ND	ND	ND	ND
Applicator dust, power duster. Total Scenarios = 2	ND	ND	ND	ND	ND	ND	ND	ND
Applicator liquids for groundboom, airblast, fogger. Total Scenarios = 4	2	2	2	2	1	0	-	-
Applicator liquids for aerial Total Scenarios = 1	ND	ND	ND	ND	ND	ND	ND	0
Flagging (for aerial) Total Scenarios = 2	0	-	-	-	-	-	-	-

Note: Total MOE for combined dermal and inhalation exposures. LOC = 100 for cholinesterase endpoint

Baseline dermal unit exposures represent long pants, long sleeved shirts, shoes, and socks
PPE1 unit exposures represent long pants, long sleeved shirts, and chemical-resistant gloves and no respirator
PPE2 unit exposures represent long pants and long sleeved shirts plus chemical-resistant gloves and dust mist respirator
PPE3 unit exposures represent long pants and long sleeved shirts plus chemical-resistant gloves and o/v respirator
PPE4 unit exposures represent coveralls worn over long pants and long sleeved shirts plus chemical-resistant gloves and no respirator
PPE5 unit exposures represent coveralls worn over long pants and long sleeved shirts plus chemical-resistant gloves and dust mist respirator
PPE6 unit exposures represent coveralls worn over long pants and long sleeved shirts plus chemical-resistant gloves and o/v respirator
Engineering controls dermal unit exposures represent long pants and long sleeved shirts. For mixers and loaders
* MOE is greater than 100 with indicated PPE, plus chemical-resistant headgear.
ND = No Data

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. Mushroom houses are a special case, where the indoor, nearly year long treatment and harvesting of multiple crop cycles result in the potential for mushroom house workers to experience long-term exposure to malathion (i.e. ≥180 days).

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 6 days. Most activities reach an MOE ≥100 on day 0. 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 Interim Reregistration Eligibility Decision (IRED) Document. (J. Arthur; D315898).

Table 9.3.3a. Summary of 'Days After Treatment' to Reach the MOE of 100 for Intermediate-term Exposure (EC, WP and RTU formulations)							
Crop Grouping (1)	Malathion Specific Crops (2)	Max Foliar Rate (lb ai/acre)	Days After Treatment where MOE ≥ 100				
			Exposure Activity Levels (3,4)				
			Very Low	Low	Medium	High	Very High
Berry, low	Blueberries (lowbush), Strawberries	1.25 - 2	N/A	0	N/A	0	N/A
Bunch / bundle	Hops, Dates	0.63 - 4.25	N/A	0	0 - 2	0 - 3	N/A
Field / row crops, low / medium	Alfalfa, Barley, Cotton, Flax, Mint, Peas (dry), Peas (green), Rice, Wheat (spring), Wheat (winter), Clover, Grasses (forage & hay), Lespedeza, Lupine, Oats, Rye, Vetch, Wild rice	0.5 - 2.5	N/A	0	0 - 3	1 - 4	N/A
Field / row crops, tall	Corn (all types), Sorghum	1.25	N/A	0	0	1	6
Trees, fruit, deciduous	Apples, Apricots, Cherries, Figs, Nectarines, Peaches, Pears, Quince	1.25 - 3.75	0	0 - 2	N/A	0 - 3	2 - 4
Trees, fruit, evergreen	Avocados, Grapefruit, Lemons, Mangos, Oranges, Papaya, Guava, Kumquat, Lime, Tangelo, Tangerines	1.25 - 6.25	0	0 - 3	1 - 5	0 - 4	N/A
Trees, nut	Macadamia nuts, Pecans, Walnuts, Chestnut	0.94 - 5	N/A	0 - 1	N/A	1 - 4	N/A
Unassigned	Mushrooms	1.7 - 2.5	0	0	0	0	0
Vegetable, cucurbit	Cantalope, Cucumbers, Melons, Squash (summer), Squash (winter), Watermelon, Chayote fruit, Pumpkin	1 - 1.88	N/A	0	1 - 2	2 - 3	N/A
Vegetable, fruiting	Eggplant, Okra, Peppers (bell), Peppers (chili), Tomatoes (fresh), Tomatoes (processed)	1.5 - 3.43	N/A	0 - 1	0 - 2	1 - 3	N/A
Vegetable, head and stem Brassica	Broccoli, Brussel sprouts, Cabbage, Cauliflower, Broccoli raab, Kohlrabi	1.25	N/A	2	3	4	N/A

Table 9.3.3a. Summary of 'Days After Treatment' to Reach the MOE of 100 for Intermediate-term Exposure (EC, WP and RTU formulations)							
Crop Grouping (1)	Malathion Specific Crops (2)	Max Foliar Rate (lb ai/acre)	Days After Treatment where MOE ≥ 100				
			Exposure Activity Levels (3,4)				
			Very Low	Low	Medium	High	Very High
Vegetable, leafy	Celery, Collards, Kale, Lettuce, Mustard greens, Parsley, Spinach, Swiss chard, Watercress, Dandelion, Endive	1.25 - 2	N/A	0	1 - 2	2 - 3	N/A
Vegetable, root	Beets (table), Carrots, Onions (dry), Onions (green), Potatoes, Sweet potatoes, Turnips, Chayote root, Garlic, Horseradish, Leeks, Parsnip, Radish, Rutabaga, Salsify, Shallots, Yams	1.25 - 1.56	N/A	0	1 - 2	2 - 3	N/A
Vegetable, stem / stalk	Asparagus, Pineapple	1.25 - 5	N/A	0	0	0 - 1	N/A
Vine / trellis (w/ girdling)	Grapes (table and raisin), Boysenberry	1.88 - 2	N/A	0	0	2 - 4	3 - 6
Vine / trellis (w/o girdling)	Blackberries, Blueberries (highbush), Grapes (juice and wine), Raspberries, Dewberry, Loganberry, Passion fruit	1.25 - 2	N/A	0	0	0 - 4	N/A
Flowers, cut	Ornamentals (flowers, shrubs, flowering plants, nursery stock, and wood plants)	2.5	N/A	0	0	0	6
Trees, fruit, evergreen	Pine trees (Pine seed orchards, Christmas trees, Slash pine plantations, shrubs, shade trees, forest trees)	2.5	0	1	3	3	N/A

Footnote:

1. Crop groupings and transfer coefficients from Science Advisory Council for Exposure: Policy Memo #003.1 'Agricultural Transfer Coefficients', August 17, 2000.

2. Maximum label rates from residue field trial studies and supported by the primary producer, Cheminova or found on end use product labels.

3. DAT = Days after treatment; DAT0 = On the day of treatment, after sprays have dried; assumed approximately 12 hours.

4. MOE = Dermal toxicity endpoint (mg/kg-day)/absorbed dermal dose (mg/kg-d) where the absorbed dose = DFR (ug/cm2) x TC (cm2/hr) x conversion factor (1 mg/1,000 ug) x exposure time (hrs) x dermal absorption / body weight (kg).

Table 9.3.3b. Summary of 'Days After Treatment' to Reach the MOE of 100 for Short-/Intermediate-term Exposure (ULV formulation)							
Crop Grouping (1)	Malathion (ULV) Specific Crops (2)	Max Foliar Rate (lb ai/acre) (2)	Days After Treatment where MOE ≥ 100				
			Exposure Activity Levels (3,4)				
			Very Low	Low	Medium	High	Very High
Berry, low	Blueberries (lowbush)	0.76	N/A	0	N/A	0	N/A
Field / row crops, low / medium	Alfalfa, Barley, Beans (dry), Beans (string), Cotton, Rice, Wheat (spring), Wheat (winter), Clover, Grasses (forage, hay), Lespedeza, Lupine, Oats, Rye, Vetch, Wild rice	0.61 - 1.22	N/A	0	0 - 1	1 - 2	N/A
Field / row crops, tall	Corn (all types), Sorghum	0.61	N/A	0	0	0	4
Trees, fruit, deciduous	Cherries	1.22	0	0	N/A	0	2
Trees, fruit, evergreen	Grapefruit, Lemons, Oranges, Kumquat, Lime, Tangelo, Tangerine	0.18 - 0.92	0	0	0 - 1	0 - 1	N/A
Vine / trellis (w/o girdling)	Blueberries (highbush)	0.76	N/A	0	0	0	N/A

Footnote:

1. Crop groupings and transfer coefficients from Science Advisory Council for Exposure: Policy Memo #003.1 'Agricultural Transfer Coefficients', August 17, 2000.

2. Maximum label rates from residue field trial studies and supported by the primary producer, Cheminova, or found on end use product labels.

3. DAT = Days after treatment; DAT0 = On the day of treatment, after sprays have dried; assumed approximately 12 hours.

4. MOE = Dermal toxicity endpoint (mg/kg-day)/absorbed dermal dose (mg/kg-d) where the absorbed dose = DFR (ug/cm2) x TC (cm2/hr) x conversion factor (1 mg/1,000 ug) x exposure time (hrs) x dermal absorption / body weight (kg).

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.

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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 -	yes	yes
	bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation -	yes	yes
	mammalian	yes	yes[2]
870.5375	Mutagenicity—Structural Chromosomal Aberrations		
870.5550	Mutagenicity—Other Genotoxic Effects		

Table 1. Data Requirements			
Test		Technical	
		Required	Satisfied
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]
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 NON-CRITICAL TOXICOLOGY STUDIES

SUBCHRONIC/CHRONIC STUDIES

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.

In a combined chronic toxicity/carcinogenicity study (MRID 43975201), 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.

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

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.

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.

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.

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.

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 and decreased habituation in PND 60/61 females. 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, increased incidences of slightly flattened gait in PND 60 males, and increased thickness of the corpus callosum in PND 63-67 males and females.

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).

1. 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.

2. 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.

3. 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.

4. 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

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.

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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)**.

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)**.

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

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

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

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.

4.0 Dissenting Opinion by Brian Dementi, Ph.D., D.A.B.T.

Hon. Stephen L. Johnson June 20, 2005
Administrator
U.S. Environmental Protection Agency
Washington, D.C. 20460

Dear Mr. Johnson:

At this stage in my role as toxicologist on the pesticide malathion, having now reviewed and submitted comments (June 13, 2005) on the latest draft of the risk assessment on this organophosphate (entitled: *"Malathion: Updated Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). PC Code: 057701. Case No.0248. DP Barcode: D315906"*), given the complexity of the analysis of several toxicology parameters and regulatory endpoints, I consider it needful to bring together in one place a listing of my principal dissenting views, each briefly stated. This is a very verbose risk assessment that in my view does not provide reliable in-depth analysis of scientific and public health issues. In numerous places, for inexplicable reasons, this risk assessment sidesteps or down plays actual evidence of toxicity of malathion, particularly in reference to carcinogenicity and neurotoxicity in the young.

It is not my intent to justify these dissenting views with rationale and documentation put forward in this brief memorandum, but refer you to my comments on the risk assessment and its associated documents [e.g. Hazard Identification Assessment Review Committee (HIARC), Carcinogenicity Assessment Review Committee (CARC), FQPA Safety Committee, Scientific Advisory Panel (SAP), etc. reports] and their many attachments for such documentation. My objective is to consolidate in one place a briefly worded expression of my overall dissenting or alternative views with respect to those of the Health Effects Division now going out in this risk assessment.

My justification in setting forth these dissenting opinions resides with my sense of duty, and in the hope the risk assessment will be suitable to protect public health, including infant/child. This pursuit derives from both a sense of duty and a commitment to perform this duty, irrespective of the stress it brings to me.

1) Having reviewed the many carcinogenicity bioassays on malathion/malaoxon, and having discussed this subject with many experts, in my view the carcinogenicity of malathion under the Agency's carcinogenicity risk assessment guidelines should be classified as *"Likely to Be Carcinogenic to Humans"*.

2) The malathion cancer assessment did not take up the question of possible enhanced child susceptibility under more recent Agency Guidelines [(Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (EPA/630/R-03/003)]. Since carcinogenicity bioassays usually involve life time testing in *adult* animals, cancer assessment must take into consideration child sensitivity, i.e. the likelihood that expressions of carcinogenicity, whatever they might be in adults, would have been enhanced, or more evident, had lifetime testing begun with young animals (offspring) rather that from the adult stage only.

3) Positive findings of carcinogenicity (leukemia; thyroid C-cell) for malaoxon in chronic bioassays of record must be acknowledged in this risk assessment as opposed to the unequivocal erroneous claims that "malaoxon is non-carcinogenic".

4) The evidence for *low dose* carcinogenic effects need further characterization.

5) Conservatively and for public health protection, in the case of malathion the quantitative risk assessment should be employed for regulatory purposes, even if the classification of carcinogenicity remains under HED's governance as *"Suggestive Evidence of Carcinogenic Potential"*. *In my view, failure of HED (and others) to invoke the cancer quantitative risk assessment for malathion is perhaps the foremost public health protection flaw or failing in the risk assessment for malathion.*

6) An External Peer Review of the entire malathion mutagenicity data base is essential to addressing the mutagenicity component of malathion carcinogenicity.

7) A principal deficiency in this malathion risk assessment is its failure to properly acknowledge and appraise the magnitude of enhanced offspring (surrogates for infants/children) brain cholinesterase inhibition, and its implications for offspring behavioral effects, as required under FQPA.

8) The risk assessment does not own up to the need for additional assessment of behavioral effects vulnerability in infants/children (and actually in adults) given that a behavioral effect was seen in rat offspring at low doses without a NOEL. Behavioral effects *at low doses* have been identified in offspring in the developmental neurotoxicity study (DNT), but further assessment of behavior is not being pursued as needed to fully characterize what could be more diverse behavioral effects, most needed to protect the nation's young population

9) The malathion DNT/cholinesterase study lately disclosed the reality, as probably expected, of behavioral effects in offspring across all doses, absent a NOEL. Since doses were already low, this study underscores the potential for low level cholinesterase inhibition to alter behavior, especially given the ubiquitous presence and neurologic function of cholinesterase within the central nervous system. However, the extent to which this effect may occur at yet lower doses, and the breadth to which behavior of varied nature may be involved, requires further definition as well in the quest to protect the nation's infants/children.

10) This risk assessment failed (for inexplicable reasons) to put forward (acknowledge) the full breadth of offspring versus adult susceptibility in spite of the wishes of Congress as manifested in the FQPA.

11) The Bench Mark Dose (BMD) method of analysis as applied to offspring cholinesterase data study (yielding "NOAELs of 13.6 mg/kg (acute) and 7.1 mg/kg/d (short-term)" (Table 4.1e in risk assessment), for the malathion developmental neurotoxicity/cholinesterase study, should not be employed for risk assessment in lieu of use of <u>actual cholinesterase inhibition</u> data in offspring showing a lower LOEL (5 mg/kg) and no NOEL (testing not performed at doses less than 5 mg/kg) that would drive a more conservative regulation of malathion. Actual cholinesterase inhibition in offspring at 5 mg/kg/d with no NOEL may drive behavioral effects also seen

as a LOEL of 5 mg/kg/d, absent a NOEL. Neither cholinesterase inhibition nor proper behavioral assessment in offspring should be short circuited by this manipulation of data. I must express my continuing disagreement with this use of the BMD to in essence undermine the essential importance of the actual low dose findings, long suspected, but now confirmed in this new DNT study. The Agency must either accept the 5 mg/kg/(d) dose level as constituting LOELs for cholinesterase inhibition and behavioral effects in offspring, or respect these findings enough to require additional low dose assays rather than resort to the BMD method as a way around the implication of these actual findings

12) Since results on offspring behavior in the DNT/cholinesterase study did not identify a NOEL, more study is needed to characterize offspring behavioral effects in the lowest dose range for the protection of infants/children under mandates of FQPA. Also, more study is needed to characterize brain cholinesterase inhibition in offspring versus adults at low doses.

13) As obtained from the DNT/cholinesterase study of malathion, the Food Quality Protection Act (FQPA) safety factor for the protection of infants/children actually exceeds 10X, and while more cholinesterase and behavioral effects data in offspring is needed to more accurately quantify the safety factor, data in hand at this time suggests the safety factor as more on the order of 90X or higher. To use 10X is inappropriate for protection of the younger population.

14) Deficiencies with regard to the recently reviewed cholinesterase inhibition study of malathion *in humans* (MRID 45125602) preclude its being used for regulatory purposes, as for example in the setting of the acute RfD for malathion.

15) OPP should avoid using a recently received cholinesterase study of malathion in humans for risk assessment until Congress has settled its current debate over the used of human testing in regulating pesticides.

16) The Moeller and Rider (1962) human cholinesterase study, employed by the Agency for many years, until recently, for establishing the malathion chronic RfD, should not be abandoned for that purpose. This human study is also worthwhile in illustrating the enhanced sensitivity of the human versus rat (surrogate test species for man) as gleaned by metabolic differences between the two.

17) Audit should be performed of Huntington Labs records of the malathion DNT/cholinesterase study, focused especially to explain the highly variable cholinergic toxicity of malathion and assessment of reported changes in the size of corpus callosum (brain region) in offspring.

18) Information has been received that upon storage, particularly at elevated temperatures, malathion product will undergo degradation, resulting in elevated levels of more toxic elements such as isomalathion. As I understand, this degradation has not been adequately investigated to know whether labeled malathion as used in large quantities for medfly eradication and boll weevil eradication, for example, remains within labeling specification at the time of application. This needs to be determined by analytical sampling and analysis before populations are exposed. There should be EPA on-site inspections during spraying until the storage issue is

resolved. Such activity might be viewed by some as impractical, but that is no excuse when faced with the responsibility to insure public confidence in the safety of the product to which they are directly exposed in various pest eradication measures.

19) a) The low order of malathion acute toxicity reflected in Toxicity Categories of III and IV claimed in the risk assessment are not reflective of the much more severe order of toxicity seen for offspring in the DNT/cholinesterase study, and absent any qualification of Toxicity Categories as presented is misleading to the public as reflective of vulnerability of infants/children. b) A statement (p.1 of risk assessment) reads: "Malathion exhibits low acute toxicity via the oral, dermal and inhalation routes (Toxicity Categories III, IV)." This statement is categorically untrue with respect to offspring (infant/child) as taken by the oral route and presumably so by the dermal and inhalation routes, though offspring have not yet been tested by the latter two routes of exposure.

20) Public expressions of health related experiences of citizens during medfly eradication, and other uses, should be responded to and clearly portrayed in the risk assessment (for example, the March 25, 1995 correspondence of Deborah Bechtel to EPA's Dr. Lynn Goldman).

21) The established HIARC (1998) requirement for a repeat subchronic inhalation study on malathion must be expedited, and certainly not withdrawn as a data requirement, particularly in view of the evidence of: nasal histopathology across all doses in the existing rat inhalation study and even after only two weeks dosing in the rat range-finding inhalation study; existing evidence of nasal tissue histopathologic effects in chronic studies; complaints by citizens of nosebleeds commensurate with medfly spraying.

22) Given my expressed concerns over the PWG (2000) for female liver tumor response in the 1996 malathion chronic toxicity/carcinogenicity bioassay (MRID 43942901), the liver histopathology slides used by the PWG should be examined by independent pathologists not in the employ of the malathion registrant. Photomicrograps of liver tumors slides from the malathion study employed by the PWG should be submitted for review of EPA's pathologists and archived within the Agency to make them available for public inspection. My principal concern in this request is that such information not be maintained only off limits in an organization's private files.

23) A subchronic dog study should be required to resolve certain tox issues in the dog, for example vulnerability to cholinesterase inhibition.

24) HED or an external entity (e.g. contractor) should re-review the malathion Guideline Reproduction Study for evidence and degree of offspring enhanced susceptibility, which I feel certain is real and substantial despite attempts within HED to water down this positive effect. The re-review is needed because when originally reviewed there was no focus driven by FQPA to identify or quantify evidence for offspring versus adult susceptibility.

25) In citing background materials, this malathion risk assessment must include the January 28, 2003 HIARC

report along with the other earlier HIARC reports listed. The most recent HIARC report appearing to be listed is that of June 13, 2002. The January 2003 report contains additional citations of my alternative opinions versus those of the HIARC, which must be in the record. Furthermore, it is in the January 28, 2003 report that HIARC affirmed as inappropriate the use of the BMD method of analysis to get around using positive evidence of low dose cholinesterase inhibition in offspring, as observed in the DNT/cholinesterase study, for regulatory purposes. Deleting reference to this HIARC report which claims as inappropriate the use of BMD methodology is of particular concern to me where transparency of the risk assessment is concerned.

26) The External Peer Review (Drs. Hartung, Decker and Douerson) (1998) on HIARC (1997) malathion toxicology issues (both Agency questions posed to the external toxicology experts and the answers they provided) must be clearly cited and represented in the malathion risk assessment so that its presence and role (if any) in the assessment is made transparent to the public, as are SAP reports of external experts which support HED's apparent downplaying the risk.

27) There should be an investigation of the *adequacy* of HED's FQPA Safety Factor Committee's consideration of the FQPA imposed 10X safety factor, and the *legitimacy* of its recommendation to remove that 10X factor for malathion (August 6, 1998 FQPA committee report on malathion). Did this FQPA Safety Factor Committee take into consideration HED's External Peer Review by three outside expert toxicologists who addressed HIARC toxicologic issues? See February 28, 2000 memorandum of B. Dementi to OPP's John Carley.

28) It should be noted in the risk assessment that the claimed use of malathion in fruit fly (medfly) control programs is not a registered use, but the use has been granted by the Agency under Emergency Exemption (Section 18) for perhaps 25 years or more, amounting to a de facto registration. This use has never satisfied the rigors of the registration process. Furthermore, I am not aware that any malathion registrant has sought registration of malathion for this purpose. It appears to be a use granted to the Department of Agriculture and states, as requested.

29) There should be a review of the Agency's laboratory audit program to determine if malathion studies have been properly audited.

30) There should be an evaluation by the FIFRA Scientific Advisory Panel on all issues reviewed by HED's Hazard Identification Assessment Review Committee (HIARC), and other toxicology issues that have arisen since the demise of the HIARC. The one External Peer Review (Drs. Decker, Douerson and Hartung) does not satisfy in fulfilling this objective, and should not be deemed so.

31) The evidence for *low dose* [< 100 ppm (mouse); < 100/50 ppm (rat)] carcinogenic effects and *low dose* [< 5 mg/kg/d (rat)] offspring behavioral effects and cholinesterase inhibition need characterization. These low dose findings are uppermost issues among my concerns, particularly given that food tolerances for malathion is 8 ppm, not that far removed from the doses possibly eliciting carcinogenic effects, and given the varied reasons why people may be more vulnerable than rats to behavioral effects given varied life styles, medications taken,

stresses, behavioral problems, age, etc. when then exposed to cholinesterase inhibiting compounds.

I address this letter to you having done all I am able within the sphere wherein I practice toxicology. All of the background documentation in support of my conclusions summarized in this letter has already been generated and submitted to various committees and panels to whom I have responded in my work. Former OPP Director, Ms Marcia Mulkey, was generous to me in allowing my dissenting scientific assessments to be appended to various committee reports, where they now reside. I will be requesting that this very letter to you summarizing my views, to also be included as an addendum to the risk assessment document.

I trust that you and your staff will seriously consider what amounts to my petition for a more reliable, public health protective, risk assessment than that which is currently on the HED launch site.

Sincerely,

Brian Dementi, Ph.D., D.A.B.T.
Senior Toxicologist
Health Effects Division/OPP

5.0 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*]
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.
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.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Cattle, meat [4] (PRE-S)	4	Revoke	Contingent upon cancellation of direct animal treatment uses.
Chayote fruit	8	0.2	Translated cucumber data.
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*]
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.
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.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
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.
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*]
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.
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.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
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*]
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.
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.
Peppermint (PRE-H)	8	2	[*Peppermint*]
Peppers (PRE-H)	8	0.5	[*Pepper*]
Pineapples (PRE-H)	8	0.2	[*Pineapple*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
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.
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.
		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.

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
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
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*]
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)*]

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
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	
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	
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	

Commodity	Tolerance Listed Under 40 CFR §180.111	Reassessed Tolerance [2]	Comment *[Correct Commodity Definition]*
Wheat, hay	None	TBD	Field trial data are required for wheat hay.
Wheat, straw	None	50	
Tolerances Listed Under 40 CFR §185.3850			
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, horses, poultry, or sheep.