Re-evaluation Decision RVD2012-10

Malathion

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Re-evaluation Decision for Malathion

After a thorough re-evaluation of the insecticide malathion, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting continued registration of products containing malathion for sale and use in Canada.

An evaluation of available scientific information found that, under the revised conditions of use:

- Certain uses of malathion products have value in Canada and do not pose unacceptable risks to human health or the environment, that includes, commercial products applied in agricultural (such as food and non-food crops in greenhouse or fields,) and non-agricultural settings (such as human habitat and recreational areas), other than those noted below. As a condition of the continued registration for these malathion uses, new risk reduction measures are required. Additional data are also being requested.

- Some uses of malathion are required for phase-out because they are not supported by the technical registrant. These uses were not included in the risk assessment:

    - Aquatic non-food sites: mosquito breeding areas and standing water;
    - Greenhouse food crops: mushroom beds and houses (wettable powder and dust formulations and application method of painting on wooden surfaces);
    - Greenhouse non-food crops: carnation, chrysanthemum, geranium, rose, snap dragon and ornamental plants (wettable powder formulation and fogging application method);
    - Seed treatments: food, feed and non-food: seeds (field and garden);
    - Terrestrial feed crops: ground ULV for alfalfa;
    - Structural: bakeries, canneries, meat processing plants, barns, pig pens, outbuildings, dairies, dairy barns, dwelling foundations (indoor), farm buildings (indoor), food processing plants, poultry houses, shipping crates, flour and feed mills;
    - Human habitat and recreational areas: farm yards, pens, feedlots, pastures, stabling areas, manure piles, garbage areas and around buildings and undergrowth to control house fly, mosquitoes, stable fly; and small flying insects as a space spray, mist, fog, aerosol and ground ULV;
    - Municipal dumps, refuse areas, sewage lines;
    - Residential outdoors: yards; and
    - Direct application to livestock for food: beef and dairy cattle, goats (non-milking), poultry, sheep, swine.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. In 1999, Health Canada announced in Re-evaluation Note REV99-01, *Re-evaluation of Organophosphate Pesticides*, that 27 organophosphate active ingredients, including malathion, would be re-evaluated in Canada. The re-evaluation of malathion draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

In 2003, the PMRA published a proposed re-evaluation consultation document (PACR2003-10, *Re-evaluation of Malathion*) for malathion use as an adulticide in mosquito abatement programs, and followed with a document (REV2003-03, *Re-evaluation of Malathion: Assessment of Use in Mosquito Abatement Programs*) which described the mitigation measures to be implemented for malathion use as an adulticide. The required label changes for related end-use products, as described in REV2003-03, have been implemented.

In addition, the technical registrant of malathion in Canada, Cheminova Canada Inc., voluntarily discontinued a number of residential uses including structural (pet quarters, indoor uses); companion animals (pet treatment); turf (broadcast turf/lawn treatment); and residential outdoors (broadcast/turf lawn treatment). The changes to the related product labels have been completed.

The regulatory approach regarding the overall re-evaluation of malathion was presented in the consultation document[1] Proposed Re-evaluation Decision PRVD2010-18, *Malathion*. This Re-evaluation Decision[2] describes this stage of the PMRA's regulatory process concerning the re-evaluation of malathion and summarizes the Agency's decision and the reasons for it.

Comments received during the consultation process were taken into consideration. These comments, however, did not result in substantial changes to the proposed regulatory decision as described in PRVD2010-18. Appendix I summarizes comments received and provides the PMRA's response.

This decision is consistent with the proposed re-evaluation decision stated in PRVD2010-18. To comply with this decision, registrants of products containing malathion will be informed of the specific requirements affecting their product registrations.

1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[3] The Act also requires that products have value[4] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Regulatory Status in Organisation for Economic Cooperation and Development Countries

Based on the available information, malathion is authorised for use in the European Union.

In the United States, malathion is registered for use in agriculture for various uses including food and feed crops, homeowner outdoor uses, ornamental nursery stock, building perimeters, pasture and rangeland, as well as regional pest eradication programs. In 2006, the United States Environmental Protection Agency (USEPA) reviewed the safety and benefits of all uses of malathion and concluded that ecological and human health risks were not of concern. Under their registration review program, the USEPA published a workplan to update the risk assessments for malathion. A final registration review decision is expected in 2015.

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3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

4 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

What is Malathion?

Malathion is a group 1B Resistance Management Mode of Action (MoA) non-systemic, broad spectrum organophosphate insecticide and acaricide. It disrupts nervous system function by inhibiting the acetylcholinesterase enzyme. It is currently used to control a broad range of insect pests on a wide variety of sites including: aquatic non-food sites; empty food storage areas; greenhouse (food and non-food crops); human habitat and recreational areas; industrial oilseed and fibre crops; livestock for food; seed treatment; stored food and feed; structural sites; terrestrial feed and food crops; outdoor ornamentals; and residential outdoor sites.

It is applied using conventional ground and aerial application equipment by farmers, farm workers, professional applicators and the general public.

Health Considerations

Can Approved Uses of Malathion Affect Human Health?

Additional risk-reduction measures are required on malathion labels. Malathion is unlikely to affect your health when used according to the revised label directions.

Potential exposure to malathion may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when malathion products are used according to label directions.

The target for malathion is the nervous system including effects on neurobehavioural parameters and acetylcholinesterase, an enzyme necessary for normal functioning of the nervous system. Overexposure may produce a variety of symptoms in animals and humans including nausea, dizziness, sweating, salivation, runny nose and watery eyes. This may progress to muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps and diarrhea in more serious poisonings. Cholinesterase inhibition has been observed with oral, dermal and inhalation exposure. Young animals have been shown to be more sensitive to this effect of malathion.

Malathion was not found to be genotoxic or teratogenic. Based on the scientific evidence, malathion is unlikely to pose a carcinogenic risk for humans. Following administration to pregnant rabbits, an increase in resorptions (embryo-fetal loss) has been observed in the presence of maternal toxicity. Due to the nature of this endpoint and its potential implications on the health of the unborn child, extra protective measures were applied during the risk assessment to further reduce the allowable level of human exposure to malathion. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern

In its evaluation of risk from the exposure of malathion and its metabolite malaoxon, the PMRA has adopted protective and conservative estimates of residues to compensate for the high potency factor of malaoxon in food and water, and for data gaps. In particular, the PMRA has compensated for malaoxon residues that were, for the most part, below analytical detection.

The PMRA has also considered exposure arising from on-site consumption of treated produce at Pick-Your-Own operation.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

For malathion, acute dietary risk for children and infants was the highest and reached 101% of reference dose, but is considered below the level of concern due to the conservative assumptions. Chronic risk for children reached 66% of reference dose and is not of concern.

Dietary exposure from Pick-Your-Own operations was estimated by adding the acute exposure from all forms of fresh fruit, in this case apple and strawberry, to the chronic exposure. Calculated MOEs exceed the target MOE for all sub-populations, and are not of concern.

Overall, the PMRA has concluded that risk to health from dietary exposure is not of concern.

Risks in Residential and Other Non-Occupational Environments

Residential risks from the use of malathion on vegetable gardens, ornamentals, and in mosquito abatement programs are not of concern.

Malathion is registered for use on residential ornamental and vegetable gardens, on exterior wall surfaces, around foundations, under fences and shrubs, and around buildings. Malathion is also registered for use in mosquito abatement programs, where bystanders could potentially be exposed by the inhalation route or by being exposed to malathion residues on turf. Estimates of exposure reach the target Margin of Exposure (MOE) for adults and children for all application and most post-application exposure scenarios, and are therefore not of concern.

Residential risks from potential exposure to malaoxon on decks and playstructures are not of concern.

Malaoxon is a degradation product of malathion which forms on hard surfaces such as decks and playstructures. Estimates of exposure for children, adolescents, and adults using default assumptions and chemical-specific monitoring data reach the target MOE, and are therefore not of concern.

Aggregate risk from exposure incurred at "Pick-Your-Own" orchard or berry facilities is not of concern.

"Pick-Your-Own (PYO)" facilities are considered commercial farming operations that allow public access for harvesting in large-scale fields or orchards treated with commercially labelled malathion products. Exposure estimates that aggregate the dermal exposure incurred during harvest and the dietary exposure from consuming fresh fruit, reached the target MOE for orchard and berry crops, and are therefore not of concern.

Occupational Risks from Handling Malathion

Occupational (mixer/loader/applicator) risks are not of concern when products are used according to revised label directions.

Most occupational risks due to malathion are not of concern for agricultural scenarios. Based on the precautions and directions for use on current labels, risk estimates associated with certain mixing, loading and applying activities reach target MOEs, and are not of concern. For those uses that do not reach the targeted MOEs, mitigation measures such as additional personal protective equipment, engineering controls, or restrictions on amount handled per day are required to reduce potential exposure and protect worker's health.

Occupational postapplication risks are not of concern.

Postapplication occupational risk assessments consider exposures of workers entering treated sites in agriculture. Most occupational postapplication risks are not of concern if proposed protective measures are followed. When the proposed mitigation measures such as lengthened restricted-entry intervals (REIs) are considered, the risk estimates for postapplication workers meet the target MOE, and are not of concern.

Environmental Considerations

What Happens When Malathion is Introduced Into the Environment?

Malathion poses a potential risk to terrestrial and aquatic organisms, therefore additional risk reduction measures need to be observed.

When malathion is released into the environment some of it can be found in soil and surface water. Malathion is very soluble in water and does not adsorb strongly to soils and therefore may leach into groundwater and enter surface water in runoff. Water monitoring has revealed malathion residues in groundwater as well as surface water, albeit infrequently and at low concentrations.

Malathion breaks down into several transformation products through hydrolysis and biotransformation at rates that depend on environmental conditions. The major transformation products, identified in biotransformation studies (mono- and dicarboxylic acid of malathion, demethyl mono and di-carboxylic acid of malathion), are expected to be non-persistent in the environment. Malaoxon, the oxidation transformation product that is primarily responsible for the toxicity of malathion, is also expected to be non-persistent. Both malathion and malaoxon readily hydrolyse under alkaline and neutral conditions, and become increasingly stable under acidic conditions. In soil, malathion is not expected to phototransform but may photolyze in natural waters containing photosensitizing agents. Malathion is not expected to volatilize significantly and is demonstrated to have low potential for bioaccumulation in fish.

Malathion poses a risk to both terrestrial and aquatic organisms. Birds are at risk in and around the site of application due to the consumption of contaminated food items, and the risk cannot be mitigated. In order to minimize the potential exposure to aquatic organisms, strips of land between the agricultural field and the aquatic areas (buffer zones) will be left unsprayed. The width of these buffer zones will be specified on the product label.

Value Considerations

What is the Value of Malathion?

Malathion is registered for use on a broad spectrum of sites for the control of a wide variety of pests

In Canada, malathion is registered to control a wide range of pests including beetles, bugs, crickets, earwigs, flies, grasshoppers, lice, mites, moths, spiders, thrips and ticks on a broad spectrum of sites.

Malathion for the control of a wide variety of chewing pests

Malathion is a non-systemic insecticide and acaricide with contact, stomach, and respiratory action. Malathion is suited for control of a wide variety of chewing insects. Chewing insects, in general, are non-selective in their feeding behaviours as they typically ingest macerated whole-leaf tissue. Insecticides with stomach-poison activity are more effective in controlling insects with chewing mouthparts such as beetles, grasshoppers and moth larvae.

Malathion contributes to insecticide resistance management

Malathion, being a MoA group 1B insecticide, plays an important role in delaying resistance when used in rotation with insecticidal active ingredients from different MoA groups. In recent years, the registrations of several carbamate and organophosphate insecticides (MoA groups 1A and 1B, respectively), have been discontinued (for example, trichlorfon, phosalone, carbofuran, etc.) or their use patterns have been amended, limiting their use to specific sites or to specific application methods (for example, diazinon). This limits the availability of other active ingredients from MoA groups 1A and 1B to rotate with insecticides with differing modes of action.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Risk-reduction measures are required to address potential risks identified in this assessment (Appendix II). These measures, in addition to those already identified on existing malathion product labels, are designed to further protect human health and the environment. The following key risk-reduction measures are required.

Additional Key Risk-Reduction Measures

Human Health

To protect mixer/loader/applicators using commercial products:
- Additional personal protective equipment.
- Restrictions on amount of active handled per day.
- Packaging of all malathion wettable powder products in water soluble packaging.

To protect workers entering treated sites, restricted-entry intervals are to be implemented.

To protect homeowners using domestic products, specification that the higher application rate of 30 g a.i./L is to be used only for dwelling foundation applications.

Environment

- Additional advisory statements to protect non-target terrestrial and aquatic organisms and to reduce the potential for malathion residues in runoff to adjacent aquatic habitats
- Buffer zones for aquatic habitats
- A statement advising that the use of malathion may result in contamination of groundwater, particularly in areas where soils are permeable and/or the depth to the water table is shallow.

What Additional Scientific Information is being Requested?

Data are required as a condition of continued registration under section 12 of the *Pest Control Products Act*. The registrants of this active ingredient must provide these data (See Appendix III) or an acceptable scientific rationale to the PMRA within the timeline specified in the decision letter.

Other Information

The relevant test data on which the decision is based are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection regarding this decision on malathion within 60 days of the date of publication of this Re-evaluation Decision. For more information regarding the basis for objection (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

Appendix I Comments and Responses

The PMRA received written comments from stakeholders including the technical registrant, Cheminova Canada Inc., relating to the Proposed Re-evaluation Decision PRVD2010-18, *Malathion*.

1.0 Comments on the Re-Evaluation Process for Malathion

1.1 Comment on a proposal for harmonization of use patterns in North America

The Canadian technical registrant proposed that the use patterns in North America should be harmonized to the fullest extent possible because the registrations of products were supported based on the same data from the technical registrant.

PMRA Response
Required by the *Pest Control Product Act*, the purpose of re-evaluation program is to re-evaluate older pesticides on a regular basis to determine whether current uses of pesticides continue to be acceptable according to modern standards. As a result of re-evaluation, use patterns on current product labels either remain the same if the risks to human health and the environment are acceptable; or certain uses or all uses will be modified or phased out due to risk concerns.

Furthermore, there are differences in the product registration between the United States and Canada, including the examples below. These differences between jurisdictions likely account for some differences in use pattern regardless of the registrant's data set.

- data requirements, for example, efficacy data required in Canada, immunotoxicity data in the United States;
- science policies with respect to risk assessment; and
- policies unique to each country, for example, the federal Toxic Substance Management Policy in Canada, and the Endangered Species Act in the United States.

Following re-evaluation, registrants can apply for new uses registered in other jurisdictions, by submitting an application for amendment with supporting information.

1.2 Comment on the PMRA re-evaluation process

The technical registrant objected to the PMRA's re-evaluation approach for malathion, including the sources of data/information used for the risk assessments and data evaluation.

PMRA Response
The PMRA, in consultation with various stakeholders, published a policy (DIR2001-03, *PMRA Re-evaluation Program*) outlining approaches to be taken for the re-evaluation of pesticides. The re-evaluation of malathion, as one of the organophosphate insecticides, was to be carried out under Program 3. Available review documents from the USEPA or other suitable international review documents from OECD member regulatory agencies were used as part of the PMRA's risk assessments. Under this approach, the PMRA may require registrants to submit data in order to fill data gaps and to address areas of concern.

Following the same approach, the PMRA had already reviewed malathion as an adulticide in mosquito abatement programs. The registrant would have been aware of the re-evaluation process because the re-evaluation decision for mosquito use had gone through the similar consultation process.

2.0 Comments Pertaining to Chemistry

2.1 Comments on the physical and chemical properties of the technical grade active ingredient

The technical registrant, Cheminova, states that the PMRA cited data that were not from Good Laboratory Practices (GLP) studies provided by them and that the PMRA should only cite and use data provided by the technical registrant. Additional information on the product chemistry was provided with the comment.

PMRA Response
The PMRA used data provided by both Cheminova (the chemistry data used to support the registration of the technical class product) and published data with respect to the chemical and physical properties of malathion (the e-Pesticide Manual, CDS Tomlin, thirteenth edition, British Crop Protection Council, version 3.1, 2004-05,492). With the exception of the octanol/water partition coefficient (K_{ow}), the chemical and physical properties of malathion cited in the PRVD are consistent with the information previously provided by the technical registrant.

For the octanol/water partition coefficient (K_{ow}), the value from the e-Pesticide manual was reported in the PRVD because it is a published and internationally accepted source of data. The octanol/water partition coefficient reported in the PRVD (log K_{ow} = 2.75) and the one provided by Cheminova (K_{ow} = 2000; log K_{ow} = 3.30) are comparable and do not change the conclusion reached in the PRVD regarding the lipophilicity of the product.

In response to PRVD2010-18, the technical registrant provided additional information with respect to the ultraviolet (UV)/visible spectrum of malathion. The UV/visible spectrum study referenced in Cheminova's comment had not been provided to the PMRA previously. Nevertheless, the values cited by Cheminova are consistent with the information reported in the PRVD for the UV/visible spectrum (not expected to absorb at $\lambda > 300$ nm).

3.0 Comments Pertaining to the Health Risk Assessments

3.1 Toxicology

3.1.1 Comment on impurity profile

The technical registrant Cheminova suggested that studies with an unknown impurity profile or differing purity/impurity profile from that of the currently manufactured should not be used in risk assessment.

PMRA Response
Available data do not support the conclusion that Cheminova's manufacturing process is producing a malathion technical with impurities that differ from the previous registrants or from what was used to conduct various pivotal toxicology studies. A revisit of reference doses established for malathion with the impurity profile in mind indicates that the current health risk assessment remains accurate, provided that the registrant adheres to current specifications.

3.1.2 Comment on an acute oral toxicity study

The technical registrant contests the use of the LD_{50} of 1580 mg/kg bw (in both sexes) from an acute oral toxicity study in Wistar rats in PRVD2010-18, because the technical used in this assay (92.2% purity) was not representative of malathion technical currently produced.

PMRA Response
The PMRA concurs that the 92.2% purity was not representative of malathion technical that is currently produced. The registrant has provided a 2003 acute toxicity study in rats, with 96.0% purity and a LD_{50} of 2382 mg/kg bw for both sexes, which is accepted (PMRA 2025101). The low acute toxicity in this study is consistent with the other available data. PRVD2010-18 stated that malathion was of low acute toxicity and did not propose any hazard label statements other than those for irritation, so no additional changes are necessary.

3.1.3 Comment on endpoints

The registrant contests the endpoints selected for dermal exposure scenarios.

PMRA Response
In the short- and intermediate-term dermal risk assessment for adults (occupational and non-occupational), an oral NOAEL of 25 mg/kg bw/day from the developmental toxicity study in rabbits was selected by the PMRA. In this study, an increase in resorptions was observed at the LOAEL. While route-specific studies are generally preferred for risk assessment, it becomes necessary to utilize oral studies when the latter identify endpoints (for example, developmental or reproductive toxicity) that have not been addressed in the existing route-specific study. The database for malathion does not include developmental or reproductive toxicity studies conducted by the dermal route. Consistent with the PMRA's approach to risk assessment, the oral (gavage) rabbit developmental toxicity study was selected to address potential toxicity to the unborn child of pregnant women.

For the short-and intermediate-term dermal risk assessment for children, a 21-day dermal study in rabbits conducted in 2006 was selected in which a $BMDL_{20}$ of 107 mg/kg bw/day for erythrocyte cholinesterase (EChE) inhibition in adult animals was selected in conjunction with an additional 3-fold factor relating to data deficiencies in characterizing the susceptibility of the young to cholinesterase inhibition from the dermal route.

As discussed in Appendix XXIII of PRVD2010-18, the PMRA chose to use the benchmark dose results from the short-term rabbit dermal assay conducted in 2006. In the PRVD, the PMRA acknowledged that the 2006 assay in rabbits was conducted in order to provide a more accurate effect level for cholinesterase inhibition, as observed in a previous study conducted by the registrant in 1998. Due to the newer age of the study, increased robustness (including increased test group sizes, increased number of dose groups, etc.) and more conservative findings in the 2006 assay, the PMRA based its assessment on the BMD from the more recent study rather than a combined BMD from the two. Furthermore, the PMRA's reliance on the 2006 study, which utilized malathion representative of current production (i.e. 96% purity) versus that of the 1998 study (94% purity) is consistent with the registrant's position on using relevant studies, as outlined in their comments.

3.1.4 Comment on the benchmark dose calculations

The registrant contests the benchmark dose calculations for the dermal risk assessment and has indicated that they are unable to reproduce the calculations conducted by the PMRA.

PMRA Response

The following outlines the PMRA's approach to deriving the BMDL20 from the 2006 dermal toxicity study. The $BMDL_{20}$ of 107 mg/kg bw/day was derived from the EChE inhibition data of the 2006 dermal toxicity study in rabbits. The following four parameter model was fit to the bioassay data using EPA's DRUtils package in R:

$$f(dose) = A - A * [P + (1 - P) * e^{-(m \times dose)^g}],$$

where *A, P, m,* and *g* are parameters to be estimated. Since there was no empirical evidence of a high dose asymptote in the EChE inhibition data, the P parameter (related to the limiting high dose cholinesterase activity) was set to zero. DRUtils reparameterizes the model in terms of BMD, which is defined as the dose which causes a specified decrease (here 20%) in the mean response of the control group. Where possible, parameters were fixed across genders. Variances were allowed to vary by dose group. Final fitted parameters for this model are shown in the following table.

Parameter	Sex	Values
A	Males	2.15
	Females	2.00
g	Males	1.09
	Females	2.39
BMD_{20} ($BMDL_{20}$)	Both	140.7 (106.7)

3.1.5 Comment on the application of *Pest Control Products Act* factor

For the following reasons, the technical registrant disagrees with the application of a 3-fold *Pest Control Products Act* factor:

a) As a matter of policy, when clear NOAELs have been established.
b) Given that the study to which the factor is applied (i.e. rabbit developmental toxicity study) was conducted with lower purity and hence a potentially more toxic malathion than current specifications.
c) Since cholinesterase inhibition in the fetus was less than that of the dam suggesting that toxicity to the rat fetus is already mitigated by the natural biological processes and that by extension, the rabbit fetus should be considered protected by the biological processes of the dam.

PMRA Response
In June of 2006, the new *Pest Control Products Act* came into force and required that the PMRA apply an additional 10-fold margin of safety to account for pre- and post- natal toxicity and completeness of the data with respect to the exposure of and toxicity to infants and children. A considerable amount of stakeholder feedback was received, including some from the registrant of malathion and taken into consideration when developing Science Policy Note SPN2008-01 *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*. While the registrant has resubmitted these comments in response to the malathion risk assessment, the PMRA does not consider it prudent, nor practical to revisit the extensive process by which the SPN was created. Instead, the PMRA chooses to ensure that the application of uncertainty factors in pesticide assessments are handled in a manner that is consistent with the SPN and across assessments.

As discussed previously in the section outlining issues relating to impurities, both the registrant and the PMRA acknowledge the requirement of an acceptable rabbit developmental toxicity study to maintain registration. While the purity (92.4%) of malathion used to conduct the study was lower than that currently produced by the technical grade active ingredient (TGAI) registrants, an additional acceptable rabbit developmental toxicity study is not available. The impact of the lower purity cannot be characterized quantitatively and therefore has tempered the need for the *Pest Control Products Act* factor.

The PMRA disagrees that the fetus can be considered protected by the biological process of the dam for a variety of reasons:

1. Studies in the peer reviewed literature have indicated that for the organophosphates, fetal cholinesterase is not necessarily affected to a lesser degree than the dam, but rather fetal cholinesterase is able to recover more quickly (Lassiter et al., 1998; Meneguz et al., 1989). Therefore, measurements in the fetus may underestimate the true cholinesterase inhibition and prevent a meaningful comparison of relative toxicity between the fetus and dam. By extension, the PMRA does not agree with the registrant that the effects on the fetus are likely secondary to any effects on the dam.

2. Species vary in their susceptibility to toxicological effects from a chemical. In fact, the disparity between the susceptibility of species is the very reason why the requirement for a developmental toxicity study in a non-rodent species came into effect for many international organizations investigating the effects of various chemicals such as pharmaceuticals and pesticides. Comments on the relationship between cholinesterase inhibition in pregnant rabbits and their fetuses are speculative in the absence of any ChE data in these populations.

3. Notwithstanding the inferences the registrant puts forth on the basis of the rat cholinesterase data, there is no information to indicate that the regulated endpoint (i.e. resorptions in rabbit fetuses) is directly attributable to cholinesterase inhibition.

Resorptions and other forms of embryo-fetal mortality are considered serious effects. Although serious effects observed in the young may justify maintaining the full 10-fold *Pest Control Products Act* factor, concern may be attenuated when observed in the presence of maternal toxicity. The PMRA has revisited the *Pest Control Products Act* factor selected for the endpoint based upon the rabbit developmental toxicity study, namely the short- and intermediate-term dermal risk assessment for adults. The application of the *Pest Control Products Act* factor was consistent with SPN2008-01 and recent risk assessments conducted by the PMRA.

3.2 Comments on the Occupational and Residential Non-Dietary Exposure Assessment

3.2.1 Comment on the assumption of area treated per day

On pages 127 and 128 of the PRVD (terrestrial feed crops), the assumed daily area treated for ULV ground applications for cereal and pasture crops (1200 ha) is inappropriate. This value corresponds to approximately 3000 acres per day (i.e. the USEPA default value for ULV ground applications for mosquito control). For ground applications to cereal crops and pasture land, the appropriate default assumption is 360 ha/day, as PMRA has assumed for other ground applications by custom applicators (updated 2009 PMRA defaults). It is inappropriate to apply a value derived for ULV mosquito control application to ground sprayer applications because the methods of application are not the same. Mosquito control applications are sprayed as a fine mist into the air along city streets and air movement is expected to take the malathion to where the pests are. For ground applications to crops, the malathion is sprayed directly onto the crop foliage as the equipment passes over the field in carefully controlled rows. Thus, a rather large effective application area can be achieved with ULV applications for mosquito control, but such a large area is not feasible for applications to crop foliage. Furthermore, it is not reasonable to assume that an ULV ground spray application could treat 1200 hectares per day for grain crops when the PMRA assumption for aerial applications to agricultural crops is 400 hectares per day.

Similar comments apply to assumptions for aerial and groundboom applications to food crops (terrestrial food crops) on pages 129 and 130. PMRA's assumptions for daily area treated with ULV applications for mosquito control in residential areas on page 132 (Human habitat and recreation areas) are appropriate, which is the only instance in which the daily area treated value for ULV mosquito control applications has been used properly.

PMRA Response
The area treated per day value used for ground ULV treatment of agricultural crops was based on the default ULV values for mosquito control in both the PMRA and the USEPA assessments. It is acknowledged that the use of 1200 ha is a high-end estimate of the area treated per day for ground ULV treatment of field crops. However, in the absence of any other information for this particular use, it was used in the assessment as a conservative assumption. Regardless of whether it is assumed that 1200 ha or 360 ha are treated in one day, the mitigation measures outlined in the PRVD are required in order to reach the target margin of exposure for this scenario since the limiting factor is the amount handled per day. These mitigation measures include additional personal protective equipment (cotton coveralls over long pants, long sleeved shirts, and chemical-resistant gloves during mixing/loading, application, clean-up, and repair), and limiting the amount of active ingredient handled per day to 95 kg per person (approximately 70 ha at a rate of 1375 g a.i./ha and 150 ha at a rate of 653 g a.i./ha).

3.2.2 Comment on re-entry exposure in mushroom houses

The PMRA states that re-entry exposures in mushrooms houses were not addressed because dislodgeable foliar residue (DFR) data and transfer coefficients are lacking. However, in the 2006 human health risk assessment for malathion that was conducted in support of the registration eligibility document, the USEPA used a DFR study involving summer squash (MRID 454919-0216) to estimate the DFR on mushrooms. From the summer squash study, the USEPA estimated a day 0 residue of 3.95 µg/cm² at an application rate of 0.95 lb a.i./A and a dissipation rate constant of -0.58322 (corresponding to 44% dissipation per day). The USEPA assumed a transfer coefficient of 400 cm²/hr for all re-entry tasks in mushroom houses and concluded that the REI for mushrooms would be 12 hours.

The label application rate for malathion on mushrooms in Canada is 0.2 g a.i./m². This corresponds to approximately 1.78 lb a.i./A. Based on this application rate, the initial DFR on mushrooms is estimated to be: 3.95 µg/cm² x (1.78/0.95) = 7.4 µg/cm². For the assumed TC of 400 cm²/hr, the estimated exposure on the day of application is:

7.4 µg/cm² × 400 cm²/hr × 8 hr/day × 10% dermal absorption / 70 kg = 33.8 µg/kg/d

The MOE, based on the long-term endpoint of 3 mg/kg/d, is 89 on the day of application. With 44% residue dissipation per day from the summer squash study, the MOE on the first day following application is 160. Thus, the minimum REI for mushrooms based on the toxicity endpoints selected by the PMRA would be 1 day (24 hours).

PMRA Response
A postapplication exposure assessment was not conducted for mushroom houses due to a lack of data. There is limited information on the activities that occur in mushroom houses following application of malathion. Therefore, in order to complete a postapplication assessment, a detailed use description and data outlining postapplication exposure estimates for workers re-entering treated mushroom houses is required. It is unknown whether activities that occur in mushroom houses are similar to other agricultural crops and whether exposure estimates generated using transfer coefficients and DFR values is appropriate for this use scenario.

The DFR study involving summer squash is not considered to be an appropriate surrogate for mushrooms grown in mushroom houses. The summer squash study was conducted outdoors where residues would be exposed to various environmental factors, which is not applicable to an indoor setting. Furthermore, residues were present on the foliage of squash. As mushrooms have no foliage, the applicability of residues from foliage to mushrooms may not be appropriate. In addition, the transfer coefficient used in the US assessment was based on performing tasks in nursery crops. It is unknown whether the amount of treated crop that a worker contacts while performing activities in mushroom houses would be similar to nursery stock.

For these reasons, the PMRA is unable to take the same approach as the USEPA, and additional information is required to support this use scenario (DACO 5.2 - Use Description/Scenario, DACO 5.6/5.7/5.9 - Postapplication).

3.2.3 Comment on potential residential exposure to malaoxon on decks and play structures

The PMRA has requested information on potential malaoxon formation in airborne spray and on surfaces (hard surfaces and turf) over a 10-30 day period following ULV application of malathion. PMRA and EPA, citing a lack of definitive data on malaoxon formation, have conducted assessments using default assumptions regarding the extent of malaoxon formation and have concluded that potential residential exposures to malaoxon on decks and play grounds are not of concern. Similar approaches could be used to evaluate potential malaoxon exposures in airborne spray and on turf without the need to generate data.

PMRA Response
The postapplication exposure assessment for potential residential exposure to malaoxon on decks and play structures relied primarily on environmental monitoring data following application of malathion mixed with a protein bait. The intent of these studies was not to quantify transferable residues of malaoxon, thus there is a degree of uncertainty in the values used. Although it is expected that malaoxon formation would be greatest on anthropogenic surfaces, confirmatory data is required to confirm the assumptions used in the risk assessment and ensure that potential exposure to malaoxon has not been underestimated.

3.3 Comments on the Dietary Exposure and Risk Assessment

3.3.1 Comment on the conservative assumptions for malaoxon residues

In Section 3.3 of the PRVD, the PMRA states the following:

> "…called for conservative assumptions. To that end, both malathion and malaoxon residues and their limits of detection were combined by converting the malaoxon residues into malathion equivalents, where one equivalent is 24 times the malaoxon residues."

The technical registrant disagrees that conservative assumptions are required here about the magnitude of malaoxon residues. A full suite of plant and animal metabolism and food/feed magnitude of the residue studies were submitted to the USEPA and were also submitted to the PMRA with their comments. These studies demonstrate that residues of malaoxon in food/feed items are very low compared to residues of malathion, and the low occurrence of malaoxon residues has been confirmed in monitoring surveys conducted in the United States as part of USDA's Pesticide Data Program. As such, there is no need for the PMRA to make conservative assumptions.

PMRA Response

The PMRA conducted a refined dietary exposure assessment for residues of malathion and malaoxon in the diet. The assessment was primarily based on surveillance data, specifically, the Canadian Food Inspection Agency's National Chemical Residue Monitoring Program (CFIA, 2002-2007) and the United States Department of Agriculture Pesticide Data Program (PDP, 2004-2005). Specific and empirical processing factors, percent crop treated information, and Canadian production of food commodities and percentages of food commodities imported from other countries were also incorporated in the dietary assessment.

In terms of malaoxon residues, the PMRA agrees with the registrant that residues were low in both the surveillance programs and the submitted field trial studies. The actual detected residues of malaoxon in the surveillance programs were used in the dietary assessment. As per PMRA policy, when malaoxon residues were reported to be below the limit of detection (LOD), the residue was assumed to be half-LOD. (Please refer to PMRA Science Policy Note SPN2003-02, *Assigning Values to Nondetected / Nonquantified Pesticide Residues in Food*.) A toxicity adjustment factor of 24-fold was used to convert both detected and non-detected residues of malaoxon into exposure equivalents of malathion.

The use of half-LOD for non-detect residues of malaoxon could be considered a conservatism in the dietary exposure assessment. However, due to the uncertainty inherent in the analytical methodology of malaoxon and the fact that malaoxon is considered to be 24 times more toxic than the parent, the impact of the non-detect values needed to be considered.

The PMRA acknowledges receipt of the submitted field trial studies. These studies were generally assessed for residues of malaoxon which were very low. As noted above, these field trial data were not used in the dietary assessment, as the surveillance data were considered to be more representative of the national food supply and would allow for a more refined exposure assessment.

3.3.2 Comment on the assumption of full conversion of malathion to malaoxon

As stated in Section 3.4 of the PRVD, a major assumption made by the PMRA was to assume that all malathion was converted to malaoxon and that no malathion (before the conversion) or malaoxon (after the conversion) dissipated further in the water treatment system. However, malathion and malaoxon have substantial hydrolysis rates at high pHs, which are present in water softening systems. Thus, significant degradation is likely to occur in the treatment system. Except for a single very limited monitoring study, the PMRA does not state its basis for assuming that all malathion was converted to malaoxon. A more scientific approach would be to use the kinetic model for malathion to malaoxon conversion in Durik et al. (2009).[5]

PMRA Response
The following studies formed the basis of the assumption of complete conversion of malathion to malaoxon in drinking water treatment plants.

Bloomquist, J. D., J. M. Denis, J. M. Cowles, J. A. Hetrick, N. B. Birtchfield, and R. D. Jones. Pesticides in selected water-supply reservoirs and finished drinking water, 1999-2000: summary of results from a pilot monitoring program. US Geological Survey, USEPA, US Geological Survey, USEPA, 2001.

Birchfield, N. Drinking water exposure modeling evaluating the effect of varying crop scenarios, Application rate, Application interval, Spray drift levels, soilhalf-life. USEPA, Office of prevention, pesticides and toxic substances, USEPA, Office of prevention, pesticides and toxic substances, 2006.

Piper, S. Revised acute, probalistic and chronic dietary (food + drinking water) exposure and risk assessment for the malathion reregistrationeligibility decision. Assessment, USEPA, 2006, 120.

Rains, D. (2005). Final Report: Results of the chlorination of dimethoate and malathion and stability characterization of their oxygen analogs, omethoate and malaoxon, in chlorinated water. US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances USEPA. Reregistration eligibility decision (RED) for malathion. Decision, US Environmental Protection Agency, 2006, 195.

Further consideration of the fate of malathion and malaoxon in drinking water treatment facilities was not necessary, as no risks of concern were identified from drinking water exposure, and for the aggregate risk assessment. For future assessments, if refinements are needed, the fate in treatment facilities and the paper by Duirk et al (2009) may be considered along with other possible refinements.

[5] Duirk, Stephen E., Lisa M. Desetto, and Gary M. Davis. "Transformation of organophosphorus pesticides in the presence of aqueous chlorine: kinetics, pathways, and structure-activity relationships." Environmental Science and Technology, 2009: 2335-2340.

3.3.3 Comments Concerning Maximum Residue Limits for Malathion in Food

As indicated in Section 8.1.1.4 of the PRVD, the PMRA states that it intends to update Canadian maximum residue limits (MRLs) and to remove MRLs that are no longer supported. The technical registrant wants to preserve established MRLs on crops grown in Canada, as well as any required MRLs on crops imported into Canada. In support of this, they also submitted a large amount of metabolism and magnitude of the residue data conducted in the United States and in EU countries, and requested the PMRA to review. Furthermore, the registrant suggested that the PMRA establish an "all crop" tolerance to cover all other uses for which residue data are not available.

PMRA Response
The PMRA does not intend to revoke or amend the MRLs for malathion, as the dietary and aggregate risks from the use of malathion on food are not of concern, and the registrant is supporting all the registered food uses of malathion. Residues in all agricultural commodities, including those approved for treatment in Canada but without a specified MRL must not exceed 0.1 ppm, a general MRL specified in subsection B.15.002(1) of the *Food and Drugs Act*. Changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*.

As part of the assessment process, the PMRA must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL). As noted in the PRVD for malathion, the PMRA requires representative residue chemistry data in order to determine the acceptability of residues on food, and consequently, of any proposed or existing MRL. The dietary and aggregate risk assessment for malathion demonstrated that the residues which may remain on food or be found in drinking water do not pose a concern. As a result, there are no risk concerns with the currently established MRLs for malathion.

In terms of establishing additional MRLs for domestic uses or for trade purposes, it is recommended that the registrant or any other interested party make that request via submission to the PMRA.

Regarding review of the submitted studies, please see Section 3.6 of this document for a response.

3.4 Comments on use patterns

The technical registrant claims that certain uses, which are proposed for phase-out because they were not supported by the technical registrant, are in fact supported. These uses are: Human habitat and recreational areas: farm yards, pens, feedlots, pastures, stabling areas, manure piles, garbage areas and around buildings and undergrowth to control house fly, mosquitoes, stable fly, and small flying insects; as a space spray, mist, fog, aerosol and ground ULV.

PMRA Response
In previous correspondence with the registrant, it was indicated that the above-noted uses were no longer supported by the registrant. Therefore, they were not included in the risk assessment and in the PRVD. At this point in the evaluation process, it is not possible to conduct a risk assessment for these uses. As a result, these uses will be removed from the labels.

In order to determine the acceptability of these uses, additional occupational exposure is required (DACO 5.4/5.5 - Mixer/Loader/Applicator, DACO 5.6/5.7/5.9 - Postapplication). Should registrants decide to register these uses, they may submit an application for amendment, including the required data.

3.5 Comments on malaoxon formation on hard and anthropogenic surfaces

The technical registrant requests the PMRA to justify the following statements by providing the primary source(s) of this information. To their knowledge, no studies or data exist to support the statement that malaoxon forms on decks and play structures.

The PMRA states the following on page 27 of its PRVD:

"Malaoxon is a degradation product of malathion, which forms on hard, anthropogenic surfaces such as decks and play structures."

"Consistent with the USEPA RED for malathion (2006), it was assumed that malathion transforms to malaoxon at a peak of 10%. This was the amount of malathion that was transformed to malaoxon in monitoring studies on any media (turf, sand, soil, stainless steel plates, and plants), and thus is considered to be an upper end estimate."

PMRA Response
The reference for the first statement is the United States, Environmental Fate and Effects Division, Reregistration Eligibility Document (US EFED RED) Chapter for Malathion (1998), which includes the results from two California Department of Pesticide Registration (DPR) studies (Ando et al., 1994; Neal et al., 1993). The primary references for the second statement are the two California DPR studies. Please see below for the full citations.

In the USEPA environmental assessment, it was observed that under many circumstances malathion degrades rapidly, usually through microbial metabolism and hydrolysis. Based on this observation, it was expected that malaoxon production would be increased when malathion contacts dry, microbially inactive and low organic content surfaces common in residential environments such as concrete, asphalt, dry soil, roofing material, and glass.

In the two California studies, the amount of malaoxon formation in water, sand, soil, plant material (tomato, lettuce), turf, and stainless steel plates, was investigated. The assumption that malathion would transform to malaoxon at a peak of 10% was based on the results of Neal et al. (1993). This was the maximum amount of malaoxon that was formed as reported in the two California studies, and refers to the amount of malaoxon that formed in soil, 21 days following application. Although decks and play structures were not directly monitored, these surfaces are examples of anthropogenic surfaces where maximum malaoxon production is expected.

Full citations:

Ando, C., Gallavan, R., Wofford, P., Bradley, A., Kim, D., Lee, D., Troiano, J. 1996. Environmental monitoring results of the Mediterranean fruit fly eradication program, Riverside County 1994. California Environmental Protection Agency, Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch, Environmental Hazards Assessment Program. Report Number EH 95-2. September 1996.

United States Environmental Protection Agency. 1998a. Environmental Fate and Effects Division Reregistration Eligibility Document Chapter for Malathion. September, 1998.

Neal, R.H., McCool, P.M., Younglove, T. February 1993. Assessment of Malathion and Malaoxon Concentrations and Persistence in Water, Sand, Soil and Plant Matrices Under Controlled Exposure Conditions. EH 93-03. Environmental Hazards Assessment Program, State of California, Environmental Protection Agency, Department of Pesticide Regulation.

3.6 Comments concerning additional data requirements

In Section 8.2 of the PRVD, the PMRA has identified a number of data requirements for malathion, which are discussed below. The technical registrant claimed that a large amount of data has been submitted along with their comment, and the PMRA should review these data to determine if any outstanding data requirements remain.

3.6.1 Comment on the requirement of an immunotoxicity study

In PRVD 2010-18, the additional scientific data was requested under section 12 of the *Pest Control Product Act* as a requirement of maintaining registration.

PMRA Response
The registrant has recently submitted an acceptable guideline immunotoxicity study which did not demonstrate an effect on the immune system of mice (PMRA 2060503). The requirement for the submission of the immunotoxicity study has been fulfilled and the data from the study does not affect the current risk assessment.

3.6.2 Comment on the requirement of use description/scenario (DACO 5.2)

The technical registrant claimed that the required use descriptions are not unique to malathion – rather, they are common to many different pesticides. As such, PMRA should already have information from consultations with growers and other registrants concerning these uses. The registrant indicated that they are not supporting the structural uses of malathion as well as direct applications to livestock.

PMRA Response
The PMRA acknowledges that the registrant is no longer supporting the use of malathion for structural uses or direct applications to livestock. These uses will be removed from the labels. The PMRA acknowledges that the use of malathion on mushroom houses is still supported.

The PMRA requested this information as there is limited information on the use of malathion in the remaining supported uses. Regardless of whether this information is unique to malathion, detailed use description information is required to complete the occupational and postapplication exposure assessment. The PMRA acknowledges that postapplication activities following application to grain elevators, grain box cars, granary bins and stored grain may be minimal; however, use pattern information is required to confirm this assumption.

It is acknowledged that Ontario Ministry of Agriculture, Food and Rural Affairs is willing to provide qualitative information for the grape vine use, which will supplement the information provided by the registrant.

3.6.3 Comment on the requirement of data for postapplication in mushroom houses (DACO 5.6/5.7/5.9)

The registrant claimed that EPA has established a procedure for evaluating potential postapplication exposure in mushroom houses. PMRA should adopt the same approach used by EPA.

PMRA Response
This data was requested as there is no data to assess potential postapplication exposure to workers re-entering mushroom houses. For the reasons outlined in section 3.2.2 of this document, the PMRA is unable to take the same approach as the USEPA, and additional information is required to support this use scenario (DACO 5.2 - Use Description/Scenario, DACO 5.6/5.7/5.9 - Postapplication).

3.6.4 Comment on the requirement of data for postapplication in structural sites

The technical registrant indicates that the use of malathion in structural sites such as flour mills is no longer supported, but the application in stored grains is supported. However, for the stored grain use,'re-entry' is not possible to silos after they are filled with grain and "re-entry" data to support the stored grain use is not appropriate.

PMRA Response
The PMRA acknowledges that the technical registrant is no longer supporting the use of malathion in structural sites such as flour mills. Therefore, this data requirement is no longer required. Stored grains are not considered to be part of the structural use-site category (USC 20), but are part of the empty food storage use-site category (USC 3). Detailed use description information (DACO 5.2) as noted above is required for stored grains to confirm the assumption that postapplication activities associated with treated grains for storage are minimal.

3.6.5 Comment on the requirement of dislodgeable/transferable residues data (DACO 5.9)

The technical registrant is in the process of conducting a study on hard surfaces to evaluate the formation and dissipation of malaoxon on these surfaces. The study was conducted on concrete, plastic and steel. Data are also being derived for soil and sand. In addition, the registrant claims that there are no validated protocols for evaluating the formation and dissipation of metabolite/degradate in airborne spray. If the PMRA can provide a validated protocol for such a study, the feasibility of conducting such a study will be considered.

PMRA Response
The PMRA acknowledges that the technical registrant is conducting a study to evaluate the formation and dissipation of malaoxon on hard surfaces. This study was expected in August 2011 and PMRA has yet to receive the study. This study should be submitted to the PMRA upon completion.

To date, the PMRA does not have a validated protocol for evaluating the formation and dissipation of metabolite/degradate in airborne spray that it can provide at this time. However, some guidance is available in Regulatory Proposal PRO98-4, *Postapplication Exposure Monitoring Test Guidelines* (September 4, 1998). It should be noted that the onus is on the registrant to conduct all method development necessary to address data requirements.

3.6.6 Comment on the requirements of metabolism studies (DACO 6.2) and field trials on livestock (DACO 7.6)

The technical registrant indicated that it is not supporting the use of malathion as a direct treatment to the skin of livestock.

PMRA Response
The technical registrant has indicated in that they are not supporting the use of malathion as a direct treatment to the skin of livestock. Therefore, data under DACO 6.2 and 7.6, metabolism studies and field trials from this use are no longer required. All references to direct application of malathion to livestock must be removed from all labels.

3.6.7 Comment on the requirement of magnitude of residue data (DACO 7.4)

The technical registrant has submitted several studies on stored grains with their comments.

PMRA Response
The PMRA received magnitude of residue data for the use on stored grains. These data were required to validate assumptions made for stored grain applications in the risk assessment. These data have been assessed by the PMRA and have been found acceptable. A review of the studies on corn and wheat showed the studies were done according to acceptable practice and yielded reliable results. New processing factors were estimated from the study data and applied to the dietary risk assessment. Re-calculations of risk did not show any significant differences in overall risk, mostly because the major contributor of exposure remained with drinking water, which was not of concern. The PMRA concludes that the dietary exposure from malathion in stored grains is understood.

3.6.8 Comment on the requirement of residue data for many crop groups

With their comments, the technical registrant has submitted the available studies including validated analytical methods for measuring residues of malathion and malaoxon in plant and animal matrices. Furthermore, validated multi-residue enforcement methods are available to PMRA via EPA and other regulatory agencies.

PMRA Response
The PMRA acknowledges the receipt of the additional metabolism and residue chemistry data. The new additions have greatly reduced the list of original requirements. The following field trials are still outstanding and required as representatives of their respective crop groups (CG):

Plums/Prune (CG 12), Barley (CG 15), Beet and Radish (CG 1AB), Beet tops (CG 2) and celery (CG 4B).

The PMRA has also reviewed an acceptable HPLC with MS/MS detection analytical method and validation for determining malathion, malaoxon and desmethyl-malathion in rapeseed, plants and pods (523 FYF) submitted by the registrant as an appendix to PMRA #2032951. The method improves greatly on older gas chromatography approaches circa 1994 which were used for the majority of studies cited by the registrant. These were all similar to the EPA recognised method EN-CAS-22/94 and its interlaboratory validation (PMRA #2032854). The PMRA also recognises that existing multi-residue methods based on MS/MS detection are adequate for quantitation of malathion and malaoxon in surveillance programs.

The data gap cited above is not sufficient to affect the present overall conclusion as to risk, but will be required as part of future requests to expand or modify usage of malathion on these crop groups. This includes analytical methodologies and their validation, equivalent or better in performance than 523 FYF cited above.

4.0 Comments Pertaining to the Environmental Assessment

The PMRA's environmental risk assessment has been partially updated based on the consideration of comments received in response to PRVD2010-18. The comments specific to the environmental risk assessment are provided below as well as the PMRA's responses; changes made to the PMRA's original environmental risk assessment that are based on consideration of new data, are integrated into the responses where appropriate.

4.1 Comment on reliance of foreign reviews

The PMRA chose to rely on outdated reviews from other regulatory agencies rather than review the relevant and more recent data themselves. On page 2 of its 2009 environmental assessment, the PMRA states the following: "This assessment is partially based on the data from the USEPA Reregistration Eligibility Decision of Malathion (USEPA Office of Pesticide Programs, Environmental Fate and Effects Division, 7507C, October 2000; PMRA 1318328) and the UK Advisory Committee on Pesticides for Malathion (Issue No. 135, August 1995; PMRA 1318327). Data used from other sources are referenced." Both of the above documents cited by the PMRA are old, therefore cannot be considered to reflect the current thinking of these regulatory agencies.

PMRA Response
The PMRA has considered data and information from more recent reviews from foreign regulatory agencies. The statement on page 2 of the PMRA's 2009 environmental assessment (an internal PMRA document) is incorrect and has since been updated to reflect data and information from more recent foreign reviews considered in the PMRA's environmental risk assessment (i.e. USEPA 2006 Reregistration Eligibility Decision for Malathion; USDA/Forest Services 2008 – Malathion: Human Health and Ecological Risk Assessment – Final Report). These two foreign reviews are cited correctly in PRVD 2010-08. The PMRA has also reviewed the Environmental Fate and Effects Division's (EFED; USEPA) 2007 ecological risk assessment to evaluate the potential for the use of malathion to affect the California Red-legged Frog (a species is listed as threatened by the U.S. Fish and Wildlife Service). However, no new information relevant to the environmental re-evaluation was found. The PMRA is aware that a revised USEPA RED for malathion was available in May 2009; this updated review was not considered by the PMRA as it was unavailable at the time that the PMRA's environmental risk assessment was completed. The PMRA has since reviewed the EPA's revised 2009 RED and did not identify any new information that would significantly alter our risk conclusions.

4.2 Comment on reliance of outdated data

The PMRA did not consider all of technical registrant's guideline data conducted according to Good Laboratory Practices (GLP) since many of those studies were not included in the older reviews conducted by those other regulatory agencies.

PMRA Response
The PMRA announced its plan and strategy for the re-evaluation of organophosphate pesticides on June 29th, 1999. Since this time, the Agency has received only four environmentally related studies from the registrant; these studies were reviewed and considered for the risk assessment. Additional data was submitted by the registrant to the PMRA on February 28, 2011, well after completion of the environmental risk assessment and the publication of the Proposed Re-evaluation Decision document (PRVD2010-18). The registrant states that these additional studies have been previously submitted to the USEPA, however, none of the studies are cited in most recent reviews conducted by the USEPA (EPA RED 2006 and 2009). The PMRA has considered the additional data submitted on February 28, 2011 in the context of its 2009 environmental risk assessment; it was determined that the additional studies do not change the overall conclusions of the original assessment.

4.3 Comment on the reliability of information used in the risk assessment

The PMRA chose to rely upon literature articles instead of using our high quality guideline GLP data. We are greatly concerned that PMRA has not identified nor adopted a scientifically defensible approach for determining the scientific validity of data reported in the open literature, grey literature, or summarized in documents published by other regulatory bodies, or for determining the reliability of such data for use in regulatory decision making. Without a well-defined and transparent evaluation process, there is little confidence that PMRA's risk assessments and regulatory decisions are based upon the best scientific and commercial data available. We consider this to be another critical flaw in the regulatory process at PMRA.

PMRA Response
As indicated in Section 1.2 of this document, the PMRA considered all available data and information that has been reviewed by OECD member regulatory agencies for malathion. OECD member regulatory agencies evaluate the quality of toxicity data following standards and guidelines that are deemed acceptable to the PMRA. If the PMRA feels that a foreign review of an environmental fate or toxicity study is inaccurate or has reason to believe that the study may be unacceptable, the PMRA will conduct a review of the original study.

In addition to the reviews of other regulatory agencies and registrant submitted data, the PMRA considers studies available in the open literature (i.e. peer reviewed journal articles). Often these studies do not follow standard guidelines (for example, OECD, USEPA), however, the PMRA will accept such studies if they are determined to be scientifically sound based on expert opinion. This approach applies equally to open source literature as well as registrant submitted studies that are non-GLP or that do not conform to existing international guidelines.

4.4 Comment on reliance of some studies conducted with malathion from another source

The PMRA has not based its risk assessments on studies that are relevant to current technical malathion. The current technical registrant claims that consideration of some of the older toxicity studies for the risk assessment is inappropriate because these studies were conducted with technical malathion produced by a formly registered American source which contained higher levels of impurities, and some of which are shown to be more toxic than malathion (isomalathion

and malaoxon). Newer studies were submitted by the registrant on February 28, 2011, such as aquatic organism (fish and aquatic invertebrate) and avian toxicology studies, using a more recent technical malathion with lower levels of impurities. The registrant claims that these studies are the most representative of the current technical malathion and, therefore, should be considered for the risk assessments.

PMRA Response
As indicated in Section 3.1.1 of this document, available data do not support the claim that Cheminova's manufacturing process is producing a malathion technical with impurities levels that differ from previous registrants.

Although the information provided by the current technical registrant indicates that lower levels of isomalathion are present within the current malathion technical compared to that of previous sources, the data is based on single batch analysis. The degree to which such small differences in impurity levels between old and new technical of malathion have on birds, aquatic invertebrates and fish is unknown.

The toxicity endpoints for species derived from studies conducted with the most recent malathion technical are shown to be either slightly more toxic, slightly less toxic or the same (i.e. overlapping confidence intervals) to those conducted with an older technical. The toxicological differences between old and most recent technical, therefore, may simply be an artefact of experimental variability. In addition, direct comparisons between studies conducted with recent and old malathion technical may be unrealistic due to differences in methods used as well as the experimental exposure conditions. As stated in a previous response, the PMRA has considered the additional data submitted February 28, 2011, in the context of its 2009 risk environmental risk assessment; it was determined that the additional studies do not change the overall conclusions of the original assessment.

4.5 Comments regarding the use of newer guideline GLP laboratory studies, mesocosm study, an aquatic field study and surface water monitoring data to refine the aquatic risk assessment.

The registrant believes that a number of refinements are necessary concerning PMRA's aquatic risk assessment. The refinements include the consideration of newer guideline GLP laboratory studies conducted with malathion technical with a lower impurity profile than that of older studies, an aquatic field and mesocosm study, and the use of water monitoring data available for malathion as a means for evaluating the likelihood and magnitude of exposures to aquatic organisms.

PMRA Response
The issue of impurities in the malathion technical has been addressed in the previous response.

Water monitoring data for malathion was considered in the PMRA's 2009 aquatic risk assessment. Additional information has become available since the original 2009 aquatic risk assessment. (i.e. water monitoring data for malathion recently reported in Environment Canada's Pesticide Science Fund (PSF) surveillance program). The PMRA has determined that inclusion of the more recent PSF data does not change the overall conclusions of its aquatic risk assessment.

The aquatic field study (Kuhadja et al. 1996; PMRA# 2025132) was submitted to the PMRA for review on February 28, 2011. The purpose of the study was to assess adverse affects to fish and aquatic invertebrates from a worst-case scenario application of malathion to cotton fields adjacent to a small creek. The PMRA considers the results of the study to be of limited value for its aquatic risk assessment based on several uncertainties (for example, the use of other pesticides in the study area including other acetyl cholinesterase inhibiting insecticides; the suitability of control site was not adequately established; physical characteristics affecting dispersion such as stream width, water depth, maximum flow rate were not reported. In addition, the results of the study are considered to be representative of flowing systems only. In flowing systems, exposure to malathion is likely reduced due to quick dispersion and downstream dilution. The results of the study, therefore, are unlikely to be representative of more static systems (for example, ponds, wetlands, lakes), aquatic environments where there is relatively little water exchange.

The results of the registrant sponsored mesocosm study (Ebke 2002 – PMRA 1326062) confirm laboratory results, that cladocerans are the most sensitive aquatic invertebrate species to malathion exposure. However, uncertainties within the mesocosm study, limit the interpretation of the study: 1) the statistical results reported cannot be confirmed or reproduced as raw data were not provided; and 2) the results are representative of alkaline aquatic systems. Malathion is shown to hydrolyse very rapidly under alkaline aquatic conditions relative to neutral or acidic conditions. The PMRA is unaware of any data that demonstrates that the rate of biotransformation of malathion in neutral or acidic freshwater environments is as fast as under alkaline conditions. As such, there is uncertainty as to whether the results of the mesocosm study are relevant to other freshwater environments in the neutral or acidic pH range, which exist in many locations in Canada.

Upon re-examination of the malathion concentration data measured in the mesocosms as well as the aerobic aquatic half-lives for malathion from aquatic biotransformation studies, the PMRA has come to the following conclusions:

1) The original aquatic risk assessment included an overly conservative aerobic water half-life of 19 days derived from an open literature study; this value should have been excluded because 18 pesticides in addition to malathion were included in a single experiment. The risk assessment has since been updated using the laboratory aerobic aquatic biotransformation half-lives. As these studies were conducted under alkaline conditions, the pH-adjusted hydrolysis rate was used to correct the DT_{50}s to pH 7; estimated environmental concentrations (EECs) for aquatic habitats used in the updated risk assessment were based on a DT_{50} of 2.76 days (the 80th percentile of whole system DT_{50}s from aerobic aquatic biotransformation studies).

2) The highest initial mesocosm exposure concentration (30 ug malathion/L nominal) is not representative of the highest estimated exposure concentration based on the Canadian use pattern (for example,an EEC of 365 ug/L is expected for the highest single airblast application rate for apples, 3952.5 g a.i./ha sprayed at a distance of 1m to a 1 ha pond of 80cm depth). The results of a similar published mesocosm study (Relyea and Diecks 2008), however, indicate that the recovery period of cladocera after exposure to a single malathion application is similar over a broad concentration exposure range (i.e. recovery occurred between 20 and 43 days after exposure to 50 and 250 ug/L malathion compared to 28 days at 10 and 30 ug/L in Ebke 2002). Collectively, the data shows that the potential for recovery is independent of the exposure concentration from a single application of malathion.

Since the Canadian use pattern includes multiple applications, the PMRA believes that consideration should be given to the potential risk to aquatic ecosystems from multiple applications. The mesocosm study reports an NOEC of 5 ug/L based on effects to the Cladoceran population at the highest test concentrations (10 and 30 ug/L); the community level NOAEC was 30 ug/L based on complete population recovery. The PMRA has refined its aquatic risk assessment using the NOEC = 5.0 ug/L. The PMRA feels that this endpoint is more appropriate for use in the risk assessment than the community level NOAEC (30 ug/L) as the recovery from multiple applications is unknown.

4.6 Comments on the feasibility of the proposed buffer zones for aerial applications

The technical registrant believes that the buffer zones proposed by the PMRA for aerial applications are not supported by legitimate concerns about risks to human health or the environment, and would lead to a de-facto ban on aerial applications of malathion in Canada. The registrant proposes that the same label restrictions imposed by EPA in the recent RED be adopted in Canada. They also believe these buffer zones imposed by EPA are reasonable and sufficient for protecting the integrity of aquatic communities.

PMRA Response
The PMRA uses different models for estimating spray drift buffer zones than those used by the USEPA. Furthermore, the PMRA does not necessarily have the same science policy with respect to endpoint selection, input parameters, and environmental protection goals as that of the USEPA. These differences between jurisdictions likely account for some of the differences in the required mitigation measures.

As stated in a previous response, the PMRA refined its aquatic risk assessment using the NOEC from the registrant sponsored mesocosm study (NOEC = 5.0 ug/L based on the highest treatment level with no effects to the cladoceran population). The spray drift buffer zones for the protection of aquatic habitats have been updated to reflect this new endpoint; the revised buffer zone related label statements for malathion agricultural product labels are shown in Appendix II.

4.7 Comment pertaining to the PMRA's bird and mammal risk assessment

The technical registrant has submitted residue data for a wide variety of plant tissues, insects and other arthropods; the data consists of malathion-specific residue data as well as pesticide (non-specific) residue data. The registrant has requested that this data be used in the PMRA's bird and mammal risk assessment to replace the non-chemical exposure estimates for dietary items relevant to birds and mammals that the PMRA obtains using the nomogram by Hoerger and Kenaga (1972) as modified according to Fletcher er al. (1994).

PMRA Response
The use of the nomogram developed from the data of Hoerger and Kenaga (1972) as well as Kenaga (1973) and modified according to Fletcher et al. (1994) is standard practice for the PMRA's avian and mammalian risk assessments in the absence of reliable pesticide-specific residue data for dietary items relevant to birds and mammals. In the PMRA's 2008 ecological risk assessment for malathion, risks were identified to birds feeding on certain food items contaminated with malathion. The PMRA has considered the submitted malathion residue data to update the bird risk assessment. Although the results of the updated assessment indicate that malathion may pose a lower risk than that was originally determined using the nomogram, risks to birds were still identified. Given that a risk to mammals was not identified in the PMRA's 2009 ecological risk assessment of malathion, the mammalian risk assessment was not updated using the submitted residue data.

5.0 Comments Pertaining to the Value Assessment

5.1 Comment on use patterns

The technical registrant had the following comments regarding the supported uses and the unsupported uses listed in PRVD2010-18 which are proposed for phase out and supported uses:

5.1.1 The technical registrant wishes to clarify that they are supporting the use of malathion in all areas needed to effectively control adult mosquitoes, biting flies, midges, as well as filth flies that are of importance for protecting human health and the health of livestock. This includes:

a. The use of malathion in human habitat and recreational areas;
b. In residential outdoor settings. (In residential outdoor settings applications may be made to ornamental shrubs, flowers, and trees and to home vegetable gardens.)
c. In municipal dumps, refuse areas and sewage lines;

The technical registrant therefore requested that these uses not be excluded from PMRA's evaluation.

5.1.2 The technical registrant is not supporting the use of malathion as a direct application to livestock.

5.1.3 The technical registrant is no longer supporting the use of malathion in or on structural sites including flour mills and feed mills.

PMRA Response

5.1.1 a) Concerning malathion use for the control of mosquitoes and flies in human habitat and recreational areas

In 2003, the PMRA published a re-evaluation consultation document (PACR2003-10) for malathion use as an adulticide in mosquito abatement programs. The PMRA determined that large-scale ultra low volume applications of malathion in residential areas for control of adult mosquitoes does not pose an unacceptable risk to bystanders and operators. The re-evaluation decision note, REV2003-03, describes the mitigation measures implemented for malathion use as an adulticide in residential areas. The PMRA subsequently published another re-evaluation consultation document (PRVD2010-18) for malathion use on the remaining food and non-food uses.

Prior to the publication of PRVD2010-18, in correspondence between the technical registrant and the PMRA, the technical registrant stated that they do not support the use of malathion as a space spray, mist, fog or aerosol, and ULV cold aerosol applicators in farm yards, pens, feedlots, pastures, stabling areas, manure piles, garbage areas and around buildings and undergrowth (excluding buildings and undergrowth in residential areas) to control house flies, mosquitoes, stable flies and small flying insects. Except for ULV ground application to pastures, these sites were not included in the risk assessment; therefore, these uses must be removed from all

Commercial Class end-use product labels. The registrant may apply to reregister these uses through the provision of data (DACO 5.4/5.5 - Mixer/Loader/Applicator, DACO 5.6/5.7/5.9 - Postapplication) to support a risk assessment under a new submission. ULV ground application of malathion on pastures was assessed for risk because the registrant supported the use of malathion on pastures to control grasshoppers, therefore, the use of malathion on pastures to control house flies, mosquitoes, and stable flies using ULV ground application will also be retained on the Commercial Class end-use product labels. The PMRA acknowledges that in Canada, there are a limited number of active ingredients registered to control pests on farm yards, pens, feedlots and stabling areas.

In response to PRVD2010-18 the registrant stated that they do not support the use of malathion in or on structural sites. The site identified on the labels as "outdoor areas (in and around buildings housing domestic animals, around processing plants and around other buildings)" to control house flies and stable flies will be removed from all Commercial Class end-use product labels because it is a structural application.

5.1.1 b) Concerning malathion use for the control of mosquitoes and flies in residential outdoor settings (i.e. yards)

The PMRA determined in REV2003-03 that large-scale adulticide applications of malathion Commercial Class end-use products using ultra low volume sprays in residential areas for control of mosquitoes does not pose an unacceptable risk to bystanders and operators. However, for all other label uses of malathion for control of adult mosquitoes in residential areas, the calculated margins of exposure for bystanders were unacceptable and these uses were no longer permitted. Therefore, the use of Domestic Class end-use product containing malathion to control mosquitoes on house foundations, exterior wall surfaces, under fences and on ornamentals, must be removed from Canadian labels. As stated above, the registrant does not support broadcast application of malathion on turf which the PMRA considers to include yards. As a result, broadcast application to turf to control mosquitoes should no longer be listed on Canadian labels.

5.1.1 c) Concerning malathion use for the control of mosquitoes and flies in municipal dumps, refuse areas and sewage lines

The only pests registered on the Canadian malathion labels for municipal dumps, refuse areas and sewage lines are cockroaches. Adult mosquitoes, biting flies, midges and filth flies are not listed as pests on the Canadian labels for these sites. Since the technical registrant does not support the use of malathion on municipal dumps, refuse areas and sewage lines to control cockroaches, these label claims will be removed from all Commercial Class end-use product labels.

5.1.2 Concerning support for direct application to livestock

Since the technical registrant no longer supports the use of malathion on livestock, this use will be removed from all Commercial Class end-use product labels. The PMRA acknowledges that in Canada, there are a limited number of active ingredients registered to control pests on livestock.

5.1.3 Concerning support for uses of malathion in structural sites

Being as the technical registrant no longer supports the use of malathion in or on structural sites including flour and feed mills, all structural uses must be removed from all Commercial Class end-use product labels. The PMRA acknowledges that in Canada, there are a limited number of active ingredients registered to control stored product pests in flour and feed mills.

5.2 Comment on outdoor residential areas

A respondent expressed concern over the loss of malathion use in outdoor residential areas, leaving products that will create more secondary pest problems (i.e. mites) and reducing resistance management options.

PMRA Response
The PMRA can confirm that malathion continues to be registered for outdoor residential use. Domestic Class end-use products containing malathion continue to be registered in Canada.

5.3 Comment on efficacy data

The technical registrant Cheminova, requested that the PMRA accept the American use patterns without requiring new efficacy data to show that coarse droplet size sprays of malathion still result in adequate product performance because the American use patterns were established based on extensive surveys of commodity groups, extension agents and individual growers that were conducted by United States Environmental Protection Agency (USEPA), United States Department of Agriculture (USDA) and Cheminova during the reregistration process in May 2009. Since these use patterns generally have been accepted by these groups, the use patterns should be considered to meet the needs of agriculture to control the important insect pests for each labelled crop.

PMRA response
The PMRA has recalculated the aerial buffer zones for malathion based on a new endpoint and medium droplet size sprays instead of the proposed coarse droplet size sprays. The PMRA requires excerpts from the surveys or copies of the surveys in lieu of efficacy data that demonstrate that medium droplet size will result in acceptable product performance.

Appendix II Revised Label Amendments for Products Containing Malathion

NOTE: The following information is divided according to product type. Please read each section carefully and make appropriate changes to your product labels.

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements given below.

A. Technical Class Products Containing Malathion

The following warning statement should appear on the **Primary** panel of the technical product labels:

Caution: Eye Irritant.

B. Commercial Class Products Containing Malathion

TOXICOLOGICAL INFORMATION

Malathion is an organophosphate that is a cholinesterase inhibitor. Typical symptoms of overexposure to cholinesterase inhibitors include headache, nausea, dizziness, sweating, salivation, runny nose and eyes. This may progress to muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps and diarrhea in more serious poisonings. A life-threatening poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression with a secondary cardiovascular component. Treat symptomatically. If exposed, plasma and red blood cell cholinesterase tests may indicate degree of exposure (baseline data are useful). Atropine, only by injection, is the preferable antidote. Oximes, such as pralidoxime chloride, may be therapeutic if used early; however, use only in conjunction with atropine. In cases of severe acute poisoning, use antidotes immediately after establishing an open airway and respiration. With oral exposure, the decision of whether to induce vomiting or not should be made by an attending physician.

STORAGE
Do not contaminate water, food, or feed by storage or disposal.

Keep in original container during storage. Isomalathion, a toxic metabolite of malathion, forms when malathion product is stored at elevated temperatures or for extended periods of time. Malathion product must be stored in a cool (<20-23°C) dry, well ventilated place away from seed, fertilizer or other pesticides and for no longer than one year.

WETTABLE POWDER IN WATER SOLUBLE PACKAGING (WSP):

The following label instructions should be added to clearly indicate directions for water soluble packaging:

PRIMARY PANEL:

NET CONTENTS (Example): 1.5 kg (20 × 75 g water soluble bag)

DIRECTIONS FOR USE
Product X MAL is a dry powder sealed within a water soluble bag. Drop intact water soluble bag directly into spray tank. The water soluble bag and pesticide will dissolve readily in water. Do not allow the water soluble bag to become wet prior to use. Do not handle individual water soluble bag with wet hands or wet gloves as this may cause breakage. Do not open or puncture water soluble bag for any reason. Do not use opened or punctured water soluble bag for any reason. If broken water soluble bags are found when container is opened, avoid contact with, and inhalation of the product. Wear chemical resistant coveralls, chemical resistant gloves and a respirator to dispose of broken water soluble bags according to DISPOSAL section.

STORAGE
Do not remove water soluble bag from container except for immediate use. Keep container closed when not in use.

USE PRECAUTIONS
There may be potential for exposure to bystanders from drift following pesticide application to agricultural areas. In the interest of promoting best management practices and to minimize human exposure from spray drift or from spray residues resulting from drift, the following label statement is required:

Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

PERSONAL PROTECTIVE EQUIPMENT

For all product labels, the following statement is required to mitigate the risk of exposure to malathion:

Wear long pants, long sleeved shirts, and chemical-resistant gloves during mixing/loading, application, clean-up and repair. Chemical-resistant gloves are not required while operating groundboom sprayers.

For product labels with stored grain uses (wheat, oats, corn, rice, rye, and barley), the following statements are required:

Dusts: Limit the amount of active ingredient handled per day to 100 kg per person (approx. 6650 metric tons at a rate of 15 g a.i./ton).

Liquids (Emulsifiable Concentrates): Limit the amount of active ingredient handled per day to 865 kg per person (approx. 28,800 metric tons at a rate of 30 g a.i./ton)

For all ULV products used for agricultural crops (food and feed crops) and wild host plants in non-agricultural land, the following is required:

For ULV Ground Applications:

Limit the amount of active ingredient handled per day to 95 kg per person (approx. 70 ha at a rate of 1375 g a.i./ha, and 150 ha at a rate of 653 g a.i./ha).

Wear cotton coveralls over long pants, long sleeved shirts, and chemical-resistant gloves during mixing/loading, application, clean-up and repair.

For ULV Aerial Applications:

Limit the amount of active ingredient handled per day to 1125 kg per person (approx. 820 ha at a rate of 1375 g a.i./ha, and 1700 ha at a rate of 653 g a.i./ha).

Wear cotton coveralls over long pants, long sleeved shirts, and chemical-resistant gloves during mixing/loading, clean-up and repair.

For product labels containing uses for dwelling foundations, the following statements are required:

> Handwand Equipment:
> Limit the amount of active ingredient handled per day to 6 kg per person (approx. 190 L at a rate of 32.5 g a.i./L).
>
> Wear chemical-resistant coveralls over long pants, long sleeved shirts, chemical-resistant gloves, and chemical-resistant footwear during mixing/loading, application, clean-up and repair.

For all commercial class labels, the following statement must be added:

> Outdoor use only in residential areas. Residential areas are defined as any use site where bystanders including children could be exposed during or after application. This includes homes, schools, public buildings or any other areas where the general public including children could be exposed.
>
> For product labels containing uses for garden areas, outside foundations and yards, the following is required:
>
> Treatment of outdoor structural foundations only, and the 1 m wide path surrounding the foundation.
>
> References to gardens and yards must be removed from all labels.

DIRECTION FOR USE

The following uses must be removed from all current commercial end-use product labels:

- Aquatic non-food sites: mosquito breeding areas and standing water;
- Greenhouse food crops: mushroom beds and houses (wettable powder and dust formulations and application method of painting on wooden surfaces);
- Greenhouse non-food crops: carnation, chrysanthemum, geranium, rose, snap dragon and ornamental plants (wettable powder formulation and fogging application method);
- Seed treatments: food, feed and non-food: seeds (field and garden);
- Terrestrial feed crops: ground ULV for alfalfa;
- Structural: bakeries, canneries, meat processing plants, barns, pig pens, outbuildings, dairies, dairy barns, dwelling foundations (indoor), farm buildings (indoor), food processing plants, poultry houses, shipping crates, flour and feed mills;
- Human habitat and recreational areas: farm yards, pens, feedlots, pastures, stabling areas, manure piles, garbage areas and around buildings and undergrowth to control house fly, mosquitoes, stable fly, and small flying insects as a space spray, mist, fog, aerosol and ground ULV;
- Municipal dumps, refuse areas, sewage lines;
- Residential outdoors: yards; and

- Direct application to livestock for food: beef and dairy cattle, goats (non-milking), poultry, sheep, swine.

Number of Applications

Based on information available for the post-application assessment, all labels must be changed to limit the maximum number of applications and provide minimum number of days between applications.

Maximum Number of Applications per Year and Minimum Application Intervals

Crop		
	Maximum Number of Applications per Year	**Minimum Interval (days)**
cereal crops (barley, oats, wheat, grasses or legumes grown for hay), wild host plants in non-agricultural land, pasture and rangeland, potato, beets (table), turnips, carrots, horseradish, parsnip, sugar beets, salsify, radish, rutabaga, onions, garlic, leek, shallot, lettuce, spinach, celery, collard, kale, parsley, Swiss chard, endive, kohlrabi, watercress, dandelion, broccoli, Brussel sprouts, cabbage, cauliflower, cucumber, melon, pumpkin, squash, peach, plum, prune plum, cherry, barley, canola (rapeseed, rape), oats, wheat, rye, wild rice (cultivated), mustard, flax, asparagus, grapes, tobacco, cranberries	1	N/A
greenhouse lettuce, raspberry, currant, gooseberry	2	10
greenhouse ornamentals, outdoor ornamentals	4	10
beans, lentils, peas, blackberry, boysenberry, dewberry, strawberry, loganberry	2	7
eggplant, pepper, tomato	4	7
apples, apricots, pears	2	10
blueberry	3	4
corn (grain, forage)	4	3
alfalfa (2 applications per cut to max 4 per year), clover, sweet clover, canary grass (for seed)	2	14

Restricted-entry Intervals

The restricted-entry intervals listed below must be added to the appropriate labels.

Recommended Restricted-entry Intervals

Activity	Proposed REI (days)
Greenhouse lettuce, cereal crops (barley, oats, wheat, grasses or legumes grown for hay), pasture and rangeland, potato, sugar beets, turnip top (greens), salsify, radish, rutabaga, onions, garlic, leek, shallot, eggplant, pepper, tomato, blackberry, boysenberry, dewberry, strawberry, loganberry, currant, gooseberry, barley, canola (rapeseed, rape), oats, wheat, rye, wild rice (cultivated), corn (grain, forage), alfalfa, clover, sweet clover, canary grass (for seed), mustard, flax, asparagus, tobacco, cranberries, wild host plants in non-agricultural land	
All activities	12 hrs
Beets, turnips, carrots, horseradish, parsnip, lettuce, spinach, celery, collard, kale, parsley, Swiss chard, endive, kohlrabi, watercress, dandelion, beans, lentils, peas, cucumber, melon, pumpkin, squash, raspberry	
All activities	1
Greenhouse ornamentals, broccoli, Brussel sprouts, cabbage, cauliflower, blueberries	
All activities	2
Outdoor ornamentals	
All activities	3
Apples, apricots, pears	
Hand thinning	3
Hand harvest, hand line irrigation	2
All other activities	12 hrs
Peach, plum, prune plum, cherry	
Hand thinning	3
All other activities	1
Grapes	
Girdling, cane turning	5
Hand harvest, training, tying, leaf pulling, hand pruning, thinning	4
All other activities	12 hrs

For all non-ULV labels:

ENVIRONMENTAL HAZARDS

TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.

TOXIC to birds.

TOXIC to bees exposed to direct treatment, drift, or residues on flowering crops or weeds. **DO NOT** apply this product to flowering crops or weeds if bees are visiting the treatment area. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site.

TOXIC to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.

To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (for example, sandy soil) and/or the depth to the water table is shallow.

DIRECTIONS FOR USE

As this product is not registered for the control of pests in aquatic systems, **DO NOT** use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 10 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop	Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Cereal crops grown for hay (barley, oats, wheat), canary grass, mustard, sugar beet, currant, gooseberry	1	1	4	2
	Mustard (condiment type only), flax, canola, tobacco, tomato, onion, pea, potato, pumpkin, sweet clover, clover, cauliflower, collards, cranberry, dandelion, endives, garlic, horseradish, kohlrabi, leek, melon, parsley, salsify, shallot, Swiss chard, watercress, pasture and rangeland, cucumber, eggplant, kale, lettuce, asparagus, bean, beet, broccoli, Brussel sprout, cabbage, carrot, radish, squash, turnip, alfalfa, barley, rye, wheat, pepper, rutabaga, lentil, wild rice	2	1	5	3
	Celery, spinach, blueberry	3	1	5	3
	Corn, strawberries, blackberry, boysenberry, dewberry, loganberry	3	1	10	4
	Raspberry	4	2	10	5

Method of application	Crop		Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Airblast	Currant, gooseberry	Early growth stage	20	5	30	20
		Late growth stage	10	3	20	15
	Blueberry	Early growth stage	25	15	40	30
		Late growth stage	20	5	30	20
	Blackberry, boysenberry, dewberry, loganberry, grape	Early growth stage	30	20	45	35
		Late growth stage	20	10	35	25
	Raspberry, prune plum	Early growth stage	35	20	45	35
		Late growth stage	25	15	35	25
	Apples, apricots, cherry, peach, plum, pear, crabapples	Early growth stage	35	25	50	40
		Late growth stage	30	15	40	30

Method of application	Crop		Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Aerial	Canary grass	Fixed wing	15	4	85	20
		Rotary wing	10	1	50	15
	Cereal crops for hay (barley, oats, wheat), mustard, flax, canola	Fixed wing	15	5	125	30
		Rotary wing	15	3	65	20
	Lentil	Fixed wing	20	5	150	35
		Rotary wing	15	5	75	25
	Wild rice	Fixed wing	25	5	150	45
		Rotary wing	20	5	75	30
	Sweet clover	Fixed wing	30	10	150	50
		Rotary wing	20	5	80	30
	Alfalfa, barley, oats, rye, wheat	Fixed wing	45	10	175	70
		Rotary wing	25	10	95	40

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The following statement is currently on malathion agricultural product labels with wild rice use (PCP 4709 and 4590) under DIRECTIONS FOR USE:

> "For control in non-fishbearing waters such as wild rice paddies".

This statement should be removed and replaced with the following statement:

> “For control in non-fishbearing waters such as cultivated or paddy grown wild rice, that are confined to the property of the user and where there is no outflow beyond the property limits".

For product labels with greenhouse and mushroom house uses:

DIRECTIONS FOR USE
DO NOT allow effluent or runoff from greenhouses or mushroom houses containing this product to enter lakes, streams, ponds or other waters.

For all ULV labels:

ENVIRONMENTAL HAZARDS
TOXIC to bees exposed to direct treatment, drift, or residues on flowering crops or weeds.

DO NOT apply this product to flowering crops or weeds if bees are visiting the treatment area. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site.

TOXIC to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.

DIRECTIONS FOR USE
DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty.

Aerial application: **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application.

C. Domestic Class Products Containing Malathion

TOXICOLOGICAL INFORMATION
This product contains a pesticide that is a cholinesterase inhibitor (anti-cholinesterase compound). Symptoms of human poisoning may include headache, weakness, sweating, blurred vision, nausea and diarrhea. Obtain medical attention or call a poison centre at once. Atropine is antidotal."

STORAGE
Do not contaminate water, food, or feed by storage or disposal. Keep in original container during storage. Isomalathion, a toxic metabolite of malathion forms when malathion product is stored at elevated temperatures or for extended periods of time. Malathion product must be stored in a cool (<20-23°C), dry, well ventilated place away from seed, fertilizer or other pesticides and for no longer than one year.

DIRECTION FOR USE
Any reference to garden areas must be removed from the label.

"Garden Area, Outdoor, Foundations" must be changed to: "Treatment of outdoor structural foundations only, and the 1 m wide path surrounding the foundation."

The following statement most be added to all labels:

For outdoor use only.

PRECAUTIONS
For best management practices, the following statement is required:

Wear rubber gloves when handling this product. Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco. Remove contaminated clothing and wash before use.

ENVIRONMENTAL HAZARDS
TOXIC to birds and aquatic organisms.

DIRECTIONS FOR USE
Avoid application of this product when winds are gusty.

DO NOT apply to any body of water.
DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

D. General Label Improvements

The current labels contain "repeat as necessary" statements for many uses. This statement should be removed and replaced by specific information indicated in the table of this appendix, titled as **Maximum Number of Applications per Year and Minimum Application Intervals**.

DIRECTIONS FOR USE

On the label for product Registration Number 5821, the heading for sections 5 and section 6 need to be changed from "Crop(s)" to "Site(s)" and from "Rate per hectare" to "Rate".

On the label for product Registration Number 8826, the heading for stored grain "ML / tonne of liquid grain protectant" must be changed to "ml of liquid grain protectant / 1000 kg of seed". Also, specific instructions must be changed from "in 10-20 litres of water per 1000 bushels" to "In 10-20 litres of water per 1000 kg of seed, apply as the grain is being loaded or turned into final storage".

On the label for product Registration Number 12073, the pest name "flat grain borer" must be changed to "flat grain beetle".

On the label for product Registration Number 13883, for use in empty granary bins, the application instruction, "apply 2 to 4 weeks before storing grain may be used within 1 day of storing grain" must be changed to "apply within 2 to 4 weeks before storing grain and may be used within 1 day of storing grain."

Appendix III Additional Data Requirements

The following studies or suitable scientific rationale are required as a condition of continued registration under section 12 of the *Pest Control Product Act*:

Data Requirements Related to Chemistry

DACO: 2.13.3	Analytical data from five recent batches of the TGAI, to 0.1% as per Section 2.13.3 of DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product* including the impurities of toxicological concern present in the TGAI at any level.

Data Requirements Related to Occupational Exposure Assessment

DACO 5.2	Use Description/Scenario (Application and Postapplication) - Information which fully describes the use of the product and human activity associated with its use in grape vines (nursery stock), stored grain, and mushroom houses.
DACO 5.6/5.7/5.9	Postapplication - Passive dosimetry or biological monitoring data and/or dislodgeable/transferable residues. Post-application exposure estimates for workers re-entering mushroom houses following application of malathion. Potential exposure to malaoxon should also be characterized.
DACO 5.9	Dislodgeable/Transferable Residues - Residue studies that measure the formation and dissipation of malaoxon in airborne spray and, particularly, in deposited surfaces such as hard surfaces (such as decks and playstructures) and turf over a 10- to 30- day period following application of ULV malathion.

References

Additional studies and information considered for the re-evaluation of malathion

Data submitted by registrant

PMRA Document Number	Reference
2025101	2003, Malathion Technical - Acute Oral Toxicity Study in Rats. DACO: 4.2.1
2088610	2011, Malaoxon Acute Oral Toxicity Up and Down Procedure in Rats., DACO: 4.2.1
2092674	Local Lymph Node Assay (LLNA) in Mice: Malathion Technical., DACO: 4.2.6
2060503	2011, Oral (Diet) Repeated Dose Six-Week Immunotoxicity Study of Malathion in Mice. DACO: 4.8(B).
2032817	Magnitude of the Residue of Malathion and Its Metabolite Malaoxon in/on Winter Wheat Processed Commodities: , DACO: 7.4.5
2032949	Magnitude of the Malathion and Malaoxon Residues in or on Stored Corn Grain and Processed Commodities: Final Report: , DACO: 7.4.1
2032950	Magnitude of the Malathion and Malaoxon Residues in or on Stored Wheat Grain and Aspirated Grain Fractions: , DACO: 7.4.1
2032951	Magnitude of the Residue of Malathion, Malaoxon, and Desmethyl Malathion in Stored Wheat Grain and Processed Commodities: Final Report., DACO: 7.4.1
2032854	Independent Laboratory Validation of the Pesticide Analytical Method for Malathion and Malaoxon: Final Report: , DACO: 7.2.1
2025135	Review on initial residue levels of pesticides in arthropods sampled in field studies. ECPA Report on Residues in Arthropods., DACO: 9.9
2025134	2011, Residues of Malathion and Malaoxon on Potential Avian and Mammalian Feed Items., DACO: 9.6.6,9.7.2
2025204	Residues of malathion and malaoxon in different feed sources for wild birds after application of CHA 3110 (Germany 2004)., DACO: 9.6.6
2025132	Impact of Malathion on Fish and Aquatic Invertebrate Communities and On Acetylcholinesterase Activity in Fishes within Stewart Creek, Fayette County, Alabama: Final Report., DACO: 9.3.6,9.5.5

Additional Information

PMRA Document Number	Reference
2079365	Lassiter, T.L. et al, 1998, Gestational Exposure to Chlorpyrifos : Apparent Protection of the Fetus - Toxicology and Applied Pharmacology, Volume 152, Pages 56 to 65, DACO: 4.8
2079368	Meneguz, Annarita, Guillermo M. Bisso, and Hanna Michalek, 1988, Alterations in the Distribution of Cholinesterase Molecular Forms in Maternal and Fetal Brain Following Diisopropyl Fluorophosphate Treatment of Pregnant Rats - Neurochemical Research, Volume 14:285-29,1 DACO: 4.8
2080063	European Food Safety Authority, 2005, Final Addendum to the Draft Assessment Report (DAR) Initial Risk Assessment Provided by the Member State Finland for the Existing Active Substance Malathion, DACO: 12.5.4
2080065	European Food Safety Authority, 2006, Conclusion Regarding the Peer Review of the Pesticide Risk Assessment of the Active Substance Malathion, DACO: 12.5.4
2080066	European Food Safety Authority, 2006, Peer Review Report on Malathion, DACO: 12.5.4
2080067	European Food Safety Authority, 2009, Conclusion on Pesticide Peer Review Peer Review of the Pesticide Risk Assessment of the Active Substance Malathion, DACO: 12.5.4