Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Acceptability for Continuing Registration

PACR2003-10

Re-evaluation of Malathion

The purpose of this document is to inform the registrant, pesticide regulatory officials and the Canadian public that the Pest Management Regulatory Agency (PMRA) has completed a re-evaluation of malathion use as an adulticide in mosquito abatement programs, pursuant to Section 19 of the Pest Control Products (PCP) Regulations. This Proposed Acceptability for Continuing Registration (PACR) document provides a summary of the data and information reviewed, and the rationale for the proposed regulatory decision.

By way of this document, the PMRA is soliciting comments from interested parties on the proposed regulatory decision for malathion for use as an adulticide in mosquito abatement programs. The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed decision. All comments should be forwarded to the Publications Coordinator at the address below.

(publié aussi en français)

September 5, 2003

This document is published by the Alternative Strategies and Regulatory Affairs Division, Pest Management Regulatory Agency. For further information, please contact:

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ISBN: 0-662-34833-8 (0-662-34834-6)
Catalogue number: H113-18/2003-9E (H113-18/2003-9E-PDF)

Foreword

The re-evaluation of the active ingredient malathion and the associated end-use products, for use as an adulticide in mosquito abatement programs in residential areas, has been completed by the Pest Management Regulatory Agency (PMRA). The registrant of the technical grade active ingredient (TGAI) is Cheminova, Inc.

The PMRA announced on June 19, 1999 in its Re-evaluation Document REV99-01, *Re-evaluation of Organophosphate Pesticides*, that organophosphate pesticides, including malathion, were subject to re-evaluation under authority of Section 19 of the Pest Control Products (PCP) Regulations.

The PMRA has carried out an assessment of available information and has concluded that the use of malathion and associated end-use products as an adulticide in mosquito abatement programs does not entail an unacceptable risk of harm to human health or the environment pursuant to Section 20 of the PCP Regulations, provided that the mitigation measures described in this document are implemented.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed re-evaluation decision for these products.

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1.0 Information used in re-evaluation

Some of the scientific information used by the PMRA in its assessment of malathion use as adulticide in a mosquito abatement program came from reviews conducted by the United States Environmental Protection Agency (USEPA). The USEPA reviews for malathion can be referenced for further details regarding scientific studies used by the PMRA. These reviews, as well as other information on the regulatory status of malathion in the United States, can be found at the website for the USEPA, http://www.epa.gov/ebtpages/pesticides.html. This does not necessarily reflect the USEPA's final risk assessment on malathion since the re-evaluation is still ongoing.

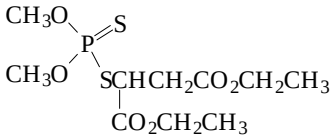
2.0 Regulatory history

Malathion is one of the organophosphate pesticides being re-evaluated by the Pest Management Regulatory Agency (PMRA), as announced on June 29, 1999, in the Agency's publication Re-evaluation Document REV99-01, *Re-evaluation of Organophosphate Pesticides.* The PMRA has developed a re-evaluation program that uses a modern scientific approach to examining older active ingredients and their end-use products to determine their continuing acceptability in relation to human health and the environment.

In light of interest by provinces and municipalities for possible large-scale application of pesticides for control of adult mosquitoes in residential areas during the upcoming season, the PMRA has completed an occupational and a bystander risk assessment for this use of malathion. The results of the assessment and the required changes to the malathion use-pattern have been outlined in Re-evaluation Document REV2003-03, *Re-evaluation of malathion: Assessment of Use in Mosquito Abatement Programs.*

3.0 The active substance

Common name:	Malathion
Chemical name:	Diethyl (dimethoxythiophosphorylthio)succinate
Chemical family:	Organophosphate
CAS registry number:	121-75-5
Molecular formula:	$C_{10}H_{19}O_6PS_2$
Molecular mass:	330.3

Structural formula:	
Purity of TGAI:	95% minimum
PCP number:	18150
Basic manufacturer:	Cheminova
Identity of relevant impurities of toxicological, environmental and(or) other significance:	Based on the manufacturing process, composition of raw materials and the chemical structure of the active ingredient, the TGAI is not expected to contain other impurities of toxicological concern as identified in section 2.13.4 of Regulatory Directive DIR98-04 or other Toxic Substances Management Policy (TSMP) Track-1 substances as identified in DIR99-03, Appendix II. However, under prolonged storage in warm conditions, malathion is known to isomerize to isomalathion.

4.0 Re-evaluation of malathion mosquito adulticide use in mosquito abatement programs

Malathion is a broad spectrum organophosphate insecticide which inhibits the enzyme acetylcholinesterase, disrupting the transmission of nerve impulses. It works by contact and ingestion action.

In Canada, malathion is registered for use on a variety of feed crops, food crops, livestock, ornamental crops, residential uses and structural sites to control a wide variety of arthropod pests. The typical use for control of adult mosquitoes is ultra-low volume (ULV) application. In the U.S., ULV applications of malathion are also used for the control of adult mosquitoes in outdoor residential areas.

4.1 Type of pesticide

Malathion is an organophosphate (OP) insecticide.

4.2 Products registered for use as adulticides in mosquito abatement programs

Malathion products registered to control adult mosquitoes are fluid formulations.

Name of product	Registration number
Products registered for ULV application	
Fyfanon ULV Ultra-Low Volume Concentrate Insecticide	9337
Gardex Malathion ULV Concentrate	16198
Malathion 95 ULV Insecticide	25638
Wilson Malathion ULV Insecticide Concentrate	14597
Products with uses other than ULV applications	
Fyfanon 50% Emulsifiable Concentrate Insecticide	4590
Malathion 50E Emulsifiable Liquid Insecticide	9975
Malathion 500E Insecticide	4709
Wilson Malathion 50 EC Liquid Insecticide	16099

4.3 Methods and rates of application

For the control of adult mosquitoes in outdoor residential areas using commercial class products, malathion may be applied by aircraft or ground application using ULV or ground spray equipment. The currently registered rates of application to control adult mosquitoes with commercial class malathion products are:

- 496.6–642.7 g a.i./ha for aerial ULV application (maximum of 233 g a.i./ha is recommended when vehicles are present)
- 26.0–60.8 g a.i./ha for ground ULV application
- 500–565.7 g a.i./ha for ground spray application.

5.0 Effects having relevance to human health

5.1 Toxicology summary

The toxicology database confirms that malathion has anticholinesterase activity in various species including rats, mice, rabbits, dogs and hens. Although clinical signs of toxicity observed in laboratory animals are typical of the organophosphate class of chemicals, they occur at relatively much higher doses with malathion compared to other organophosphates.

Following oral administration to rats, malathion was rapidly absorbed and eliminated, mainly in the urine with lesser amounts excreted in the feces. The major metabolic pathway is hydrolysis of the carboxyester by tissue, liver or plasma carboxylesterases, resulting in alpha and beta monocarboxyacid. A proposed metabolic pathway postulates the oxidative desulphuration of malathion by microsomal enzymes to malaoxon which is excreted in the urine or further metabolised by phosphatases. Greater than 80% of the radioactivity in urine was represented by the diacid (DCA) and monoacid (MCA) metabolites. It was determined that between 4% and 6% of the administered dose was converted to malaoxon, the active cholinesterase-inhibiting metabolite of malathion.

Malathion did not accumulate in tissues following single or multiple exposure. There did not appear to be any dose-related or sex-related differences in the metabolism of malathion.

Malathion exhibits low acute toxicity via the oral, dermal and inhalation routes. Acute toxicity signs were consistent with cholinesterase inhibition and included: tremors, convulsions, salivation and dyspnea. Based on a comparison of the malaoxon oral LD_{50} value with the oral LD_{50} for malathion, malaoxon appears to be approximately 10 to 30 times more acutely toxic than malathion by the oral route in rats. Malathion exhibits slight eye and dermal irritation and is not dermally sensitizing.

Like other organophosphate pesticides, the mode of toxic action for malathion is the inhibition of plasma, erythrocyte or brain cholinesterase activity. Dose-related inhibition of plasma, erythrocyte and brain cholinesterase activity occurs by all routes and following exposures of various durations. In repeat dose studies with malathion, plasma and erythrocyte cholinesterase inhibition were exhibited at various lowest observed adverse effect levels (LOAELs) following oral (mouse, rat, dog), inhalation (rat) and dermal (rabbit) exposure. Brain cholinesterase inhibition typically occurred at higher doses in all species following oral and inhalation exposure. Generally speaking, in non-acute studies, erythrocyte cholinesterase was qualitatively and(or) quantitatively preferentially affected followed by inhibition of plasma cholinesterase then by brain cholinesterase. Treatment-related effects also included clinical signs, increases in liver, kidney and thyroid/parathyroid weights and hematological effects (oral exposure) in rats and dogs. With long-term oral exposure, mice and rats exhibited microscopic lesions of the nasal cavity and larynx at high doses. Although these could be attributed to direct contact with malathion (by volatilization from the feed or by inhalation of the feed through the nose), the possibility that these lesions could be due to systemic toxicity could not be ruled out. Short-term inhalation exposure in the rat produced similar lesions of the nasal cavity and larynx albeit at a much lower systemic dose level.

Chronic dosing studies with malaoxon in the rat showed inhibition of erythrocyte and brain cholinesterase to occur at much lower dose levels than with malathion (LOAELs of 1.0 and 327 mg/kg bw/day for erythrocyte cholinesterase and 57 and 327 mg/kg bw/day for brain cholinesterase in malaoxon and malathion, respectively). Effect levels of inhibition of plasma cholinesterase were comparable between malaoxon and malathion. The liver and nasal cavity epithelium were also identified as target organs of toxicity in studies with malaoxon.

Assessment of the relative sensitivity of cholinesterase activity reveals no appreciable species differences between mice, rats and dogs. Studies of various durations in the rat indicate that the female may be more sensitive to the toxic effects of malathion than the male is, however, no consistent pattern was seen (often increase in magnitude of effect but at the same LOAEL). Females do appear to be more sensitive to the inhibition of brain cholinesterase by malathion but only at high doses. A comparison of the results of subchronic and chronic studies demonstrate that duration of dosing has an impact on

toxicity. In the F-344 rat, the chronic no observed adverse effect level (NOAEL) is almost 20-fold lower than the NOAEL in the subchronic studies for the same effects (liver/kidney effects, brain cholinesterase) indicating a cumulative toxicity response over time. An increase in toxicity of malathion with increased study duration was also indicated in the dog studies by the manifestation of liver, kidney, thyroid/parathyroid and hematological effects (other than cholinesterase inhibition) in the 1-year study at similar dose levels that in the 28-day study in dog caused only clinical signs, plasma and erythrocyte cholinesterase inhibition and minimal suppression of body weight gain.

Neurobehavioural observations are typically associated with exposure to malathion. While no frank neuropathological changes were seen in the majority of mammalian toxicity studies, lumbar dorsal root axonal degeneration, tibial nerve pathology, retinal rosette formation (acute neurotoxicity study) and sciatic nerve demyelination, lumbar dorsal root and peroneal nerve pathology (subchronic neurotoxicity study) were observed in male rats given malathion at very high doses (exceeding 1500 mg/kg bw day). There was no evidence of delayed-type neurotoxicity in the hen study (neurotoxic esterase was not measured).

Results of the guideline genetic toxicology studies with malathion indicated that the test material did not cause gene mutations in bacteria or unscheduled DNA synthesis in cultured rat hepatocytes. Similarly, malathion was neither clastogenic nor aneugenic up to doses that showed clear cytotoxicity for the target tissue in vivo in rats. Some in vitro and in vivo mutagenicity studies with malathion obtained from published literature have shown positive evidence of clastogenicity. However, the relevance of these findings are not clear since the positive results were seen usually at cytotoxic doses or the types of induced aberrations were asymmetric and, therefore, not consistent with cell survival. In addition, the identity and(or) purity of the test substance was an issue in some studies (i.e., unknown purity or of lesser purity than current specifications; test substance obtained from numerous and(or) unknown suppliers bring into question their chemical equivalencies). Although the structure of malathion suggests electrophilicity, the overall weight of the evidence supports neither a genotoxic hazard nor a role for genotoxicity in the carcinogenicity associated with malathion.

The consensus from reviews of the open literature is that malaoxon is not mutagenic in bacteria but is positive in the mouse lymphoma assay without metabolic activation. Malaoxon was weakly clastogenic in cultured Chinese hamster ovary (CHO) cells; however, the findings from the mouse lymphoma assay suggest that malaoxon may induce both gene mutations and chromosome aberrations. Malaoxon is structurally similar to malathion and, therefore, concerns for possible electrophilicity also apply to malaoxon. Nevertheless, malaoxon is not carcinogenic in male or female Fischer 344 rats.

In chronic/oncogenicity studies performed with malathion in mice and rats, treatment-related increased tumour incidences were observed in the liver (mouse, rat) and in the nasal/oral cavity (rat). The USEPA has classified malathion based on the weight of the

evidence as having “suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential”.

The PMRA concurs with the USEPA assessment that the liver tumours in both sexes of mice and in female rats occur at excessive doses of malathion which exceed the maximum tolerated dose (MTD). From the weight of the evidence, the PMRA concluded that malathion is unlikely to possess carcinogenic potential for humans based on the following information:

1. The MTD was exceeded in mid and high dose male and female mice and in high dose rats i.e., increased mortality, decreased body weight gain > 10%.
2. No evidence of progression from non-neoplastic (i.e., hyperplasia) to neoplastic lesions.
3. All tumours were benign i.e., no progression from benign to malignant.
4. No dose-response in tumour incidence at dose levels below those deemed to be excessively toxic.
5. No evidence of decrease in tumour latency.
6. The liver is the site of metabolism of malathion and is demonstrating signs of metabolic overload.
7. Liver tumours are a common neoplasm in mice.
8. The organophosphates as a chemical class are not, generally speaking, known to be carcinogenic.
9. Overall, the data does not indicate that malathion is genotoxic.
10. Malaoxon (the active metabolite) did not induce tumors in a long-term rat study.

The single incidences of nasal/oral tumours cannot be distinguished as treatment-related or due to random occurrence. In view of the rare nasal/oral cavity tumours observed in the rat in the dietary study and the fact that moderate-to-severe lesions of the nasal cavity and larynx were observed in a 2-week range-finding inhalation exposure study, the PMRA has a concern that no carcinogenicity study via the inhalation route is available for evaluation. This lack of information is taken into consideration in the risk assessment particularly for workers who may be occupationally exposed to malathion.

Malathion was evaluated for developmental toxicity in rats and rabbits. In rabbits, developmental effects (slightly increased incidence of dams with resorption sites) were noted at 50 mg/kg/day where maternal toxicity was also observed. A slightly increased incidence of dams with resorption sites was noted in rats at the highest dose tested (800 mg/kg/day) also in the presence of maternal toxicity. The data also demonstrated no apparent increased sensitivity of rats or rabbits with only in utero exposure to malathion. Maternal toxicity (cholinergic signs and(or) reduced weight gains) was observed in both species at the same dose levels that caused fetal toxicity. Malathion did not induce reproductive toxicity in rats at the highest dose tested. Although the offspring NOAEL was lower than the parental systemic NOAEL, offspring toxicity as evidenced by pup body weight decrements was primarily observed at postnatal day 21. This could be related to the increased food intake (on a body weight basis) compared to adults and hence

increased compound intake. However, the relative sensitivities of adults and pups to cholinesterase inhibition by malathion were not determined in either the developmental or reproduction studies precluding a definitive conclusion on potential sensitivity of the young. There was no evidence of abnormalities in the development of the fetal nervous system in any of these studies.

Recently conducted developmental neurotoxicity (DNT) and related comparative cholinesterase studies with malathion showed definite evidence of quantitative and qualitative sensitivity of juvenile rats. Overall, this susceptibility was observed in terms of the dose level at which effects were observed (i.e., the NOAELs for cholinesterase inhibition were up to 20× lower for juveniles than for adults), the compartments in which a response was elicited (e.g., brain cholinesterase was inhibited in offspring but was not observed in adults up to the highest dose tested), and the magnitude of the responses (i.e., when inhibition was noted for both age groups at the same level, the percent inhibition was substantially greater for pups than for young adults). This susceptibility was observed following both single and repeat-dosing regimes. At low doses these studies also demonstrated behavioural effects in juvenile rats which were absent in adult animals. This knowledge of the differential susceptibility of juvenile animals is reflected in the human health risk assessment for malathion.

There was limited evidence in the database to suggest that malathion has an adverse effect on the endocrine system in mammals (altered thyroid/parathyroid weights in the 2-year rat carcinogenicity study—increased in males, decreased in females; increased thyroid/parathyroid weights in male and female dogs). These weight changes were not accompanied by corresponding histopathology. There is some indication that malathion may also affect the immune response in humans. Although there is some indication in the published literature that malathion may induce a human allergic or irritative response, guideline dermal sensitivity studies conducted in laboratory animals show it to be a non-sensitizer. For the effects of malathion on humoral immunity, the results reported in literature studies are inconclusive. Therefore, guideline immunotoxicity studies are required in order to fully characterize the effect of malathion on immune response.

Reference doses have been set based on NOAELs for the most sensitive indicator of toxicity. These reference doses incorporate various uncertainty factors to account for extrapolating between rats and humans and for variability within human populations as well as additional uncertainty or safety factors to account for an extra level of protection that is warranted by the data.

5.2 Residential (bystander) exposure and risk assessment

Residential risk assessment is concerned with estimating risks to the general population, including children, during or after pesticide application. Residential risk is estimated by comparing the amount of pesticide to which an individual may be exposed to endpoints from the most relevant toxicology studies with respect to route and duration to estimate a margin of exposure (MOE). This is compared to a target MOE that incorporates safety

factors protective of the most sensitive populations. If the MOE is less than the target MOE, it does not necessarily mean exposure will result in adverse effects. However, mitigation measures will be necessary to reduce exposure.

The duration of exposure for bystanders would be acute- to short-term (i.e., from one to several days), since malathion does not persist in the environment and would not accumulate between applications. A separate acute assessment was not conducted as high-end exposure/risk values were considered in the short-term assessment.

Toxicology endpoints and target MOEs selected for adults and children are summarized in Table 1. For **short- and intermediate-term dermal risk assessment** for **adults,** the assessment was driven by the most sensitive adult subpopulation of pregnant women. The oral NOAEL of 25 mg/kg bw/day from a rabbit developmental study was selected based on the increased incidence of does with resorptions in the presence of maternal toxicity (reduced mean body weight gain) at 50 mg/kg bw/day. The target **MOE** selected when using this study is **300**; this accounts for standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability. In addition, an additional 3× safety factor is warranted due to the severity of the endpoint (resorptions = embryofetal deaths). This target MOE would, therefore, be considered protective of pregnant women and their unborn children.

A 10% dermal absorption value was incorporated into the dermal estimates of exposure for all scenarios, based on the weight-of-evidence from published studies (Feldmann & Maibach, 1970; 1974; Maibach et al., 1971; Wester et al., 1983; Reifenrath et al., 1984; Zendzian, 1993). This is consistent with that used by the USEPA (USEPA, 2000a).

For **short- and intermediate-term inhalation risk assessment** for **adults**, the LOAEL of 25.8 mg/kg bw/day (0.1 mg/L) was selected from a 90-day inhalation toxicity study in rats. The LOAEL was established based on the observation of lesions in the nasal respiratory epithelium. The NOAEL for erythrocyte and brain cholinesterase depression occurred at this dose. The target **MOE** selected when using this study is **1000**; this accounts for standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability, with an additional uncertainty/safety factor of 10 because a NOAEL was not identified and because of the severity of the nasal lesions also observed at the LOAEL in a 2-week range-finding study and concern for the potential for development of nasal cavity tumours with chronic exposure via the inhalation route. This would provide an intrinsic margin of safety of > 960 to the developmental NOAEL of 25 mg/kg bw/day. This target MOE would therefore be considered protective of pregnant women and their unborn children.

For **short- and intermediate-term dermal, inhalation and non-dietary oral ingestion by children**, the oral LOAEL of 5 mg/kg bw/day from the comparative cholinesterase study in rats was selected based on inhibition of erythrocyte cholinesterase in PND 11 or PND 21 pups following single or repeated dosing. The target **MOE** selected when using this study is **1000**; this accounts for the standard uncertainty factors of 10 for interspecies

extrapolation and 10 for intraspecies variability, as well as an additional 10× uncertainty/safety factor due to the use of a LOAEL and for the potential increased sensitivity of younger populations. As in the adult assessment, a dermal absorption value of 10% was incorporated for exposure by the dermal route.

Table 1 Toxicity endpoints and target MOEs used to estimate bystander risk for commercial mosquito control application

Population	Route of exposure	Duration of exposure	Toxicity endpoint	Target MOE
Adult (62 kg female)	Dermal	short-term	oral NOAEL = 25 mg/kg bw/day*	300
	Inhalation	short-term	inhalation LOAEL = 25.8 mg/kg bw/day	1000
	Combined routes	short-term	oral NOAEL = 25 mg/kg bw/day	300
Toddler and adolescent	Dermal	short-term	oral LOAEL = 5 mg/kg bw/day*	1000
	Non-dietary oral (toddlers only)	short-term	oral LOAEL = 5 mg/kg bw/day	1000
	Inhalation	short-term	oral LOAEL = 5 mg/kg bw/day**	1000
	Combined routes	short-term	oral NOAEL = 5 mg/kg bw/day	1000

* Since an oral study is used to estimate risk for dermal exposure, a dermal absorption value of 10% is applied to dermal exposure estimates.

** It is assumed that inhalation absorption is the same as oral absorption.

5.2.1 Mixer/loader/applicator exposure

Homeowner exposure during mixing/loading and application was not assessed for residents since only commercial applicators would apply commercial products.

5.2.2 Bystander exposure and risk assessment during and after application

There is potential for exposure to adults and children during or immediately following application of malathion as a commercially applied mosquitocide (e.g., people re-entering treated lawns or gardens).

Post-application exposure estimates were generated following the USEPA *Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments* and the recommended revisions by the USEPA Science Advisory Council (USEPA, 1997; 2001). The assumptions outlined in the SOP generally result in high-end estimates of exposure. Exposure estimates were generated for a 62 kg adult, 39 kg child (adolescent) and a 15 kg toddler. The assumptions and inputs used to estimate bystander exposure are tabulated in Appendix I.

Two general exposure scenarios were considered: 1) exposure to adults and toddlers while on turf during or immediately after application, and 2) exposure to adults and adolescents while gardening during or immediately after application. Adolescents were assessed for exposure from gardening activities, since they could potentially have higher exposure than adults due to lower body weights. Toddlers are not expected to have post-application exposure from gardening activities. Dermal exposure was assessed for all population groups. Non-dietary oral exposure, resulting from hand-to-mouth transfer and direct ingestion of soil or turf was also assessed for toddlers. Finally, inhalation exposure was assessed for all population groups.

Estimates of exposure and risk are presented in Table 2. The MOE combined for exposure from all routes was also calculated when acceptable MOEs were obtained for the route-specific exposures.

Table 2 Bystander exposure estimates and MOEs for malathion commercial mosquito control use in residential areas

Scenario	Application method	Dermal exposure absorbed (µg/kg/d)	Inhalation exposure (µg/kg/d)	Total oral exposure µg/kg/d	Dermal MOE[f]	Inhalation MOE	Oral MOE	Combined MOE
Adult (62 kg female)								
Garden	ground ULV	0.124	0.647	n/a	201 000	39 900	n/a	32 400
	ground non-ULV	1.12	5.85		22 300	4410		3580
	aerial ULV	1.24	2.87E-04		20 200	8.98E+07		20 200
Turf	ground ULV	0.192	0.647		130 000	39 900		29 800
	ground non-ULV	1.74	5.85		14 400	4410		3290
	aerial ULV	1.92	2.87E-04		13 100	8.98E+07		13 000
Adolescent (39 kg)								
garden	ground ULV	0.151	1.03	n/a	33 100	4860	n/a	4240
	ground non-ULV	1.37	9.31		3660	537		n/a

Scenario	Application method	Dermal exposure absorbed (µg/kg/d)	Inhalation exposure (µg/kg/d)	Total oral exposure µg/kg/d	Dermal MOE[f]	Inhalation MOE	Oral MOE	Combined MOE
	aerial ULV	1.51	4.57E-04		3320	1.09E+07		3320
Toddler (15 kg)								
turf	ground ULV	0.316	1.87	0.126	15 800	2670	39 700	2160
	ground non-ULV	2.86	16.94	1.14	1750	295	4393	n/a
	aerial ULV	3.15	0.001	1.255	1580	5.00E+06	3990	1130

Bystander risk estimates are above the target MOE for all exposure routes and scenarios associated with either ground ULV or aerial ULV applications. The MOEs that were attained were sufficiently large and thus are anticipated to provide further accommodation for those with environmental sensitivities. The MOEs would be further enhanced through measures such as remaining indoors during and immediately after spraying. Following non-ULV ground application at higher rates, unacceptable MOEs are obtained for inhalation exposures for adolescents and toddlers.

5.3 Dietary/drinking water risk assessment

Since the mosquito control use of malathion does not involve direct spray of agricultural crops, a dietary risk assessment for this specific use was not conducted. A dietary risk assessment will be conducted at the time of re-evaluation of the agricultural uses. Assessment of exposure from drinking water will also be considered at that time. Preliminary estimates of chronic dietary and drinking water exposures were made to incorporate into the aggregate risk assessment (below).

5.4 Aggregate risk assessment

As a commitment to ensuring protection of human health, the PMRA assesses risk on the basis of aggregate exposure from all non-occupational sources. Aggregate exposure is the total exposure to a single pesticide that may occur from all sources and routes of exposure, including food, drinking water, residential, and any other exposures.

Short-term aggregate risk assessments were conducted as there is potential for short-term exposure to malathion from residential mosquito control use. The exposure from use of malathion in a mosquito control program was assumed to co-occur with background (chronic) dietary and drinking water exposure to adults, adolescents and toddlers. Mosquito control uses which did not have MOEs above the PMRA target (i.e., ground non-ULV applications) were not incorporated into the aggregate risk assessment as risk mitigation is required for these uses.

Ideally, toxicity data reflecting the hazard associated with repeated exposure for periods of up to one week by each of the oral, dermal and inhalation routes would be relevant for the aggregate risk assessment. In the absence of this data, extrapolation from other toxicity data is required. For short-term aggregate assessment for adults, the assessment was driven by the most sensitive subpopulation of pregnant women. Due to the duration of exposure (12 days) in the rabbit oral developmental study, the endpoints and target MOEs are believed to be relevant for the short-term aggregate assessment. It is assumed that the effects in this study could be manifested by either the oral, dermal or inhalation routes. Thus, the oral NOAEL of 25 mg/kg bw/day from a rabbit developmental study selected was based on increased incidence of does with resorptions in the presence of maternal toxicity (reduced mean body weight gain) at 50 mg/kg bw/day. The selection of this study is considered protective of the potential inhibition of cholinesterase that could occur in an adult population. The target MOE selected when using this study is 300; this accounts for standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability. In addition, an additional 3× safety factor is warranted due to the severity of the endpoint (resorptions = embryofetal deaths). This target MOE would, therefore, be considered protective of all adults including pregnant women and their unborn children.

For short-term aggregate assessment for children, the oral LOAEL of 5 mg/kg bw/day from the comparative cholinesterase study in rats was selected based on inhibition of erythrocyte cholinesterase in PND 21 pups following repeated dosing. The target MOE selected when using this study is 1000; this accounts for the standard uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability, as well as an additional 10× uncertainty/safety factor due to the use of a LOAEL and for the potential increased sensitivity of younger populations.

The aggregate assessments are considered to be preliminary as the dietary exposure assessment has not been fully refined. Actual dietary exposure is likely lower than estimated. Even so, acceptable aggregate MOEs were obtained for ground and aerial ULV application of malathion.

5.5 Occupational exposure and risk assessment

Occupational risk is estimated by comparing the potential exposure of persons mixing, loading and applying pesticides to endpoints from the most relevant toxicology studies with respect to route and duration to estimate an MOE. This is compared to a target MOE that incorporates safety factors protective of the most sensitive population. If the MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, mitigation measures will be necessary to reduce exposure.

For the occupational risk assessment, operators using commercial class products in residential areas were considered. These would include municipal workers applying malathion for large scale mosquito control, as well as pest control operators hired by homeowners to treat their properties. For this scenario, mixer/loaders and applicators

have potential for short- to intermediate-term exposure (i.e., up to several months). A separate acute exposure assessment was not required as high-end exposure values were considered in the short- to intermediate-term assessment.

Toxicity endpoints used for the adult bystanders were also used for workers (Table 1). As in the bystander assessment, a dermal absorption value of 10% was incorporated for exposure by the dermal route.

5.5.1 Mixer/loader/applicator exposure and risk assessment

For commercial application of malathion to control mosquitoes in residential areas, dermal and inhalation exposure estimates for mixer/loaders and applicators are based on data from the Pesticide Handlers Exposure Database Version 1.1 (PHED).

PHED is a compilation of generic mixer/loader applicator passive dosimetry data. To estimate exposure for each use scenario, appropriate subsets were created from the mixer/loader and applicator database files of PHED. Exposure estimates are calculated on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part which is most appropriate to the distribution of data for that body part. Exposure estimates were calculated for mixer/loaders and applicators wearing long sleeves, long pants and gloves. Exposure was calculated as the product of the unit exposure for a given scenario, the application rate and the area treated per day divided by the body weight. The average body weight of adult females was used because pregnant women were considered to be the most sensitive adult population.

Estimated MOEs for occupational exposure are presented in Table 3.

Table 3 Commercial mixer/loader/applicator: Exposure estimates and MOEs for commercial mosquito control use in residential areas

Application method and rate	Population	Dermal exposure µg/kg/day	Inhalation Exposure µg/kg/day	Dermal MOE	Inhalation MOE	Combined (dermal + inhal.) MOE
Ground ULV (0.0608 kg a.i./ha)	M/L/A	64.91	8.71	385	2960	340
Ground non-ULV (0.55 kg a.i./ha)	M/L/A	587.19	78.77	43	328	n/a
	M/L/A coveralls and respirator	498.62	7.88	50	3275	n/a

Application method and rate	Population	Dermal exposure µg/kg/day	Inhalation Exposure µg/kg/day	Dermal MOE	Inhalation MOE	Combined (dermal + inhal.) MOE
Aerial ULV (0.260 kg a.i./ha)	M/L	57.91	20.13	430	1280	320
	applicator	12.15	0.89	2060	28 880	1900

M/L/A = mixer/loader/applicator (i.e., one person mixing/loading and applying)
M/L - mixer/loader only

MOEs for ground and aerial ULV applications are above the target MOEs of 300 and 1000 for dermal and inhalation exposure, respectively. In addition, the MOE for combined exposure from the dermal and inhalation routes is greater than the target of 300. This is with personal protective equipment typically worn by mixer/loaders and applicators (i.e., long-sleeved shirt, long pants and gloves). However, for ground non-ULV applications, the dermal MOE is less than the target MOE even with mitigation through the use of extra personal protective equipment.

5.5.2 Post-application exposure

Post-application exposure for workers in residential sites is assessed under residential/bystander exposure (Section 5.2.2).

6.0 Effects having relevance to the environment

Malathion for control of adult mosquitoes will be applied as ultra-low volume (ULV) sprays and these are characterized by fine droplets and are applied in urban residential areas, at night when adult mosquitoes are most active.

When applied as ULV and according to the other label directions, adverse effects on the environment will be limited, for the following reasons. Malathion degrades rapidly in the environment with a half-life in soil of < 1 day and in water of 0.5 to 19 days. The toxicity to birds and mammals is low and in view of short-lived nature of malathion in the environment, the risk to these organisms is limited. Although malathion is highly toxic to insects including beneficial ones such as honey bees, the potential impact on any honey bees or other pollinators, that may be present in the residential areas, is minimized, since the mosquito spray programs are conducted at night, when the bees are not active. Some individuals of non-target insects and other arthropods, that are present in the residential areas and that are active at spraying times, may be affected, but it is expected that the effects on the populations will not be permanent due to recolonization from rural unsprayed areas.

Malathion is highly toxic to fish and aquatic invertebrates. However, the impact on these aquatic organisms will be limited in view of the ULV method of spray application. The droplets of pesticide are very small and do not drift or deposit like larger droplets. Spray

droplets may evaporate during this period of suspension in the air, and so, not deposit at all. Thus, deposit into aquatic systems from this type of application is reduced, exposure is minimized and adverse effects are, as a result, limited. As per currently registered labels, users are advised to take care not to contaminate sensitive aquatic environments such as sloughs, ponds, prairie potholes, lakes, rivers, streams and wetlands when cleaning and rinsing spraying equipment and containers.

Since as a health mitigation measure, non-ULV uses of malathion for mosquito control in residential areas is not permitted, an environmental assessment of these non-ULV use patterns was not conducted.

7.0 Usage of malathion in mosquito abatement programs

7.1 Evaluation method

The importance of malathion commercial class end-use products for managing adult mosquitoes in outdoor residential areas was evaluated based on the availability of registered alternative pesticides. The extent of use of commercial class malathion products in residential adult mosquito control in Canada was assessed by the PMRA in 2001 by a survey of provincial governments. Responses were received from British Columbia, New Brunswick, Nova Scotia and PEI extension specialists. Information on the extent of malathion use for mosquito control was obtained from Winnipeg, Manitoba in 2002.

7.2 Evaluation results

In Canada, most of the malathion to control adult mosquitoes in outdoor residential areas has been used in Winnipeg, Manitoba where there are generally two applications per year. From 1993 to 2002, the amount of malathion used per season in Winnipeg ranged from none in 1994–1996 to 8033 kg a.i. in 2001. Typical use involved ground ULV application.

Due to its short persistence, malathion is the preferred active ingredient for adult mosquito abatement programs in residential areas of Winnipeg. The following are currently registered active ingredients for adult mosquito abatement programs in residential areas: propoxur (carbamate), d-trans allethrin, permethrin and resmethrin (synthetic pyrethroids), pyrethrins (botanical), dichlorvos and [1]naled (organophosphates) and [1]methoxychlor (organochlorine).

In the past, malathion usage was reported in the Okanagan and Fraser Valleys of British Columbia (two to three applications per year) for the fogging of adult mosquitoes. In

[1] These uses of naled and methoxychlor will be phased out by August 31, 2004 and December 31, 2005, respectively.

recent years, malathion has not been used in British Columbia against adult mosquitoes because the focus of the British Columbia mosquito abatement program has moved to larval control.

No other regions of Canada have reported the use of malathion in residential adult mosquito abatement programs in recent years.

8.0 Regulatory conclusions

The PMRA has determined that large-scale applications of malathion in residential areas for control of adult mosquitoes do not pose an unacceptable risk to bystanders and operators (mixer/loaders and applicators) when used in the following manner:

- ground applications are made with ultra-low volume (ULV) equipment at the currently registered rate of up to 60.8 g a.i/ha.

- aerial applications are made with ULV equipment at a rate up to 260 g a.i/ha.

- operators wear long pants, long-sleeved shirts and chemical-resistant gloves during mixing/loading, application, clean-up and repair.

Based on consultation with the provinces/territories, these scenarios reflect the typical use pattern for malathion when/if used in provincial/territorial/municipal mosquito abatement programs.

For other current label uses of malathion for control of adult mosquitoes in residential areas (e.g. higher rate of application, spray, thermal fog), the calculated margins of exposure for bystanders are unacceptable. As a result, these uses are no longer permitted.

The regulatory position outlined in this document describes the outcome of the re-evaluation by the PMRA of the adulticide use of malathion in mosquito abatement programs. The label changes noted below have been agreed to and implemented by the registrants. The PMRA will accept written comments up to 60 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed re-evaluation decision for these products. The PMRA will continue with the re-evaluation of the remaining uses for malathion. The outcome of this assessment will be the subject of a future PMRA consultation document.

9.0 Label changes

Products with uses other than ULV application
Fyfanon 50% Emulsifiable Concentrate Insecticide, Reg. No. 4590
Malathion 50E Emulsifiable Liquid Insecticide, Reg. No. 9975
Malathion 500E Insecticide, Reg. No. 4709
Wilson Malathion 50 EC Liquid Insecticide, Reg. No. 16099

a. Removal of all malathion non-ULV use for mosquito control in residential areas (e.g. spray, thermal fog at higher rates) from the label

b. Addition of the following statements to the label:
   - "Do not apply as a fog, aerosol, mist or space spray in residential areas"
   - "Residential areas are defined as sites where bystanders including children may be potentially exposed during or after spraying. This includes around homes, school, parks, playgrounds, playing fields, public buildings or any other areas where the general public including children could be exposed".

Products registered for ULV application
Fyfanon ULV Ultra-Low Volume Concentrate Insecticide, Reg. No. 9337
Gardex Malathion ULV Concentrate, Reg. No. 16198
Malathion 95 ULV Insecticide, Reg. No. 25638
Wilson Malathion ULV Insecticide Concentrate, Reg. No. 14597

Addition of the following statements to the section of the label pertaining to aerial application for mosquito control:

1. "In residential areas, rates must not exceed 260 g a.i./ha"
2. "Residential areas are defined as sites where bystanders including children may be potentially exposed during or after spraying. This includes around homes, school, parks, playgrounds, playing fields, public buildings or any other areas where the general public including children could be exposed"
3. "Consult provincial/territorial pesticide regulatory officials for required authorization"

Label amendments are not required for products registered for ground ULV application.

10.0 Additional data requirements

Since high-end model assumptions were used to estimate bystander exposure, the PMRA is requesting data to refine estimates of risk. Specifically, air concentration and deposition data for both ground and aerial ULV applications under typical use conditions. It is anticipated that these data will provide a more realistic assessment and lower estimate of risk.

Toxicology and Chemistry data requirements pertain to all uses of malathion and will be communicated in a future PMRA document reporting the results of the re-evaluation of the remaining uses of malathion.

11.0 Implementation

The PMRA has notified registrants of end-use products of the regulatory conclusions outlined in this document. The mitigation measures are to be implemented by the 2003 spray season:

Registrants have amended their labels on product to be formulated packaged and sold for use during the 2003 use-season.

Packaged product that has the current registered label which is in the hands of the registrants and distributors will be overstickered in a place which is obvious to users to indicate the statements listed above.

Applicators of products for mosquito control are advised not to use products which do not carry the revised use directions. Further label changes will probably be required pending the completion of the re-evaluation of all the uses of malathion.

List of abbreviations

a.i.	active ingredient
CHO	Chinese hamster ovary
DCA	diacid
DNT	developmental neurotoxicity
g	gram
h	hour
ha	hectare
kg	kilogram
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
MCA	monoacid
MTD	maximum tolerated dose
MOE	margin of exposure
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
OP	organophosphate insecticide
PEI	Prince Edward Island
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
Reg. No.	*Pest Control Products Act* Registration Number
SOP	standard operating procedure
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
ULV	ultra-low volume
USEPA	United States Environmental Protection Agency

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Appendix I Inputs used to estimate bystander exposure

Parameter	Input	Descriptor	Reference
Application rate Ground ULV Aerial ULV Ground non-ULV	 60.8 g a.i./ha 260 g a.i./ha* 550 g a.i./ha	 maximum typical maximum	 product labels
Receptor body weights Adult Youth Toddler	 62 kg female (most sensitive) 39 kg 15 kg	 central central central	 NAFTA, 1999
Receptor inhalation rates Adult Youth Toddler	 1.0 m^3/hr (light activity) 1.0 m^3/hr (light activity) 0.7 m^3/hr (light activity)	 central central central	 NAFTA, 1999
Dermal absorption	10%	not applicable	published studies
Turf transferable residue	5% of application rate	maximum	USEPA, 1997; 2001
Turf dermal transfer coefficients Adult Youth Toddler	 13 051 cm^2/h (adjusted for surface area) 9986 cm^2/h (adjusted for surface area) 5200 cm^2/h	 central	 USEPA, 1997; 2001
Exposure time on turf	2 hours/day	maximum	USEPA, 1997; 2001
Ornamental transferable residue	20% of application rate	maximum	USEPA, 1997; 2001
Ornamental dermal transfer coefficients Adult Youth	 6300 cm^2/h (adjusted for surface area) 4821 cm^2/h (adjusted for surface area)	 maximum	 USEPA, 1997; 2001
Exposure time in ornamentals	40 minutes	maximum	USEPA, 1997; 2001

Parameter	Input	Descriptor	Reference
Surface area of hands for hand-to-mouth transfer in toddler	20 cm^2	central	USEPA, 1997; 2001
Saliva extraction factor from hand	50%	not applicable	USEPA, 1997; 2001
Hand-to-mouth activity for toddlers	20 events/h	maximum	USEPA, 1997; 2001
Area of grass consumed by toddlers	25 cm^2/day	maximum	USEPA, 1997; 2001
Deposition rate Ground Aerial	 15% 35%	 maximum maximum	published studies; AgDRIFT® model (aerial)
Exposure time for inhalation exposure (during application)	20 minutes	maximum	
Air concentrations following ground ULV applications	full rate available in breathing zone immediately after application with 1% dilution rate	maximum	USEPA, 1997; 2001
Air concentration following aerial ULV applications Helicopter Adult (6 ft) Toddler (3 ft) Fixed-Wing Adult (6 ft) Toddler (3 ft)	 0.054 mg/m^3 0.065 mg/m^3 0.022 mg/m^3 0.025 mg/m^3	maximum	AgDRIFT® model

* Although aerial application is registered at a rate of up to 642.7 g a.i./ha, due to the presence of vehicles in residential areas, lower application rates are typically used. Therefore, for residential areas, the rate of aerial application assessed was up to 260 g a.i./ha, which is the registered rate in the U.S.