Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Acceptability for Continuing Registration

PACR2003-05

Re-evaluation of Fenthion

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 fenthion pursuant to Section 19 of the Pest Control Products 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 fenthion. 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.

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Foreword

The re-evaluation of the active ingredient fenthion and the associated end-use products (EPs) has been completed by the Pest Management Regulatory Agency (PMRA). The registrant of the technical grade active ingredient is Bayer CropScience Chemicals Division.

The PMRA announced in June 1999 that organophosphate active ingredients, including fenthion, were subject to re-evaluation under authority of Section 19 of the Pest Control Product (PCP) Regulations[1].

Subsequent to that announcement, Bayer CropScience, primary registrant of fenthion in Canada, indicated that it intended to provide continued support for products containing fenthion on beef cattle and non-lactating dairy cattle.

The PMRA has carried out an assessment of available information and has concluded that the use of fenthion and its end-use products on cattle does not entail an unacceptable risk to human health and the environment pursuant to Section 20 of the PCP Regulations, provided that the proposed mitigation measures described in the document are implemented.

It is proposed that the Food and Drug Regulations be amended so that, with the exception of meat, meat by-products and fat of cattle, food with quantifiable residues of fenthion cannot be sold in Canada once Canadian use has been phased out, unless additional data to support fenthion residues in imported food are provided.

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

[1] Re-evaluation Document REV99-01, *Re-evaluation of organophosphate pesticides*

Table of Contents

1.0 Purpose

This document describes the outcome of the Pest Management Regulatory Agency's re-evaluation of the insecticide fenthion and its end-use products (EPs). It includes a human health assessment, an environmental assessment and information on the value of fenthion to pest management in Canada. By way of this document, the Agency is soliciting comments from interested parties on the decisions and mitigation measures proposed.

2.0 General background of re-evaluation

The PMRA is re-evaluating, under Section 19 of the Regulations pursuant to the *Pest Control Products Act* (PCPA), all pesticides, both active ingredients (a.i.) and formulated end-use products (EPs), that were registered prior to 1995. As outlined in Regulatory Directive DIR2001-03 *PMRA Re-evaluation Program*, a modern scientific approach is used to determine the continuing acceptability of older active ingredients in relation to human health and the environment. Fenthion is under reassessment in the U.S. (United States of America) as a result of the *Food Quality Protection Act* and is therefore being re-evaluated by PMRA under Program 3. The following components are addressed and considered in this re-evaluation:

Risk to human health: The initial focus of the re-evaluation of a pest control product in Program 3 is the risk to human health. As indicated in Regulatory Directive DIR2001-03, the reassessment in Program 3 pays particular attention to:

- pest control products with a common mechanism of toxicity
- aggregate exposure to a pesticide arising from its residues in food and in drinking water, and from non-occupational exposure, such as from treatments in and around homes
- susceptibility and exposure of infants and children that may be different from that of adults during critical developmental stages

The re-evaluation of risks to human health also includes a re-examination of the acceptability of risks resulting from occupational exposure. Once the reassessments of all the individual organophosphates have been completed, a cumulative assessment of all the remaining uses of organophosphates will be conducted.

Risk to the environment: The environmental assessments will be tiered, with refined environmental risk assessments taking place only on those actives, products or uses that pass the cumulative health risk assessment or, for unique mechanisms of toxicity, that are acceptable from a human health perspective. At the first tier, based on an identification of hazards to non-target organisms, measures to reduce environmental exposure will be implemented where warranted. These measures may include removing uses which are obsolete, reducing the number of applications, requiring buffer zones to protect sensitive habitats, and taking regulatory action against uses that have been determined to be extremely high risk to organisms in the environment. In general, uses which remain after the first tier assessment will be revisited when the results of refined environmental assessments are available.

A tiered approach is necessary for several reasons. For some products, initial environmental assessments indicate a high hazard. However, there is considerable uncertainty with regard to the frequency and magnitude of exposure and effects. For some products there is also little data on field concentrations and (or) adverse effects. A tiered approach to environmental risk assessment would allow time for development and implementation of refined ecological risk assessment methods, for additional data to be provided to refine the environmental exposure assessments, and for consideration of the preferability of existing alternatives and the development of new ones. In addition, a tiered approach would make most efficient use of assessment resources.

Value: The PMRA seeks to understand, as early as possible in the re-evaluation process, the current uses of products under review and their importance for pest management in agriculture, the nursery trades, forestry and public health. The PMRA relies to a great extent on provincial and territorial government input. Registrants and users are also an important source of information. Environment Canada, the Department of Foreign Affairs and International Trade, the Canadian Food Inspection Agency (CFIA) and Agriculture and Agri-Food Canada are also contacted during the re-evaluation process, as needed, for information specific to their areas of expertise.

The outcome of the re-evaluation of each pesticide, including proposed risk mitigation measures, will be published in a consultation document at the end of the aggregate human health risk assessment and the first tier environmental assessment. In some cases, the PMRA will implement changes in regulatory status of products prior to public consultation, especially where the PMRA considers risk mitigation ineffective or impractical, or where registrants have opted for voluntary discontinuation of the sale of products.

3.0 Re-evaluation of fenthion

Fenthion is one of 27 organophosphate pesticides subject to re-evaluation in Canada. The re-evaluation of fenthion was announced in Re-evaluation Document REV99-01 *Re-evaluation of organophosphate pesticides*. Fenthion is a broad spectrum organophosphate insecticide which inhibits the enzyme acetylcholinesterase, interrupting the transmission of nerve impulses. It works by systemic action. Pest control products containing fenthion were first registered in Canada in 1961. Currently, the primary use of fenthion is for insect control on livestock. Previously registered uses for fenthion (e.g., mosquito and fly control, bird control, and insect control in ornamental crops, forestry, companion animals, and agricultural, industrial and residential buildings) have been voluntarily discontinued by registrants. The currently registered products containing fenthion are listed in Appendix I.

Much of the scientific information used by the PMRA in its assessment of fenthion came from reviews conducted by the United States Environmental Protection Agency (EPA). The EPA reviews of fenthion can be referenced for further details regarding the scientific studies used by the PMRA. These reviews, as well as other information on the regulatory status of fenthion in the United States, can be found at the website of the Environmental Protection Agency, http://www.epa.gov/pesticides/op/status.htm.

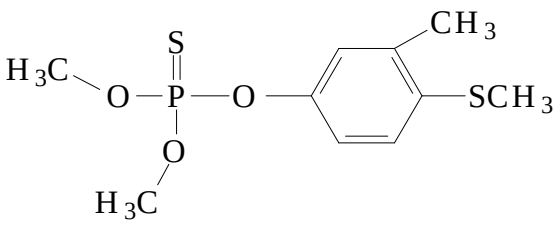
3.1 Chemical identification

Chemical name
International Union of
Pure and Applied Chemistry: O,O-Dimethyl O-4-methylthio-m-tolyl phosphorothioate

or

Chemical name
Chemical Abstracts Service: O,O-Dimethyl O-[3- methyl-4-(methylthio)phenyl] phosphorothioate

Molecular formula: $C_{10}H_{15}O_3PS_2$



3.2 Description of current registered uses

The following information is based on the currently registered uses of fenthion.

Type of pesticide: insecticide

Summary of use sites:
Livestock: beef cattle, non-lactating dairy cattle.

In the U.S., uses on livestock were discontinued by registrants.

Target pests:
Anoplura: sucking lice.
Diptera: cattle grub (warble).
Mallophaga: chewing lice.

Formulation types registered: solution.

Method and rates of application:
Equipment: On livestock, pour-on solution.

Method and rate: On cattle, pour-on application 440–1184 mg a.i./100 kg body weight. One (cattle grub) or two (lice) applications 28–35 days apart can be made per season. Applications can be made up to 10 days prior to milking, 35 days prior to slaughter (lower application rate or single application) or 45 days prior to slaughter (higher application rate or two applications).

4.0 Effect having relevance to human health

4.1 Toxicology summary

The toxicology database supporting fenthion is based primarily on studies available from the registrant. In laboratory animals, fenthion was highly toxic via the oral and moderately toxic via the dermal and inhalation routes of exposure. Fenthion was non-irritating to the skin and minimally or non-irritating to the eye and not considered a dermal sensitizer. With oral exposure, fenthion was readily absorbed and extensively metabolized with little tissue retention. Metabolites were rapidly eliminated primarily via the urine with the major metabolite group composed of the three phenols and their sulphoxide, sulphone and glucoronide conjugates. Four desmethyl metabolites were also identified with the oxygen analogue sulphoxide constituting a minor amount.

Following both single and repeated dosing, the most sensitive indicator of toxicity was the inhibition of acetylcholinesterase, an enzyme necessary for the proper functioning of the nervous system, or clinical signs of cholinergic toxicity. Acetylcholinesterase was affected by oral, dermal and inhalation routes with no appreciable species or gender differences. On the basis of the available toxicity studies, fenthion is anticipated to have high dermal absorption potential. In repeat–dose studies, there was no indication that longer duration of dosing increased toxicity in the rat. Fenthion did not cause any apparent delayed neurotoxicity and there was no evidence of histopathological effects on the central or peripheral nervous system in any of the available neurotoxicity studies. In the chronic rat study, there was corneal scarring, corneal neovascularization and mineralization, retinal atrophy, subcapsular cataracts and optic nerve atrophy at the highest dose. Females at the high and mid dose had suppression of the electroretinogram. Fenthion showed no evidence of tumorigenicity in either rats or mice following chronic dosing. While most genotoxicity studies showed no significant response, positive results were obtained in a mouse micronucleus and unscheduled DNA synthesis assay.

There was no evidence of teratogenicity in rats or rabbits up to the highest dose tested or additional sensitivity of the fetus following in utero exposure to fenthion in the developmental studies. Reproductive effects observed at the highest dose in the 2-generation reproduction study included reductions in fertility, number of implantations sites/dam, number of litters and litter size, and increases in the number of stillborn pups/litter, but at a dose level eliciting significant reductions in cholinesterase activity in the parental animals. Effects observed in the high dose offspring included reduced viability and weaning indices as well as reductions in cholinesterase activity. Based on the results of this study, there is no evidence of increased sensitivity of the offspring compared to the adults due to treatment with fenthion. The only effects indicative of endocrine disruption were the observations of epididymal vacuolation in the chronic and reproduction rat studies however these observations were noted at levels higher than those which elicited significant cholinesterase depression.

Reference doses have been set based on no observed adverse effect level (NOAELs) for the most sensitive indicator of toxicity, namely acetylcholinesterase inhibition and (or) cholinergic signs of toxicity. These reference doses incorporate various uncertainty factors to account for extrapolating between laboratory animals and humans and for variability within the human populations. Additional uncertainty factors have been used where the most relevant study has not demonstrated a NOAEL.

The toxicology end points used in the risk assessment of fenthion are summarized in Appendix II.

4.2 Occupational risk assessment

Occupational risk is estimated by comparing the potential exposure of persons mixing, loading and applying pesticides to the most relevant end points from toxicology studies to generate a margin of exposure (MOE). The risk exceeds the PMRA's level of concern if the MOE is less than the desired or target MOE.

For short-term dermal risk assessment, the most suitable toxicology study for risk assessment was the 23-month oral toxicity study in monkeys. In this study, erythrocyte cholinesterase was not inhibited at 0.2 mg/kg bw/d in the first week of the study but was subsequently affected at 0.07 mg/kg bw/d after the first week of the study. Although this study had limitations that precluded its use as a full chronic study, a NOAEL of 0.2 (short-term, 1–7 days) could be established for cholinesterase inhibition, which was identified in the remainder of the database as the most sensitive end point. A target MOE of 100 was established based on standard uncertainty factors of 10× for interspecies extrapolation and 10× for intraspecies variability.

The 3-week inhalation toxicity study in rats was used for short-term (1–7 days) risk assessment, with a NOAEL of 0.001 mg/L (0.27 mg/kg bw/d) based on clinical signs of neurotoxicity at the next higher dose. A target MOE of 100 was established based on standard uncertainty factors of 10× for interspecies extrapolation and 10× for intraspecies variability.

A dermal absorption value was required in the dermal risk assessment. There were no studies available in the scientific literature. Based on the use pattern, it was concluded that using a conservative default of 100% for dermal absorption was sufficient to support fenthion's continued use.

4.2.1 Mixer/loader/applicator exposure

For livestock application, workers can be exposed occupationally to fenthion through mixing, loading and applying the registered products during normal use. Applicators are expected to have intermittent short-term exposure. Based on the use patterns of fenthion, two major exposure scenarios were identified: 1) applying ready-to-use solutions (pour-on); and 2) mixing, loading and applying liquids via ladling. Dermal and inhalation exposure estimates for mixing and loading liquids 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 with associated software which facilitates the generation of scenario-specific exposure estimates. To estimate exposure for each use scenario, appropriate subsets were created from the mixer/loader and applicator database files of PHED. All data were normalized for the amount of active ingredient handled. Exposure estimates were 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. As the PHED data subset are not specifically for animal treatments, there is some uncertainty associated with the exposure

estimates. However, the PHED data provide a reasonable frame of reference to approximately assess the risks.

Exposure is calculated as the product of the unit exposure (mg/kg a.i. handled) for a given scenario and the amount of active ingredient handled per day divided by the body weight. Occupational risk is estimated by comparing a calculated margin of exposure to a target MOE incorporating safety factors protective of the most sensitive sub-population. MOEs greater than or equal to 100 do not require risk mitigation.

MOEs for all occupational mixers, loaders and applicators, based on the current label personal protective equipment requirements are above 100. Although MOEs are above the Agency target, a chemical resistant apron and long chemical resistant gloves are recommended for all scenarios due to the uncertainties that result from using PHED data for animal treatment scenarios and the potential for splashes.

4.2.2 Post-application exposure

The labels prohibit treatment to cattle 10 days before or after shipping, weaning, or dehorning, and no lactating dairy cattle are to be treated. Contact with treated animals after application is complete would probably result in exposures much lower than handlers would receive. Therefore a quantitative post-application exposure assessment was not conducted. However, the product labels should instruct users to avoid contact with treated animals until the liquid has dried.

4.3 Residential risk assessment

Since uses of fenthion in residential areas have been discontinued, a residential risk assessment was not required.

4.4 Dietary risk assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested as part of the daily diet. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life. For example, assessments take into account children’s greater consumption of fruit, vegetables and juices for their body weight compared with adults.

Acute dietary risk is calculated by considering food consumption and residue values in food. A probabilistic statistical analysis allows all possible combinations of consumption and residue levels to be combined to estimate a distribution of the amount of fenthion residue that might be eaten in a day. A value representing the high end (99.9^{th} percentile) of this distribution is compared to the Acute Reference Dose (ARfD), which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake from residues is less than the ARfD, the expected intake is not considered to be of concern.

The chronic dietary risk is calculated by using the average consumption of different foods, and average residue values on those foods, over a 70-year lifetime. This expected intake of residues is compared to the Acceptable Daily Intake (ADI), which is the dose at which an individual could be exposed over the course of a lifetime and expect no adverse health effects. When the expected intake from residues is less than the ADI, the expected intake is not considered to be of concern.

To estimate acute dietary risk (1-day exposure) for the general population, the 23-month monkey study was selected where it was determined that there was no inhibition of erythrocyte cholinesterase during the first week of the study at doses up to and including 0.2 mg/kg bw/d, establishing this as an acute NOAEL. Standard uncertainty factors of 10× for interspecies extrapolation and 10× for intraspecies variability were applied for an overall factor of 100. The ARfD was calculated to be 0.002 mg/kg bw (0.2 mg/kg bw ÷ 100). This value was considered to be protective of infants and children.

To estimate risk from repeat dietary exposure, the lowest observed adverse effect dose level (LOAEL) of 0.03 mg/kg bw/d from the 102-week dietary study in mice was selected for risk assessment. This chronic LOAEL was based on depression of brain cholinesterase in males in this dose group. Standard uncertainty factors of 10× for intraspecies variability and 10× for interspecies extrapolation as well as an additional uncertainty factor of 3× for use of a LOAEL were applied. Thus the ADI was calculated to be 0.0001 mg/kg bw/d (0.03 mg/kg bw/d ÷ 300). This value was considered to be protective of infants and children.

4.4.1 Dietary exposure

Currently, Canadian MRLs for meat and milk are covered by Subsection B.15.002(1) of the Food and Drug Regulations at 0.1 ppm, with no formal definition of the residue(s) of concern (ROC).

The U.S. currently lists the tolerance for fenthion as the sum of fenthion and its cholinesterase-inhibiting metabolites (40 CFR 180.214, 2001). The ROC for fenthion defined by Codex (1999) is the sum of fenthion, its oxygen analogue, and their sulfoxides and sulfones. The acute and chronic dietary exposure and risk estimates for fenthion were performed with the ROC defined as the sum of fenthion, its oxygen analogue, and their sulfoxides and sulfones.

Acute and chronic dietary exposure and risk estimates were generated using the Dietary Exposure Evaluation Model (DEEM®) software and updated consumption data from the FDA's Continuing Surveys of Food Intake of Individuals, CSFII (1994–1998).

The acute dietary exposure was assessed using a refined assessment. Refinements included (where appropriate) generating residue distribution files (RDFs) which incorporated empirical data from magnitude of residue (MOR) studies, percent livestock treated (%LT) estimates, CFIA and FDA monitoring data, and percent crop imported from countries with potential use of fenthion (for commodities with an established Codex MRL). The acute PDI accounted for < 75% (99.9^{th} percentile) of the acute reference dose (ARfD) for all sub-populations, with children 1–6 years old being the most highly exposed sub-population.

The chronic dietary exposure was assessed using a refined assessment. Refinements included (where appropriate) incorporating mean residues from MOR studies, %LT estimates, CFIA and FDA monitoring data, and percent crop imported from countries with potential use of fenthion (for commodities with an established Codex MRL). The chronic PDI accounted for < 90% of the acceptable daily intake (ADI) for all sub-populations, with children 1–6 years old being the most highly exposed sub-population.

These chronic and acute dietary risk assessments demonstrated that there were no concerns for any population subgroup in Canada, including infants, children, teenagers, adults and seniors. In addition, no dietary concerns were evident for nursing or pregnant females or based on gender in general.

4.5 Aggregate risk assessment

There are no longer residential uses of fenthion and residues in drinking water are expected to be negligible (see Section 5.3), so an aggregate risk assessment was not conducted.

5.0 Environmental assessment

5.1 Environmental fate

This assessment is mainly based on the data from the U.S. EPA Re-registration Eligibility Decision of fenthion (Environmental Fate and Effects Division (EFED) RED chapter for fenthion, Aug., 1996).

The vapour pressure for fenthion was determined to be 0.37 mPa (2.8×10^{-6} mm Hg), which indicated that fenthion has a low potential to volatilize. The calculated Henry's Law Constant ($K = 2.4 \times 10^{-7}$ atm m^3/mole) indicated that fenthion is unlikely to volatilize from moist soil or water.

Fenthion is unlikely to persist in the environment (aerobic biotransformation DT_{50} < 1 day). Fenthion has low mobility in soil, and is thus unlikely to impact on groundwater resources (K_{OC} = 946–2179). An aged fenthion leaching study indicated that the transformation products of fenthion are more mobile than the parent fenthion and may potentially leach to levels that may affect groundwater resources. However, quantities of fenthion that are applied to each individual animal are small and are unlikely to reach the soil surface unless the product is spilled.

Fenthion has a low solubility (4.2 mg/L), high K_{ow} (69 000) and high K_{oc} (946–2179), thus, if fenthion enters the aquatic environment it is expected to adsorb to organic particles in the water column or partition into sediments. The high K_{ow} also indicates that fenthion has a potential to bioaccumulate.

Phototransformation is an important route of transformation of fenthion in surface waters. The phototransformation is dependent on temperature, although the half-life was determined to be less than one hour at all temperatures tested. The hydrolysis of fenthion and its major transformation products were studied and it was concluded that hydrolysis is not an important route of transformation of fenthion and its transformation products at neutral and basic pH (hydrolysis at acid pH was not tested) ($t_{½}$ = 59 d for fenthion at pH 7, $t_{½}$ > 16 d for all transformation products tested). In an aerobic water/sediment biotransformation study it was determined that fenthion preferentially partitions to the sediment resulting in a DT_{50} of < 2 d in water, 20 d in sediment and 16 d in the total system. Thus, fenthion is not persistent in water and slightly persistent in sediment. The anaerobic biotransformation DT_{50} of 11 d indicates that fenthion will not persist under anaerobic conditions in the aquatic environment.

5.2 Environmental toxicology

Fenthion is classified as highly to very highly toxic to birds on an acute oral basis (LD_{50} = 25.9–2.5 mg a.i./kg bw), whereas it is moderately toxic to mammals (LD_{50} = 405–566 mg a.i./kg bw). On a dietary basis fenthion is slightly to very highly toxic to birds (LC_{50} = 1259–30 mg a.i./kg diet). The two major transformation products tested (fenthion phenol sulfoxide and fenthion phenol sulfone) were identified as practically non-toxic to birds on an acute oral basis (LD_{50} = > 2000 mg a.i./kg bw).

On an acute basis fenthion was determined to be very highly toxic to freshwater invertebrates (LC_{50} = 0.024–350 µg a.i./L), moderately to highly toxic to freshwater fish (1700–299 µg a.i./L), highly to very highly toxic to estuarine and marine invertebrates (LC_{50} = 340–0.15 µg a.i./L) and moderately toxic to estuarine and marine fish (LC_{50} = 1200–1900 µg a.i./L). Chronic toxicity values are presented although chronic exposure to fenthion is not expected. Toxicity testing using aquatic plants indicates that fenthion is not particularly toxic to plants (EC_{50} = 360 µg a.i./L).

5.3 Concentrations in drinking water

Fenthion is expected to have limited impact on drinking water sources in Canada because of its limited use pattern. Fenthion is sparingly soluble with a high log K_{ow}. These physicochemical properties combined with the high organic carbon coefficients determined in laboratory studies and the rapid dissipation from soil indicate that fenthion is unlikely to leach to sufficient depths nor run-off independently from the application area. Fenthion may leave the treatment site if precipitation results in soil erosion although, given the limited use pattern (i.e. applied directly to the back of livestock), fenthion is unlikely to reach the soil. Fenthion may enter the aquatic environment if freshly treated cattle are allowed to wade into aquatic areas. Upon entering a water body there is the potential for a portion of the fenthion applied to the cattle to wash off into the water. If fenthion enters the aquatic environment it is not likely to persist. Laboratory studies indicate that fenthion is highly susceptible to phototransformation in surface waters and is not persistent under aerobic and anaerobic aquatic conditions.

5.4 Terrestrial assessment

A suitable method for quantifying the risk to non-target organisms from the application of pesticides to livestock is currently not available. A risk to birds may exist from direct exposure to freshly treated cattle or through secondary exposure from consuming contaminated carcasses. The primary exposure can result from dermal contact with fenthion when birds perch on freshly treated cattle and through ingestion of contaminated hair or insects.

Two avian mortality incidents directly related to the use of fenthion as a livestock application in the U.S. have been reported to the U.S. EPA. Numerous other mortality incidents have been linked to the use of fenthion in the U.S. through other application methods (i.e., Rid-A-Bird Perch (no longer registered in the U.S.) and mosquito control) in addition to other incidents, including one reported in Canada, where the use pattern is not known.

5.5 Aquatic assessment

Aquatic organisms can be exposed to livestock pesticides as a result of spills or run-off from the treatment site in addition to the pesticide washing off freshly treated animals that wade into a body of water. However, there is evidence from another organophosphate pesticide used for the same purpose that the amount available to wash-off the hide after 24 hours of air drying is minimal. Environmental exposure is expected to be limited as use of fenthion is restricted to treatment of livestock.

5.6 Toxic substances policy statement

During the review of fenthion, the PMRA has taken into account the federal Toxic Substances Management Policy[2] (TSMP) and has followed its Regulatory Directive DIR99-03[3]. The following were considered:

- Fenthion has the potential to bioaccumulate. The log octanol-water partition coefficient (log K_{ow}) is 4.8, which is below the TSMP Track-1 cut-off criterion of log $K_{ow} \geq 5.0$.

- Fenthion does not meet the criteria for persistence as its DT_{50} value in soil is < 1d which does not meet the TSMP Track-1 cut-off criteria of ≥ 182 d. Fenthion does not meet the TSMP Track-1 cut-off of ≥182 d in water as the aerobic DT_{50} in water is < 2 d, the DT_{50} in soil = 20 d and the anaerobic DT_{50} = 11 d. No data were available to assess the persistence in air although the current use pattern is not expected to result in the volatilization of fenthion.

- The toxicity of fenthion is described in chapters 4 and 5.2.

- No data were available to assess the major transformation products according to the TSMP policy.

It has been determined that this active (fenthion) does not meet TSMP Track-1 criteria because it does not meet the criteria for bioaccumulation (log $K_{ow} \geq 5$) and persistence (DT_{50} = 182 d). Further information is required to assess the major transformation products (see Section 8.4).

5.7 Formulants in pest control products

Formulant issues are being addressed through PMRA formulant initiatives or the formulant policy under development, including:

- List 1 formulants are subject to removal from products as communicated to registrants of affected products in September 2001.

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[2] The federal Toxic Substances Management Policy is available through Environment Canada's Website at : http://www.ec.gc.ca/toxics

[3] The PMRA's Strategy for Implementing the Toxic Substances Management Policy, Regulatory Directive DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; E-Mail pminfoserv@hc-sc.gc.ca or through our Website at http://www.hc-sc.gc.ca/pmra-arla

- Registrants of products containing nonylphenol ethoxylates are requested to replace nonylphenol ethoxylates with less harmful alternatives.

- Other formulants including List 2 formulants, formulation preservatives, and allergens will be subject to future regulatory action as outlined in the PMRA's Regulatory Proposal, PRO2000-04 *Formulant Policy* (soon to be issued as a regulatory directive).

No EPA or PMRA List 1 formulants of toxicological concern were identified in the end-use products containing fenthion.

5.8 Environmental assessment conclusions

Although acceptable methods for conducting a quantitative environmental assessment were not available, the evidence suggests that there is a potential risk to wild birds and aquatic organisms from the use of fenthion on livestock. This active is highly toxic to both birds and aquatic invertebrates and thus, if there is exposure to fenthion, it will result in non-target effects.

Reports of avian mortality have occurred in both Canada and the U.S. that are directly related to livestock application of fenthion. In addition, a number of the incidents have been reported in the U.S. where the use pattern resulting in the mortality was not clearly defined. It is clear that birds are being exposed to fenthion and mortality is occurring. General label statements regarding environmental toxicity are required (see Chapter 7.2).

6.0 Value

6.1 Evaluation method

The importance of fenthion end-use products for managing specific pests on specific crops in Canada was evaluated based on:

- the availability of registered alternative pesticides that are potential substitutes

- current field use of fenthion in agriculture in Canada as measured by a survey of organophosphate (OP) use conducted in 1998 (the "1998 OP Survey") with the cooperation of provincial governments, and from consultations with crop production specialists

- expert opinion of provincial agricultural officials, grower groups, and other stakeholders.

Uses of fenthion were divided into four value classes as follows:

Key Uses:
Based on the results from the 1998 OP Survey and the availability of effective registered alternative pesticides, some uses of fenthion were considered "key uses" because they matched one or more of the following criteria:

- a User Requested Minor Use Label Expansion (URMULE) was granted after the 1998 OP Survey and there are no registered alternatives, OR
- there was reported use of at least 10% and there are no registered alternatives, OR
- there was reported use of at least 10% and the alternatives are other organophosphate (OP) insecticides and fenthion is the preferred active, OR
- maintaining registration was considered key for resistance management and (or) plays an important role in IPM programs, OR
- the site of use is of large importance to the economy of Canada.

Important Uses:
Based on the 1998 OP Survey some uses of fenthion were considered "important uses" because they matched the following criteria:

- at least 10% of the given site has been reported to receive treatment with fenthion in some provinces, AND
- non-OP alternatives to fenthion are registered for each of these uses, however, fenthion was reported to be either the primary pest control product for that use, or one of the preferred products for that use.

Other Reported Uses:
Based on the 1998 OP Survey some uses of fenthion were considered "other reported uses" because they matched one of the following criteria:

- greater than 5% of the given site was treated in some provinces, non-OP alternatives to fenthion are registered for each of these uses, and the alternatives were reported to be used to treat a greater percentage of crop/site than fenthion, OR
- less than 5% of the given crop was treated or there was no reported use but there was an URMULE for the pest issued after the 1998 OP Survey and there are registered non-OP alternatives.

Little or No Reported Use:
Based on the 1998 OP Survey some uses of fenthion were considered to have "little or no reported use" because they matched one of the following criteria:

- less than 5% of the site in any province was reported to be treated with fenthion, OR

- fenthion is registered for use on certain sites for which the PMRA has received no information regarding the extent of use in the 1998 OP Survey.

6.2 Evaluation results

All registered uses of fenthion are categorized as "important uses"

- cattle (beef, non-lactating dairy): for control of cattle grub (warble)
- cattle (beef, non-lactating dairy): for control of cattle lice (chewing and sucking).

7.0 Proposed regulatory action

The PMRA has determined that the aggregate risks for fenthion are acceptable provided that the mitigation measures proposed below are adopted. The acceptable uses for fenthion products, together with proposed mitigation measures and use limitations, are presented in Appendix III. Registrants will be rquired to submit label amendments within 90 days of the finalization of the decision.

7.1 Proposed regulatory action relating to human health

1. Labels of pesticide products carry statements regarding symptoms of poisoning and treatment, which are especially important for those who may be overexposed when working with the product in a commercial or industrial setting e.g., mixers/loaders who handle more concentrated forms. Based on the toxicological assessments, the label text of the fenthion-containing products should be expanded and (or) standardized, as follows:

   "Toxicological Information

   Fenthion 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."

2. For those products which contain more than 10% petroleum distillates, the following text should also be added to the Toxicological Information section (placed at the end of the paragraph presented above), as an additional aid to the attending physician:

   "NOTE: Product contains a petroleum distillate solvent."

3. Label requirements:

   a. Measures to protect mixer, loaders, applicators (all liquid pour-on solutions):

      - mixers, loaders and applicators must wear chemical resistant apron over long pants and long sleeved shirt, long chemical resistant gloves or gauntlets, shoes and socks

   b. Measures to protect workers post-application:

      - no contact with treated animals until liquid has dried.

7.2 Proposed regulatory actions relating to dietary risk

Currently, there are no specific maximum residue limits (MRLs) for fenthion in food. Consequently, any residues on imported or domestic commodities must not exceed 0.1 ppm, a default value specified by the Food and Drugs Regulations, subsection B.15.002(1).

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to prevent unauthorized use of the pesticide by recommending new MRLs at the limit of quantitation for any agricultural commodities not approved for continued treatment in Canada. Additional MRLs for import purposes will be considered if sufficient data are provided by interested parties to allow a reassessment of those residues. The U.S. EPA undertakes similar action in such circumstances. Proposed amendments to the Food and Drugs Regulations reflecting these MRLs will be published in the Canada Gazette.

In the case of fenthion, continuing registration is proposed only for products used to treat beef. Based on the available information, the PMRA will recommend the following:

- that the residue of concern for fenthion be defined as fenthion, its oxygen analogue, and their sulfoxides and sulfones;

- that an MRL of 0.1 ppm be established for the sum of these residues in meat, meat by-products and fat of cattle; and

- that an MRL be established at the limit of quantitation of fenthion residues for all other raw agricultural commodities, unless additional data are provided to support additional import MRLs.

A proposal to amend the MRLs will appear in the Canada Gazette. Parties interested in supporting an MRL to allow imports of other commodities treated with fenthion should contact the PMRA to discuss the submission of appropriate data.

In the U.S., uses of fenthion on cattle have been discontinued by the registrant as a result of re-evaluation. Users of fenthion on commodities that may be exported to the U.S. should be aware of the actions taken by the U.S. EPA regarding revocation of tolerance (Federal Register Volume 67, Number 147 of July 31, 2002). The U.S. EPA is revoking the tolerances for residues of fenthion and its cholinesterase-inhibiting metabolites in or on cattle fat, cattle meet and cattle meet byproducts with an expiration/revocation date of April 1, 2006.

7.3 Proposed regulatory action relating to environment

A potential hazard to wild birds exists, but it is difficult to mitigate this hazard short of scaring away birds that may frequent areas where fenthion is applied. In addition, a potential hazard to aquatic organisms was identified. General label statements regarding environmental toxicity are required. The following wording is suggested:

- This pesticide is toxic to birds, fish and aquatic invertebrates. Do not apply directly to any body of water. Do not contaminate water when disposing of used containers.

The following label statements will reduce the risk associated with aquatic exposure to fenthion:

- Do not use this product near lakes, streams, ponds, or other aquatic systems.

- This product should not be applied when rain is forecast in order to reduce run-off from the treatment site.

8.0 Additional data requirements

As also indicated in 7.2, residue data are needed to determine appropriate import MRLs for any commodity other than beef meat, meat by-products and fat.

Data needed to support continued registration of existing uses of fenthion are noted below. Scientifically based rationales for data waivers may be acceptable for some of the following data requirements.

8.1 Data requirements related to chemistry

No additional data are required.

8.2 Data requirements related to toxicology

The following confirmatory data would be required to support the continued registration of fenthion and to support any expansion of fenthion use:

- a developmental neurotoxicity study (DACO 4.5.12)
- a dominant lethal study (DACO 4.5.8)

Although not critical to the current fenthion re-evaluation, the following data may be required to support any expansion of fenthion use:

- a short-term dermal toxicity study (DACO 4.3.3 or 4.3.4).

8.3 Data requirements related to exposure

Although not critical to the re-evaluation of current uses of fenthion, the following data may be required to support any expansion of fenthion use:

- Storage stability data should be submitted for all metabolites that will be included in the ROC definition, in the matrices that they will be expected to occur.

- The reviewed animal MOR studies should be updated by including the recovery data at spiking levels at or near the limit of quantitation (LOQ) of 0.02 ppm for all metabolites that will be included in the ROC definition.

- Data are required to determine appropriate MRLs for any commodity other than beef meat, meat by-products and fat

8.4 Data requirements relating to environmental risks

Even though the environmental fate database is limited, additional fate data are not required for the active ingredient, fenthion, at this time, given the limited environmental

exposure expected in the terrestrial and aquatic environments from the livestock use of fenthion. For expansion of use of fenthion, the data requirements will be revisited and data gaps may be identified at that time.

In order to complete the review of the livestock uses, K_{ow} values for the following transformation products are required:

- fenthion sulphoxide
- fenthion oxygen analogue
- fenthion oxygen analogue sulphoxide
- fenthion phenol
- fenthion phenol sulphoxide
- fenthion phenol sulphone

9.0 Proposed re-evaluation decision

The PMRA has carried out an assessment of available information and has concluded that the use of fenthion and its end-use products on cattle does not entail an unacceptable risk to human health and the environment pursuant to Section 20 of the PCP Regulations, provided that the proposed mitigation measures described in the document are implemented. Further measures may be necessary/proposed pending the outcome of the cumulative risk assessment for all organophosphates, which share a common mechanism of toxicity, and pending refinements to environmental risk assessment methodologies.

It is proposed that the Food and Drug Regulations be amended so that, with the exception of meat, meat by-products and fat of cattle, food with quantifiable residues of fenthion cannot be sold in Canada once Canadian use has been phased out, unless additional data to support fenthion residues in imported food are provided.

The PMRA will accept written comments of 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.

List of abbreviations

%LT	Percent Livestock Treated
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
CFIA	Canadian Food Inspection Agency
CFSII	Continuing Survey of Food Intakes by Individuals
DEEM®	Dietary Exposure Evaluation Model
EPA	Environmental Protection Agency
FDA	United States Food and Drug Administration
atm	atmospheres
bw	body weight
d	day(s)
DT_{50}	dissipation time to 50%
EC_{50}	effective concentration to 50%
EEC	expected environmental concentration
EFED	Environmental Fate and Effects Division (U.S. EPA)
EP	end-use product
g	gram(s)
h	hour(s)
ha	hectare
K	Henry's Law constant
K_d	adsorption coefficient
Kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol–water partition coefficient
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
L	litre
LOAEC	lowest observed adverse effect concentration [mg a.i./kg diet or mg a.i./L]
LOAEL	lowest observed adverse effect dose level [mg a.i./kg bw]
LOD	limit of detection
LOEC	lowest observed effect concentration [mg a.i./kg diet or mg a.i./L]
LOEL	lowest observed effect level [mg a.i./kg bw]
LOQ	limit of quantitation
min	minute(s)
mg	milligram
mm Hg	millimetre mercury
mL	millilitre
MOE	margin of exposure
mol	moles
MOR	magnitude of residue
mPa	MilliPascals
MRL	maximum residue limit
NOAEL	no observed adverse effect level

NOEC	no observed effect concentration
NOEL	no observed effect level
nm	nanometre
OC	organic carbon
OM	organic matter
OP	organophosphate insecticide
PDI	potential daily intake
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers' Exposure Database
pKa	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
ra	radioactivity applied
RDF	Residue Distribution File
Reg. No.	*Pest Control Products Act* Registration Number
R_f	retention time value
ROC	residue(s) of concern
$t_{1/2}$	first-order half-life
TGAI	technical grade active ingredient
TSMP	Toxic Substance Management Policy
URMULE	User Requested Minor Use Label Expansion
U.S.	United States of America
U.S. EPA	United States Environmental Protection Agency
µg	Microgram
vp	vapour pressure
UV	ultraviolet
wk	week(s)

Appendix I Fenthion products currently registered:

Registrant	Registration Number	Guarantee	Product Name	Class
Bayer CropScience Chemical Division	24631	95%	Tiguvon Technical Insecticide	Technical
Bayer CropScience Chemical Division	13250	20%	Spotton Cattle Insecticide	Commercial
Bayer CropScience Chemical Division	15360	7.6%	Lysoff Pour-on for Lice	Commercial
Bayer CropScience Chemical Division	24129	3%	Tiguvon Pour-on Cattle Insecticide	Commercial

Appendix II Toxicology end points for health risk assessment for fenthion

EXPOSURE SCENARIO	DOSE (mg/kg bw/d)	ENDPOINT	STUDY	UF/SF or MOE[b]
Acute Dietary	NOAEL = 0.2	No erythrocyte cholinesterase inhibition in first week of study	23-Month Oral Toxicity - Monkey	100
	ARfD = 0.002 mg/kg bw			
Chronic Dietary	LOAEL = 0.03	Brain cholinesterase inhibition	102-Week Dietary Chronic Toxicity and Oncogenicity—Mouse	300
	ADI = 0.0001 mg/kg bw/d			
Short-Term[a] Dermal[c]	Oral NOAEL = 0.2	No erythrocyte cholinesterase inhibition in first week of study	23-Month Oral Toxicity— Monkey	100
Short-Term[a] Inhalation	Inhalation NOAEL = 0.27	Clinical signs of neurotoxicity	3-Week Inhalation Toxicity—Rat	100

[a] Duration of exposure is 1–7 days

[b] UF/SF refers to total of uncertainty and (or) safety factors for dietary assessments, MOE refers to desired margin of exposure for occupational or residential assessments

[c] Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) should be used in route-to-route extrapolation

Appendix III Use standard for commercial class products containing fenthion

(**NOTE:** The information in this appendix summarizes the acceptable uses, limitations and precautions for commercial class products containing fenthion, but does not identify all label requirements for such products. Registrants are referred to the PMRA Registration Handbook for further guidance on label requirements for pest control products.)

COMMON NAME: fenthion

CHEMICAL NAME: *O,O*-dimethyl *O*-[4-(methylthio)-m-tolyl]phosphorothioate

FORMULATION TYPE: EC emulsifiable concentrate
SN solution

SITE CATEGORIES: Livestock for food 08

GENERAL LIMITATIONS:

Avoid contact with treated animals until the liquid has dried.

TOXICOLOGICAL INFORMATION: Fenthion 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 should be made by an attending physician.

[For those products which contain greater than 10% petroleum distillates, the following text should also be added to TOXICOLOGICAL INFORMATION section (placed at the end of the paragraph presented above), as an additional aid to the attending physician:

NOTE: Product contains a petroleum distillate solvent.]

PROTECTIVE CLOTHING AND EQUIPMENT:

Workers who mix, load, apply or otherwise handle solutions containing fenthion must wear a chemical resistant apron over long pants and a long sleeved shirt, long chemical resistant gloves or gauntlets and shoes and socks.

ENVIRONMENTAL HAZARDS:

This pesticide is toxic to birds, fish and aquatic invertebrates. Do not apply directly to any body of water. Do not contaminate water when disposing of used containers.

Do not use this product near lakes, streams, ponds, or other aquatic systems.
This product should not be applied when rain is forecast in order to reduce run-off from the treatment site.

ACCEPTABLE USES FOR FENTHION

SITES, PESTS	RATES (AS ACTIVE) AND DIRECTIONS
1. LIVESTOCK FOR FOOD	
BEEF CATTLE, NON LACTATING DAIRY CATTLE	Do not give a second treatment sooner than 35 days after the first. Do not treat lactating dairy cattle, animals less than 3 months old, sick, convalescent, or stressed livestock. Do not treat non-lactating dairy cattle within 10 days of freshening. If freshening should occur within 10 days of treatment, do not use milk as human food for the balance of the 10-day interval. Do not treat animals for 10 days before or after shipping, weaning, dehorning, or after exposure to contagious or infectious diseases. Do not use this product on animals simultaneously with, or within a few days before or after treatment with or exposure to, cholinesterase-inhibiting drugs, pesticides or chemicals. Do not slaughter cattle within 35 days of a single treatment. If a second application is made for louse control, do not slaughter within 45 days of the second treatment. The second treatment should not be applied sooner than 35 days after the first treatment. Host-parasite reactions such as bloat, salivation, staggering and paralysis may sometimes occur when cattle are treated while the common cattle grub *Hypoderma lineatum* is in the gullet, or while the northern cattle grub *H. bovis* is in the area of the spinal cord. Cattle should be treated either BEFORE or AFTER these stages of grub development. Host-parasite reactions are most prevalent during the winter months. Therefore, if treatment cannot be made before the end of November, treatment during the winter months of December, January and February should be made only under the supervision of a veterinarian. Consult your provincial recommendations regarding the timing of treatment
Cattle grub, lice (reduction)	Spot application: SN formulation, 0.59–1.18 g (from 20 %solution)/100kg body weight. Apply the solution to a single location on the middle of the animal's back. Only one application per season is needed for grub control and reduction of lice. Pour-on: SN formulation, 0.975 g (from 3% solution)/100kg body weight. Treat as soon as possible after heel fly activity ceases. Pour the correct amount of solution uniformly along the animal's back. Only one properly-timed application per season is required for grub control.
Lice	Pour-on: SN formulation, 0.54 g (from 3% solution)/100 kg body weight. EC formulation, 0.53 g (from 0.74% emulsion)/100 kg body weight. Treat when lice become a problem or when the existence of lice has been confirmed. Pour the correct amount of solution uniformly along the animal's back. Repeat if necessary. Treat every animal in the heard (except those under three months of age) to reduce sources of re-infection. Cattle previously treated for grubs with a systemic insecticide may be treated again later in the season should the lice become a problem.