Proposed Re-evaluation Decision PRVD2017-07

Phosmet

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Executive Summary

Health Canada's Pest Management Regulatory Agency (PMRA)

Health Canada's primary objective in regulating pesticides is to protect Canadians' health and their environment. Pesticides must be registered by Health Canada's Pest Management Regulatory Agency (PMRA) before they can be imported, sold, or used in Canada. Before being approved for registration, pesticides must go through rigorous science-based human health, environmental and value assessments.

Under the *Pest Control Products Act*, all registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure that they continue to meet modern health and environmental safety standards and continue to have value. This may happen sooner if there have been changes in the required information or to the risk assessment methodology. Re-evaluations may result in:

- changes to how products are used;
- changes to product labels to meet current health and environmental standards; or,
- removing products from the market to prevent future harm to health or the environment.

The re-evaluation considers all available information, including data from pesticide manufacturers, published scientific reports, information from other regulatory agencies and other available, relevant information. To reach its decisions, the PMRA applies internationally accepted hazard and risk assessment methods and modern risk management approaches and policies. For more information on how the PMRA regulates pesticides, as well as the assessment process, please visit the Pesticides and Pest Management portion the Canada.ca website.

Re-evaluation of Phosmet

Phosmet is an insecticide used to control insect pests on ornamental plants and a wide variety of agricultural crops including alfalfa, fruits and vegetables.

This document (Proposed Re-evaluation Decision PRVD2017-07, *Phosmet*) presents an updated human health risk assessment for phosmet, based on the additional information submitted to the PMRA by the registrant.

Key Findings

When considering all the currently available information, the human health risk assessment identified concerns for workers handling phosmet during its application and for people conducting post-application activities such as hand harvesting and thinning. The level of precaution needed to lower potential post-application risks to an acceptable level is not feasible. Therefore, PMRA is proposing to phase-out the registration of phosmet products.

Next Steps

The proposed re-evaluation decision is now open for public consultation for 90 days from the date of the publication of Proposed Re-evaluation Decision PRVD2017-07, *Phosmet*. Once the PMRA considers the comments and any information received during the public consultation period, it will publish a final decision.

Overview

What is the Proposed Re-evaluation Decision for Phosmet?

Using all currently available information and most recent risk assessment methods, the PMRA has identified potential risks of concern to human health that cannot be reduced through feasible label directions. For this reason, the PMRA is proposing to phase out all uses of phosmet.

Before making a final re-evaluation decision on phosmet, the PMRA will accept and consider written comments and additional data received up to 90 days from the date of this publication. Please forward all comments to Publications. The PMRA will consider any additional data/information submitted during the consultation period in the final decision.

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

Under the *Pest Control Products Act*, all registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure that they continue to meet modern health and environmental safety standards and continue to have value. The re-evaluation considers data from pesticide manufacturers, published scientific reports, information from other regulatory agencies and other available, relevant information. To reach its decisions, the PMRA applies internationally accepted hazard and risk assessment methods and modern risk management approaches and policies.

For more information on how the PMRA regulates pesticides, as well as the assessment process, please visit the Pesticides and Pest Management portion of the Canada.ca website at healthcanada.gc.ca/pmra.

What is Phosmet?

Phosmet is an organophosphate insecticide used to control insect pests on ornamental plants and a wide variety of agricultural crops including alfalfa, fruits and vegetables. There are currently two end-use products containing phosmet registered for commercial use in Canada:

- IMIDAN 50-WP INSTAPAK (Registration Number 23006)
- IMIDAN 70-WP INSTAPAK (Registration Number 29064)

Health Considerations

Can Approved Uses of Phosmet Affect Human Health?

PMRA's assessment identified risks of concern for workers entering treated sites, and from residential exposures to phosmet. Based on the currently available information, there are no feasible measures to address these concerns. Therefore, all uses of phosmet are proposed for phase-out.

Potential exposure to phosmet may occur through the diet (food and drinking water), when handling and applying products containing phosmet or when coming in contact with treated plants. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risk are established to protect the most sensitive human population (that is, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which exposure is well below the levels that cause no effects in animal testing are considered acceptable for registration.

In laboratory animals, phosmet had high acute toxicity via the oral route of exposure, moderate acute toxicity via the inhalation route and low acute toxicity via the dermal route. Phosmet caused moderate eye irritation and did not cause allergic skin reactions.

The PMRA assessed short- term and long-term (lifetime) animal toxicity tests supplied by the registrant as well as information from published scientific literature to evaluate the potential of phosmet to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The risk assessment takes these potential effects into account in determining the allowable level of human exposure to phosmet.

Residues in Food and Drinking Water

Dietary risks from food and drinking water are not of concern.

The dietary assessment took into consideration the potential for exposure to phosmet residues in treated crops and animal commodities (including imports), and drinking water for the general population and different subpopulations. No acute, chronic and cancer risks of concern were identified.

Occupational Risks

Risks to handlers are of concern for some uses, but these potential risks can be mitigated.

Risks to farmers and workers who mix, load and apply phosmet for crops (fruits, vegetables, ornamentals and alfalfa) are of concern for some scenarios. However, these potential risks can be effectively mitigated using additional personal protective clothing and engineering controls (such as protective headgear and/or closed cabs). In some cases, limiting the amount of product that can be used per day can mitigate the risks.

Risks to workers entering treated sites are of concern, and mitigation is not considered to be feasible. In order to address these potential concerns, all uses of phosmet are proposed for phase-out.

Occupational post-application risk assessments consider exposure to workers entering treated sites in agriculture and other scenarios. Based on the precautions and directions for use on the current product labels, post-application risks to workers performing activities such as thinning, pruning and harvesting of crops are of concern. Occupational post-application risks can be mitigated by increasing the amount of time before safely re-entering a treated site. However, the restricted entry intervals (REIs) proposed to mitigate post-application risks range from 12 hours to 79 days and are not considered to be feasible. As a result, all uses of phosmet are proposed for phase-out.

Risks in Residential and Other Non-Occupational Environments

Residential risks are of concern following commercial application to fruit trees and gardens in residential areas. In order to address these concerns, these uses of phosmet are proposed for phase-out.

There are currently no domestic phosmet products registered in Canada. Therefore, a risk assessment for residential handlers was not required.

Commercial application of phosmet to residential ornamentals and fruit trees could lead to exposure for people working in their home gardens. Risk assessments for such activities identified cancer and non-cancer risks of concern. Consequently, commercial application to residential ornamentals and fruit trees is proposed for phase-out.

Exposure to people who enter pick-your-own establishments following commercial application of phosmet to fruit trees or berries was not assessed, since the proposed REIs for commercial post-application workers (orchards, blueberries) are already not considered to be feasible.

Agricultural application of phosmet may result in spray drift. Studies that sampled the air surrounding agricultural areas in the United States during the spray season indicate that phosmet can be present in ambient air. Non-cancer and cancer risk estimates based on phosmet air concentrations are not of concern.

Aggregate risk estimates were not conducted due to existing non-cancer and cancer risk concerns from non-occupational exposures.

Environmental Considerations

When used according to the proposed label directions, phosmet is not expected to pose risks of concern to the environment.

The environmental fate and toxicity of phosmet was previously considered in PACR2004-38 and REV2007-14. Label statements for the protection of pollinators would need to be updated to meet current standards. However, at this time, the PMRA is proposing to phase out all uses of phosmet as a result of the human health risk assessment.

Value Considerations

What is the Value of Phosmet?

Phosmet plays an important role in insect pest management in Canadian agricultural production.

Phosmet is used on a wide variety of agricultural crops, including alfalfa, fruits and vegetables, and is also used on ornamental plants. For some crops, phosmet is the only approved insecticide to control specific pests. Furthermore, phosmet contributes to insecticide resistance management by helping to delay the development of insect resistance when used in rotation with insecticides having a different mode of action.

Proposed Measures to Minimize Risk

Based on the currently available information and most recent risk assessment methods, there are no feasible measures to reduce the risk to an acceptable level for people entering treated sites to conduct activities such as hand harvesting and thinning. Therefore, the PMRA is proposing to phase out all uses of phosmet.

What Additional Scientific Information Is Requested?

Since the phase-out of all uses is proposed as a result of the human health risk assessment, no additional data are required at this time.

Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments, which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period, for advice on studies or information that could be submitted to help refine the relevant risk assessments. Consideration of any additional data/information submitted during the consultation period to further refine the health risk assessment may or may not result in a change to this proposal.

Before making a final re-evaluation decision on phosmet, the PMRA will consider any comments received from the public in response to Proposed Re-evaluation Decision PRVD2017-07, *Phosmet*[1]. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments. Once the final decision is made, manufacturers will be required to implement the decision according to the schedule established in the decision document.

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

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

Science Evaluation

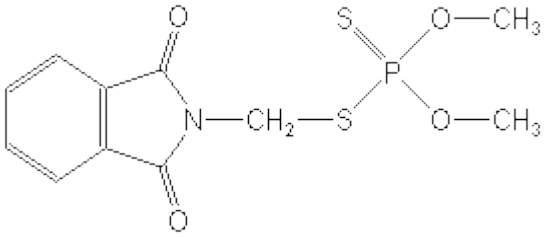
1.0 Introduction

Phosmet is a broad spectrum organophosphate insecticide that acts as an acetylcholinesterase inhibitor in the insect nervous system. It is a non-systemic insecticide with predominantly contact action.

Following the re-evaluation announcement for phosmet, the registrant of the technical grade active ingredient indicated their support to continue registration of all uses included on the labels of end-use products (EPs) containing phosmet in Canada.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Phosmet
Function	Insecticide
Chemical Family	Organophosphate
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	*O,O*-dimethyl *S*-phthalimidomethyl phosphorodithioate or *N*-(dimethoxyphosphinothioylthiomethyl)phthalimide
2 Chemical Abstracts Service (CAS)	*S*-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl] *O,O*-dimethyl phosphorodithioate
CAS Registry Number	732-11-6
Molecular Formula	$C_{11}H_{12}NO_4PS_2$
Structural Formula	
Molecular Weight	317.3
Purity of the Technical Grade Active Ingredient	96.0%
Registration Number	23055

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	0.065 mPa
Ultraviolet (UV) / visible spectrum	Not expected to absorb at λ >300 nm
Solubility in water at 20-25°C	25.0 mg/L
n-Octanol/water partition coefficient	log K_{ow} = 2.95
Dissociation constant	Not applicable

2.3 Description of Registered Phosmet Uses

Appendix I lists all phosmet products that are registered under the authority of the *Pest Control Products Act* as of January 13, 2017. Appendix II lists all commercial uses for which phosmet is presently registered. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of phosmet.

Uses of phosmet belong to the following use-site categories: terrestrial feed crops, terrestrial food crops and outdoor ornamentals.

3.0 Impact on Human Health

A detailed review of the phosmet toxicology database was previously conducted by the PMRA in Proposed Acceptability for Continuing Registration PACR2004-38, *Re-evaluation of Phosmet*. The registrant then submitted an acute "time-to-peak effect" cholinesterase inhibition study in rat pups, an acute oral comparative cholinesterase study in neonatal and adult rats and a repeat-dose oral comparative cholinesterase study in neonatal and adult rats.

In addition, the registrant submitted two 21-day dermal toxicity studies in rats, a dermal sensitization study in guinea pigs, a human clinical study and an in vitro unscheduled DNA synthesis study, which were reviewed by the PMRA. The phosmet toxicology database was also amended to include benchmark dose analysis, where possible.

The toxicological reference values for phosmet were re-examined and all were revised in light of these new toxicology data, and current PMRA policy including the application of the *Pest Control Products Act* factor.

3.1 Toxicology Summary

Since a detailed review of the toxicological database for phosmet was previously conducted and published under PACR2004-38, only a brief synopsis is included herein. The new toxicology studies for phosmet are summarized below and an updated toxicology table is included in Table 1 of Appendix III. The toxicology endpoints used in the human health risk assessment of

phosmet are summarized in Table 2 of Appendix III. The scientific quality of the data for phosmet was high and the database was considered adequate to define the majority of the toxic effects that may result from exposure to phosmet.

As described in PACR2004-38, phosmet was of high acute toxicity via the oral route of exposure, moderate acute toxicity via the inhalation route and low acute toxicity via the dermal route in laboratory animals. Phosmet caused moderate eye irritation, but was not a skin sensitizer in a modified Buehler assay submitted in response to PACR2004-38. No dermal irritation study was available. The most sensitive endpoints for risk assessment were effects on the nervous system. In vitro genotoxicity studies demonstrated that phosmet can be a direct-acting mutagen, but no genotoxicity was evident in in vivo studies. Longer-term oral dosing with phosmet resulted in liver tumors in mice, in addition to decreased reproductive organ weights (testes, ovary), gastrointestinal effects, and mineralization of the thyroid. No carcinogenicity was observed in long-term oral studies conducted in rats. Phosmet did not cause malformations and produced developmental toxicity in offspring only at doses which were maternally-toxic. It should be noted that no toxicology data were available on the transformation product, phosmet oxon (see section 3.3.1).

The new cholinesterase studies confirmed the nervous system as the target for toxicity. In the oral acute- and repeat-dose comparative cholinesterase inhibition studies, erythrocyte and brain cholinesterase inhibition were noted in juvenile and adult rats treated with phosmet. Sensitivity of the young was evident in both the acute- and repeat-dose studies, as indicated by erythrocyte and brain cholinesterase inhibition at lower oral doses in rat pups, compared to adults. A durational effect was also evident, based on the observation of cholinesterase inhibition at lower doses in the 7-day oral comparative cholinesterase study, than in the acute oral comparative study. In contrast, a durational effect on cholinesterase inhibition was not observed in longer-term repeat-dose studies conducted with phosmet.

The remaining new studies provided further information relevant to the toxicological assessment. Dermal administration in rats over a 21-day period did not result in dermal irritation, clinical signs of toxicity or effects on haematological parameters, body weight, organ weights, gross pathology or histopathology. However, brain cholinesterase inhibition was noted at low doses in both sexes. A second 21-day dermal study was considered unacceptable for hazard assessment. Phosmet was negative for induction of unscheduled DNA synthesis in rat hepatocytes in an in vivo study. The double-blind, placebo-controlled clinical study was previously submitted to the PMRA and was addressed in REV2007-14. This study involved the intentional dosing of humans with phosmet for the purpose of identifying a no observed adverse effect level (NOAEL). Consistent with PMRA's current policy on the use of human studies with pesticides (Science Policy Note SPN2016-01, *Restricted Use of Human Studies with Pesticides for Regulatory Purposes*), this systemic toxicity study was not used in the assessment of phosmet.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account the completeness of the data with respect to the exposure of, and toxicity to, infants and children as well as potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicology database for the assessment of risk to infants and children, there was a range of adequate studies including oral developmental toxicity studies in rats and rabbits, a 2-generation reproductive toxicity study in rats and acute- and repeat-dose oral comparative cholinesterase studies in juvenile and adult rats. No comparative cholinesterase data were available for dams exposed gestationally and their fetuses. Although a DNT study was not submitted, the PMRA considers the acute- and repeat-dose comparative cholinesterase studies to be appropriate for the purpose of this risk assessment.

With respect to identified concerns related to the assessment of risks to the young, sensitivity of the young was not identified in developmental toxicity studies conducted in rats or rabbits, or in the 2-generation reproductive toxicity study in rats. However, in the acute- and repeat-dose oral comparative cholinesterase studies in rat pups and adults, erythrocyte and brain cholinesterase inhibition were noted in pups at doses which were up to 5-fold lower than adults. Given this sensitivity, a 3-fold uncertainty factor for database deficiency was applied where the endpoint from testing in the sensitive population (that is, the young) was not available for risk assessment purposes. In the absence of data to suggest otherwise, it is assumed that the fetus is as sensitive as juvenile animals. Since residual concerns for sensitivity of the young were addressed through the application of an uncertainty factor, the *Pest Control Products Act* factor was reduced to 1-fold for all relevant exposure scenarios.

3.2 Dietary Exposure and 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 with the daily diet. Exposure to phosmet from potentially treated imported foods is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose or the lifetime cancer risk estimate exceeds 1×10^{-6} (one-in-a-million). PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Residue estimates used in the dietary risk assessment may be based conservatively (using upper bound estimates) on the maximum residue limits (MRLs) or field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture's (USDA) Pesticide Data Program (PDP). Theoretical and experimental processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

Sufficient information was available to adequately assess the dietary exposure and risk to phosmet. Acute, chronic and cancer dietary exposure and risk assessments for phosmet were conducted using the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02, 05-10-c) program which incorporates food consumption data from the National Health and Nutrition Examination Survey/"What We Eat in America" for the years 2005-2010, available through the Centers for Disease Control and Prevention's National Center for Health Statistics. Acute and chronic dietary exposures were estimated from residues of phosmet in treated crops and animal commodities (including imports), and from drinking water.

The acute, chronic and cancer exposure estimates are considered to be highly refined (more precise) as monitoring residues, percent crop treated (PCT), and domestic/import data were used to the extent possible. For more information on dietary risk estimates or residue chemistry information used in the dietary exposure assessment, see Appendices IV and V.

3.2.1 Determination of Acute Reference Dose (ARfD)

General Population (including pregnant women, infants and children):

To estimate acute dietary risk, the acute oral comparative cholinesterase study in rats was selected with a point of departure based on the $BMDL_{10}$ (benchmark dose 95% lower confidence limit at the 10% effect level) of 1.26 mg/kg bw for brain cholinesterase inhibition in pups on PND (postnatal day) 11. A composite assessment factor of 100 was applied to the $BMDL_{10}$ to account for uncertainty factors for inter-species extrapolation (10-fold) and intra-species variability (10-fold). As outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold.

$$\text{ARfD} = \frac{1.26 \text{ mg/kg bw}}{100} = 0.01 \text{ mg/kg bw}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk (from food and drinking water) was calculated considering the highest ingestion of phosmet that would be likely on any one day, and using food and drinking water consumption, and food and drinking water residue values. The expected intake of residues is compared to the 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 of residues is less than the ARfD, the acute dietary exposure is not of concern.

The acute probabilistic risk assessment was conducted for the general population and all subpopulations using available residue monitoring data from the CFIA and the USDA's PDP. The PMRA's and United States Environmental Protection Agency's (USEPA) policies were used for crop translations when necessary. The general maximum residue limit (GMRL) of 0.1 ppm or the US Tolerance was used for a few commodities for which no monitoring data were available. In addition, the following inputs were incorporated where available: percent crop treated (PCT) information in Canada; 100% crop treated for commodities for which no PCT information was available; available information on domestic production and import supply; and available theoretical processing factors. Drinking water contribution to the exposure was accounted for by direct incorporation of the estimated environmental concentrations (EECs) distribution, obtained from water modelling (see section 3.3) into the dietary exposure evaluation model (DEEM).

The acute dietary exposure (from food and drinking water) estimates for the general population and all subpopulations, at the 99.9^{th} percentile, ranged from 11% of the ARfD (females 13-49 years of age) to 47% of the ARfD (children 1-2 years of age). Drinking water was shown to be only a minor contributor to the acute risk assessment, accounting for less than 6% of the total exposure for the most exposed subpopulation. Acute dietary exposure is, therefore, not of concern.

3.2.3 Determination of Acceptable Daily Intake (ADI)

General Population (including pregnant women, infants and children):

To estimate the risk from repeated dietary exposure, the 7-day oral comparative cholinesterase study in rats was selected with a point of departure based on the $BMDL_{10}$ of 0.58 mg/kg bw/day for brain cholinesterase inhibition in PND 17 pups. The lowest observed adverse effect level (LOAEL) of 1 mg/kg bw/day from the 2-year dietary mouse study was not selected for risk assessment purposes due to limitations in the dose-response data for the critical endpoint (brain cholinesterase inhibition). A composite assessment factor of 100 was applied to the $BMDL_{10}$ to account for uncertainty factors for inter-species extrapolation (10-fold) and intra-species variability (10-fold). The *Pest Control Products Act* factor was reduced to 1-fold, as outlined in the *Pest Control Products Act* Hazard Characterization section. An additional uncertainty factor to account for the use of a short-term oral study for a chronic scenario was not required due to the absence of a durational effect in rats exposed to phosmet in repeat-dose studies of varying durations.

$$ADI = \frac{0.58 \text{ mg/kg bw/day}}{100} = 0.006 \text{ mg/kg bw/day}$$

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk (from food and drinking water) was calculated by using the average consumption of different foods and drinking water, and the average residue values on those foods and drinking water. This estimated exposure to phosmet was then compared to the ADI. The ADI is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The chronic assessment was conducted for the general population and all subpopulations using average residues from the same CFIA and PDP monitoring data used in the acute assessment, adjusted with PCT data and domestic production/import statistics; the GMRL of 0.1 ppm or the US Tolerance for commodities for which no monitoring data were available; the available theoretical processing factors; and the chronic drinking water EEC point estimate obtained from modelling (see section 3.3).

The chronic exposure estimates for the general population and all subpopulations ranged from 1% (females 13-49 years of age) to 5% (children 1-2 years of age) of the ADI. Chronic dietary exposure is, therefore, not of concern.

3.2.5 Cancer Potency Factor

A cancer potency factor (q_1*) of 1.06×10^{-2} $(\text{mg/kg bw/day})^{-1}$ was generated based on the statistically significant, increased incidence of hepatocellular adenomas/carcinomas in male mice, which had an apparent early onset. Female mice also had a significant dose-related trend for liver tumours, but there was no evidence of carcinogenicity in rats. Phosmet also demonstrated mutagenic potential in a number of in vitro assays but not in in vivo assays.

3.2.6 Cancer Dietary Exposure and Risk Assessment

The dietary cancer risk (from food and drinking water) was conducted for the general population by using the same residues for chronic assessment as described in section 3.2.4 and the chronic drinking water EEC point estimate obtained from modelling (see section 3.3).

The dietary cancer risk is determined by multiplying the estimated lifetime exposure by the cancer potency factor (q_1*). A lifetime cancer risk that is equal to or below 1×10^{-6} (one-in-a million) usually does not indicate a risk of concern for the general population when exposure occurs through pesticide residues in or on food, or to otherwise unintentionally exposed persons. Based on the q_1* approach, the lifetime cancer risk estimate from exposure to phosmet through food and drinking water is approximately 1×10^{-6} and is, therefore, not of concern.

3.3 Exposure from Drinking Water

3.3.1 Concentrations in Drinking Water

Phosmet EECs in drinking water are intended to include both phosmet and phosmet oxon. Data on phosmet oxon were insufficient to model its formation and decline quantitatively. Therefore, a highly conservative estimate was used in the human health risk assessment: the reported EECs were assumed to consist entirely of phosmet oxon. A published study (PMRA No. 2687816) indicates that on chlorination, all available phosmet converts to phosmet oxon in approximately one hour and that phosmet oxon degrades after approximately four hours. Consequently, it is likely that the actual EECs would be lower than those predicted by water modelling.

Phosmet EECs in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. EECs of phosmet in groundwater were calculated using the Pesticide Root Zone Model Groundwater (PRZM-GW) model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are average concentrations in the top 1 metre of the water table. EECs of phosmet in surface water were calculated using the Surface Water Concentration Calculator (SWCC) model, which simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

Only EECs in surface water were considered, as concentrations in groundwater were practically zero. The Level 2 (refined) surface water modelling was conducted for two different use rates reflecting those specified for the treatment of apples and potatoes. The daily surface concentration distribution from the apple scenario was used in the acute exposure assessment. The highest yearly average concentration of 0.00023 ppm was used in chronic (non-cancer) and cancer exposure assessments.

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with daily surface EECs distribution and the highest yearly average point estimate incorporated directly in the acute and chronic dietary assessments, respectively. Please refer to sections 3.2.2, 3.2.4 and 3.2.6.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Non-Cancer Risk Assessment:

Occupational and non-occupational non-cancer risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

If a common toxic effect (for example, cholinesterase inhibition) occurs with multiple routes of exposure, risks from these routes are aggregated using an aggregate risk index (ARI). The ARI is a method of measuring combined risk when exposure occurs via multiple routes or pathways and different toxicological points of departure and uncertainty factors are established for each route. The ARI is an extension of the MOE concept. As with the MOE, risk increases as the ARI decreases. ARIs greater than or equal to 1 do not require risk mitigation. If the calculated ARI is less than 1, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Cancer Risk Assessment:

The cancer risk is determined by calculating the lifetime average daily dose (LADD) from dermal, inhalation and/or oral exposure. The LADD is multiplied by the cancer potency factor (q_1*) to obtain a lifetime cancer risk estimate, which is a measurement of probability. A lifetime cancer risk in the range of 1×10^{-5} in worker populations and in the range of 1×10^{-6} in residential populations is generally acceptable.

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

Dermal Exposure:

For short- and intermediate-term dermal exposures, the $BMDL_{10}$ of 7.7 mg/kg bw/day in the 21-day dermal toxicity study conducted in adult rats was selected based on brain cholinesterase inhibition. A target MOE of 300 was selected to account for uncertainty factors for inter-species extrapolation (10-fold) and intra-species variability (10-fold) as well as an uncertainty factor of 3-fold for database deficiencies. Since the dermal study was conducted in adult animals, there was uncertainty as to whether the sensitivity observed via oral exposure in the young would also be manifested with the dermal route. Additional uncertainty arises as to whether sensitivity can occur in the fetus or nursing infant as a result of indirect exposure via the mother. As the population of interest could include pregnant or lactating women, the 3-fold factor for database deficiencies was employed to address concerns related to sensitivity of the young. For the residential risk assessment, since a 3-fold uncertainty factor for database deficiency was applied to address residual concern regarding sensitivity of the young, the *Pest Control Products Act* factor was reduced to 1-fold, as outlined in the *Pest Control Products Act* Hazard Characterization section.

Inhalation Exposure:

Repeat-dose inhalation toxicity studies were not available. For short- and intermediate-term inhalation exposures, the 7-day oral comparative cholinesterase assay in rats was selected with a point of departure based on the $BMDL_{10}$ of 0.58 mg/kg bw/day for brain cholinesterase inhibition in PND 17 pups. A target MOE of 100 was selected to account for inter-species extrapolation (10-fold) and intra-species variability (10-fold). For the residential risk assessment, the *Pest Control Products Act* factor was reduced to 1-fold, as outlined in the *Pest Control Products Act* Hazard Characterization section.

Non-Dietary Incidental Oral Ingestion (Short-Term, Intermediate-Term):

For the assessment of non-dietary (incidental) oral exposure, the 7-day oral comparative cholinesterase study in rats was selected with a point of departure based on the $BMDL_{10}$ of 0.58 mg/kg bw/day for brain cholinesterase inhibition in PND 17 pups. A target MOE of 100 was selected to account for uncertainty factors for inter-species extrapolation (10-fold) and intra-species variability (10-fold). The *Pest Control Products Act* factor was reduced to 1-fold, as outlined in the *Pest Control Products Act* Hazard Characterization section.

Cancer Assessment:

See section 3.2.5.

3.4.2 Dermal Absorption

The estimated dermal absorption is based on an in vivo rat dermal absorption study. A dermal absorption value of 10% was used in estimating the systemic dose from dermal exposure for the cancer risk assessment. A dermal absorption value was not required for the non-cancer assessment, since the toxicological points of departure were based on dermal studies.

This dermal absorption value was used for the PMRA risk assessments discussed in PACR2004-38 and REV2007-14. Since that time, an in vitro dermal absorption study in rat and human skin was submitted, which the PMRA considered along with the rat in vivo study to determine if the dermal absorption value could be refined. However, the in vitro study did not meet the criteria for the triple pack approach. The PMRA did not consider this approach appropriate for the phosmet update given the limitations in the available data.

3.4.3 Occupational Exposure and Risk Assessment

Workers can be exposed to phosmet through mixing, loading, or applying products containing the pesticide, and when entering a treated site to conduct activities, such as scouting and hand harvesting.

3.4.3.1 Mixer, Loader, and Applicator Exposure and Risk Assessment

The following exposure scenarios were considered:

- Mixing/loading of wettable powder in water soluble packaging (Instapack)
- Airblast liquid application to fruit trees, blueberries, cranberries, grapes, and ornamentals
- Groundboom liquid application to blueberries, carrots, celery, cranberries, alfalfa, potatoes, and ornamentals
- Chemigation liquid application to cranberries
- Manually pressurized handwand liquid applications to blueberries, cranberries, grapes, and ornamentals

- Mechanically pressurized handgun liquid applications to blueberries, cranberries, grapes, and ornamentals
- Backpack liquid application to blueberries, cranberries, grapes, and ornamentals

Based on the number of applications and timing of application, farmers and custom applicators applying phosmet would generally have a short-intermediate term duration of exposure. For the cancer assessment, the LADD was calculated assuming 40 years of exposure (that is, a career in agriculture of 40 years) over a 78-year lifetime. Farmer and custom applicators were assumed to be exposed for up to a total of 30 days per year based on the number of applications per year.

The PMRA estimated handler exposure is based on different levels of personal protective equipment (PPE) and engineering controls:

- Baseline PPE: Long pants, long-sleeved shirt and chemical-resistant gloves (unless specified otherwise). For groundboom application, this scenario does not include gloves, as the data quality was better for non-gloved scenarios than gloved scenarios.
- Mid-Level PPE: Cotton coveralls over long pants, long-sleeved shirt and chemical-resistant gloves.
- Maximum PPE: Chemical-resistant coveralls over long-sleeved shirt, long pants and chemical-resistant gloves.
- Engineering Controls: Represents the use of appropriate engineering controls, such as closed cab tractor. For groundboom and airblast applicators, the engineering controls were comprised of closed cab and baseline PPE. Engineering controls are limited for handheld application methods.
- Headgear [airblast application only]: Open cab, chemical-resistant coveralls over long sleeved shirt, long pants, chemical-resistant headgear that covers the neck (for example, Sou'Wester hat, rain hat) and chemical-resistant gloves.
- Respirator: with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides.

No appropriate chemical-specific handler exposure data were available for phosmet; therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, and the Agricultural Handler Exposure Task Force (AHETF).

The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE. In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing coveralls, chemical-resistant coveralls or a respirator. This was estimated by incorporating a 75% clothing protection factor for coveralls, a 90% clothing protection factor for chemical-resistant coveralls, and a 90% protection factor for a respirator into the unit exposure values. As there were no handheld scenarios for wettable powder in water soluble packaging, the data for a liquid product was used as a surrogate. Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack applicator scenarios, which were based on moderate inhalation rates (27 L/min).

The unit exposures for the open cab airblast scenario were available from the AHETF database. Inhalation unit exposures are based on light inhalation rates (17 L/min) unless otherwise stated.

Mixer/loader/applicator exposure estimates are based on the best available data at this time.

The generation of exposure data representative of modern application equipment and engineering controls may potentially refine the risk assessment. Biological monitoring data could also further refine the assessment.

Occupational non-cancer risk estimates associated with mixing, loading, and applying phosmet were calculated and the proposed mitigation is summarized in Appendix VI. For some uses, based on the current label PPE and application rates, the calculated ARIs are below the target of 1. However, ARIs of 1 or greater are achieved with the proposed mitigation measures listed in Appendix VI, such as additional PPE or engineering controls.

For all uses, based on the current label PPE and application rates, the calculated cancer risk estimates are below 1×10^{-5} and are not of concern.

3.4.3.2 Post-application Worker Exposure and Risk Assessment

The post-application occupational risk assessment considers exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, pruning, thinning, harvesting or scouting). Based on the phosmet use pattern, there is potential for short-to-intermediate term (>1 day to several weeks) post-application dermal exposure for most worker activities.

The PMRA is primarily concerned with the potential for dermal exposure for workers performing post-application activities in crops treated with a foliar spray. Based on the vapour pressure of phosmet, inhalation exposure is not likely to be of concern provided that the minimum 12-hour REI is followed.

Potential dermal exposure to post-application workers was estimated using updated activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural work clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used. Post-application exposure activities for agricultural crops include (but are not limited to): harvesting, pruning, scouting and thinning. For more information about estimating worker post-application exposure, refer to PMRA's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Exposure to Pesticides.*

Chemical-specific DFR studies were used for the current assessment. The study and site selected to estimate the DFR on registered Canadian crops used the study peak DFR and predicted percent dissipation per day following the final application. However, although these studies

reflected the current use pattern of phosmet, the study design precluded estimating exposure when possible mitigation measures are considered (that is, reduced number of applications and increased application intervals). Estimated DFR values were adjusted proportionally for maximum and/or typical Canadian application rates.

Due to the limited number of acceptable DFR studies available to the PMRA for the post-application risk assessment, the extrapolation of study DFR data to a wide variety of crops was required. Extrapolation was based on a comparison of general crop morphology, application equipment, application regime, foliage types, application rates, study conditions and climatic zones. Since the studies available are not necessarily representative of some Canadian crops, this extrapolation represents an uncertainty in the post-application assessment. This approach is consistent with PACR2004-38.

For workers entering a treated site, REIs are calculated to determine the minimum length of time required before workers can enter after application to perform tasks involving hand labour. An REI is the duration of time that must elapse in order to allow residues to decline to a level where there are no risks of concern for post-application worker activities (for example, in the case of phosmet, performance of a specific activity that results in exposures above the target MOE of 300 for dermal exposure, or below the cancer threshold of 1×10^{-5}).

For the current label uses, most REIs would need to be significantly increased in duration in order to achieve the target MOE or the cancer threshold for post-application workers in agricultural scenarios. Calculated REIs ranged from 12 hours to 79 days for outdoor uses. Appendix VI summarizes the proposed REIs based on the post-application exposure risk assessment. The majority of the proposed REIs are not considered to be agronomically feasible. As a result, all uses of phosmet are proposed for phase-out.

3.4.4 Non-Occupational Exposure and Risk Assessment

The non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

The USEPA has generated standard data-based default assumptions for developing residential exposure assessments for post-application exposures when chemical- and/or site-specific field data are limited. The assumptions and algorithms may be used in the absence of, or as a supplement to, chemical- and/or site-specific data and generally result in high-end estimates of exposure. The assumptions and algorithms relevant to the phosmet re-evaluation are outlined in the Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessments 2012 under “Section 4: Gardens and Trees”.

3.4.4.1 Residential Applicator Exposure and Risk Assessment

A residential applicator refers to an adult who applies a domestic-class product in or around the home. Domestic-class products containing phosmet are not registered in Canada. Therefore, a residential applicator assessment was not required.

3.4.4.2 Residential Post-application Exposure and Risk Assessment

Residential post-application exposure occurs when an individual is exposed through dermal, inhalation and/or incidental oral (non-dietary ingestion) routes as a result of activities occurring in a residential environment that has been previously treated with a pesticide. For phosmet, this scenario could apply to areas where a commercial applicator was hired to treat trees in a residential area, where phosmet could have drifted from nearby commercial uses, or where people could have visited a pick-your-own facility that was previously treated.

Based on the number of applications and timing of application, residential exposure to phosmet would generally have a short-term (<30 days) duration of exposure.

The following scenarios were considered for residential exposure to phosmet:

- Dermal exposure for adults, youth and children resulting from activities in treated gardens and fruit trees
- Inhalation exposure for adults, youth and children resulting from phosmet in ambient air due to commercial applications nearby
- Exposure to adults, youth, and children from visiting phosmet treated 'pick-your-own' facilities

The quantitative estimate of exposure for residential gardens and fruit trees that have been treated with phosmet utilized the USEPA SOPs along with chemical specific DFR studies discussed in section 3.4.3. The risk assessment did not meet the target MOE for adults, youth and children and exceeded the cancer threshold for total lifetime cancer risk. Therefore, residential post-application risks from activities in treated gardens and fruit trees are of concern.

Residential inhalation exposure and risk from agricultural uses of phosmet near residential areas were calculated based on literature data and study report data from California. Although phosmet was rarely detected in ambient air, point estimates were used to create a high end estimate of potential exposure. The quantitative estimate of exposure from inhaling phosmet arising from drift from commercial applications to nearby fields results in MOEs that are greater than the target MOE and a lifetime cancer risk that is below the threshold. Therefore, residential post-application risks from commercial application to nearby fields are not of concern.

'Pick-Your-Own' facilities are considered to be commercial farming operations that allow public access for harvesting in large-scale fields or orchards; these areas may be treated with commercially labelled pesticides. This scenario assesses the combination of risks resulting from dermal and dietary exposures in commercial agricultural settings where the public may hand harvest crops for personal consumption. However, a pick-your-own assessment was not conducted for phosmet since the REIs for commercial post-application orchard and blueberry workers are already not considered to be agronomically feasible.

Based on the residential post-application exposure and risk assessment (Appendix VII), it is proposed to phase out the commercial use of phosmet on ornamental and fruit trees in residential areas.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

For aggregate exposure to phosmet (of any duration), the common toxicological effect was brain cholinesterase inhibition. For oral and inhalation aggregate risk assessment of the general population (including pregnant women, infants and children), the 7-day oral comparative cholinesterase study in rats was selected with a point of departure based on the $BMDL_{10}$ of 0.58 mg/kg bw/day for brain cholinesterase inhibition in PND 17 pups. The target MOE for both routes of exposure is 100, reflecting uncertainty factors of 10-fold for inter-species extrapolation, 10-fold for intra-species variability and a *Pest Control Products Act* factor of 1-fold.

For dermal aggregate risk assessment of the general population (including pregnant women, infants and children), the $BMDL_{10}$ of 7.7 mg/kg bw/day in the 21-day dermal toxicity study conducted in adult rats was selected based on brain cholinesterase inhibition. A target MOE of 300 was selected to account for uncertainty factors for inter-species extrapolation (10-fold) and intra-species variability (10-fold) as well as an uncertainty factor of 3-fold for database deficiencies; a *Pest Control Products Act* factor of 1-fold was further applied.

Cancer Assessment:

See section 3.2.5, above.

3.5.2 Residential, Non-Occupational, and Dietary Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated.

An aggregate assessment (non-cancer and cancer) for phosmet was not conducted, as risk concerns were already identified from dermal exposure alone in residential areas.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative exposure to pesticides with a common mechanism of toxicity. Phosmet belongs to a group of pesticides classified as organophosphates. Organophosphates have a common mechanism of toxicity wherein they bind to and phosphorylate acetylcholinesterase, ultimately leading to neurotoxicity. A cumulative risk assessment will be undertaken upon completion of the re-evaluation of the individual chemicals in the organophosphate group.

4.0 Impact on the Environment

The environmental fate and toxicity of phosmet was previously considered in PACR2004-38 and REV2007-14. Label statements for the protection of pollinators would need to be updated to meet current standards (Appendix VIII). However, at this time, the PMRA is proposing to phase out all uses of phosmet as a result of the human health risk assessment.

5.0 Value

Please refer to the Value Considerations part of the Overview. Appendix IX lists phosmet uses for which a limited number of alternative active ingredients are registered in Canada.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

Phosmet and two of its major transformation products, phosmet oxon and phthalamic acid, were previously assessed in PACR2004-38. It was determined that phosmet oxon and phthalamic acid do not meet TSMP Track 1 criteria.

7.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report pesticide incidents, including adverse effects to health and the environment, to the PMRA. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of the Canada.ca website.

As of December 17, 2015, one human and one domestic animal incident were submitted to the PMRA. An individual developed flu-like symptoms following exposure to phosmet during mixing and loading of the product without wearing any personal protective equipment. In the domestic animal incident, undiluted insecticidal spray was applied to a young steer that subsequently died. Both the human and domestic animal incidents had a high degree of association with exposure to phosmet, but in both cases, the label directions were not followed.

The incident report data were incorporated into the evaluation of phosmet.

8.0 Organisation for Economic Co-operation and Development Status of Phosmet

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which groups member countries and provides a forum in which governments can work together to share experiences and seek solutions to common problems.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member country to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

Phosmet is currently acceptable for use in other OECD member countries, including Australia and the United States. As of 24 June 2016, no decision by an OECD member country to prohibit all uses of phosmet for health or environmental reasons has been identified.

9.0 Proposed Regulatory Decision

9.1 Proposed Regulatory Action

9.1.1 Proposed Regulatory Action Related to Human Health

After a re-evaluation of the insecticide phosmet, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing the phase-out of all phosmet uses based on risks associated with human health.

9.1.1.1 Residue Definition for Risk Assessment and Enforcement

Currently, the residue definition for phosmet in Canada is S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl] O,O-dimethyl phosphorodithioate, for both enforcement and risk assessment. No change is proposed to this residue definition *per se* as a result of this update to the re-evaluation. However, the residue definition for MRL enforcement will be revised to clarify residues are to be measured as **phosmet (**S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl] O,O-dimethyl phosphorodithioate**)**.

9.2 Additional Data Requirements

Human Health

Since phase-out of all uses is proposed as a result of the human health risk assessment, no additional data are required at this time.

The PMRA will consider additional data submitted during the 90-day consultation period to further refine the health risk assessment, should that become available. It is recommended that registrants interested in submitting additional data during the 90-day consultation period first consult with the Agency.

List of Abbreviations

↑	increased
↓	decreased
♀	females
♂	males
AAFC	Agriculture and Agri-Food Canada
a.i.	active ingredient
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Re-Entry Task Force
BChE	brain acetylcholinesterase
BMD	benchmark dose
BMDL	benchmark dose 95% lower confidence limit
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CalDPR	California Environmental Protection Agency Department of Pesticide Regulation
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CFIA	Canadian Food Inspection Agency
ChE	acetylcholinesterase
cm	centimetre(s)
CR	chemical resistant
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
DER	Data Evaluation Record
DFR	dislodgeable foliar residue
DNT	developmental neurotoxicity
EChE	erythrocyte acetylcholinesterase
EEC	estimated environmental concentration
F_0	parental generation
F_1	first filial generation
g	gram(s)
GMRL	general maximum residue limit
ha	hectare
hr	hour
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
Kow	n-octanol/water partition coefficient at 25°C
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest adverse effect level
max	maximum

mg	milligram(s)
mL	millilitre(s)
MOE	margin of exposure
mPa	millipascal(s)
MRID	USEPA's master record identifier number
MRL	maximum residue limit
NCHS	National Center for Health Statistics
NIOSH	National Institute for Occupation Safety and Health
nm	nanometre(s)
NOAEL	no observed adverse effect level
NTE	neuropathy target esterase
PACR	Proposed Acceptability for Continuing Registration
PChE	plasma acetylcholinesterase
PCT	percent crop treated
PDP	Pesticide Data Program
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	post natal day
PPE	personal protective equipment
ppm	parts per million
PRZM-GW	Pesticide Root Zone Model Groundwater
REI	restricted entry interval
RfD	reference dose
SOP	standard operating procedures
SWCC	Surface Water Concentration Calculator
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
USDA	United States Department of Agriculture
wk	week
wt	weight
µg	microgram(s)

Appendix I Registered Phosmet Products[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Net Contents	Guarantee
23055	Technical Grade Active Ingredient	Gowan Company LLC	Phosmet Technical	Solid	Not available	Phosmet 96%
23006	Commercial		Imidan 50-WP Instapack	Wettable powder	2kg (2x 1kg water soluble sachets)	Phosmet 50%
29064			Imidan 70-WP Instapack		2.265 kg (5x 0.453kg water soluble sachets)	Phosmet 70%

[1]as of January 13, 2017, excluding discontinued products or products with a submission for discontinuation

Appendix II Registered Commercial Class Uses of Phosmet in Canada[1]

Site(s)	Pest(s)	Application Methods and Equipment	Application Rate	Maximum Number of Applications per Year	Minimum Application Interval (Days)
			Single		
Alfalfa	alfalfa blotch leafminer, alfalfa weevil	Ground: foliar spray	1120 to 1125 g a.i./ha	3	Not stated on label
Apples	apple aphid apple maggot codling moth Eastern tent caterpillar elm spanworm European red mite eye-spotted bud moth green fruitworm gypsy moth Japanese beetle obliquebanded leafroller plum curculio redbanded leafroller San José scale spotted tentiform leafminer spotted wing drosophila spring cankerworm tarnished plant bug twospotted spider mite	Ground: foliar spray	1875 g a.i./ha	5	Not stated on label
Blueberries	blueberry maggot blueberry spanworm Japanese beetle Spotted wing drosophila	Ground foliar spray	1120 to 1125 g a.i./ha	2	Not stated on label
Carrots, Celery	carrot weevil	Ground: foliar spray	1120 to 1125 g a.i./ha	2	Not stated on label
Cherries, sour	cherry fruit fly Eastern tent caterpillar Elm spanworm European red mite gypsy moth Japanese beetle peach twig borer plum curculio redbanded leafroller spotted wing drosophila spring cankerworm twospotted spider mite	Ground: foliar spray	1875 g a.i./ha	4	Not stated on label
Cranberries	blackheaded fire worm	Ground: chemigation	1100 g a.i./ha	4	5
Grapes	Eastern tent caterpillar elm spanworm grape berry moth gypsy moth Japanese beetle spotted wing drosophila spring cankerworm	Ground: foliar spray	950 to 1550 g a.i./ha	3	Not stated on label

Site(s)	Pest(s)	Application Methods and Equipment	Application Rate	Maximum Number of Applications per Year	Minimum Application Interval (Days)
			Single		
Peaches	Eastern tent caterpillar elm spanworm European red mite green fruitworm gypsy moth Japanese beetle obliquebanded leafroller Oriental fruit moth peach twig borer plum curculio spotted wing drosophila spring cankerworm tarnished plant bug twospotted spider mite	Ground: foliar spray	1875 g a.i./ha	4	Not stated on label
Pears	codling moth Eastern tent caterpillar elm spanworm European red mite green fruitworm gypsy moth Japanese beetle obliquebanded leafroller pear psylla plum curculio redbanded leafroller rust mite spotted wing drosophila spring cankerworm twospotted spider mite			5	
Plums	apple maggot Eastern tent caterpillar elm spanworm European red mite gypsy moth Japanese beetle plum curculio redbanded leafroller spotted wing drosophila spring cankerworm twospotted spider mite			3	
Potatoes	Colorado potato beetle potato aphid potato flea beetle potato leafhopper	Ground: foliar spray	1120 to 1125 g a.i./ha	5	Not stated on label
Deciduous shade and ornamental trees (ash, beech, birch, dogwood, elm, hawthorn, hickory, maple, oak, willow)	birch leafminer (birch only) Eastern tent caterpillar elm spanworm gypsy moth Japanese beetle spring cankerworm	Ground: foliar spray	625 g a.i./ha	3	14
Woody evergreens (arborvitae, azalea, boxwood, camellia, cedar, fir, hemlock, hydrangea, juniper, lilac, pine, privet, rose, spruce, yew)	Elm spanwormgypsy moth Japanese beetle	Ground: foliar spray	625 g a.i./ha	3	14

Site(s)	Pest(s)	Application Methods and Equipment	Application Rate	Maximum Number of Applications per Year	Minimum Application Interval (Days)
			Single		
Herbaceous plants (chrysanthemum, cosmos, geranium, four o'clock, marigold, petunia, portulaca, zinnia)					

[1]as of January 13, 2017

Appendix III Toxicology Profile and Endpoints for Health Risk Assessment

The following table includes studies which were previously published in PACR2004-38 (in plain text), in addition to studies with review amendments and new toxicology studies (**in bold text**). Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight changes refer to both relative and absolute weights, unless otherwise indicated. Studies lacking a PMRA# utilized foreign study evaluations**.**

Table 1 Toxicology Profile for Phosmet

Study/Species	Results/Effects
Toxicokinetic and Metabolism Studies	
Absorption, Distribution, Elimination - Gavage Sprague-Dawley Rat PMRA#1052680 PMRA#1052681	Single oral dose of 1 or 25 mg/kg bw ^{14}C-Imidan™ Absorption: Rapidly absorbed. Peak blood levels observed at 0.5 hr Distribution: Low levels in carcass (1.2% to 2.1%) Elimination: Rapidly eliminated via urine (> 70% after 24 hrs; 81% to 89% after 96 hrs). The primary metabolites in urine were N-(methylsulfinylmethyl) phthalamic acid (52% to 66%) and N-(methylsulfonylmethyl) phthalamic acid (8% to 26%); greater elimination of methylsulfonylmethyl phthalamic acid in ♂, compared to ♀. Minimal faecal elimination (6% to 13%).
Metabolism, Elimination Long-Evans Rat	Single oral dose of 23 to 35.2 mg/kg bw ^{14}C-phosmet Metabolism: < 1% ^{14}C-phosmet detected in urine (as phosmet or phosmet oxon) Elimination: 79% in urine, 19% in faeces, < 0.04% in expired air
Acute Toxicity Studies	
Acute Oral Toxicity Mouse	LD_{50} = 20 to 60 mg/kg bw HIGH ORAL TOXICITY
Acute Oral Toxicity Rat	LD_{50} = 92 to 310 mg/kg bw Tremors, salivation, lacrimation, excessive mastication, urine staining, exophthalmia, bloody eye, nose and mouth exudate, dyspnea, depression and diarrhoea were noted. HIGH ORAL TOXICITY
Acute Oral Toxicity Guinea Pig	LD_{50} = 200 mg/kg bw HIGH ORAL TOXICITY
Acute Dermal Toxicity Rabbit	LD_{50} ~ 3160 to > 5000 mg/kg bw Mucous discharge from mouth and nose and mild dermal irritation (characterized by slight to moderate patchy erythema) were noted. LOW DERMAL TOXICITY

Study/Species	Results/Effects
Acute Inhalation Toxicity Rat	LC_{50} > 0.152 mg/L MODERATE INHALATION TOXICITY
Eye Irritation Rabbit	Erythema of the lid, vascularization of the sclera and nictitating membrane and slight edema of the lower lid were noted. Note: only 3 mg test material was used. MODERATE EYE IRRITATION
Dermal Sensitization – Modified Buehler Assay **Dunkin-Hartley Guinea Pig** **PMRA#1211439**	Repeated application of test substance did not cause skin reactions during the induction phase. Challenge/re-challenge with Imidan™ technical did not cause sensitization. NOT A DERMAL SENSITIZER
Subchronic Toxicity Studies	
4-Week Oral Toxicity B6C3F1 Mouse	NOAEL = 2.25 mg/kg bw/day ≥ 7.5 mg/kg bw/day: ↓ EChE ≥ 22.5 mg/kg bw/day: ↑ relative liver wt; ↓ food consumption (♂) 75.0 mg/kg bw/day: ↓ food consumption, ↑ relative kidney wt, ↑ relative liver wt, ↓ BChE (♀)
14-Week Oral Toxicity Rat	NOAEL = 2.0 mg/kg bw/day ≥ 10.0 mg/kg bw/day: ↓ EChE, ↓ PChE, ↓ BChE 50.0 mg/kg bw/day: ↓ bwg; mortality (♂)
16-Week Oral Toxicity Charles River Rat	LOAEL = 22.5 mg/kg bw/day ≥ 22.5 mg/kg bw/day: ↓ EChE, ↓ PChE, ↓ BChE, clinical signs ≥ 40 mg/kg bw/day: mortality, ↓ bwg, ↑ relative liver wt, ↑ relative adrenal wt, hepatic degenerative changes, adrenal hypertrophy
14-Week Oral Toxicity Beagle Dog	NOAEL = 1.9 mg/kg bw/day 14 mg/kg bw/day: ↓ BChE, ↓ EChE, ↓ PChE
21-Day Dermal Toxicity **Sprague-Dawley Rat** **PMRA#1995291** **PMRA#1995270**	The following benchmark dose values were derived for ↓ BChE in adult rats: BMD_{10} ($BMDL_{10}$) = 16.6 (13.3) mg a.i./kg bw/day (♂) BMD_{10} ($BMDL_{10}$) = 10.2 (7.7) mg a.i./kg bw/day (♀) Note: Data were inadequate to determine BMD values for EChE inhibition
Neurotoxicity Studies	
Acute Oral Neurotoxicity Sprague-Dawley Rat	NOAEL = 4.5 mg/kg bw 22.5 mg/kg bw/day: ↓ BChE, ↓ PChE, ↓ EChE, ↓ motor activity
Acute Oral Neurotoxicity - Gavage **Range-Finding Study** **Sprague-Dawley Rat**	Supplemental due to range-finding study 15 mg/kg bw: ↓ BChE, ↓ EChE, ↓ PChE at all-time points In both sexes, peak BChE, EChE and PChE inhibition were noted 2- to 4-hrs post-dosing; 4-hrs was considered the "time-to-peak effect" in PND 11

Study/Species	Results/Effects
PND 11 Pup **PMRA#1715584** **PMRA#1715586**	pups.
Acute Oral Neurotoxicity - Gavage **Sprague-Dawley Rat** **Adult and PND 11 Pup** **PMRA#1715583** **PMRA#1715586**	The following benchmark dose values were derived for ↓ ChE in adults and pups: <u>Adult (mg/kg bw):</u> BChE $BMD_{10}/BMDL_{10}$ = 6.82/5.15 EChE BMD_{20} /$BMDL_{20}$ = 5.14/4.09 <u>PND 11 Pup (mg/kg bw):</u> BChE $BMD_{10}/BMDL_{10}$ = 1.48/1.26 EChE BMD_{20} /$BMDL_{20}$= 3.61/2.95 Evidence of sensitivity of the young
7-Day Oral Comparative Cholinesterase Assay - Gavage **Sprague-Dawley Rat** **Adult, PND 11 Pup** **PMRA#1840659** **PMRA#1995268**	The following benchmark dose values were derived for ↓ ChE in adults and pups: <u>Adults (mg/kg bw/day):</u> BChE $BMD_{10}/BMDL_{10}$ = 2.94/2.21 EChE BMD_{20} /$BMDL_{20}$ = 2.40/2.04 <u>PND 17 Pups (mg/kg bw/day):</u> BChE $BMD_{10}/BMDL_{10}$ = 0.62/0.58 EChE BMD_{20} /$BMDL_{20}$ = 1.19/1.03 Note: There is less confidence in the EChE data due to analytical issues. Evidence of sensitivity of the young
13-Week Oral Neurotoxicity - Diet **Sprague-Dawley Rat** **PMRA#1995276** **PMRA#1995281** **PMRA#1995283** **PMRA#1995285** **PMRA#1995288**	The following BMD values were derived for ↓ BChE in adult rats: <u>Whole Brain BChE (mg/kg bw/day):</u> wk 3 ($BMD_{10}/BMDL_{10}$): 2.94/ 2.02(♂/♀) wk 7 ($BMD_{10}/BMDL_{10}$): 1.53/1.33 (♂); 1.03 /0.94 (♀) <u>Olfactory Bulb BChE (mg/kg bw/day):</u> wk 13 ($BMD_{10}/BMDL_{10}$): 1.83/1.19 (♂); 1.04/0.85 (♀) <u>Brain Stem BChE (mg/kg bw/day):</u> wk 13 ($BMD_{10}/BMDL_{10}$): 2.01/1.75 (♂/♀) <u>Mid-Brain BChE (mg/kg bw/day):</u> wk 13 ($BMD_{10}/BMDL_{10}$): 1.49/1.30 (♂/♀) <u>Cerebellum BChE (mg/kg bw/day):</u> wk 13 ($BMD_{10}/BMDL_{10}$): 5.06/3.35 (♂/♀) <u>Cortex BChE (mg/kg bw/day):</u> wk 13 ($BMD_{10}/BMDL_{10}$): 3.18/1.97 (♂/♀) <u>Hippocampus BChE (mg/kg bw/day):</u> wk 13 ($BMD_{10}/BMDL_{10}$): 1.20/1.00 (♂/♀)
Acute Delayed Neurotoxicity - Gelatin Capsule	≥ 200 mg/kg bw: limp comb, non-vocal, motor impairment, signs of cholinergic toxicity

Study/Species	Results/Effects
White Leghorn Hen PMRA#1232946	2050 mg/kg bw: ptosis
Acute Delayed Neurotoxicity Hen	600 mg/kg bw: ↓ BChE, unsteadiness, subdued behaviour, recumbency, salivation No ↓ NTE activity and no histopathological evidence of delayed neuropathy.
Chronic Toxicity/Carcinogenicity Studies	
Two-Year Chronic Toxicity/ Carcinogenicity - Diet **B6C3F1 Mouse** **PMRA#1243149** **PMRA#1254691** **PMRA#1206187** **PMRA#1148296**	LOAEL = 1.0 mg/kg bw/day ≥ 1.0/1.2 mg/kg bw/day: ↓ BChE (both sexes at interim; ♀ at termination) ≥ 4/5 mg/kg bw/day: convulsions (♂); ↑ liver wt (♀) 14/18 mg/kg bw/day: ↑ hepatocellular adenomas, ↑ degenerative vacuolation of liver, ↑ relative liver wt, ↑ perivasculitis of muscle, hyperplasia of stomach mucosa, testicular atrophy (♂); ↑ hepatocellular carcinomas, necrotizing inflammation of stomach, duodenum and myometrical atrophy (♀) Note: Data were unsuitable for BMD modelling. Evidence of carcinogenicity in mice
Two-Year Chronic Toxicity/ Carcinogenicity - Diet **Sprague-Dawley Rat** **PMRA#1173005** **PMRA#1173004**	≥ 9.4/10.9 mg/kg bw/day: ↓ BChE, ↓ EChE, ↓ PChE, fatty changes in liver; ↑ hepatic foci, hyperkeratosis of stomach (♂); mineralization of thyroid (♀) 23/27 mg/kg bw/day: ↓ bwg, ↓ kidney wt, ↑ BUN (♀) The following BMD values were derived for ↓ BChE in adult rats: <u>12-Month Interim Sacrifice</u>**:** BMD_{10} ($BMDL_{10}$) = 3.27 (2.44) (♂/♀) <u>Terminal Sacrifice</u>**:** BMD_{10} ($BMDL_{10}$) = 7.29 (5.43) (♂/♀) No evidence of carcinogenicity in rats
Reproductive and Developmental Toxicity Studies	
Two-Generation Reproductive Toxicity - Diet Sprague-Dawley Rat 2 litters/generation PMRA#1172963	<u>Parental</u> NOAEL = 1.4 mg/kg bw/day ≥ 5.8/6.1 mg/kg bw/day: ↓ bwg (F_0); ↓ EChE (F_0, F_1) (♂); dehydration (F_0), ↓ relative liver wt (F_0), ↓ relative adrenal wt (F_0), ↓ relative spleen wt (F_1), ↓ relative thymus wt (F_1), ↓ PChE (F_0), ↓ EChE (F_0, F_1) (♀) 22.3/25.4 mg/kg bw/day: ↓ bwg (F_1); ↓ absolute testes wt (F_0, F_1), ↓ absolute spleen wt (F_1), ↑ hepatic vacuolation (F_1) (♂); dehydration (F_0), chromorhinorrhea (F_1), ↓ relative spleen wt, ↓ relative adrenal wt and ↓ relative ovary wt (F_0), ↓ PChE and ↓ EChE (F_0, F_1) (♀) <u>Reproductive</u> NOAEL = 1.4 mg/kg bw/day ≥ 5.8/6.1 mg/kg bw/day: ↓ mating, ↓ fertility (2nd mating of F_0; both

Study/Species	Results/Effects
	matings of F_1) Offspring NOAEL = 6.1 mg/kg bw/day 25.4 mg/kg bw/day: ↓ pups/litter, ↓ pup wt, ↓ pup survival (by PND 14) Note: BChE was not assessed. No evidence of sensitivity of the young.
Developmental Toxicity - Gavage Wistar Rat PMRA#1173013	Maternal NOAEL = 10 mg/kg bw/day ≥ 5 mg/kg bw/day: ↑ urinary incontinence ≥10 mg/kg bw/day: ↓ bwg 15 mg/kg bw/day: ↓ food consumption, shaking, piloerection, staining around mouth Developmental NOAEL = 10 mg/kg bw/day 15 mg/kg bw/day: ↑ skeletal variations No evidence of teratogenicity or sensitivity of the young
Developmental Toxicity - Gavage New Zealand White Rabbit PMRA#1173014	Maternal NOAEL = 5 mg/kg bw/day 15 mg/kg bw/day: unsteady gait, shaking, salivation, irregular breathing, ↓ bwg Developmental NOAEL = 5 mg/kg bw/day 15 mg/kg bw/day: delayed fetal skeletal ossification No evidence of teratogenicity or sensitivity of the young
In Vitro Genotoxicity Studies	
Reverse Mutation *S. typhimurium* (TA98, TA100, TA1535, TA1537) PMRA#1207883	Positive in TA100 at ≥ 0.625 mg/plate without activation, and positive in TA 100 at ≥ 0.313 mg/plate with activation.
Reverse Mutation *S. typhimurium* (TA1535, TA1536, TA1537, TA1538)	Negative in all strains up to 20 µg/plate
Reverse Mutation S. *typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Positive in TA 100 only, with and without activation

Study/Species	Results/Effects
Reverse Mutation *B. subtillis* H17	Negative up to 20 µg/plate
Reverse Mutation *E. coli* WP2 *hcr*	Negative up to 20 µg/plate
Reverse Mutation *E. coli* WP2 *hcr*	Negative up to 5000 mg/plate
Forward Mutation Mouse lymphoma TK +/- PMRA#1207884	Positive at ≥ 0.08 mg/mL without activation, and negative up to 0.04 mg/L with activation.
Cell Transformation Mouse Balb/3T3 PMRA#1207888	Negative up to 0.014 mg/mL without activation.
DNA Repair Human Fibroblasts PMRA#1207887	Negative up to 1 mg/mL with or without activation.
Sister Chromatid Exchange Mouse Lymphoma L1578Y PMRA#1207885	Positive at ≥ 0.04 mg/L without activation, and positive at ≥ 0.008 mg/L with activation.
Chromosomal Aberrations Mouse Lymphoma L1578Y PMRA#1207885	Negative up to 0.04 mg/mL without activation, and negative up to 0.1 mg/mL with activation.
In Vivo Genotoxicity Studies	
Unscheduled DNA Synthesis - Gavage Sprague-Dawley Rat Hepatocytes PMRA#1052686	Negative up to 50 mg/kg bw.
Unscheduled DNA Synthesis - Gavage **Sprague-Dawley Rat Hepatocytes** **PMRA#1052687**	Negative up to 180 mg/kg bw.
Micronucleus Test COBS CD1 (ICR) BR Mouse Bone Marrow PMRA#1211436	Negative up to 17 mg/kg bw. Mortality was noted at ≥ 20 mg/kg bw in a preliminary assay.

Table 2 Updated Toxicology Endpoints for Use in the Health Risk Assessment of Phosmet

Exposure Scenario	RfD	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute Dietary	ARfD = 0.01 mg/kg bw	$BMDL_{10}$ = 1.26 mg/kg bw acute oral comparative cholinesterase study in rats (↓ brain cholinesterase activity in PND 11 pups)	100
Chronic Dietary	ADI = 0.006 mg/kg bw/day	$BMDL_{10}$ = 0.58 mg/kg bw/day 7-day oral comparative cholinesterase study in rats (↓ brain cholinesterase activity in PND 17 pups)	100
Short- and Intermediate-Term Dermal	-	$BMDL_{10}$ = 7.7 mg/kg bw/day 21-day dermal toxicity study in rats (↓ brain cholinesterase activity in adult rats)	300
Short- and Intermediate-Term Inhalation[2]	-	$BMDL_{10}$ = 0.58 mg/kg bw/day 7-day oral comparative cholinesterase study in rats (↓ brain cholinesterase activity in PND 17 pups)	100
Short- and Intermediate-Term Non-Dietary Incidental Oral Ingestion	-	$BMDL_{10}$ = 0.58 mg/kg bw/day 7-day oral comparative cholinesterase study in rats (↓ brain cholinesterase activity in PND 17 pups)	100
Aggregate Risk - Oral (based on ↓ brain cholinesterase activity)	-	$BMDL_{10}$ = 0.58 mg/kg bw/day 7-day oral comparative cholinesterase study in rats (↓ brain cholinesterase activity in PND 17 pups)	100
Aggregate Risk - Inhalation[2] (based on ↓ brain cholinesterase activity)	-	$BMDL_{10}$ = 0.58 mg/kg bw/day 7-day oral comparative cholinesterase study in rats (↓ brain cholinesterase activity in PND 17 pups)	100
Aggregate Risk - Dermal (based on ↓ brain cholinesterase activity)	-	$BMDL_{10}$ = 7.7 mg/kg bw/day 21-day dermal toxicity study in rats (↓ brain cholinesterase activity in adult rats)	300
Carcinogenicity [3]	q_1^* = 1.06×10^{-2} $(mg/kg\ bw/day)^{-1}$ based on hepatocellular adenomas/carcinomas in male mice following oral administration.		

[1]CAF (Composite assessment factor) refers to the total uncertainty and *Pest Control Products Act* factors for dietary and residential risk assessment; MOE refers to the target margin of exposure for occupational assessment.
[2]Since an oral BMDL was selected, an inhalation absorption factor of 100% (default value) was used in the route to route extrapolation.
[3] Since the q_1^* was based on an oral study, a dermal absorption value of 10% was used in the dermal cancer assessment.

Appendix IV Dietary Exposure and Risk Estimates for Phosmet

Table 1 Summary of Acute Dietary Exposure and Risk from Phosmet

Subpopulations	Acute – 99.9th Percentile			
	Food Only		Food and Drinking Water	
	Exposure (mg/kg bw)	%ARfD[1]	Exposure (mg/kg bw)	%ARfD[1]
General Population	0.001701	17	0.001829	18
All Infants (< 1 year old)	0.002955	30	0.003734	37
Children 1-2 years old	**0.004434**	**44**	**0.004713**	**47**
Children 3-5 years old	0.003026	30	0.003125	31
Children 6-12 years old	0.001691	17	0.001777	18
Youth 13-19 years old	0.001094	11	0.001156	12
Adults 20-49 years old	0.001028	10	0.001208	12
Adults 50+ years old	0.001183	12	0.001383	14
Females 13-49 years old	0.000921	9	0.001140	11

[1]Acute Reference Dose (ARfD): 0.01 mg/kg bw

Table 2 Summary of Chronic Dietary Exposure and Risk from Phosmet

Subpopulations	Chronic			
	Food Only		Food and Drinking Water	
	Exposure (mg/kg bw/day)	%ADI[1]	Exposure (mg/kg bw/day)	%ADI[1]
General Population	0.000096	1.6	0.000101	1.7
All Infants (< 1 year old)	0.000168	2.8	0.000185	3.1
Children 1-2 years old	**0.000300**	**5.0**	**0.000306**	**5.1**
Children 3-5 years old	0.000225	3.7	0.000230	3.8
Children 6-12 years old	0.000136	2.3	0.000140	2.3
Youth 13-19 years old	0.000084	1.4	0.000087	1.4
Adults 20-49 years old	0.000077	1.3	0.000082	1.4
Adults 50+ years old	0.000075	1.2	0.000079	1.3
Females 13-49 years old	0.000067	1.1	0.000071	1.2

[1] Acceptable Daily Intake (ADI): 0.006 mg/kg bw/day

Table 3 Summary of Cancer Risk from Phosmet

Population Subgroup	Food Only		Food and Drinking Water	
	Exposure (mg/kg bw/day)	Cancer Risk	Exposure (mg/kg bw/day)	Cancer Risk
General Population	0.000096	1E-06	0.000101	1E-06
$q_1^* = 0.0106$ (mg/kg bw/day)$^{-1}$				

Appendix V Food Residue Chemistry Summary

Since a review of the residue chemistry database for phosmet was previously conducted and published under PACR2004-38, only a brief summary is included herein.

Most of the scientific information used by the PMRA for the residue chemistry re-evaluation and the dietary risk assessment of phosmet was based on the USEPA re-registration review document dated September 8, 1999. With regard to the assessment of the adequacy and completeness of the residue chemistry database for phosmet, it was concluded that there was very limited data on file. In most cases, the existing residue data did not fully satisfy the requirements as described in the Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*. As such, the following data requirements were included in PACR2004-38 to support the continued registration of phosmet and to support any expansion of phosmet use:

- Residue field trials following good agricultural practices for cranberries (DACO 7.4.1)
- Freezer storage stability tests or USEPA Data Evaluation Records (DERs) for all commodities on which phosmet is registered for use (DACO 7.3)
- Livestock and plant metabolism studies or USEPA DERs (DACO 6.2 and 6.3)
- Confirmation that residue data for all commodities meet contemporary standards, as per DIR98-02 (DACO 7.4 to 7.6)

It was also recommended, based on USEPA reviews, that a 30-day plant-back interval be added to phosmet product labels.

Data Gaps

In addition to the residue chemistry data requirements identified for phosmet in PACR2004-38, data on the toxicity of phosmet oxon and its formation in the presence of chlorine are required, or an acceptable rationale for a waiver. Since the phase-out of all uses is proposed as a result of occupational and non-occupational risks of concern, these data will not be requested.

Appendix VI Occupational Exposure Risk Assessment for Phosmet

Table 1 Wettable Powder in Water Soluble Packaging: Occupational Dermal and Inhalation

Exposure Risk Assessment Summary

Scenario		Mixer/Loader/Applicator Proposed Mitigation	Post-Application Proposed REIs[2] (days)
USC	Crop		
13	Alfalfa	Groundboom Farmer: ML with mid-level PPE, A with closed cab + mid-level PPE Groundboom Custom: ML with max level PPE, A with closed cab + mid-level PPE + limited use (150 kg ai/day)	39 moving irrigation pipes by hand 32 scouting
14	Apples	Airblast: ML with mid-level PPE, A with closed cab + baseline PPE OR MLA with max level PPE + CR hat + limited used (13 kg ai/day)	59 thinning 48 hand harvesting 34 hand pruning, scouting, training 8 hand weeding, propping, orchard maintenance
	Blueberries	Airblast: ML with mid-level PPE, A with closed cab + baseline PPE OR MLA with max level PPE + CR hat + limited used (13 kg ai/day) Groundboom: MLA baseline PPE Manually pressurized handwand: MLA baseline PPE Backpack: MLA baseline PPE Mechanically pressurized handgun: MLA max level PPE with respirator + limited use (1 kg/day)	43 moving irrigation pipes by hand 39 highbush: hand harvesting 36 lowbush; hand harvesting, scouting 28 high bush: scouting, hand pruning, hand weeding, tying, training, frost control, bird control 0.5 low bush: hand weeding
	Carrots	Groundboom: MLA baseline PPE	43 moving irrigation pipes by hand 36 hand harvesting 12 scouting 0.5 hand weeding
	Celery	Groundboom: MLA baseline PPE	43 moving irrigation pipes by hand 36 hand harvesting 12 scouting 0.5 hand weeding
	Cherries (sour)	Airblast: MLA with max level PPE + CR hat	43 moving irrigation pipes by hand 29 hand harvesting 3 hand weeding, propping, bird control, orchard maintenance
	Cranberries	Chemigation: Midlevel PPE Groundboom: MLA baseline PPE Airblast: ML with mid-level PPE, A with closed cab + baseline PPE OR MLA with max level PPE + CR hat + limited used (13 kg ai/day) Manually pressurized handwand: MLA baseline PPE Backpack: MLA baseline PPE Mechanically pressurized handgun: MLA max level PPE with respirator + limited use (1 kg/day)	43 hand harvesting (raking), scouting 3 hand pruning (shears), hand weeding
	Grapes	Airblast: ML with mid-level PPE, A with closed cab + baseline PPE OR MLA with max level PPE + CR hat + limited used (13kg ai/day) Manually pressurized handwand: MLA baseline PPE	79 table grapes: turning, girdling 67 hand harvesting, training, tying, leaf pulling 44 moving irrigation pipes by hand

Scenario		Mixer/Loader/Applicator Proposed Mitigation	Post-Application Proposed REIs[2] (days)
USC	Crop		
		Backpack: MLA baseline PPE Mechanically pressurized handgun: MLA max level PPE with respirator + limited use (1kg/day)	30 scouting, hand weeding, hand pruning, propagating, bird control, trellis repair
	Peaches	Airblast: ML with mid-level PPE, A with closed cab + baseline PPE OR MLA with max level PPE + CR hat + limited used (13 kg ai/day)	55 thinning 44 hand harvesting 31 hand pruning, scouting, training 4 hand weeding, propping, orchard maintenance
	Pears	Airblast: MLA with mid-level PPE + CR hat	59 thinning 48 hand harvesting 34 hand pruning, scouting, training 8 hand weeding, propping, orchard maintenance
	Plums	Airblast: MLA with mid-level PPE + CR hat	54 thinning 43 hand harvesting 29 hand pruning, scouting, training 3 hand weeding, propping, orchard maintenance
	Potatoes	Groundboom Farmer: ML with mid-level PPE, A with closed cab + mid-level PPE Groundboom Custom: ML with max level PPE, A with closed cab + mid-level PPE and limited use (150 kg ai/day)	49 moving irrigation pipes by hand 41 roguing 18 scouting 2 hand weeding
27	Ornamentals[1]	Airblast: MLA with max level PPE + CR hat Groundboom: MLA baseline PPE Manually pressurized handwand: MLA baseline PPE Backpack: MLA baseline PPE Mechanically pressurized handgun: MLA max level PPE with respirator + limited use (1 kg/day)	46 cut flowers: hand harvesting, disbudding, hand pruning 34 moving irrigation pipes by hand 5 potted plants: all activities (except handset irrigation)

[1]These include the following ornamentals: shade trees (ash, beech, birch, dogwood, elm, hawthorn, hickory, maple, oak, willow), herbaceous plants (cosmos, chrysanthemum, four-o'clock, geranium, marigold, petunia, portulaca, zinnia), woody shrubs (arborvitae, azalea, boxwood, camellia, cedar, fir, hemlock, hydrangea, juniper, lilac, pine, privet, rose, spruce, yew)

[2]REIs from individual tasks are grouped together.

CR: chemical resistant; PPE: personal protective equipment [Baseline PPE: long sleeved shirt + long pants + CR gloves; Mid-level PPE: cotton coveralls over long sleeved shirt + long pants + CR gloves; Max level PPE: CR coveralls over long sleeved shirt + long pants + CR gloves]; MLA: Mixer/Loader/Applicator; REI: Restricted Entry Interval USC: Use Site Category

Appendix VII Non-Occupational Exposure Risk Assessment for Phosmet

Table 1 Wettable Powder in Water Soluble Packaging: Non-Occupational Risk Assessment

Summary

Use Site	Sub-population	Applicator Risk Summary	Post-Application Risk Summary	Proposed Mitigation
Ornamentals [1] in residential gardens	Adult	Not applicable [3]	Non-cancer and cancer concerns	Do not use product on ornamentals in residential areas.
	Youth			
	Child			
Fruit trees [2] in residential areas	Adult	Not applicable [3]	Non-cancer concerns	Do not use product on fruit trees in residential areas.
	Youth			
	Child			
Ornamental trees [1] in residential areas	Adult	Not applicable [3]	Non-cancer and cancer concerns	Do not use product on ornamentals in residential areas.
	Youth			
	Child			
Bystander Inhalation	Adult	Not applicable [3]	No concerns with limited data	None.
	Youth			
	Child			
Pick-your-own facility	All ages	Not applicable [3]	Not conducted	Do not use product on fruit trees or berries in PYO facilities.

[1]These may include the following ornamentals: shade trees (ash, beech, birch, dogwood, elm, hawthorn, hickory, maple, oak, willow), herbaceous plants (cosmos, chrysanthemum, four-o'clock, geranium, marigold, petunia, portulaca, zinnia), woody shrubs (arborvitae, azalea, boxwood, camellia, cedar, fir, hemlock, hydrangea, juniper, lilac, pine, privet, rose, spruce, yew)
[3]These may include the following fruit trees: apples, cherries, peaches, pears, plums
[3] Not applicable because there are no domestic products.

Appendix VIII Label Amendments Related to the Environment for Products Containing Phosmet

Label statements for the protection of pollinators would need to be updated to meet current standards. However, at this time, the PMRA is proposing to phase out all uses of phosmet as a result of the human health risk assessment.

The following statements are proposed to be added under **ENVIRONMENTAL PRECAUTIONS**:

"TOXIC to birds and small wild mammals."

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

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

"TOXIC to bees. Bees may be exposed through direct spray, spray drift, and residues on leaves, pollen and nectar in flowering crops and weeds. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Avoid applications when bees are foraging in the treatment area in ground cover containing blooming weeds. To further minimize exposure to pollinators, refer to the complete guidance "Protecting Pollinators during Pesticide Spraying – Best Management Practices" on Canada.ca (https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/growers-commercial-users/pollinator-protection.html). Follow crop specific directions for application timing."

"For applications on crops that are highly attractive to pollinators (alfalfa, apples, blueberry, cherry, cranberry, pear, peach, plum, and trees and flowering shrubs/ornamentals/herbaceous plants (excluding coniferous evergreens)), or when using managed bees for pollination services: DO NOT apply during the crop blooming period."

"For applications on all other crops: Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to evening when most bees are not foraging."

Runoff

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

"Avoid application when heavy rain is forecast."

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

The following statements are proposed to be added under **DIRECTIONS FOR USE**:

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

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

"DO NOT apply by air."

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

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

Buffer zones:

"Use of the following spray methods or equipment **DOES NOT** require a buffer zone: handheld or backpack sprayer and spot treatment."

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

Method of application	Crop	Buffer Zones (metres) Required for the Protection of:			
		Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer*	Alfalfa , blueberry, carrot, celery, cranberry, potato	15	4	10	5
Airblast (early growth stage)	Apple, grapes, peach, pear, plum, sour cherry	45	35	45	35
	Ornamentals (deciduous shade trees, woody evergreen trees and shrubs)	35	20	35	25
Airblast (late growth stage)	Apple, grapes, peach, pear, plum, sour cherry	35	25	35	25
	Ornamentals (deciduous shade trees, woody evergreen trees and shrubs)	25	15	25	15

> "For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners."
>
> "The buffer zones for [insert product name] can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site."

For use on cranberries, the following statement is proposed to be added under **DIRECTIONS FOR USE**:

> "To minimize surface water contamination by phosmet applied on cranberries, all effluent water must be impounded and released after a period of 4 days."

The following statement for pollinator protection is proposed to be added under **DIRECTIONS FOR USE**:

> "To protect pollinators, follow the instructions regarding bees in the Environmental Precautions section."

For alfalfa, apples, blueberry, cherry, cranberry, pear, peach, plum and deciduous shade and ornamental trees (ash, beach, oak, dogwood, willow, hickory, hawthorn, birch, elm, maple), herbaceous plants (chrysanthemum, geranium, zinnia, petunia, portulaca, four-o'clock, marigold,

cosmos), and some woody evergreen trees and shrubs (azalea, camellia, hydrangea, lilac, rose, privet), the following statement for pollinator protection is proposed to be added under **DIRECTIONS FOR USE**:

> "TOXIC to bees. DO NOT apply during the crop blooming period."

For grapes and potatoes, the following statement for pollinator protection is proposed to be added under **DIRECTIONS FOR USE**:

> "TOXIC to bees. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to evening when most bees are not foraging. When using managed bees for pollination services, DO NOT apply during the crop blooming period."

No specific use directions are required for coniferous evergreens (arborvitae, boxwood, spruce, yew, cedar, fir, hemlock, juniper, pine), as these are not attractive to pollinators.

No specific use directions are required for carrot and celery as they are harvested prior to bloom and therefore not attractive to pollinators.

Appendix IX Phosmet Uses with Limited Registered Alternative Active Ingredients[1]

Site(s)	Pest(s)	Mode of Action[2]: Registered Alternatives in Canada[3]	Comments
Apples	elm spanworm gypsy moth	None	-
	spotted wing drosophila	None	
	spring cankerworm	11: *Bacillus thuringiensis* var *aizawai*	Phosmet is of value for rotation with *Bacillus thuringiensis* for insecticide resistance management.
	tarnished plant bug	1A: carbaryl, oxamyl (non-bearing apples) 3: cypermethrin, lambda-cyhalothrin, permethrin Other: kaolin clay	Carbaryl uses on apples will be phased out as stated in RVD2016-02, dated March 31, 2016. Cypermethrin, lambda-cyhalothrin and permethrin are currently under re-evaluation.
Celery	carrot weevil	None	-
Cherries	Eastern tent caterpillar	1A: carbaryl	Carbaryl uses on cherry will be phased out as stated in RVD2016-02 dated March 31, 2016.
	elm spanworm gypsy moth spring cankerworm	None	-
	Japanese beetle	28: chlorantraniliprole cyantraniliprole	Phosmet is of value for rotation with chlorantraniliprole and cyantraniliprole for insecticide resistance management.
Grapes	elm spanworm	18: methoxyfenozide	Phosmet is of value for rotation with the methoxyfenozide for insecticide resistance management.
	gypsy moth spotted wing drosophila spring cankerworm	None	-
Peaches	Eastern tent caterpillar elm spanworm gypsy moth spring cankerworm	None	-
	Japanese beetle	28: chlorantraniliprole cyantraniliprole	Phosmet is of value for rotation with chlorantraniliprole and cyantraniliprole for insecticide resistance management.
Pears	Elm spanworm gypsy moth	None	-
	spotted wing drosophila	None	
	spring cankerworm	11: *Bacillus thuringiensis* ssp. *aizawai* (cankerworm)	Phosmet is of value for rotation with *Bacillus thuringiensis* for insecticide resistance management.

Site(s)	Pest(s)	Mode of Action[2]: Registered Alternatives in Canada[3]	Comments
Plums	apple maggot	1A: carbaryl Other: kaolin clay	Carbaryl uses on plums will be phased out as stated in RVD2016-02 dated March 31, 2016.
	Eastern tent caterpillar	1A: carbaryl	
	elm spanworm gypsy moth spring cankerworm	None	-
	Japanese beetle	28: chlorantraniliprole cyantraniliprole	Phosmet is of value for rotation with chlorantraniliprole and cyantraniliprole for insecticide resistance management.
Deciduous shade trees	spring cankerworm	1A: carbaryl (birch, dogwood, elm, maple, oak)	The use of carbaryl on ornamentals in residential areas is proposed to be phased out as stated in RVD2016-02 dated March 31, 2016.
		1B: acephate (birch, hawthorn, linden, maple, municipal parks, oak, rights of way, shelter belts, tree nurseries)	Acephate is currently under re-evaluation.
		3: pyrethrins / piperonyl butoxide (dogwood, elm, oak)	Pyrethrins/piperonyl butoxide is packaged into a spray can. As a result, it is only viable for use to treat very small ornamental trees and bushes. In addition, pyrethrin and piperonyl butoxide are currently under re-evaluation.
		11: *Bacillus thuringiensis*	*Bacillus thuringiensis* is registered for use on all types of deciduous shade and ornamental trees.

Site(s)	Pest(s)	Mode of Action[2]: Registered Alternatives in Canada[3]	Comments
Deciduous shade trees, woody evergreens and herbaceous plants	elm spanworm	1A: carbaryl (arborvitae, azalea, birch, boxwood, chrysanthemum, dogwood, elm, hydrangea, juniper, lilac, maple, oak, pine, rose and zinnia) 1B: acephate (beech, elm, hickory, maple, oak) 11: *Bacillus thuringiensis*	Carbaryl uses on ornamentals in residential areas will be phased out as stated in RVD2016-02 dated March 31, 2016. Acephate is registered for control of elm spanworm when applied as an implant cartridge to trees with a minimum trunk diameter of 7.5 cm. As a result, acephate cannot be used on small trees, shrubs or herbaceous plants. In addition, acephate is currently under re-evaluation.

[1] as of January 13, 2017.

[2] Insecticide and Acaricide Resistance Management Group Numbers based on Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance Management Labelling based on Target Site/Mode of Action*, with updates from the Insecticide Resistance Action Committee Mode of Action Classification Scheme v8.0 December 2015. Available at http://www.irac-online.org.

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Information Considered in the Chemistry Assessment

A. Studies/Information Submitted by the Registrant

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1674144	2003. Validation of Analytical Methodology for the Assay of Phosmet and Structurally Related Significant Impurities of Phosmet and Subsequent 5-Batch Analysis of Phosmet TGAI, DACO 2.13.3.
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1855269	1997. Analysis and Certification of Product Ingredients in Five Batches of Technical Grade Phosmet, DACO 2.13.
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Information Considered in the Toxicological Assessment

A. Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
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1995291	1999. A 21-Day Dermal Toxicity Study of Imidan in Rats. MPI Research, 54943 Main, Mattawan, MI. Laboratory Study Identification Number 815-002, DACO 4.3.5.
1840663	2007. Cholinesterase Response of Crl:CD(SD) Rats Following Repeated Dermal Application of Imidan 70-W at Multiple Dose Levels in Rats. Charles River Laboratories Preclinical Services, Horsham, PA. Laboratory

PMRA Document Number	Reference
	Project Identification Number WJI00021, DACO 4.5.
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1715583	2007. Oral (Gavage) Acute Dose Relative Sensitivity of Phosmet Technical in Neonatal Rats and Adult Rats. Charles River Laboratories Pre-Clinical Services, Horsham, PA. Protocol No. WJ100011, DACO 4.5.14.
1840659	2009. Oral (Gavage) Repeat Dose Relative Sensitivity Study of Phosmet Technical in Neonatal Rats and Adult Rats. Charles River Laboratories Preclinical Services, Horsham PA Protocol No. WJ100013, DACO 4.3.8.
1995283, 1995276, 1995281, 1995285, 1995288	1999. A dietary Subchronic (90-day) Neurotoxicity Study of Phosmet in Rats. Laboratory Study Number WIL-331002. WIL Research Laboratories, Inc. Ashland, OH, DACO 4.3.1.
1243149	1984. Two-Year Dietary Oncogenicity Study in Mice. Stauffer Chemical Company, Environmental Health Centre, Farmington, CT, DACO 4.4.2.
1206187	1986. Unpublished Addendum I (Error Correction). Two Year Dietary Oncogenicity Study in Mice with Imidan Technical. Stauffer Environmental Health Centre, Stauffer Chemical Co., CT, USA, DACO 4.4.2.
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1173004, 1173005	1991. Final Report: 2 Year Chronic Toxicity/Oncogenicity Study with R-1504 in Rats. Ciba-Geigy Corp., Agricultural Division, Environmental Health Centre. T-13241, DACO 4.4.4.
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B. Additional Information Considered

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PMRA Document Number	Reference
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Information Considered in the Dietary Assessment

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
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2220509	2006. Validation of the Analytical Method for the Determination of Phosmet and Phosmet Oxon Residue in Peaches, Oranges (Fruit, Peel and Flesh), Apples and Olives, DACO 7.2.1, 7.2.3.

PMRA Document Number	Reference
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2220514	1994. Determination of the Magnitude of Residues of Phosmet and its Oxygen Analog in Potato Tuber RACs Treated with Imidan 50-WP, DACO 7.2.1, 7.3, 7.4.1.
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2220531	1974. Crop Residue Report - Imidan 70-WP + Oil - Oranges (Variety Navel), DACO 7.4.1.
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2220533	1976. Crop Residue Report - Imidan 50-WP and 5-P - Sweet Potatoes, DACO 7.4.1.
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B. Additional Information Considered

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