Re-evaluation Note REV2024-02

Organophosphate Pesticides – Cumulative Health Risk Scoping Assessment, Problem Formulation and Planned Approach of Analysis

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Organophosphate Pesticides – Cumulative Health Risk Scoping Assessment, Problem Formulation and Planned Approach of Analysis

In Canada, the cumulative health risk assessment of active ingredients belonging to the organophosphate (OP) class of pesticides, as described in SPN2018-02, *Cumulative Health Risk Assessment Framework*, was initiated in May 2022.

Under the authority of section 16 of the *Pest Control Products Act*, the Canadian registrants of 11 OP pesticides were notified of the initiation of the cumulative risk assessment (CRA) of this class of compounds. Following notification, the registrants indicated support for all uses included on the labels of the end-use products for 10 of the 11 OP pesticides registered in Canada at the time of initiation. Registrants of one OP pesticide chose to discontinue registration. This CRA includes 10 OP pesticides that are registered in Canada: acephate, azamethiphos, bensulide, dichlorvos, dimethoate, malathion, naled, phorate, phosmet and tetrachlorvinphos.

As outlined in SPN2018-02, cumulative risk assessments are aimed at evaluating human health risks associated with co-exposure to two or more pesticides that have a common mechanism of toxicity, based on available information. It may consist of a quantitative or qualitative cumulative risk assessment or result in a determination that a cumulative risk assessment is not required, for example, in situations that do not involve co-exposures.

Metabolites/Transformation Products: For the OP pesticides, the common mechanism of toxicity relates to their shared ability to irreversibly bind to and phosphorylate the acetylcholinesterase (AChE) enzyme in mammalian central and peripheral nervous systems. Some transformation products of the OP pesticides also inhibit AChE and will thus be considered in the cumulative risk assessment if there is potential for exposure to these chemicals. For example, when formed, oxon metabolites of OP pesticides are known to inhibit AChE. Some of these oxon metabolites were previously determined to be relevant in the individual Health Canada assessments for several OP pesticides and will be considered in the OP CRA (as outlined in Appendix I, Tables 1 and 2). Methamidophos, an OP pesticide registered in other countries, is also a metabolite of acephate, and will be considered in the CRA. The relevance of other transformation products of OP pesticides in the CRA will be further considered during the full review.

A quantitative approach will be used in this CRA to assess risk from major exposure pathways, routes, and uses of OP pesticides. This will include deterministic and/or probabilistic assessments, as required. The results of this complex analysis must be interpreted with a full understanding of the assumptions made and the uncertainties introduced as a result of these assumptions. Qualitative assessments will also be used to assess risk from minor exposure pathways, routes, and uses of OP pesticides.

The process Health Canada's Pest Management Regulatory Agency (PMRA) undertook to identify available evidence relating to a common mechanism of toxicity for the OP pesticides, their co-exposure and their potential to result in a material contribution to non-occupational (dietary and residential) exposure, in order to define the cumulative assessment group (CAG), is outlined in the appendices.

A scoping assessment is included in Appendix I; a decision tree is included in Appendix II; and the planned approach for analysis of the OP CRA is included in Appendix III.

Scoping Assessment: The anticipated exposure scenarios resulting from the uses of each of the 10 OP pesticides registered in Canada are provided in Table 1, Appendix I. Additional OP pesticides that belong to the OP common mechanism group are listed in Table 2, Appendix I. Although these OP pesticides are not registered in Canada, the active ingredients could be present on imported food commodities, and accordingly, are included in the scoping assessment. The decision tree used by Health Canada to determine which active ingredients would be included (quantitatively or qualitatively), or excluded, from the dietary exposure cumulative assessment group (CAG) is presented in Appendix II. This 5-step process was used to categorize the 42 OP pesticides that are listed in Appendix I, Table 2 into the three categories described below:

- OP pesticides not registered in Canada that will be quantitatively included in the cumulative assessment group,
- OP pesticides not registered in Canada and determined to be minor contributors to overall cumulative exposure to OP pesticides and will be considered qualitatively in the cumulative assessment group, and
- OP pesticides not registered in Canada that will be excluded from the cumulative assessment group as their food residues are not relevant to dietary exposure based on the available Canadian food supply.

Problem Formulation and CRA Analysis: The planned approach for analyzing the OP CRA is presented in Table I, Appendix III to clearly identify and describe the problem formulation elements that will be considered in the OP CRA, and to summarize the key information that will be used to support Health Canada's assessment.

Appendix I Scoping assessment for the cumulative health risk assessment of organophosphate pesticides

Background

Health Canada follows the approach to cumulative health risk assessment for pesticides described in SPN2018-02.[1] The purpose of the scoping assessment is to identify the available information relating to evidence of a common mechanism of toxicity, use pattern, and likelihood of co-exposure to the pesticides being considered. The information collected at this stage allows Health Canada to confirm whether a CRA is required, and if so, to identify the scope and depth of the necessary analysis. Data types and information sources are also identified at this step.

Common mechanism of toxicity

As indicated in SPN2018-02, Health Canada leverages cumulative assessments undertaken by other regulators, provided that the assessments are relevant to the Canadian context. The USEPA has established the OPs as a common mechanism group based on a common toxic effect by the same major biochemical event (2002)[2,3]. Given the well-established and distinct common mechanism of toxicity of the OP pesticides, related to their irreversible binding and phosphorylation of the serine residue of the AChE enzyme in mammalian central and peripheral nervous systems, Health Canada agrees that there is scientific validity in establishing the OP pesticides as a common mechanism group, consistent with the approach outlined in SPN2018-02.

OP pesticides, use patterns and potential exposure pathways

OP pesticides are generally used for insect control. Table 1 lists the 10 OP pesticides (active ingredients) currently registered in Canada and the anticipated exposure scenarios resulting from the uses for each OP. Additional pesticides that belong to the OP common mechanism group are listed in Table 2. Although these OP pesticides are not registered in Canada, residues of the active ingredients could be present on imported food commodities and accordingly, are included in the scoping assessment.

1 Health Canada. 2018. Pest Management Regulatory Agency Science Policy Note (SPN2018-02) Cumulative Health Risk Assessment Framework. Science Policy Note SPN2018-02, Cumulative Health Risk Assessment Framework - Canada.ca

2 USEPA Office of Pesticide Programs (2002). Status of Cumulative Risk Assessment for Organophosphate Pesticides. https://archive.epa.gov/epa/sites/production/files/2015-07/documents/guidefinal_4-new.pdf

3 USEPA (2002). Revised OP (Organophosphate) Cumulative Risk Assessment. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100BFLL.TXT

Table 1 Summary of uses and exposure pathways for organophosphate pesticides registered in Canada and to be included in the cumulative assessment group

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
Acephate (and Methamidophos[1])	Agricultural crops (commercial-class products)	yes	yes	no
	Outdoor and greenhouse ornamentals (commercial-class products)	no	yes	yes
	Forests and woodlots (foliar application), shelterbelts and rights-of-way (commercial-class products)	no	yes	yes
	Ornamental trees in residential areas, rural lands, farms, businesses, shopping complexes, etc. (trunk injection) (commercial-class products)	no	no	yes
Azamethiphos	Farmed Atlantic salmon (restricted-class products)	yes	no	no
Bensulide (and Bensulide oxon)	Field cucumbers (commercial-class products)	yes	yes	no
	Turf (residential lawns, golf course tees and putting greens) (commercial-class products)	no	yes	yes
Dichlorvos	Indoor commercial food containing warehouses, food processing plants, industrial plants, theatres (restricted-class products)	yes	no	yes
	Insecticidal strip in fruit and vegetable crops only (commercial-class products)	yes	no	no
Dimethoate (and Omethoate)	Agricultural crops (commercial-class products)	yes	yes	no
	Pastures and wastelands (commercial-class products)	yes	yes	no
	Outdoor ornamentals (commercial-class products)	no	yes	yes

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
	Forests and woodlots (commercial- and restricted-class products)	no	yes	yes
Malathion (and Malaoxon)	Agricultural crops (commercial-class products) and residential fruit and vegetable gardens (domestic-class products)	yes	yes	yes
	Greenhouse food crops (commercial-class products)	yes	no	no
	Greenhouse ornamentals (commercial-class products)	no	no	yes
	Outdoor ornamentals (commercial- and domestic-class products)	no	yes	yes
	Outdoor structural foundations (commercial- and domestic-class products)	no	no	yes
	Outdoor non-structural including agricultural, commercial, industrial (commercial-class products) and residential (domestic-class products)	no	yes	yes
	Grain elevator, granary bins, grain box cars (when empty) (commercial-class products)	no	no	no
	Stored grains (commercial-class products)	yes	no	no
Naled	Agricultural crops (commercial-class products)	yes	yes	no
	Outdoor ornamentals (commercial-class products)	no	yes	yes
	Livestock pastures, feedlots pastures with dairy cattle present (commercial-class products)	yes	yes	no
	Corrals, adjacent pastures, holding pens with animals present (commercial-class products)	yes	no	yes
Phorate (and Phorate oxon)	Potato (restricted-class products)	yes	yes	no

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
Phosmet (and Phosmet oxon)	Agricultural crops (commercial-class products)	yes	yes	no
	Outdoor ornamentals[2] (commercial-class products)	no	yes	yes
Tetrachlorvinphos	Cats and dogs (domestic-class products)	no	no	yes
	Poultry (commercial-class products)	yes	no	yes
	Poultry housing, dairy barns, swine barns, other animal buildings (commercial-class products)	no	no	yes

[1] Methamidophos is the principal metabolite of acephate, and it is also a pesticide registered in other countries (refer to Table 2).
[2] Outdoor ornamentals grown for cut flowers have a last date of use of 30 October 2024; therefore, will not be included in the CRA.

A complete list of all Health Canada published documents including public consultations, final decisions and updates for each registered organophosphate pesticide listed in Table 1 is included in Appendix IV.

Table 2 Summary of organophosphate pesticides that are not registered in Canada to be considered for dietary exposure from imported foods[1]

Active ingredient	Potential exposure pathway
OP active ingredient residues quantitatively included in the cumulative assessment group	
Chlorpyrifos[2] (and chlorpyrifos oxon)	Imported foods
Diazinon (and diazoxon)	
Methamidophos[3]	
Methidathion	
Oxydemeton-methyl	
OP active ingredient residues qualitatively included in the cumulative assessment group	
Azinphos-methyl	Imported foods
Cadusafos	
Chlorpyriphos-methyl	
Coumaphos[4]	
Dicrotophos	
Ethion	
Ethoprop/Ethoprophos	
Monocrotophos	
Phosalone	
Pirimiphos-methyl	
Profenofos	
Propetamphos	
Terbufos	
Trichlorfon	
OP active ingredient residues excluded from the cumulative assessment group	
Bromophos-ethyl	Imported foods
Chlorethoxyfos/Chlorethoxyphos	
Chlorfenvinphos	
Chlorthiophos	
Dialifor	
Dioxathion	
Disulfoton	
Fenamiphos	
Fenitrothion	
Fenthion	
Fonofos	
Fosthiazate	
Isazophos	
Isofenphos	
Mevinphos	
Parathion Ethyl	
Parathion Methyl	
Phosphamidon	

Active ingredient	Potential exposure pathway
OP active ingredient residues quantitatively included in the cumulative assessment group	
Phostebupirim (tebupirimphos)	
Sulfotep	
Sulprofos/Sulfprophos	
Temephos	
Tribufos/Tribuphos	

[1] For detailed information on how the pesticides listed in this table were identified for inclusion in the cumulative assessment group see Appendix II, Decision tree for determining which pesticides to include in the dietary exposure cumulative assessment group.
[2] The last date of use for all uses/products of this OP active ingredient was 10 December 2023; however, it will still be considered in the cumulative risk assessment as residues could be present in/on imported food commodities.
[3] Methamidophos is the principal metabolite of acephate and it is also a pesticide registered in other countries (refer to Table 1).
[4] The last date of use for all uses/products of this OP active ingredient was 1 November 2023; however, it will still be considered in the cumulative risk assessment as residues could be present in/on imported food commodities.

A complete list of all public consultation, final decision and update documents published by Health Canada for each organophosphate pesticide list in Table 2 previously registered in Canada is included in Appendix IV.

Toxicity assessment

For the hazard analysis of the OP CAG, Health Canada anticipates using the relative potency factor method outlined in SPN2018-02 and used by the USEPA (2006).[4] This approach relies upon the selection of an index chemical within the CAG, against which the other members of the OP pesticides included quantitatively in the CRA are compared, in order to convert exposures of all OP pesticides into exposure equivalents of this index chemical for estimating cumulative exposure and risks.

As previously noted, the common mechanism of toxicity for the OP pesticides involves inhibition of the AChE enzyme through phosphorylation of the serine residue at the active site of the enzyme. This results in irreversible inhibition of bound AChE, and leads to accumulation of acetylcholine, and subsequent neurotoxicity, in the central and/or peripheral nervous system. Health Canada anticipates using AChE inhibition data, a direct measure of the mechanism of toxicity, to identify the index chemical and establish relative potency factors for each individual OP pesticide included quantitatively in the CRA. Consistent with the approach used by the USEPA, the AChE inhibition data from available in vivo toxicity studies in adult and juvenile animals, from relevant routes of exposure, will be analysed using benchmark dose (BMD) analysis. BMD estimates will be used to establish relative potency factors, determine points of departure for risk assessment, and inform the magnitude of the Pest Control Products Act (PCPA) factors used in the CRA.

[4] US EPA (2006). Organophosphorus Cumulative Risk Assessment. 2006 Update. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002

Exposure assessment – Food

The CRA for the OP pesticides will examine potential exposures that may occur through the dietary pathway. This approach is similar to that used for the single chemical aggregate assessments, in that the cumulative risk assessment will evaluate residues on foods treated with OP pesticides belonging to the CAG, as well as those residues that may occur in drinking water. Residues on foods may occur as a result of registered uses in Canada, or through residues on foods imported into Canada. As such, the dietary exposure assessment considers Canadian and international food use registrations of pesticides.

The specific food/pesticide combinations that will be included in the CRA are based on an analysis of Maximum Residue Limits (MRLs)/US tolerances, food use registrations, as well as food residue monitoring data, as presented in the decision tree of Appendix II. Certain OP pesticides were excluded from the cumulative risk assessment/cumulative assessment group when it was determined that their residues were not relevant to the dietary exposure, based on the available Canadian food supply (see Table 2 above). The data sources used to inform the scoping assessment include the North American pesticide registration status, food residue monitoring data (Canadian Food Inspection Agency National Chemical Residue Monitoring Program and United States Department of Agriculture Pesticide Data Program), Canadian crop production information, and trade data.

Exposure assessment – Drinking water

For OP pesticides that are registered in Canada, potential exposure from drinking water will be assessed through modelling and available relevant water monitoring information (for example, monitoring data from Health Canada's Water Monitoring Program for Pesticides). Modelling for OP pesticides registered in Canada previously completed as part of the individual pesticide re-evaluations will be used and updated, as required. For OP pesticides that are not registered in Canada, but potentially present on imported foods only, consideration of drinking water contribution is not required, as their lack of use in Canada means these will not be present in drinking water.

The OP pesticides have the potential to undergo oxidation to their respective oxon metabolites and/or other oxidation analogues. Some OP pesticides may not be stable in chlorinated water and may form the more stable oxon metabolites. As such, the oxon metabolites will be considered in the CRA through exposure from drinking water sources.

Exposure assessment – Residential

The CRA for OP pesticides will consider all non-occupational sources, pathways and routes of exposures that could contribute materially to a person's total exposure. Several of the OP pesticides registered in Canada include use sites that can be accessed by Canadians, and this may result in potential residential dermal and inhalation exposure (for example, via application of domestic-class products, postapplication activities in treated areas), and postapplication incidental oral ingestion (for example, hand-to-mouth activities) for children. Some postapplication exposure scenarios (for example, outdoor structural foundation application, tree injection) will result in low or negligible exposure and will be assessed qualitatively.

Data sources that will be used to inform the assessment include pesticide use data, Canadian national and provincial percent crop treated data, chemical-specific residue data, and residential exposure and survey data (for example, Outdoor Residential Exposure Task Force, Residential Joint Venture homeowner survey, and USEPA Standard Operating Procedures). The regionality and temporality of the residential exposure are important factors that will be considered to determine if co-occurrence of exposure is expected and plausible.

Conclusion

Given a common mechanism of toxicity has been identified and there is potential for co-exposure to the OP pesticides within the CAG, a cumulative risk assessment is required. The cumulative assessment group that will be considered in the OP CRA will include 29 active ingredients and their relevant metabolites, where applicable, 14 of which will be considered qualitatively as outlined in Tables 1 and 2 above. The potential for co-exposure of the pesticides in the CAG will be considered for the oral (dietary and incidental oral), dermal and inhalation routes.

Data Gathering

Following initiation of this cumulative assessment, the registrants of the OP pesticides registered in Canada provided Health Canada with lists of available studies (including planned and/or in-progress studies). Health Canada will make use of available information, including registrant-supplied data, foreign reviews, as well as relevant data from the open scientific literature. An Announcement of Data Call-In, outlining the information required from registrants, will be placed in the Public Registry under Application Number 2022-1065.

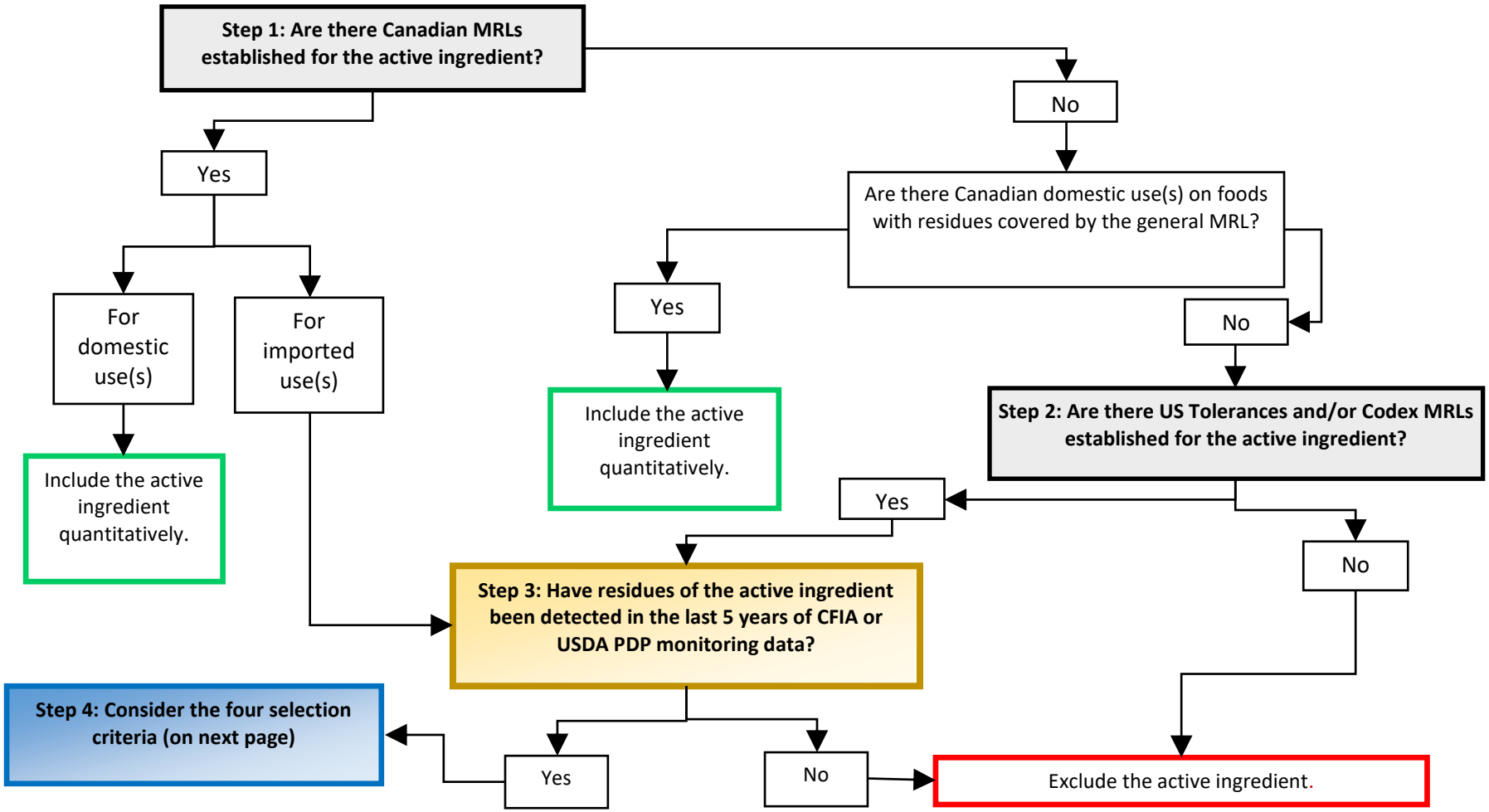
As noted above, although some OPs are not registered in Canada, they may contribute to cumulative risk through residues on imported food commodities. For the hazard analysis of these pesticides, toxicology data in the open scientific literature will be used to the extent possible; however, Health Canada also encourages registrants of the organophosphate pesticides to submit relevant toxicity data (specific to measurement of cholinesterase inhibition), if available.

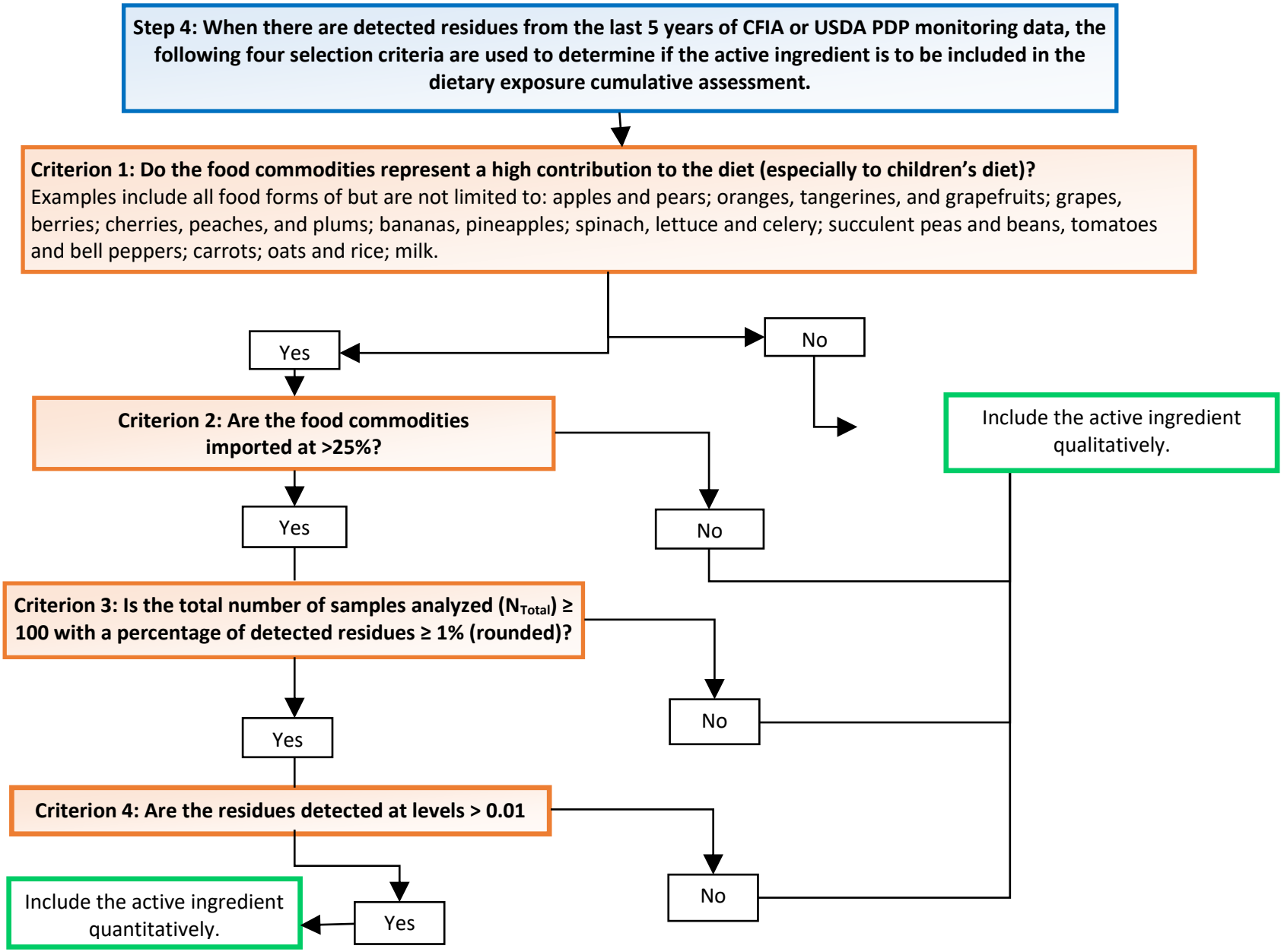
Next steps

Following examination of the extent of available data and information, Health Canada will publish a workplan for the cumulative risk assessment and initiate the full review. The workplan will include target dates for the publication of the proposed cumulative health risk assessment for consultation, as well as for the final decision.

Appendix II Decision Tree for determining which pesticides to include in the dietary exposure cumulative assessment group

Pesticides that will be considered for inclusion in the cumulative assessment group (CAG) to account for the main contributors to the Canadian diet (including imported foods) are pesticides with Canadian registrations, pesticides with Canadian MRLs on imported foods, pesticides with US tolerances and pesticides with Codex MRLs.




Step 4: When there are detected residues from the last 5 years of CFIA or USDA PDP monitoring data, the following four selection criteria are used to determine if the active ingredient is to be included in the dietary exposure cumulative assessment.
Criterion 1: Do the food commodities represent a high contribution to the diet (especially to children's diet)?
Examples include all food forms of but are not limited to: apples and pears; oranges, tangerines, and grapefruits; grapes, berries; cherries, peaches, and plums; bananas, pineapples; spinach, lettuce and celery; succulent peas and beans, tomatoes and bell peppers; carrots; oats and rice; milk.
Yes
No
Criterion 2: Are the food commodities imported at >25%?
Yes
No
Include the active ingredient qualitatively.
Criterion 3: Is the total number of samples analyzed (N_{Total}) ≥ 100 with a percentage of detected residues ≥ 1% (rounded)?
Yes
No
Criterion 4: Are the residues detected at levels > 0.01
Yes
No
Include the active ingredient quantitatively.

Appendix III Problem formulation and planned approach of analysis for the organophosphate pesticides cumulative risk assessment

Problem formulation element	Description	Information related to the organophosphate CRA

Risk assessment questions	Specific questions to be addressed	a) What are the health risks to the general population of Canada (including vulnerable subpopulations) from cumulative dietary exposure and/or non-occupational dermal and/or inhalation exposures to organophosphate (OP) pesticide residues in food, drinking water and treated residential areas, given the ability of OP pesticides to inhibit acetylcholinesterase (AChE) via a common mechanism of toxicity?
		
		b) What exposure pathway contributes the most to the cumulative risk of OP pesticides in Canada (in other words, what are the risk drivers) and for which OP active ingredients? Sensitivity analyzes can help to discern whether risks are driven by exposure from one pesticide in the common mechanism group, or by certain uses for one or more pesticides, a specific pathway of exposure, or other factors, such as whether risks are specific to a certain population.
		
		c) What food-pesticide combination(s) contribute(s) the most to dietary exposure and cumulative risk of OP pesticides in Canada?
		
		If the protection goals are not met (in other words, MOEs for the determined threshold percentile are below the target MOE),
		
		• It may trigger the need for a higher tier (in other words, more refined) assessment and the generation of additional data to obtain a CRA that is more reflective of real-world exposure (for example, biomonitoring data, pesticide use surveys, residue transfer studies, air monitoring data).
		• The results from the OP CRA will be used to inform risk management decisions to protect human health such as:
		  ○ implementing risk mitigation measures, which includes a number of possible measures ranging from label amendments to cancellation of uses or products;
		  ○ setting or amending regulatory standards (for example, risk-based MRLs);
		  ○ consideration as part of the proportional effort classification for these pesticides; and,

Problem formulation element	Description	Information related to the organophosphate CRA
		○ prioritization of the active ingredients to inform continuous oversight monitoring. Further, the implementation of risk mitigation measures or amendments of regulatory standards could inform the prioritization of compliance verification by the Regulatory Operations and Enforcement Branch (ROEB).
Description of the cumulative assessment group (CAG)	Evidence for the common toxicological effect of the mixture component included in the CAG	AChE inhibition is a consistent effect in toxicity studies of OP pesticides and some of their transformation products conducted in vivo.
	Evidence of co-exposure	**Food**: Monitoring data show that North American foods contain low levels of several OP pesticide residues concurrently in the same sample. **Drinking water**: Water monitoring data using multi-residue methods analyzing several OP pesticide residues concurrently in the same sample will inform the potential for co-occurrence of OP pesticide residues in drinking water sources (for example, acephate, bensulide, dimethoate, dichlorvos and malathion are included in the water monitoring framework). **Residential exposure**: Several OP pesticides are registered for use in Canada on different use sites that can be accessed by the Canadian general population resulting in potential residential dermal, inhalation and incidental oral exposure. When conducting a cumulative risk assessment, the regionality and temporality of exposure is important to determine if co-occurrence of exposure is expected and plausible. Data such as Provincial Percent Crop Treated (PCT) data and use pattern information will inform the potential for co-exposure of the different OPs.
Conceptual model	Regulatory framework	*Pest Control Products Act* (PCPA), SPN2018-02
	Substances categories	Pesticides
	Exposure sources	Non-occupational exposure: Food, drinking water and residential exposure

Problem formulation element	Description	Information related to the organophosphate CRA
	Exposure routes	Oral, dermal and inhalation
	Population groups	General population in Canada, including vulnerable populations of children, pregnant people, and the elderly
	Population age groups	Infants, children 1–2 years old, children 3–5 years old, children 6–12 years old, youth 13–19 years old, females 13–49 years old, adults and seniors
	Toxicological effect	Inhibition of AChE
	Level of grouping	Common mechanism of toxicity/adverse outcome pathway
Toxicology methodology	Data availability for toxicity described in general terms, including the type of data	Available information, including registrant-supplied data, foreign reviews, as well as relevant data from the open scientific literature will be used. Data from toxicity studies in adult and juvenile animals measuring AChE inhibition following various exposure scenarios will be evaluated. These data will be used to determine relative potency factors, points of departure and inform the magnitude of the PCPA factor.
	Use of adverse outcome pathway networks and/or mode of action information to support grouping of substances into assessment groups and/or identification of measurable effect/key events	The grouping of OP pesticides is based on their shared ability to inhibit AChE through a common mechanism of toxicity. The initiating event in this adverse outcome pathway involves inhibition of AChE via irreversible phosphorylation of the active site, which leads to accumulation of acetylcholine, and subsequent neurotoxicity, in the central and/or peripheral nervous system.
	Collection of additional toxicity data from literature	Literature searches will be conducted to identify in vivo toxicology data measuring AChE inhibition for all OP pesticides included quantitatively in the Canadian cumulative risk assessment, as well as for relevant transformation products (including the oxon metabolites). Although some OPs are not registered in Canada, they may contribute to cumulative risk through

Problem formulation element	Description	Information related to the organophosphate CRA
		residues on imported food commodities. Toxicology data in the open-scientific literature will be used to the extent possible for these OP pesticides; however, Health Canada also encourages the submission of relevant toxicity data, if available, from registrants.
	Grouping of substances based on toxicological considerations	Data from in vivo toxicity studies that assess AChE inhibition, a direct measure of the mechanism of toxicity, will be used to conduct the cumulative risk assessment.
	Calculation of RPFs, choice of index substance and selection of POD	It is anticipated that the relative potency factor (RPF) method outlined in SPN2018-02 and used by the USEPA (2006) for the cumulative risk assessment of the OPs will be followed. The use of RPFs will allow conversion of exposures of all the chemicals in the OP common assessment group into exposure equivalents of an index chemical, to be selected from the list of OPs included quantitatively in CRA. AChE inhibition data, a direct measure of the mechanism of toxicity, will be used to identify an index chemical and establish RPFs for each OP pesticide included quantitatively in the CRA. The AChE inhibition data from the available in vivo toxicity studies in adult and juvenile animals, from relevant routes of exposure, will be analysed using benchmark dose (BMD) analysis. BMD estimates will be used to establish RPFs, to determine points of departure (POD) for risk assessment, and to inform the magnitude of the PCPA factors that will be used in the CRA.
Dietary food exposure methodology	Data availability for dietary food exposure described in general terms, including the type of data	Consumption data from NHANES in the United States (national dietary survey on two non-consecutive days); Concentrations from Canadian and American monitoring data; and Biomonitoring data.
	Collection of consumption data	Food consumption surveys for the population in the United States, using 24 h-recall on two

Problem formulation element	Description	Information related to the organophosphate CRA
		non-consecutive days.
	Collection of concentration data	Concentration data from North American monitoring programs (Canadian CFIA and USDA PDP), using objective or selective sampling.
	Non-detects, concentration measurements below the limit of detection	Use zero value.
	Approach for dealing with lack of food concentration data	Extrapolation of measured data from other foods and using residue data.
	Conversion of food-as-eaten to food-as-measured and processing factors	FCID recipes incorporated into DEEM (Version 4.02); and Experimental processing factors, where available, for the processed commodities that do not have specific monitoring data.
	Acute or chronic model for dietary exposure assessment	Acute and chronic models since AChE inhibition is caused by both acute and repeated exposure.
	Model for dietary exposure assessment (deterministic or probabilistic)	Probabilistic model
Drinking water exposure methodology	Data availability for drinking water exposure described in general terms, including the type of data	Where available, concentrations in drinking water from monitoring data in surface water and groundwater sources throughout Canada (either directly or as a weight-of-evidence); and Biomonitoring data.
	Approach for dealing with lack of	Water modelling can be based on available crop location data. Each OP pesticide can be modelled for each use pattern, those use patterns matched with crops, and therefore an EEC assigned to

Problem formulation element	Description	Information related to the organophosphate CRA
	concentration data	location. An average concentration over a standard area can then be calculated and the maximum for each region reported. In cases where more than one OP pesticide can be used on the same crop, both would be modelled, and the results added together.
	Most representative drinking water concentration	Either use the point estimate concentration, the distribution of concentrations, or region-specific concentrations
Residential exposure methodology	Residential Scenarios	Turf (golf courses and residential lawns), outdoor and greenhouse ornamentals, residential fruit and vegetable gardens, indoor commercial buildings and animal premises, recreational areas, outdoor structural foundations, outdoor non-structural uses (including management of mosquitoes), forests and woodlots, and pets.
	Exposure Routes	Domestic-class products: • Applicator dermal and inhalation route for adults Domestic- and commercial-class products: • Postapplication oral route of exposure by incidental oral ingestion (for example, hand-to-mouth) activity of children (1–2 and 3–5 years old) • Postapplication dermal route of exposure for children and adults • Postapplication inhalation route of exposure for children and adults
	Dermal Absorption Data	Where available, chemical-specific dermal absorption data.
	Data for residential exposure described in general terms	• Pesticide use data, National and Provincial Percent Crop Treated data • Residue concentration and dissipation/decay data • Residue contact and exposure factor data • Residential Exposure Joint Venture (REJV) data

Problem formulation element	Description	Information related to the organophosphate CRA
		• Chemical-specific data related to dermal and inhalation exposures, including: dislodgeable residue data (DFR), turf transferrable residue (TTR) data, ambient air monitoring data, biomonitoring data and any other relevant data (either submitted by registrants or available in the public domain/scientific literature)
	Data availability for the lawn scenario and for the golf course scenario	• Task force data (ORETF) including the Johnson homeowner survey. • USEPA Residential SOP (2012)[5] • Where available, chemical-specific TTR, biomonitoring data.
	Data availability for the outdoor non-structural (management of mosquitoes) use scenario	• USEPA Residential SOP (2012) • Where available, chemical-specific DFR, TTR, air monitoring data, biomonitoring.
	Data availability for the residential garden scenario (vegetable garden and ornamentals)	• USEPA Residential SOP (2012) • Task force data (ORETF) including the Johnson homeowner survey. • Where available, chemical-specific DFR.
	Data availability for the pet use scenario	• USEPA Residential SOP (2012) • Where available, chemical-specific dislodgeable residue data from pet fur.
	Model for residential exposure assessment (deterministic or probabilistic)	Lower tier quantitative assessment will use a deterministic model. If a higher tier quantitative assessment is required, a probabilistic model may be used.
Risk assessment results	Risk metrics to be used and different percentiles of the	**Qualitative assessment** Risk resulting from minor exposure pathways, routes or uses will not be included in the quantitative CRA and will be assessed qualitatively. A detailed rationale will be provided to justify

[5] USEPA (2012). Standard Operating Procedure for Residential Exposure and Risk Assessment for Pesticides https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedure-residential-exposure

Problem formulation element	Description	Information related to the organophosphate CRA
and characterization	exposure distribution to be used	the exclusion from the quantitative risk assessment. **Quantitative assessment** Deterministic Assessment (for lower tier, if applicable): Margins of exposure (MOEs) Probabilistic Assessment (higher tier): Margins of exposure (MOEs) using different percentiles up to 99.9 percentile. Quantitative cumulative risk assessment is a complex analysis, and the results are not a collection of numbers. The results need to be interpreted with a full understanding of the assumptions made and the uncertainties introduced by making these assumptions. Therefore, it is especially important to consider the risk characterization section of the framework to get a full understanding of the results.
	Methodology to identify risk drivers	MOEs at 99.9 percentile below the target MOE
	Higher tiers to be used when lower tier assessment does not provide sufficient protection	This may result in the need to generate additional hazard, food and drinking water concentration data and exposure data for residential scenarios.
	Method(s) for uncertainty analysis (for example, qualitatively or quantitatively)	Uncertainties listed and quantified, when possible.

Appendix IV Reference list of Health Canada's Pest Management Regulatory Agency public consultations, decisions and updates for organophosphate pesticides registered in Canada.

Table 1 Summary of Health Canada's Pest Management Regulatory Agency public consultations, decisions and updates for organophosphate pesticides registered in Canada

Active ingredient	Document number, document type, title
Acephate (for methamidophos refer to Table 2)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2004-40, Proposed Acceptability for Continuing Registration, Acephate • REV2007-02, Re-evaluation Note, Acephate Interim Measures • PRVD2016-01, Proposed Re-evaluation Decision, Acephate REV2016-16, Re-evaluation Note, Special Review of Acephate: Proposed Decision for Consultation • PRVD2019-04, Proposed Re-evaluation Decision, Acephate and Its Associated End-use Products, Updated Environmental Risk Assessment • SRD2020-01, Special Review Decision, Acephate • RVD2020-07, Re-evaluation Decision, Acephate
Azamethiphos	• PRD2016-25, Proposed Registration Decision, Azamethiphos • RD2017-13, Registration Decision, Azamethiphos
Bensulide (and Bensulide oxon)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-06, Proposed Acceptability for Continuing Registration, Bensulide • RRD2004-22, Re-evaluation Decision, Re-evaluation of Bensulide
Dichlorvos	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2008-04, Re-evaluation Note, Dichlorvos Interim Measures • PRVD2017-16, Proposed Re-evaluation Decision, Dichlorvos REV2018-01, Re-evaluation Note, Dichlorvos • SRD2020-02, Special Review Decision, Special review decision: dichlorvos RVD2020-08, Re-evaluation Decision, Dichlorvos and its Associated End-use Products
Dimethoate (and Omethoate)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PRVD2011-12, Proposed Re-evaluation Decision, Dimethoate • RVD2015-04, Re-evaluation Decision, Dimethoate

Active	Document number, document type, title
Malathion (and Malaoxon)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-10, Proposed Acceptability for Continuing Registration, Malathion • REV2000-06, Re-evaluation Note, Update on the Re-evaluation of Malathion in Canada • REV2003-03, Re-evaluation Note, Re-evaluation of malathion Assessment of use in mosquito abatement programs • PRVD2010-18, Proposed Re-evaluation Decision, Malathion • RVD2012-10, Re-evaluation Decision, Malathion
Naled	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2004-33, Proposed Acceptability for Continuing Registration, Naled • RRD2006-24, Re-evaluation Decision, Naled • PSRD2019-02, Proposed Special Review Decision, Special Review of Naled and Its Associated End-use Product under subsection 17(1) of Pest Control Products Act • PSRD2019-03, Proposed Special Review Decision, Special Review of Naled and Its Associated End-use Product under subsection 17(2) of Pest Control Products Act • SRD2022-01, Special Review Decision, Special Review Decisions: Naled
Phorate (and Phorate oxon)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-01, Proposed Acceptability for Continuing Registration, Phorate • RRD2004-11, Re-evaluation Decision, Phorate • REV2006-05, Re-evaluation Note, Update on the Use of Phorate on Potatoes • REV2007-07, Re-evaluation Note, Update on the Use of Phorate on Potatoes • REV2008-05, Re-evaluation Note, Update on the Use of Phorate on Potatoes • REV2012-01, Re-evaluation Note, Update on the Use of Phorate on Potatoes
Phosmet (and Phosmet oxon)	• PACR2004-38, Proposed Acceptability for Continuing Registration, Phosmet • REV2007-14, Re-evaluation Note, Re-evaluation of Phosmet Interim Measures • PRVD2017-07, Proposed Re-evaluation Decision, Phosmet • RVD2020-11, Re-evaluation Decision, Re-evaluation of Phosmet and its associated end-use products

Active	Document number, document type, title
Tetrachlorvinphos	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-09, Proposed Acceptability for Continuing Registration, Tetrachlorvinphos • RRD2004-14, Re-evaluation Decision, Re-evaluation of Tetrachlorvinphos • PSRD2019-04, Proposed Special Review Decision, Special Review of Tetrachlorvinphos and Its Associated End-use Products • SRD2021-01, Special Review Decision, Special Review of Tetrachlorvinphos and its Associated End-use Products

Table 2 Summary of Health Canada's Pest Management Regulatory Agency public consultations, decisions and updates for organophosphate pesticides previously registered in Canada

Active ingredient	Document number, document type, title
OP active ingredient residues quantitatively included in the CAG[1]	
Chlorpyrifos (and chlorpyrifos oxon)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2000-01, Re-evaluation Note, Update on the Re-evaluation of Chlorpyrifos in Canada • REV2000-05, Re-evaluation Note, Chlorpyrifos • PACR2003-03, Proposed Acceptability for Continuing Registration, Phase 2 of the Re-evaluation of Chlorpyrifos • REV2007-01, Re-evaluation Note, Update on the Re-evaluation of Chlorpyrifos • PRVD2019-05, Proposed Re-evaluation Decision, Chlorpyrifos and Its Associated End-use Products • RVD2020-14, Revaluation Decision, Chlorpyrifos • REV2021-02, Re-evaluation Note, Update on the Re-evaluation of Chlorpyrifos • REV2021-04, Re-evaluation Note, Cancellation of remaining chlorpyrifos registrations under paragraph 20(1)(a) of the Pest Control Products Act

Active ingredient	Document number, document type, title
Diazinon (and diazoxon)	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2000-07, Re-evaluation Note, Update on Re-evaluation of Diazinon in Canada • REV2000-08, Re-evaluation Note, Update on Re-evaluation of Diazinon in Canada • REV2005-06, Re-evaluation Note, Preliminary Risk and Value Assessments of Diazinon • PRVD2007-16, Proposed Re-evaluation Decision, Diazinon • RVD2009-18, Re-evaluation Decision, Diazinon • REV2013-01, Re-evaluation Note, Diazinon Risk Management Plan • REV2016-18, Re-evaluation Note, Special Review of Diazinon – Subsection 17(1) of Pest Control Products Act: Proposed Decision for Consultation • REV2016-19, Re-evaluation Note, Special Review of Diazinon – Subsection 17(2) of Pest Control Products Act: Proposed Decision for Consultation • REV2017-12, Special Review Decision, Special Review Decision: Diazinon – Subsection 17(1) of Pest Control Products Act • REV2017-13, Special Review Decision, Special Review Decision: Diazinon – Subsection 17(2) of Pest Control Products Act
Methamidophos	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2007-11, Re-evaluation Note, Preliminary Risk and Value Assessments of Methamidophos
Methidathion	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2001-01, Re-evaluation Note, Discontinuation of the Organophosphate Insecticide Methidathion
Oxydemeton-methyl	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides
OP active ingredient residues qualitatively included in the CAG	
Azinphos-methyl	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-07, Proposed Acceptability for Continuing Registration, Azinphos-methyl • RRD2004-05, Re-evaluation Decision, Azinphos-methyl • REV2006-04, Re-evaluation Note, Update on Re-evaluation of Azinphos-methyl • REV2007-08, Re-evaluation Note, Update on Re-evaluation of Azinphos-methyl

Active ingredient	Document number, document type, title
Coumaphos	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-04, Proposed Acceptability for Continuing Registration, Coumaphos • RRD2004-21, Re-evaluation Decision, Re-evaluation of Coumaphos
Ethion	• REV2001-03, Re-evaluation Note, Discontinuation of the Organophosphate Insecticide Ethion
Phosalone	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2005-02, Proposed Acceptability for Continuing Registration, Phosalone • REV2006-13, Re-evaluation Note, Re-opening Consultation for Phosalone
Propetamphos	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2003-01, Re-evaluation Note, Re-evaluation of Propetamphos
Terbufos	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • PACR2003-02, Proposed Acceptability for Continuing Registration, Terbufos • RRD2004-04, Re-evaluation Decision, Re-evaluation of Terbufos • REV2008-06, Re-evaluation Note, Update on the Use of Terbufos on Sugar Beets
Trichlorfon	• REV99-01, Re-evaluation Document, Re-evaluation of Organophosphate Pesticides • REV2007-05, Re-evaluation Note, Preliminary Risk Assessment of Trichlorfon • PRVD2008-14, Proposed Re-evaluation Decision, Trichlorfon • RVD2008-27, Re-evaluation Decision, Trichlorfon

[1]CAG: Cumulative Assessment Group

Appendix V List of abbreviations

AChE	acetylcholinesterase
BMD	benchmark dose
CAG	cumulative assessment group
CFIA	Canadian Food Inspection Agency
CRA	cumulative risk assessment
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable residue data
EEC	estimated environmental concentration
FCID	Food Commodity Intake Database
MOE	margin of exposure
MRL	maximum residue limits
NHANES	National Health and Nutrition Examination Survey
OP	organophosphate
ORETF	Outdoor Residential Exposure Task Force
PACR	Proposed Acceptability for Continuing Registration
PCPA	*Pest Control Products Act*
PCT	percent crop treated
PMRA	Pest Management Regulatory Agency
POD	point of departure
PRD	Proposed Registration Decision
PRVD	Proposed Re-evaluation Decision
PSRD	Proposed Special Review Decision
RD	Registration Decision.
REJV	Residential exposure joint venture
REV	Re-evaluation Note
ROEB	Regulatory Operations and Enforcement Branch

RPF	relative potency factor
RRD	Re-evaluation Decision Document
RVD	Re-evaluation Decision
SOP	standard operating procedure
SRD	Special Review Decision
TTR	turf transferable residue
USDA PDP	United States Department of Agriculture’s Pesticide Data Program
USEPA	United States Environmental Protection Agency