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Re-evaluation Note

REV2026-02

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

(publié aussi en français)

1 June 2026

This document is published by the Health Canada Healthy Environments and Consumer Safety Branch.
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ISSN: 1925-0630 (print)
1925-0649 (online)

Catalogue number: H113-25/2026-2E (print version)
H113-25/2026-2E-PDF (PDF version)

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Triazole 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 triazole class of pesticides, as described in SPN2018-02, *Cumulative Health Risk Assessment Framework*, was initiated in October 2024.

Under the authority of section 16 of the *Pest Control Products Act*, the Canadian registrants of 13 triazole 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 13 of the 13 triazole pesticides registered in Canada at the time of initiation. This CRA includes 13 triazole pesticides that are registered in Canada: difenoconazole, flutriafol, ipconazole, mefentrifluconazole, metconazole, myclobutanil, paclobutrazol, propiconazole, prothioconazole, tebuconazole, tetraconazole, triticonazole and uniconazole-p. In addition to the triazole pesticides registered in Canada, using the decision tree included in Appendix II, residues of 8 other triazole pesticides may be present on imported food commodities, namely bitertanol, cyproconazole, epoxiconazole, fenbuconazole, flusilazole, penconazole, triadimefon, and triadimenol. These triazole pesticides will also be considered in the CRA.

Common metabolites of the triazole pesticides include 1,2,4-triazole, triazole alanine, triazole acetic acid, triazole lactic acid (triazole hydroxy propionic acid) and are typically referred to as triazole-derivative metabolites (TDMs). The CRA will also consider assessment of TDMs in conjunction with the CRA for the parent triazole pesticides.

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.

A quantitative approach will be used in this CRA to assess risk from major exposure pathways, routes, and uses of triazole 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 triazole pesticides.

The process Health Canada undertook to identify available evidence relating to a common mechanism of toxicity for the triazole 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 triazole CRA is included in Appendix III.

Scoping Assessment: The anticipated exposure scenarios resulting from the uses of each of the 13 triazole pesticides registered in Canada are provided in Appendix I, Table 1. Additional triazole pesticides that could be present on imported food commodities are listed in Appendix I, Table 2. The decision tree used by Health Canada to determine which of these active ingredients would be included (quantitatively or qualitatively), or excluded, from the dietary exposure cumulative assessment is presented in Appendix II. This 4-step process was used to categorize the 24 triazole pesticides that are listed in Appendix I, Table 2 into the three categories described below:

- Triazole pesticides not registered in Canada that will be quantitatively included in the cumulative assessment (7 triazoles),
- Triazole pesticides not registered in Canada and determined to be minor contributors to overall cumulative exposure to triazole pesticides and will be considered qualitatively in the cumulative assessment (1 triazole), and
- Triazole pesticides not registered in Canada that will be excluded from the cumulative assessment as their food residues are not relevant to dietary exposure based on the available Canadian food supply (16 triazoles).

Problem Formulation and CRA Analysis: The planned approach for analysing the triazoles CRA is presented in Appendix III, Table 1 to clearly identify and describe the problem formulation elements that will be considered in the triazole 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 triazole 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 European Food Safety Authority (EFSA) established a common mechanism group (CMG) for triazole pesticides in 2009 based on a common toxic effect potentially produced by the same major biochemical events.² The U.S. Environmental Protection Agency (USEPA), under the 2024 Interim Registration Review Decision for Triadimefon, also noted an intention to apply its 2016 framework to determine whether a CMG can be established for triazole pesticides.³ Given that triazole pesticides are structurally similar and share similar general mechanism of toxicity in pests, and considering that common toxic effects have been observed in mammals, Health Canada agrees that there is scientific validity in determining whether a CMG can be established. As part of this CRA, all potential CMGs will be explored for the triazoles; however, Health Canada is prioritizing establishing CMGs for serious effects in sensitive subpopulations that may result from a single acute exposure event.

Developmental craniofacial effects, including craniofacial malformations, have been observed in test animals across several triazole pesticides and some of their metabolites and transformation products. The World Health Organization (WHO) has defined craniofacial anomalies as a group of congenital anomalies named after the anatomical location of a given defect present at birth.⁴ It is expected that craniofacial effects in a sensitive subpopulation (in other words, the developing young) can occur as a result of acute exposure. As such, Health Canada is prioritizing the potential for a CMG to be established for craniofacial effects. Consistent with other regulatory authorities, including EFSA (2009), the review phase will also examine the scientific basis for establishing and assessing additional CMGs, including liver toxicity via Constitutive Androstane Receptor (CAR) activation.

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

² Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health - 2009 - EFSA Journal - Wiley Online Library

³ Regulations.gov

⁴ World Health Organization Registry Meeting on Craniofacial Anomalies, 2001. Global registry and database on craniofacial anomalies. Global registry and database on craniofacial anomalies : report of a WHO Registry Meeting on Craniofacial Anomalies / Main editors: P. Mossey, E. Castilla

Triazole pesticides, use patterns and potential exposure pathways

Triazole pesticides are generally used as antifungal agents. Table 1 lists the 13 triazole pesticides (active ingredients) currently registered in Canada and the anticipated exposure scenarios resulting from the uses for each triazole. Additional pesticides that belong to the triazole group are listed in Appendix II, Table 2. Although these triazole 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.

Toxicology assessment of triazole-derivative metabolites (TDMs)

As described in SPN2018-02, a mechanistic similarity that would support a finding of a common toxic mechanism is the occurrence of similar metabolic transformations that yield common or structurally analogous metabolites. Triazole technical grade active ingredients yield common metabolites, the TDMs, which include 1,2,4-triazole, triazole alanine, triazole acetic acid and triazole lactic acid (triazole hydroxy propionic acid). Due to the possibility for the TDMs to cause a common effect from the same mechanism as triazole technical grade active ingredients, Health Canada intends to conduct a toxicology assessment for TDMs. Internationally, the EFSA⁵ and USEPA⁶ have completed assessments of the TDMs listed above.

As a residual starting material in the manufacture of triazole products, 1,2,4-triazole is also considered an impurity of toxicological concern,⁷ Health Canada intends to determine an acceptable limit of 1,2,4-triazole as an impurity in triazole technical grade active ingredients following completion of the toxicology assessment for 1,2,4-triazole.

Antimicrobial Resistance (AMR)

Health Canada intends to address the AMR potential for triazole pesticides in a separate assessment, leveraging both existing Health Canada work as well as international partnerships.

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

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
Difenoconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
	Pome and stone fruit trees in residential settings (commercial-class products)	Yes	Yes	Yes
	Turfgrass (golf course) (commercial-class products)	No	Yes	Yes

⁵ Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted | EFSA

⁶ Regulations.gov

⁷ Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1, 2, 3, 4, 5, 6, 7 and 10

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
Flutriafol	Agricultural crops (commercial-class products)	Yes	Yes	No
	Apples trees in residential settings (commercial-class products)	Yes	Yes	Yes
Ipconazole	Commercial seed treatment, and for on-farm treatment (commercial-class products)	Yes	Yes	No
Mefentrifluconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
	Pome and stone fruit trees in residential settings	Yes	Yes	Yes
	Turfgrass (golf course) (commercial-class products)	No	Yes	No
Metconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
	Stone fruit trees in residential settings (commercial-class products)	Yes	Yes	Yes
	Turfgrass (golf course, sod farms) (commercial-class products)	No	Yes	Yes
Myclobutanil	Agricultural crops (commercial-class products)	Yes	Yes	No
	Pome and stone fruit trees in residential settings (commercial-class products)	Yes	Yes	Yes
	Greenhouse food crops (commercial-class products)	Yes	No	No
	Outdoor ornamentals (commercial-class products)	No	Yes	No
	Turfgrass (golf course) (commercial-class products)	No	Yes	Yes
	Greenhouse ornamentals (commercial-class products)	No	No	No
Paclobutrazol	Turfgrass (golf course, greens and tees) (commercial-class products)	No	Yes	No
	Greenhouse ornamentals (commercial-class products)	No	No	No

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
Propiconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
	Stone fruit trees in residential settings (commercial-class products)	Yes	Yes	Yes
	Outdoor ornamentals (commercial-class products)	No	Yes	No
	Christmas tree plantations and nurseries (commercial-class products)	No	Yes	No
	Antimicrobial – Freshly cut lumber in transit and storage, new lumber used above-ground and wood joinery products (commercial-class products)	No	No	Yes
	Turfgrass (golf course, sod farms)	No	Yes	Yes
Prothioconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
Tebuconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
	Tree plantations (commercial-class products)	No	Yes	No
	Antimicrobial – Freshly cut lumber in transit and storage, new lumber used above-ground, wood joinery products and residential construction (Commercial-class products)	No	No	Yes
Tetraconazole	Agricultural crops (commercial-class products)	Yes	Yes	No
Triticonazole	Agricultural crops (commercial-class products)	Yes	Yes	No
	Turfgrass (golf course) (commercial-class products)	No	Yes	Yes
Uniconazole-P	Greenhouse food crops (commercial-class products)	Yes	No	No

Active ingredient	Pesticide uses	Potential exposure pathways		
		Food	Drinking water	Residential
	Greenhouse ornamentals (commercial-class products)	No	No	No

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

Table 2 Summary of triazole pesticides that are not registered in Canada to be considered for dietary exposure from imported foods¹

Active ingredient	Potential exposure pathway
Triazole active ingredient residues quantitatively included in the dietary cumulative assessment	
Bitertanol	Imported foods
Epoxiconazole	
Fenbuconazole	
Flusilazole	
Penconazole	
Triadimefon	
Triadimenol	
Triazole active ingredient residues qualitatively included in the dietary cumulative assessment	
Cyproconazole	Imported foods
Triazole active ingredient residues excluded from the dietary cumulative assessment	
Amisulbrom	Imported foods
Azaconazole	
Bromuconazole	
Diclobutrazol	
Diniconazole	
Etaconazole	
Fluotrimazole	
Fluquinconazole	
Furconazole	
Hexaconazole	
Huanjunzuo	
Imibenconazole	
Ipfentrifluconazole	
Quinconazole	
Simeconazole	
Triazbutil	

¹ For detailed information on how the pesticides listed in this table were identified for inclusion in the dietary cumulative assessment see Appendix II, Decision tree for determining which pesticides to include in the dietary exposure cumulative assessment.

A complete list of all public consultation, final decision and update documents published by Health Canada for each triazole pesticide not registered in Canada is included in Appendix IV, Table 2.

Toxicity assessment

For the analysis of the triazole CMGs, Health Canada anticipates using methods outlined in SPN2018-02 and used by the EFSA (2009). For example, Health Canada will consider the feasibility of relying on an index triazole pesticide within the CMG, in order to convert exposures of all relevant triazole pesticides into exposure equivalents of this index chemical to estimate cumulative exposure and risks.

Exposure assessment – Food

The CRA for the triazole 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 triazole 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 triazole pesticides were excluded from the cumulative risk assessment when it was determined that their residues were not relevant to the dietary exposure, based on the available Canadian food supply (see Appendix I, Table 2). 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 triazole 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 triazole pesticides registered in Canada previously completed as part of the individual pesticide assessments will be used and updated, as required. For triazole 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 sources.

Exposure assessment – Residential

The CRA for triazole 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 triazole pesticides registered in Canada include use sites that can be accessed by Canadians, and this may result in potential residential dermal exposure (for example, postapplication activities in treated

areas), and postapplication incidental oral ingestion (for example, hand-to-mouth activities) for children. Some postapplication exposure scenarios (for example, pick-your-own activities, handling treated retail plants) 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

Health Canada has identified the need to conduct a cumulative risk assessment for triazole pesticides given the potential for a common mechanism of toxicity resulting in common health effects and the potential for co-exposure to the triazole pesticides. The cumulative assessment group that will be considered in the triazole CRA will potentially include 21 active ingredients and their relevant metabolites, where applicable, 1 of which will be considered qualitatively as outlined in Appendix I, Tables 1 and 2. Given the potential acute risks and in consideration of sensitive subpopulations, Health Canada is prioritizing the review of toxicological mechanisms by which the pesticides in the CAG may cause craniofacial effects. While priority will be given to defining a CMG for craniofacial effects, the review phase will also examine the scientific basis for establishing and assessing other potential CMGs. Once defined, the pesticides in the CMG will be considered for potential co-exposure that could occur via the oral (dietary and incidental oral), and dermal routes to conduct the cumulative health risk assessment.

Data gathering

Following initiation of this cumulative assessment, the registrants of the triazole pesticides registered in Canada provided Health Canada with lists of available studies (including studies planned and/or in-progress). 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 2024-1674.

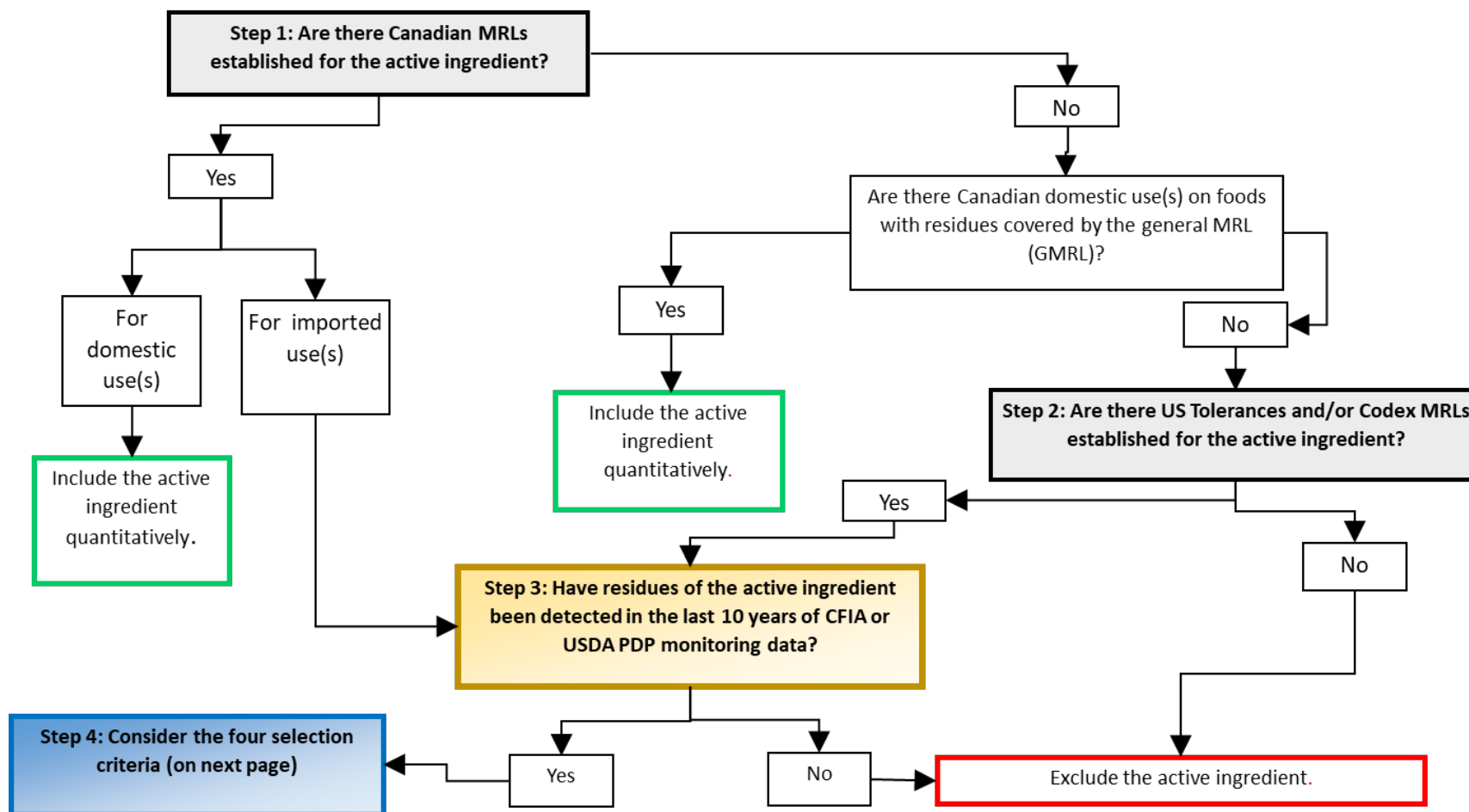
As noted above, although some triazole pesticides are not registered in Canada, they may contribute to cumulative risk through residues on imported food commodities. Toxicology data in the published scientific literature will be used to the extent possible; however, Health Canada also encourages registrants of the triazole pesticides to submit relevant toxicity data, if available.

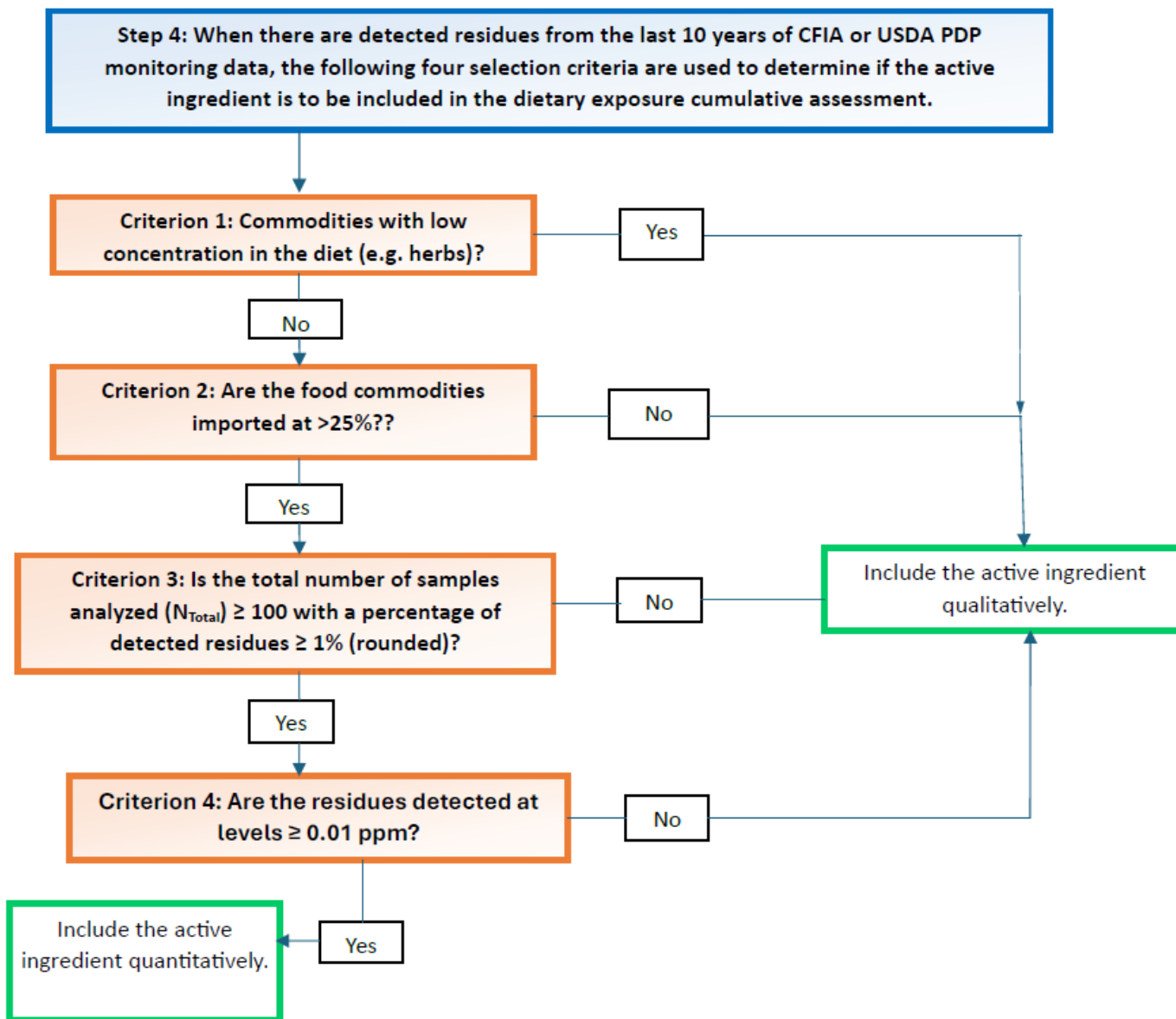
Next steps

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 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.





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

Problem formulation element	Description	Information related to the triazole pesticides CRA
Risk assessment questions	Specific questions to be addressed	<p>a) What potential common mechanism groups are possible for triazole pesticides and their common metabolites?</p> <p>b) What are the known health effects of common triazole-derivative metabolites (TDMs), and is their toxicity fundamentally different from the parent triazole pesticides?</p> <p>c) What are the health risks to the general population of Canada (including sensitive subpopulations) from exposure to the common TDMs?</p> <p>d) What are the health risks to the general population of Canada (including sensitive subpopulations) from cumulative dietary exposure and/or non-occupational dermal exposures to triazole pesticide including TDM residues in food, drinking water and treated residential areas?</p> <p>e) What exposure pathway contributes the most to the cumulative risk of triazole pesticides in Canada (in other words, what are the risk drivers) and for which triazole active ingredients? Sensitivity analyses 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.</p> <p>If the protection goals are not met (in other words, MOEs for the determined threshold percentile are below the target MOE),</p> <ul style="list-style-type: none"> • 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 triazole pesticides CRA will be used to inform risk management decisions to protect human health such as: <ul style="list-style-type: none"> ○ 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);

Problem formulation element	Description	Information related to the triazole pesticides CRA
		<ul style="list-style-type: none"> ○ consideration as part of the proportional effort classification for these pesticides; and, ○ prioritization of the active ingredients to inform continuous oversight monitoring. <p>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).</p>
Description of the cumulative assessment group (CAG)	Evidence for the common toxicological effect of the mixture component included in the CAG	Developmental craniofacial effects are a recurring finding across triazole pesticides and some of their metabolites and transformation products. It is expected that these serious effects can occur following acute exposure in a sensitive subpopulation (in other words, the developing young). As such, Health Canada will prioritize exploring the potential for a CMG to be established for craniofacial effects potentially produced through a common mechanism of action. While priority will be given to evaluating craniofacial effects, the review phase will also examine the scientific basis for establishing and assessing other potential CMGs, such as liver toxicity via Constitutive Androstane Receptor (CAR) activation.
	Evidence of co-exposure	<p>Food: Monitoring data show that North American foods contain low levels of several triazole pesticide residues. Further analysis will inform the potential for co-exposure of the different triazoles.</p> <p>Drinking water: Water monitoring data using multi-residue methods analyzing several triazole pesticide residues concurrently in the same sample will inform the potential for co-occurrence of triazole pesticide residues in drinking water sources. Several triazoles registered in Canada are included in the water monitoring program.</p> <p>Residential exposure: Several triazole 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 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 triazoles.</p>

Problem formulation element	Description	Information related to the triazole pesticides CRA
Conceptual model	Regulatory framework	<i>Pest Control Products Act (PCPA)</i> , SPN2018-02
	Substances categories	Pesticides
	Exposure sources	Non-occupational exposure: Food, drinking water and residential exposure
	Exposure routes	Oral and dermal
	Population groups	General population in Canada, including sensitive subpopulations 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	Craniofacial effects will be prioritized
	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 considered. Craniofacial effects reported in developmental toxicity studies will be evaluated as well as epidemiology studies, mechanistic data (for example, in vivo, in vitro, in silico) and international reviews relevant for the assessment of craniofacial effects. This information 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 (MOA) information to support grouping of substances into assessment groups and/or identification of measurable effect/key events	The grouping of triazole pesticides is based on structural similarity, similarity of general mechanism of toxicity in pests and their shared ability to cause craniofacial effects in rodents. A potential molecular initiating event involves inhibition of CYP 26 activity leading to altered retinoic acid metabolism, which can lead to impact on neural crest cell migration and impact on branchial defects resulting in developmental craniofacial effects. ⁸ This MOA will be prioritized for review, while other potential MOAs will also be explored to determine the potential for other common mechanism groups.
	Collection of additional toxicity data from literature	Literature searches will be conducted to identify in vivo toxicology, epidemiology and mechanistic data relevant for the assessment of craniofacial effects.

⁸ An adverse outcome pathway on the disruption of retinoic acid metabolism leading to developmental craniofacial defects - PubMed

Problem formulation element	Description	Information related to the triazole pesticides CRA
		Although some triazoles are not registered in Canada, they may contribute to cumulative risk through residues on imported food commodities. Toxicology data in the published scientific literature will be used to the extent possible for these triazole pesticides; however, Health Canada also encourages the submission of relevant toxicity data, if available, as noted in the Data Gathering section above.
	Grouping of substances based on toxicological considerations	Data from in vivo toxicity and other types of studies that assess key events of the pathway leading to developmental craniofacial effects will be used to conduct the CRA.
	Calculation of RPFs, choice of index substance and selection of POD	<p>It is anticipated that the most appropriate method, such as relative potency factor (RPF) outlined in SPN2018-02 and/or used by the EFSA (2009) for CRA of triazoles will be followed. For example, the use of RPFs will allow conversion of exposures of all chemicals in the triazole common assessment group into exposure equivalents of an index chemical, to be selected from the list of triazoles included quantitatively in CRA.</p> <p>Developmental craniofacial effects, a direct measure of the mechanism of toxicity, will be used to identify an index chemical and could be used to establish RPFs for each triazole pesticide included quantitatively in the CRA. The developmental craniofacial effects data from the available in vivo toxicity studies, from relevant route of exposure, could 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.</p>
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 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	Use zero value.

Problem formulation element	Description	Information related to the triazole pesticides CRA
	below the limit of detection	
	Approach for dealing with lack of food concentration data	Extrapolation of measured data from other foods and using residue and monitoring 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 craniofacial effects are relevant for acute exposure scenarios, but are also appropriate for chronic 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 concentration data	Water modelling can be based on available crop location data. Each triazole pesticide can be modelled for each use pattern, those use patterns matched with crops, and therefore an EEC assigned to 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 triazole 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), pome and stone fruits in residential settings, treated lumber
	Exposure routes	Commercial-class products: <ul style="list-style-type: none"> • Postapplication oral route of exposure by incidental oral ingestion (for example, hand-to-mouth) activity of children (1–2 years old)

Problem formulation element	Description	Information related to the triazole pesticides CRA
		<ul style="list-style-type: none"> Postapplication dermal 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	<ul style="list-style-type: none"> 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 Chemical-specific data related to dermal exposures, including: dislodgeable residue data (DFR), turf transferrable residue (TTR) data, transferrable residue (TR) from treated wood, 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 golf course scenario	<ul style="list-style-type: none"> Task force data (ORETF) USEPA Residential SOP (2012)⁹ Where available, chemical-specific TTR, biomonitoring data.
	Data availability for the treated wood scenario	<ul style="list-style-type: none"> USEPA Residential SOP (2012) Where available, chemical-specific TR data, biomonitoring.
	Data availability for the scenario of fruit trees in residential settings	<ul style="list-style-type: none"> USEPA Residential SOP (2012) Where available, chemical-specific DFR.
	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 and characterization	Risk metrics to be used and different percentiles of the exposure distribution to be used	<p>Qualitative assessment</p> <p>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 the exclusion from the quantitative risk assessment.</p> <p>Quantitative assessment</p>

⁹ 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 triazole pesticides CRA
		<p>Deterministic Assessment (for lower tier, if applicable): Margins of exposure (MOEs)</p> <p>Probabilistic Assessment (higher tier, if applicable): Margins of exposure (MOEs) using different percentiles up to 99.9th percentile.</p> <p>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.</p>
	Methodology to identify risk drivers	MOEs at 99.9 th 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 List of Health Canada's public consultations, decisions and updates for triazole pesticides.

Table 1 Summary of Health Canada's public consultations, decisions and updates for triazole pesticides registered in Canada

Active ingredient	Document number, document type, title
Difenoconazole	<ul style="list-style-type: none"> • RVD2022-05, Re-evaluation Decision, Difenoconazole • PRVD2021-06, Proposed Re-evaluation Decision, Difenoconazole • REV2018-14, Re-evaluation Project Plan for Difenoconazole • RD2016-07, Registration Decision, Difenoconazole • PRD2015-29, Proposed Registration Decision, Difenoconazole • REV2015-02, Re-evaluation Note, Special Review Update for Difenoconazole • RD2015-15, Registration Decision, Difenoconazole • PRD2015-10, Proposed Registration Decision, Difenoconazole • ERC2011-06, Evaluation Report, Difenoconazole • RDD2001-04, Regulatory Decision Document, Difenoconazole Fungicide • PRDD99-01, Proposed Regulatory Decision Document, Difenoconazole
Flutriafol	<ul style="list-style-type: none"> • PRD2014-16, Proposed Registration Decision, Flutriafol • RD2015-06, Registration Decision, Flutriafol
Metconazole	<ul style="list-style-type: none"> • RD2015-01, Registration Decision, Metconazole • RD2015-02, Registration Decision, Metconazole • RD2015-05, Registration Decision, Metconazole • PRD2014-24, Proposed Registration Decision, Metconazole • PRD2014-14, Proposed Registration Decision, Metconazole • PRD2013-11, Proposed Registration Decision, Metconazole • ERC2011-02, Evaluation Report, Metconazole
Ipconazole	<ul style="list-style-type: none"> • RD2013-24, Registration Decision, Ipconazole • PRD2012-05, Proposed Registration Decision, Ipconazole • ERC2011-04, Evaluation Report, Ipconazole
Mefentrifluconazole	<ul style="list-style-type: none"> • RD2019-17, Registration Decision, Mefentrifluconazole • PRD2019-09, Proposed Registration Decision, Mefentrifluconazole
Myclobutanil	<ul style="list-style-type: none"> • RVD2013-01, Re-evaluation Decision, Myclobutanil • PRVD2010-14, Proposed Re-evaluation Decision, Myclobutanil • E93-01, Decision Document, Myclobutanil
Paclobutrazol	<ul style="list-style-type: none"> • RD2024-02, Registration Decision, Paclobutrazol • PRD2023-10, Proposed Registration Decision, Paclobutrazol • RVD2014-06, Re-evaluation Decision, Paclobutrazol • PRVD2013-04, Proposed Re-evaluation Decision, Paclobutrazol

Active ingredient	Document number, document type, title
Propiconazole	<ul style="list-style-type: none"> RVD2017-03, Re-evaluation Decision for Antisapstain and Joinery Uses of Propiconazole RVD2012-02, Re-evaluation Decision, Propiconazole PRVD2011-02, Proposed Re-evaluation Decision, Propiconazole REG2000-06, Regulatory Note, Propiconazole D87-05, Decision Document, Propiconazole
Prothioconazole	<ul style="list-style-type: none"> RD2012-01, Registration Decision, Prothioconazole PRD2011-07, Proposed Registration Decision, Prothioconazole RD2010-13, Registration Decision, Prothioconazole PRD2010-08, Proposed Registration Decision, Prothioconazole REG2007-03, Regulatory Note, Prothioconazole
Tebuconazole	<ul style="list-style-type: none"> RVD2024-09, Re-evaluation Decision, Tebuconazole PRVD2021-08, Proposed Re-evaluation Decision, Tebuconazole RVD2017-06, Re-evaluation Decision, Tebuconazole RD2017-04, Registration Decision, Tebuconazole PRD2016-33, Proposed Registration Decision, Tebuconazole PRVD2016-21, Proposed Re-evaluation Decision, Tebuconazole REG2006-11, Regulatory Note, Tebuconazole
Triticonazole	<ul style="list-style-type: none"> RVD2022-02, Re-evaluation Decision, Triticonazole PRVD2021-05, Proposed Re-evaluation Decision, Triticonazole RDD2005-01, Regulatory Decision Document, Triticonazole Charter Seed Treatment, Charter PB Seed Treatment PRDD2004-06, Proposed Regulatory Decision Document, Triticonazole
Tetraconazole	<ul style="list-style-type: none"> RD2013-08, Registration Decision, Tetraconazole PRD2012-29, Proposed Registration Decision, Tetraconazole
Uniconazole-p	<ul style="list-style-type: none"> RVD2020-03, Re-evaluation Decision, Uniconazole-P PRVD2019-09, Proposed Re-evaluation Decision, Uniconazole-P

Table 2 Summary of Health Canada’s public consultations, decisions and updates for triazole pesticides not registered in Canada but to be included in the CRA

Active ingredient	Document number, document type, title
Triazole active ingredient residues to be quantitatively included	
Bitertanol	None
Epoxiconazole	None
Fenbuconazole	REG2003-03, Regulatory Note, Fenbuconazole PRDD2005-03, Proposed Regulatory Decision Document, Fenbuconazole RDD2006-02, Regulatory Decision Document, Fenbuconazole
Flusilazole	None
Penconazole	None
Triadimefon	D87-03, Decision Document, Triadimefon
Triadimenol	None

Active ingredient	Document number, document type, title
Triazole active ingredient residues to be qualitatively included	
Cyproconazole	None

List of abbreviations

AMR	Antimicrobial Resistance
CAG	Cumulative Assessment Group
CAR	Constitutive Androstane Receptor
CFIA	Canadian Food Inspection Agency
CMG	Common Mechanism Group
CRA	Cumulative Risk Assessment
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Residue Data
EEC	Estimated Environmental Concentration
EFSA	European Food Safety Authority
FCID	Food Commodity Intake Database
h	Hour(s)
MOA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limits
NHANES	National Health and Nutrition Examination Survey
ORETF	Outdoor Residential Exposure Task Force
PACR	Proposed Acceptability for Continuing Registration
PCPA	<i>Pest Control Products Act</i>
PCT	Percent Crop Treated
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
TDM	Triazole-derivative Metabolite
TR	Transferable Residue
TTR	Turf Transferable Residue
USDA PDP	United States Department of Agriculture's Pesticide Data Program
USEPA	United States Environmental Protection Agency
WHO	World Health Organization