Registration Decision RD2023-04

Pyraziflumid and Parade Fungicide

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Under the authority of the *Pest Control Products Act,* pesticides must be assessed before they are sold or used in Canada in order to determine that they do not pose unacceptable risks to humans or the environment and have value when used according to the label instructions. The pre-market assessment considers available data and information[1] from pesticide registrants, published scientific reports, other governments, and international regulatory agencies, as well as comments if received during public consultations. Health Canada applies internationally accepted current risk assessment methods as well as risk management approaches and policies. More details, on the legislative requirements, risk assessment and risk management approach, are provided under the section of Evaluation Approach of this document.

Registration Decision Statement[2] for pyraziflumid

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting registration for the sale and use of Pyraziflumid Technical and Parade Fungicide containing the technical grade active ingredient pyraziflumid to control powdery mildew and scab on apples.

The Proposed Registration Decision PRD2022-04, *Pyraziflumid and Parade Fungicide,* containing the detailed evaluation of the information submitted in support of this registration, underwent a 45 day consultation period ending on 14 April 2022. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control product are acceptable. Health Canada received comments relating to the health and environmental assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*.

Comments and responses

Comment on the cumulative risk assessment

Ecojustice objected to the registration of pyraziflumid on the basis that subsection 7(7)(i) of the *Pest Control Products Act* requires that a cumulative risk assessment be conducted prior to registering a product. As Health Canada has identified a potential common mechanism of toxicity, Ecojustice requests that Health Canada require additional information to address the issue before pyraziflumid is registered for use in Canada.

Health Canada response

The Cumulative Assessment section of PRD2022-04 did note that pyraziflumid belongs to the class of fungicides known as the succinate dehydrogenase inhibitors (SDHI). Pyraziflumid contains a 3-(trifluoromethyl) pyrazine-2-carboxamide group, which is unique for this compound within the SDHI group. Other structurally similar SDHI fungicides include benzovindiflupyr, bixafen, fluxapyroxad, inpyrfluxam, isopyrazam, penflufen, penthiopyrad, sedaxane (pyrazole-carboxamides), pydiflumetofen (*N*-methoxy-(phenyl-ethyl)-pyrazole-carboxamides), and

[1] Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*

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

boscalid (pyridinecarboxamides). Liver and thyroid toxicity linked to hepatic enzyme induction appears to be a common mode/mechanism of action (MOA) for several SDHI fungicides. In PRD2022-04, Health Canada noted that structurally related SDHI fungicides share a common mechanism of toxicity related to hepatic enzyme induction. This mechanism can result in tumour formation in the liver or thyroid in rats. While the mechanism involved in tumour formation specifically was determined not to be relevant to humans for some SDHI fungicides, the relevance of this mechanism for non-tumour effects in humans (in other words, liver and thyroid toxicity) has not been fully elucidated. Thus, in light of this uncertainty, given the MOA is consistent across this class of fungicides, the current cumulative risk assessment (CRA) considers the available information for all SDHI fungicides.

In addition to identifying a common mechanism of toxicity, other important considerations must be explored as part of the process in determining the need to conduct a CRA. These considerations include defining and comparing the use patterns of the different chemicals belonging to a class of pesticides with a common mechanism of toxicity to determine if the same uses are registered, whether the uses are wide-ranging, if there are residential uses, the potential routes of exposure and the potential for co-occurrence of exposure to the different chemicals. In addition, monitoring data from the Canadian Food Inspection Agency (CFIA) and/or the United States Department of Agriculture (USDA) Pesticide Data Program (PDP), as well as drinking water monitoring information, are important sources of real-world data for dietary exposure assessment, and are key in order to conduct realistic CRAs.

Table A Summary of uses and exposure pathways for registered SDHI fungicides and for SDHI fungicides with established MRLs on imported commodities

Active ingredient	PMRA published document	Pesticide uses	Potential exposure pathways		
			Food	Drinking water	Residential
Benzovindiflupyr	PRD2015-17 RD2015-27	Foliar use (potatoes, sugarbeets, CSG 6C, soybeans, fruiting vegetables, cucurbits, pome fruits, berries, cereals, canola, onions)	Yes	Yes [EEC[1]]	Yes (Golf course)
Bixafen	PRD2019-04 RD2019-13	Foliar use (cereals and soybeans; imported CSG1A, CSG1C and peanuts)	Yes	Yes [EEC[1]]	No
Boscalid	PRD2011-16 RD2012-06 and PRD2009-08 RD2009-12	Foliar use (fruits, vegetables, potatoes, legumes, oilseeds) Seed Treatment (canola, oilseed mustard)	Yes	Yes [EEC[1]]	Yes (Golf course)

Active ingredient	PMRA published document	Pesticide uses	Potential exposure pathways		
			Food	Drinking water	Residential
Carbathiin/ Carboxin	PRVD2008-25 RVD2009-11	Seed Treatment (cereals, legumes, canola and flax)	Yes	Yes [EEC[1]]	No
Fluopyram	PRD2016-11 RD2016-25 and PRD2016-05 RD2016-15 and ERC2014-02	Foliar use (fruits, vegetables, roots and tubers, legumes, oilseeds, corn, hops) Seed Treatment (soybeans, oilseeds)	Yes	Yes [EEC[1]]	Yes (Golf course)
Flutolanil	-	**Not registered** in Canada (MRLs on imported potatoes and peanuts)	Yes	-	-
Fluxapyroxad	PRD2020-09 RD2020-12 and PRD2012-09 RD2012-31	Foliar use (fruits, vegetables, roots and tubers, legumes, cereals, oilseeds) Seed Treatment (soybeans, oilseeds)	Yes	Yes [EEC[1]]	Yes (Golf course)
Inpyrfluxam	PRD2020-10 RD2020-11	Foliar use (apples, soybeans, sugarbeets) Seed Treatment (cereals, legumes, canola, sugarbeets)	Yes	Yes [EEC[1]]	No
Isofetamid	PRD2014-19 RD2016-19	Foliar use (grapes, lettuce, oilseeds, berries, stone fruits, apples, legumes)	Yes	Yes [EEC[1]]	Yes (Golf course)
Isopyrazam	-	**Not registered** in Canada (MRLs on imported apples and dried apples, bananas, cucurbits and fruiting veg, peanuts)	Yes	-	-
Oxycarboxin	PRVD2008-25 RVD2009-11	**No longer registered** in Canada. Historical use on turf and ornamentals – Oxycarboxin does not contribute to cumulative exposure	No Canadian MRLs, no US tolerances and no Codex MRLs	-	-

Active ingredient	PMRA published document	Pesticide uses	Potential exposure pathways		
			Food	Drinking water	Residential
Penflufen	PRD2012-02 RD2012-17	Seed Treatment (cereals, legumes, oilseeds, alfalfa, sugarbeets and onions) In-furrow treatment of potatoes	Yes	Yes [EEC[1]]	No
Penthiopyrad	PRD2014-01 RD2014-17 and PRD2011-26 RD2012-14	Foliar use (fruits, vegetables, roots and tubers, legumes, oilseeds) Seed Treatment (oilseeds, corn, soybeans)	Yes	Yes [EEC[1]]	Yes (Golf course)
Pydiflumetofen	PRD2020-08 RD2020-10 and PRD2018-06 RD2018-08	Foliar use (grapes, vegetables, cereals, corn, legumes, oilseeds) Seed Treatment (oilseeds, corn, soybeans)	Yes	Yes [EEC[1]]	Yes (Golf course)
Sedaxane	PRD2015-03 RD2015-10 and ERC2012-01	Seed Treatment (CSG 1C, sugarbeets, cereals, soybeans, CSG 6C, oilseeds, corn; imported peanuts, rice and cottonseeds)	Yes	Yes [EEC[1]]	No
Pyraziflumid	PRD2022-04	Foliar use – Apple	Yes	Yes [EEC[1]]	No

[1] EEC = estimated environmental concentration; based on conservative modelling of pesticide residues in drinking water sources.
CSG = crop subgroup

Co-occurrence of exposure

There is a potential for co-occurrence of exposure for all registered end-use products in the SDHI class and for the SDHI fungicides with established Canadian maximum residue limits (MRLs) on imported commodities.

Non-dietary exposure

Pyraziflumid is for use only on apples in Canada. As no residential uses are proposed for pyraziflumid, no residential (non-dietary) exposure is anticipated. Accordingly, the potential contribution of pyraziflumid to the cumulative exposure of SDHI fungicides is through dietary exposure alone.

There are no residential uses for the currently registered actives in this class. However, seven SDHI active ingredients are registered in Canada for use on golf course turf. Given one of the SDHI fungicides (boscalid) is under re-evaluation, the cumulative exposure contribution to the CRA from use on golf course turf will be investigated further during the re-evaluation.

Dietary exposure

Several of the SDHI fungicides are registered as seed treatments only (carbathiin, flutolanil, penflufen, sedaxane) or as a combination of seed and foliar treatments (inpyrfluxam, pydiflumetofen, penthiopyrad, fluxapyroxad and fluopyram). Seed treatment uses generally have minimal contribution to food residue and drinking water exposure, and food residues from foliar uses are often related to timing of application.

Food monitoring data are available for most of the SDHI fungicides. Of the fourteen food use SDHI active ingredients, there are only two for which no monitoring data are available at this time, given their recent registrations: bixafen (registered in September 2019) and inpyrfluxam (registered in August 2020). Over a decade of monitoring data (**>480 000 samples**) for the remaining ten currently registered SDHI fungicides and the two SDHI fungicides with Canadian MRLs on imported commodities are listed below in Table B. For the vast majority of samples, **no detectable residues** were observed. Only 3% of samples had residues above or equal to the limit of detection, and all of these residues were well below the established MRLs. Therefore, the potential cumulative exposure to SDHI fungicides from dietary sources is not of concern.

Table B Summary of residue monitoring data by the Canadian Food Inspection Agency (CFIA, 2008–2017) and the USEPA Pesticide Data Program (PDP, 2010–2019) for SDHI fungicides for various food commodities.

Pest control product	Data source	# Samples tested	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)	LOD (ppm) range in different commodities
1. Benzovindiflupyr	CFIA	No data				
	PDP	3,068	5 [Hot peppers only; mean residues of 0.003 ppm]	0.16%	0.010	0.001–0.006
2. Bixafen	CFIA	No data				
	PDP	No data				
3. Boscalid	CFIA	15 780	1810 [Mean residues greater than 0.01 ppm observed only in: Blueberries Carrots Cherries	11.5%	0.0004–3.78 [Maximum residues of 3.78 ppm were observed in blackberries; MRL of 6 ppm]	0–0.01

Pest control product	Data source	# Samples tested	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)	LOD (ppm) range in different commodities
			Grapes Leaf lettuce Papayas Peaches Bell peppers Raspberries Strawberries]			
	PDP	102 144	9050 [Mean residues greater than 0.01 ppm observed only in: Blueberries Carrots Cherries Cherry tomatoes Cilantro Collards Grapes Kale Papayas Peaches Pears Raisins Raspberries Bell peppers]	8.9%	0.001–15.7 [Maximum residues of 15.7 ppm were observed in kale; MRL of 50 ppm]	0.000007–0.03
4. Carbathiin	CFIA	50 335	2 [Other herbs only; mean residues of 0.003 ppm]	0.004%	0.0002–0.094	0–0.0032
	PDP	32 262	4 [Soybeans only; mean residues of 0.0005 ppm]	0.012%	0.001–0.002	0.001–0.061
5. Fluopyram	CFIA	No data				
	PDP	40 525	1,194 [Mean residues greater than 0.01 ppm observed only in: Mustard Greens Raisins]	3.0%	0.001–2.94 [Maximum residues of 2.94 ppm were observed in kale; MRL of 50 ppm]	0.001–0.04

Pest control product	Data source	# Samples tested	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)	LOD (ppm) range in different commodities
6. Flutolanil [No Canadian registration]	CFIA	34 369	53	0.15%	0.0004–0.098	0.0009–0.009
	PDP	38 637	1 [Lettuce; mean residues at 0.001 ppm]	0.0026%	0.15	0.001–0.1
7. Fluxapyroxad	CFIA	No data				
	PDP	39 181	970 [Mean residues greater than 0.01 ppm observed only in: Kale Spinach Strawberries]	2.5%	0.001–2.0 [Maximum residues of 2.0 ppm were observed in spinach; MRL of 30 ppm]	0.000007–0.25
8. Inpyrfluxam	CFIA	No data				
	PDP	No data				
9. Isofetamid	CFIA	No data				
	PDP	3130	0	0%	NA	0.001–0.002
10. Isopyrazam [No Canadian registration]	CFIA	No data				
	PDP	3125	0	0%	NA	0.001–0.005
11. Oxycarboxin[1] [No registration in Canada and the United States - no food uses]	CFIA	39 852	13	0.032%	0.0003–0.16 [Maximum residues of 0.16 ppm in 1 sample (out of 409) were observed in succulent beans; no MRL]	0–0.010
	PDP	265	0	0%	NA	0.001
12. Penflufen	CFIA	No data				
	PDP	18 253	0	0%	NA	0.001–0.003
13. Penthiopyrad	CFIA	No dat				
	PDP	46 080	1284 [Mean residues greater than 0.01 ppm observed only in: Kale Mustard greens Spinach]	2.8%	0.001–14.7 [Maximum residues of 14.7 ppm were observed in kale; MRL of 50 ppm]	0.000007–0.25
14. Pydiflumetofen	CFIA	No data				
	PDP	1211	0	0%	NA	0.001–0.005

Pest control product	Data source	# Samples tested	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)	LOD (ppm) range in different commodities
15. Sedaxane	CFIA	No data				
	PDP	12 048	0	0%	NA	0.005–0.05
Overall	**Canada (CFIA)**	**140 336**	**1878**	**1.3%**	**NA**	**NA**
	USA (PDP)	**339 929**	**12 508**	**3.7%**	**NA**	**NA**
	Overall	**480 265**	**14 386**	**3.0%**	**NA**	**NA**

[1] Monitoring data for oxycarboxin confirm that there are no food uses that need to be considered in the cumulative risk assessment.
LOD = limit of detection; NA = not applicable

Based on conservatively modelled estimated environmental concentrations (EECs), the contribution of SDHI fungicides to drinking water is relatively low, therefore, measured levels via drinking water monitoring are anticipated to be even lower. This will be confirmed as real-world drinking water monitoring information becomes available.

With the current registration of pyraziflumid, the dietary contribution of this SDHI to the cumulative risk assessment would be from Canadian-grown apples only and therefore very low. The contribution of pyraziflumid in drinking water to the CRA is also relatively low, based on a conservatively modelled estimate of 0.07 ppm,[3] with actual levels also expected to be much lower.

Consideration of the **available information,** as required under section 7(7)(b)(i) of the *Pest Control Products Act,* indicates a very low proportion of detectable residues observed in the food monitoring data for all the SDHI fungicides. Any detectable residues were observed at low levels and well below the MRLs, with low levels also anticipated for drinking water. Thus, no cumulative health effects of concern have been identified for pyraziflumid and other pest control products with a common mechanism of toxicity that would prevent the registration of pyraziflumid. Currently, there are no concerns to warrant additional information prior to the registration of pyraziflumid for use on apples.

The PMRA will continue to monitor the available information on this class of pesticides. Given one of the SDHI fungicides (boscalid) is under re-evaluation, the CRA will be updated during the re-evaluation in accordance with the process described in PMRA's framework on cumulative health risk assessment (SPN2018-02).

[3] The modelled conservative value of 0.07 ppm represents approximately 0.1–0.3% of the ARfD and 5–10% of ADI for most subpopulations except infants at 26% of the ADI.

Comments on the environmental risk assessment

Comment 1: Concerns that no harm will occur to environment

Ecojustice raised concerns that "The PMRA does not have reasonable certainty that no harm will occur to the environment," with specific concerns outlined for risks to terrestrial plants, honeybees and marine invertebrates. These specific concerns were identified because the screening level risk quotients (RQ) slightly exceeded the level of concern (LOC) for these groups of organisms.

Health Canada response

Explanation of general environmental risk assessment processes

The PMRA uses a tiered approach to assess environmental risks to non-target terrestrial and aquatic wildlife from exposure to pesticides. The first tier, known as screening-level risk assessment, uses scientific data (basic studies describing fate, behaviour and hazards/toxicity) and conservative assumptions to identify pesticides that pose a negligible environmental risk. When evaluating a particular pesticide, the screening-level risk assessment quickly and efficiently identifies which groups of non-target organisms are not at risk when exposed to the pesticide through its proposed uses (in other words, RQ<LOC), and which groups of organisms may be under potential risk (RQ≥LOC). If a potential risk is identified, the PMRA moves to higher-tiered assessments. Thus, the screening level risk assessment ensures that the PMRA focuses its efforts and time on where a risk may exist.

Compared to the screening level, higher tiers of the environmental risk assessment incorporate more realistic information on exposure and toxicity. Refinements may use computer-based modelling techniques, monitoring data, more realistic toxicity studies or field research. In higher tiers, the PMRA may also include qualitative information to further characterize the risk. As part of the higher-tier assessments, the PMRA will also evaluate measures to mitigate expected risks. If the risk is not acceptable and cannot be mitigated, the pest control product will not be registered.

To address the specific concerns, further explanations and rationales are provided by the PMRA as responses to comments 2, 3 and 4 below.

Comment 2: Concerns for non-target terrestrial plants

Ecojustice stated, "The proposed decision does not cite any evidence in support of the use of buffer zones or a "toxic" label to mitigate the risks to terrestrial plants." Further, Ecojustice noted, "the uncertainty factor was only 1 for terrestrial plants."

Health Canada response

As described in the PRD2022-04, the screening level RQ for non-target terrestrial plants at the seedling emergence stage may exceed the LOC (RQ <1.9), suggesting a potential risk. Further characterization considers off-field exposure from spray drift. Depending on the timing of application, RQs were <1.4 and <1.1 for early season and late season airblast applications, respectively. These "less than" RQ values indicate uncertainties in whether or not the LOC is exceeded. In the seedling emergence toxicity study, the measured application rate was 118.5 g a.i./ha, lower than the target application rate of 150 g a.i./ha, but greater than the maximum single application rate of 75 g a.i./ha on the label. Even though no statistically significant inhibitions compared to controls were observed for any of the tested endpoints in ten crop species at the measured test application rate, the effective concentration on 25% of the population (EC_{25}) of >118.5 g a.i./ha presents some uncertainties since the maximum yearly application rate of 225 g a.i./ha on the label and the cumulative airblast spray drift rates are higher than this value. Therefore, as a precautionary measure, a statement of toxic to terrestrial plants and requirements to observe no-spray buffer zones of 2 and 1 metres for early and late season airblast applications, respectively, are placed on the label. The no-spray buffer zones are determined using a spray drift model, which takes into account mode of application (early- and late-season airblast) and American Society of Agricultural Engineers spray quality. Based on the modelling results, the estimated environmental concentrations would not exceed the level of concern for non-target plants when the addition of 1–2 m spray buffer zones are observed.

For plant toxicity, the endpoint considered for risk assessment is EC_{25} for sub-lethal effects. The EC_{25} is considered the lowest effects level that can be distinguished compared to the control for the plant parameters (for example, dry weight, shoot height) and was originally intended for crop protection. As such, the EC_{25} can be viewed as a protective endpoint for plants, equivalent to a no-observed-effect concentration (NOEC), and an uncertainty factor of one is therefore used. If an EC_{50} were to be used, an uncertainty factor of two would be applied to the toxicity endpoint. It should be noted that when endpoints from a statistically sufficient number of plant species are available (especially during re-evaluation), the PMRA may also consider an HC_5 value from a species sensitivity distribution (the 5^{th} percentile of the SSD). The HC_5 value is an estimate of the concentration that would be protective of 95% of species at the effects level considered (*e.g.*, LC_{50}, NOEC, EC_{25}, EC_{50}).

Comment 3: Concerns for pollinators (honeybees)

Ecojustice stated, "The LOC was exceeded for honeybee. If the assumptions used in these assessments were conservative they need to be refined prior to registration. The PMRA should require information to perform refined assessments for these biota prior to registration as is required under section 7 of the Act and under PMRA risk assessment policies."

Health Canada response

For the honeybee risk assessment, five studies were evaluated. The studies included acute oral and contact toxicity tests and a 10-day chronic toxicity test for adult bees, and an acute oral test and a 22-day chronic toxicity test for larvae. As described in the PRD2022-04, pyraziflumid is classified as practically non-toxic to adult bees. Though no toxicity hazard classification scheme is set for larva, given that the acute LD_{50} is higher than that for the adult bees, this suggests that larva is less sensitive to pyraziflumid than adult bees.

On an acute exposure basis, no risk quotients exceeded the level of concern at the screening level, indicating acute risk to adult and larval bees is negligible.

On a chronic exposure basis, adult bees and larvae were continuously fed with food containing pyraziflumid. The resulting no observed adverse effect level (NOAEL) was 55 µg a.i./bee/day for adults. At the lowest observed adverse effect level (LOAEL) of 78 µg a.i./bee/day for adults, which is the next highest dose above the NOAEL, there were effects on adult bee weight and food consumption. For larvae, the NOAEL was 0.85 µg a.i./larva/day and the LOAEL was 2.8 µg a.i./larva/day based on effects on adult emergence. Using these NOAEL endpoints, the screening level RQ for adult bees did not exceed the LOC for chronic exposure; whereas, for larvae, the screening level RQ was 1.07, just above the LOC of 1 for chronic exposure. As explained in the PRD2022-04, at the screening level, the exposure is based on conservative (highest possible) estimates of pyraziflumid concentrations in nectar and pollen immediately following spray application. It also assumes that adult bees would only collect freshly contaminated pollen and nectar at the highest residue level and bring them back to the hive. It further assumes that larvae would have the opportunity to consume these highly contaminated pollen and nectar at the highest food consumption rates over multiple days during the larval growth stage. These combined high-end exposure assumptions are very conservative for larval consumption. Additionally, it is noted that the high-end exposure assumptions do not result in reaching or exceeding the LOAEL. Overall, the screening level RQ exceedance is minimal and is based on highly conservative assumptions. Furthermore, there is a lack of any effects of pyraziflumid to adult bees, acute effects on larvae, or any other arthropods. Therefore, the PMRA concluded that the risk to bee larvae is acceptable.

Comment 4: Concerns for marine invertebrates

Ecojustice identified similar concerns for marine invertebrates as for bees, and indicated that: “If the assumptions used in these assessments were conservative they need to be refined prior to registration.”

Health Canada response

As discussed in the PRD2022-04, for marine invertebrates, the screening level RQ for acute exposure to pyraziflumid did not exceed the LOC, but the screening level RQ for chronic exposure exceeded the LOC. The screening level exposure considered direct application to water at the cumulative maximum annual application rate and does not consider tidal flushing. It is highly unlikely that the maximum level of cumulative exposure could be maintained in a marine environment to cause chronic effects. Tidal activity is expected to dilute the concentrations in the

coastal environment and make it negligible at the time of subsequent applications. Therefore, further characterization of the risk considers the single maximum application rate. For this refined exposure estimate, the RQ for chronic exposure did not exceed the LOC, indicating that the risk associated with the use of pyraziflumid is acceptable for marine invertebrates.

The PMRA acknowledges that the RQ for risk refinement was not presented in a table format (only as a footnote to the screening risk assessment, Table 23 of PRD2022-04), inconsistent with those for other organisms. Therefore, a table of refinement for marine invertebrates is provided below.

Table 1 Refined risk assessment of pyraziflumid for marine pelagic invertebrate

Organism	Exposure	Effect metric (mg a.i./L)	EEC[1] (mg a.i./L)	RQ	Level of concern
Marine species					
Pelagic invertebrate	Chronic – a.i.	NOAEC: 0.012	0.009	0.78	Not exceeded

[1] For refinement, the EEC in water was calculated for direct spray application at the highest single application rate of 75 g a.i./ha to an 80-cm deep body of water. The resulting EEC is 0.009 mg a.i./L.

Note on maximum residue limits for imported commodities

Maximum residue limits (MRLs) for pyraziflumid were proposed for the imported commodities – Pome fruits (crop group 11-09), Stone fruits (crop group 12-09), Caneberries (crop subgroup 13-07A), Bushberries (crop subgroup 13-07B), Small fruits vine climbing, except fuzzy kiwifruit (crop subgroup 13-07F), Tree nuts (crop group 14-11) and raisins, as per the Proposed Maximum Residue Limit (PMRL2022-02) document published on 28 February 2022. However, due to delays in the registration decision for pyraziflumid and the associated end-use product, NNF-0721 20SC Fungicide, in the United States, the MRLs cannot be established for the above imported commodities at this time.

Once the decision on pyraziflumid is finalized, the established MRL on apples will be legally in effect as of the date that it is entered into the MRL database.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2022-04, *Pyraziflumid and Parade Fungicide*) are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection[4] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section of the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[4] As per subsection 35(1) of the *Pest Control Products Act.*

Evaluation approach

Legislative framework

The Minister of Health's primary objective under the *Pest Control Products Act* subsection 4(1) is to prevent unacceptable risks to individuals and the environment from the use of pest control products.

As noted in the preamble of the Act, it is in the national interest that the attainment of the objectives of the federal regulatory system continue to be pursued through a scientifically-based national registration system that addresses risks to human health, the environment and value both before and after registration and applies to the regulation of pest control products throughout Canada; and that pest control products with acceptable risk and value be registered for use only if it is shown that their use would be efficacious and if conditions of registration can be established to prevent unacceptable risk impact to human health and the environment.

For the purposes of the Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions of registration as per subsection 2(2) of the *Pest Control Products Act*.

Risk for the human health and environment, and value are defined under the Act subsection 2(1) as follows:

> **Health risk**, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Environmental risk**, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Value**, in respect of a pest control product, means the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact.

When evaluating the health and environmental risks of a pesticide and determining whether those risks are acceptable, subsection 19(2) of the *Pest Control Products Act* requires Health Canada to apply a scientifically-based approach. The science-based approach to assessing pesticides considers both the toxicity and the level of exposure of a pesticide in order to fully characterize risk.

Pre-market assessments are based on a required set of scientific data that must be provided by the applicants for pesticide registrations. Additional information from published scientific reports, other government departments and international regulatory agencies are also considered.[5]

Risk and value assessment framework

Health Canada uses a comprehensive body of modern scientific methods and evidence to determine the nature as well as the magnitude of potential risks posed by pesticides. This approach allows for the protection of human health and the environment through the application of appropriate and effective risk management strategies, consistent with the purpose described in the preambular text set out above.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[6] A high-level overview is provided below.

i) Assessing potential health risks

With respect to the evaluation and management of potential health risks, Health Canada's risk assessments follow a structured, predictable process that is consistent with international approaches and the Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks[7].

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.[8]

Assessments estimate potential health risks to defined populations[9] under specific exposure conditions. They are conducted in the context of the proposed or registered conditions of use, such as the use of a pesticide on a particular field crop using specified application rates, methods and equipment. Potential exposure scenarios consider exposures during and after application of

5 Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*

6 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*

7 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000

8 Science Policy Note: *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*

9 Consideration of Sex and Gender in Pesticide Risk Assessment

the pesticide in occupational or residential settings, food and drinking water exposure, or exposure when interacting with treated pets. Also considered are the anticipated durations (short-, intermediate- or long-term) and routes of exposure (oral, inhalation, or skin contact). In addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

With respect to the evaluation of environmental risks, Health Canada's environmental risk assessments follow a structured, tiered approach to determine the likelihood that exposure to a pesticide can cause adverse effects on individual organisms, populations, or ecological systems. This involves screening assessments starting with simple methods, conservative exposure scenarios and sensitive toxicity effects metrics, then moving on, where required, to more refined assessments that can include exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The environmental assessment considers both the exposure (environmental fate, chemistry, and behaviour, along with the application rates and methods) and hazard (toxic effects on organisms) of a pesticide. The exposure assessment examines the movement of the pesticide in soil, water, sediments and air, as well as the potential for uptake by plants or animals and transfer through the food web. The possibility for the pesticide to move into sensitive environmental compartments such as groundwater or lakes and rivers, as well as the potential for atmospheric transport, is also examined. The hazard assessment examines effects on a large number of internationally recognized indicator species of plants and animals (terrestrial organisms include invertebrates such as bees, beneficial arthropods, and earthworms, birds, mammals, plants; aquatic organisms include invertebrates, amphibians, fish, plants and algae), and includes considering effects on biodiversity and the food chain. Acute and chronic effects endpoints are derived from laboratory and field studies that characterize the toxic response and the dose–effect relationship of the pesticide.

The characterization of environmental risk requires the integration of information on environmental exposure and effects to identify which, if any, organisms or environmental compartments may be at risk, as well as any uncertainties in characterizing the risk.

iii) Value assessment

Value assessments consist of two components: an assessment of the performance of a pest control product and its benefits.

Assessing pesticide performance involves an evaluation of the pesticide's efficacy in controlling the target pest and the potential for the pesticide to damage host crops or use sites. Where the efficacy of a pesticide is acceptable, the assessment serves to establish appropriate label claims and directions and an application rate (or rate range) that is effective without being excessive, and with no unacceptable damage to the use site or host organism/crop (and subsequent hosts or crops) under normal use conditions.

In many cases, proof of performance alone is sufficient to establish the value of the pesticide, so that an in-depth or extensive evaluation of benefits may not be required. However, a more thorough assessment of benefits may be undertaken in particular cases where performance alone does not sufficiently demonstrate value, or while developing risk management options.

Risk management

The outcomes of the assessments of risks to human health and the environment, and the assessment of value, form the basis for identifying risk management strategies. These include appropriate risk mitigation measures and are a key part of decision-making on whether health and environmental risks are acceptable. The development of risk management strategies take place within the context of the pesticide's conditions of registration. Conditions can relate to, among other things, the specific use (for example, application rates, timing and frequency of application, and method of application), personal protective equipment, pre-harvest intervals, restricted entry intervals, buffer zones, spray drift and runoff mitigation measures, handling, manufacture, storage or distribution of a pesticide. If feasible conditions of use that have acceptable risk and value cannot be identified, the pesticide use will not be eligible for registration.

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*. Implementation of post-market decisions follow the framework articulated in the Policy on Cancellations and Amendments Following Re-evaluation and Special Review[10].

Following a decision, continuous oversight activities such as post-market assessments, monitoring and surveillance, including incident reporting, all play an essential role to help ensure the continued acceptability of risks and value of registered pesticides.

[10] PMRA Regulatory Directive DIR2018-01 *Policy on Cancellations and Amendments Following Re-evaluation and Special Review*

List of abbreviations

<	less than
>	greater than
µg	microgram(s)
a.i	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
CAG	cumulative assessment group
CFIA	Canadian Food Inspection Agency
cm	centimetre
CRA	cumulative risk assessment
CSG	crop subgroup
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental concentration
ERC	Evaluation Report Consultation
g	gram(s)
ha	hectare
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
m	metre(s)
mg	milligram(s)
MOA	mode/mechanism of action
MRL	maximum residue limit
NA	not applicable
NOAEL	no observed adverse effect level
NOEC	no-observed-effect concentration
PDP	Pesticide Data Program
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PRD	Proposed Registration Decision
RD	Registration Decision
RQ	risk quotient
SDHI	succinate dehydrogenase inhibitor
SPN	Science Policy Note
SSD	species sensitivity distribution
USDA	United States Department of Agriculture