Registration Decision RD2026-20

Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide

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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 written comments directly related to the proposed decision, such as comments directed to the science evaluation, 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 Evaluation approach Section of this document.

Registration Decision Statement[2] for Epyrifenacil

Health Canada, pursuant to subsection 8(1) of the *Pest Control Products Act*, is granting registration for the sale and use of S-3100 Technical (Rapidicil Technical), S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, containing the active ingredient epyrifenacil. S-3100 0.46 EC Herbicide is to be applied pre-plant surface to canola, field corn, spring and winter wheat, and pre-plant surface and pre-emergence to soybean. V-10488 0.94 SE Herbicide is to be applied pre-plant surface to spring wheat and pre-emergence to soybean. Both products can also be used in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for industrial vegetation management (IVM).

This decision is consistent with the Proposed Registration Decision PRD2026-13, *Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide,* containing the detailed evaluation of the information submitted in support of this registration, which underwent a 30-day consultation period ending on 20 September 2026. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control product(s) are acceptable. Health Canada received written comments relating to the health, environmental and value assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*. However, some of the comments were not directly related to the proposed decision in PRD2026-13, *Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide*.

[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.*

Comments and responses

Health Canada received comments from a non-governmental organization on the health, environmental and value assessments. The responses are provided in this section.

1. Comment related to the registration decision being issued in advance of the MRL consultation

The commenter stated that MRLs should be established as an integral part of the registration decision process, and pointed out that the separate consultation processes for PMRL2026-08 and PRD2026-13 undermined the ability of commenters to address the complete record.

Health Canada response

Health Canada has considered the comment that the assessment in PRD2026-13 and the associated proposed maximum residue limit (PMRL) document should be combined into a single consultation process. Health Canada will consider this feedback for exploring ways to improve the consultation process for how Proposed Registration Decisions (PRDs) and PMRLs are consulted. However, a potential change in the consultation process would only be implemented after careful consideration and would not be implemented retroactively for previously published proposed decisions. As such, this comment is appreciated and will be considered for improving future process, but does not impact the current decision.

Human health assessment

2. Comment related to the toxicological endpoints and the PCPA factor

The commenter stated that PRD2026-13 does not provide the scientific data required under the *Pest Control Products Act* to justify reducing the default 10-fold PCPA factor to threefold for the acute reference dose (ARfD) and onefold for the acceptable daily intake (ADI). The commenter further stated that PRD2026-13 does not explain the scientific or methodological basis for selecting a threefold factor for the ARfD and onefold for the ADI specifically. The commenter also questioned the exclusion of the mouse data from the point-of-departure selection given the mouse's greater sensitivity to potential epyrifenacil toxicity compared to other species, including humans.

Health Canada response

Health Canada has considered the comments related to the reduction of the PCPA factor from the presumptive 10-fold value to threefold for developmental toxicity endpoints and onefold for other toxicity endpoints, as well as the exclusion of the mouse data from point-of departure selection. Additional clarification and justification for this approach is provided herein.

As described in PRD2026-13, Health Canada conducted an assessment of the available toxicology database to determine whether there was evidence of increased sensitivity of the young and whether the database was complete and adequate for characterizing that sensitivity. This assessment also considered the nature of the findings. The assessment concluded that the database was adequate for determining potential sensitivity of the young, and no sensitivity of the young was identified. Although the observed developmental and reproductive effects in

offspring (supernumerary lumbar vertebra, reduced anogenital distance, F1 male mortality) were serious, concern was tempered by the fact that they occurred in the presence of maternal toxicity. Health Canada is aware of the cited *Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment, Second Edition* (final publication date: 11 August 2026) and concur with the OECD guidance that it may not be possible to determine from the available toxicological data whether an observed fetal effect is attributable to associated maternal toxicity or a direct adverse effect on development. That said, the Toxicology Reference Values (TRVs) selected for health risk assessment protect against the effects noted in the toxicology database and there are protective margins from these TRVs to observed effects across the database.

Health Canada's ADI of 0.01 mg/kg bw/day was based on the lowest no-observed-adverse-effect-level (NOAEL) in the database for effects considered relevant to humans. While the established ADI was calculated with a PCPA factor of onefold, there is nevertheless a margin of 680 from this value to the NOAEL for offspring toxicity in the 2-generation reproductive toxicity study (6.8 mg/kg bw/day) and an even larger margin of 2100 to the dose where young F1 male mortality was observed (21 mg/kg bw/day). These margins represent the magnitude of separation between the ADI (the dose to which an individual could be exposed over the course of a lifetime and expect no adverse health effects) and the NOAEL or dose associated with adverse effects after epyrifenacil treatment, respectively. Overall, these margins were considered to be protective of the effects of concern observed in the young after epyrifenacil treatment, and the retention of an additional PCPA factor was not required for the endpoint selected for the ADI as there is already a built-in protective margin to account for infants and children in this risk assessment.

The reduction of the PCPA factor to threefold for scenarios in which these endpoints (supernumerary lumbar vertebra, reduced anogenital distance, F1 male mortality) are used to establish the point of departure for risk assessment is consistent with the framework described in SPN2008-01. This Science Policy Note indicates that a different factor than the default 10-fold PCPA factor may be determined where reliable scientific data support such a decision. Several lines of evidence are considered to characterize the level of concern for effects in the young. The principal components in determining this level of concern are sensitivity of the young noted in the database and seriousness of the prenatal or postnatal effects. In addition to the nature and severity of the developmental findings, other factors that are taken into account include the dose-response relationship, confidence in the endpoint, and the overall completeness of the database.

Overall, the database is adequate for determining the sensitivity of the young. Effects in the young are well-characterized and occurred at dose levels also producing maternal toxicity. The supernumerary lumbar vertebra in rabbits, decreased anogenital distance in F2 rats and increased mortality in young F1 male rats were considered serious effects, though concern was tempered by the fact that they were observed at dose levels also producing maternal toxicity. Accordingly, a threefold PCPA factor was retained for risk assessments based on supernumerary lumbar vertebra, reduced anogenital distance or F1 male mortality. Health Canada considers this approach to be consistent with SPN2008-01 and protective of sensitive populations, including pregnant women, infants, and children, while reflecting the weight of scientific evidence available for epyrifenacil.

An extensive package of mechanistic toxicology data, including in vitro studies with hepatocytes from multiple species and in vivo data with humanized chimeric mice and in the standard toxicology studies, was used to evaluate the toxicity profile and mode of action (MOA) of

epyrifenacil and its principal metabolite, S-3100-CA. The available data indicated that mice, and rodents more broadly, exhibit substantially greater sensitivity to protoporphyrinogen oxidase (PPO) inhibition than other tested species, including humans. As outlined in PRD2026-13, based on the overall scientific evidence, mouse PPO inhibition was not considered to be a suitable model for health risk assessment in humans nor for establishing TRVs.

3. Comment related to the tumour mode-of-action assessment

The commenter stated that PRD2026-13 does not explain the scientific or methodological basis for the conclusion that there is adequate evidence for a threshold MOA for the observed liver tumours in male mice and that existing TRVs are protective of these findings. The commenter requested that Health Canada disclose the cancer weight-of-evidence approach taken for the epyrifenacil cancer assessment, including an analysis addressing each criterion of the IPCS/Sonich-Mullin Human Relevance Framework or an equivalent recognized framework and the basis on which the applicant-generated interspecies sensitivity data were accepted by Health Canada.

Health Canada response

Health Canada has considered the comment related to the reporting of the review of the MOA framework for liver tumours in PRD2026-13, and herein provides additional clarification on the review that was undertaken.

Health Canada's approach to assessing the potential carcinogenicity of pesticides is described in the guidance document *A Framework for Risk Assessment and Risk Management of Pest Control Products*. In summary, the cancer assessment for pesticides is based on evidence from cancer studies in at least two species together with evidence from in vitro and in vivo genotoxicity studies. These studies are typically carried out at dose levels that are much higher than expected human exposures. In many cases these are also complemented with studies that shed light on the mechanism or biological mode of action by which the pesticide causes cancer. The outcome of the animal studies together with mechanistic considerations are used in a weight-of-evidence approach to determine if a pesticide is likely to pose a cancer hazard to humans. If a potential cancer hazard is identified, a cancer risk assessment is conducted to ensure that exposure to the pesticide will not result in unacceptable risk to humans. This type of approach is consistent with that used by other international authorities. Although the general cancer risk assessment approach used by the United States Environmental Protection Agency (USEPA), as cited by the commenter, is consistent with that of Health Canada, the USEPA also employs a classification system and applies a descriptor, such as "carcinogenic to humans" or "suggestive evidence of carcinogenic potential", based on several lines of evidence, which then determines how the USEPA will regulate the pesticide. The lines of evidence used by the USEPA are also taken into consideration by Health Canada in assessing cancer effects. In summary, Health Canada's approach is to identify whether a pesticide has carcinogenic potential based on the weight of evidence, and to ensure adequate protection regardless of the tumour type, species, or sex of the animal affected through the cancer risk assessment. Health Canada also considers published international guidance from other authorities, including the cited IPCS/Sonich-Mullin Human Relevance Framework.

The epyrifenacil tumourigenic dose identified in male mice after long term dosing with epyrifenacil was consistent in the Health Canada and USEPA assessments at 15 ppm (1.7 mg/kg bw/day). The tumour incidences of hepatocellular adenomas and carcinomas combined was 7, 3, 4, 14, 19 in the 0, 1, 5, 15, 40 ppm (0, 0.1, 0.5, 1.7, 4.7 mg/kg bw/day) groups, respectively.

An MOA related to PPO inhibition, porphyrin accumulation, hepatocyte injury, regenerative proliferation was proposed by the applicant for hepatocellular adenoma and carcinoma formation. Health Canada's analysis included data from several mechanistic MOA studies (in vitro and in vivo), 90-day and 18-month mouse studies and a standard battery of genotoxicity studies in which results were negative. Both dose concordance and temporal concordance were well-supported and consistent across the available studies. Other known liver tumour MOAs were ruled out. Although there was a lack of data pertaining to the reversibility of the key events, based on the strong dose and temporal concordance of the key events leading to tumour formation and the negative genotoxicity results, the animal MOA was considered plausible. Although mice have been shown to be considerably more sensitive to the liver tumour precursor events than humans, this tumourigenic MOA was not excluded from being relevant to humans.

Overall, there was adequate evidence to support a threshold-based mechanism for the liver tumours in male mice in the dietary oncogenicity study. The selected TRVs provide sufficient margins to not only the doses at which these tumours were observed, but also the precursor toxicological events that lead to tumour formation. Therefore, the TRVs selected for use in the non-cancer risk assessment are considered to be protective of any residual concerns regarding the carcinogenic potential of epyrifenacil. This conclusion aligns with that of the USEPA review as outlined in their Cancer Assessment Document.

4. Comment related to the cumulative risk assessment

The commenter stated that epyrifenacil's residue profile was used to support the absence of tiafenacil monitoring data in the cumulative risk assessment (CRA). The commenter also requested clarification on several aspects of the CRA, such as why the chronic risk of epyrifenacil from drinking water was not incorporated, why relative potency factors based on the shared hematopoietic effects were not used to calculate cumulative risk of protoporphyrinogen IX oxidase (PPO) inhibitors, and why an acute reference dose (ARfD) for the general population was not established by Health Canada for epyrifenacil.

Health Canada response

Health Canada would like to clarify that the residue profile of epyrifenacil was not used to support the absence of tiafenacil monitoring data in the CRA for PPO inhibitors. Food monitoring data for tiafenacil were not available since it was only first registered in 2020 in the United States and 2022 in Canada. Epyrifenacil recently received approved registration in the United States in June 2026. Therefore, the available monitoring data at the time of review for the proposed use of epyrifenacil did not include tiafenacil or epyrifenacil. Nevertheless, crop field trial data of these two PPO inhibitors showed no quantifiable residues in food and feed commodities. Residues of pyraclonil, a PPO inhibitor registered in the US with no available monitoring data, were also not detectable based on the USEPA conclusion from crop field trials. It is noted that crop trials are conducted in accordance with Health Canada's residue chemistry requirements and are designed to reflect pesticide use patterns that lead to the highest possible

residues. Taking this into account, as well as the available monitoring data that showed the residues of individual PPO inhibitors were detectable in only 0.021% of samples, Health Canada concluded that no co-occurrence of quantifiable residues originating from any of the herbicides in the PPO inhibitor group are expected on any food commodities.

In addition, Health Canada has considered the comment related to the lack of incorporation of the chronic drinking water risk of epyrifenacil into the PPO inhibitor CRA. It should be clarified that it was taken into account in PRD2026-13, but not added to the maximum drinking water contribution of cumulative exposure of PPO inhibitors that was calculated from drinking water monitoring data. The chronic dietary risk of epyrifenacil from drinking water was estimated using a basic Tier 1 analysis with a modelled estimated environmental concentration (EEC) and is expected overestimate the actual drinking water concentration of epyrifenacil, considering that maximum concentrations of individual PPO inhibitors from monitoring data were 3–190 × lower than their respective modelled EECs. As such, the cumulative risk of PPO inhibitors from drinking water would also be overestimated if 1) the chronic risk of epyrifenacil from drinking water were summed with 2) the maximum drinking water contribution of cumulative exposure of PPO inhibitors calculated from drinking water monitoring data. Nevertheless, if this very conservative approach were taken and the Tier 1 chronic drinking water risk estimates of the PPO inhibitors that do not have water monitoring data (epyrifenacil and trifludimoxazin at 74% and 0.6% of their ADIs, respectively) were to be added to the maximum drinking water contribution of cumulative exposure of PPO inhibitors calculated from available drinking water monitoring data (6.2% of the human health reference value of the index chemical fomesafen), it would be evident that cumulative risk of PPO inhibitors from drinking water does not exceed 100% of the risk cup.

As stated in PRD2026-13, no significant residential (non-dietary) exposure is anticipated for PPO inhibitors. Also as explained in PRD2026-13 and reiterated in this Registration Decision document, 1) no co-occurrence of quantifiable residues originating from any of the herbicides in the PPO inhibitor group are expected on any food commodities and 2) cumulative risk of PPO inhibitors from drinking water does not exceed 100% of the risk cup based on a very conservative approach. Taking all potential routes of exposure into consideration, cumulative health risks are acceptable for all subpopulations.

The cumulative health risk was found to be acceptable, even though in the drinking water risk assessment with the monitoring data, the relative potency factors for each PPO inhibitor were calculated using the most conservative points of departure. Hematopoietic effects for PPO inhibitors were observed at doses higher than the NOAELs used to establish toxicological reference point for the respective PPO inhibitors. Consequently, if relative potency factors were further refined to be based on the shared hematopoietic effects of PPO inhibitors, the risk estimate would be lower than that calculated in PRD2026-13 and thus continue to represent acceptable cumulative health risk.

Health Canada has also considered the comment related to the lack of an ARfD for the general population in PRD2026-13, and herein provides additional clarification on the review that was undertaken.

Health Canada establishes each ARfD through a structured, weight of evidence-based process designed to identify an estimated maximum amount of a pesticide in food and/or drinking water

a person can ingest within a period of 24 hours or less without appreciable health risk to the consumer; this approach aligns with international guidance such as those published by OECD and Solecki et al. 2005. This differs from an ADI, which is often a lesser quantity, and represents a continuous dietary exposure of a pesticide in food and/or drinking water over a lifetime. In the case of epyrifenacil, there were no toxicological effects identified that were considered acutely hazardous to the general population (excluding females aged 13–49) as identified in the available single dose and repeat dose toxicity studies that meet the requirements of internationally recognized test guidelines. Hemolytic anemias induced by mechanical damage, immune mediated anemia, oxidative injury to red blood cells and non-oxidative damage are considered to be less relevant for ARfD derivation since the severity of such effects appear to generally depend on prolonged exposure. A similar approach is taken for liver toxicity observed in repeat dose studies. These toxicological effects were considered in establishing the ADI for epyrifenacil.

As indicated in PRD2026-13, only chronic exposure was assessed in the CRA since PPO inhibition or any other associated blood effects were not considered relevant to acute exposure.

5. Comment related to the dietary exposure assessments

5a) The commenter stated that acute and chronic dietary risk assessments used the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 4.02), which incorporates consumption data from the U.S. National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for 2005–2010 to conduct the assessments, and asked if more recent Canadian consumption data were considered in the assessment.

Health Canada response

Health Canada's dietary exposure assessments for new active ingredients, re-evaluations, and new uses to registered active ingredients, such as for epyrifenacil, rely upon the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™). The software incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/WWEIA) conducted in the US from 2005 to 2010.

Health Canada conducted a detailed analysis of the consumption datasets available for North America (in other words, the United States National Health and Nutrition Examination Survey – NHANES and the Canadian Community Health Survey – CCHS) and published the Information Note on comparing food and drink consumption data from Canada and the United States to explain why Health Canada uses NHANES data. For example, amongst others, comparison of the total consumption levels determined for NHANES and CCHS shows a very similar pattern between the US and Canada (see Figure 1 in the Information Note). The average food consumption level for NHANES is 2% higher compared to the CCHS, while drinking water consumption is 7% higher.

Further, Health Canada selected NHANES data for use in pesticide dietary risk assessments, over the CCHS, after carefully considering several factors (refer to SPN2014-01, *General Exposure Factor Inputs for Dietary, Occupational, and Residential Exposure Assessments*) including the quality and accessibility of the data, relevance to the Canadian population, and inclusion of vulnerable populations.

Based on these factors, Health Canada has determined that using the NHANES dataset which is a component of DEEM-FCID, is most appropriate for determining exposure levels to pesticides in the diets of Canadians. It should be noted, however, that Health Canada continually monitors revisions to both NHANES and CCHS consumption data and will continue to ensure that the data used in dietary exposure and risk assessments for pesticides are appropriate and protective of people in Canada.

5b) The commenter stated that Health Canada only conducted a Tier 1 basic deterministic dietary exposure assessment and did not refine the assessment nor consider a probabilistic assessment given that the highest result obtained for the chronic exposure assessment was 76% of the ADI for the infant subpopulation.

Health Canada response

In assessing the exposure to pesticide in food and drinking water, Health Canada typically uses a tiered or multi-level approach where an initial assessment is conducted using "worst-case" scenarios (such as the assumption that 100% of ingested crop commodities have been treated and contain residues at the MRL levels, which were determined based on the maximum registered application rate). If risks from pesticide residues in food are not of health concern using the basic exposure estimates, refinements are not required. This provides a more conservative estimate of expected dietary exposure to pesticide residues. Health Canada would consider refining risk assessments when the estimated dietary exposure exceeds 100% of the ADI for chronic assessments or 100% of the ARfD for acute assessments. In the case of epyrifenacil, contribution to exposure from food residues was low (in other words, <6% ADI and <1% ARfD), with the vast majority of exposure coming from drinking water sources, which used the EEC derived from a conservative modelling. Within this context, further refinements of exposure associated with food residues would have had little impact on the outcome of the dietary exposure assessment.

In addition, it should be noted that a probabilistic assessment is only conducted to refine an acute (single-day) dietary risk assessment (SPN2003-03), and is not applicable in this case.

5c) The commenter stated that an acute dietary exposure assessment was not conducted for the general population and most subgroups.

Health Canada response

Health Canada has considered the comment related to the lack of an ARfD for the general population in PRD2026-13, and herein provides additional clarification on the review that was undertaken.

For further information on how Health Canada establishes ARfDs for pesticides, refer to the response to Item 4. No toxicological effects were identified for epyrifenacil that were considered acutely hazardous to the general population (excluding females aged 13–49 years for which there is a population-specific ARfD established) based on available single-dose and repeat-dose studies conducted in accordance with internationally recognized test guidelines. These toxicological effects relevant to repeated exposures were considered in establishing the ADI for epyrifenacil.

6. Comment related to the livestock dietary burden calculations

6a) The commenter stated that only the dietary burden values of 0.009 ppm (beef cattle), 0.02 ppm (dairy cattle), 0.006 ppm (poultry) and 0.006 ppm (swine) were disclosed, and enquired about how these values were determined.

Health Canada response

The dietary burden is the estimation of total exposure of livestock to a pesticide through feed items expressed in ppm (mg pesticide per kg feed). In this calculation, the livestock diet and the amount of pesticide in various feed items are considered.

The Maximum Reasonably Balanced Diet (MRBD), also called the More Balanced Diet (MBD), is a livestock feeding program, which represents a well-balanced diet that contains essential nutrients in appropriate amounts and ratios. It comprises sources of carbohydrate concentrate [CC], roughage [R] and protein concentrate [PC], while allowing livestock to have steady weight gain, high milk volume and consistently high egg production. As the livestock grow, their nutritional requirements change, and their diet is adjusted to allow adequate growth and maintenance.

To calculate the livestock dietary burden in a consistent and efficient fashion, Health Canada uses the Dietary Burden Calculator, which is an Excel-based spreadsheet developed internally. The calculator includes the MBD and the feedstuffs presented in the OECD Guidance Document on Overview of Residue Chemistry Studies (as revised in 2009) for reference livestock animals, including dairy cattle, beef cattle, poultry, and swine. Calculated dietary burdens for beef and dairy cattle are extrapolated to goats, horses and sheep.

Epyrifenacil residues were not quantifiable in all crop field trial and processing studies for canola, corn, soybean, and wheat. All residues were below LOQ (0.005 ppm or 0.01 ppm depending on the crop matrix). Therefore, these LOQ values were used in the dietary burden calculator.

The following feed items and residue levels were input into the Dietary Burden Calculator:

Crop[1]	Feed Commodity	Residue Input (ppm)	Standard Residue Input	Feed Class[3]
Canola (Rape)	Forage	-[4]	Median	R
Canola (Rape)	Meal	0.005	Median	PC
Corn, field	Forage/Silage	0.01	HAFT[2]	R
Corn, field	Stover	0.01	HAFT	R
Corn, field	Grain	0.005	Median	CC
Corn, field	Milled byproducts	0.005	Median	CC
Soybean	Forage	0.01	HAFT	R
Soybean	Hay	0.01	HAFT	R
Soybean	Hulls	0.005	Median	R
Soybean	Silage	-[4]	HAFT	R
Soybean	Meal	0.005	Median	PC

Crop[1]	Feed Commodity	Residue Input (ppm)	Standard Residue Input	Feed Class[3]
Soybean	Seed	0.005	Median	PC
Wheat/Triticale	Forage	0.01	HAFT	R
Wheat/Triticale	Hay	0.01	HAFT	R
Wheat/Triticale	Straw	0.01	HAFT	R
Wheat/Triticale	Grain	0.005	Median	CC
Wheat	Milled byproducts	0.005	Median	CC

[1] Data taken from crop field trial and processed commodity studies (Submission # 2022-0053/0054/0055).
[2] HAFT = highest average field trial residues; Median = median field trial residues
[3] R = roughage; PC = processed commodity; CC = Concentrate commodity
[4] No residue data available.

The following livestock dietary contributions (in other words, dietary burdens) were calculated based on the Dietary Burden Calculator:

More Balanced Diet (MBD)							
Crop	Feed Commodity	Feed Class[1]	Residue[2,3]		%DM	%Diet	Dietary Contribution (ppm)
			ppm	Input			
Beef - Total Dietary Contribution						**100**	**0.009**
Corn, field	Forage/Silage	R	0.01	HAFT	40	15	0.004
Corn, field	Milled byproducts	CC	0.005	Median	85	50	0.003
Corn, field	Grain	CC	0.005	Median	88	30	0.002
Canola (Rape)	Meal	PC	0.005	Median	88	5	0.0003
Dairy - Total Dietary Contribution						**100**	**0.02**
Wheat/Triticale	Forage	R	0.01	HAFT	25	20	0.008
Corn, field	Forage/Silage	R	0.01	HAFT	40	25	0.006
Corn, field	Milled byproducts	CC	0.005	Median	85	25	0.001
Corn, field	Grain	CC	0.005	Median	88	20	0.001
Canola (Rape)	Meal	PC	0.005	Median	88	10	0.0006
Poultry - Total Dietary Contribution						**100**	**0.006**
Corn, field	Milled byproducts	CC	0.005	Median	85	50	0.003
Corn, field	Grain	CC	0.005	Median	88	25	0.001
Canola (Rape)	Meal	PC	0.005	Median	88	15	0.0009
Soybean	Seed	PC	0.005	Median	89	10	0.0006
Swine - Total Dietary Contribution						**100**	**0.006**
Corn, field	Milled byproducts	CC	0.005	Median	85	60	0.004
Corn, field	Grain	CC	0.005	Median	88	25	0.001
Canola (Rape)	Meal	PC	0.005	Median	88	15	0.0009

[1] R = roughage; PC = processed commodity; CC = Concentrate commodity
[2] Data taken from crop field trial and processed commodity studies (Submission # 2022-0053/0054/0055).
[3] HAFT = highest average field trial residues; Median = median field trial residues

6b) The commenter expressed concern with respect to exclusion of TFA (trifluoroacetic acid) from the dietary burden calculation.

Health Canada response

Crop field trial data for the preplant soil application of epyrifenacil in soybean, field corn, wheat, and canola as well as processing studies for epyrifenacil in soybean, field corn, wheat, and canola included analysis of TFA. TFA concentrations in crops grown in treated soil were comparable to those observed in crops grown in the untreated control plots. As a result, it was demonstrated that TFA residue levels were comparable in both treated and untreated samples.

Based on these findings, it was concluded that preplant soil application of epyrifenacil at proposed application rates do not contribute substantially to the background levels of TFA already present in the environment and that TFA residues are not expected to concentrate during processing of wheat, corn, soybean and canola. Therefore, the dietary burden calculation included residues of epyrifenacil (parent only) in the feed commodities.

Please refer to the response to Item 7 for further discussion on TFA.

7. Comment related to maximum residue limits, cumulative assessment, transformation products, and other countries' assessments of CF3-containing active ingredients

7a) The commenter stated that the MRLs for every commodity were established at the LOQ of the enforcement analytical method and asked if Health Canada could clarify if the OECD MRL Calculator was used.

Health Canada response

Health Canada uses a statistical MRL calculation tool, adopted internationally by the Organisation for Economic Co-operation and Development (OECD) countries and regulatory authorities, such as the European Union, to calculate MRLs. Health Canada scientists collaborated with other OECD scientists to develop this OECD MRL calculator. The calculator is also used by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Meeting on Pesticide Residues (JMPR) to recommend MRLs for adoption by the Codex Committee on Pesticide Residues (CCPR) to protect consumer health and promote fair practices in food trade.

The OECD White Paper, which explains this Calculator, notes that for fully censored datasets (in other words, where all residue values are below the limit of quantitation [LOQ]), the MRL Calculator cannot be used and the MRL is to be set at the LOQ of the method used to analyze the data.

All crop field trials for soybean seed (20 independent trials), field corn grain (20 independent trials), wheat grain (20 independent trials), and canola seed (13 independent trials) had epyrifenacil residues below the LOQ of 0.005 ppm. Therefore, the OECD MRL Calculator was not required and MRLs of 0.005 ppm are being proposed for these crops.

7b) The commenter stated that TFA was excluded from the dietary residue definition even though it was measured in field trial samples.

Health Canada response

Crop field trial data for the preplant soil application of epyrifenacil in soybean, field corn, wheat, and canola included analysis of TFA. TFA concentrations in crops grown in treated soil were comparable to those observed in crops grown in the untreated control plots, and in some cases, were higher in the control samples. Based on these findings, it is concluded that preplant soil application of epyrifenacil at proposed application rates do not contribute substantially to the background levels of TFA already present in the environment. Accordingly, TFA was not included in the residue definition for epyrifenacil in primary crops.

Field rotational crop trials conducted in wheat, lettuce and radish also included analysis of TFA. TFA concentrations in the commodities harvested from rotational crops grown in treated aged soil were comparable to those detected in crops grown in the untreated control plots, and in some instances, were higher in the control samples. These results indicate that application of epyrifenacil to rotational crops at the proposed rates do not contribute substantially to the background levels of TFA already present in the environment. Accordingly, TFA was not included in the residue definition for epyrifenacil in secondary (rotational) crops.

The human health risk assessment of TFA, taking into account the multiple pesticidal sources, is currently in the initial planning phase. The status of the TFA risk assessment is captured in the Cumulative Health Risk Assessment Operational Planning Framework that was published in December 2025.

7c) Comment related to toxicology reference values for TFA established by an international regulatory authority: The commenter compared the TFA reference values from the European Food Safety Authority (EFSA) and the epyrifenacil reference values from Health Canada, noting that although the ADI values are similar, and the ARfD for epyrifenacil is lower for females aged 13–49 years, the values are based on different toxicological endpoints. The commenter stated that a TFA-specific quantitative risk assessment is warranted.

Health Canada response

Health Canada is aware of the EFSA's recent assessment of TFA. Health Canada's assessments are based on an independent evaluation of the complete data package and are conducted in accordance with the requirements of the *Pest Control Products Act* and Health Canada's established science policies and risk assessment framework.

In the rat metabolism study, the radiolabeled administered dose of epyrifenacil was well-excreted and not absorbed within 48 hours and nearly all (>93%) of the radiolabelled administered dose was identified as epyrifenacil metabolites that retained the TFA component within their structure. This suggests that potential TFA exposure from epyrifenacil intake is expected to be low. Combined with health risk assessment of TFA conclusions outlined in PRD2026-13 (section 3.8), based on the weight of scientific evidence, the epyrifenacil TRVs established by Health Canada are considered to be protective of any potential treatment-related adverse effects related to exposure to epyrifenacil-derived TFA.

7d) Comment related to toxicological data/information available for epyrifenacil's major transformation products: The commenter expressed concern that the toxicological database for epyrifenacil does not provide sufficient chemical-specific toxicological characterization of its

numerous environmental transformation products to support the general assertion that major transformation products are less toxic than unchanged epyrifenacil.

Health Canada response

Review summaries of the available major metabolite/transformation product toxicological data for S-3100-DA, S-3100-DP-Me, S-3100-CA-RD, S-3100-PR, 4”-OH-S-3100-CA, S-3100-UR, APPE, S-3100 BFP and S-3100-DP are reported in Appendix I, Table 4 of PRD2026-13. The toxicological database for the individual transformation products was limited compared to that of epyrifenacil; however, the evidence was sufficient to show that the observed toxicity including PPO inhibition occurred at higher dose levels than with unchanged epyrifenacil, suggesting that the tested metabolites are not expected to be more toxic than epyrifenacil. In the rat metabolism study, nine metabolites were identified: S-3100-CA, S-3100-CA-UR, S-3100-CA-RD, 4"-OH-S-3100-CA, S-3100-CA-AM, S-3100-DA, S-3100-DP, S-3100-DA-UR, and (S)-TFP-Glu. As such, the results from the animal toxicology studies that were conducted with epyrifenacil, which included subchronic and reproductive toxicity tests, reflect systemic exposure to these metabolites and thus account for their contribution to the toxicity profile from exposure to epyrifenacil.

7e) The commenter pointed out recent European assessments (2025) for other active ingredients, specifically that the European Commission declined to renew flufenacet’s EU approval, and that Denmark had withdrawn six active ingredients: fluazinam, fluopyram, diflufenican, mefentrifluconazole, tau-fluvalinate and flonicamid.

Health Canada response

Flufenacet has been cancelled by Health Canada because human health risks were shown to be unacceptable (RVD2024-10, 29 November 2024).

The commenter also requested that Health Canada confirm whether Denmark's 15 July 2025 withdrawal of market authorization for six active ingredients, fluazinam, fluopyram, diflufenican, mefentrifluconazole, tau-fluvalinate, and flonicamid – specifically because of trifluoroacetic acid (TFA) formation (a PFAS compound) and groundwater contamination, has triggered, or will trigger, mandatory special reviews of those Canadian registrations under subsection 17(2) of the *Pest Control Products Act*. Health Canada acknowledges the request and will examine Denmark’s initiative on its withdrawal of market authorization for the six active ingredients for potential formation of TFA to determine appropriate action with respect to Canadian registrations.

8. Comment related to dietary exposure from the co-formulated product

The commenter requested that Health Canada disclose whether an aggregate dietary exposure assessment has been performed for epyrifenacil, flumioxazin and pyroxasulfone to take into account the exposure from all three active ingredients in the co-formulated product. They would also like to know why pyroxasulfone is excluded from a cumulative exposure assessment.

Health Canada response

Science Policy Note SPN2003-04 states that "Aggregate exposure and risk assessments involve the analysis of exposure to a single chemical by multiple pathways (for example, food, drinking water, and residential uses) and routes (ingestion, dermal, and inhalation)." Consequently, aggregate assessments were conducted for exposure to a chemical through multiple routes and pathways and have concluded that all these chemicals have acceptable aggregate risk assessments when used as proposed. Similarly, Science Policy Note SPN2018-02 states that the cumulative health risk assessments involve the analysis of co-exposure to two or more pesticides that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (in other words, a common mechanism of toxicity). The cumulative assessment focused on pesticides with a common mechanism of toxicity. See the response to Question 4 related to the cumulative risk assessment.

9. Comment related to repeat-dose toxicology

The commenter stated that the previously identified hematological findings in repeated dose oral toxicity studies and portal-of-entry respiratory tract effects from repeated inhalation exposure were not considered as distinct hazards on their own, and they requested that Health Canada disclose a dedicated hazard characterization hematotoxicity and inhalation toxicity observed after epyrifenacil treatment, and their relationship to the endpoints selected for the ADI and ARfD.

Health Canada response

Health Canada has considered the comment regarding the hematological findings in the epyrifenacil toxicological database, and herein provides additional clarification on the approach undertaken for the review of these findings.

Health Canada agrees that evidence of treatment-related adverse hematotoxicity was present across the toxicological database for epyrifenacil. Effects on PPO inhibition were examined and reported both throughout the standard toxicology studies and in numerous mechanistic studies. A significantly increased sensitivity to PPO inhibition was observed in mice compared to other tested species. These effects were summarized in PRD2026-13 within the study summaries and the toxicology results table (Table 4, pages 65-86). The observed hematotoxicity was considered a precursor to several observed treatment-related adverse effects, especially in the liver. During Health Canada's study reviews, NOAELs were selected for each study to be protective of hematotoxicity and other adverse toxicological effects observed at higher doses. The ADI was established based on the rat 2-year oncogenicity study which listed liver, blood and heart effects as a basis of the lowest-observed-adverse-effect-level (LOAEL); the selected NOAEL was 1.4 mg/kg bw/day. Based on the above, Health Canada confirms that treatment-related adverse effects in the hematological system were considered in the hazard characterization of epyrifenacil.

Regarding the comment on the relevance of the effects observed in the rat 90-day inhalation toxicity study, the calculated mg/kg bw/day compound intake values resulted in a higher NOAEL (13 mg/kg bw/day) than from the rat 2-generation reproductive toxicity study (NOAEL 6.8 mg/kg bw/day), so the latter study was used by Health Canada for risk assessment for short- and intermediate-term inhalation scenarios. The selection of this study and target margin of

exposure (MOE) of 300 is considered to be protective of all populations, including the unborn children and nursing infants of exposed female workers. Not only are the selected TRVs protective of the effects in the rat 2-generation toxicity study, they provide a margin of 570 to the NOAEL for the 90-day inhalation toxicity study.

10. Comment related to possible effects on the human or animal gut microbiome

The commenter requested disclosure about whether the potential effects of epyrifenacil or its transformation products on the human or animal gut microbiome were considered, given the compound's confirmed translocation into the harvested seed.

Health Canada response

Health Canada has considered the comment inquiring whether the epyrifenacil toxicological evaluation considered potential effects on the animal gut microbiome, and herein provides additional clarification on the approach undertaken for the review of these findings.

The gut microbiome is not directly evaluated in routine toxicity testing for pesticides such as epyrifenacil; however, the gastrointestinal tract as well as the normal function of all other organs and tissues that could be potentially influenced by a disrupted microbiome are routinely examined by gross and/or histopathological evaluations in required toxicity studies as recommended by internationally recognized test guidelines (for example, OECD). The risk assessment protects against the effects noted in the epyrifenacil database by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Recently, various global scientific organizations [3,4,5,6,7] have been increasingly exploring the scientific merits of including direct intestinal microbiome evaluations as part of the human health assessment for a broad range of chemicals, including pesticides. The findings from these global research initiatives underscore the need for further scientific exploration to better understand the factors contributing to variation in the human and animal gut microbiome within non-adverse ranges, ultimately establishing a normal baseline. This foundational knowledge is essential for assessing when a change in structure, function and/or relative abundance of the microbiome extend beyond normal variations, potentially resulting in adverse biological effects on the host. Specific microbial groups that serve as a proxy for the gut microbiome as a whole also need to be

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3 Garrido-Romero, M., Pazos, F., Sánchez-Martínez, E., Benito, C., Gómez-Ruiz, J. Á., Borrego-Yaniz, G., … Moreno, F. J. (2024). Relevance of gut microbiome research in food safety assessment. *Gut Microbes*, *16*(1). https://doi.org/10.1080/19490976.2024.2410476

4 Merten, C., Schoonjans, R., Di Gioia, D., et al. Editorial: Exploring the need to include microbiomes into EFSA's scientific assessments. *EFSA Journal, 18*(6), e18061 (2020). https://doi.org/10.2903/j.efsa.2020.e18061

5 Food and Agriculture Organization of the United Nations (FAO). The impact of pesticide residues on the gut microbiome and human health - A food Safety perspective. Food Safety and Quality Series, No. 19. (2023).https://www.fao.org/documents/card/en/c/cc5306en

6 United States National Academy of Sciences, Engineering, and Medicine. Environmental chemicals, the human microbiome, and health risk – a research strategy. The National Academies Press. (2018). https://doi.org/10.17226/24960

7 Moreno, F.J., Pazos, F., Garrido-Romero, M., et al. Roadmap for the integration of gastro-intestinal (GI) tract microbiomes (human and domestic animal) in risk assessments under EFSA's remit. *EFSA Supporting Publication*, 21(2):EN-8597 (2024). doi:10.2903/sp.efsa.2024.EN-8597

defined to establish a standardized starting point for testing protocols to examine potential connections with microbial diversity, metabolic functions, and interactions with chemical exposures. While multi-omics approaches hold potential to unravel links between compromised microbiome and adverse effects on the host, more experimental work is necessary to determine causality. This involves demonstrating that changes in microbiome are causally-linked, rather than potentially correlatively-linked, to various health effects and disease states such as autism, gluten intolerance, and inflammatory bowel disease.

Epyrifenacil's pesticidal mode of action involves a metabolic pathway that has correlates within very diverse lifeforms. During the review of epyrifenacil, no data on the potential specific toxicity to animal or human gut microbiota were located in the public literature. Through continuous oversight, Health Canada proactively monitors scientific literature and regulatory information for new findings related to human health risks of currently registered pesticides, including epyrifenacil.

Environmental assessment

Correction for the environmental risk assessment: An incorrect endpoint for *Lemna gibba* (EC_{50} =1.4 mg a.i./L) was used in the screening-level risk assessment in PRD2026-13. The correct endpoint, which is reported in Appendix I, Table 17 of PRD2026-13, is an EC_{50} of 0.0022 mg a.i./L. The corrected endpoint and corresponding effects metric (0.0011 mg a.i./L) results in a screening-level risk quotient of 9.1, which exceeds the level of concern. This correction does not affect the overall risk assessment conclusions, as aquatic risk is driven by freshwater algae and the required mitigation measures are protective of aquatic vascular plants, including *Lemna gibba*. Risks remain acceptable when epyrifenacil is used according to label directions, which include required risk mitigation measures.

11. Comment related to the TSMP Track 1 determination

The commenter asserts that in the TSMP assessment, Health Canada evaluated the individual transformation products (TPs) based on the rapid dissipation of epyrifenacil rather than data for each compound individually. The commenter notes that some of the TPs meet the persistence criterion and objects to Health Canada's single, blended statement that "epyrifenacil and its transformation products do not meet all of the TSMP Track 1 criteria". The commenter requests that Health Canada disclose a substance-by-substance TSMP Track 1 determination for each TP identified in Table 27 of PRD2026-13 rather than a single blended conclusion. They also request that Health Canada confirm whether trifluoroacetic acid (TFA) has been, or will be, assessed separately against TSMP Track 1 criteria, and to disclose the TPs for which Track 1 persistence data are recorded as "not available" and whether data will be obtained.

Health Canada response

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that are CEPA-toxic, as defined under the *Canadian Environmental Protection Act* (CEPA), or equivalent; predominantly anthropogenic; persistent; and bioaccumulative). If all four TSMP

Track 1 criteria are met, the substance will be deemed Track 1. In evaluating pest control products, the Minister shall give effect to the TSMP.

As presented in Table 27 of PRD2026-13, epyrifenacil and each of its 18 major TPs, including TFA, were assessed individually against the TSMP criteria based on the available data; the assessment was summarized for presentation. As noted by the commenter, Health Canada determined that epyrifenacil and all of its TPs meet the CEPA toxic or CEPA toxic equivalent, and the predominantly anthropogenic criteria.

For the persistence criteria, empirical data are available for the following major TPs:

- **Soil**: S-3100-CA, S-3100-CA-RD, S-3100-DA, S-3100-CA-UR and S-3100-DA-RD.
    - None of these TPs meet the persistence criteria for soil. As stated in PRD2026-13, soil persistence data are not available for the other major TPs (4"-OH-S-3100-CA, S-3100-DP, S-3100-DA-UR, S-3100-CA-RD-RO, S-3100-DA-RD-RO, S-3100-DP-UR, S-3100-DA-RO1, S-3100-CA-RO1, S-3100-CA-RO2, 1,1,1-trifluoroacetone, S-3100-BFP, 4'-OH-S-3100 and TFA). Soil persistence data for these major TPs are not required for the TSMP assessment because the TPs do not meet the bioaccumulation criteria.
- **Water/sediment**: S-3100-CA and S-3100-CA-UR.
    - S-3100-CA-UR was found to meet the persistence criteria for water/sediment, while S-3100-CA did not. As noted in PRD2026-13, aquatic persistence data are not available for the other major TPs (S-3100-DA, S-3100-CA-RD, 4"-OH-S-3100-CA, S-3100-DA-RD, S-3100-DP, S-3100-DA-UR, S-3100-CA-RD-RO, S-3100-DA-RD-RO, S-3100-DP-UR, S-3100-DA-RO1, S-3100-CA-RO1, S-3100-CA-RO2, 1,1,1-trifluoroacetone, S-3100-BFP, 4'-OH-S-3100 and TFA). Aquatic persistence data for these major TPs are not required for the TSMP assessment because the TPs do not meet the bioaccumulation criteria.
- **Air**: EPISuite (AOPWIN) modelling was used to estimate the atmospheric half-life of all of the major TPs. This is standard procedure for Health Canada's TSMP assessment for pesticides when empirical data are not available. Out of the 18 major TPs, two (1,1,1-trifluoracetone and TFA) met the criterion for persistence in air. The model was not suited for predicting the half-lives of the other major TPs. Additional air persistence data for the major TPs are not required for the TSMP assessment because the TPs do not meet the bioaccumulation criteria.

None of the major TPs, including TFA, were found to meet the bioaccumulation criteria given that all of their log K_{ow} values were estimated to be <2.02, which is below the TSMP criterion of log $K_{ow} \geq 5$. Additionally, the bioconcentration factors (BCFs) in fish for epyrifenacil and the TPs that formed in fish tissues during the study (S-3100-CA and S-3100-DA) ranged from 45.89 to 112.07 L/kg, which is below the TSMP criterion of BCF $\geq$ 5000.

A chemical must meet all four criteria to be deemed a TSMP Track 1 substance designated for virtual elimination. Given that none of the major TPs meet the bioaccumulation criteria, they do not meet the criteria for TSMP Track 1 and further assessment under TSMP is not required. The information provided in Table 27 of PRD2026-13 is sufficient to show the assessment for each TP. There is no need to obtain further data on the major TPs at this time.

12. Comment related to risk to non-target terrestrial organisms

12a) Comments related to risk to non-target terrestrial plants and spray buffer zones: The commenter notes that the calculated spray buffer zones to protect terrestrial habitat are extrapolated from a single modelled point and do not represent a directly modelled or tested distance. The commenter does not contest the underlying ecotoxicological data or spray buffer zone calculation methodology but finds it difficult to reconcile a spray buffer zone of 275 metres with the realities of Canadian farmland, where adjacent sensitive terrestrial habitat could occur within the spray buffer zone distance. In the commenter's opinion, a spray buffer zone of 275 metres would preclude treatment of a substantial portion of the field. They also note that PRD2026-13 does not disclose how compliance with a mitigation measure of this magnitude would be verified. According to the commenter, modelled spray buffer zone requirements can be substantially different from buffer zone distances validated under realistic field conditions, citing a peer-reviewed study (*Integrated Environmental Assessment and Management* 2022;18:757–769) which determined that smaller spray buffer zones were sufficient for an unrelated chemical when tested under field conditions. The commenter requests that Health Canada disclose whether any field-validation study of the modelled buffer distance exists or is planned for epyrifenacil.

Health Canada response

When appropriate, Health Canada mitigates spray drift by requiring spray buffer zones (SBZs) on product labels and by encouraging best application and land management practices to minimize off-site exposures. The need for SBZs is determined based on the results of the environmental risk assessment. As described in PMRA Guidance Document, *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products*, Health Canada uses a tiered environmental risk assessment framework for pest control products.

In the risk assessment, toxicity endpoints for the seedling emergence and vegetative vigour (ER_{25} values) of non-target terrestrial plants were used as the effects metrics (uncertainty factor of 1). The foliar and soil EECs were compared to the effects metrics to calculate risk quotients (RQs). In the first tier of the risk assessment for non-target terrestrial plants (in other words, screening-level), on-field risk is evaluated based on the maximum proposed cumulative application rate. If the on-field RQs are below the level of concern (LOC) of 1, risk is considered to be acceptable and no further assessment or mitigation measures are required.

If on-field RQs exceed the LOC of 1, the assessment is refined by conducting a spray drift assessment that evaluates risk off-field, 1-metre downwind of the site of application based on spray drift from the maximum proposed cumulative application rate. If the off-field RQs do not exceed the LOC, no further assessment is needed and a 1-metre SBZ is required to mitigate risk to non-target terrestrial plants off-field. If the off-field RQs exceed the LOC, larger SBZs are required to mitigate risk and are calculated based on the crop/use site, application rate and application method(s).

Health Canada uses three different models to calculate SBZs, depending on the type of application equipment used. For ground application, empirical drift models are used that are

based on field data collected for field sprayer (Wolf and Caldwell, 2001[8]) and airblast (Ganzelmeier et al., 1995[9]) application equipment. For aerial application, the mechanistic model AGDISP v. 8.29[10] is used. Since its release in the 1980's, AGDISP has been continually calibrated using field data and updated to current practices. The calculated SBZs are thus derived from models that are based on, and/or have been calibrated using, real-world field spray deposition data. They are not simply an extrapolation from the spray drift fraction at 1-m downwind used in the refined risk assessment.

The SBZ requirements are also based on validated laboratory fate and ecotoxicological data specific to the chemical. The results of chemical-specific field studies are not considered when determining SBZ requirements, and a field-validation study for SBZs is not planned for epyrifenacil. Additional information regarding Drift mitigation webpage on Canada.ca.

In the case of epyrifenacil, terrestrial SBZs ranging from 3 to 275 metres were calculated based on the crop/use site, application rate and application method. The 275 metre SBZ applies only to the end-use product, S-3100 EC Herbicide (containing 55.1 g epyrifenacil/L), when it is applied to bare ground non-crop areas and for industrial vegetation management using aerial application equipment. Pesticide applicators can use the Spray buffer zone calculator on the Drift mitigation portion of the Canada.ca website to modify the SBZ requirement for epyrifenacil based on weather conditions and spray equipment configuration at the time of application.

A pesticide label is a legal document that informs users of a product's proper use and its potential hazards. Users must comply with the label instructions and minimize the risks associated with the product's use. If the 275 m SBZ requirement for application of S-3100 EC Herbicide to bare ground non-crop areas or industrial vegetative management sites via aerial application equipment is not feasible at a site, the pesticide applicator has several options:

- Use the Spray Buffer Zone Calculator to calculate a site-specific SBZ based on the weather conditions and spray equipment configuration at the time of application;
- Choose to apply the product via field sprayer, which has a much smaller SBZ requirement to protect terrestrial habitat (5 metres for epyrifenacil), rather than using aerial application.
- Choose to use a different product with smaller SBZ requirements.

Health Canada's Pesticide Compliance Program is responsible for enforcing compliance with the *Pest Control Products Act* and its regulations. The Pesticide Compliance Program operates under the Regulatory Operations and Enforcement Branch (ROEB) of Health Canada. ROEB carries out compliance promotion and monitoring, and takes enforcement actions that follow applicable laws, policies and guidance documents through teams of inspectors and analysts designated under the *Pest Control Products Act*. For more information, please see the Pesticides compliance

[8] Wolf, T and B.C. Caldwell, 2001. Development of a Canadian spray drift model for the determination of buffer zone distances. In Expert Committee on Weeds, Proceedings of the 2001 National Meeting, Quebec City, Sainte Anne de Bellevue, Quebec: ECW-CEM. D. Bernier, DRA Campbell, D. Cloutier, Eds.

[9] Ganzelmeier, H, D. Rautmann, R. Spangenberg, M. Streloke, M. Herrmann, H-J. Wenzelburger, and H-F. Walter. 1995. Studies on the spray drift of plant protection products: Results of a test program carried out throughout the Federal Republic of Germany. Report Number 305 from the Biologischen Bundesanstalt fhr Land- und Forstwirtschaft, Berlin-Dahlem. Blackwell Wissenschafts-Verlag GmbH, Berlin/Vienna.

[10] AGDISP v. 8.29. USDA Forest Service Spray Modeling Software.

and enforcement: Overview and Compliance and enforcement policy for pesticides webpages on Canada.ca.

12b) Comments related to the fate assessment and uncertainties regarding property-based predictions: The commenter states that the environmental fate data presented in PRD2026-13 undermine confidence in the property-based predictions used in the assessment because several major TPs were found to partition to sediment in the aquatic biotransformation studies even though they were expected to be mainly found in water based on their water solubilities, log K_{ow} values and K_{oc}/K_d values. Given that the physico-chemical properties do not accurately predict partitioning to sediment, the commenter questions the validity of using property-based predictions for the major TPs elsewhere in the fate assessment, such as for bioaccumulation. The commenter requests that Health Canada disclose the empirical basis, beyond log K_{ow} predictions alone, that supports the conclusion that the major TPs of epyrifenacil do not bioaccumulate given that a property-based approach did not correctly predict water/sediment partitioning.

Health Canada response

There are inherent uncertainties when using physico-chemical properties to estimate environmental fate. Differences between laboratory and field studies are also common because physico-chemical properties are measured under controlled conditions or estimated using models, rather than under the dynamic conditions found in the environment. Factors such as temperature, pH, light, water quality, organic matter, and microbial activity can influence a chemical's fate and may lead to different outcomes between the laboratory and the field. Consequently, environmental risk assessments generally use a weight-of-evidence approach that integrates multiple lines of evidence. For epyrifenacil, the environmental risk assessment was conducted with the assumption that the TPs would partition to sediment based on the results of the laboratory studies.

It is standard procedure, both for Health Canada and other jurisdictions, to consider the log K_{ow} value of a chemical as a line of evidence to determine if bioconcentration/bioaccumulation data with living organisms is required. The available bioconcentration in fish study for epyrifenacil showed that total radioactive residues (TRR) of epyrifenacil, which included the formation of S-3100-CA and S-3100-DA, were rapidly metabolized in fish tissues. More than 99% of the TRR was depurated by Day 3 of the depuration phase. Based on this study, Health Canada calculated BCFs ranging from 45.89 to 112.07 L/kg for the TRR of epyrifenacil, which is well below the TSMP BCF criterion of ≥ 5000.

Health Canada has committed to reducing vertebrate animal testing: Strategy to replace, reduce or refine animal testing under the Canadian Environmental Protection Act, 1999 (CEPA). The major TPs all have higher water solubilities than epyrifenacil, maintain components of the parental structure and are estimated to have lower log K_{ow} values than epyrifenacil. No functional groups that would promote bioconcentration/bioaccumulation have been added to the molecular structures of the TPs. Based on the available evidence, there is no apparent reason to conclude that bioconcentration/bioaccumulation is a concern for the major TPs, and that additional bioconcentration/bioaccumulation testing is required.

12c) Comments related to volatility of 1,1,1-trifluoroacetone and TFA: The commenter notes that 1,1,1-trifluoroacetone and TFA have intermediate to high volatilities and that TFA is

expected to be slightly volatile from water surfaces and moist soils while 1,1,1-trifluoroacetone is expected to be rapidly lost from a water surface or moist soil, as reported in PRD2026-13. The commenter concludes that this atmospheric mobility is a distinct exposure and persistence pathway from the aquatic and groundwater pathways addressed elsewhere in PRD2026-13, and demonstrates that TFA generated by epyrifenacil could enter the atmospheric transport and redeposition cycle already implicated as a major source of environmental TFA loading generally. The commenter requests that Health Canada address the atmospheric transport and redeposition implications of the volatility of TFA and 1,1,1-trifluoroacetone.

Health Canada response

1,1,1-trifluoroacetone and TFA are produced from the hydrolysis and/or biotransformation of epyrifenacil in aquatic systems. Based on their vapour pressures and Henry's law constants, it is expected that these TPs will have a degree of volatility in the field; however, this does not mean that these TPs would be found entirely in air.

Fugacity models predict how a chemical partitions between major environmental compartments (air, water, soil, and sediment) using a simplified representation of the environment. The Level III fugacity model available in the USEPA EPI Suite Program Interface assumes steady-state conditions and homogeneous environmental compartments. Although these assumptions are unlikely to be fully realized in natural systems and limit the model's ability to predict site-specific concentrations, fugacity models are useful for estimating the environmental distribution and overall fate of chemicals. Assuming that 1,1,1-trifluoroacetone is produced 50% in soil and 50% in water, and that TFA is produced 100% in water, the Level III fugacity model in EPI Suite predicts that the majority of these TPs will be found in soil and/or water, with only a small proportion partitioning to air:

- 1,1,1-trifluoroacetone: 1.07% in air, 43.6% in water, 55.2% in soil and 0.1% in sediment.
- TFA: 0.003% in air, 99.8% in water, 0.04% in soil and 0.2% in sediment.

Even if assuming that TFA is produced 100% in soil, which is not supported by the environmental fate studies, the fugacity model predicts that only 0.22% would partition to air.

The environmental risk assessment for epyrifenacil was conducted in accordance with PMRA Guidance Document, *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products*, and evaluated risks to non-target terrestrial and aquatic organisms exposed to epyrifenacil and/or its major TPs. Risk from exposure to the major TPs was evaluated in two manners:

- Given that ecotoxicity data are not available for all major TPs or taxa, a conservative approach was used to calculate the screening-level EECs in soil and water. Screening-level EECs are generally calculated based on a direct application of the active ingredient to soil or water at the maximum cumulative seasonal application rate, taking into account dissipation of the active ingredient between applications; however, for epyrifenacil, the screening-level EECs were calculated assuming no dissipation to ensure that they represent a worst-case estimate of the concentration of epyrifenacil and any of its major TPs that form in soil or water. The available data show that epyrifenacil is more toxic to non-target organisms than its major TPs so toxicity is expected to decrease with the formation of the TPs.

- When ecotoxicity data are available for the individual major TPs, risk was assessed directly, assuming that 100% of the applied epyrifenacil transformed into the major TP on a molar basis, with no dissipation of either the parent or TP. This is a conservative assumption because, with the exception of S-3100-CA, the maximum levels of the major TPs formed in the laboratory fate studies were much lower than 100% of the applied parent.
    - Aquatic toxicity data for TFA are available for freshwater invertebrates, fish, algae and vascular aquatic plants. Risks to these taxa from exposure to TFA were determined to be acceptable at the screening-level, as reported in PRD2026-13.
    - Ecotoxicity data for 1,1,1-trifluoracetone are not available; however, the Material Safety Data Sheet for this chemical[11] reports a 48-h EC_{50} value of 46 mg/L for water fleas (daphnids). Assuming 100% transformation of epyrifenacil to 1,1,1-trifluoroacetone on a molar basis, the screening-level EEC for 1,1,1-trifluoroacetone in water would be 0.002 mg/L. Considering an effects metric of 23 mg/L (48-h EC_{50} of 46 mg/L divided by an uncertainty factor of 2), the screening-level RQ for 1,1,1-trifluoroacetone would be 0.00009, significantly below the LOC of 1. Based on this information, the risk assessment for epyrifenacil, which used an effects metric for freshwater invertebrates based on a 48-h $EC_{50} > 3.2$ mg a.i./L, is protective of risk to freshwater invertebrates from exposure to 1,1,1-trifluoroacetone, and further information/assessment is not required.

The environmental risk assessment presented in PRD2026-13 is considered to be protective of non-target organisms exposed to epyrifenacil and its major TPs off-site, including from redeposition following atmospheric transport. Neither TP is expected to biomagnify in the food web; therefore, environmental exposure is expected to be significantly higher at, and surrounding, the site of use than at remote sites exposed via deposition of residues transported via the atmosphere.

TFA is ubiquitous in the environment. Health Canada acknowledges that, to some extent, the use of epyrifenacil is expected to contribute to TFA levels in the environment; however, this is not expected to change the risk characterization of epyrifenacil products as per the Health Canada's current environmental risk assessment framework given that TFA is not currently known to be harmful to organisms in the environment.

12d) Comments related to leaching: The commenter states that a label statement to advise users of the potential of the major TPs of epyrifenacil to leach to groundwater is not a verified mitigation measure, and that Health Canada has not disclosed how compliance with the label statement will be verified. They also note that an unverified mitigation measure for TPs leaching to groundwater affects human exposure given that groundwater is a source of drinking water. The commenter requests that Health Canada disclose the compliance verification mechanism, if any, for the leaching label statement.

Health Canada response

The leaching potential of epyrifenacil and its TPs was characterized using a weight-of-evidence approach as part of the fate assessment. The available weight-of-evidence (in other words, field

[11] 2025, Safety Data Sheet for 1,1,1-Trifluoroacetone: https://www.fishersci.com/store/msds?partNumber=AC139740250&countryCode=US&language=en

studies, mobility information, leaching criteria of Cohen et al., (1984), groundwater ubiquity scores (GUS), and groundwater modelling) indicates that while epyrifenacil itself is not expected to leach to groundwater, its major TPs may do so. Based on this information, and because the major TPs are included in the drinking water residue definition, PRD2026-13 proposed an advisory label statement to inform users that the use of products containing epyrifenacil in areas where the soils are permeable, particularly where the water table is shallow, could result in groundwater contamination.

Best management practice label statements are a standard method used by Health Canada to reflect the results of the scientific evaluation and explain how to further reduce any potential risks to human health or the environment. When leaching potential is determined to be a concern, Health Canada uses an advisory label statement to inform users of the conditions where leaching to groundwater is likely. The requirement for a leaching label statement is based on potential for exposure rather than risk. As reported in PRD2026-13, dietary risks from aggregate exposure to food and drinking water are acceptable. This conclusion was made without considering the potential effect of a leaching label statement. Even though risk to human health from exposure to drinking water is acceptable, the leaching label statement is required on the labels of epyrifenacil products as a Health Canada guideline to inform users of the potential for movement of epyrifenacil residues from the terrestrial environment to groundwater under certain conditions. The leaching label statement is advisory in nature and is not intended to be subject to enforcement. As such, compliance verification mechanisms are not required.

12e) Comments related to risk to earthworms: The commenter requests that Health Canada disclose the toxicity data for the transformation products not captured by the 56-day earthworm test window.

Health Canada response

The available ecotoxicity data for earthworms are reported in PRD2026-13: a chronic 56-day study with epyrifenacil. As noted in PRD2026-13, the formation of some of the major TPs in soil is expected to have occurred during the study, and any toxicity related to these TPs is included in the results of the study. However, the study would not include effects from exposure to major TPs expected to form or persist later than 56 days after application of epyrifenacil to soil (such as 4”-OH-S-3100-CA, S-3100-CA-RD and S-3100-CA-UR, which were produced from the dissipation of epyrifenacil in the biotransformation in aerobic soil laboratory studies at mean maximum concentrations of 23.1, 42.28 and 19.6% AR, respectively). Due to this, a conservative approach was used to calculate the screening-level EEC in soil, assuming that 100% of the applied epyrifenacil would reach soil and persist, with no dissipation between applications.

While earthworm toxicity data are not available for all of the major TPs, the screening-level EEC in soil, considering no dissipation of epyrifenacil in the environment, is orders of magnitude lower than the no-observed effects concentration (NOEC) from the available earthworm toxicity study (EEC of 0.036 mg a.i./kg dw soil compared to a 56-day NOEC of 484 mg a.i./kg dw soil). It is highly unlikely that additional earthworm toxicity studies for the major TPs would change the conclusion of the risk assessment for epyrifenacil. Additionally, none of the major TPs have been found to be more toxic than epyrifenacil based on the available ecotoxicity data for other taxa (freshwater invertebrates, fish, algae). Based on these, additional earthworm toxicity studies for the major TPs are not required.

12f) Comments related to toxicity to bees: The commenter notes that for bees, PRD2026-13 reports that "adverse effects on survival were observed in the larval toxicity and adult chronic toxicity laboratory tests", even though the compound's classification is "practically non-toxic to adult bees on an acute contact basis". The commenter believes that this classification is based on an exposure-margin argument rather than an absence of demonstrated lethality.

Health Canada response:

The classification of epyrifenacil as 'practically non-toxic to adult bees on an acute basis' is based solely on the results of the acute bee toxicity studies and does not consider either exposure or the results of larval or chronic adult bee toxicity studies. The toxicity classification is consistent with the USEPA toxicity categories, which do not include toxicity categories for larval bees, or chronic toxicity to adult bees.

13. Comment related to aquatic runoff risk assessment

13a) Comments related to the runoff assessment: The commenter disputes Health Canada's use of a qualitative rationale to determine that risk to aquatic organisms based on a maximum RQ of 39 is acceptable and believes that additional modelling is needed to support the rationale. The commenter states that a qualitative expectation that real-world risk is lower than the screening estimate is not a substitute for a quantified refinement when resolving LOC exceedances. The commenter requests that Health Canada disclose a transformation-product-weighted quantitative recalculation of the runoff risk assessment for aquatic organisms, rather than the qualitative assertion that the runoff RQs overestimate risk.

Health Canada response

As outlined in PRD2026-13, there are several assumptions specific to epyrifenacil in the runoff assessment that are considered to be conservative and are expected to result in an overestimation of exposure and, consequently, risk:

- Several representative scenarios for each use pattern were modelled for different regions of Canada using the maximum application rate for each crop. The highest EECs for all of the modelled scenarios were used in the risk assessment.
- The combined residue of epyrifenacil, S-3100-CA, S-3100-DA and S-3100-DP was used to calculate the EECs. The modelling used the most conservative fate assumptions available for these compounds to represent the combined residue. This resulted in the assumption that the combined residue is relatively stable, with limited dissipation over time. Epyrifenacil is non-persistent in soil and water with half-lives of <1 and <3 days, respectively. As such, limited amounts of epyrifenacil are expected to reach surface water via runoff due to its rapid dissipation in the environment. The TP, S-3100-CA, which is at least 9 times less toxic than epyrifenacil based on the available data, is expected to make up the majority (>85%) of the EEC. Despite this, the runoff assessment conservatively used effects metrics for epyrifenacil, overestimating risk.
- The maximum RQ in the runoff assessment presented in PRD2026-13 is 39 for freshwater algae and marine diatoms. This was calculated by comparing the peak EEC of 0.0092 mg a.i./L in 80-cm deep water (based on 2 applications of 40 g a.i./ha to bare ground in Prince Edward Island) to the epyrifenacil effects metric for the marine diatom, *Skeletonema*

costatum. The marine diatom was used as a surrogate to represent freshwater algae and marine diatoms to simplify presentation of the runoff assessment because it was the most sensitive species. The available data show that the magnitude of toxicity of epyrifenacil to freshwater algae and marine diatoms is similar, with endpoints ranging from 0.0005 to 0.0009 mg a.i./L. Given that the majority of the EEC is expected to be composed of S-3100-CA, it would be more appropriate to use an effects metric based on S-3100-CA rather than epyrifenacil.

- Marine diatom data for S-3100-CA are not available, but assuming that the toxicity of S-3100-CA to freshwater algae is also similar to marine diatoms, the maximum RQ for S-3100-CA would be 2.2 based on an EEC of 0.0087 mg/L (the combined residue EEC of 0.0092 mg a.i./L corrected to mg S-3100-CA/L on a molar basis using a conversion factor of 0.95[12]) and an effects metric of 0.004 mg/L, as reported in PRD2026-13. S-3100-DA and D-3100-DP are slightly more toxic than S-3100-CA, and each have an effects metric for algae of 0.001 mg/L. Assuming that the runoff EEC of 0.0092 mg a.i./L is composed of 30% S-3100-DA and 10% S-3100-DP (the maximum concentrations of these TPs measured in the environmental fate studies), corrected on a molar basis, the resulting RQs for these TPs would be 3.1 and 1.0. All of these RQs are significantly below 39, without considering the other conservative assumptions in the risk assessment.

Furthermore, there are additional conservative assumptions inherent to the runoff water modelling approach that are expected to result in overestimation of EECs, including:

- All runoff water, eroded soil, and associated pesticide transported from the treated field are assumed to enter the adjacent water body without accounting for attenuation processes that may occur along the transport pathway.
- The receiving water body is represented by a standardized water body with limited dilution capacity and simplified hydrologic characteristics, rather than site-specific watershed and hydrologic conditions.
- Applications may be simulated to occur immediately before major precipitation events, resulting in substantial runoff and potential soil erosion. In practice, growers may defer applications when heavy rainfall is forecast to ensure efficacy of the treatment.
- Tillage practices can influence pesticide transport by affecting runoff, erosion, and soil incorporation. The model assumes that all fields are conventionally tilled, except for tree and turf.
- Ecological modeling is conducted using region- and crop-specific scenarios. The highest labelled/proposed application rate is modeled, and the application timing is specific to the labelled/proposed use pattern for each crop and region. These assumptions are intended to represent a conservative exposure scenario for the assessment.

[12] The EECs for the TPs were corrected from mg a.i./L to mg TP/L on a molar basis, using the same correction factors used in PRD2026-13: 0.95 for S-3100-CA, 0.83 for S-3100-DA and 0.65 for S-3100-DP. Given that S-3100-CA was observed at >90% in some of the environmental fate studies, it was assumed that the combined residue EEC would be composed of 100% S-3100-CA. Additionally, the EEC was adjusted to consider that it could be composed of 30% S-3100-DA and 10% S-3100-DP. The maximum mean concentrations of these TPs measured in the environmental fate studies, resulting in TP-specific EECs of 0.002 and 0.0006 mg/L for S-3100-DA and S-3100-DP, respectively.

Taken together, the conservative assumptions used in the water modelling for the runoff assessment are considered to overestimate risk and additional modelling is not required to further refine the runoff assessment. Risks to aquatic organisms are considered to be acceptable when label directions are followed, including best management practices to mitigate runoff.

13b) Comments related to refinement for the estuarine/marine risk assessment: The commenter asserts that the protocol to consider only a single application of epyrifenacil for the estuarine/marine spray drift assessment because small, salt marshes are expected to be flushed and recharged by tidal action is based on an unverified hydrological assumption. They note that this is not true of every estuarine or marsh configuration the label's use pattern could reach – restricted-flow, diked, or otherwise low-exchange marshes would not necessarily flush on the timescale the assumption requires. The commenter is concerned that SBZs of up to 125 metres for freshwater habitat are required while the SBZs for estuarine/marine habitats are only up to 60 metres. The commenter requests that Health Canada disclose the site-specific hydrological basis for assuming tidal flushing prevents accumulation of spray drift residues in all estuarine and marsh habitats within the scope of the proposed label.

Health Canada response

Health Canada acknowledges that different estuarine/marine water bodies will have variable tides and refill times based on their morphology, connectivity to rivers and/or the ocean, location and water renewal time. Site-specific data for all estuarine and marine habitats in Canada located adjacent to pesticide application sites are not available.

To represent the estuarine/marine environment in the environmental risk assessment, Health Canada uses a simple, standard, conceptual site model based on a 1-ha, 80-cm deep waterbody exposed to a direct overspray of a pest control product and/or spray drift and runoff. As noted by the commenter, the spray drift assessment considers a single pesticide application for spray drift because estuarine/marine environments, including small, salt marshes, are expected to be flushed and recharged by tidal action.

Small, salt marshes are typically found in the upper intertidal zone between the mean sea level and high tide. As such, tidal recharge of these small, salt marshes would occur 1 to 2 times per day, depending on their location and the strength of the tide. While it is possible that restricted- or low-exchange salt marshes would have longer recharge rates, it is expected that the majority will be regularly flushed and recharged. Many former salt marshes in Canada have been isolated from direct tidal influence by human activity (for example, building dykes or roads), shifting the ecosystems into freshwater or terrestrial systems that would be protected from spray drift by freshwater or terrestrial SBZs rather than the estuarine/marine SBZs.

The minimum retreatment interval proposed for epyrifenacil end-use products is 14 to 30 days. It is considered likely that estuarine/marine habitat will be flushed and recharged between applications of epyrifenacil, when it is used according to its label directions. As such, for epyrifenacil, the assumption that the estuarine/marine environment will be flushed and recharged by tidal action is appropriate.

Health Canada conducts stringent, science-based risk assessments for pesticides, and strives to use up-to-date, sound, and evidence-based information in its assessments. This comment will be

considered in determining whether updates to the estuarine/marine risk assessment framework are required in the future.

13c) Comments related to consideration of exposure to groundwater in the environmental risk assessment: The commenter notes that the aquatic risk assessment considered exposure of aquatic organisms to residues of epyrifenacil and its major TPs in surface water as a result of runoff but did not consider exposure to residues in groundwater. As such, the ecological risk assessment did not consider risk to groundwater-dependent aquatic organisms or ecosystems, such as groundwater-fed wetlands or hyporheic zone communities, from the major TPs of epyrifenacil that have been identified as potentially leaching to groundwater. The commenter requests that Health Canada disclose whether ecological risk to groundwater-dependent aquatic organisms and ecosystems from transformation product leaching has been, or will be, assessed.

Health Canada response

Consistent with international pesticide risk assessment frameworks, such as the USEPA, Health Canada's aquatic risk assessment framework does not currently consider exposure of aquatic organisms directly to pesticide residues in groundwater. As noted in Section 13b, Health Canada conducts stringent, science-based risk assessments for pesticides, and strives to use up-to-date, sound, and evidence-based information in its assessment. This comment will be considered in determining whether updates to the aquatic risk assessment framework are required in the future.

14. Comment related to species-at-risk information

The commenter notes that PRD2026-13 does not mention species at risk or the *Species at Risk Act* even though the United States Environmental Protection Agency (USEPA) conducted an Endangered Species Act Biological Evaluation for epyrifenacil, which concluded that the proposed use of epyrifenacil products "may affect and are likely to adversely affect multiple listed species and designated critical habitats", and that the USEPA registration of epyrifenacil included mitigation measures tied to the presence of listed species and critical habitat. The commenter notes that there is overlap between the listed species identified as likely to be affected by epyrifenacil in the USEPA assessment and species listed under *Species at Risk Act* in Canada. The commenter also notes that Health Canada has previously acknowledged that its risk assessments warrant strengthening regarding species at risk in Notice of Intent NOI2023-01 (June 2023) and the subsequent Canada Gazette, Part I proposal (15 June 2024), both of which proposed giving the Minister of Health "explicit authority to require registrants and applicants to submit available information on species at risk". The commenter requests that Health Canada confirm whether species-at-risk information, including USEPA's Endangered Species Act finding that epyrifenacil use is likely to adversely affect multiple listed species and designated critical habitats, was considered in the preparation of PRD2026-13, and if not, explain why.

Health Canada response:

Under the *Pest Control Products Act*, "environment" encompasses biodiversity and wildlife, including species at risk. To protect the environment, Health Canada currently takes a tiered approach for the environmental risk assessment, as described in PMRA Guidance Document, *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products*. Health Canada's current science-based environmental risk assessments are intended to prevent

unacceptable risk to non-target plant and animal species in the environment. Additionally, when there are specific concerns for a particular species at risk related to the use of a pest control product, this is considered and incorporated into the environmental risk assessment and related mitigation measures. Pest control product users are required to respect provisions of other legislation that are implicated when using pest control products, notably the *Species at Risk Act* and the *Fisheries Act* at the federal level.

Species at risk/endangered species legislation differs between Canada and the United States. In Canada, most agricultural lands would be subject to provincial species at risk legislation rather than *Species At Risk Act*. The *Pest Control Products Act* and Health Canada's environmental risk assessment framework does not currently include a species at risk evaluation similar to the USEPA.

For epyrifenacil, the USEPA Endangered Species Act Biological Evaluation for epyrifenacil identified exceedances of the LOC for terrestrial, wetland and aquatic plants based on the mitigations initially proposed by the applicant and ultimately predicted a potential likelihood of jeopardy for 9 species requiring mitigation measures, such as SBZs. It should be noted that the 9 species of flowering plants (*Warea carteri*, *Rhodiola integrifolia ssp. Leedyi, Polygala lewtonii*, *Asclepias meadii*, *Cordylanthus palmatus*, *Eryngium cuneifolium*, *Lesquerella perforate*, *Physaria douglasii ssp. Tuplashensis*, *Helianthus verticillatus*) are largely endemic to localized regions in the southern United States, and that none are native to Canada. As such, specific mitigation measures to protect these species are not required in Canada.

The two epyrifenacil end-use products proposed for registration in Canada are also registered in the United States. In the United States, products containing epyrifenacil require the following environmental mitigation measures: (1) statements advising users of toxicity to plants and aquatic invertebrates; (2) a prohibition on application to water; (3) instructions not to apply when weather conditions favour spray drift; (4) a leaching statement; (5) SBZs of 3 to 7.6 metres for ground application, and 15 to 33.4 metres for aerial application. Users are also required to obtain applicable Endangered Species Protection Bulletins prior to application and follow all directions and restrictions therein.

While Health Canada does not have an Endangered Species Protection Bulletin program like the United States, the other mitigation measures proposed for the epyrifenacil products are similar to the American requirements. The Canadian label advises users of toxicity to aquatic organisms and non-target terrestrial plants, prohibits application to water, includes a leaching statement and spray drift buffer zones and provides instructions to reduce spray drift. In Canada, SBZ requirements are presented separately for protection of freshwater, estuarine/marine and terrestrial habitats while one SBZ is presented per application rate/method/spray quality on the American labels. For S-3100 EC Herbicide, the proposed spray buffer zones in Canada range from 1 to 5 metres for ground application, and 1 to 275 metres for aerial application, based on the crop or use site. For V-10488 0.94 SE Herbicide, proposed only for ground application, SBZs of 1 to 35 metres are required based on the crop or use site. The proposed environmental mitigation measures for epyrifenacil products are considered to be appropriate to protect non-target species in Canada in accordance with the protection goals outlined in PMRA Guidance Document, *Health Canada's Approach to Environmental Risk Assessment for Pest Control*. When used according to the label directions, the environmental risks associated with epyrifenacil and its end-use products are acceptable.

Value assessment

15. Comment related to benefits, and social and economic impacts

The commenter stated that the value assessment omits the mandatory health, safety and environmental benefits and social/economic impact components of the definition of "value", as found in the *Pest Control Products Act* s.2(1).

Health Canada response

One of the ancillary objectives of the *Pest Control Products Act* is to ensure that only those pest control products that are determined to be of acceptable value are approved for use in Canada (s.4(2)(d)). The *Pest Control Products Act* defines the value of a pest control product as 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. Details regarding the different types of information that could be considered for each of the three components can be found in the PMRA Guidance Document, *Value Assessment of Pest Control Products*.

Value assessment consists of two general aspects: an assessment of the performance of a pest control product (items (a) and (b) in the paragraph above) and its benefits (item (c)). 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 and rotational 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 and rotational crops under normal use conditions. As a weight of evidence approach is used in determining acceptable value, in many cases proof of performance alone is sufficient to establish that the value of the pesticide is acceptable, 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.

In the case of epyrifenacil, an assessment based primarily on efficacy and effects on host and rotational crops was sufficient to determine acceptable value, and any additional health, safety and environmental benefits and social and economic impact would only add to this weight of evidence. Although specific sections were not included in PRD2026-13 for health, safety and environmental benefits and social and economic impact, information related to these was included throughout the section related to the value assessment. This included information related to the fit for epyrifenacil in conservation tillage and IPM systems (with the associated economic benefits), and it's unique binding mechanism with both contact and systemic herbicidal activity that contributes to resistance management.

16. Comment related to market-access/trade risk

16a) The commenter stated that the value assessment does not address the market-access and trade risk created by epyrifenacil's MRL matching United Stated tolerances with no Codex or European Union equivalent.

Health Canada response

Whenever a new pesticide active ingredient is registered, it is not unusual for MRLs to be absent from some export markets, or different from those to be established for Canada. While these can serve as trade irritants for those markets, the impact is not significant enough to result in the value of the pest control products to be found unacceptable.

In the case of epyrifenacil, harmonized MRLs between Canada and the United States would allow for trade of treated commodities between the two countries and there is potential for the establishment of MRLs in additional export markets in the future that could align with these.

16b) The commenter stated that they are concerned about the market-access and trade risk associated by establishing MRLs for epyrifenacil equivalent to the US tolerances with no Codex or European MRLs.

Health Canada response

While Health Canada considers the Codex MRLs and tolerances established by the United States Environmental Protection Agency (USEPA) in proposing MRLs, this is not a legal requirement. The requirement of the *Pest Control Products Act* to establish an MRL for a submission is an acceptable level of health risk associated with the MRLs specified. The health risks associated with epyrifenacil and associated end-use products are considered acceptable (PRD2026-13).

Additionally, the Codex MRL process requires that for the Joint Meeting on Pesticide Residues (JMPR, the scientific body providing independent advice to Codex Committee on Pesticide Residues) to review an active ingredient for proposing Codex MRLs, the pesticide must first be registered in a member state and have a Good Agricultural Practice established (FAO Plant Production and Protection Paper 225). In other words, a member country must first establish MRLs for an active ingredient before Codex MRLs can be established. Consequently, not registering a product in the absence of Codex MRLs is neither practical nor necessary. Additionally, as the MRLs for epyrifenacil are proposed at the limit of quantitation, the objector's argument of a potential trade implication that could arise from residue enforcement by importing countries at the limit of quantitation in the absence of the product registration within their jurisdiction is moot.

17. Comment related to efficacy and rotational crop claims

The commenter stated that the value assessment's efficacy and rotational-crop claims are not reconciled with documented crop injury, and the practical meaning of certain claimed uses is not explained. The commenter requested that Health Canada clarify the mechanism by which a herbicide is claimed to manage pathogen, insect, and rodent pest issues; disclose the yield outcome associated with the documented moderate canola rotational injury and confirm whether affected crops are typically replanted or removed; disclose whether canola rotational crop tolerance data specific to the lowest application rate and shortest re-cropping interval exist; and disclose whether multi-year, repeated-application rotational crop tolerance data have been considered given the persistence of several transformation products.

Health Canada response

As a broad-spectrum non-selective herbicide, epyrifenacil has herbicidal activity on a broad range of weeds. The primary benefit of this is removal of competition with crops. However, removal of the weeds also has the potential to reduce plant pathogens and insects that use the weeds as alternate hosts, or as a food source. Similarly, the removal of weeds removes cover used by rodents. This indirect effect is considered as part of the broader definition of value in the *Pest Control Products Act* but does not result in an explicit claim on the product labels.

Yield data were not collected in the trials that evaluated canola as a rotational crop following application of S-3100 0.46 EC Herbicide. The initial moderate visual crop injury observed in the rotational crop trials declined over time, consistent with that observed in the host crop tolerance trials for similar application rates and timings, in which moderate crop injury was observed for canola in the early season but declined overtime, and crop yield was unaffected. The early observations of crop injury were less than 20% injury, and are not severe enough that the crop would be replanted or removed. The yield effect on canola as a host crop was extrapolated to canola as a rotational crop, in consideration of the weight of evidence. To advise users of the early-season injury potential to canola as a rotational crop, a warning statement is included on the product label.

Rotational crop injury data are not available for canola as a rotational crop for the lowest application rate and shortest recropping interval. However, this application rate (182 mL/ha) and interval (3 days between application and planting) is supported based on crop tolerance data for the use of S-3100 0.46 EC Herbicide on canola as a host crop for the same application rate and interval between application and planting.

Multi-year, repeated-application rotational crop tolerance data have not been considered and are not required as not all transformation products have herbicidal activity, and as exaggerated rates up to 1452 mL/ha (double the maximum application rate) were evaluated in the single-year rotational crop trials. Additionally, the same field should not be treated in successive years when the resistance management best practices appearing on the product label are followed.

Other information

Inspection of confidential test data

The relevant confidential test data on which the decision is based (as referenced in PRD2026-13, *Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide*) are available for public inspection, upon application, in the Pesticides Regulatory Directorate's Reading Room. For more information, please contact the Pesticides Information Service.

Notice of Objection

Any person may file a notice of objection,[13] which must be based on scientific grounds, regarding this registration decision on *Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide,* within 60 days from the date of publication of this Registration Decision through

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

the Public Engagement Portal (Public Engagement Portal forms – Notice of Objection). The request for reconsideration must include the Notice of Objection form, the scientific explanation of the objection and the supporting scientific evidence in possession of the requestor that wouldn't already be in Health Canada's possession or cite specific Health Canada documentation they wish to rely on as supporting evidence (for example, scientific reports) in the form of electronic copies of cited references. Each of the references provided or cited must be clearly associated with the objection it supports. Failure to provide a complete package may result in the Notice of Objection being considered ineligible for further consideration by Health Canada. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and pest management portion of the Canada.ca website or contact the Pesticides Information Service.

Proportional Effort

Active ingredients registered in Canada are categorized based on criteria in Health Canada's Policy on Proportional Effort. The categorization is used to inform Health Canada's allocation of resources related to pesticide reviews in alignment with the required level of regulatory effort. Epyrifenacil is categorized as higher Proportional Effort based on the environmental criteria. Information on the risk assessment conclusions that resulted in the categorization is included in the proposed regulatory decision PRD2026-13. The Proportional Effort categorization will be used to inform the scope and level of effort needed for future reviews.

Continuous Oversight

Health Canada's Policy on continuous oversight of pesticides and the associated information note describe the process by which Health Canada monitors published scientific literature for active ingredients registered in Canada, and the criteria used to determine which active ingredients will be monitored when a final regulatory decision is made. The criteria have been met, therefore, scientific literature and regulatory information will be monitored as part of continuous oversight for this active ingredient.

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 *Pest Control Products 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 there is acceptable risk to human health and the environment, taking into account the conditions of registration.

For the purposes of the *Pest Control Products 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.[14]

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.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[15] A high-level overview is provided in the following sections.

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.[16]

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.[17]

Assessments estimate potential health risks to defined populations[18] 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 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

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14 Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*.
15 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*.
16 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000.
17 Science Policy Note: *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*.
18 Consideration of Sex and Gender in Pesticide Risk Assessment.

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, as presented in PMRA Guidance Document, *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products*. 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. For pesticide use scenarios that are expected to have negligible exposure, no environmental review is conducted. When environmental exposure is expected, 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 takes 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*.

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.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
AR	applied radioactivity
ARfD	acute reference dose
CEPA	*Canadian Environmental Protection Act*
CRA	cumulative risk assessment
dw	dry weight
EEC	estimated environmental concentration
K_{oc}	organic-carbon partition coefficient
K_{ow}	n-octanol-water partition coefficient
kg	kilogram
LOC	level of concern
mg	milligram
NOAEL	no-observed-adverse-effect-level
NOEC	no-observed effects level
PPO	protoporphyrinogen IX oxidase
ROEB	Regulatory Operations and Enforcement Branch
RQ	risk quotient
SBZ	spray buffer zone
TFA	trifluoroacetic acid
TP	transformation product
TRR	total radioactive residues
TSMP	Toxic substances Management Policy
USEPA	United States Environmental Protection Agency