



Registration Decision

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Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2

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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 information¹ 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 section of Evaluation Approach of this document.

Registration Decision Statement² for Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2

Health Canada's Pest Management Regulatory Agency (PMRA), pursuant to subsection 8(1) of the *Pest Control Products Act*, is granting registration for the sale and use of Cyclobutrifluram Technical, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, containing the technical grade active ingredient cyclobutrifluram, a nematicide and fungicide for use on romaine lettuce and as a soybean seed treatment.

The Proposed Registration Decision PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, containing the detailed evaluation of the information submitted in support of this registration, underwent a 30-day consultation period ending on 12 October 2025. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products 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*.

Comments and responses

Health Canada received comments from a non-governmental organization and the responses are provided below.

1. Comment related to the approach taken for the human health cancer risk assessment

This comment expressed concern over the approach taken for the cancer risk assessment, and stated that “The dismissal of linear carcinogenic risk modelling in the face of data limitations with the threshold approach is not justifiable.”

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*.

Further, the mode of action (MOA) for the liver tumours was noted as not being well supported and therefore there was disagreement with Health Canada's conclusion that it was "plausible" that the tumours were forming via a threshold mechanism and that the linear low dose extrapolation (q_1^*) approach would be overly conservative.

Health Canada response

As outlined in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, despite the limitations identified, support the proposed MOA for liver tumours in mice, Health Canada used a weight of evidence approach and concluded that the tumours are likely forming via a threshold mechanism. This was based on the partially supportive results from the mechanistic studies, coupled with the lack of genotoxic potential of cyclobutrifluram and existing knowledge that these tumour types develop via a threshold mechanism in mice. In view of the totality of the available information, it was considered that a threshold approach to the cancer risk assessment would be sufficiently health protective (and a linear dose extrapolation (q_1^*) approach would be overly conservative).

2. Comment related to the differences between animal doses and human exposure

There was expressed concern with the statement in the consultation document that "the risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests". This comment also noted that "This statement pointing to differences between animal doses and human effects is not appropriate and does not reflect a scientifically based approach. The methodology of the scientifically based approach as applied in risk assessments uses animals as a proxy for harms to humans, and then applies uncertainty factors to adjust for the differences between animals and humans."

Health Canada response

The statement in question reflects the scientifically based approach to human health risk assessment that is taken by Health Canada and is an internationally recognized approach in chemical regulatory frameworks. In the human health assessment, animal toxicity studies are designed to assess a pesticide's potential to cause adverse health effects, including, but not limited to, target organ toxicity, effects on the developing fetus through exposure via the maternal animal, impairment in the animal's ability to reproduce, and cancer. Results from these animal toxicity studies are used to extrapolate to potential human health risks by identifying the dose level at which no adverse effects are observed in animal studies. This is then compared to levels at which humans are normally exposed when pesticide products are used according to label directions. For a pesticide to be considered acceptable for registration, a sufficient margin of safety (typically at least 100-fold) must exist between the dose levels at which there are no adverse health effects noted in animals and the estimated human exposure under approved conditions of use. This 100-fold margin of safety is composed of a 10-fold uncertainty factor (UF) to account for differences between animal species and humans, as well as a 10-fold UF to account for variability that may exist within the human population. This 100-fold UF was applied when deriving the toxicology reference values selected for use in the human health risk assessments for cyclobutrifluram.

3. Comment related to assessment of endocrine disruption

This comment noted how the PMRA “did not give due consideration to disruption of the endocrine system” and noted that cyclobutrifluram caused effects in the thyroid glands, which was evidence of endocrine disruption. They further commented that the application of a threefold uncertainty factor in the human health risk assessment was “not enough, since higher doses may have revealed additional effects.”

Health Canada response

In accordance with the PMRA framework for a science-based risk assessment, Health Canada characterizes adverse effects across the pesticide database, including potential effects on the endocrine system, and considers these in the weight of evidence for the hazard assessment to ensure protection from the most sensitive effects regardless of their mode of action. As outlined in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, the toxicology database for cyclobutrifluram includes reproductive and developmental toxicity studies in rats and/or rabbits that were conducted according to international standards. These studies investigated several endocrine-related endpoints that may arise from exposure during sensitive periods of development. These endpoints are considered adequate to define the majority of potential endocrine-mediated effects that may result from exposure to cyclobutrifluram. By selecting the most sensitive endpoint in the available toxicology database as a point of departure (POD) for human health risk assessment, the dose levels chosen for risk assessment purposes are protective of effects observed at higher dose levels.

4. Comment related to reproductive and developmental toxicity concerns

With respect to the rat developmental toxicity study, this comment noted that there was evidence of qualitative sensitivity of the young and that the inadequate dose selection in the study meant that the NOAEL in the study could be “artificially high”. There was also expressed concern that “The efforts to have this reflected in the POD and UF is not appropriate” and that data could have been requested to “rectify this shortcoming”. It was further commented that the reduced fertility in the F1 males at the highest dose level tested in the rat reproductive toxicity study should be considered an indicator of reproductive toxicity and that historical control data should not be used to discount or diminish the finding.

Health Canada response

As stated in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, an additional uncertainty factor was applied in the human health risk assessment “to afford sufficient protection to potential serious developmental effects occurring in the absence of maternal toxicity if higher dose levels were tested in the rat developmental toxicity study”. Thus, the points of departure chosen for risk assessment are considered protective of potential effects that may have been observed had higher dose levels been used, and the need for further animal testing is not justified. This approach is in alignment with the framework outlined in the Science Policy note, SPN 2008-01, *the Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*.

With respect to the reduced fertility observed in the F1 males, at the highest dose level, in the reproductive toxicity study, Health Canada considered this finding to be an indication of reproductive toxicity. As such this it was taken into consideration during the selection of the PODs used for risk assessment, which are considered protective of the effects observed at higher dose levels. In addition, the low level of concern for the seriousness of this finding was not solely based on the fact that it was within the historical control data range for the parameter. As stated in PRD2025-06, the weight of evidence for concern for reproductive effects included the fact that “there were no other concerns for effects on reproductive parameters, including sperm and ovarian follicle measurements, or endocrine tissues in the database, the decreased fertility index was within the historical control range, and there was no effect on fertility in the P generation.”

5. Comment related to the lack of subchronic or reproductive toxicity testing on two major metabolites

This comment noted how the major metabolites SYN549104 and SYN510275 “reached higher systemic concentrations than the parent compound, but that acute and genotoxicity testing was limited and conducted only on SYN549104.” It was also stated that the assessment was insufficient since no subchronic or reproductive toxicity data were available on these metabolites.

Health Canada response

Both SYN549104 and SYN510275 are major metabolites formed in mammals during the biotransformation of cyclobutrifluram. As such, the results from the animal toxicology studies that were conducted with cyclobutrifluram, 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 cyclobutrifluram.

6. Comment related to the hazard assessment of end-use products

This comment noted how the hazard assessment was only conducted on the active ingredient, and that the end-use products need to be assessed for hazard as well.

Health Canada response

Health Canada considers acute hazards associated with end-use products and requires that formulators within end-use products meet certain regulatory requirements outlined in Regulatory Directive: *Formulants Policy and Implementation Guidance Document*.

With respect to toxicity information on formulated end-use products, Health Canada requires acute toxicity studies to determine the potential hazards from acute exposures. Acute data are used for classification purposes and for the development of appropriate precautionary statements for product labels. Acute studies identify relative acute toxicities by different routes of exposure as well as the potential to produce irritation and sensitization.

With respect to formulants in pest control products, applicants must provide Health Canada with information about all components of a pesticide, including active ingredients and formulants. These are assessed during the evaluation process. Health Canada may require that formulants of concern be eliminated from pest control products registered in Canada, or may limit the amount of formulant in a product.

7. Comment related to the application of the *Pest Control Products Act* (PCPA) factor in the dietary risk assessment

The commenter noted that there were “no reliable scientific data” provided to reduce the PCPA factor from 10-fold, adding that the database for developmental and reproductive toxicity was not sufficient and that there were concerns with qualitative sensitivity.

Health Canada response

As outlined in the Science Policy note, SPN 2008-01, *the Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*, the PMRA must apply a default 10-fold factor (the PCPA factor) for the protection of infants and children, unless the PMRA concludes, based on reliable data, that a different factor is appropriate. Determination of the magnitude of the factor involves evaluating the completeness of the data with respect to exposure of and toxicity to infants and children as well as potential for prenatal or postnatal toxicity. Incomplete toxicology databases are not equally incomplete and all prenatal and postnatal toxicities are not of equal concern. For these reasons, the PMRA makes specific case-by-case determinations as to the magnitude of the PCPA factor if reliable data permit. An integrative approach is taken to optimize the use of all available information.

With respect to the completeness of the data, as discussed in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, developmental toxicity studies in both rats and rabbits, as well as a 2-generation reproductive toxicity study in rats, were available for cyclobutrifluram to characterize the potential for toxicity to infants and children. Although it was acknowledged that dose level selection in the rat developmental toxicity study may not have been adequate, this study limitation was taken into account during the selection of the PODs and UFs for use in the risk assessment.

It is acknowledged that completeness of the data with respect to exposure of and toxicity to infants and children is a consideration in the determination of the magnitude of the PCPA factor. However, there is overlap between the use of an uncertainty factor to account for database deficiencies and a PCPA factor to account for the completeness of the data with respect to the toxicity to infants and children. Accordingly, as outlined in the Science Policy Note, SPN2008-01, it is Health Canada’s practice to address most uncertainties relating to the completeness of data with respect to the toxicity to infants and children (or for any subpopulation) through the application of an appropriate uncertainty factor for database deficiency. Therefore, as part of the review of the cyclobutrifluram toxicology database, consideration was given to the acceptability of the rat developmental toxicity study in the context of the overall uncertainty in the hazard characterization.

As such, it was concluded that an additional uncertainty factor was warranted to account for the limitation in the rat developmental toxicity study in order to afford sufficient protection to potential serious developmental effects occurring in the absence of maternal toxicity if higher dose levels were tested in the rat developmental toxicity study.

With respect to the comment raised concerning qualitative sensitivity, as noted in PRD2025-06, it was concluded that there was no evidence of increased sensitivity of the young compared to the adult animals observed in the cyclobutylfluram database. The PODs selected for the risk assessment are considered adequately protective of effects that were observed in the young. Therefore, reduction of the PCPA factor to onefold is justified, based on the lack of sensitivity in the young in all relevant studies that were reviewed.

8. Comment related to dietary exposure

This comment noted that the consumption data for the dietary risk assessment is based on DEEM, which measures what Americans, not Canadians consume.

Health Canada response

The PMRA has 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 an Information Note on comparing food and drink consumption data from Canada and the United States to explain why Health Canada’s PMRA uses NHANES data.

Based on this analysis, the total consumption levels determined for NHANES and CCHS shows a very similar pattern between the USA and Canada. Further, the PMRA selected NHANES data for use in dietary risk assessments for pesticides over the CCHS after carefully considering several factors (as noted in SPN2014-01, General Exposure Factor Inputs for Dietary, Occupational, and Residential Exposure Assessments) including relevance for people in Canada and the need to have foods “as eaten” converted to the raw agricultural commodity (RAC). Both NHANES and the CCHS collect consumption data “as eaten” foods, but only NHANES data is broken down further to RACs within the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ program (DEEM-FCID™, Version 4.02, 05-10-c). This is extremely important because both the consumption data and pesticide residue concentration must be based on RACs to most accurately estimate dietary exposure for a pesticide.

Based on the above, the PMRA has determined that using the NHANES is most appropriate for determining exposure levels to pesticides in the diets of Canadians. The Agency continues to monitor this area to ensure that the data used in the dietary exposure and risk assessments for pesticides are appropriate, reflective of modern day dietary trends, and protective of people in Canada.

9. Comment related to field trial data

The comment on the field trial data was related to lettuce and soybean and how these trials were conducted in the US and Brazil. These regions differ in terms of climate and applications from Canada, rendering the trials inadequate for the Canadian context.

Health Canada response

As per the Updated Residue Chemistry Guidelines, the total number of crop field trials required for a given crop is determined by the total production area and the dietary share, and the specific locations of the field trials are distributed according to the share of total crop area reported in each North American region.

Field trials conducted in the United States, in the equivalent growing region, can be used to fulfill Canadian requirements provided the use pattern is the same as the one proposed in Canada. Residue data generated from outside of North America may be accepted on a case-by-case basis.

Science Policy Note SPN2017-02, Joint Canada/United States Field Trial Requirements provides additional insights relevant to the current context. That is, joint residue trial projects intended to support simultaneous domestic registration applications in both the United States (US) and Canada (as is the case with cyclobutrifluram). The trial requirements for the representative crops in the NAFTA Residue Chemistry Crop Groups were developed in collaboration with the USEPA (see section 40 CFR 180.41 of the eCFR website and Residue Chemistry Crop Groups on Canada.ca). Consequently, as long as field trials provided for a given crop or for a representative crop of the subject crop have been conducted in growing regions according to SPN2017-02, the location of these trials are acceptable to support registrations in both the US and in Canada. The submitted field trial data for cyclobutrifluram met these criteria.

With regard to the Brazilian soybean trials, as mentioned above, additional trials conducted in jurisdictions outside of North America can also be considered and accepted on a case-by-case basis, particularly if agronomic practices and treatment and harvest regimes align with those proposed. The Brazilian soybean trials were considered to be supplemental since an acceptable number of trials conducted in major growing regions in North America were provided. The Brazilian trials were conducted in major soybean production regions in this country and according to the use directions on the relevant proposed Canadian product labels. As such, these trials were considered to provide useful additional information for consideration in the final decision-making process.

10. Comment related to occupational-residential exposure

With regards to dermal and inhalation exposure, this comment noted that the dermal absorption factors (2–6%) were extrapolated from a single formulation and study, not compound-specific field data.

Health Canada response

As reported in Section 3.3 of the PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, the PMRA relied on multiple compound-specific dermal absorption studies to support the occupational exposure and risk assessments conducted for these cyclobutrifluram submissions.

The PMRA reviewed four in vitro dermal absorption studies, conducted in 2020. These studies were based on three of the four end-use products proposed for registration: A22011 Crop (to represent both A22011 Crop and A23156 Crop), 22417 ST (now called VICTRATO) and A22417 ST Red (now called VICTRATO 2). Out of these studies, there were two human in vitro studies: one for each of the aforementioned seed treatment products (A22417 ST and A22417 ST Red). In addition, there was one human in vitro dermal absorption study and one rat in vitro dermal absorption study conducted with one of the soil-directed products (A22011 Crop).

Although only one of the two soil-directed products was used in these studies, a full comparison of the ingredients found in each of the products showed that the formulation of A23156 Crop (untested) was sufficiently similar to the formulation of A22011 Crop (tested) that the results of the tested formulation could be extrapolated to the untested formulation. For the soil-directed products, there were a human skin in vitro study and a rat skin in vitro study; however, given that rat skin is known to be more permeable than human skin and results from this study would more likely overestimate dermal absorption in vivo, the human skin in vitro study was selected to obtain more realistic values.

Overall, the four studies were considered acceptable for the selection of dermal absorption values based on an analysis of the various factors that can impact dermal absorption, including formulation type, product formulants, dose levels, skin site variability, tape stripes, skin wash and replicates. For the seed treatment products and the soil-directed products, activity-specific dermal absorption values were selected for scenarios where the concentrate or diluted end-use products were handled, as presented in Appendix I, Table 7 of PRD2025-06. Tables 8 and 9 of Appendix I also summarized the PMRA's analysis of these four studies.

11. Comment related to occupational-residential exposure

This comment was on the assumptions for re-entry exposure and how they were used, without back data – no measured dislodgeable residue data was provided.

Health Canada response

For the two seed treatment products of soybeans, VICTRATO and VICTRATO 2, dislodgeable foliar residue data are not relevant given that they are not applied as foliar postemergence sprays and there is no expectation of cyclobutrifluram residues being deposited on the crops during their growth stages following planting and up to harvest. The products are used to treat the seeds prior to planting and the risk assessments are conducted to estimate workers' exposure during the treatment of soybean seeds in commercial facilities (including mobile treaters) and on-farm settings, as well as during planting or handling of the treated seeds.

For the two soil-directed products in Romaine lettuce fields, A22011 Crop and A23156 Crop, the labels specify that they must be applied to the soil to protect the roots from infection. The products are not to be applied as over-the-top postemergence sprays on the crops. They must rather be applied via drench (including transplant water), low pressure drip, trickle or equivalent equipment, or via surface or soil-directed banded sprays. Therefore, postapplication dermal exposure to workers from contact with cyclobutrifluram residues deposited on lettuce leaves is expected to be minimal.

Nonetheless, as a worst-case scenario, the PMRA conducted a postapplication risk assessment to estimate workers' dermal exposure during the activities of handset irrigation, hand harvesting, transplanting, hand weeding and scouting. These activities are considered to have the highest transfer coefficients for the exposure scenarios relevant to leaf lettuce.

Given that chemical-specific dislodgeable foliar residue (DFR) data were not submitted for cyclobutrifluram, the default values of 25% dislodged residues on the day of the application and 10% daily dissipation for the following days were used in this risk assessment, which is presented in Appendix I, Table 12 of PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*. When postapplication activities are performed on the same day as the single application, calculated MOEs ranged from 3429 to 26087, compared to a target MOE of 100. Consequently, no health risks of concern were identified for any of the postapplication activities and the minimum restricted-entry interval (REI) of 12 hours is recommended to allow residues to dry, suspended particles to settle, and vapours to dissipate.

Please see the Science Policy Note, SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferrable Residues in Occupational and Residential Postapplication Exposure Assessments* for further details on how the PMRA uses default DFR values.

12. Related to occupational-residential exposure

As treated seeds are known to be dusty, this comment questioned how the PMRA determined that the inhalation exposure during seed treatment or planting was negligible without providing supporting evidence.

Health Canada response

The PMRA did not consider the inhalation exposure as negligible in the seed treatment risk assessments conducted for VICTRATO and VICTRATO 2. For all seed treatment exposure scenarios, including commercial seed treatment workers, on-farm seed treatment workers and planters, as well as planters of commercially-treated seeds, the PMRA estimated the inhalation and dermal exposures to VICTRATO and VICTRATO 2 based on the actual dermal and inhalation exposure values obtained from selected seed treatment surrogate exposure studies owned by the Agricultural Handler Exposure Task Force (AHETF), of which the applicant is a member and has full access.

As described in Sections 3.4.2.3.2 to 3.4.2.3.5 of PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, in support of using these surrogate data, the PMRA also reviewed a dust-off study in which the dustiness of VICTRATO - and VICTRATO

2-treated soybean seeds was shown to be lower than the dust levels measured in untreated soybean seeds, or in other seeds and various formulations used in surrogate exposure studies. These comparisons served to demonstrate that the use of surrogate exposure studies would not underestimate workers' exposure.

As demonstrated in Appendix I, Tables 13, 14 and 15 of PRD2025-06, when comparing the estimated exposures from both the dermal and inhalation routes with the toxicological reference values, the calculated margins of exposure (MOEs) were higher than the target MOEs of 100. More specifically, for commercial treaters and handlers (Table 13), calculated dermal and inhalation MOEs ranged from 571 to 8929; for on-farm treaters and handlers (Table 14), calculated MOEs were 6546 for dermal exposure and 686 for inhalation exposure; and for planters of commercially-treated seeds (Table 15), calculated MOEs were 1660 for dermal exposure and 1890 for inhalation exposure. Therefore, it was concluded that no health risks of concern were identified for all seed treatment workers.

13. Comments related to cumulative risk assessment

This comment noted how a quantitative cumulative exposure model is required to be protective.

Health Canada response

As outlined in the Science Policy Note SPN2018-02, *Cumulative Health Risk Assessment Framework*, the PMRA uses a tiered approach in conducting cumulative health risk assessments (CHRA), with each tier being more refined (that is, less conservative and uncertain) than the previous tier.

Succinate dehydrogenase inhibitors (SDHI)

Based on this tiered approach, a more refined quantitative risk assessment was not required for the SDHI, since the less refined semi-quantitative risk assessment, conducted in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, demonstrated that the cumulative health risks from the potential co-exposure to SDHIs through food, drinking water and residential exposure are acceptable.

The semi-quantitative CHRA took into account the co-occurrence of SDHIs detected in monitoring of food and water. For the monitored samples that had co-occurrence, using fluopyram as an index chemical, residues of each SDHI detected were adjusted for relative potency and molecular weight equivalency and summed to calculate the total SDHI residue level in fluopyram equivalents. The mean total SDHI residue level in each food commodity and water was calculated for the cumulative SDHI dietary exposure assessment (DEA) and then compared to the residue inputs of the existing fluopyram DEA.

When the cumulative dietary exposure assessment (DEA) for the common mechanism group (CMG) results in exposure estimates that are lower than those derived from the previously conducted index chemical DEA, it can be inferred that dietary exposures based on residue monitoring data for the entire group are also lower than those considered in the existing risk assessment for the index chemical. Under these conditions, the cumulative exposure is not considered to pose a health concern.

If further refinement is warranted, one approach is to update the DEA by replacing the residue inputs with the mean total residues of the CMG across all commodities. This adjustment provides a more representative estimate of cumulative exposure based on empirical monitoring data, while maintaining alignment with the toxicological framework established through the index chemical. This was done in the SDHI CHRA, which estimated risk to be 71.0% and 13.8% of the ADI of fluopyram in food and drinking water, respectively. These risk estimates were lower compared to the existing fluopyram DEA (80.7% and 16.6% of the ADI, respectively). The approach taken for the SDHI cumulative DEA had several conservatisms, since 1) it only considered samples with detection and co-occurrence, 2) maximum concentrations were used for the risk analysis from drinking water, which is a conservative assumption for a chronic dietary exposure assessment, and 3) the relative potency factors used for the risk assessment for each SDHI were calculated using the most conservative points of departure, that are not necessarily based on common effects of liver and thyroid toxicity (which are likely to be higher).

In addition, residential exposure from the registered use of SDHIs contributes to no more than 5.1% of the risk cup. This risk estimate was calculated using the most conservative point of departure, which is not based on common effects of liver and thyroid toxicity for the exposure duration and routes relevant for the residential exposure scenarios of SDHIs.

As such, based on this semi-quantitative assessment, the cumulative risks from potential co-exposure to SDHIs through food, drinking water and residential exposure, where relevant, are acceptable. Conducting a quantitative risk assessment for the SDHIs, which will remove the conservatisms listed above, would result in cumulative exposure and risk estimates lower than those from the semi-quantitative assessment and thus continue to represent acceptable cumulative health risk.

Trifluoroacetic acid (TFA)

Similarly for TFA, since the qualitative risk assessment conducted in PRD2025-06 demonstrates that health risk is not of concern, a quantitative risk assessment is not required.

The qualitative risk assessment for TFA considered the following:

- The DEA for cyclobutifluram: The contribution of TFA to the cyclobutifluram DEA was low – 1% of the ADI and <0.04% of the ARfD of cyclobutifluram.
- The 2014 EFSA comprehensive dietary exposure assessment for TFA: Conducted during the assessment of the pesticide saflufenacil, it took into account all sources of the environmental degradate (from pesticides and other environmental contaminants) and did not identify risks of concern.

Therefore, it was concluded that exposure to TFA from pesticidal sources is not considered to be a health risk of concern.

It is noted that TFA is an environmental degradate generated from multiple pesticidal sources and does not share a common mechanism of toxicity with the parent active ingredients. As such, in the Cumulative Health Risk Assessment Operational Planning Framework,³ TFA was identified as a common metabolite that requires a separate health risk assessment. As indicated in the PRD2025-06, the PMRA will prioritize the work in consideration with the resources available and leverage the assessment completed by EFSA in 2014.

14. Comments related to the environmental fate and hazard assessments

The commenter noted that there is no discussion of the environmental effects or hazard of cyclobutrifluram in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, and thus, evidence is lacking for the assessment of risk using a scientifically based approach. Specifically, they reported that they find the fate assessment to be lacking because a phototransformation in air study was not conducted. This comment also noted how the assessment was based on limited data on volatilization, adsorption/desorption and hydrolysis, and that the potential for long-range transport cannot be understood. Additionally, there was disagreement with the use of modelled estimates rather than empirical evidence, which the commenter claims is contrary to a scientifically based approach that uses evidence.

Health Canada response

The PMRA completed the environmental risk assessment as described in PMRA Guidance Document (2023) Health Canada's Approach to Environmental Risk Assessment for Pest Control Products, and considered both environmental exposure and ecotoxicology information. Details of the environmental risk assessment are in Section 4.0 of PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*. As presented in Appendix I, Table 19 of PRD2025-06, the environmental fate assessment considered the studies identified in this table.

A comprehensive review of the environmental fate and ecotoxicology data for cyclobutrifluram was conducted by the PMRA to inform the risk characterization. The fate and behaviour of cyclobutrifluram in the environment is discussed in Section 4.1 of PRD2025-06. The results of the various fate studies were considered in the environmental risk assessment, and fate parameters from these studies were used in drinking water modelling, as appropriate.

While PRD2025-06 does not include a standalone hazard assessment section, a hazard assessment was conducted as part of the assessment and the ecotoxicity data for non-target species used in the risk assessment are presented in Appendix I, Table 22 of PRD2025-06.

³ The Cumulative Health Risk Assessment Operational Planning Framework is pending publication (December 2025). However, the underlying science is complete and has been taken into consideration with respect to the comments received for the Proposed Registration Decision and this Registration Decision.

A phototransformation in air study was not required based on the physico-chemical properties of cyclobutrifluram, which indicate that cyclobutrifluram is expected to be non-volatile. This is supported by the results of the laboratory fate studies, which showed limited production of volatile compounds. The only volatile compounds observed in the fate studies were:

- The transformation product, SYN551241, was shown to be volatile in the phototransformation in water study. AOPWIN modelling for the Toxic Substances Management Policy (TSMP) assessment concluded that SYN551241 is not persistent in air, with an estimated half-life of 0.393 days. Given that phototransformation only occurs in the upper layer of clear water columns and that SYN551241 was not formed in any of the other studies, SYN551241 was considered to have limited environmental relevance.
- Carbon dioxide was produced at $\leq 6.4\%$ applied radioactivity (% AR) in the environmental fate studies. Carbon dioxide is a terminal transformation product, indicating that some cyclobutrifluram is expected to be completely transformed by microorganisms or abiotic processes in the environment.

Based on the above, significant long-range transport of cyclobutrifluram and its transformation products is not expected.

15. Comment related to the leaching and runoff assessments

This comment noted that cyclobutrifluram has several major transformation products (SYN510275, SYN549104, TFA) that are highly mobile, persistent, and have the potential to leach to groundwater. Further, despite noting that there is potential for leaching to groundwater and runoff, the PMRA nevertheless considered the risk to be acceptable. Therefore, the commenter did not consider this finding to be consistent with an evidence-based approach, which would have used quantitative groundwater modelling based on accurate input or field data validation. The commenter also did not consider that an environmental risk characterization, which integrated environmental exposure and effects, occurred. Additionally, the commenter stated that best management practice label statements to reduce leaching to groundwater and runoff are insufficient to mitigate risk and that detailed, enforceable standards are needed.

Health Canada response

The PMRA conducted a tiered, science-based environmental risk assessment for cyclobutrifluram, as described in the response to Comment 16. This included consideration of the environmental fate of cyclobutrifluram, and a comparison of estimated environmental concentrations based on the maximum application rate (in other words, exposure) to effect metrics calculated from ecotoxicological data from laboratory studies (in other words, effects).

Risks to aquatic organisms were determined to be acceptable at the screening level as outlined in Section 4.2.2 of the PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*. Therefore, further characterization, such as a spray drift or runoff assessment, is not required.

The leaching potential of cyclobutrifluram and its transformation products was characterized as part of the fate assessment using a weight-of-evidence approach. The available weight-of-evidence (in other words, field studies, mobility information, leaching criteria of Cohen et al., (1984), groundwater ubiquity scores (GUS), and groundwater modelling) indicates that cyclobutrifluram and its transformation products may leach from soil to groundwater.

Although further characterization of risk to aquatic organisms is not required given the results of the screening level risk assessment, the human health assessment considered exposure to cyclobutrifluram and several of its transformation products (SYN510275, CGA177291, SYN549104 and trifluoroacetic acid (TFA)) in drinking water sources. The estimated environmental concentrations of the combined residue of these compounds in drinking water was modelled using the Pesticide in Water Calculator (PWC) version 2.001 based on fate parameters from the laboratory studies outlined in the response to Comment 14. As noted in PRD2025-06, residues of cyclobutrifluram and its transformation products in food and drinking water are not a health concern.

Best management practice label statements are a standard method used by the PMRA to reflect the results of the Scientific evaluation and explain how to further reduce any potential risks to human health or the environment. The conditions that could promote the runoff of a chemical (for example, steep slope, heavy rain) may exist, regardless of its attributes. As such, a label statement providing best management practices to reduce runoff is required on the labels of all products used outdoors in a manner where runoff could occur. Due to the leaching potential of cyclobutrifluram, a label statement to inform users of best management practices to reduce leaching was also required. Even though risks to aquatic organisms and from exposure through drinking water are acceptable, these statements are Health Canada guidelines and were included to inform users of the potential for movement of cyclobutrifluram and its transformation products from the terrestrial environment to surface and groundwater and of practices to further reduce the potential risks.

16. Comments related to the risk assessment for aquatic invertebrates

The commenter noted that a chronic risk assessment for aquatic invertebrates was not conducted even though they are the most sensitive taxa. Instead, only a screening level risk assessment was conducted. Additionally, this comment stated that the aquatic toxicity of transformation products was not assessed, even though some are more persistent and more soluble in water than the parent.

Health Canada response

The PMRA uses a tiered risk assessment approach, as described in the PMRA Guidance Document (2023) *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products*. The first tier, known as a screening level risk assessment, uses conservative exposure assumptions and effects metrics (based on endpoints from laboratory ecotoxicology studies) to identify whether a pest control product poses an acceptable risk to the environment or requires additional characterization to determine the acceptability of risk. The screening level risk assessment includes evaluation of both acute and chronic risks. If risks are determined to be acceptable at the screening level, no further characterization is required.

For aquatic organisms, the screening level risk assessment assumed a direct overspray of cyclobutrifluram to surface water at the maximum proposed application rate. This is a conservative assumption because cyclobutrifluram is not permitted to be applied directly to water. The risk assessment for aquatic invertebrates included consideration of acute and/or chronic data for several species (water flea (*Daphnia magna*), midge (*Chironomus dilutus*), freshwater amphipod (*Hyalella azteca*), mysid shrimp (*Americamysis bahia*) and the estuarine amphipod (*Leptocheirus plumulosus*).

An acute study exposing *Daphnia magna* to the major transformation product, SYN510275, was also considered in the assessment. SYN510275 is less toxic than cyclobutrifluram based on the available data. SYN510275 was determined to be the only transformation product relevant to the aquatic risk assessment. The risk quotients calculated in the screening level risk assessment for cyclobutrifluram and SYN510275 were below the level of concern of 1 for aquatic invertebrates. As such, risks were determined to be acceptable, and no further assessment is required.

The risk assessment of cyclobutrifluram and SYN510275 is considered to be protective of the other transformation products so they were not quantitatively assessed for the proposed decision based on the following considerations. SYN551231 and SYN551241 were not considered to be environmentally relevant. These major transformation products are only formed via phototransformation in water after several days of continuous irradiation (2 and 4 days, respectively). Phototransformation only occurs in the upper layer of clear water columns. CGA177291 and EXC8199 are only formed at low levels via phototransformation on soil (14.1 and 11.6% AR, respectively). Low levels (10.6% AR) of trifluoroacetic acid (TFA) are produced via biotransformation in aerobic soil. While runoff of the transformation products produced in soil to the aquatic environment can occur, the levels reaching water are expected to be low.

Empirical ecotoxicological data for TFA are available in the scientific literature and were also considered as part of the re-evaluation of flufenacet (PRVD2021-01 *Flufenacet and Its Associated End-use Products*). The data show that TFA is less toxic than cyclobutrifluram to most aquatic taxa (Table 1). In the case of algae, TFA has a similar, but slightly higher, toxicity; however, the exposure of algae to TFA from the use of cyclobutrifluram is expected to be significantly lower than that from cyclobutrifluram since the biotransformation of cyclobutrifluram results in the formation of only 10.6% AR as TFA.

ECOSAR modelling was used to predict the toxicity of SYN551231, SYN551241, CGA177291 and EXC8199 to aquatic organisms (Table 2). SYN551231 (with the exception of algae), CGA177291 and EXC8199 were predicted to be less toxic than cyclobutrifluram. SYN551241 was predicted to be more toxic than cyclobutrifluram to aquatic organisms while SYN551231 was predicted to have a slightly higher toxicity to green algae. As noted above, SYN551231 and SYN551241 are not considered to be environmentally relevant because they are only formed under very specific environmental conditions (phototransformation in water). Based on the above, the risk assessment for cyclobutrifluram is considered to be protective of the exposure of the environment to its transformation products. Assuming 100% transformation of cyclobutrifluram to both SYN551231 and SYN551241 on a molar basis, which overestimates the formation of both transformation products, the estimated environmental concentrations for these transformation products are an order of magnitude below the predicted toxicity values (Table 3). No updates to the aquatic risk assessment are required.

Table 1 Comparison of ecotoxicological endpoints for cyclobutrifluram and TFA

| Organism | Exposure | Test substance | Endpoint value | Reference/PMRA No. |
|---|------------|---------------------------------|---|---------------------------------|
| <i>Daphnia magna</i> | 48-h Acute | Cyclobutrifluram | EC ₅₀ >27 mg a.i./L | 3273313 |
| | | Sodium trifluoroacetate (NaTFA) | EC ₅₀ > 1200 mg NaTFA/L equivalent to >1008 mg TFA/L | 3648595, 3014765 ⁽²⁾ |
| Fathead minnow (<i>Pimephales promelas</i>) ⁽¹⁾ | 96-h Acute | Cyclobutrifluram | LC ₅₀ >11 mg a.i./L | 3273304 |
| Zebrafish (<i>Danio rerio</i>) | | Sodium trifluoroacetate (NaTFA) | LC ₅₀ >1200 mg NaTFA/L equivalent to >1008 mg TFA/L | 3648595, 3014765 ⁽²⁾ |
| Freshwater algae (<i>Rhaphidocelis subcapitata</i>) ⁽¹⁾ | 96-h Acute | Cyclobutrifluram | EC ₅₀ = 6.4 mg a.i./L | 3273323 |
| | 72-h Acute | Sodium trifluoroacetate (NaTFA) | EC ₅₀ = 4.19 mg TFA/L | 3014765 ⁽²⁾ |
| | | Sodium trifluoroacetate (NaTFA) | EC ₅₀ > 1.2 mg TFA/L | 3014765 ⁽²⁾ |
| Duckweed (<i>Lemna gibba</i>) | 7-d | Cyclobutrifluram | EC ₅₀ = 11 mg a.i./L | 3273330 |
| | | Sodium trifluoroacetate (NaTFA) | EC ₅₀ = 769 mg TFA/L | 3014765 ⁽²⁾ |
| <p>(1) The most sensitive acute fish and algae endpoints from PRD2025-06, <i>Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2</i> are presented.</p> <p>(2) These endpoints were also published in PRVD2021-01 <i>Flufenacet and Its Associated End-use Products</i>).</p> | | | | |

Table 2 Comparison of ECOSAR-modelled ecotoxicological endpoints for SYN551231, SYN551241, CGA177291 and EXC8199 to empirical data for cyclobutrifluram

| Organism | Exposure | Test substance | Endpoint value | Reference/PMRA No. |
|--|-----------------------|------------------|-----------------------------------|------------------------|
| Freshwater organisms | | | | |
| <i>Daphnia magna</i> | 48-h Acute | Cyclobutrifluram | EC ₅₀ >27 mg a.i./L | 3273313 |
| | 21-d Chronic | | NOEC = 2.6 mg a.i./L | 3273287 |
| Daphnid | 48-h Acute | SYN551231 | LC ₅₀ = 290 mg/L | Predicted using ECOSAR |
| | | SYN551241 | LC ₅₀ = 1.08 mg/L | |
| | | CGA177291 | LC ₅₀ = 176 mg./L | |
| | | EXC8199 | EC ₅₀ = 232 mg/L | |
| | Chronic | SYN551231 | ChV = 10.5 mg/L | |
| | | SYN551241 | ChV = 0.18 mg/L | |
| | | CGA177291 | ChV = 21.2 mg/L | |
| EXC8199 | ChV = 27.2 mg/L | | | |
| Fathead minnow (<i>Pimephales promelas</i>) ⁽¹⁾ | 96-h Acute | Cyclobutrifluram | LC ₅₀ >11 mg a.i./L | 3273304 |
| | 32-d Early life stage | | NOEC = 1.9 mg/L | 3273306 |
| Fish | 96-h Acute | SYN551231 | LC ₅₀ = 194 mg/L | Predicted using ECOSAR |
| | | SYN551241 | LC ₅₀ = 1.55 mg/L | |
| | | CGA177291 | LC ₅₀ = 287 mg/L | |
| | | EXC8199 | LC ₅₀ = 382 mg/L | |
| | Chronic | SYN551231 | ChV = 64.1 mg/L | |
| | | SYN551241 | ChV = 0.19 mg/L | |
| | | CGA177291 | ChV = 30.7 mg/L | |
| EXC8199 | ChV = 40.4 mg/L | | | |
| Green algae (<i>Rhaphidocelis subcapitata</i>) ⁽¹⁾ | 96-h Acute | Cyclobutrifluram | EC ₅₀ = 6.4 mg a.i./L | 3273323 |
| Green algae | 96-h Acute | SYN551231 | EC ₅₀ = 5.3 mg/L | Predicted using ECOSAR |
| | | SYN551241 | EC ₅₀ = 1.55 mg/L | |
| | | CGA177291 | EC ₅₀ = 179 mg/L | |
| | | EXC8199 | EC ₅₀ = 227 mg/L | |
| Estuarine/marine organisms | | | | |
| Mysid shrimp (<i>Americamysis bahia</i>) | 96-h Acute | Cyclobutrifluram | LC ₅₀ > 8.0 mg a.i./L | 3273279 |
| | 28-d Chronic | | NOEC = 1.3 mg a.i./L | 3273289 |
| Eastern oyster (<i>Crassostrea virginica</i>) | 96-h Acute | | IC ₅₀ = 0.33 mg a.i./L | 3273287 |
| Saltwater mysid | 96-h Acute | SYN551231 | LC ₅₀ = 8.7 mg/L | Predicted using ECOSAR |
| | | SYN551241 | LC ₅₀ = 0.34 mg/L | |
| | | CGA177291 | LC ₅₀ = 155 mg/L | |
| | | EXC8199 | LC ₅₀ = 221 mg/L | |
| | Chronic | SYN551231 | Not estimated | |
| | | SYN551241 | LC ₅₀ = 0.02 mg/L | |
| | | CGA177291 | ChV = 10.5 mg/L | |
| EXC8199 | ChV = 15.4 mg/L | | | |
| Sheepshead minnow (<i>Cyprinodon</i>) | 96-h Acute | Cyclobutrifluram | LC ₅₀ > 18 mg a.i./L | 3273285 |
| | 34-d Early-life stage | | NOEC = 0.43 mg a.i./L | 3273282 |

| Organism | Exposure | Test substance | Endpoint value | Reference/PMRA No. |
|---|---------------------------------|----------------|------------------------------|------------------------|
| <i>variegatus</i>) | | | | |
| Saltwater fish | 96-h Acute | SYN551231 | LC ₅₀ = 193 mg/L | Predicted using ECOSAR |
| | | SYN551241 | LC ₅₀ = 1.98 mg/L | |
| | | CGA177291 | LC ₅₀ = 364 mg/L | |
| | | EXC8199 | LC ₅₀ = 483 mg/L | |
| | Chronic (duration not reported) | SYN551231 | ChV = 0.223 mg/L | |
| | | SYN551241 | ChV = 0.816 mg/L | |
| | | CGA177291 | ChV = 65.1 mg/L | |
| | | EXC8199 | ChV = 81.3 mg/L | |
| ChV: Chronic value, is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC). The PMRA uses NOEC values to assess chronic risk. (1) The most sensitive endpoints for cyclobutrifluram are presented when data for multiple species are reported in PRD2025-06, <i>Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2</i> . | | | | |

Table 3 Estimated environmental concentrations of SYN551231 and SYN551241 in water

| Transformation product | Estimated environmental concentration (mg/L) | | Notes |
|------------------------|--|-------|---|
| | 15 cm | 80 cm | |
| SYN551231 | 0.037 | 0.007 | EECs of the major transformation products in surface water were calculated considering a direct overspray of 100 g a.i./ha cyclobutrifluram to a one-hectare wetland with depths of 15 and 80 cm. The calculation assumed 100% transformation of the cyclobutrifluram to each transformation product on a molar basis. Dissipation of the parent or transformation products was not considered. |
| SYN551241 | 0.030 | 0.006 | The molecular weights of cyclobutrifluram, SYN551231 and SYN551241 are 389.2, 216.16 and 173.04 g/mol, respectively. EECs in surface water at 15-cm depth are used to determine risk to amphibians (using fish as a surrogate) while the 80-cm depth EECs are used to evaluate risks to all other aquatic organisms. |

17. Comment related to the environmental cumulative analysis of TFA

This comment noted that the environmental assessment defers the cumulative analysis of TFA, even though the PMRA acknowledges its persistence and occurrence from multiple pesticides. The commenter feels that this deferral is not justified and that the proposed decision cannot be approved until the cumulative analysis is conducted.

Health Canada response

The PMRA acknowledges that, to some extent, cyclobutrifluram is expected to contribute to TFA levels in the environment; however, this is not expected to change the risk characterization of cyclobutrifluram products, given that TFA is not currently known to be harmful to organisms in the environment.

Although there is some uncertainty regarding the total contribution of pest control products to TFA in the environment over time, this does not change the environmental risk assessment conclusions for cyclobutrifluram, as per the PMRA's current environmental risk assessment practices. The consideration of cumulative environmental effects from multiple sources of active ingredients and transformation products is not currently considered in the environmental risk assessment framework for pesticides in Canada. The cumulative risk assessment for TFA discussed in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2* relates to the human health assessment.

18. Comments related to the assessment of nanoparticles in seed treatments

The commenter stated that an assessment of potential harms and risks requires an assessment of the interaction of the pest control product with the constituents of the seed treatment. This comment cited several articles to infer that harm to the environment from nanomaterials in seed treatments could occur. The commenter also noted that the constituents of the seed treatment were not described and that it appears that an assessment was not conducted. The commenter believes that at a minimum, field trial data are required to assess the impacts of seed treatments on soil and ecosystems. Additionally, even though treated seeds are known to be dusty, the PMRA determined that inhalation exposure during seed treatment or planting was negligible without providing supporting evidence.

Health Canada response

There is no indication that cyclobutrifluram Technical and its end-use products, A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2, contain nanomaterials. As such, the references cited by the commenter are not applicable to the assessment of cyclobutrifluram. The formulations of pest control products are confidential business information, and as such, are not published by the PMRA. However, a review of the proposed product formulations was conducted. The PMRA concluded that cyclobutrifluram and its end-use products, A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. More information on the List can be found in Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act*.

The commenter notes concerns that treated seeds are known to be dusty. While the current environmental risk assessment framework does not generally include evaluation of inhalation by non-target organisms, seed-treatment specific considerations were evaluated where appropriate in the assessment for cyclobutrifluram (in other words, for bees, beneficial arthropods, birds and mammals).

19. Comment related to risk reduction measures for aquatic organisms

This comment noted that the precautionary label statement to inform users of the toxicity of cyclobutrifluram to aquatic organisms is not mitigation.

Health Canada response

A “toxic to aquatic organisms” label statement is required for products containing cyclobutrifluram due to its inherent toxicity (acute $EC_{50}/LC_{50} < 1$ mg/L for at least one of the assessed species). The use of precautionary label statements is a standard method that the PMRA uses to inform users of hazards associated with pest control products. As discussed in the response to Comment 16, risks to aquatic organisms from cyclobutrifluram were determined to be acceptable at the screening level. As such, measures to mitigate risks to aquatic organisms from cyclobutrifluram and its transformation products are not required.

20. Comments related to best management practices for seed treatment

The commenter noted that the best management practice label statement to clean up spilled seed is insufficient and that detailed standards that are enforceable are needed.

Health Canada response

The required statement for seed treatments “any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned up from the soil surface” is a label direction and not a best management practice. The *Pest Control Products Act* states that no person shall use a pest control product in a way that is inconsistent with the directions on the label.

21. Comment related to the value assessment

This comment reported how the value assessment was lacking in that there was no need for the pest control products provided, and the three criteria for value set out in the *Pest Control Products Act* were not established. (Under section 2(1) of the *Pest Control Products Act*, “value” includes: (a) efficacy, (b) effects on host organisms, and (c) health, safety, environmental, social and economic impacts). Value requires demonstration of tangible benefits, but these have not been shown.

Health Canada response

The *Pest Control Products Act* recognizes a pest control product’s actual or potential contribution to pest management in its definition of value.

The detrimental socio-economic impact of the subject diseases on Canadian growers is well documented and the expected contribution to the management of these pests from the new active ingredient formed the basis for the finding of acceptable value.

Soybean cyst nematodes are a major cause of yield loss in Canada and are considered the most destructive soybean disease in the world. Sudden death syndrome is now reported as the second most devastating soybean disease in major soybean-growing regions of Canada. These diseases frequently co-occur in fields and lead to significant yield reductions and economic loss.

Root knot nematodes are a major pest of horticultural and field crops in Canada. A broad range of crop plants are susceptible to their damaging effects, including lettuce. Reductions in crop yield and quality caused by nematode infection, and the resulting economic loss, is a growing concern among Canadian producers.

The value information described in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*, established a reasonable expectation of cyclobutrifluram product performance in managing the detrimental effects of these pests, including the absence of adverse effects on host organisms.

The PMRA recognizes value in access to new pest control products that offer either a first solution to emerging pest problems or an addition to existing alternatives that increase grower options, which, among other benefits, enables rotation of effective pesticide products and facilitates responsible disease resistance management.

Further detail on the approach to value assessments of pesticides is provided in the PMRA guidance documents *Value Guidelines for New Plant Protection Products and Label Amendments (2023)* and *Value Assessment of Pest Control Products (2022)*.

22. Comment on efficacy data

The commenter noted that efficacy and yield data were primarily from the US and Brazilian trials, with no published or peer-reviewed Canadian field performance.

Health Canada response

Evidence of product performance from Canadian field trials was supplemented by trials conducted outside of the country; in other words, the US and Brazil. All of the trials considered in support of the value of the proposed claims were determined to have been conducted using acceptable scientific methodology. Some of the US trials were conducted in northern states with growing conditions that are comparable to those found in Canadian growing regions. While some trial regions, such as Brazil, have higher annual temperatures than those typical to Canadian growing regions, some target pests are favoured by warmer humid conditions. Consequently, the efficacy data obtained outside of Canada could reasonably be expected to represent a worst-case scenario, which in fact emphasizes the expectations of product performance under Canadian conditions.

Peer-reviewed publication of efficacy trial data submitted to support value is not required by the PMRA.

23. Comment on acceptable risk

The commenter noted that the PMRA did not adequately assess the risk arising to human health and the environment.

Health Canada response

With regard to the points raised in the conclusion of the comment received, the PMRA has concluded that the risks of cyclobutrifluram are acceptable under the *Pest Control Products Act*. In other words, based on the health and environmental risk assessments for this product, the PMRA is reasonably certain that no harm to human health, future generations or the environment will result from exposure to or use of this product, taking into account its conditions of registration. When determining whether a product's risks are acceptable, the PMRA factors into its assessment that persons will comply with a product's mandatory conditions of registration. Pest control product labels include mandatory conditions for use which mitigate against otherwise unacceptable risks. Under the *Pest Control Products Act*, it is an offence to use a pest control product in a way that is inconsistent with the directions on the label. This offence is punishable by significant fine and/or imprisonment. The section "Evaluation Approach" of this document contains further details.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2025-06, *Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2*) are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection,⁴ which must be based on scientific grounds, regarding this registration decision on cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 within 60 days from the date of publication of this Registration Decision through 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 would not already be in the PMRA's possession or cite specific PMRA 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 the PMRA. 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 PMRA's Pest Management Information Service.

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

Evaluation approach

Legislative framework

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

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

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

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

Health risk, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.

Environmental risk, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.

Value, in respect of a pest control product, means the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact.

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

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

Risk and value assessment framework

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

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

i) Assessing potential health risks

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

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.⁸

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

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

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

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

Assessments estimate potential health risks to defined populations⁹ 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 addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

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

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

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

iii) Value assessment

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

⁹ Consideration of Sex and Gender in Pesticide Risk Assessment.

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

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

Risk management

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

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*.

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

| | |
|------------------|---|
| % | percent |
| a.i. | active ingredient |
| ADI | acceptable daily intake |
| AHETF | Agricultural Handlers Exposure Task Force |
| AOPWIN | Atmospheric Oxidation Program for Windows |
| AR | applied radioactivity |
| ARfD | acute reference dose |
| CCHS | Canadian Community Health Survey |
| CHRA | cumulative health risk assessment |
| ChV | chronic value |
| CFR | Code of Federal Regulations |
| cm | centimetre |
| CMG | common mechanism group |
| d | day |
| DEA | dietary exposure assessment |
| DEEM | Dietary Exposure Evaluation Model |
| DFR | dislodgeable foliar residue |
| EC ₅₀ | effective concentration on 50% of the population |
| ECOSAR | Ecological Structure Activity Relationships |
| EEC | estimated environmental concentration |
| EFSA | European Food Safety Authority |
| F1 | first filial generation |
| FCID | Food Commodity Intake Database |
| g | gram |
| GUS | groundwater ubiquity scores |
| h | hour |
| ha | hectare |
| IC ₅₀ | inhibitory concentration to 50% of the population |
| L | litre |
| LC ₅₀ | lethal concentration to 50% of the population |
| LOEC | lowest observed effect concentration |
| mg | milligram |
| mol | mole |
| MOA | mode of action |
| NaTFA | sodium trifluoroacetate |
| NAFTA | North American Free Trade Agreement |
| NHANCES | National Health and Nutrition Examination Survey |
| NOAEL | no observed adverse effect level |
| NOEC | no-observed effect concentration |
| P | parental generation |
| PCPA | <i>Pest Control Products Act</i> |
| PMRA | Pest Management Regulatory Agency |
| POD | point of departure |
| PRD | Proposed Registration Decision |
| PWC | Pesticide in Water Calculator |
| q ₁ * | cancer potency facto |

| | |
|-------|---|
| RAC | raw agricultural commodity |
| REI | restricted-entry interval |
| SDHI | succinate dehydrogenase inhibitors |
| SPN | Science Policy Note |
| TFA | trifluoroacetic acid |
| TSMP | Toxic Substances Management Policy |
| UF | uncertainty factor |
| US | United States |
| USEPA | United States Environmental Protection Agency |

References

A. List of studies/information submitted by registrant

None

B. Additional information considered

PMRA

Document

Number

Reference

| | |
|---------|---|
| 3014765 | 2017, European Commission. Draft renewal assessment report prepared according to the Commission Regulation (EU) No 1107/2009. Flufenacet. Vol. 1. DACO: 12.5.4. |
| 3648595 | Berends et al., 1999, Toxicity of trifluoroacetate to aquatic organisms, Env. Tox. and Chem. 18:1053-1059. DACO: 9.9. |