



# COMMENTS ON PROPOSED REGISTRATION DECISION FOR CYCLOBUTRIFLURAM, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 UNDER PRD 2025-06

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## Introduction

We herein provide comments to PRD 2025-06 concerning Cyclobutrifluram Technical (Active), and the end-use products A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2. The Active is a new conventional ingredient for nematode and fungal disease management, which works on contact and by systemic feeding activity on certain nematodes to disrupt ATP (adenosine triphosphate) production in nematode mitochondria. Cyclobutrifluram is also a systemic and selective fungicide that inhibits spore germination and mycelial growth of certain fungal pathogens.

The proposal is to register the Active and end-use products for use on romaine lettuce and as a soybean seed treatment.

## Background: Appropriate PMRA Approach

The legislative goal under the PCPA is for the Minister of Health/ PMRA to have a 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 or proposed conditions of registration. This goal sets the legislative standard for “acceptable risk” (See Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks and Section 1(2), 4 and 7(6) of the PCPA).

A pest control product (PCP) is defined as either the active ingredient, the end-product, or both. The PMRA, on behalf of the Minister of Health, must apply a scientifically based approach when evaluating the risks of the PCP. A scientifically based approach considers both the toxicity or hazard and the level of exposure to characterize risk ([PMRA Guidance Document, a Framework for Risk Assessment and Risk Management of Pest Control Products](#)).

Because the approach is “scientifically based”, it gathers knowing using the scientific method and is evidence-based. The scientific method develops and then test theories/hypothesis with scientific data and evidence. The method consists of gathering evidence through rigorous repeatable procedures, and the evidence must be empirical, interpretable according to the scientific method, and capable of being verified or falsified through observation and experimentation.

PMRA reflects this approach in its Mission, which is: “To protect the health and environment of Canadians by using modern, evidence-based, scientific approaches to pesticide regulation, in an open and transparent manner”.

## Additional Information Requested

We have requested and are awaiting information from Access to Information. We may have additional comments following our receipt of such information.

## Health Risk Assessment Concerns

### Results of Studies

The results of the health risk assessment were the Active caused liver tumours in mice and thyroid tumours in rats. A mode of action (MOA) was proposed (p.17 PRD), but this MOA and supporting mechanistic studies had the limitation that the application of dose-response for these tumours was not well supported, in that “the concordance of the dose-response relationship for some of the key events was not well supported, and the key event related to clonal expansion leading to altered foci was not investigated”. Despite these shortcomings, PMRA found it was “plausible” that the tumours were forming via a threshold mechanism and that the linear low dose extrapolation (q1\*) approach would be overly conservative. Plausibility is not adequate in a scientifically based approach, and when it comes to the q1\* cancer approach, the requirements for using such an approach set out in the PMRA Framework have been met. The dismissal of linear carcinogenic risk modelling in the face of data limitations with the threshold approach is not justifiable.



With respect to these concerns, PMRA states 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 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.

In addition to the tumours, there were effects on body weight, sexual development and fertility and the lung. These are evidence of toxicity as well.

PMRA did not give due consideration to disruption of the endocrine system. The Active caused thyroid follicular cell hypertrophy, increased the weight of glands, and evidenced tumours, all of which align with disruption of the endocrine system. The application of only a 3× uncertainty factor is not enough, since higher doses may have revealed additional effects.

With respect to reproductive/developmental toxicity, there were concerns. There were treatment related effects in the offspring, and the fact that the same dose saw effects in the parent may not be evidence of quantitative sensitivity of the young, but there was evidence of qualitative sensitivity. In addition, PMRA acknowledged that the rat developmental toxicity study had inadequate dose selection, which means the NOAEL could be artificially high. The efforts to have this reflected in the POD and UF is not appropriate, particularly when data could have been requested to rectify this shortcoming.

There was a finding of reduced fertility in F1 males at the highest dose level, which is the determinative finding. A reference to “historical control data” is available to contextualize this finding, not discount or diminish it, such that these results should be considered an indicator of reproductive toxicity.

### Metabolites

Regarding the major metabolites SYN549104, SYN510275 reached higher systemic concentrations than the parent compound, but acute and genotoxicity testing was limited and conducted only on SYN549104. No subchronic or reproductive toxicity data was put forward, hence the assessments are insufficient.

### Cumulative Risk

Because there is a common mechanism of toxicity, PMRA is required under the Act to conduct a cumulative risk assessment. There are no other considerations to be explored apart from the legal requirement for the assessment, and the determination of the need for a cumulative risk assessment is not permitted when the law requires it.

The assessment acknowledged both SDHI fungicides and TFA (trifluoroacetic acid) as common exposure pathways but performed only qualitative screens. The persistence of TFA in the environment is shown, and its occurrence is widespread. A quantitative cumulative exposure model is required in order to be protective.

### Bystander Risk

Regarding dermal and inhalation exposure, the dermal absorption factors (2–6%) were extrapolated from a single formulation and study, not compound-specific field data. Plus assumptions for re-entry exposure were used, without back data - no measured dislodgeable residue data was provided.



## End-product differences

The hazard assessment was conducted only on the Active, but there are different effects arising between the Active and the end products. The end-products need to be assessed for hazard as well.

## Concerns with the Dietary Risk Assessment

Uncertainties and problems with the dietary risk assessment include the following.

- the PCPA Factor of 10 was not applied, even though the Act requires it. No “reliable scientific data” was provided to reduce the factor. Even the requirements based on PMRA’s own interpretation are not met: the database on developmental/reproductive toxicity was not sufficient, and there were concerns with qualitative sensitivity.
- the consumption data is based on DEEM, which measures what Americans, not Canadians consume.

## Field Trial Data

The field trial data for lettuce and soybean were conducted in, respectively, the US, and the US and Brazil. These regions differ in terms of climate and applications than Canada, rendering the trials inadequate for the Canadian context.

## Environmental Risk Assessment

- The Active breaks down in soil or water in the presence of light and forms major transformation products and one minor. These can move through soil and reach groundwater, and also runoff to reach surface water.
- There is no discussion of the environmental effects or hazards, and as such, the evidence is lacking for an the assessment of risk using a scientifically based approach.
- Several major transformation products (SYN510275, SYN549104, TFA) are highly mobile ( $K_{oc} \leq 10$ ) and persistent, and have the potential to leach into groundwater. The PMRA itself notes concerns with leaching and runoff, but nevertheless considers the risk “acceptable”. This finding was not backed up using an evidenced based approach, which would have used quantitative groundwater modeling based on accurate inputs or field data validation. Environmental risk characterization integrates the exposure (environmental fate and behaviour) and effects (ecotoxicological data) information, as stated in the PMRA Framework. This characterization did not occur.
- Evidence on the fate of the PCP was not adequate. No phototransformation in air study was conducted. There was only limited data on volatilization, adsorption/desorption, and hydrolysis, so the long-range transport potential cannot be understood. The PMRA also relied on modeled estimates rather than empirical evidence, contrary to the scientifically based approach that uses evidence.
- The most sensitive taxa were aquatic invertebrates, yet no refined chronic assessment was conducted—only screening-level risk quotients. Plus transformation products were not assessed for aquatic toxicity, even though some are more persistent and water-soluble than the parent.
- The assessment explicitly defers cumulative analysis of TFA, even though PMRA acknowledges its persistence and occurrence from multiple pesticides. This deferral is not justified, and the PRD cannot be approved until this analysis is



conducted. The lack of integrated modeling of TFA accumulation represents a major scientific gap in long-term environmental risk characterization

## Failure to Assess Use as a Seed Treatment

An assessment of potential harms and risks requires assessment of the interaction of the PCPs with constituents of the seed treatment, and also an assessment of the treatment constituents themselves, since they can cause effects as well. Science shows nanomaterials used in seed treatments can enter the environment and soil systems through seed treatment strategies, and they must therefore be critically assessed and managed. (Shelar A, Nile SH, Singh AV, Rothenstein D, Bill J, Xiao J, Chaskar M, Kai G, Patil R. Recent Advances in Nano-Enabled Seed Treatment Strategies for Sustainable Agriculture: Challenges, Risk Assessment, and Future Perspectives. *Nanomicro Lett.* 2023 Feb 16;15(1):54. doi: 10.1007/s40820-023-01025-5. PMID: 36795339; PMCID: PMC9935810.)

The authors show that “an adverse effect of nanomaterials on soil microbiota can occur when they interact with the soil”, and “Nanoparticles can inhibit critical steps in nutrient recycling such as ammonification, denitrification, nitrogen fixation, phosphate solubilization, and plant growth-promoting activities, all crucial for maintaining soil fertility and the ecosystem”. Also “nitrogen, carbohydrate, and phosphorus cycles are of high environmental importance, and nanomaterials appear to interfere with them”, and “It is well established that nanomaterials considerably impact the soil microbiome, including their abundance, diversity, and essential microbial processes, such as nitrogen fixation, mineralization, and plant growth-promoting activities [190, 191]..190: Patisaul HB. Endocrine disruption by dietary phyto-oestrogens: Impact on dimorphic sexual systems and behaviours. *Proc. Nutri. Soci.* 2017;76(2):130–144. doi: 10.1017/S0029665116000677 191: Khan ST, Adil SF, Shaik MR, Alkathlan HZ, Khan M, et al. Engineered nanomaterials in soil: their impact on soil microbiome and plant health. *Plants.* 2021;11(1):109. doi: 10.3390/plants11010109

It is possible for nanomaterial-based agrochemicals can seep into water bodies and enter the food chain (bioaccumulation). {O.Murali M, Gowtham HG, Singh SB, Shilpa N, Aiyaz M, et al. Fate, bioaccumulation and toxicity of engineered nanomaterials in plants: current challenges and future prospects. *Sci. Total Environ.* 2022;811:152249. doi: 10.1016/j.scitotenv.2021.152249. [DOI] [PubMed] [Google Scholar]

The constituents of the treatment were not set out, and it appears no assessment of them was conducted. At a minimum, field trial data is required that assesses the impacts of seed treatments on soil and ecosystems.

Treated seeds are known to be dusty, but PMRA saw the inhalation exposure during seed treatment or planting was as negligible without providing supporting evidence.

## Value Assessment

The PRD describes the value it will provide growers with a new mode of action to manage nematode infection and fungal diseases on the crops listed on the product label. There was no discussion set out that showed that that infection and disease on these crops is a concern such that there is a need for the PCP. In order to align with two of the ancillary objective set out in the Act s. 4(2), firstly supporting sustainable development so as to meet the needs of the present without harming the ability for future generations to meet their own needs, and secondly to minimize health and environmental risks posed by pest control products and encourage the development and implementation of innovative, sustainable pest management strategies by appropriate measure, it is incumbent on PMRA to be responding to a proven need in order to approve a PCP. This requirement is more heightened because the PCP is new, and so the effects cannot be fully known at this time but only over time.



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.

In addition, PMRA must demonstrate that an evaluation under at least these 3 criteria was conducted before accepting the new use pattern on hops. On this point:

- (a) efficacy: - efficacy and yield data primarily from U.S. and Brazilian trials, with no published or peer-reviewed Canadian field performance. Environmental and climatic differences could materially affect nematode suppression and residue behaviour.
- (b) Health, safety, environmental, social and economic impacts: the claims of “economic advantage” or “fumigant replacement” were supported by cost-benefit, yield-gain, or sustainability metrics or information. Value requires demonstration of tangible benefits, but these have not been shown.

## Risk Reduction Measures

As indicated, if the assessment finds a health or environmental risk arises from a PCP, the mitigation strategy/ risk reduction measure must remove the potential of the risk to cause harm, in order to align with the “no harm” standard which is the legislated goal under the PCPA.

The key risk reduction measures for the environment were the following, and we have the itemized comments/ concerns:

- Precautionary label statements to inform users of the toxicity of cyclobutirfluram to aquatic organisms.  
- Comment: Information is not mitigation.
- Best management practice label statements to instruct users to avoid using the end-use products in areas more conducive to leaching to groundwater (in other words, where the soils are permeable and particularly where the water table is shallow).  
- Comments: detailed standards and directions for ascertaining are required to be instructive and enforceable need to be set out
- Best management practice label statements to reduce runoff entering sensitive aquatic habitats  
- Comment: “best management” means “try your best”. This does not ensure risk mitigation to the “no harm” standard.
- Best management practice label statements to inform users to clean up spilled seed when cyclobutirfluram is used as a seed treatment.  
- Comment: “best management” means “try your best”. This does not ensure risk mitigation to the “no harm” standard.



## Conclusion

The scientific evaluation did not adequately assess the risk arising to human health and the environment from the Active and its end-products, or showed that they pose risks to human health and the environment. Mitigation by labels does not guarantee the “no harm” standard. The value assessment was lacking in that there was no need for the PCP provided, and also the 3 criteria for value set out in the Act were not established.

Safe Food Matters urges PMRA to not register this Active or its end-products, given these problems with the risk and value assessment.