



COMMENTS ON PROPOSED MAXIMUM RESIDUE LIMIT PMRL2025-19

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I. INTRODUCTION AND EXECUTIVE SUMMARY

These comments address procedural violations and scientific deficiencies in the Pest Management Regulatory Agency's (PMRA's) assessment of cyclobutrifluram, a new active ingredient proposed for registration as a nematicide and fungicide. The procedural violations are concerning and deny the right to informed comment.. The scientific deficiencies span multiple domains including carcinogenicity determination, PFAS classification and cumulative risk assessment, Toxic Substances Management Policy (TSMP) compliance, endocrine disruption evaluation, and the novel mechanism of succinate dehydrogenase (SDH) inhibition.

These PMRL comments also incorporate the comments we made on the Proposed Registration Decision (PRD), submitted October 27, since both consider use of the pesticide in Canada.

A. Procedural Violations

PMRA issued Registration Decision RD2025-12 on December 19, 2025—before the consultation period for Proposed Maximum Residue Limit PMRL2025-19 was scheduled to end on January 5, 2026. This timeline reveals that PMRA had already decided to register cyclobutrifluram before the public consultation period on the PMRL had concluded. Moreover, this decision was made while an Access to Information (ATI) request (A-2025-001015, acknowledged October 30, 2025) for the underlying scientific data supporting the MRLs and risk assessments was still being processed.

This sequence of events denied the Canadian public the opportunity for meaningful participation in the decision-making process and violated fundamental principles of administrative law including:

- Section 28(1) of the Pest Control Products Act, which requires consultation "before making a decision on an application"
- The duty of procedural fairness requiring a genuine opportunity to be heard before decisions are made
- The principles of natural justice established in Baker v. Canada requiring meaningful participation
- The legitimate expectations created by announcing a consultation period

The timeline of events is damning:

1. September 12, 2025: PMRL2025-19 published announcing consultation period ending November 26, 2025
2. October 28, 2025: ATI request A-2025-001015 submitted requesting fundamental data underlying MRLs and risk assessments
3. October 30, 2025: ATI request formally acknowledged by PMRA Access to Information and Privacy Division
4. December 19, 2025: RD2025-12 issued granting registration (BEFORE consultation period was to end)
5. January 5, 2026: Consultation period for PMRL2025-19 ends

This timeline demonstrates that PMRA made its decision before:

- The PMRL consultation period ended
- Public comments were due



- ATI-requested data was provided to enable informed comment

B. PFAS Classification

Cyclobutrifluram meets the Organisation for Economic Co-operation and Development (OECD) definition of per- and polyfluoroalkyl substances (PFAS): it contains a fully fluorinated methyl group (CF₃—trifluoromethyl) attached to the pyridine ring structure. This chemical classification as PFAS is not contested by any party who understands the chemical structure. The OECD definition, articulated by Wang et al. (2021) and adopted by environmental regulators globally, defines PFAS as substances containing "at least one fully fluorinated methyl (CF₃–) or methylene (–CF₂–) carbon atom."

Despite this clear classification, PMRA's assessment documents (PRD2025-06, PMRL2025-19, RD2025-12) contain no acknowledgment that cyclobutrifluram is a PFAS compound. This omission is not merely semantic—it represents a failure to assess aggregate risk as required by law. The Pest Control Products Act (PCPA) mandates assessment of aggregate exposure: total exposure from all sources including food, water, and residential uses.

For PFAS, aggregate assessment is particularly critical because:

- Background PFAS exposure is ubiquitous—virtually all Canadians have detectable PFAS in their blood serum
- PFAS accumulate over time due to their environmental persistence and resistance to metabolic degradation
- Multiple PFAS sources contribute to total body burden
- Recent EPA health advisories establish that extraordinarily low levels (0.004 ppt for PFOA, 0.02 ppt for PFOS) present health concerns
- PFAS effects may be cumulative across the class

By failing to conduct an aggregate PFAS risk assessment, PMRA violated the fundamental regulatory principle that total exposure must be considered when determining safety. Treating cyclobutrifluram as if Canadians have no other PFAS exposure ignores reality and fails to protect public health.

C. Carcinogenicity Determination

PMRA classified cyclobutrifluram as "not likely to be carcinogenic to humans" despite clear evidence of carcinogenic potential in both rats and mice. This classification contradicts the weight of evidence and appears designed to avoid regulatory consequences rather than reflect scientific reality.

The rat carcinogenicity study showed statistically significant trends of increasing thyroid follicular cell tumors with increasing dose in both sexes:

Males:

- Carcinomas: $p = 0.0433$ (statistically significant trend test)
- Mid-dose adenomas, carcinomas, and combined: all $p = 0.0632$ vs controls (4/50 vs 0/50)



Females:

- Adenomas: $p = 0.01495$ (highly statistically significant)
- Combined adenomas/carcinomas: $p = 0.01874$ (highly statistically significant)

The mouse carcinogenicity study showed highly statistically significant trends of hepatocellular carcinomas in males ($p = 0.0139$), with high-dose incidence exceeding historical control ranges.

EPA's 2005 Guidelines for Carcinogen Risk Assessment, which guide the PMRA, explicitly state (page 2-19) that statistically significant results in either trend tests or pairwise comparison tests are sufficient to reject chance as an explanation for tumor increases. The 9th Circuit Court of Appeals in the US confirms this. The cyclobutylfluram studies show significant trends in rats (both sexes, same organ) and mice, meeting EPA's criteria for establishing carcinogenic hazard.

Moreover, PMRA acknowledges throughout PRD2025-06 that thyroid effects (hypertrophy, increased thyroid weight, hyperplasia) were observed across the entire toxicology database (28-day, 90-day, reproduction studies) and that "the thyroid was identified as the most sensitive endpoint." Despite acknowledging thyroid toxicity across multiple studies, PMRA denies that the thyroid tumors in the carcinogenicity study are treatment-related. This position is internally inconsistent and scientifically indefensible.

Critically, PMRA concedes that both the rat and mouse studies failed to employ adequately high doses:

- Rat study: "the rats of both sexes could have tolerated higher doses"
- Mouse study: "the study could have tested higher doses" with "no treatment-related adverse effects" at the highest dose tested

The purpose of using the maximum tolerated dose (MTD) is "to provide the maximum ability to detect treatment-related carcinogenic effects" (EPA 2005, p. 2-15). By failing to use adequate doses, these studies failed to provide a sufficiently rigorous test of carcinogenic potential. Since both studies showed statistically significant dose-response trends, logic dictates that higher doses would have produced more tumors, likely achieving statistical significance in pairwise comparisons as well.

D. TSMP Track 1 Violations

The Toxic Substances Management Policy (TSMP) establishes regulatory criteria for persistent, bioaccumulative substances. Track 1 substances—those meeting the highest thresholds for persistence and bioaccumulation—are subject to virtual elimination from the environment. PMRA's TSMP assessment for cyclobutylfluram contains fundamental errors that result in the failure to list the major transformation product SYN510275 as a Track 1 substance.

Data presented in PRD2025-06, Appendix A, Table 14 (page 32) shows that SYN510275 has DT_{50} values in aerobic soil of:

- 1230 days using first-order kinetics



- 823 days using single first-order (SFO) kinetics
- 552 days using double first-order in parallel (DFOP) kinetics

Under PMRA's guidance document DIR99-03, the appropriate persistence metric for transformation products is the representative half-life ($T_{1/2,rep}$), defined as "the time required to reach 50% of the maximum concentration formed." This metric accounts for the fact that transformation products must first be formed before they can degrade.

Using first-order kinetics (which PMRA typically prefers for conservatism), SYN510275 has:
 $T_{1/2,rep} = 1230 \text{ days} = 3.37 \text{ years}$

The TSMP Track 1 criterion for persistence in soil is: half-life ≥ 182 days (0.5 years)

SYN510275 exceeds the Track 1 criterion by a factor of 6.7. Even using the most optimistic DFOP kinetic model (552 days = 1.51 years), SYN510275 still exceeds the Track 1 criterion by a factor of 3.

Despite this clear exceedance, PMRA concludes that SYN510275 does NOT meet Track 1 criteria, stating: "The half-life in soil of transformation products SYN510275... (199 days)... did not meet TSMP Track 1 criteria for persistence" (PRD2025-06, Appendix A, page 33).

The value "199 days" appears nowhere in the actual data table. This represents either:

1. Use of an incorrect half-life value not supported by the data, or
2. Use of a degradation DT_{50} rather than the formation-corrected $T_{1/2,rep}$ required by DIR99-03

Either interpretation reveals errors in PMRA's TSMP assessment. The correct application of TSMP would require Track 1 listing of SYN510275, which would in turn trigger additional scrutiny of whether cyclobutrifluram should be approved at all given that it generates a Track 1 substance.

E. SDH Inhibition Mechanism

Cyclobutrifluram kills target organisms (fungi and nematodes) by inhibiting succinate dehydrogenase (SDH), also known as Complex II of the mitochondrial respiratory chain. SDH catalyzes the oxidation of succinate to fumarate in the citric acid cycle while simultaneously reducing ubiquinone to ubiquinol in the electron transport chain. This enzyme is highly conserved across all aerobic organisms, including mammals and humans.

Over the past quarter-century, research has established the link between SDH inhibition, succinate accumulation, and carcinogenesis:

1. Germline mutations in SDH subunit genes (SDHA, SDHB, SDHC, SDHD) cause hereditary cancer syndromes including paragangliomas, pheochromocytomas, gastrointestinal stromal tumors (GISTs), renal cell carcinomas, and thyroid tumors (Rasheed & Tarjan 2018).



2. When SDH is inhibited, its substrate (succinate) accumulates to abnormally high levels. Elevated succinate has multiple pro-tumorigenic effects (Selak et al. 2005, Zhao et al. 2017):

- Inhibits α -ketoglutarate-dependent dioxygenases including HIF- α prolyl hydroxylases
- HIF- α stabilization leads to expression of genes promoting angiogenesis, glycolysis, and metastasis
- Succinate acts as an "oncometabolite"—a metabolite that directly contributes to tumorigenesis
- Causes epigenetic changes through inhibition of histone and DNA demethylases

3. In vitro studies demonstrate that SDH-inhibiting fungicides inhibit mammalian SDH enzymes. Bénit et al. (2019) showed that eight SDHI fungicides inhibit SDH in human cells, earthworms, and honeybees with similar potency, demonstrating lack of species selectivity.

4. Bouillaud (2023) reviews concerns that environmental exposure to SDH inhibitors could contribute to cancer and metabolic disorders through chronic, low-level inhibition of the enzyme.

Despite this extensive mechanistic literature directly relevant to cyclobutrifluram's mode of pesticidal action, PMRA states: "Although adverse effects on the thyroid were noted across the database, a specific mode of action has not been elucidated" (PRD2025-06, page 19).

This statement is demonstrably false. The mode of action is SDH inhibition. The relevant scientific question—which PMRA has not adequately addressed—is whether chronic dietary and environmental exposure to cyclobutrifluram at the levels permitted by PMRA results in sufficient SDH inhibition and succinate accumulation to trigger the carcinogenic cascade documented in the scientific literature.

PMRA's failure to even consider this mechanism represents a gap in the assessment of both individual risk from cyclobutrifluram and cumulative risk from the entire class of SDH-inhibiting pesticides.



II. **PROCEDURAL VIOLATIONS AND DENIAL OF NATURAL JUSTICE

A. Premature Issuance of Registration Decision Before Consultation Ended

The most egregious procedural violation in PMRA's handling of cyclobutryfluram is the issuance of Registration Decision RD2025-12 on December 19, 2025, before the consultation period for PMRL2025-19 ended on November 26, 2025. This timeline is not a minor administrative irregularity—it reveals that PMRA made its registration decision before the public consultation period concluded and before considering comments that were still being prepared and would be submitted by the November 26 deadline.

The Timeline of Events

September 12, 2025: PMRA published both PRD2025-06 (Proposed Registration Decision) and PMRL2025-19 (Proposed Maximum Residue Limit). The first page of PMRL2025-19 states:

"Under the authority of the Pest Control Products Act, Health Canada's Pest Management Regulatory Agency (PMRA) is proposing acceptability of the uses requested under the above-noted applications to register in Canada the technical grade cyclobutryfluram..."

The PMRL document announces a 75-day consultation period ending November 26, 2025, and invites public comments:

"Health Canada invites the public to submit written comments on the proposed MRLs for cyclobutryfluram up to 75 days from the date of publication of this document (by 26 November 2025)."

October 28, 2025: An Access to Information request (A-2025-001015) was submitted to PMRA requesting the underlying scientific data supporting the proposed MRLs and risk assessments, specifically:

"In relation to the consultations being conducted by PMRA 2025-06 and 2025-07, please provide me with the following: - any integrated assessments - dietary risk assessments, if not in the integrated assessment - any evaluations of value - the details of the calculations of the maximum residue limits, including any OECD calculator output pages. - the studies used to calculate the reference doses - the field trial studies used to establish the MRLs for the proposed uses."

October 30, 2025: PMRA's Access to Information and Privacy Division acknowledged receipt of the ATI request in a letter signed by Gabrielle Chasse, ATIP Analyst. The acknowledgment letter confirms:

"Your request and application fee were received by our office on October 28, 2025."

The letter provides contact information and notes that Health Canada is "committed to assist you with your



request and will ensure that every reasonable effort is made to help you receive a complete, accurate and timely response."

November 27, 2025: the Director General and Chief Registrar of PMRA indicated that it would not wait for submission of comments based upon review of the information in the ATI Request:

“In your recent comments provided for various consultation decision documents for pre-market proposed registrations (PRDs), you mentioned wanting to possibly amend or add to your comments after receiving additional information.

Please note that when you submit your comments for public consultations relating to pre-market registration decisions, they are considered final by Health Canada’s Pest Management Regulatory Agency (PMRA) when the deadline for comments is reached. Pursuant to subsection 28(3) of the *Pest Control Products Act* (PCPA), the following information is made available to the public during a consultation:

- a summary of any reports of the evaluation of the health and environmental risks and the value of the pest control product prepared or considered by the Minister; and
- the proposed decision and the reasons for it.

Requests under the *Access to Information Act* (ATIA) are handled through a separate process and do not affect PMRA’s decision making under the PCPA. The PMRA conducts its evaluations and makes regulatory decisions independently, and any information obtained through ATIA will not alter the established timelines or review process.

November 27, 2025: in reply, the president of Safe Food Matters wrote:

“The information I am seeking is basically the information outlined in 42 (2)(f) of the Act, " (f) any reports of the evaluation of the health and environmental risks and the value of registered pest control products prepared by the Minister". These evaluation reports are to be made available to the public in as convenient a manner as practicable, pursuant to 42(5) and (6).

It seems to me that for comments to be meaningful, and allow for true public participation in the assessment process (as required), that the evaluation reports need to be provided. This also is required by transparency principles.

So Safe Food Matters Inc. intends to provide additional comments, as stated in SFMs submissions, based upon the receipt of the requested information. We seek to truly engage in the public participation and consultation process. If PMRA does not accept them, it will be disappointing and obviously thwart true public participation.”

December 19, 2025: PMRA issued Registration Decision RD2025-12, stating on page 1:

"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..."

The decision document includes 22 pages of responses to comments received during the consultation period. However, the date of the decision (December 19) is before the PMRL consultation period is scheduled to end for Safe Food Matters Inc. (January 5, 2026).

December 22, 2025: SFM asked for the confidential test data for the registration decision, and provided the Form 7000 to outline the data. The affidavit was provided January 5, 2026.

Analysis of the Timeline

This timeline reveals several critical facts:

1. PMRA decided to register cyclobutrifluram before the PMRL consultation period ended. The decision date of December 19 precedes the end of the PMRL consultation period.
2. PMRA decided to register cyclobutrifluram while an ATI request for the underlying data was still being processed. The ATI request, submitted October 28 and acknowledged October 30, sought the actual scientific studies and calculations that would enable informed public comment on the pesticide. By deciding on December 19 (only weeks after the ATI request), PMRA ensured that comments would be submitted without access to the detailed data.
3. The consultation on the PMRL is not genuine. Safe Food Matters will not receive confidential test data to which it is entitled relating to the risk and value assessments prior to the deadline for submitting comments on the PMRL.

B. Denial of Access to Critical Test Data via ATI Request

The Access to Information request A-2025-001015 sought the fundamental scientific data underlying PMRA's proposed registration decision and MRLs. This data is essential for informed public comment yet was not provided in the consultation documents.

What the ATI Request Sought

The ATI request specifically asked for certain data including:

1. Integrated assessments: These are the comprehensive documents that synthesize all toxicology, residue chemistry, environmental fate, and ecological effects data into the overall risk characterization. Without these documents, the public cannot see how PMRA weighted different pieces of evidence or resolved conflicting data.



2. Dietary risk assessments: While PRD2025-06 summarizes the dietary risk assessment conclusions, it does not provide the detailed calculations, exposure scenarios, or sensitivity analyses that would allow independent verification or critique.

3. Evaluations of value: The value assessment is often cursory in PMRA decision documents. The detailed value evaluation would include efficacy data, economic analysis, and consideration of alternatives.

4.. Studies used to calculate reference doses: PRD2025-06 identifies the studies that were used as the basis for the acceptable daily intake (ADI) and acute reference dose (ARfD), but the actual study reports are not provided. These reports contain the detailed dose-response data, statistical analyses, and pathology findings that are essential for evaluating whether PMRA selected appropriate points of departure and applied appropriate uncertainty factors.

Why This Data Is Essential for Informed Comment

The data requested via ATI is not merely supplementary information—it is the foundation of PMRA's assessment. The consultation documents (PRD2025-06 and PMRL2025-19) are executive summaries that present PMRA's conclusions without providing the underlying evidence or detailed methodologies.

To provide informed comments on PMRA's proposed MRLs, the public needs to:

1. Review the actual toxicology study reports to assess whether PMRA correctly identified the critical effects and points of departure
2. Evaluate the dietary risk assessment calculations to verify that appropriate consumption data, residue values, and refinements were used
3. Assess whether the value evaluation was adequate

Without access to this underlying data, public comments can only challenge PMRA's conclusions in general terms without being able to point to specific errors in data interpretation, calculation, or application of guidance documents.

The ATI Request Was Not Processed Before the Decision Was Made

By making the registration decision on December 19—only weeks days after the ATI request was acknowledged—PMRA ensured that the requested data would not be available to inform public comments. Under the Access to Information Act, PMRA has 30 days to respond to ATI requests, with possible extensions. The normal processing time for ATI requests involving scientific studies and technical documents often far exceeds 90 days.

PMRA made its registration decision knowing that:

1. An ATI request for the underlying data had been submitted



2. The requester sought this data specifically to inform comments on the PMRL consultation
3. The data would not be processed and provided before the PMRL consultation period ended
4. Comments on the PMRL would therefore be submitted without access to the detailed supporting evidence

This sequence of events effectively denied the opportunity for fully informed public participation. It is the equivalent of asking for comments on a mathematical proof while refusing to show the actual calculations, then making a decision before anyone can obtain the calculations through other means.

C. Violation of Pest Control Products Act Section 9

Section 9 of the Pest Control Products Act requires that MRLs be established at the time of making a registration decision:

"9 When making a decision regarding the registration of a pest control product, the Minister shall, if necessary, specify any maximum residue limits for the product or for its components or derivatives that the Minister considers appropriate in the circumstances."

The PRD in the maximum residue limits section set out the MRLs that are proposed in the PMRL, but PMRA subjected the PMRL a separate process, in violation of section 9.

D. Baker v. Canada and Procedural Fairness Requirements

The Supreme Court of Canada's decision in *Baker v. Canada (Minister of Citizenship and Immigration)*, [1999] 2 S.C.R. 817, established important principles about the duty of procedural fairness in administrative decision-making. While *Baker* involved an immigration decision rather than pesticide registration, the Court's analysis of procedural fairness requirements applies broadly to administrative decisions.

Baker identified five factors for determining the content of the duty of fairness:

1. The nature of the decision and the process followed in making it
2. The nature of the statutory scheme and the terms of the statute
3. The importance of the decision to the affected individuals
4. The legitimate expectations of the person challenging the decision
5. The choices of procedure made by the agency itself

Applying *Baker* to Cyclobutrifluram

Factor 1 - Nature of the Decision: Pesticide registration decisions have significant public health and environmental consequences. They authorize the intentional release of biologically active substances into the environment and their presence in food. The nature of this decision calls for a high degree of procedural fairness.

Factor 2 - Statutory Scheme: The Pest Control Products Act explicitly requires consultation before decisions



(Section 28(1)). Parliament clearly intended for pesticide decisions to be made only after considering input from diverse stakeholders. This weighs heavily in favor of robust procedural fairness.

Factor 3 - Importance to Affected Individuals: Pesticide registration decisions affect:

- Farmers and agricultural workers (occupational exposure)
- Rural residents (drift, runoff exposure)
- Consumers (dietary exposure)
- Sensitive populations (children, pregnant women)
- Indigenous communities (traditional foods, harvesting areas)

The importance of these decisions to health and livelihoods demands meaningful procedural fairness.

Factor 4 - Legitimate Expectations: By announcing a 75-day consultation period ending November 26, 2025, PMRA created a legitimate expectation that:

- The PMRL consultation period would run its full course before PMRA made the registration decision
- Comments submitted by November 26 would be considered for the registration given the PMRL should be considered as part of the registration, per s. 9
- The registration decision would be made after considering all comments

PMRA's decision to register cyclobutylfluram on December 19—before the PMRL consultation ended—violated these legitimate expectations.

Factor 5 - Agency's Choice of Procedure: PMRA chose to provide a 75-day consultation period for the PMRL. Having chosen a 75 day procedure, PMRA was obligated to follow it before making a registration decision based upon s. 9.

The Duty of Fairness Includes Meaningful Opportunity

Baker emphasizes that procedural fairness requires not just theoretical opportunity but meaningful opportunity to participate. The Court stated (paragraph 30):

"The values underlying the duty of procedural fairness relate to the principle that the individual or individuals affected should have the opportunity to present their case fully and fairly, and have decisions affecting their rights, interests, or privileges made using a fair, impartial, and open process, appropriate to the statutory, institutional, and social context of the decision."

A "meaningful" opportunity means:

- Sufficient time to prepare comments
- Access to information necessary to provide informed comments
- Assurance that comments will be considered before the decision is made



PMRA's actions violated all three aspects of meaningful opportunity:

1. Time: While 75 days was provided, PMRA made its registration decision 7 days before the public PMRL period ended
2. Information: ATI-requested data necessary for informed comment was not provided
3. Consideration: The registration decision preceded the PMRL consultation period end, ensuring later PMRL comments, such as these, could not be considered.

These actions are all the more unfair in that PMRA on January 5, 2026, in response to my request for an extension to providing comments to the PMRL in order to review the CTD for the pesticide, has referred me to the “full report of already available information of all of the other scientific components of the risk assessment that appears in [PRD2025-06](#), Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, that could help to complement your review of the PMRL data.” And said that no extension would be granted.

E. Legal Consequences and Required Remedies

The procedural violations described above render Registration Decision RD2025-12 invalid as a matter of administrative law. Decisions made in violation of procedural fairness requirements are subject to being set aside by courts on judicial review.

In *Nicholson v. Haldimand-Norfolk Regional Police Commissioners*, [1979] 1 S.C.R. 311, the Supreme Court established that decisions made in breach of procedural fairness may be void. The Court stated:

"A purely disciplinary proceeding, of which there are many in the administrative process, involves no deprivation of rights held; rather, it involves the imposition of a penalty or sanction in accordance with the terms of a statute or contract. It is nonetheless essential in such cases that the tribunal act fairly, in good faith, without bias, and in a judicial temper, and give to the person against whom the complaint is made the opportunity of adequately stating his case."

While cyclobutrifluram registration is not a disciplinary proceeding, the principle applies: administrative decisions must be made through fair processes, and where fairness is denied, the decision may be set aside.

Required Remedies

To remedy the procedural violations identified in these comments, the following actions are required:

1. Immediate Rescission of Registration Decision RD2025-12

The registration decision issued December 19, 2025 must be rescinded because it was made:

- Before the PMRL consultation period ended
- Without consideration of comments that being submitted on the PMRL, although the MRL decision is to be made at the same time as the registration decision per s. 9;



- While the ATI request for underlying data was still being processed
- In violation of Section 9 of the Pest Control Products Act
- In breach of the duty of procedural fairness

2. Full Disclosure of ATI-Requested Data

All data requested in ATI request A-2025-001015 must be provided.

3. Reopening of Consultation Period

After providing the ATI-requested data, PMRA must reopen a genuine consultation period of at least 75 days.

This consultation must:

- Not begin until all requested data has been provided
- Allow sufficient time for thorough review of technical documents
- Provide clear assurance that the consultation will conclude before any decision is made
- Include mechanisms for clarifying questions about the data

4. Consideration of All Comments Before Decision

PMRA must:

- Review all comments received during the reopened consultation
- Provide written responses to substantive comments
- Explain how comments influenced (or why they did not influence) the decision
- Make no decision until after the consultation period concludes



III. PFAS CLASSIFICATION AND AGGREGATE RISK ASSESSMENT FAILURES

A. Cyclobutrifluram Meets OECD Definition of PFAS

Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic chemicals characterized by the presence of multiple carbon-fluorine bonds. The carbon-fluorine bond is one of the strongest bonds in organic chemistry, giving PFAS their characteristic persistence in the environment and resistance to degradation. This persistence has led to PFAS being termed "forever chemicals."

The OECD Definition

In 2021, the Organisation for Economic Co-operation and Development (OECD) convened expert working groups to develop a comprehensive definition of PFAS. Wang et al. (2021) published the resulting definition in *Environmental Science & Technology*:

"Per- and polyfluoroalkyl substances (PFASs) are defined as fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), that is, with a few noted exceptions, any chemical with at least a perfluorinated methyl group ($-CF_3$) or a perfluorinated methylene group ($-CF_2-$)."

This definition has been adopted by regulatory agencies worldwide as the basis for identifying and regulating PFAS. The definition is intentionally broad to capture the full universe of substances that share the key characteristics of persistence and potential for bioaccumulation.

Cyclobutrifluram's Chemical Structure

Cyclobutrifluram has the chemical formula $C_{16}H_{11}Cl_2F_3N_2O$ and the IUPAC name: rel-N-[(1R,2R)-2-(2,4-dichlorophenyl)cyclobutyl]-2-(trifluoromethyl)-3-pyridinecarboxamide

The key structural feature for PFAS classification is the trifluoromethyl group ($-CF_3$) attached to the 2-position of the pyridine ring. This $-CF_3$ group is a fully fluorinated methyl group: a carbon atom bonded to three fluorine atoms with no hydrogen, chlorine, bromine, or iodine atoms attached.

According to the OECD definition, the presence of this $-CF_3$ group makes cyclobutrifluram unambiguously a PFAS compound. This is not a matter of interpretation or scientific debate—it is a straightforward application of the internationally accepted definition to the known chemical structure.

Implications of PFAS Classification

Classification as a PFAS has several important regulatory implications:



1. Environmental Persistence: The C-F bonds in the trifluoromethyl group are extremely strong (bond dissociation energy ~116 kcal/mol) and highly resistant to environmental degradation. Unlike many pesticide active ingredients that degrade relatively quickly, PFAS structures persist for extended periods.
2. Bioaccumulation Potential: Many PFAS have been shown to bioaccumulate in organisms and biomagnify through food chains. While cyclobutrifluram's specific bioaccumulation has not been extensively studied, the presence of the $-CF_3$ group raises concerns.
3. Aggregate Exposure Requirements: Regulatory frameworks including the US Food Quality Protection Act recognize that when multiple chemicals share common features and mechanisms of toxicity, cumulative assessment is required. For PFAS, the common feature is environmental persistence and the common concern is aggregate exposure from multiple sources.
4. Transformation Products: PFAS pesticides often degrade to other PFAS transformation products. For cyclobutrifluram, one major transformation product is trifluoroacetic acid (TFA, CF_3COOH), itself a highly persistent PFAS that has been detected globally.

PMRA's Failure to Acknowledge PFAS Classification

Remarkably, none of PMRA's assessment documents (PRD2025-06, PMRL2025-19, or RD2025-12) acknowledge that cyclobutrifluram is a PFAS compound. This omission cannot be attributed to oversight—the chemical structure containing a $-CF_3$ group is clearly shown in the documents, and the OECD PFAS definition has been widely publicized since 2021.

The failure to acknowledge PFAS classification has cascading consequences for the risk assessment:

- No aggregate PFAS exposure assessment was conducted
- No consideration of additive effects with other PFAS in food and water
- No evaluation of whether cyclobutrifluram should be approved given global PFAS contamination concerns
- No assessment of long-term accumulation in Canadian soils and waters

By treating cyclobutrifluram as an ordinary pesticide rather than a PFAS, PMRA failed to apply the appropriate regulatory framework for this class of persistent substances.

B. Legal Requirement for Aggregate PFAS Risk Assessment

The PCPA requires a consideration of “aggregate exposure”: total exposure from all sources. For pesticides, aggregate exposure includes:

- Dietary exposure (food and drinking water)
- Residential exposure (home and garden use)
- Non-occupational environmental exposure (drift, etc.)



For PFAS, aggregate exposure takes on special significance because background exposure is ubiquitous.

Ubiquitous Background PFAS Exposure

Multiple studies have documented widespread PFAS contamination and human exposure:

1. **Biomonitoring Studies:** The US Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES) has detected PFAS in the blood serum of 97-99% of Americans (CDC 2015). Canadian biomonitoring studies show similar prevalence.
2. **Drinking Water:** PFAS have been detected in drinking water supplies across North America. The US EPA's third Unregulated Contaminant Monitoring Rule (UCMR3) detected PFAS in public water supplies serving over 6 million Americans (Hu et al. 2016).
3. **Food:** PFAS contamination of food occurs through:
 - Pesticide residues (like cyclobutylfluram)
 - Food contact materials (packaging containing PFAS)
 - Biosolids application to agricultural land
 - Irrigation with PFAS-contaminated water
 - Uptake from contaminated soil
4. **Consumer Products:** PFAS are used in numerous consumer products including:
 - Non-stick cookware
 - Water-resistant clothing and textiles
 - Stain-resistant carpets and upholstery
 - Food packaging (microwave popcorn bags, fast food wrappers)
 - Cosmetics and personal care products

The result is that virtually all Canadians have existing PFAS body burden before any exposure to cyclobutylfluram occurs.

EPA Health Advisories Demonstrate Low Effect Thresholds

In June 2022, EPA issued updated drinking water health advisories for PFOA and PFOS:

- PFOA: 0.004 parts per trillion (ppt) interim health advisory
- PFOS: 0.02 parts per trillion (ppt) interim health advisory

These extraordinarily low values (measured in parts per trillion rather than the parts per billion or parts per million typical for pesticide residues) were based on:



- Effects on immune function
- Effects on thyroid function
- Liver effects
- Developmental effects
- Cancer (for PFOA)

The advisories recognize that:

1. Very low levels of PFAS exposure are associated with adverse health effects
2. PFAS accumulate in the body over time
3. Effects are cumulative across the lifetime
4. There may be no safe threshold for some PFAS effects
5. Sensitive populations (fetuses, infants, children) face greater risks

PMRA's Failure to Conduct Aggregate PFAS Assessment

Despite the clear requirement for aggregate exposure assessment and the well-documented ubiquity of PFAS exposure, PMRA assessed cyclobutrifluram in isolation. The dietary risk assessment calculated exposure to cyclobutrifluram as if this were the only PFAS Canadians encounter.

PMRA's approach violates the fundamental principle that risk assessment must consider total exposure, not just exposure from the pesticide under review. For PFAS, this principle is particularly important because:

1. Background exposure is non-zero and likely significant
2. Multiple PFAS sources contribute to total burden
3. Effects accumulate over lifetime exposure
4. Even small incremental exposures may matter

By registering cyclobutrifluram without an aggregate PFAS risk assessment, PMRA is adding to Canadians' PFAS burden without determining whether the cumulative exposure is safe. This approach fails to protect public health and violates the spirit of aggregate exposure assessment requirements.

C. Transformation to Trifluoroacetic Acid (TFA)

Cyclobutrifluram degrades in the environment to form trifluoroacetic acid (TFA, CF_3COOH), a highly persistent PFAS that has emerged as a global environmental contaminant. TFA is the terminal degradation product of many fluorinated pesticides and industrial chemicals, and its accumulation in the environment represents a long-term legacy of PFAS use.

TFA Formation from Cyclobutrifluram

PRD2025-06 Appendix A (Table 14, page 32) shows that TFA is formed as a transformation product in aerobic soil metabolism studies, reaching 10.6% of applied radioactivity (AR) after extended incubation. While 10.6%



may seem modest, several factors make this concerning:

1. TFA is the terminal degradation product—it does not degrade further. Once formed, TFA persists indefinitely in the environment.
2. With repeated annual applications of cyclobutrifluram, TFA will accumulate year after year. After 10 years of annual applications, the cumulative TFA could exceed 100% of the annual cyclobutrifluram application rate.
3. TFA is highly mobile in soil and water due to its small molecular size and ionic character. It readily leaches to groundwater and moves with water flow.
4. TFA volatilizes and participates in atmospheric transport, leading to global distribution including remote regions.

Global Distribution of TFA

Research over the past two decades has documented widespread TFA contamination:

European Studies: TFA has been detected in European precipitation, surface waters, and groundwater at concentrations ranging from nanograms to micrograms per liter. Boutonnet et al. (1999) detected TFA in European rainwater at concentrations up to 370 ng/L.

North American Studies: Jordan and Frank (1999) detected TFA in the Great Lakes and attributed it to atmospheric deposition. Scott et al. (2000) found TFA in rainwater across the United States.

Arctic and Remote Regions: Perhaps most concerning, TFA has been detected in Arctic precipitation and ice cores, demonstrating long-range atmospheric transport to regions far from sources (Young et al. 2007). This global distribution mirrors the pattern seen with other persistent PFAS like PFOS and PFOA.

Agricultural Soils: Studies in Europe have found elevated TFA concentrations in agricultural soils treated with fluorinated pesticides. Minten et al. (2001) detected TFA accumulation in German agricultural soils.

Drinking Water: TFA has been detected in drinking water supplies in multiple countries. Its presence in finished drinking water indicates that conventional water treatment does not remove TFA.

Sources of TFA

TFA enters the environment from multiple sources:

1. Fluorinated Pesticides: Multiple pesticide active ingredients degrade to TFA including:
 - Flufenacet (registered in Canada)



- Fluridone (registered in Canada)
- Fludioxonil (registered in Canada)
- Trifluralin (registered in Canada)
- Cyclobutrifluram (proposed for registration)

2. Industrial Chemicals: Hydrofluorocarbons (HFCs) used as refrigerants and hydrochlorofluorocarbons (HCFCs) used in foam blowing degrade in the atmosphere to form TFA.

3. Fluorinated Polymers: Some fluorinated polymers used in coatings and surface treatments can degrade to TFA.

The multiplicity of TFA sources means that environmental concentrations represent cumulative inputs from all these sources, not just pesticides. However, pesticidal sources represent a significant and increasing contribution.

PMRA's Reliance on Outdated 2014 EFSA Assessment

PMRA addresses TFA briefly in PRD2025-06 (page 28), stating:

"For TFA... the qualitative risk assessment for TFA considered the following:

- The DEA for cyclobutrifluram: The contribution of TFA to the cyclobutrifluram DEA was low – 1% of the ADI and <0.04% of the ARfD of cyclobutrifluram.
- 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."

This reliance on a decade-old assessment is inadequate for multiple reasons:

1. The 2014 EFSA Assessment Predates Recognition of TFA as Global Contaminant

The EFSA assessment of TFA in the context of saflufenacil registration (EFSA 2014) was conducted before:

- Full recognition of TFA's global distribution
- Understanding of TFA accumulation in remote environments
- Discovery of multiple new pesticidal sources of TFA
- Research on TFA ecotoxicity and environmental effects
- Current understanding of PFAS as a class

2. Multiple New Pesticidal Sources Approved Since 2014



Since the 2014 EFSA assessment, multiple pesticides that degrade to TFA have been newly registered or had their uses expanded:

- Florpyrauxifen-benzyl (2018)
- Cyclobutrifluram (proposed 2025)
- Use expansions for existing TFA-forming pesticides

These new sources were not considered in the 2014 assessment and have increased the cumulative pesticidal contribution to environmental TFA.

3. Recent Research Shows TFA Effects on Aquatic and Terrestrial Ecosystems

Research published since 2014 has identified TFA effects including:

Aquatic Toxicity: TFA shows toxicity to sensitive aquatic species. Thompson et al. (2021) found effects on fish liver function at environmentally relevant concentrations.

Phytotoxicity: Some plant species show sensitivity to TFA. Boutonnet et al. (1999) documented phytotoxic effects on sensitive crop varieties.

Soil Accumulation: Studies show TFA accumulates in agricultural soils with repeated pesticide applications. Hader et al. (2024) documented increasing soil TFA concentrations.

PMRA has a legal obligation to consider and document its assessment of recent public literature on pesticides when making decisions. It has apparently not done so.

4. TFA Contribution to Overall PFAS Burden Not Assessed

The 2014 EFSA assessment treated TFA in isolation. It did not consider:

- TFA's contribution to aggregate PFAS exposure
- Potential additive effects with other PFAS
- Cumulative exposure through multiple pathways
- Long-term accumulation in the body

Need for Updated TFA Assessment

A comprehensive, current assessment of TFA must:

1. Quantify all sources: pesticidal, industrial, and other sources
2. Model global distribution and accumulation trends
3. Assess effects on sensitive species and ecosystems



4. Evaluate human health effects including:
 - Liver toxicity
 - Developmental effects
 - Endocrine disruption
 - Cumulative PFAS effects
5. Consider cumulative exposure through food, water, and environmental pathways
6. Establish protective environmental and health criteria

PMRA's Promised Future Assessment

PMRA acknowledges the need for better TFA assessment, stating (PRD2025-06, page 28):

"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, 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."

This statement admits that:

1. TFA requires a separate comprehensive assessment
2. The assessment has not yet been done
3. The assessment is being "prioritized" but no timeline is provided
4. PMRA will "leverage" the outdated 2014 EFSA assessment

The problem with this approach is that PMRA is approving cyclobutylfluram NOW (Registration Decision RD2025-12 issued December 19, 2025) while promising to assess TFA later. This stepwise and backwards sequence means:

- Cyclobutylfluram is generating TFA before TFA safety is established
- If future TFA assessment identifies concerns, the damage is already done
- TFA's environmental persistence means it will remain even if cyclobutylfluram is later restricted

This approach is not acceptable and no in line with the protective primary objection of the Act, or with the precautionary principle.

D. Beyond Pesticides Comments Demonstrate PFAS Concerns

The comments submitted by Beyond Pesticides during the U.S. EPA consultation on cyclobutylfluram (Docket EPA-HQ-OPP-2022-0003, submitted May 6, 2025) provide important context for understanding the PFAS classification issues and aggregate risk concerns.

Beyond Pesticides identified cyclobutylfluram as PFAS based on its trifluoromethyl group and raised several critical points:



PFAS Definition and Classification

Beyond Pesticides stated: "Based on cyclobutryfluram's structure, with one of the carbons fully fluorinated as a trifluoromethyl group, the chemical falls under the widely accepted definition of PFAS. This definition is utilized, by EPA and other associations, as a basis for risk assessments for compounds that all fall into this class of 'forever chemicals.'"

This statement is correct and applies equally to PMRA's assessment. The OECD definition used by EPA and other international regulators unambiguously classifies cyclobutryfluram as PFAS.

Call for Aggregate Assessment

Beyond Pesticides argued: "Given EPA's mandatory duty under the Food Quality Protection Act to consider aggregate risk from dietary and non-dietary exposure, the addition of a new PFAS-classified pesticide (cyclobutryfluram) without an aggregate risk assessment—taking into account uncertainties associated with the agency's still limited characterization of exposure and the impact on vulnerable populations—would constitute a violation of law."

This argument applies with equal force to PMRA's registration under the Pest Control Products Act. The requirement to consider aggregate exposure is not unique to FQPA—it is a fundamental principle of risk assessment that PMRA claims to follow.

TFA Concerns

Beyond Pesticides noted research on TFA including: "this chemical breaks down into trifluoroacetic acid (TFA), which studies find threatens aquatic and terrestrial ecosystems as well as health through liver toxicity and 'possible harmful impacts on the development of embryos in humans and mammals.'"

This echoes concerns about PMRA's reliance on the outdated 2014 EFSA TFA assessment.

Recommendation for Organic Agriculture

Beyond Pesticides recommended: "We urge the agency to not register cyclobutryfluram as an active ingredient, or any additional pesticides that are classified as PFAS, based on the unreasonable risks to health and the environment and the availability of alternative practices."

The comment highlighted that organic agriculture systems prohibit synthetic pesticides including PFAS compounds, and argued that organic production offers a viable alternative that avoids PFAS contamination.

Relevance to Canadian Assessment



While Beyond Pesticides' comments were directed to EPA, the concerns apply equally to PMRA's assessment:

1. The chemical structure and PFAS classification are identical
2. The aggregate exposure concerns are the same (Canadians also have background PFAS exposure)
3. The TFA formation and persistence concerns apply to Canadian use
4. The availability of alternatives (organic production) is the same in Canada

The fact that substantive PFAS concerns were raised during U.S. consultation makes PMRA's failure to acknowledge PFAS classification even more problematic. PMRA was or should have been aware of these concerns yet proceeded without addressing them.

E. Comment to PMRA Response on PFAS Assessment (RD2025-12, Comment 13)

RD2025-12 contains PMRA's response to public comments on cumulative risk assessment (pages 10-12, Comment 13). While this response primarily addresses SDH inhibitor cumulative assessment, it also touches on TFA. PMRA's response is inadequate on multiple levels:

PMRA's Position on SDH Cumulative Assessment

PMRA argues: "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, Cyclobutryfluram, 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."

This response conflates two distinct issues:

1. SDH inhibitor cumulative assessment (mechanism-based grouping)
2. PFAS aggregate assessment (class-based exposure consideration)

These are not interchangeable. The fact that SDHIs as a mechanism group may have acceptable cumulative risk does not address whether cyclobutryfluram as a PFAS contributes to unacceptable aggregate PFAS exposure.

PMRA Must Conduct Both Assessments

PMRA needs to conduct:

1. **SDH Inhibitor Cumulative Assessment:** Groups cyclobutryfluram with other SDH inhibitors based on common mechanism. Assesses cumulative risk from combined exposure to all SDHIs.
2. **PFAS Aggregate Assessment:** Groups cyclobutryfluram with other PFAS based on common chemical structure and persistence. Assesses aggregate exposure from all PFAS sources (not just pesticides).



PMRA has attempted only the first assessment and ignored the second. Both are required.

PMRA's Response on TFA

PMRA states: "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."

This response is circular reasoning:

1. PMRA conducts a "qualitative" assessment (essentially, citing the old EFSA study)
2. The qualitative assessment concludes "no concern"
3. Therefore, PMRA argues, no quantitative assessment is needed

But the qualitative assessment was inadequate because:

- It relied on a 2014 EFSA assessment that is outdated
- It did not consider new pesticidal sources of TFA approved since 2014
- It did not account for recent research on TFA ecotoxicity
- It did not evaluate TFA's contribution to aggregate PFAS exposure

Conservatism in PMRA's Assessment Are Irrelevant

PMRA argues that its SDH cumulative assessment had "several conservatisms" including:

- Only considering samples with detection and co-occurrence
- Using maximum concentrations for drinking water
- Using conservative relative potency factors

These conservatisms relate to the SDH assessment, not PFAS aggregate assessment. PMRA is defending an assessment it actually conducted (SDHs) rather than addressing the assessment it failed to conduct (PFAS aggregate).

PMRA's Approach Violates Precautionary Principle

PMRA's decision to approve cyclobutylfluram while promising to assess TFA later violates the precautionary principle. When faced with:

- Scientific uncertainty about cumulative PFAS risks
- Outdated safety assessments (2014 EFSA)
- Known global PFAS distribution and persistence
- Recognized bioaccumulation potential

The protective mandate of the PMRA, which it has stated is more strong than the precautionary principle, comes into play. PMRA has:



1. Approved cyclobutrifluram first (RD2025-12)
2. Promised to assess cumulative TFA effects later (unspecified timeline)
3. Acknowledged that TFA assessment has not been done

This backwards approach—expose first, assess later—fails to protect public health and environment.

What PMRA Should Have Done

Before approving cyclobutrifluram, PMRA should have:

1. Acknowledged cyclobutrifluram is PFAS (based on OECD definition)
2. Conducted aggregate PFAS assessment:
 - Quantified Canadian background PFAS exposure from biomonitoring data
 - Estimated cyclobutrifluram's contribution to total PFAS burden
 - Assessed whether cumulative exposure is acceptable
 - Considered sensitive populations (fetuses, infants, children)
3. Conducted current TFA assessment:
 - Updated the 2014 EFSA assessment with recent research
 - Quantified all TFA sources (pesticidal and non-pesticidal)
 - Modeled environmental accumulation with multiple sources
 - Established protective criteria for TFA in food and water
 - Assessed contribution to aggregate PFAS exposure
4. Applied protective /precautionary principle:
 - If aggregate PFAS assessment showed concerns, delay approval
 - If TFA assessment showed concerns, reconsider approval
 - If uncertainties remain, require additional data before approval
5. Considered alternatives:
 - Evaluated whether cyclobutrifluram is necessary given existing nematicides
 - Assessed whether PFAS-free alternatives are available
 - Considered whether value justifies adding new PFAS to environment

PMRA did none of these things. Instead, it employed an approach that is the opposite of protective:

- Failed to acknowledge PFAS classification
- Conducted no aggregate PFAS assessment
- Relied on outdated TFA assessment
- Approved cyclobutrifluram despite uncertainties
- Promised to address issues later (no timeline provided)



IV. CARCINOGENICITY: "NOT LIKELY" DETERMINATION IS SCIENTIFICALLY UNJUSTIFIED

A. Rat Study: Statistically Significant Thyroid Follicular Cell Tumors

The rat carcinogenicity study provides clear evidence that cyclobutylfluram induces thyroid follicular cell tumors in both male and female rats. PMRA's dismissal of these tumors as not treatment-related contradicts the statistical evidence and the biological plausibility of thyroid carcinogenicity for a compound showing thyroid toxicity across the entire toxicology database.

Study Design and Findings

The rat carcinogenicity study (PMRA No. 3273270, cited in PRD2025-06) tested cyclobutylfluram at dietary concentrations of 0, 50, 150, and 500 ppm. The achieved doses were:

- Males: 0, 2.3, 7.0, 23 mg/kg/day
- Females: 0, 3.0, 9.1, 30 mg/kg/day

The study duration was 24 months with 50 rats per sex per dose group.

Thyroid Follicular Cell Tumor Incidences

Male Rats - Follicular Cell Adenomas:

- Control (0 ppm): 0/50 (0%)
- Low dose (50 ppm): 1/50 (2%)
- Mid dose (150 ppm): 4/50 (8%)
- High dose (500 ppm): 2/50 (4%)

Male Rats - Follicular Cell Carcinomas:

- Control (0 ppm): 0/50 (0%)
- Low dose (50 ppm): 1/50 (2%)
- Mid dose (150 ppm): 4/50 (8%)
- High dose (500 ppm): 3/50 (6%)

Male Rats - Combined Adenomas or Carcinomas:

- Control (0 ppm): 0/50 (0%)
- Low dose (50 ppm): 2/50 (4%)
- Mid dose (150 ppm): 8/50 (16%)
- High dose (500 ppm): 5/50 (10%)

Female Rats - Follicular Cell Adenomas:

- Control (0 ppm): 0/50 (0%)
- Low dose (50 ppm): 2/50 (4%)



- Mid dose (150 ppm): 4/50 (8%)
- High dose (500 ppm): 6/50 (12%)

Female Rats - Follicular Cell Carcinomas:

- Control (0 ppm): 0/50 (0%)
- Low dose (50 ppm): 0/50 (0%)
- Mid dose (150 ppm): 0/50 (0%)
- High dose (500 ppm): 0/50 (0%)

Female Rats - Combined Adenomas or Carcinomas:

- Control (0 ppm): 0/50 (0%)
- Low dose (50 ppm): 2/50 (4%)
- Mid dose (150 ppm): 4/50 (8%)
- High dose (500 ppm): 6/50 (12%)

Statistical Analysis

EPA's Cancer Assessment Review Committee (CARC) report (EPA 4/15/25) presents statistical analyses:

Males:

- Adenomas: Cochran-Armitage trend test $p = 0.105$ (not significant)
- Carcinomas: Cochran-Armitage trend test $p = 0.0433$ (SIGNIFICANT)
- Combined: Cochran-Armitage trend test $p = 0.0539$ (marginally significant)
- Mid-dose adenomas vs control: Fisher's exact test $p = 0.0632$
- Mid-dose carcinomas vs control: Fisher's exact test $p = 0.0632$
- Mid-dose combined vs control: Fisher's exact test $p = 0.0632$

Females:

- Adenomas: Cochran-Armitage trend test $p = 0.01495$ (HIGHLY SIGNIFICANT)
- Carcinomas: No carcinomas observed (0% incidence all groups)
- Combined: Cochran-Armitage trend test $p = 0.01874$ (HIGHLY SIGNIFICANT)

Interpretation Under EPA Guidelines, adopted by PMRA

EPA's 2005 Guidelines for Carcinogen Risk Assessment state (page 2-19):

"A statistically significant positive trend or a significantly elevated tumor incidence at one or more doses (compared with the control group) generally indicates an association between the increased tumor incidence and the exposure under study."

The Guidelines further state:



"When a trend test or a pairwise comparison test is statistically significant (usually less than 0.05), this means that chance is unlikely (less than 5% probability) to have caused the observed differences. When such a significant result is observed, the conclusion is that the increased tumors are associated with exposure to the agent."

Applied to cyclobutrifluram:

1. Male carcinomas show SIGNIFICANT trend ($p = 0.0433 < 0.05$)
 - Conclusion: Increased carcinomas are associated with cyclobutrifluram exposure
 - Chance is unlikely to have caused this result
2. Female adenomas show HIGHLY SIGNIFICANT trend ($p = 0.01495 < 0.05$)
 - Conclusion: Increased adenomas are associated with cyclobutrifluram exposure
 - Chance is very unlikely to have caused this result
3. Female combined tumors show HIGHLY SIGNIFICANT trend ($p = 0.01874 < 0.05$)
 - Conclusion: Increased tumors are associated with cyclobutrifluram exposure
 - Chance is very unlikely to have caused this result
4. Male mid-dose tumors show marginally significant pairwise comparisons ($p = 0.0632$)
 - While this exceeds the conventional 0.05 cutoff, it represents 8/50 rats vs 0/50 controls
 - The probability that this occurred by chance is only 6.3%
 - In context of significant trends and female tumors, this supports treatment-relation

EPA Guidelines Require Weight of Evidence

The Guidelines emphasize that statistical significance is necessary but not sufficient—weight of evidence must be considered:

"Tumor responses are considered in the light of a number of factors including: the background rate, the shape of the dose-response curve, the consistency of the response across sexes or species, the presence of preneoplastic lesions, the progression from benign to malignant tumors, the plausibility of underlying mechanisms, and consistency across different studies."

Applying weight of evidence factors:

Background Rate: Both sexes showed 0% thyroid follicular cell tumors in concurrent controls. This is consistent with historical control ranges. The fact that controls had zero tumors makes any tumor increase more concerning, not less.



Dose-Response: The trend tests demonstrate dose-response relationships. While not perfectly monotonic (mid-dose males showed numerically higher incidence than high-dose), significant trends indicate general dose-response.

Consistency Across Sexes: BOTH sexes showed significant tumor trends. Males had significant carcinoma trend, females had significant adenoma and combined tumor trends. This consistency strengthens the conclusion of treatment-relation.

Preneoplastic Lesions: The study found thyroid follicular cell hyperplasia in males:

- Control: 4/50 (8%) - minimal severity
- Low dose: 6/50 (12%) - minimal severity
- Mid dose: NOTE - Table 3 shows inconsistent count
- High dose: 11/50 (22%) - minimal to moderate severity

The progression from normal → hyperplasia → adenoma → carcinoma represents the classic carcinogenic sequence. The presence of hyperplasia at increased incidence in treated groups supports that tumors are treatment-related.

Biological Plausibility: Thyroid effects were seen throughout the toxicology database (addressed in Section IV.C below). The biological plausibility of thyroid carcinogenicity is high for a compound showing chronic thyroid toxicity.

PMRA's Dismissal of the Tumor Findings

Despite this evidence, PMRA classified cyclobutylfluram as "not likely to be carcinogenic to humans." EPA's CARC report (cited in PMRA documents) concluded the thyroid tumors were "likely not treatment-related."

This conclusion appears to be based primarily on the fact that pairwise comparisons of high-dose vs control did not achieve statistical significance. However, this reasoning is flawed:

1. EPA Guidelines state that EITHER trend OR pairwise significance indicates treatment-relation. This is supported by the 9th Circuit Court of Appeals decision on glyphosate. Both males (carcinomas) and females (adenomas, combined) showed significant TRENDS.
2. The lack of pairwise significance at high dose likely reflects inadequate dosing (see Section IV.D). Higher doses would likely have produced more tumors achieving pairwise significance.
3. The mid-dose male tumors (8/50 vs 0/50, $p = 0.0632$) nearly achieved significance and strongly suggest treatment-relation.
4. Dismissing significant trends because pairwise tests were not significant violates EPA's own Guidelines



requiring weight of evidence consideration.

Historical Control Data Does Not Negate Findings

PMRA may argue that tumor incidences were within historical control ranges. However, EPA Guidelines address this:

"If the tumors in treated animals occur at an incidence that is within the historical control range, this may indicate that the tumors are not related to treatment. However, this is not conclusive, and other factors such as a significant dose-response trend and biological plausibility must still be considered."

In this case:

- Significant dose-response trends exist
- Biological plausibility is high (thyroid toxicity across database)
- Both sexes show tumor increases
- Preneoplastic lesions support progression

Therefore, even if incidences are within historical ranges, the weight of evidence supports treatment-relation.

B. Mouse Study: Statistically Significant Hepatocellular Carcinomas

The mouse carcinogenicity study provides strong evidence that cyclobutylfluram induces liver tumors in male mice. The highly significant dose-response trend, incidences exceeding historical control ranges, and supporting preneoplastic lesions establish treatment-relation under EPA Guidelines.

Study Design

The mouse carcinogenicity study (PMRA No. 3273295) tested cyclobutylfluram at dietary concentrations of 0, 50, 150, and 500 ppm. Achieved doses were:

- Males: 0, 6.1, 19, 48 mg/kg/day
- Females: 0, 7.4, 23, 54 mg/kg/day

Duration was 18 months with 50 mice per sex per group.

Hepatocellular Tumor Incidences

Male Mice - Hepatocellular Adenomas:

- Control: 6/50 (12%)
- Low: 8/50 (16%)
- Mid: 6/50 (12%)
- High: 9/50 (18%)
- Trend test: $p = 0.287$ (not significant)



Male Mice - Hepatocellular Carcinomas:

- Control: 8/50 (16%)
- Low: 14/50 (28%)
- Mid: 16/50 (32%)
- High: 20/50 (40%)
- Cochran-Armitage trend: $p = 0.0139$ (HIGHLY SIGNIFICANT)

Male Mice - Combined Adenomas or Carcinomas:

- Control: 14/50 (28%)
- Low: 22/50 (44%)
- Mid: 22/50 (44%)
- High: 29/50 (58%)
- Trend test: $p = 0.0030$ (HIGHLY SIGNIFICANT)

Female Mice: No significant increases in liver tumors

Preneoplastic Liver Lesions

The study documented "foci of cellular alteration" (preneoplastic liver lesions) in male mice:

- Control: 3/50 (6%)
- Low: 7/50 (14%)
- Mid: 10/50 (20%)
- High: 14/50 (28%)

This monotonic dose-related increase in preneoplastic lesions supports that carcinomas are treatment-related and part of a progressive disease process.

Statistical Significance and Interpretation

The male hepatocellular carcinoma trend test p-value of 0.0139 is highly statistically significant (< 0.05). Under EPA Guidelines, this establishes association between cyclobutylfluram exposure and liver carcinomas.

Moreover, the combined adenomas/carcinomas trend ($p = 0.0030$) is even more significant, indicating a clear dose-response for total liver neoplasia.

Historical Control Exceedance

EPA's CARC report notes that high-dose male hepatocellular carcinoma incidence (40%, 20/50) exceeded the historical control range. This exceedance strengthens the conclusion of treatment-relation—when incidence exceeds historical ranges AND shows significant dose-response, treatment-relation is clear.



Consistency with Open Literature Study

Syngenta scientists published an open-literature study on cyclobutylfluram carcinogenicity (cited in EPA CARC report, Appendix A page 39). This study also showed dose-responsive increases in hepatocellular carcinomas in male CD-1 mice, confirming the regulatory study findings.

The consistency between two independent studies using different mouse strains strengthens the conclusion that cyclobutylfluram is hepatocarcinogenic in mice.

Sex-Specificity Does Not Negate Findings

The liver tumors occurred only in males, not females. PMRA may argue this sex-specificity suggests the tumors are not relevant to humans. However:

1. Sex-specific carcinogenicity is common in rodent studies and does not automatically indicate lack of human relevance. Many human carcinogens show sex-specific effects in rodents.
2. The sex-specificity may reflect toxicokinetic differences (males may achieve higher internal doses) or sex differences in metabolic enzyme expression, not fundamental mechanistic differences.
3. EPA Guidelines require weight-of-evidence assessment. The highly significant trends, historical control exceedance, preneoplastic lesion progression, and consistency across studies outweigh any concern about sex-specificity.
4. The mouse liver tumors occur in addition to rat thyroid tumors—two tumor types in two species strengthens rather than weakens the carcinogenicity determination.

C. Supporting Evidence Across Toxicology Database

PMRA acknowledges throughout PRD2025-06 that thyroid effects occurred across the cyclobutylfluram toxicology database. This consistent pattern of thyroid toxicity provides biological plausibility for the thyroid tumors observed in the rat carcinogenicity study.

Evidence from Short-Term Studies

28-Day Rat Study (PMRA No. 3273245): "Thyroid follicular cell hypertrophy was noted in males and females at ≥ 100 mg/kg/day" (PRD2025-06, Table 3, page 16).

90-Day Rat Study (PMRA No. 3273246): "Thyroid follicular cell hypertrophy was observed in males and females at ≥ 500 ppm (30/36 mg/kg/day [M/F])" (PRD2025-06, Table 3, page 16).



These short-term studies establish that cyclobutylfluram affects thyroid follicular cells—the same cell type that developed tumors in the carcinogenicity study—at relatively high doses after only weeks of exposure.

Evidence from Reproduction Study

Two-Generation Rat Reproduction Study (PMRA No. 3273263): The study found:

- Increased absolute thyroid weight in F0 parental males at 1000 ppm (PRD2025-06, Table 4, page 17)
- Thyroid follicular cell hypertrophy in F0 and F1 males at 1000 ppm
- Thyroid follicular cell hypertrophy in F0 and F1 females at 1000 ppm

The increased absolute thyroid weight is particularly significant. Organ weight increases often indicate sustained toxicity and adaptive responses. When coupled with follicular cell hypertrophy, increased thyroid weight suggests the gland is being chronically stressed.

PMRA's Acknowledgment of Thyroid as Sensitive Target

PRD2025-06 states (page 19): "there were effects noted on the thyroid across the cyclobutylfluram toxicity database" and "the thyroid was identified as the most sensitive endpoint in the cyclobutylfluram toxicity database."

PMRA further notes that this thyroid sensitivity formed the basis for setting the chronic reference dose: "Health Canada's PMRA based the chronic reference dose on the LOAEL for thyroid follicular cell hypertrophy and increased absolute thyroid weights in the two-generation reproduction study" (PRD2025-06, page 23).

The Inconsistency in PMRA's Position

PMRA's position contains a fundamental inconsistency:

On one hand, PMRA acknowledges:

- Thyroid effects across entire database
- Thyroid is most sensitive endpoint
- Thyroid toxicity formed basis for chronic RfD

On the other hand, PMRA denies:

- Thyroid tumors in rat carcinogenicity study are treatment-related
- Cyclobutylfluram has carcinogenic potential

This inconsistency is scientifically indefensible. When a chemical shows:

1. Hypertrophy (adaptive cellular response) in short-term studies
2. Increased organ weight (sustained effect) in chronic studies
3. Hyperplasia (preneoplastic proliferation) in carcinogenicity study



4. Adenomas (benign tumors) with significant dose-response
5. Carcinomas (malignant tumors) with significant dose-response

...all in the SAME CELL TYPE (thyroid follicular cells), the only reasonable conclusion is that the chemical is carcinogenic to that tissue.

The Mode of Action Progression

The Nielsen et al. (2012) framework for thyroid carcinogenicity describes a "combined mode of action" for chemicals affecting thyroid follicular cells:

- Stage 1: Hypertrophy (adaptive response to increased TSH or other stimulation)
- Stage 2: Hyperplasia (increased cell proliferation)
- Stage 3: Adenomas (benign neoplasms)
- Stage 4: Carcinomas (malignant neoplasms)

Cyclobutylfluram shows ALL FOUR STAGES:

- Hypertrophy: 28-day, 90-day, reproduction studies
- Hyperplasia: Carcinogenicity study preneoplastic lesions
- Adenomas: Carcinogenicity study, significant trends both sexes
- Carcinomas: Carcinogenicity study, significant trend in males

This progression through all stages of thyroid carcinogenesis provides overwhelming support for treatment-relation of the tumors.

D. Inadequate Dosing Masked Full Carcinogenic Potential

PMRA concedes in multiple documents that both the rat and mouse carcinogenicity studies failed to employ adequately high doses. This dosing failure biased the studies toward underestimating carcinogenic potential.

PMRA Admits Inadequate Dosing

Rat Study: EPA's CARC report (EPA 4/15/25, page 6) states: "the rats of both sexes could have tolerated higher doses."

PMRA further notes (EPA 4/15/25, page 11): "no adverse toxicological effects were observed up to the highest dose tested (23/30 mg/kg/day [M/F] (500 ppm))."

Mouse Study: EPA CARC report (EPA 4/15/25, page 16) states: "the [mouse] study could have tested higher doses" and details:

"there were no treatment-related adverse effects on survival observed for either male or female mice. No treatment-related adverse effects to body weight, body weight gain, or hematology were observed up to and



including the highest dose tested (48/54 mg/kg/day).... Based on the aforementioned results, the carcinogenicity study in mice could have tested higher doses."

Purpose of Maximum Tolerated Dose

The maximum tolerated dose (MTD) concept is fundamental to carcinogenicity testing. EPA's 2005 Guidelines state (page 2-15):

"The MTD is defined as the highest dose that causes no more than a 10% weight decrement, as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural lifespan."

The rationale for using MTD is (EPA 2005, page 2-15): "to provide the maximum ability to detect treatment-related carcinogenic effects by increasing the likelihood that an agent will produce tumors if it has the potential to do so."

Without MTD dosing, the study lacks sufficient sensitivity to detect carcinogenic potential. This is particularly problematic for cyclobutylfluram because the studies DID show tumors despite inadequate dosing.

Implications of Inadequate Dosing

When studies show significant tumor trends despite failing to use MTD, the logical conclusion is that MTD dosing would have shown STRONGER effects:

1. Both rat and mouse studies showed statistically significant dose-response TRENDS
2. Trends indicate that higher doses would produce more tumors
3. If MTD had been used, tumor incidences would likely have been higher
4. Higher incidences would likely have achieved pairwise statistical significance vs controls
5. The carcinogenic potential would have been even more apparent

In other words, inadequate dosing MASKED the full extent of carcinogenic potential. PMRA's admission of dosing inadequacy should have led to repeat studies with proper MTD, not to dismissal of the positive tumor findings.

Why MTD Was Not Achieved

The failure to achieve MTD in both species suggests either:

1. Poor dose selection in study design (did not test high enough)
2. Cyclobutylfluram has very low acute toxicity making MTD difficult to find
3. Protocol violations (should have added higher dose groups)



Regardless of reason, the result is the same: studies were inadequately sensitive to detect full carcinogenic potential.

PMRA's Illogical Response to Inadequate Dosing

PMRA attempts to defend the inadequate dosing by arguing the studies were "adequate" despite not reaching MTD. This defense is internally contradictory:

Argument 1: "No adverse effects at highest dose means study is adequate"

Counter: The ABSENCE of adverse effects at highest dose is precisely what demonstrates the dose was too low! MTD is defined by presence of moderate toxicity.

Argument 2: "Tumors occurred, so studies had sufficient sensitivity"

Counter: Tumors occurred DESPITE inadequate dosing. With proper MTD, even more tumors would have been observed, providing clearer evidence.

Argument 3: "Guidelines don't require MTD in all cases"

Counter: Guidelines allow flexibility but the rationale for MTD (maximize detection) applies especially when positive tumor responses are observed.

The fundamental principle is: if you're going to do a carcinogenicity study, do it right. Inadequate dosing wastes resources, animal lives, and produces ambiguous results. When studies show tumor increases despite inadequate dosing, the appropriate response is to conduct proper studies, not to dismiss the findings.

F. SDH Inhibition Mechanism and Carcinogenesis

The most critical gap in PMRA's carcinogenicity assessment is the failure to consider cyclobutirfluram's mechanism of action: inhibition of succinate dehydrogenase (SDH). Over the past 25 years, research has established clear mechanistic links between SDH inhibition, succinate accumulation, and carcinogenesis. PMRA's claim that "a specific mode of action has not been elucidated" (PRD2025-06, page 19) ignores this extensive literature.

SDH Function and Evolutionary Conservation

Succinate dehydrogenase (SDH), also known as Complex II, catalyzes two crucial reactions:

1. In the citric acid cycle (TCA cycle/Krebs cycle): Oxidizes succinate to fumarate
2. In the electron transport chain: Reduces ubiquinone (CoQ) to ubiquinol (CoQH₂)

SDH is the only enzyme complex that participates in both the TCA cycle and the electron transport chain, making it essential for cellular energy metabolism.



Critically, SDH is highly conserved across all aerobic organisms. The enzyme structure and function are essentially identical in:

- Fungi (cyclobutrifluram's target pests)
- Nematodes (cyclobutrifluram's target pests)
- Mammals including humans
- Other vertebrates and invertebrates

This conservation means that inhibitors of fungal/nematode SDH also inhibit mammalian SDH. Bénit et al. (2019) demonstrated this experimentally, showing that eight SDHI fungicides inhibit human SDH with similar potency to their inhibition of target organism SDH.

Hereditary SDH Mutations Cause Cancer Syndromes

The link between SDH deficiency and cancer was established through study of hereditary cancer syndromes caused by germline mutations in SDH subunit genes:

SDHB Mutations: Cause hereditary paraganglioma-pheochromocytoma syndrome. Patients with SDHB mutations develop:

- Paragangliomas (tumors of parasympathetic ganglia)
- Pheochromocytomas (adrenal medulla tumors)
- Renal cell carcinomas
- Risk of malignant transformation

SDHD Mutations: Also cause paraganglioma-pheochromocytoma syndrome with high penetrance.

SDHC Mutations: Cause paragangliomas with lower penetrance.

SDHA Mutations: Cause paragangliomas and gastrointestinal stromal tumors (GISTs).

SDH-Deficient Thyroid Tumors: Mu et al. (2021) review the role of SDH deficiency in thyroid cancer. SDH-deficient thyroid tumors have been identified in humans, showing that SDH dysfunction can contribute to thyroid carcinogenesis—directly relevant to cyclobutrifluram's induction of thyroid tumors in rats.

These hereditary syndromes establish that SDH deficiency is causally linked to tumor development in humans.

Mechanism: Succinate as an Oncometabolite

When SDH is inhibited or deficient, its substrate (succinate) accumulates. Research has established that elevated succinate acts as an "oncometabolite"—a metabolite that directly promotes tumorigenesis through multiple mechanisms:



Mechanism 1: HIF- α Stabilization (Selak et al. 2005)

Succinate inhibits prolyl hydroxylase domain-containing proteins (PHDs), which normally hydroxylate hypoxia-inducible factor alpha (HIF- α), marking it for degradation. When succinate accumulates:

- PHDs are inhibited
- HIF- α is not hydroxylated
- HIF- α is stabilized and enters nucleus
- HIF- α activates transcription of genes promoting:
 - Angiogenesis (new blood vessel formation to feed tumors)
 - Glycolysis (altered metabolism supporting rapid growth)
 - Cell survival and proliferation
 - Metastasis

This "pseudohypoxic" state mimics oxygen deprivation and drives tumor-promoting gene expression even when oxygen is available.

Mechanism 2: Epigenetic Modifications (Zhao et al. 2017)

Succinate inhibits α -ketoglutarate (α -KG)-dependent dioxygenases including:

- Ten-eleven translocation (TET) enzymes (DNA demethylases)
- Jumonji C domain-containing histone demethylases (JHDMS)

When these enzymes are inhibited:

- DNA hypermethylation occurs (especially at CpG islands)
- Histone methylation patterns change
- Gene expression is altered (often silencing tumor suppressors)
- Cells acquire cancer-like epigenetic landscape

These epigenetic changes can persist even if succinate levels later normalize, creating a "memory" of SDH inhibition.

Mechanism 3: Oxidative Stress and DNA Damage

SDH inhibition impairs electron transport chain function, leading to:

- Increased reactive oxygen species (ROS) generation
- Oxidative damage to DNA, proteins, and lipids
- Accumulation of DNA mutations
- Genomic instability supporting tumorigenesis

Mechanism 4: Metabolic Reprogramming



The "Warburg effect" describes cancer cells' preference for glycolysis even when oxygen is available. SDH inhibition contributes to this metabolic reprogramming:

- Impaired oxidative phosphorylation
- Shift to glycolytic metabolism
- Altered nutrient utilization supporting rapid proliferation

Environmental SDH Inhibitors and Cancer Risk

The question for cyclobutylfluram is: can chronic, low-level environmental exposure to SDH inhibitors cause sufficient succinate accumulation to trigger these carcinogenic mechanisms?

Bouillaud (2023) reviews this question, noting:

"SDH inhibition from environmental pesticides could contribute to metabolic disorders and potentially cancer through chronic interference with cellular energy metabolism."

Bénit et al. (2019) found that SDHI fungicides inhibit mammalian SDH at concentrations potentially achievable through dietary and environmental exposure. They concluded:

"This evolutionarily conserved susceptibility... raises concerns about the safety of SDHI use."

Critical Gap in PMRA's Assessment

Despite this extensive mechanistic literature, PMRA states (PRD2025-06, page 19):

"Although adverse effects on the thyroid were noted across the database, a specific mode of action has not been elucidated."

This statement is demonstrably false. The mode of action is known: SDH inhibition. The relevant questions PMRA failed to address are:

1. What are tissue-specific SDH activities and succinate levels in treated rats?
2. Do the doses causing tumors produce measurable SDH inhibition?
3. Do succinate levels increase in thyroid and liver of treated animals?
4. Are the HIF- α and epigenetic markers of succinate accumulation present?
5. Can the tumor induction be prevented by interventions that reduce succinate?

These are answerable scientific questions. PMRA's failure to even consider them represents a critical gap. Instead of investigating the mechanism, PMRA dismissed the tumors as "not treatment-related" despite statistical significance and biological plausibility.



Implications for Risk Assessment

If cyclobutirfluram-induced tumors occur via SDH inhibition and succinate accumulation:

1. The mechanism is relevant to humans (SDH is identical)
2. No clear threshold may exist (any SDH inhibition produces some succinate)
3. Cumulative exposure matters (multiple SDHIs contribute to total inhibition)
4. Sensitive life stages matter (developing organisms may be more susceptible)
5. Linear dose-response may be appropriate (no clear threshold mechanism)

PMRA's assessment assumed a threshold mechanism allowing calculation of a "safe" chronic RfD. If the actual mechanism is non-threshold or involves cumulative succinate accumulation, this approach underprotects health.

H. Comments to PMRA Responses on Carcinogenicity (RD2025-12, Comments 1-6)

RD2025-12 contains PMRA's responses to six comments related to carcinogenicity received during the consultation period (pages 1-7). These responses are inadequate and fail to address the fundamental scientific concerns about cyclobutirfluram's carcinogenic potential.

Comment to Response to Comment 1: Cancer Risk Assessment Approach

Comment 1 (summarized): Concerns about the dismissal of linear carcinogenic risk modeling and that the threshold approach is not justifiable given data limitations.

PMRA Response (page 1-2): PMRA states it used a "weight of evidence approach" and concluded tumors are "likely forming via a threshold mechanism" based on:

- "Partially supportive results from mechanistic studies"
- Lack of genotoxic potential
- Knowledge that these tumor types develop via threshold mechanism in mice

Comment:

First, PMRA admits mechanistic studies were only "partially supportive"—meaning they did NOT conclusively demonstrate a threshold mode of action. When mechanism is unclear, EPA Guidelines require that tumors be assumed to be relevant to humans.

Second, the "lack of genotoxic potential" is a red herring. Many human carcinogens (including hormones and immunosuppressants) are non-genotoxic yet clearly carcinogenic. Non-genotoxic does not mean non-carcinogenic.

Third, PMRA's claim that "these tumor types develop via a threshold mechanism" contradicts the SDH



inhibition mechanism. As detailed in Section IV.F, SDH inhibition leads to succinate accumulation with multiple pro-carcinogenic effects including HIF- α stabilization and epigenetic modifications. These effects may occur at any level of SDH inhibition—there is no clear biological threshold.

Fourth, EPA's 2005 Guidelines state that when mode of action is "not adequately determined," a linear approach may be more appropriate than assuming a threshold. PMRA's mechanistic data was admittedly "partially supportive"—hardly sufficient to assume a threshold.

Fifth, the fundamental issue is that PMRA dismissed statistically significant tumor findings based on speculation about mechanism without solid mechanistic data. This violates the principle that statistical evidence of carcinogenicity should not be dismissed without compelling evidence.

Comment to Response to Comment 2: Animal Doses vs Human Exposure

Comment 2: Concerns that PMRA's statement about animal doses being higher than human exposure is inappropriate and doesn't reflect a scientifically based approach.

PMRA Response (page 2): PMRA defends its risk assessment approach using uncertainty factors to extrapolate from animal studies.

Comment:

The commenter's point was not about the uncertainty factor methodology but about PMRA's misleading public communication. PMRA's statement creates the false impression that animal effects are irrelevant to humans because "doses are different."

More fundamentally, PMRA's response evades the core issue: even with uncertainty factors, if tumors are treatment-related (which statistics indicate), they represent a carcinogenic HAZARD that should be acknowledged. The question is not whether the hazard exists (it does) but whether human exposure levels are sufficiently below the hazardous levels.

By classifying cyclobutylfluram as "not likely carcinogenic," PMRA denies the hazard exists. This is scientifically incorrect and prevents proper risk characterization.

Comment to Response to Comment 3: Endocrine Disruption Assessment

Comment 3: Concerns that PMRA did not give due consideration to endocrine disruption, particularly thyroid effects, and that a 3-fold uncertainty factor is insufficient.

PMRA Response (page 3): PMRA argues that reproduction and developmental studies are adequate to characterize endocrine effects and that the point of departure selection protects against effects at higher doses.



Comment:

First, reproduction and developmental studies do NOT substitute for specific endocrine disruption screening. The Endocrine Disruptor Screening Program (EDSP) was mandated by Congress precisely because standard toxicity studies miss endocrine effects.

Second, for a chemical showing thyroid effects across the ENTIRE database (28-day, 90-day, reproduction, carcinogenicity), failure to conduct EDSP testing is indefensible. PMRA acknowledged "the thyroid was identified as the most sensitive endpoint" (PRD2025-06, page 19) yet refused to require thyroid-specific testing.

Third, PMRA's claim that "the POD selected is protective of effects at higher doses" is circular reasoning. The question is whether the POD adequately accounts for endocrine effects, particularly given:

- Inadequate dosing in developmental study (PMRA admits 250 mg/kg/day may not be appropriate top dose)
- No valid thyroid hormone data
- No EDSP testing

Fourth, the 3-fold uncertainty factor for database deficiency does NOT compensate for missing data.

Uncertainty factors account for known variability, not for effects that were never measured. Without EDSP data, PMRA cannot know whether 3-fold is adequate.

Comment to Response to Comment 4: Reproductive Toxicity Concerns

Comment 4: Concerns about qualitative sensitivity in developmental study and reduced fertility in F1 males being indicators of reproductive toxicity.

PMRA Response (page 3-4): PMRA argues the additional uncertainty factor addresses developmental study limitations and that reduced fertility was within historical control range.

Comment:

PMRA's response acknowledges the concern but claims it was addressed through uncertainty factors. However, uncertainty factors are blunt instruments. The appropriate response to a study with inadequate top dose is to require a repeat study with proper dosing, not to apply a fudge factor.

Regarding reduced fertility in F1 males, PMRA dismisses it as "within historical control range." But the fertility index decreased from 100% (control) to 82% (high dose). While this may be within the range observed in other studies, it represents an 18-point decrease from controls in THIS study. The consistency within a study is more relevant than historical ranges across different studies.

Furthermore, the "low level of concern" is based on absence of other reproductive effects. But reduced fertility



IS a reproductive effect. The fact that it's the only one observed doesn't make it less concerning—it makes cyclobutrifluram selective for this endpoint.

Comment to Response to Comment 5: Metabolite Testing

Comment 5: Concerns that major metabolites SYN549104 and SYN510275 reached higher systemic concentrations than parent but lacked subchronic and reproductive toxicity testing.

PMRA Response (page 4): PMRA argues that parent compound studies include metabolite exposure so additional testing is unnecessary.

Comment:

This response conflates two different types of testing:

Type 1: Testing parent compound (which generates metabolites in vivo)

Type 2: Testing isolated metabolites directly

PMRA is correct that Type 1 testing captures toxicity from metabolites formed during parent compound exposure. However, when metabolites reach HIGHER concentrations than parent, and when they're likely to have different toxicity profiles, Type 2 testing is warranted.

The concern is particularly acute for SYN510275, which has a half-life exceeding 3 years and will accumulate to steady-state levels far higher than acute parent compound exposure produces. This long-term, high-level metabolite exposure is NOT adequately represented in parent compound studies.

Comment to Response to Comment 6: Hazard Assessment of End-Use Products

Comment 6: Concerns that hazard assessment was only conducted on active ingredient, not end-use products.

PMRA Response (page 4-5): PMRA explains it requires acute toxicity testing of end-use products and that formulants must meet regulatory requirements.

Comment:

PMRA's response addresses acute hazards but not chronic hazards. The concern about end-use product assessment is whether formulants might:

- Increase dermal absorption of active ingredient
- Have synergistic toxic effects with active ingredient
- Add their own chronic toxicity



These questions are not answered by acute toxicity tests alone. For a potentially carcinogenic active ingredient, end-use product chronic studies take on added importance.



V. TSMP TRACK 1 VIOLATIONS FOR SYN510275

A. SYN510275 Meets Track 1 Persistence Criteria

The Toxic Substances Management Policy (TSMP) establishes regulatory criteria for persistent, bioaccumulative, and toxic substances. Track 1 substances are those meeting the HIGHEST criteria for persistence and bioaccumulation and are subject to virtual elimination from the environment. PMRA's assessment of cyclobutrifluram's major transformation product SYN510275 contains fundamental errors that resulted in failure to recognize its Track 1 status.

TSMP Background and Criteria

The TSMP was adopted by the federal government in 1995 and applies to all federal departments and agencies including Health Canada. The policy recognizes that persistent substances:

- Remain in the environment for extended periods
- May bioaccumulate in organisms and food chains
- Can be transported long distances from sources
- Present ongoing exposure to humans and ecosystems

Track 1 substances are those meeting criteria indicating VIRTUAL ELIMINATION is warranted:

Persistence Criteria (any environmental compartment):

- Half-life in air ≥ 2 days
- Half-life in water ≥ 182 days (6 months)
- Half-life in sediment ≥ 365 days (1 year)
- Half-life in soil ≥ 182 days (6 months)

Bioaccumulation Criterion:

- Bioconcentration factor (BCF) ≥ 5000
- OR Bioaccumulation factor (BAF) ≥ 5000

Toxicity Criterion:

- Meets Canadian Environmental Protection Act toxicity criteria

A substance need only meet the persistence criterion in ONE environmental compartment and the bioaccumulation criterion to be Track 1. Toxicity is separately assessed.

DIR99-03: PMRA's TSMP Implementation

PMRA's guidance document DIR99-03 ("The Pest Management Regulatory Agency's Approach to Implementing the Toxic Substances Management Policy under the Pest Control Products Act") establishes how



TSMP applies to pesticides.

DIR99-03 Section 3.2.1 addresses persistence assessment for transformation products:

"For transformation products, a representative $T_{1/2}$ value should be based on kinetic modeling, which should be calculated as the time required to reach 50% of the maximum concentration formed."

This definition recognizes that transformation products are not present initially—they must first be formed from the parent compound. The relevant half-life is not the time to 50% dissipation (DT_{50}) but the time for concentration to decline to 50% of the maximum formed ($T_{1/2,rep}$).

SYN510275 Formation and Degradation Data

PRD2025-06, Appendix A, Table 14 (page 32) presents aerobic soil metabolism data for cyclobutrifluram. The study followed radiolabeled cyclobutrifluram in four soils over 360 days.

SYN510275 was identified as a major transformation product, reaching maximum concentrations of:

- Soil 1: 47.9% AR at day 180
- Soil 2: 41.6% AR at day 120
- Soil 3: 36.5% AR at day 120
- Soil 4: 27.8% AR at day 120

DT_{50} values for SYN510275 dissipation (Table 14, page 32):

- 1230 days (first-order kinetics)
- 823 days (SFO kinetics)
- 552 days (DFOP kinetics)

Calculating $T_{1/2,rep}$ for SYN510275

Following DIR99-03 guidance, $T_{1/2,rep}$ is calculated as time to reach 50% of maximum concentration.

Using first-order kinetics (PMRA's typically preferred approach for conservatism):

- Maximum SYN510275 concentration: ~47.9% AR (Soil 1, day 180)
- 50% of maximum: 23.95% AR
- DT_{50} from maximum: 1230 days

Therefore: $T_{1/2,rep} = 1230 \text{ days} = 3.37 \text{ years}$

TSMP Track 1 criterion for soil persistence: Half-life ≥ 182 days (0.5 years)

SYN510275 $T_{1/2,rep}$ of 1230 days EXCEEDS the Track 1 criterion by a factor of 6.7



Even using the most optimistic DFOP kinetics:

- $DT_{50} = 552$ days = 1.51 years
- Exceeds Track 1 criterion by a factor of 3.0

By any kinetic model, SYN510275 meets TSMP Track 1 persistence criteria for soil.

Comparison to Other Track 1 Pesticides

To put SYN510275's persistence in context:

DDT:

- Half-life in soil: 2-15 years (varies by conditions)
- Track 1 listed, virtually eliminated in Canada

Dieldrin:

- Half-life in soil: 3-7 years
- Track 1 listed, use prohibited

Toxaphene:

- Half-life in soil: 10+ years
- Track 1 listed, virtually eliminated

SYN510275:

- $T_{1/2,rep}$ in soil: 1.51-3.37 years (by different kinetic models)
- Should be Track 1 listed but PMRA says it doesn't meet criteria

SYN510275's persistence is comparable to classic persistent organic pollutants (POPs) that Canada has phased out under TSMP and international agreements.

B. PMRA TSMP Assessment Contains Multiple Errors

PMRA's conclusion that SYN510275 does NOT meet Track 1 criteria is based on multiple errors in data analysis and interpretation.

Error 1: Use of Incorrect Half-Life Values

PRD2025-06, Appendix A states (page 33):

"The half-life in soil of transformation products SYN510275, SYN551231, SYN551241, and CGA177291 (199, 164, 46, and 61 days respectively)... did not meet TSMP Track 1 criteria for persistence (half-life in soil \geq 182 days)."



The value "199 days" for SYN510275 appears NOWHERE in Table 14 (page 32), which presents the actual study data. The table shows DT_{50} values of:

- 1230 days (first-order)
- 823 days (SFO)
- 552 days (DFOP)

Where did "199 days" come from?

Possibility 1: PMRA used a formation half-life rather than a dissipation half-life. But this would be backwards—TSMF requires assessment of how long the substance persists, not how quickly it forms.

Possibility 2: PMRA used a DT_{50} value from a different study not presented in the PRD. But this would violate transparency requirements—all data supporting regulatory decisions should be presented.

Possibility 3: PMRA made a calculation or transcription error. This is troubling but appears most likely given the value appears unsupported by presented data.

Regardless of explanation, PMRA's use of "199 days" is not supported by the data in Table 14.

Error 2: Use of DT_{50} Instead of $T_{1/2,rep}$

Even if 199 days were a correct DT_{50} value, using DT_{50} for transformation products violates DIR99-03 guidance.

DIR99-03 explicitly requires $T_{1/2,rep}$ for transformation products: "the time required to reach 50% of the maximum concentration formed."

This is conceptually different from DT_{50} :

DT_{50} : Time for concentration to decline 50% from its current level

$T_{1/2,rep}$: Time for concentration to decline to 50% of the MAXIMUM level reached

For transformation products that form slowly:

- Formation may take 120-180 days to reach maximum
- DT_{50} measures dissipation from that maximum
- $T_{1/2,rep}$ measures total time at $\geq 50\%$ of maximum (formation + dissipation)

$T_{1/2,rep}$ is always longer than DT_{50} for transformation products. By using DT_{50} (or an even shorter value), PMRA systematically underestimates transformation product persistence.



Error 3: Failure to Use Conservative Kinetic Model

When multiple kinetic models are available, PMRA should use the most conservative (longest half-life) for TSMP assessment. This is consistent with TSMP's precautionary approach.

Yet PMRA appears to have used (or calculated) a value shorter than any of the DT_{50} values in Table 14:

- First-order DT_{50} : 1230 days
- SFO DT_{50} : 823 days
- DFOP DT_{50} : 552 days
- PMRA value: "199 days" (unsupported)

If PMRA had used first-order kinetics (most conservative), SYN510275 would clearly be Track 1. Even using DFOP kinetics (least conservative), it would still be Track 1 (552 days > 182 days).

Error 4: No Consideration of Representative Half-Life Calculation

DIR99-03 requires using "kinetic modeling" to calculate $T_{1/2,rep}$. This means:

1. Fit kinetic model to formation and dissipation data
2. Identify time of maximum concentration
3. Calculate time to reach 50% of that maximum

PMRA presents no evidence of having done this calculation. Table 14 shows DT_{50} values but not $T_{1/2,rep}$ values. The TSMP assessment section (Appendix A, pages 31-33) makes no mention of $T_{1/2,rep}$ calculation methodology.

This suggests PMRA either:

- Did not perform the required calculation, or
- Performed it incorrectly, or
- Performed it but didn't report it

Any of these possibilities represents a procedural failure.

C. Misapplication of DIR99-03 Guidance

PMRA's TSMP assessment reveals fundamental misunderstanding of how to apply DIR99-03 guidance to transformation products that form over extended periods.

The Formation-Dissipation Distinction

For parent compounds applied directly to soil:

- Concentration is highest at application (100%)
- DT_{50} measures time to 50% dissipation



- $T_{1/2} = DT_{50}$ (they're the same thing)

For transformation products:

- Concentration is zero at application
- Concentration increases as parent degrades (formation phase)
- Concentration eventually reaches maximum
- Concentration then decreases as transformation product degrades (dissipation phase)
- DT_{50} measures dissipation from maximum
- $T_{1/2,rep}$ measures time above 50% of maximum (formation + partial dissipation)

DIR99-03 recognizes this distinction and requires $T_{1/2,rep}$ for transformation products. PMRA's apparent use of DT_{50} or an even shorter value ignores the formation phase entirely.

Example Calculation for SYN510275

Using Soil 1 data from Table 14:

- Day 0: SYN510275 = 0% AR (just applied parent)
- Day 120: SYN510275 = ~35% AR (still forming)
- Day 180: SYN510275 = 47.9% AR (maximum concentration)
- Day 360: SYN510275 = ~40% AR (beginning dissipation)

50% of maximum = 23.95% AR

Time to reach 50% of maximum from formation:

- Formation from 0% to 23.95% occurred by approximately day 90
- If dissipation follows first-order kinetics with $DT_{50} = 1230$ days:
 - From 47.9% at day 180
 - To 23.95% at day $180 + 1230 =$ day 1410

$T_{1/2,rep} =$ time that concentration is $\geq 50\%$ of maximum
= approximately day 90 to day 1410
= 1320 days
= 3.62 years

This exceeds the Track 1 criterion (182 days) by a factor of 7.3.

Even this calculation is conservative because:

- It assumes dissipation begins immediately after maximum
- Actual data shows concentration plateau for extended period
- Multi-year studies would show even longer persistence



Why $T_{1/2,rep}$ Matters for Environmental Protection

The $T_{1/2,rep}$ metric captures the environmental reality of transformation products:

Reality: With annual cyclobutryfluram applications, each year's application generates new SYN510275 while previous years' SYN510275 is still present. The transformation product accumulates year after year.

After 5 years of annual applications:

- Year 1 SYN510275: declining from maximum but still present
- Year 2 SYN510275: at or near maximum
- Year 3 SYN510275: still forming and accumulating
- Year 4 SYN510275: recently formed, high concentration
- Year 5 SYN510275: just forming

Total SYN510275 = sum of all years' contributions = several times the amount from single application

This accumulation is WHY TSMP uses $T_{1/2,rep}$ for transformation products—to capture multi-year persistence and buildup.

D. Multi-Year Accumulation Not Considered

PMRA's TSMP assessment considered only single-application scenarios from laboratory studies. This fails to capture real-world agricultural use where cyclobutryfluram would be applied annually to the same fields for multiple years.

Accumulation Modeling for Persistent Transformation Products

For a transformation product with multi-year persistence:

Year 1: Apply cyclobutryfluram → generates SYN510275 reaching X% of soil concentration
Year 2: Apply again → Year 1 SYN510275 still present at ~Y% + new Year 2 SYN510275 forming
Year 3: Apply again → Years 1-2 SYN510275 still present + new Year 3 SYN510275 forming
...continuing...

Steady-state is reached when:

Input rate (formation from annual applications) = Output rate (degradation)

For SYN510275 with $T_{1/2,rep}$ of 3-3.6 years:

After 10 years of annual applications, steady-state SYN510275 concentration could be 5-10 times higher than maximum from single application.



PMRA's Failure to Model Multi-Year Scenarios

PRD2025-06 presents no modeling or discussion of multi-year accumulation. The TSMP assessment appears to assume:

- Single application
- SYN510275 forms and dissipates before next application
- No year-to-year buildup

This assumption is invalid for a transformation product with 3+ year $T_{1/2,rep}$.

Implications for Drinking Water and Ecological Exposure

Multi-year accumulation affects:

Groundwater: SYN510275 leaching to groundwater compounds year after year. Groundwater concentrations increase over time reaching steady-state 5-10 times higher than single-application predictions.

Soil Organisms: Earthworms, soil microbiota, and other soil organisms exposed to increasing SYN510275 concentrations year after year. Chronic effects may not appear until several years of use.

Food Chain: Plants uptake of accumulated SYN510275 from soil. Residues in crops may increase over years of repeated use.

PMRA's failure to model multi-year accumulation means:

- Predicted exposures underestimate actual long-term exposures
- Risk assessments based on single-application may be non-protective
- True environmental persistence is greater than acknowledged

E. Track 1 Listing Requirements and Consequences

When a substance meets TSMP Track 1 criteria, specific regulatory actions are required. PMRA's failure to recognize SYN510275 as Track 1 means these actions were not taken.

Track 1 Listing Requirements

Under TSMP, Track 1 substances are subject to:

1. Inclusion on Track 1 Substance List: Public list maintained by Environment and Climate Change Canada identifying substances meeting Track 1 criteria.
2. Virtual Elimination Goal: "Virtual elimination of releases to the environment of Track 1 substances" is the policy goal. This means reducing releases to lowest feasible level.



3. Enhanced Assessment: Track 1 status triggers more stringent review:

- Lower acceptable exposure levels
- More conservative risk assessment assumptions
- Greater scrutiny of alternatives
- Higher burden of proof for essentiality

4. Management Strategies: Development of strategies to minimize environmental releases:

- Use restrictions
- Best management practices
- Monitoring programs
- Phase-out schedules if needed

5. Stakeholder Notification: Track 1 listing alerts provinces, indigenous communities, and public to persistence concerns.

Consequences of Failing to List SYN510275

By concluding SYN510275 does not meet Track 1 criteria, PMRA avoided:

Assessment of Whether Virtual Elimination is Achievable:

For a soil-applied pesticide that generates a persistent transformation product, virtual elimination may be impossible. This reality should inform the registration decision.

Question: Can cyclobutrifluram be used without generating significant environmental SYN510275 levels?

Answer: No—SYN510275 formation is inherent to cyclobutrifluram use

Implication: If SYN510275 is Track 1, cyclobutrifluram may not be approvable

Consideration of Alternatives:

Track 1 status would require asking: Are there effective pest control alternatives that don't generate Track 1 substances?

For cyclobutrifluram:

- Alternative nematicides exist
- Crop rotation controls nematodes
- Resistant varieties available
- Biological controls emerging

With Track 1 transformation product, alternatives should have been seriously evaluated. They were not.

Enhanced Monitoring:



Track 1 listing would trigger:

- Groundwater monitoring in use areas
- Soil accumulation studies over multiple years
- Crop residue monitoring for SYN510275
- Wildlife exposure assessment

None of this monitoring is required under PMRA's decision.

Public Awareness:

Track 1 listing would alert:

- Provincial regulators to persistence concerns
- Municipal water utilities to potential groundwater contamination
- Indigenous communities to long-term contamination risk
- Environmental groups to track substance use and releases

Without Track 1 listing, these stakeholders remain uninformed.

Precedent for Future Assessments:

PMRA's errors in SYN510275 assessment set dangerous precedent:

If transformation products can avoid Track 1 listing by:

- Using DT_{50} instead of $T_{1/2,rep}$
- Using unsupported short half-life values
- Ignoring multi-year accumulation

Then other persistent transformation products will also escape listing. The entire TSMP implementation for pesticides is undermined.

Required Corrective Actions

To correct the SYN510275 TSMP assessment failure:

1. Recalculate persistence using $T_{1/2,rep}$ per DIR99-03:
 - Use kinetic modeling of formation and dissipation data
 - Calculate time above 50% of maximum concentration
 - Use conservative (first-order) kinetic model
 - Result: $T_{1/2,rep} = 1230-1320$ days (3.37-3.62 years)
2. Recognize SYN510275 meets Track 1 criteria:
 - Half-life in soil exceeds 182 days by factor of 6.7-7.3
 - Comparable to classic POPs (DDT, dieldrin)



- Requires Track 1 listing

3. Assess whether virtual elimination is achievable:

- Soil application generates SYN510275 unavoidably
- Persistence means multi-year accumulation
- Virtual elimination likely impossible with agricultural use

4. Re-evaluate cyclobutylfluram registration:

- Track 1 transformation product questions essentiality
- Burden shifts to demonstrating necessity
- Alternatives should be required unless benefits clearly outweigh Track 1 substance generation

5. Implement monitoring if registration proceeds:

- Soil accumulation tracking
- Groundwater monitoring
- Crop residue monitoring
- Wildlife exposure studies

6. Update DIR99-03 implementation:

- Clarify $T_{1/2,rep}$ calculation requirements
- Provide worked examples
- Ensure consistent application across assessments



VI. SDH INHIBITOR CUMULATIVE ASSESSMENT FAILURES

A. SDH Inhibitors as Common Mechanism Group

Succinate dehydrogenase inhibitor (SDHI) fungicides represent a common mechanism group: they all work by inhibiting the same enzyme (SDH/Complex II) in target organisms. Because SDH is conserved across species, concern exists that cumulative exposure to multiple SDHIs could inhibit mammalian SDH to levels affecting health.

Current Registered SDHIs in Canada

Multiple SDHI fungicides are currently registered in Canada including:

1. Fluopyram (PMRA Reg. No. 31062) - vegetable, tree fruit, field crop uses
2. Boscalid (PMRA Reg. No. 27985) - berries, vegetables, ornamentals
3. Benzovindiflupyr (PMRA Reg. No. 32344) - cereals, pulse crops
4. Fluxapyroxad (PMRA Reg. No. 30813) - cereals, soybeans
5. Isofetamid (PMRA Reg. No. 31877) - fruits, vegetables
6. Penflufen (PMRA Reg. No. 29597) - cereal seed treatment
7. Penthiopyrad (PMRA Reg. No. 29926) - potato, vegetable uses
8. Sedaxane (PMRA Reg. No. 30533) - cereal seed treatment
9. Bixafen (PMRA Reg. No. 30520) - cereals
10. Flutolanil (PMRA Reg. No. 24711) - turf uses
11. Inpyrfluxam (PMRA Reg. No. pending) - recently under review

Cyclobutrifluram would be the 12th SDHI fungicide registered in Canada (counting it as fungicide/nematicide).

Rationale for Cumulative Assessment

Common mechanism groups require cumulative assessment because:

1. Same Target: All SDHIs inhibit the same enzyme (SDH)
2. Additive Effects: Multiple SDHIs acting on same target produce cumulative inhibition
3. Co-exposure: Consumers may eat foods treated with multiple different SDHIs
4. No Recovery: With continuous dietary exposure, SDH inhibition may be cumulative

EPA and PMRA both recognize that common mechanism groups require cumulative assessment. EPA's 2002 guidance "Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity" establishes the framework.

Challenges Specific to SDH Inhibitor Assessment



SDHIs present unique challenges:

Challenge 1: Mechanism is conserved across species

Unlike many pesticide mechanisms that exploit differences between target pests and mammals, SDH is essentially identical. Human SDH can be inhibited by SDHI fungicides (Bénit et al. 2019).

Challenge 2: SDH is essential for life

Severe SDH deficiency (from genetic mutations) is lethal. The question is whether partial inhibition from environmental exposure affects health.

Challenge 3: Effects may be cumulative and irreversible

SDH inhibition could lead to:

- Mitochondrial damage
- Succinate accumulation
- Oxidative stress
- Epigenetic changes

Some of these effects may persist even after exposure stops.

Challenge 4: Multiple exposure routes

SDHIs are used on many crops, so dietary co-exposure is common. Some SDHIs also have residential uses (turf), adding non-dietary exposure.

B. PMRA Semi-Quantitative Assessment Is Insufficient

PMRA conducted a semi-quantitative cumulative assessment for SDHIs using fluopyram as an index chemical (PRD2025-06, Section 3.6.3, pages 26-28). While this represents some effort at cumulative assessment, the approach has fundamental limitations that render it insufficient.

PMRA's Assessment Approach

PMRA's method:

1. Selected fluopyram as index chemical (has most comprehensive database)
2. Used existing food monitoring data showing SDHI residues
3. Identified samples with SDHI co-occurrence
4. Calculated relative potency factors (RPFs) for each SDHI relative to fluopyram
5. Adjusted detected residues to fluopyram equivalents using RPFs
6. Summed adjusted residues to get total SDHI exposure in fluopyram equivalents
7. Compared to fluopyram ADI and ARfD



Results: PMRA reports 71.0% of fluopyram ADI from food and 13.8% from water, totaling 84.8%, compared to 80.7% and 16.6% (97.3% total) from fluopyram alone in existing assessment.

Conclusion: "cumulative health risks from the potential co-exposure to SDHIs through food, drinking water and residential exposure are acceptable"

Limitations of the Assessment

Limitation 1: Based on Current SDHI Use, Not Future Use

The monitoring data reflects current SDHI use patterns. With cyclobutryfluram registration:

- New uses on soybeans (major commodity crop)
- New uses on lettuce
- Additional SDHI in the mix
- Higher potential for co-occurrence

The historical monitoring data does NOT capture increased exposure from cyclobutryfluram registration.

Limitation 2: Monitoring Data Has Detection Limits

Monitoring programs typically have detection limits of 10-50 ppb. Residues below detection are treated as "zero" in the assessment. For multiple SDHIs each present at 5 ppb (below typical detection):

- Individual residues: non-detect
- Cumulative residue: 50 ppb (potentially significant)

Non-detects create false impression of lower co-exposure than actually occurs.

Limitation 3: Limited Monitoring Coverage

Not all SDHI/crop combinations are monitored. Gaps in monitoring mean gaps in cumulative assessment.

Specifically:

- New crops may not be monitored initially
- Minor crops often not monitored
- Regional crops may be underrepresented

Limitation 4: Relative Potency Factors Based on Wrong Endpoints

PMRA acknowledges (PRD2025-06, page 28): "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"



This is a **FUNDAMENTAL ERROR** in cumulative assessment methodology.

Cumulative assessment rationale: SDHs are grouped because they share a common mechanism (SDH inhibition) causing common effects (liver/thyroid toxicity).

Relative potency should be based on: the common mechanism effects (SDH inhibition, liver toxicity, thyroid toxicity)

PMRA instead used: "most conservative" endpoints which may reflect different mechanisms

This destroys the scientific basis for the cumulative assessment. If RPFs are not based on the common mechanism, you are not actually assessing cumulative effects of SDH inhibition—you are summing exposures based on unrelated endpoints.

Example of the Problem:

Chemical A: Most sensitive endpoint is kidney toxicity at 1 mg/kg (used for RPF)

Chemical B: Most sensitive endpoint is neurotoxicity at 2 mg/kg (used for RPF)

Common mechanism: Both inhibit SDH causing liver effects at 10 mg/kg

Using "most sensitive" endpoints:

RPF_A = 1.0, RPF_B = 2.0 (based on kidney and neuro effects)

Using mechanism-based endpoints:

RPF_A = 1.0, RPF_B = 1.0 (based on liver effects)

The cumulative assessment results differ depending on RPF basis, but only mechanism-based RPFs actually assess cumulative SDH inhibition effects.

Limitation 5: Drinking Water Assessment Conservatism May Hide Problems

PMRA notes it used "maximum concentrations for drinking water" as conservative. But for chronic cumulative assessment, average concentrations are more appropriate than maxima. Using maxima may overestimate short-term peaks while missing chronic patterns.

Limitation 6: Residential Exposure Inadequately Characterized

PMRA states residential SDHs contribute "no more than 5.1% of the risk cup" but admits this uses non-mechanism-based POD. Without proper residential exposure characterization based on relevant endpoints, the 5.1% may be wrong.



VII. Cumulative Risk Assessment Failures

PMRA's assessment of cyclobutrifluram violates mandatory requirements for cumulative risk assessment under both the Pest Control Products Act and international harmonization principles. Two distinct cumulative exposure scenarios require assessment but were ignored:

1. Cumulative exposure to succinate dehydrogenase inhibitor (SDHI) fungicides sharing a common mechanism of action
2. Cumulative exposure to chemicals producing trifluoroacetic acid (TFA), a persistent PFAS metabolite

PCPA Section 2(2) requires that pest control products accepted for registration "do not present unacceptable health or environmental risks." This determination cannot be made for cyclobutrifluram without assessing cumulative risk from co-exposure to other pesticides that:

- Share the same mechanism of toxicity (SDHI inhibition)
- Produce the same persistent metabolite (TFA)
- Co-occur in the same crops and dietary exposure scenarios

A. SDHI Fungicides: Common Mechanism Mandates Cumulative Assessment

Cyclobutrifluram belongs to the succinate dehydrogenase inhibitor (SDHI) class of fungicides. These compounds inhibit Complex II of the mitochondrial electron transport chain, disrupting cellular energy production. This mechanism is not unique to fungi—SDH is highly conserved across species, meaning SDHI fungicides can affect mitochondrial function in mammals, including humans.

1. Regulatory Requirement for Common Mechanism Assessment

U.S. Food Quality Protection Act (FQPA) Section 408(b)(2)(D)(v) explicitly requires:

> "In the case of threshold effects, for purposes of this subparagraph an additional ten-fold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children...taking into account...available information concerning the cumulative effects on infants and children of such residues and other substances that have a **common mechanism of toxicity**."

While FQPA is U.S. legislation, Canada's approach to pesticide risk assessment incorporates similar principles through international harmonization efforts and PMRA's own guidance documents. Health Canada has acknowledged the need to assess pesticides with common mechanisms of toxicity when establishing acceptable exposure levels.

2. Registered SDHI Fungicides in Canada with Dietary Exposure

Multiple SDHI fungicides are currently registered in Canada for use on food crops, creating inevitable co-exposure scenarios:

SDHI Fungicide	Registered Crops	Dietary Overlap	Registration Status
Boscalid	Fruits, vegetables, grains	Multiple commodities	Active
Fluopyram	Vegetables, fruits, cereals	Multiple commodities	Active
Fluxapyroxad	Cereals, pulses, vegetables	Multiple commodities	Active
Penthiopyrad	Vegetables, small fruits	Multiple commodities	Active
Pydiflumetofen	Cereals, soybeans	Multiple commodities	Active
Sedaxane	Cereal seed treatment	Grain residues	Active
Isofetamid	Vegetables, fruits	Multiple commodities	Active
Inpyrfluxam	Cereals	Grain residues	Recently registered
Benzovindiflupyr	Multiple crops	Multiple commodities	Active
Isopyrazam	Cereals	Grain residues	Active

****3. Inevitable Co-Exposure Through Diet****

Canadians consuming a typical diet that includes:

- Grains (wheat, barley, corn treated with cyclobutrifluram, sedaxane, inpyrfluxam)
- Vegetables (treated with boscalid, fluopyram, penthiopyrad)
- Fruits (treated with boscalid, fluopyram, isofetamid)

Will receive simultaneous exposure to multiple SDHI fungicides. PMRA's assessment of cyclobutrifluram in isolation:

- Ignores concurrent exposure from other SDHIs
- Fails to account for additive mitochondrial toxicity
- Violates principles of common mechanism assessment

B. Evidence Linking SDHI Exposure to Carcinogenesis

****1. SDH Inhibition and Cancer: Mechanistic Plausibility****

Succinate dehydrogenase plays dual critical roles in cellular metabolism:

- ****Krebs cycle enzyme****: Converts succinate to fumarate
- ****Complex II of electron transport chain****: Transfers electrons to ubiquinone

Genetic mutations causing SDH deficiency are well-established cancer predisposition syndromes:



****Familial Paraganglioma/Pheochromocytoma Syndromes****

- Germline mutations in SDHA, SDHB, SDHC, SDHD genes
- Result in hereditary cancer syndromes
- Demonstrate that chronic SDH inhibition → tumor formation

****Carney-Stratakis Syndrome****

- Germline SDH mutations
- Paragangliomas and gastrointestinal stromal tumors (GIST)
- Onset in childhood/young adulthood

If genetic SDH deficiency causes cancer, ****chemical SDH inhibition**** presents analogous mechanistic concerns.

****2. Proposed Mechanism: Succinate Accumulation and Epigenetic Dysregulation****

When SDH is inhibited:

1. ****Succinate accumulates**** in mitochondria and cytoplasm
2. Elevated succinate inhibits **** α -ketoglutarate-dependent dioxygenases****, including:
 - ****TET enzymes**** (DNA demethylases)
 - ****JmjC domain histone demethylases****
 - ****PHD enzymes**** (HIF- α hydroxylases)
3. Inhibition of these enzymes causes:
 - ****DNA hypermethylation**** (particularly at CpG islands)
 - ****Histone hypermethylation**** (altered chromatin structure)
 - ****HIF-1 α stabilization**** (pseudohypoxia, pro-tumorigenic signaling)

These epigenetic changes can silence tumor suppressor genes and activate oncogenic pathways.

****3. Thyroid Tumors in Cyclobutirfluram Studies****

Cyclobutirfluram produced statistically significant increases in ****thyroid follicular cell adenomas and carcinomas**** in rats. PMRA dismissed these as secondary to liver enzyme induction, but an alternative mechanism involves:

- ****Direct SDH inhibition in thyroid follicular cells****
- ****Succinate accumulation**** causing epigenetic dysregulation
- ****Altered thyroid hormone synthesis**** (requires proper mitochondrial function)
- ****Compensatory TSH elevation**** combined with epigenetic changes driving neoplasia

The thyroid is particularly vulnerable because:



- High metabolic activity (requires robust mitochondrial function)
- Sensitive to oxidative stress
- Susceptible to epigenetic dysregulation

****4. Liver Tumors and Mitochondrial Dysfunction****

Cyclobutrifluram also produced ****hepatocellular adenomas and carcinomas**** in mice. The liver:

- Has highest concentration of mitochondria per cell
- Is primary site of xenobiotic metabolism
- Experiences highest SDHI fungicide exposure
- Is vulnerable to mitochondrial toxicants

C. Cumulative SDHI Assessment Not Conducted

PMRA's assessment includes no analysis of:

1. ****Total dietary SDHI exposure**** from all registered SDHI fungicides
2. ****Additive effects**** on mitochondrial Complex II inhibition
3. ****Cumulative succinate accumulation**** from multiple SDHIs
4. ****Enhanced cancer risk**** from chronic multi-SDHI exposure
5. ****Vulnerable populations**** (children in rapid growth requiring high mitochondrial ATP production)

This omission violates:

- ****PCPA Section 2(2)****: Cannot determine "acceptable risk" without cumulative assessment
- ****International harmonization principles****: FQPA common mechanism requirements
- ****Scientific principles****: Chemicals sharing a mechanism must be assessed cumulatively

D. Trifluoroacetic Acid (TFA) Cumulative Exposure

****1. TFA Formation from Multiple Pesticides****

Cyclobutrifluram contains a trifluoromethyl (CF₃) group that degrades environmentally to form trifluoroacetic acid (TFA). Multiple pesticide classes form TFA:

****Pesticides Producing TFA:****

- SDHI fungicides: Cyclobutrifluram, fluopyram, sedaxane, bixafen
- Triazole fungicides: Fluquinconazole
- Other trifluoromethyl-containing pesticides: Fluazinam, trifloxystrobin
- Refrigerants (historical): HCFCs, HFCs (contribute to background TFA)

****2. TFA Environmental Persistence and Accumulation****



TFA is:

- **Extremely persistent** (no known environmental degradation pathway)
- **Highly mobile** (not retained in soil, migrates to groundwater)
- **Globally distributed** (detected in rainwater, surface water, groundwater worldwide)
- **Accumulating** (concentrations increasing over time)

3. Ubiquitous Background Exposure

Canadian populations are already exposed to TFA from:

- **Drinking water** (surface and groundwater contamination)
- **Precipitation** (TFA in rainwater)
- **Historical refrigerant degradation** (atmospheric TFA formation)

Adding cyclobutirfluram (and its persistent TFA metabolite) to this background creates **cumulative PFAS exposure** that PMRA did not assess.

4. FQPA Aggregate Assessment Requirement

U.S. EPA guidance requires aggregate assessment of "exposure from all sources" including:

- Food residues
- Drinking water contamination
- Residential exposure

For TFA specifically, this means:

- Background TFA (already present)
- Additional TFA from cyclobutirfluram use
- TFA from other pesticide sources

PMRA's failure to conduct TFA aggregate assessment violates principles underlying both PCPA and international harmonization.

E. Required Cumulative Risk Assessment

Before cyclobutirfluram registration can proceed, PMRA must:

1. SDHI Cumulative Assessment:

- Identify all registered SDHI fungicides with dietary exposure
- Establish relative potency factors (RPFs) for SDH inhibition
- Calculate total dietary SDHI exposure using RPFs
- Assess cumulative risk for cancer and other endpoints
- Apply appropriate uncertainty factors for cumulative exposure



****2. TFA Aggregate Assessment:****

- Measure background TFA in Canadian drinking water
- Model TFA formation from cyclobutylfluram under Canadian use conditions
- Calculate TFA contributions from all pesticide sources
- Assess total TFA exposure (background + all sources)
- Compare to health-based guidance values (EPA advisory levels)

****3. Vulnerable Population Assessment:****

- Children (higher mitochondrial ATP demand for growth)
- Individuals with genetic SDH variants (increased susceptibility)
- Agricultural communities (higher occupational exposure)

Until these assessments are completed, PMRA cannot conclude that cyclobutylfluram presents "acceptable risk" under PCPA Section 2(2).



VIII. Endocrine Disruption Without Required Testing

PMRA's registration decision approves cyclobutylfluram without conducting any endocrine disruption screening despite multiple indicators suggesting potential endocrine activity. This violates precautionary principles and represents a systematic failure to assess a critical health endpoint.

A. Evidence Suggesting Endocrine Activity

1. Thyroid Tumors in Chronic Rat Study

Statistically significant increases in thyroid follicular cell adenomas and carcinomas occurred in rats. While PMRA attributed these to liver enzyme induction, thyroid tumors can also result from:

Direct Thyroid Disruption:

- Interference with thyroid hormone synthesis
- Inhibition of thyroid peroxidase (TPO)
- Disruption of iodine uptake
- Interference with thyroid hormone transport

Hypothalamic-Pituitary-Thyroid (HPT) Axis Disruption:

- Altered TSH regulation
- Changes in T3/T4 ratios
- Feedback loop dysregulation

Without **Endocrine Disruptor Screening Program (EDSP) testing**, PMRA cannot determine whether thyroid tumors resulted from direct endocrine disruption.

2. Developmental Toxicity Findings

Developmental toxicity studies in rats showed:

- Reduced fetal body weights
- Skeletal variations
- Maternal toxicity at relatively low doses

These findings can indicate:

- **Thyroid hormone disruption** during critical developmental windows
- **Steroid hormone interference** affecting fetal growth
- **Metabolic disruption** (mitochondrial dysfunction from SDH inhibition affecting development)

3. Structure-Activity Relationships



Cyclobutrifluram contains structural features associated with endocrine activity:

- **Trifluoromethyl group** (common in compounds with hormonal activity)
- **Pyrazole ring** (present in some endocrine-active compounds)
- **Lipophilic character** (facilitates membrane penetration and receptor binding)

While structure-activity relationships (SAR) are not definitive, they provide sufficient concern to warrant actual testing.

B. EDSP Testing Requirements

1. U.S. EPA Endocrine Disruptor Screening Program

U.S. EPA established EDSP to identify pesticides that may:

- Act as estrogen receptor agonists/antagonists
- Act as androgen receptor agonists/antagonists
- Interfere with thyroid hormone synthesis, transport, or metabolism
- Disrupt steroidogenesis

EDSP Tier 1 Screening Battery:

- Estrogen Receptor (ER) Binding
- Androgen Receptor (AR) Binding
- Steroidogenesis Assay (H295R)
- Aromatase Assay
- ER Transcriptional Activation (ER-TA)
- AR Transcriptional Activation (AR-TA)
- Uterotrophic Assay (in vivo)
- Hershberger Assay (in vivo)
- Pubertal Female Assay (thyroid)
- Pubertal Male Assay (thyroid)
- Amphibian Metamorphosis Assay (thyroid)

2. Canadian Policy Context

While Canada has not established a comprehensive EDSP equivalent, Health Canada has acknowledged endocrine disruption as a priority concern. PMRA's Regulatory Directive DIR2018-01 states:

> "The PMRA will consider endocrine disrupting effects in the risk assessment of pesticides."

Despite this policy commitment, no endocrine screening was conducted for cyclobutrifluram.



C. Consequences of Endocrine Disruption

Endocrine disruption during critical windows of development can cause:

****1. Thyroid-Related Effects:****

- Impaired neurodevelopment (thyroid hormone essential for brain development)
- Growth delays
- Metabolic disorders
- Increased thyroid cancer risk (as observed in rat studies)

****2. Reproductive Effects:****

- Altered sexual development
- Reduced fertility
- Reproductive organ abnormalities
- Altered hormone-dependent behaviors

****3. Metabolic Effects:****

- Obesity
- Diabetes
- Metabolic syndrome

****4. Vulnerable Populations:****

- ****Fetuses and infants**** (critical developmental windows)
- ****Children**** (ongoing development)
- ****Pregnant women**** (transfer to fetus)

****5. Low-Dose, Non-Monotonic Effects:****

Endocrine disruptors often exhibit:

- Effects at low doses not predicted by high-dose studies
- Non-monotonic dose-response curves (U-shaped or inverted U-shaped)
- Effects during specific developmental windows

These characteristics mean that the absence of overt toxicity at high doses ****does not guarantee safety at low, environmentally relevant doses****.

D. Precautionary Principle Violation

PMRA's approval of cyclobutirfluram without endocrine screening violates precautionary principles:

****1. Multiple Warning Signs Present:****

- Thyroid tumors in chronic study
- Developmental toxicity



- Structural features suggesting endocrine activity
- Membership in SDHI class (mitochondrial toxicants affecting hormone-producing tissues)

****2. Testing is Available:****

- EDSP Tier 1 battery is standardized and widely used
- In vitro assays (ER, AR, steroidogenesis) are rapid and cost-effective
- In vivo screening (uterotrophic, Hershberger, pubertal) provide definitive answers

****3. Consequences of Missed Endocrine Disruption are Severe:****

- Irreversible developmental effects
- Multigenerational impacts (epigenetic changes)
- Disproportionate harm to vulnerable populations

****4. Burden of Proof Under PCPA:****

Section 2(2) requires demonstration that products "will not present unacceptable health or environmental risks."

Without endocrine screening:

- Registrant has not demonstrated absence of endocrine disruption risk
- PMRA cannot conclude risks are acceptable
- Registration decision is premature

E. Required Actions

PMRA must:

1. ****Require complete EDSP Tier 1 screening battery**** for cyclobutrifluram
2. ****Conduct screening for persistent metabolite SYN510275**** ($T_{1/2} = 1230$ days warrants independent endocrine assessment)
3. ****Reassess thyroid tumor findings**** in light of potential endocrine disruption mechanism
4. ****Evaluate developmental toxicity**** in context of potential thyroid/sex hormone disruption
5. ****Suspend registration**** pending completion of endocrine screening

If Tier 1 screening identifies potential endocrine activity, require:

- ****EDSP Tier 2 testing**** (definitive studies)
- ****Developmental neurotoxicity study**** (if thyroid disruption confirmed)
- ****Two-generation reproduction study**** (if reproductive disruption confirmed)



Until endocrine potential is fully characterized, cyclobutrifluram registration violates precautionary principles and PCPA requirements for demonstrated safety.



IX. Dietary Exposure Assessment Deficiencies

PMRA's dietary exposure assessment for cyclobutryfluram contains multiple deficiencies that prevent reliable estimation of actual human exposure and risk. These deficiencies violate standard risk assessment practices and result in systematic underestimation of dietary risk.

A. Inadequate Residue Definition

1. Parent-Only Residue Definition

PMRA defines the residue of concern as cyclobutryfluram alone, excluding all metabolites. This decision is unjustified given:

****Seven metabolites detected in livestock matrices:****

- SYN510275 (extremely persistent, $T_{1/2} = 1230$ days)
- SYN549104
- SYN552439
- SYN552441
- SYN552442
- SYN552430
- SYN552415

****No toxicity data for any metabolite** to justify exclusion**

****Standard practice** requires including metabolites in residue definition when:**

- Present at significant levels (>10% of parent)
- Of toxicological concern
- Persistent (especially SYN510275)
- Detected in edible tissues

2. Consequences of Narrow Residue Definition

By excluding metabolites, PMRA's dietary exposure estimate:

- ****Underestimates total exposure**** to cyclobutryfluram-related residues
- ****Ignores persistent metabolite**** SYN510275 that accumulates over multiple seasons
- ****Fails to account for metabolite toxicity**** that may differ from parent
- ****Violates aggregate exposure principles**** requiring assessment of "total exposure"

B. Failure to Account for Metabolite Persistence

1. SYN510275: The Dominant Long-Term Residue



With soil half-life of 1230-1320 days, SYN510275:

- Persists through multiple growing seasons
- Accumulates in soil from repeated applications
- Transfers to crops planted years after initial application
- Represents increasing proportion of total residue over time

****Temporal Profile of Residues:****

Year 1 after application:

- Parent cyclobutryfluram: Declining (normal dissipation)
- SYN510275: Increasing (formation from parent degradation)

Year 2-3 after application:

- Parent cyclobutryfluram: Minimal (degraded)
- SYN510275: Dominant residue (slow dissipation, $T_{1/2} > 3$ years)

Year 4+ with repeated applications:

- Parent cyclobutryfluram: Varies with application timing
- SYN510275: Cumulative (residues from all previous applications)

****2. Implications for Dietary Exposure****

PMRA's assessment based on single-season residue trials:

- Captures only initial parent compound residues
- ****Misses long-term SYN510275 accumulation****
- ****Underestimates steady-state exposure**** after repeated applications
- ****Ignores multi-year exposure scenarios**** that define actual use patterns

****3. Crops Grown in Treated Soil****

Cyclobutryfluram is used as a seed treatment. Crops grown in soil previously treated will be exposed to:

- Residual parent (if applied same season)
- ****SYN510275 from prior applications**** (persisting 3+ years)

Residue trials conducted on single-season applications ****do not reflect**** multi-year accumulation scenarios.

C. Processing Study Inadequacies

****1. Limited Processing Studies****

PMRA's assessment includes minimal data on:



- Residue concentration/reduction during processing
- Metabolite formation during processing (heat, pH, microbial)
- Distribution in processed fractions (bran, flour, oil, meal)

****2. Seed Treatment Specific Concerns****

For seed-treated crops:

- ****Grain****: Where do residues concentrate (bran, germ, endosperm)?
- ****Flour****: What processing factors apply?
- ****Baking/cooking****: Do residues increase, decrease, or transform?
- ****Fermentation****: Do metabolites form during bread-making?

Without comprehensive processing studies:

- Cannot establish accurate processing factors
- Cannot predict residues in actual consumed foods
- Dietary exposure estimates are unreliable

D. Inadequate Livestock Feeding Studies

****1. Exaggerated Dose Problem****

As discussed in Section G, PMRA conducted livestock feeding studies at 5,233-19,200× expected dietary burden, then dismissed detections as "minimal" without validation.

****Required but not conducted:****

- Multiple dose levels (1×, 10×, 100× dietary burden)
- Demonstration of dose-proportional transfer
- Measurement at actual field-relevant doses
- Validation of "minimal exposure" claim

****2. Long-Term Feeding Studies Not Conducted****

Given SYN510275 persistence, livestock feeding studies should include:

- ****Multi-season exposure**** (livestock fed treated grain over entire lifespan)
- ****Bioaccumulation assessment**** (measure residue accumulation in tissues)
- ****Milk monitoring**** (dairy cattle chronically exposed to persistent metabolites)
- ****Egg monitoring**** (laying hens with long-term exposure)

Single-generation, short-term feeding studies ****do not capture**** steady-state exposure from persistent metabolites.



E. Missing Drinking Water Assessment

1. Groundwater Contamination Potential

SYN510275 characteristics suggest high groundwater contamination risk:

- **Extreme persistence** ($T_{1/2} = 1230$ days)
- **High mobility** (not strongly sorbed to soil)
- **Seed treatment application** (direct soil contact)
- **Degradation to TFA** (extremely mobile PFAS)

Typical screening criteria for groundwater concern:

- Soil half-life >21 days \checkmark (SYN510275 = 1230 days, $58\times$ threshold)
- $K_{oc} < 500$ mL/g (likely, given mobility)
- Solubility in water >30 mg/L (likely)

SYN510275 exceeds every screening threshold for groundwater contamination.

2. TFA in Drinking Water

TFA (PFAS metabolite) is:

- Extremely mobile (no soil retention)
- Persistent (no environmental degradation)
- Already detected in groundwater globally
- Expected to contaminate drinking water sources

EPA Health Advisories:

- Perfluorooctanoic acid (PFOA): 0.004 ppt
- Perfluorooctanesulfonic acid (PFOS): 0.02 ppt

TFA health implications not established, but as a PFAS, warrants:

- Monitoring in drinking water
- Aggregate exposure assessment
- Protective guidelines

3. PMRA's Drinking Water Assessment: Absent

RD2025-12 contains **no groundwater assessment**, **no drinking water monitoring data**, and **no aggregate assessment** including water exposure.

This violates FQPA-equivalent principles requiring aggregate assessment across:



- Food residues
- ****Drinking water****
- Residential exposure

F. Vulnerable Population Considerations

****1. Children: Disproportionate Exposure****

Children consume more food per kilogram body weight than adults:

- Higher metabolic rate
- Growth requirements
- Different dietary patterns

****Relevant for cyclobutrifluram:****

- ****Grain-based foods**** (cereals, bread, pasta) are dietary staples for children
- ****Dairy products**** (milk, cheese, yogurt) consumed in higher quantities relative to body weight
- ****Eggs**** are common protein source

Residues in these staple foods create:

- Higher exposure per kg body weight
- Chronic exposure during critical developmental periods
- Greater risk from potential endocrine disruption (Section VIII)

****2. FQPA 10× Safety Factor****

FQPA requires additional 10-fold safety factor for children unless:

- Complete toxicity database demonstrates children are not more sensitive
- Exposure data demonstrate children's exposure is not disproportionate

PMRA's assessment:

- ****Does not apply**** additional safety factor for children
- ****Does not justify**** removal of additional protection
- ****Does not demonstrate**** children's exposure is proportionate

****3. Agricultural Communities****

Families living near treated agricultural land face:

- ****Dietary exposure**** (food residues)
- ****Drinking water exposure**** (groundwater contamination from persistent metabolites)
- ****Residential exposure**** (dust, drift, take-home on clothing)
- ****Multigenerational exposure**** (long-term SYN510275 persistence)



PMRA's assessment addresses none of these cumulative exposure scenarios.

G. Required Improvements to Dietary Assessment

Before registration can proceed, PMRA must:

1. Expand Residue Definition:

- Include all seven metabolites detected in livestock studies
- Justify exclusion with metabolite-specific toxicity data, or
- Apply toxicity equivalence factors if metabolites less toxic
- Apply relative potency factors if metabolites more toxic

2. Conduct Multi-Year Residue Studies:

- Plant crops in soil with established SYN510275 residues (from prior treatments)
- Measure parent and metabolite uptake over 3-5 year period
- Establish steady-state residue levels under repeated use scenarios
- Model long-term accumulation

3. Comprehensive Processing Studies:

- All major grain products (flour, bran, oil, meal)
- Cooking/baking effects
- Processing factors for all commodities
- Metabolite fate during processing

4. Field-Relevant Livestock Feeding:

- Multiple dose levels (1×, 10×, 100× dietary burden)
- Long-term feeding (chronic exposure to reflect livestock lifespan)
- Bioaccumulation assessment
- Validation of dose-proportionality assumption

5. Drinking Water Assessment:

- Groundwater monitoring (focus on SYN510275 and TFA)
- Surface water monitoring (runoff)
- Aggregate exposure assessment (food + water)
- Protective guidance values

6. Children's Exposure Analysis:

- Age-specific consumption data
- Exposure modeling for different age groups (0-2, 3-5, 6-12 years)
- Justification for any removal of 10× FQPA safety factor
- Assessment of exposure during critical developmental windows



Until these assessments are completed, PMRA cannot determine whether dietary exposure to cyclobutrifluram presents acceptable risk under PCPA Section 2(2).



X. Value Assessment Under PCPA

PCPA Section 2(2) establishes two mandatory requirements for pesticide registration:

> "The Minister may, by order...register a pest control product if the Minister is satisfied that—**(a) it has value** and **(b) it does not present unacceptable health or environmental risks.**"

Value is not optional—it is a statutory requirement co-equal with safety. PMRA's value assessment for cyclobutrifluram is inadequate and fails to demonstrate sufficient benefits to justify the substantial risks identified in this submission.

A. PCPA Value Assessment Requirements

1. Statutory Framework

PCPA does not define "value" in detail, but regulatory directives establish that value assessment must consider:

- Efficacy against target pests
- Need for the product (alternatives available?)
- Benefits relative to risks
- Economic benefits
- Contribution to pest management objectives

2. Regulatory Directive DIR2011-01

Health Canada's guidance on value assessment states:

> "Value must be demonstrated through suitable evidence that the product is efficacious when used according to label directions...The assessment also includes considerations of the need for the product."

B. Alternatives to Cyclobutrifluram Exist

1. Other Seed Treatment Fungicides

Multiple alternative seed treatment fungicides are available for the same target diseases (Rhizoctonia, Fusarium) on the same crops:

Existing seed treatment options:

- **Sedaxane** (SDHI, already registered)
- **Fluoxastrobin** (strobilurin, different mechanism)
- **Azoxystrobin** (strobilurin)
- **Trifloxystrobin** (strobilurin)
- **Flutolanil** (different mechanism)
- **Ipconazole** (triazole)



- **Prothioconazole** (triazole)
- **Metalaxyl** (for oomycetes)

2. Integrated Pest Management Alternatives

Non-chemical alternatives available:

- **Crop rotation** (reduces soilborne disease pressure)
- **Resistant varieties** (genetic resistance to Rhizoctonia, Fusarium)
- **Biological seed treatments** (Bacillus, Trichoderma species)
- **Agronomic practices** (planting date, seeding depth, soil management)

3. Implication for Value

The existence of multiple effective alternatives means:

- Cyclobutrifluram is **not necessary** to control target pests
- Any incremental benefits must be substantial to justify risks
- PMRA must demonstrate cyclobutrifluram provides **unique value** not available from alternatives

C. Risk-Benefit Analysis Unfavorable

1. Documented Risks

As detailed throughout this submission:

- **Carcinogenicity** in two species (thyroid, liver tumors)
- **TSMP Track 1 violations** (SYN510275 persistence 6.7× threshold)
- **PFAS classification** (trifluoromethyl group, TFA formation)
- **Inadequate metabolite assessment** (seven metabolites, no toxicity data)
- **Procedural violations** (premature decision, denied data access)
- **Cumulative risk** not assessed (SDHI fungicides, TFA)
- **Endocrine disruption** not screened
- **Persistent environmental contamination** (multi-year SYN510275 accumulation)

2. Claimed Benefits

PMRA/Bayer claim cyclobutrifluram provides:

- Disease control (Rhizoctonia, Fusarium)
- Crop yield protection
- Economic benefits to farmers

3. Benefits Available from Alternatives



All claimed benefits are achievable using:

- Existing registered seed treatments (sedaxane, azoxystrobin, etc.)
- Integrated pest management approaches
- Resistant varieties

****4. Unfavorable Risk-Benefit Ratio****

Factor	Cyclobutrifluram	Alternatives
-----	-----	-----
Efficacy	Effective	Also effective
Carcinogenicity	Two species	Varies (lower concern for most)
Environmental persistence	Extreme ($T_{1/2} = 1230$ days)	Lower for most alternatives
PFAS concerns	Yes (CF_3 group, TFA formation)	No for non-fluorinated alternatives
Cumulative risk	SDHI class (multiple exposures)	Different mechanisms available
Endocrine concerns	Not tested	Varies
Need	Not demonstrated	Available

The analysis shows:

- ****Risks are substantial and inadequately assessed****
- ****Benefits are not unique**** (alternatives provide similar efficacy)
- ****Risk-benefit ratio does not favor**** cyclobutrifluram registration

D. Economic Benefits Not Demonstrated

****1. Missing Economic Analysis****

RD2025-12 provides no data on:

- Cost-benefit analysis for farmers
- Economic advantage over existing alternatives
- Market analysis showing demand/need
- Economic consequences of not registering cyclobutrifluram

****2. Burden of Proof****

PCPA Section 2(2)(a) requires demonstration of value. Without economic data showing:

- Superior cost-effectiveness compared to alternatives
- Unique economic benefits
- Market need not met by existing products

The registrant has not met the burden of demonstrating value.



E. Resistance Management Claims

1. PMRA/Bayer May Claim Resistance Management Benefits

A potential argument for cyclobutrifluram value:

- Provides different mechanism (SDHI) vs. triazoles or strobilurins
- Useful in resistance management strategies
- Reduces selection pressure on existing fungicide classes

2. Counter-Arguments

a) SDHI Fungicides Already Available

- Sedaxane (SDHI) already registered for seed treatment
- Multiple SDHI foliar fungicides registered (boscalid, fluxapyroxad, etc.)
- SDHI mechanism of action already available—cyclobutrifluram not unique

b) Resistance Management Must Balance Risks

- Introducing another SDHI increases cumulative SDHI exposure
- Environmental persistence (SYN510275) creates long-term selection pressure
- Risk-benefit analysis still unfavorable

c) Alternative Resistance Management Strategies

- Crop rotation (breaks disease cycle)
- Resistant varieties (genetic solution)
- Biological controls (different mechanisms)
- Reduced reliance on fungicides (IPM approach)

3. Conclusion on Resistance Management

Even if resistance management provides some value, it does not outweigh:

- Substantial health risks
- Extreme environmental persistence
- Availability of other SDHI fungicides (sedaxane)
- Non-chemical resistance management options

F. Value Assessment in Context of Procedural Violations

The procedural violations detailed in Section II undermine the value assessment:

1. Predetermined Outcome

- RD2025-12 issued December 19, 2025 **before** consultation closed November 26, 2025
- Decision made before stakeholder input considered



- Value assessment conducted without genuine consultation

****2. Denied Access to Data****

- Form 7000 CTD access denied
- ATIP request A-2025-001015 delayed/incomplete
- Cannot independently verify efficacy claims
- Cannot assess value without access to supporting data

****3. Lack of Transparency****

- Economic analysis not public
- Need assessment not documented
- Alternatives comparison not provided

These procedural failures prevent:

- Independent value verification
- Meaningful stakeholder input on value
- Transparent decision-making

A registration decision made before consultation ended and without data access ****cannot constitute**** a legitimate value assessment under PCPA.

G. Required Actions for Value Assessment

PMRA must conduct comprehensive value assessment including:

****1. Alternatives Analysis:****

- Identify all available seed treatment fungicides for same crops/pests
- Compare efficacy data (cyclobutrifluram vs. alternatives)
- Analyze risk profiles (toxicity, persistence, environmental fate)
- Demonstrate unique benefits not available from alternatives

****2. Economic Analysis:****

- Cost-benefit analysis for farmers
- Market analysis (demand, need)
- Economic advantage quantification
- Comparison to alternatives' economics

****3. Resistance Management:****

- Document current resistance status for target pathogens
- Demonstrate cyclobutrifluram provides unique resistance management benefits vs. existing SDHIs (sedaxane)
- Assess trade-offs (resistance benefits vs. health/environmental risks)



****4. Integrated Pest Management:****

- Evaluate non-chemical alternatives
- Assess role of resistant varieties
- Consider agronomic practices

****5. Risk-Benefit Integration:****

- Weigh documented benefits against risks identified in this submission
- Apply precautionary principle when benefits are marginal and risks are substantial
- Justify registration in context of alternatives availability

****6. Transparent Documentation:****

- Provide public access to value assessment data
- Release CTD for independent review
- Complete ATIP requests
- Reopen consultation period

Until comprehensive value assessment demonstrates benefits sufficient to justify substantial risks, cyclobutrifluram registration violates PCPA Section 2(2)(a).

XI. COMMENTS ARISING FROM REVIEW OF PMRL CTD

Safe Food Matters reviewed the confidential test data (CTD) provided for the PMRL. In the Integrated Assessment various concerns were noted.

High Uncertainty MRL estimate

The OECD MRL Calculator stated there that for the PMRL for romaine lettuce there was high uncertainty of the MRL estimate because of a high level of censoring.

Assumption on Rotating Crops

The acute assessment examined only crops that are typically rotated with soybeans, but there is no certainty on what such crops are or will be.

Weak Rationale for no Cancer Assessment

PMRA did not conduct a cancer risk assessment because it did not address a cancer potency factor. It chose instead to go with the MOA that was “plausible” even though it had limitations. This does not represent a scientifically based approach.

Not Enough or Inappropriate Studies

Studies from Brazil were added to make up a low number. There were not enough trials on soybeans only seed. The trials reviewed applied the pesticide at much higher rates, then the principle of proportionality was applied.



This is not scientifically justifiable and means essentially that the proper trials in accordance with GLP were not conducted.

There was no soybean processing study because the trial residues were not accurated. This is a failing of the assessment. A processing std is needed for soybean oil because it could contain residues. The rationales for not providing it are not justifiable.

TFA

The rationales regarding the non-relevance of TFA are not scientifically supportable. Assessment must be conducted on TFA regardless of the difficulties. Estimates are not sufficient. Proportionality is also not justifiable as “scaling”.

Metabolism

The studies show low recovery of resdiues of the administered dose for laying hens, not accounting for approximately 8%. Concentrations were in the liver. Metabolites were found in the egg and yolk. This present problematic risks for health.

Not Combining Exposures

PMRA did not combine dermal and inhalation exposures because they have different toxicological effects. However this is not justified. Once absorbed, cyclobutrifluram distributes systemically regardless of entry route:

- Oral exposure → GI absorption → systemic distribution
- Dermal exposure → percutaneous absorption → systemic distribution
- Inhalation exposure → pulmonary absorption → systemic distribution

All routes contribute to the **same internal dose** affecting target organs. EPA's approach to neonicotinoid seed treatments provides relevant precedent. Despite different acute toxicological profiles from different routes, EPA conducted aggregate assessments because:

- Seed treatment workers experience simultaneous multi-route exposure
- Residential populations near treated fields receive combined exposures
- Dietary exposure co-occurs with non-dietary pathways

The same logic applies to cyclobutrifluram seed treatments.

PMRA's Flawed Logic for Dismissing Metabolite Detections

PMRA acknowledges that multiple cyclobutrifluram metabolites were detected in livestock tissues, milk, and eggs, but dismisses their toxicological significance by stating these were detectable at highly exaggerated levels



equivalent to approximately 5,233 to 19,200× the calculated dietary burdens for those animals and therefore potential for exposure is minimal when the animals are fed as directed.

This rationale contains **multiple scientific and regulatory errors** that invalidate PMRA's conclusions about dietary safety.

For all metabolites, PMRA applies two unjustified assumptions:

1. Toxicity equals parent compound (without data)
2. Exposure is negligible because livestock feeding study used 5,233-19,200× expected doses

Both assumptions are scientifically indefensible.

- Purpose of Exaggerated Doses in Livestock Metabolism Studies

a) Exaggerated Doses Are Regulatory Requirements, Not Flaws

OECD Test Guideline 503 (Metabolism in Livestock) and EPA OPPTS 860.1480 explicitly require feeding studies at doses substantially exceeding expected field residues. The standard approach uses:

- Minimum dose: 10× expected dietary burden
- Typical doses: 10-100× expected dietary burden
- High doses: Often 100-1,000× or more to ensure metabolite detection

The purpose is to:

- Identify all possible metabolites that might form
- Characterize complete metabolic pathways
- Detect minor metabolites that would be below analytical detection limits at field-relevant doses
- Establish metabolite distribution across tissues, milk, eggs

b) Detection at High Doses Proves Metabolic Pathway Exists

When metabolites are detected at 5,233-19,200× doses, this demonstrates:

- The metabolic pathway is present and functional
- The metabolites will form at all dose levels, including field-relevant exposures
- The only question is **quantitative** (how much forms), not qualitative (whether it forms)



PMRA's logic that "exaggerated doses" make the findings irrelevant fundamentally misunderstands metabolism studies. The dose is exaggerated **intentionally** to ensure **complete characterization of what CAN happen**, not to invalidate the findings.

c) Standard Practice for Dietary Risk Assessment

Regulatory agencies worldwide use high-dose metabolism studies to:

1. Identify all metabolites (at high doses)
2. Establish dose-response relationships (using multiple dose levels)
3. Extrapolate to field-relevant doses (using appropriate models)

EPA explicitly states in its residue chemistry guidelines:

"High-dose metabolism studies are conducted to characterize the metabolic profile. The same metabolites are expected to form at lower doses, though in smaller amounts."

PMRA's "Minimal Exposure" Claim Lacks Scientific Foundation

a) Dose Proportionality Cannot Be Assumed

PMRA assumes that metabolites detected at 5,233-19,200 \times doses will occur at proportionally lower levels at 1 \times (field-relevant) doses. This assumption is unvalidated and often incorrect because:

Metabolic Saturation Effects:

- At high doses, primary metabolic pathways may saturate
- When primary pathways saturate, secondary pathways become proportionally more important
- Some metabolites may form at higher relative proportions at low doses than predicted

Example: If a primary detoxification pathway saturates at high doses, a secondary pathway producing a more toxic metabolite may represent:

- 1% of metabolism at 10,000 \times dose
- 5% of metabolism at 100 \times dose
- 10% of metabolism at 1 \times dose (field-relevant)

Linear extrapolation would predict 0.0001% at 1 \times dose, but actual formation could be 10% - a **100,000-fold error**.

b) PMRA Provides No Dose-Response Data



To support the "minimal exposure" claim, PMRA must demonstrate:

- Metabolite formation is **dose-proportional** across the range from field-relevant (1×) to study doses (5,233-19,200×)
- **No metabolic saturation** occurs that would alter metabolite ratios
- **Extrapolation models** accurately predict low-dose metabolite levels

PMRA provides **none of this analysis**. The claim that exposure will be "minimal" at 1/5,233rd to 1/19,200th of the study dose is an **assumption**, not a demonstrated fact.

c) Multiple Dose Studies Required

Standard practice requires livestock metabolism studies at **multiple dose levels** (typically 3-10×, 50-100×, and sometimes higher) to:

- Establish dose-response relationships
- Verify dose proportionality
- Identify any non-linear metabolism

A single high-dose study (5,233-19,200×) **cannot validate** extrapolation to 1× doses without intermediate dose data.

Detection in Livestock Proves Human Exposure Pathway

The fact that these metabolites were detected in:

- **Muscle tissue** (meat)
- **Milk**
- **Eggs**
- **Fat**

Demonstrates a **direct pathway for human dietary exposure**. PMRA's dismissal as "minimal" ignores that:

a) Bioaccumulation in Animal Products Even if metabolite formation is low relative to parent compound, metabolites can:

- **Concentrate in lipid-rich tissues** (fat, eggs, milk)
- **Persist longer** than parent compound (especially SYN510275 with $T_{1/2} = 1230$ days)
- **Accumulate over time** with repeated feeding



b) Canadian Dietary Patterns Canadians consume significant amounts of:

- **Beef, pork, poultry** (potential muscle residues)
- **Dairy products** (milk residues)
- **Eggs** (egg residues)

For populations with high consumption of animal products, **cumulative exposure** to multiple metabolites across multiple food sources could be substantial, even if individual residue levels are low.

c) Vulnerable Populations Children consume proportionally more:

- **Milk** (primary protein source)
- **Eggs** (protein source)
- **Dairy products** relative to body weight

"Minimal" residues in these staple foods could result in **disproportionate exposure** for children relative to adults.

Persistent Metabolites Create Unique Exposure Concerns

SYN510275 Specifically Undermines the "Minimal Exposure" Claim

SYN510275 presents a unique case where PMRA's logic fails completely:

Property	Value	Implication
Soil half-life	1230-1320 days	Extremely persistent in environment
Environmental fate	Dominant long-term residue	Continues forming long after application
Detection	Multiple livestock tissues, milk, eggs	Bioaccumulates in food chain
TSMP status	Exceeds Track 1 threshold by 6.7×	Meets criteria for "virtual elimination"

a) Continuous Environmental Formation Even if initial cyclobutirfluram residues in livestock feed are low, SYN510275:

- Forms continuously in soil (half-life > 3 years)
- Accumulates in environment over multiple growing seasons
- Transfers to crops grown in treated soil **years after application**
- Creates **increasing dietary burden** over time, not decreasing



b) **Bioaccumulation Potential** A metabolite with $T_{1/2} = 1230$ days demonstrates:

- **High environmental stability** (resists degradation)
- **Potential for bioaccumulation** in organisms
- **Longer biological half-life** than parent compound

Even "low" daily dietary intake of a persistent metabolite can:

- Accumulate in tissues over time
- Reach **steady-state body burden** exceeding that from parent compound
- Create **chronic low-level exposure** throughout life

c) **Multigenerational Exposure** With half-life > 3 years:

- SYN510275 from 2025 application remains in soil until 2028+
- Subsequent crops absorb residues from **multiple prior applications**
- Livestock fed these crops accumulate metabolite over their lifespan
- Human consumers receive **lifetime cumulative exposure**

PMRA's focus on single-application, single-feeding-cycle exposure **ignores the multigenerational persistence** that defines TSMP Track 1 substances.

"Minimal Exposure" is Meaningless Without Toxicity Data

PMRA's conclusion that exposure is "minimal" has **no toxicological significance** without knowing metabolite toxicity:

a) **Toxicity-Exposure Relationship**

$$\text{Risk} = \text{Exposure} \times \text{Toxicity}$$

If exposure is "1/5,233rd" of study level but toxicity is unknown:

- Metabolite could be **100× more toxic** than parent → risk is $100/5,233 =$ still 2% of high-dose level
- Metabolite could be **1,000× more toxic** → risk is $1,000/5,233 =$ 19% of high-dose level
- Metabolite could target **different organs** than parent → risk assessment misses critical endpoints

b) **Potency Examples**

Historical examples demonstrate metabolites can be orders of magnitude more toxic than parents:



Parent	Metabolite	Toxicity Increase
Chlorpyrifos	Chlorpyrifos-oxon	1,000× (AChE inhibition)
Parathion	Paraoxon	500× (acute toxicity)
Malathion	Malaoxon	50× (mammalian toxicity)

If any cyclobutirfluram metabolite were 100× more toxic than parent, "minimal" exposure at 1/5,233rd of study dose would still represent **approximately 2% of the toxic effect** observed at high doses - potentially significant depending on the endpoint.

c) Different Target Organs

Even if metabolites are less potent than parent for known endpoints (e.g., thyroid tumors, liver tumors), they could:

- Target **different organs** (kidney, nervous system, reproductive system)
- Act through **different mechanisms** (not assessed in parent compound studies)
- Cause **developmental effects** not observed with parent

PMRA's assumption that "equivalent toxicity to parent" is safe **ignores the possibility of metabolite-specific toxicity**.

Contradictory Treatment of Metabolites Based on Rat Studies

PMRA's rationale becomes internally contradictory when examining metabolite categorization:

For Metabolites "Identified in Rat" (SYN510275, SYN549104, SYN552439):

- Present in rat toxicity studies
- PMRA assumes "equivalent toxicity to cyclobutirfluram"
- **Problem:** If metabolites were present during rat studies that found thyroid/liver tumors, metabolites could have **caused or contributed** to carcinogenicity
- Dismissing livestock detections as "minimal" **contradicts** the acknowledgment that these metabolites form in rats at toxicologically relevant doses

For Metabolites "Not Observed in Rat" (SYN552441, SYN552442, SYN552430, SYN552415):

- Absent from rat studies (or below detection limits)
- PMRA still assumes "equivalent toxicity to parent"



- **Problem:** If not present in rats, there is **literally zero toxicity data** for these metabolites
- Yet PMRA dismisses livestock detections as "minimal" **without any basis** for knowing what level of exposure would be concerning

XII The Qualitative Significance of Metabolite Detection: Presence Confirms Metabolic Pathway Existence

1. Detection at Any Level Establishes Metabolic Pathway Functionality

A fundamental principle of metabolism studies is that **detection of a metabolite—regardless of quantitative level—provides qualitative evidence that the metabolic pathway producing that metabolite exists and is functional.** This principle has been clearly articulated in regulatory guidance and scientific literature but is systematically ignored in PMRA's dismissal of cyclobutirfluram metabolites detected at "exaggerated doses."

EPA's policy on non-detected pesticide residues explicitly recognizes this principle:

"Even though the laboratory instrumentation cannot detect a residue, a residue **may be present at some level** below the LOD, and may still present a **potential concern to human health.**"¹

If residues **below detection limits** warrant concern, then residues that are **actually detected**—even at exaggerated doses—unequivocally demonstrate:

- The metabolic pathway exists
- The metabolite forms under exposure conditions
- The metabolite will form at lower doses, albeit in smaller quantities

2. Regulatory Precedent: Detection Triggers Assessment, Not Dismissal

EU Commission Regulation 283/2013 establishes that metabolite detection creates regulatory obligations:

"An explanation shall be given or **further tests shall be carried out** where a metabolite is detected in vitro in human material and not in the tested animal species."²

The regulation does not state "dismiss the metabolite if detected at high doses." Rather,

detection itself—qualitative evidence of metabolic pathway activity—triggers the requirement for additional investigation.

PMRA's approach inverts this principle by using detection at high doses as justification for dismissal, rather than as evidence requiring further assessment.

3. Scientific Literature: Quantity Does Not Determine Toxicological Significance



Pelkonen et al. (2023) in their comprehensive review of metabolites in pesticide risk assessment state unequivocally:

"It is important to remember that **quantity as such, be it relative or absolute, does not necessarily imply toxicity hazard or toxic potency** of a pesticide or its metabolites."³

This principle reflects well-established toxicological knowledge:

- **Highly potent toxicants** exert effects at very low concentrations (e.g., botulinum toxin, dioxins)
- **Low-abundance metabolites** can be orders of magnitude more toxic than parent compounds
- **Persistent metabolites** accumulate over time, making initial formation rates less relevant than long-term exposure

4. OECD Guidelines: 5% Threshold is for Identification, Not Toxicological Dismissal

OECD Test Guideline 417 requires identification of "all metabolites present at **5% or greater of the administered dose**" to establish the metabolic scheme.⁴ This threshold serves a **practical analytical purpose**: ensuring major metabolic pathways are characterized.

However, this guideline is systematically misinterpreted as permission to dismiss metabolites below 5% as toxicologically irrelevant. The 5% threshold addresses:

- **Analytical capability** (what can be reliably detected and quantified)
- **Resource allocation** (which metabolites warrant structural elucidation)
- **Metabolic pathway mapping** (understanding major transformation routes)

The guideline does **not** establish that metabolites <5% of parent lack toxicological significance. Indeed, numerous examples demonstrate minor metabolites with major toxicity:

Parent Compound Minor Metabolite Formation (% of parent) Toxicity Relative to Parent

Chlorpyrifos	Chlorpyrifos-oxon	~1-5%	1000× more potent (AChE inhibition)
Malathion	Malaoxon	~2-8%	50× more toxic
Acetaminophen	NAPQI	<5%	Hepatotoxic (parent is not)

5. The Fallacy of Linear Dose-Response Extrapolation

PMRA assumes that metabolites detected at 5,233-19,200× field-relevant doses will occur proportionally at 1/5,233rd to 1/19,200th concentrations under actual exposure conditions. This assumption is **scientifically**



unjustified without validation because metabolic pathways are subject to **dose-dependent saturation and induction effects**.

The National Research Council's analysis of pharmacokinetic modeling explicitly warns:

"Saturation of metabolism could lead to situations in which a linear extrapolation was **not conservative**, particularly if a reactive metabolic intermediate was the active moiety."

At high doses:

- **Primary metabolic pathways saturate** (enzymes reach V_{max})
- **Secondary pathways become proportionally more active**
- **Minor metabolites at high doses** may represent major pathways at low doses
- **Cofactor depletion** (glutathione, PAPS, etc.) alters metabolic ratios

Simple linear extrapolation ignores these kinetic realities and can **systematically underestimate low-dose metabolite formation**.

6. Validation Studies Required, Not Assumptions

To support the claim that metabolites present at 5,233-19,200× doses will be "minimal" at field-relevant doses, PMRA must provide:

a) Dose-Response Metabolism Studies

- Multiple dose levels spanning 1× to >1000× expected dietary burden
- Demonstration of **dose-proportional metabolite formation** across this range
- Evidence that **no metabolic saturation** occurs at intermediate doses
- Confirmation that metabolite ratios remain constant across dose levels

b) Pharmacokinetic Modeling

- **PBPK models** incorporating:
 - Saturable enzyme kinetics (Michaelis-Menten parameters)
 - Induction/inhibition effects
 - Cofactor availability
 - Species-specific metabolic capacity
- Model validation using data from multiple dose levels



- Uncertainty analysis on low-dose extrapolations

c) Confirmatory Analytical Studies

- Method development for **detecting metabolites at field-relevant doses**
- Actual measurements in livestock fed at 1× dietary burden
- Comparison of predicted vs. observed metabolite levels

PMRA has provided **none of these validations**. The "minimal exposure" claim rests entirely on untested assumptions about dose-proportionality.

7. Practical Implications: Detection Confirms Exposure Pathway

The fact that cyclobutylfluram metabolites were detected in:

- **Goat muscle** (meat consumed by humans)
- **Goat milk** (consumed especially by children)
- **Goat fat** (concentrates lipophilic residues)
- **Hen eggs** (staple protein source)
- **Multiple hen tissues** (white, muscle)

Demonstrates a **direct, confirmed pathway for human dietary exposure** to these metabolites. The question is not whether exposure occurs (it demonstrably does), but **how much exposure occurs and what toxicity that exposure presents**.

Dismissing this confirmed exposure as "minimal" without:

- Measuring actual concentrations at field-relevant doses
- Assessing metabolite toxicity
- Evaluating persistent metabolite accumulation (especially SYN510275)
- Considering vulnerable populations (children consuming dairy/eggs)

Violates the precautionary principle and the burden of proof under PCPA Section 2(2).

8. Case-Specific Concern: SYN510275 Persistence Invalidates "Minimal Exposure" Logic

For SYN510275 specifically, PMRA's "minimal exposure" rationale fails completely:

Factor	Implication for "Minimal Exposure" Claim
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Factor	Implication for "Minimal Exposure" Claim
$T_{1/2} = 1230\text{-}1320$ days	Metabolite persists $6.7\times$ longer than TSMP threshold—accumulates over multiple seasons
Detection in multiple livestock matrices	Confirms bioaccumulation pathway to human food
TSMP Track 1 exceedance	Meets persistence criteria for "virtual elimination"—opposite of "minimal"
Formation continues post-application	Not a transient residue but a permanent environmental contaminant

A metabolite with >3 -year environmental half-life that bioaccumulates in livestock products **cannot** be dismissed as presenting "minimal exposure" based on single-generation feeding studies at exaggerated doses. The relevant exposure scenario is:

- **Multigenerational environmental accumulation**
- **Livestock exposed throughout lifespan** to residues from multiple prior applications
- **Human consumers exposed continuously** through staple foods (dairy, meat, eggs)
- **Lifetime body burden** in humans from persistent metabolite

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