COMMENTS ON PMRL2025-21

Proposed Maximum Residue Limits for Isocycloseram

Contents

Introduction

We herein provide comments to PMRL 2025-09 concerning Isocycloseram (IS). PMRL2025-21 proposes MRLs for isocycloseram as part of submissions 2021-3038, 2021-3045, and 2021-3048 for seed treatment products A22241ST and A23128 ST on barley, oats, rye, triticale, and wheat to control or suppress various insects and seed- and soil-borne diseases. This is a new pest control product (PCP).

The PMRA in the proposal document indicated the end-use products have value and the risks are acceptable. The document also asserts that "dietary risks from the consumption of foods listed in Table 1 were shown to be acceptable when isocycloseram is used according to the supported label directions." We disagree with these conclusions.

The proposed MRLs are for the food commodities including the meat of cattle, goats, hogs, horses, poultry and sheep; meat by-products of cattle, goats, horses, sheep and hogs and poultry; fat of cattle, goats, horses and sheep, eggs, milk, barley, oats, rye, triticale, wheat.

There are no MRLs established elsewhere in the world for IS. They are only being proposed in the US. As such, there is no history of use of the product, and effects in the real worlds are not known. A precautionary approach is therefore required.

PMRA has not provided or made available any evidence concerning the establishment of the MRLs. We asked for details of the assessment of dietary risks conducted so as to put forward this MRLs, and PMRA did not provide any. Instead, it stated: pre

> *MRLs for isocycloseram are being proposed in 2 separate phases. The first phase is for seed treatment uses, and the corresponding proposed MRLs are listed in PMRL2025-21. The second phase is for foliar application uses, where the proposed MRLs will be published in an upcoming PMRL. The internal documentation for dietary exposure is a consolidation of both phases and will be finalized and available for disclosure after Phase 2 is complete.*

The failure to provide evidence to support the proposed MRLs is a failure of the pillar of public participation in risk assessments, which is codified in the Pest Control Products Act (the Act) and case law. As such, it is unlawful.

The splitting of proposals for MRLs into two phases is also unlawful.

The proposed MRLs are predicated on a flawed dietary risk assessment, inadequate toxicity testing, misclassification of a PFAS substance under the Toxic Substances Management Policy, and violations of the Pest Control Products Act's requirement to establish "reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the pest control product."

I. INTRODUCTION AND REGULATORY CONTEXT

A. PMRL2025-21 Consultation Scope

PMRL2025-21, published October 9, 2025, proposes the following MRLs for isocycloseram:

- 0.04 ppm: Fat of cattle, goats, horses, sheep

- 0.015 ppm: Meat by-products of cattle, goats, horses, sheep

- 0.01 ppm: Fat of hogs/poultry; meat of cattle/goats/hogs/horses/poultry/sheep; meat by-products of hogs/poultry; eggs, milk, barley, oats, rye, triticale, wheat

The PMRL states that these MRLs are being proposed "as part of the following applications for Canadian use, under submission numbers 2021-3038; 2021-3045; 2021-3048" for technical grade isocycloseram and end-use products A22241ST (isocycloseram only) and A23128 ST (isocycloseram + difenoconazole + sedaxane + metalaxyl-M + fludioxonil) as seed treatments on barley, oats, rye, triticale, and wheat.

The PMRL references Proposed Registration Decision PRD2025-11 for details regarding the applications, stating that "the evaluation of these isocycloseram applications indicated that the end-use products have value, and the human health and environmental risks associated with their proposed uses are acceptable."

B. Pest Control Products Act Requirements

The Pest Control Products Act (PCPA) establishes the legal framework for pesticide registration in Canada. Section 1(2) states:

"The purpose of this Act is to prevent unacceptable risks to people and the environment from the use of pest control products."

Section 4 requires that no person shall manufacture, possess, handle, store, transport, import, distribute or use a registered pest control product under conditions other than those specified in its registration.

Section 7(6) provides the core standard for registration:

"In deciding whether to grant registration or an amendment to a registration, the Minister must determine whether the product, if used in the manner and under the circumstances specified in the proposed registration, will meet the standard specified in subsection (2)."

Section 7(2) states:

"For the purposes of this Act, a product meets the standard if it is determined, in accordance with this Act, the regulations and any document or regulatory rule that are applicable, that there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions or proposed conditions of registration."

This is the fundamental legal standard that PMRA must satisfy before establishing MRLs or registering any pest control product. The standard requires "reasonable certainty" - not merely a probability or likelihood - that "no harm" will result to human health, future generations, or the environment.

C. Maximum Residue Limits as Regulatory Tools

As defined in PMRL2025-21, "A maximum residue limit (MRL) is the maximum amount of residue that may remain in or on food when a pesticide is used according to label directions."

The PMRL states: "Before registering a pesticide for food use in Canada, Health Canada must determine the quantity of residues that could remain in or on the food when the pesticide is used according to label directions and that such residues will not be a concern to human health."

This determination requires completion of a four-step dietary health assessment process:

1. Identifying toxicology hazards

2. Determining acceptable dietary levels protective of all vulnerable populations

3. Estimating human dietary exposure from all sources

4. Characterizing health risk by comparing exposure to acceptable levels

The PMRL concludes: "If estimated human exposure is less than or equal to the acceptable level... Health Canada concludes that consuming residues resulting from use according to approved label directions is not a health concern."

Safe Food Matters contends that PMRA has failed to properly complete this four-step process for isocycloseram, and that the proposed MRLs are therefore not supportable.

D. Relationship Between PMRL2025-21 and PRD2025-11

PMRL2025-21 cannot be evaluated in isolation from PRD2025-11. The PMRL explicitly references the PRD as containing "details regarding these applications" and relies on the PRD's conclusion that "human health and environmental risks associated with their proposed uses are acceptable."

However, PRD2025-11 contains fundamental scientific and legal deficiencies that undermine any dietary risk assessment or MRL proposal. These deficiencies include:

- Misclassification of isocycloseram and its transformation products under the Toxic Substances Management Policy

- Inadequate assessment of cancer, developmental toxicity, and immunotoxicity risks

- Failure to conduct toxicity testing on 35 of 36 metabolites/degradates

- Waiver of critical toxicity studies without scientific justification

- Underdosing of cancer and developmental toxicity studies in violation of EPA test guidelines

- Inadequate cumulative risk assessment

- Use of mitigation measures to compensate for failure to establish reasonable certainty of no harm

- Jurisdictional overreach in regulating prophylactic seed coatings

These deficiencies in PRD2025-11 directly affect the validity of the dietary risk assessment and proposed MRLs in PMRL2025-21. If the underlying toxicity assessment is flawed, the "acceptable dietary levels" derived from that assessment are unreliable, and the proposed MRLs lack scientific foundation.

Moreover, even if the dietary risk assessment were adequate (which it is not), PMRA cannot legally establish MRLs for a pesticide that fails to meet the PCPA Section 7(2) standard of "reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product."

The classification of isocycloseram as a PFAS "forever chemical" that will persist indefinitely in the environment and human bodies fundamentally precludes any finding of "no harm to future generations" - regardless of calculated dietary exposure levels or proposed MRLs.

II. ISOCYCLOSERAM AS A PFAS "FOREVER CHEMICAL"

A. Chemical Structure and PFAS Classification

Isocycloseram's chemical structure contains critical fluorine-bearing components that definitively classify it as a per- and polyfluoroalkyl substance (PFAS):

Chemical name: 4-[5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-(2-ethyl-3-oxo-4-isoxazolidinyl)-2-methylbenzamide

The molecule contains:

1. A trifluoromethyl group (-CF_3): This is a fully fluorinated carbon atom bonded to three fluorine atoms

2. A dichloro-fluorophenyl group: A phenyl ring with two chlorine atoms and one fluorine atom

These structural features meet the widely accepted Organisation for Economic Co-operation and Development (OECD) definition of PFAS, which includes any chemical containing at least one fully fluorinated carbon atom.

This classification is not disputed in the scientific or regulatory community. As documented in EPA and scientific literature:

- Wang et al. (2021) identify isocycloseram as a PFAS pesticide

- PubChem (CID 87323565) confirms the presence of perfluorinated moieties

- EPA's assessment acknowledges the fluorinated structure

The PFAS classification of isocycloseram has profound implications for human health, environmental fate, and regulatory decision-making. PFAS are termed "forever chemicals" because:

1. The carbon-fluorine bond is one of the strongest in organic chemistry

2. These compounds resist environmental degradation

3. They persist indefinitely in both environmental and biological systems

4. They bioaccumulate in organisms and biomagnify through food chains

B. Ubiquitous PFAS Contamination

PFAS contamination is now recognized as a pervasive global environmental and public health crisis. The scientific evidence demonstrates:

1. Human Exposure Is Universal

- Centers for Disease Control and Prevention (CDC) biomonitoring data show PFAS are detected in the bloodstream of nearly all Americans

- Similar findings documented in Canadian populations

- Exposure occurs through multiple pathways: drinking water, food, consumer products, occupational exposures, contaminated environments

2. Environmental Persistence and Mobility

- PFAS detected in remote environments far from sources: Arctic ice, Antarctic snow, Tibetan Plateau glaciers

- Contamination of agricultural land through:

* Application of PFAS-containing pesticides

* Use of sewage sludge (biosolids) as fertilizer

* Irrigation with contaminated water

* Atmospheric deposition

- Surface water and groundwater contamination widespread, including drinking water sources

3. Agricultural Land Contamination

- PFAS accumulation in agricultural soils creates long-term food safety concerns

- Crops grown in contaminated soil take up PFAS, transferring contamination to food supply

- Livestock consuming contaminated feed bioaccumulate PFAS in meat, milk, eggs

- Once agricultural land is contaminated, remediation is extremely difficult or impossible

- Threatens farmers' livelihoods and land values

4. Disproportionate Environmental Justice Impacts

- California data show PFAS drinking water contamination disproportionately affects communities of color

- Low-income communities often face higher PFAS exposure burdens

- Agricultural workers face occupational PFAS exposure

5. Health Effects at Extremely Low Levels

- EPA health advisories for PFOA and PFOS: 0.004 parts per trillion (ppt) and 0.02 ppt respectively

- These advisory levels reflect current scientific understanding of health risks at extraordinarily low concentrations

- Effects documented include: immune system suppression, cancer, thyroid disease, reproductive/developmental effects, liver damage, increased cholesterol

C. Implications for MRL Setting

The PFAS nature of isocycloseram fundamentally undermines the premise of setting MRLs. The traditional MRL paradigm assumes:

1. Pesticide residues degrade over time

2. Human exposure is transient

3. The body can eliminate pesticide residues

4. Risks can be managed through exposure limits

None of these assumptions hold for PFAS "forever chemicals":

1. Isocycloseram and its degradates will not meaningfully degrade - they persist indefinitely

2. Human exposure accumulates over lifetime rather than being transient

3. PFAS have long biological half-lives; the body cannot effectively eliminate them

4. Each additional source of PFAS exposure adds to the irreversible body burden

Establishing MRLs for isocycloseram means authorizing the deliberate addition of a persistent pollutant to the food supply that will:

- Add to Canadians' existing PFAS body burden

- Remain in the environment indefinitely

- Contaminate agricultural land for generations

- Accumulate in livestock and wildlife

- Transfer to future generations through various exposure pathways

This is fundamentally incompatible with the PCPA Section 7(2) requirement for "reasonable certainty that no harm to... future generations" will result.

D. Aggregate PFAS Exposure Not Assessed

1. PMRA's dietary risk assessment for isocycloseram evaluated exposure to isocycloseram in isolation. This approach is scientifically inadequate for a PFAS compound because it ignores non-diietary PFAS exposure sources.

Canadians are exposed to PFAS through numerous non-food pathways:

- Drinking water

- Consumer products: non-stick cookware, food packaging, personal care products, textiles, carpets

- House dust

- Indoor air

- Outdoor air

- Soil contact

- Occupational exposures

2. Legacy PFAS Body Burden

All Canadians already carry a body burden of PFAS from decades of environmental contamination. Adding dietary exposure to isocycloseram increases this burden without consideration of:

- Current blood serum PFAS levels in the population

- Variations in body burden across demographic groups

- Cumulative health risks from total PFAS exposure

3. Additive and Synergistic Effects

PFAS may exert additive or synergistic toxic effects when present as mixtures. The health effects of exposure to multiple PFAS compounds simultaneously may differ from effects predicted based on individual compound assessments.

EPA's own Federal Register notices for PFAS regulations acknowledge the importance of aggregate exposure assessment. For example, in setting drinking water standards for PFOA and PFOS, EPA considered:

- Multiple exposure routes

- Cumulative risks from PFAS mixtures

- Existing body burdens

- Vulnerable populations including pregnant women and children

PMRA has failed to conduct any parallel aggregate PFAS exposure assessment for isocycloseram. The dietary risk assessment assumes zero background PFAS exposure and zero non-dietary PFAS exposure - assumptions that are demonstrably false for every Canadian.

E. Global Regulatory Trend Toward PFAS Restrictions

The regulatory landscape for PFAS is rapidly shifting toward greater restrictions and phase-outs:

1. European Union

- Broad restriction proposal under REACH regulation to ban manufacture, use, and placing on market of thousands of PFAS

- Proposal covers intentionally added PFAS in consumer products

- Would affect agricultural uses including pesticides

2. United States

- EPA designated PFOA and PFOS as hazardous substances under CERCLA

- EPA established Maximum Contaminant Levels for six PFAS in drinking water

- Multiple states enacted PFAS restrictions in food packaging, firefighting foam, other products

- Growing momentum for Federal PFAS restrictions

3. Canada

- Environment and Climate Change Canada designated certain PFAS as toxic under CEPA

- Drinking water guidelines under development

- Provincial actions on PFAS in consumer products

4. International Bodies

- Stockholm Convention evaluating certain PFAS for listing as persistent organic pollutants (POPs)

- OECD working groups addressing PFAS contamination and risk assessment

The clear global regulatory direction is toward reducing PFAS use and exposure, not introducing new PFAS into commerce and the environment. PMRA's proposal to register isocycloseram and establish MRLs runs counter to this international consensus.

F. PCPA Section 7(2) Cannot Be Satisfied for PFAS

The PCPA Section 7(2) standard requires "reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product."

For a PFAS "forever chemical" like isocycloseram, this standard cannot be met because:

1. Harm to Future Generations Is Certain

- Isocycloseram will persist in the environment indefinitely

- Contamination of agricultural land will affect future food production

- PFAS in water, soil, and biota will expose future generations

- Bioaccumulation means exposure increases over time

- Remediation is not technically or economically feasible

The harm to future generations is not speculative - it is a chemical certainty based on the persistent nature of PFAS compounds.

2. Environmental Harm Is Inevitable

- Irreversible environmental contamination

- Disruption of ecosystem functions

- Threats to biodiversity from bioaccumulation

- Soil degradation from binding of persistent compounds

- Water quality impairment

3. Uncertainty About Long-Term Health Effects

- Limited data on chronic health effects of most PFAS

- Emerging science continues to identify new health concerns at lower exposure levels

- Mixtures effects poorly understood

- Vulnerable populations may be at greater risk

- Trans-generational effects possible

Given these certainties and uncertainties, PMRA cannot reach a conclusion of "reasonable certainty that no harm" will result. The most scientifically and legally defensible conclusion is that harm is certain, particularly to future generations.

III. DIETARY RISK ASSESSMENT DEFICIENCIES

A. Use of Inappropriate Consumption Data

PMRL2025-21 states that dietary risk assessment was conducted to evaluate safety of the proposed MRLs. However, fundamental problems exist with the consumption data used in this assessment.

1. U.S. Data Used Instead of Canadian Data

The dietary exposure assessment for isocycloseram relied on consumption data from the United States National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005-2010.

This presents multiple problems:

a) Wrong Population: NHANES/WWEIA measures what Americans consume, not Canadians. While food consumption patterns overlap between the two countries, significant differences exist in:

- Dietary preferences and food culture

- Availability of certain food products

- Serving sizes and meal patterns

- Demographic composition

- Geographic and climatic influences on diet

Using U.S. consumption data to assess risks to Canadians violates the PCPA requirement for a scientifically-based approach specific to the Canadian population.

b) Outdated Data: The 2005-2010 NHANES/WWEIA data is now 15-20 years old. Food consumption patterns have changed substantially over this period due to:

- Changing dietary trends (e.g., plant-based diets, organic foods, gluten-free products)

- Shifts in grain consumption

- Changes in livestock product consumption

- Evolving food availability and marketing

- Economic factors affecting food purchases

Using data from 2005-2010 to make regulatory decisions in 2025 does not reflect current exposure conditions.

c) Canadian Consumption Data Available: Health Canada conducts the Canadian Community Health Survey (CCHS) - Nutrition, which provides Canadian-specific food consumption data. There is no legitimate reason to rely on foreign, outdated consumption data when Canadian data exists.

2. Scientific Basis Requirement

The PCPA and regulatory guidance documents require PMRA to apply a scientifically based approach using empirical evidence gathered through rigorous, repeatable procedures. Using inappropriate consumption data fundamentally undermines the scientific basis of the dietary risk assessment.

If the consumption estimates are wrong - whether overestimated or underestimated - the dietary exposure estimates and risk characterization are correspondingly wrong. This means PMRA cannot have reasonable certainty about whether the proposed MRLs are protective of Canadian health.

B. Insufficient Field Trial Data and MRL Uncertainty

1. Field Trial Data has not been provided

PMRL2025-21 proposes MRLs derived from field trial data, but PMRA has not made the data available. The MRLs were calculated using the OECD MRL Calculator, a statistical tool designed to estimate MRLs from supervised field trial datasets.

2. Uncertain datasets

However, the OECD Calculator is sensitive to dataset size and quality. The OECD MRL Calculator White Paper explicitly warns:

"For trials numbered 3-7, there is 'High uncertainty of MRL estimate. [Small dataset]'"

For isocycloseram, PMRA conducted only 5 field trials for each of the following crops:

- Barley: 5 trials

- Oats: 5 trials

- Rye: 5 trials

- Triticale: 5 trials

- Wheat: 5 trials (each for spring/durum and winter varieties)

With only 5 trials per crop, the dataset falls squarely within the OECD's "high uncertainty" range. The OECD acknowledges that with such small datasets:

- Statistical variability is high

- The calculated MRL may not reliably represent actual residue distributions

- Outlier values can disproportionately affect the MRL estimate

- The MRL may be inflated by algorithmic rounding or statistical treatment

3. Implications for Dietary Risk Assessment

The MRL values directly affect dietary exposure estimates. If the MRLs are uncertain or inflated due to small dataset size, the dietary exposure assessment inherits this uncertainty.

The four-step dietary risk assessment process described in PMRL2025-21 requires:

Step 3: "Estimating human dietary exposure to the pesticide from all applicable sources"

Step 4: "Characterizing health risk by comparing the estimated human dietary exposure to the acceptable dietary level"

If the exposure estimates in Step 3 are based on uncertain MRLs derived from insufficient field trial data, the risk characterization in Step 4 is unreliable.

Moreover, for seed treatments like isocycloseram, residue distributions can be highly variable depending on:

- Seed coating application uniformity

- Planting conditions and depth

- Soil characteristics affecting uptake

- Weather conditions during growing season

- Time from planting to harvest

Five trials per crop is inadequate to capture this variability across the diverse growing regions and conditions in Canada.

4. Information Requested but Not Provided

Safe Food Matters has requested from PMRA the OECD MRL Calculator output pages showing detailed calculations and information on the field trials.

- The MRLs are scientifically justified

- The dataset size creates unacceptable uncertainty

- The MRLs are inflated by statistical artifacts

- Additional field trials are needed

PMRA has not provided this information. Without transparency regarding the MRL derivation, stakeholders cannot verify the scientific validity of the proposed limits.

C. Metabolite Toxicity: Critical Data Gaps

1. Thirty-Six Metabolites, Minimal Testing

As documented in EPA materials (EPA 8/2/22, Appendix A), isocycloseram breaks down into 36 distinct metabolites and degradation products. Of these 36 compounds:

- 24 are classified as "major" metabolites (≥10% of parent compound)

- 11 of the 24 major degradates pose human health concerns in drinking water

- Only ONE metabolite (SYN548569) has received any toxicity testing

- That single tested metabolite was evaluated only in limited genotoxicity assays

- The genotoxicity assays were POSITIVE, indicating potential DNA damage

The remaining 35 metabolites have received NO toxicity testing whatsoever. Their potential to cause the following is completely unknown:

- Cancer

- Developmental toxicity

- Reproductive toxicity

- Immunotoxicity

- Neurotoxicity

- Endocrine disruption

- Other adverse health effects

2. PMRA's Assumption-Based Approach

PMRA explicitly acknowledges this data gap in PRD2025-11, stating:

"Generally, the metabolites have similar structure as the parent isocycloseram, so are assumed to have similar toxicity to the parent compound."

This is assumption, not science. The statement reveals that PMRA is proceeding with registration and MRL-setting based on untested assumptions about metabolite toxicity rather than empirical data.

3. Evidence That Assumption Is False

The assumption that metabolites have "similar toxicity to the parent" is contradicted by PMRA's own data on isocycloseram metabolites:

Honey Bee Toxicity Data:

- Metabolite isomer SYN549106 is 4 times more toxic to honey bees than the parent compound on an acute contact basis

- SYN549106 is 1.5 times more toxic on an oral exposure basis

This demonstrates that metabolites CAN be substantially more toxic than the parent compound. If SYN549106 is 4-fold more toxic to bees, what is its toxicity to mammals? What about the other 35 untested metabolites?

4. Bioaccumulation and Slow Elimination

Radiolabeled isocycloseram studies in rats show:

- Slow elimination of radioactivity (representing isocycloseram + metabolites)

- After 1 week: 10-20% of initial dose retained in male rats

- After 1 week: 20-30% of initial dose retained in female rats

This long residence time in the body means:

- Metabolites accumulate over time with repeated exposure

- Chronic exposure effects are accentuated

- Occupational users could accumulate pesticide and metabolites throughout a spraying season

- The body burden of metabolites may exceed that of the parent compound

5. Implications for Dietary Risk Assessment

The "acceptable dietary level" determined in Step 2 of the dietary risk assessment is based on toxicity data for the parent compound, isocycloseram. PMRA has:

- NOT established acceptable dietary levels for the 36 metabolites

- NOT quantified metabolite residues in food commodities

- NOT assessed dietary exposure to metabolites

- NOT characterized health risks from metabolite exposure

Yet metabolites WILL be present in food commodities. The MRL residue definition in PMRL2025-21 specifies only the parent compound isocycloseram. This means:

- Metabolite residues are NOT counted toward the MRL

- Metabolite exposure is NOT limited by the MRL

- Actual total pesticide-related residues (parent + metabolites) may substantially exceed the MRL

- Dietary exposure and risk are underestimated

6. Requirement for Metabolite Testing

A scientifically based approach requires toxicity testing of all major metabolites (at minimum). The EPA test guidelines and PMRA's own guidance emphasize the importance of metabolite toxicity assessment when:

- Metabolites represent ≥10% of parent compound (all 24 "major" metabolites meet this criterion)

- Metabolites have structural features suggesting potential toxicity (e.g., SYN548569 tested positive for genotoxicity)

- Metabolites persist longer than parent (many isocycloseram degradates are more persistent)

- Metabolites are present in edible commodities

Without this testing, PMRA cannot establish "reasonable certainty that no harm" will result from dietary exposure to isocycloseram residues - because the residues include untested metabolites of unknown toxicity.

D. Inadequate Toxicity Database

The dietary risk assessment's Step 2 - determining "acceptable dietary level" - depends entirely on the quality and comprehensiveness of the toxicity database. For isocycloseram, this database has critical deficiencies.

1. Waived Studies

PMRA allowed waivers for two critical toxicity studies:

a) Developmental Neurotoxicity Study

- Isocycloseram's mode of action involves blocking neurotransmission at GABA-gated chloride channel receptors

- This is inherently a neurological mechanism

- The developing nervous system is far more sensitive to chemical disruption during critical windows of development

- Effects on the developing nervous system can have permanent consequences "quite unlike the chemical's effects in adults"

- Isocycloseram DID show evidence of neurotoxicity:

* Male dogs: slight body tremor and vomiting at 80 mg/kg/day

* Male rats: 17% lower forelimb grip strength at 22 mg/kg/day (dismissed by EPA as "not adverse")

Despite this evidence and the neurological mode of action, PMRA waived the developmental neurotoxicity study. The subchronic neurotoxicity study that was conducted used extremely low dosing: high dose of only 25/33 mg/kg/day (M/F) compared to the limit dose of 1,000 mg/kg/day - more than 30-fold lower.

b) Immunotoxicity Study

- Toxicological data suggested possible immune system toxicity requiring further investigation:

* Plasmacytosis/plasma cell infiltration of lymph nodes, spleen, thymus in 80-week mouse study

* Leucocyte (white blood cell) counts increased in multiple studies: 28-day oral rat, 28-day dermal rat, 90-day oral mouse, 90-day oral rat

* Australian APVMA noted "lymphocytic leucocytosis" and "leucocytosis"

* APVMA characterized response as "lymphatic and non-lymphatic plasmacytosis" and used this to establish Acceptable Daily Intake

* APVMA noted "[n]o data were available on immunotoxicity" preventing determination of effects on T- and B-cells

* Aberrant immune system responses can indicate lymphomas or other blood-borne cancers

Despite this evidence, PMRA waived the immunotoxicity study based on a <1 page EPA rationale claiming negative findings for "Hematology indicators (WBC changes)" and "organ weight indicators (spleen, thymus)" - directly contradicting the documented evidence of white blood cell changes and organ effects.

Immunotoxicity testing is otherwise required of all pesticides used with food crops under 40 CFR 158, Subpart F, 158.500 (EPA Toxicology data requirements table).

2. Underdosed Cancer Studies

a) Mouse Carcinogenicity Study

- Three groups administered 2, 7, or 23/24 (M/F) mg/kg bw/day for 80 weeks

- EPA found NO adverse effects in any group, even at the highest dose

- The highest dose was designated as the NOAEL (no-observed adverse effect level)

- EPA Cancer Test Guidelines require that the highest dose "elicit signs of toxicity without substantially altering life span due to effects other than tumors"

- Intermediate doses should "produce gradation of toxic effects"

- Only the lowest dose should not have toxic effects

- The study was classified as "non-guideline because no LOAEL identified... and animals not dosed up to limit dose"

- The high dose of 23/24 mg/kg/day is less than 2.5% of the limit dose (1,000 mg/kg/day)

An entirely new mouse carcinogenicity study is required with substantially higher doses per EPA Cancer Test Guidelines.

b) Rat Carcinogenicity Study

- High-dose group received just 7/9 mg/kg/day (M/F)

- Less than 1% of the limit dose

- It is not surprising there was a finding of no isocycloseram-related tumors given the incredibly low doses

- Study should be repeated at substantially higher doses

The inadequate dosing means that the cancer assessment is based on studies that did not properly test for carcinogenic potential. The "acceptable dietary level" derived from these studies may not be protective against cancer. This is very concerning, particularly since this pesticide will be present in meat and may be highly consumed by Canadians.

3. Underdosed Developmental Toxicity Studies

a) Rat and Rabbit Studies

- EPA freely concedes: "rat and rabbit definitive developmental studies did not test up to limit dose and there is potential for susceptibility at higher doses..."

- Both studies classified as "non-guideline because no LOAEL identified in study, and animals not dosed up to limit dose"

- A key attribute of a developmental toxin is that it exerts adverse effects on the fetal/infant organism at doses lower than those harming the maternal animal

- EPA maintains this increased "susceptibility" [of fetus/infant] vis-à-vis mother might have been found "at higher doses," potentially "up to limit dose"

- EPA Prenatal Developmental Toxicity Study Test Guidelines specify: "highest dose should be chosen with aim to induce some developmental and/or maternal toxicity but not death or severe suffering" and "highest dose tested need not exceed 1,000 mg/kg/day"

b) Australian Findings

- Australian Pesticides and Veterinary Medicines Authority (APVMA) found isocycloseram caused a rare skeletal malformation (bifid sternum) in the rat developmental study

- Pregnant rats dosed with 15 mg/kg/day produced two fetuses in two separate litters with bifid sternum

- Bifid sternum is a rare congenital anomaly resulting from sternum fusion failure; in humans it requires surgery to protect the heart and major blood vessels

- Australian reviewers were confident isocycloseram caused this birth defect and established an acute reference dose (ARfD) for women of child-bearing age on this basis

- Critical consideration: isocycloseram caused a birth defect in rats; developmental toxicity may manifest differently in humans

c) DEREK System Alerts

- EPA's expert system DEREK identified SYN551324 as a potential developmental toxin

- Produced equivocal alerts for teratogenicity for six metabolites (SYN549433, SYN549554, SYN550455, SYN550602, SYN551113, SYN551190) based on glucocorticoid receptor activity

d) Related Compound Evidence

- Fluralaner (80% structural similarity to isocycloseram, same mode of action) is a developmental toxin

- Caused skeletal/visceral malformations in two rabbit developmental toxicity studies

- Caused adverse neonatal effects and postimplantation loss in two-generation rat study

- Carries hazard statement "Suspected of damaging the unborn child"

4. Weight of Evidence on Developmental Toxicity

The weight of evidence indicates serious concerns about developmental toxicity:

- Australian authorities identified clear birth defects (bifid sternum)

- EPA's DEREK system flagged seven metabolites as potential teratogens

- Closely related compound (fluralaner) classified as suspected of causing birth defects

- EPA concedes "potential for susceptibility at higher doses" in inadequately dosed studies

Yet PMRA has established MRLs without resolving these concerns through properly dosed, guideline-compliant developmental toxicity studies.

5. Equivocal Cancer Evidence

a) Mouse Study Findings

- Increased incidence of ovarian luteomas in female mice

- PMRA dismissed as "not statistically significant"

- Dismissed because "no progression to malignant tumors"

- Observed in "only one sex and one species"

b) Rat Study Findings

- Slight increase in Leydig cell tumors in male rats

- Also dismissed as equivocal and "low concern"

c) Lack of Scientific Justification

- PMRA provided NO scientific authority to justify dismissing these tumor findings as non-treatment-related

- Regulatory cancer assessment guidelines emphasize biological relevance over strict statistical significance

- The alignment between mouse and rat studies (both showing tumors, albeit in different organs) supports biological plausibility

- Progression to malignancy is NOT required by cancer assessment guidelines - benign tumors are considered relevant

d) Mode of Action Unknown

- PMRA does not understand the mechanics or mode of action (MOA) of the potential carcinogenic effects

- Cancer assessment guidelines emphasize the importance of understanding MOA to determine human relevance

- Lack of MOA clarity fundamentally limits the cancer assessment

e) Inappropriate Reliance on Non-Cancer Values

- PMRA states it will rely on "non-cancer risk assessment values to address concerns of tumorigenicity" without justification

- This is inappropriate because:

* Toxicity assessment employs dose-response analysis; carcinogenicity assessment does not

* No evidence provided that toxicity values adequately address tumorigenicity concerns

* Different mechanisms require different safety thresholds

f) Related Compound Carcinogenicity

- EPA classified broflanilide (55% structural similarity, same mode of action) as "likely to be carcinogenic to humans"

- Broflanilide caused Leydig cell tumors in male rats at 709 mg/kg/day (approaching limit dose)

- EPA classified fluxametamide (76% structural similarity, same mode of action) as having "suggestive evidence of carcinogenic potential"

- Fluxametamide caused thyroid tumors in male rats and liver tumors in male mice at doses approaching 900 mg/kg/day

The fact that two closely related compounds with the same mode of action are classified as likely or suggestive carcinogens when tested at adequate doses strongly suggests that isocycloseram would show similar carcinogenic potential if tested at adequate doses.

6. Implications for "Acceptable Dietary Level"

Given these critical deficiencies in the toxicity database:

- The Reference Dose (RfD) and other toxicity values may not be protective against cancer, developmental toxicity, immunotoxicity, or neurotoxicity. A precautionary approach should be applied.

- The "acceptable dietary level" determined in Step 2 of the dietary risk assessment is unreliable

- PMRA cannot have "reasonable certainty" that dietary exposure below the proposed MRLs will not cause harm

A scientifically based approach requires:

- Properly dosed, guideline-compliant cancer studies in at least two animal species

- Guideline-compliant developmental toxicity studies dosed up to the limit dose

- Developmental neurotoxicity study given the neurological mode of action

- Immunotoxicity study given the evidence of immune system effects

- Toxicity testing of all major metabolites

Without these studies, the toxicity database is inadequate to support MRL-setting or dietary risk assessment.

E. Inadequate Cumulative Risk Assessment

1. Limited Scope

PMRA's cumulative risk assessment for isocycloseram considered only three pesticides:

- Isocycloseram

- Broflanilide

- Fluxametamide

All three are Group 30 pesticides (GABA-gated chloride channel allosteric modulators). The assessment excluded cyproflanilide due to lack of registered uses in Canada/U.S.

However, SPN2018-02 (PMRA guidance on cumulative risk assessment) indicates the importance of considering ALL pesticides with a common mechanism of toxicity regardless of registration status.

2. Qualitative vs. Quantitative

PMRA used a qualitative rather than quantitative approach to cumulative risk assessment. A qualitative approach may not accurately capture actual cumulative exposure levels or risks.

SPN2018-02 emphasizes the importance of quantitative approaches, especially when multiple pesticides share a common mechanism of toxicity and significant exposure occurs.

3. Exposure Pathways

The cumulative assessment focused only on dietary exposure and excluded residential exposure. SPN2018-02 indicates that all relevant exposure pathways (occupational, residential) should be considered.

The assessment also did not address sensitive subpopulations or acute exposure scenarios.

4. Other Cumulative Risk Potentials Not Assessed

Apart from common mechanism of toxicity, other cumulative risk scenarios exist that were not assessed:

a) Common Cellular Outcomes

- If two compounds independently cause the same cellular outcome (e.g., mitochondrial dysfunction, oxidative stress), effects can be additive

- Example: Sedaxane (SDHI fungicide in A23128 ST formulation) causes mitochondrial dysfunction

- Another chemical causing oxidative/mitochondrial stress could produce additive or synergistic effects

b) Toxicokinetic Interactions

- Azoles (difenoconazole in A23128 ST formulation) frequently inhibit mammalian CYP enzymes

- CYP inhibition can raise internal exposures (blood/tissue concentrations) of co-exposed chemicals that are CYP substrates

- This produces apparent synergy

- Azoles repeatedly implicated in drug/pesticide interaction cases

- SDHIs (sedaxane in A23128 ST formulation) predicted/observed to affect human drug transporters (e.g., OAT3)

- Might change elimination of co-exposures, creating another kinetic interaction route

c) Mixture-Level Stress

- Pesticides independently causing cellular stress often produce greater-than-additive effects in some endpoints/species

- Defense pathways become overwhelmed

- Particular classes (azoles, cholinesterase inhibitors) feature in many reported synergistic interactions

5. Implications for A23128 ST Formulation

The A23128 ST formulation contains five active ingredients:

- Isocycloseram (insecticide, GABA channel modulator)

- Difenoconazole (fungicide, azole, CYP inhibitor)

- Sedaxane (fungicide, SDHI, mitochondrial complex II inhibitor)

- Metalaxyl-M (fungicide, RNA polymerase inhibitor)

- Fludioxonil (fungicide, HOG pathway)

Potential interactions include:

- Difenoconazole (azole): Potential "hotspot" for interactions due to CYP inhibition - could increase internal levels and toxicity of other actives if metabolized by CYPs

- Sedaxane (SDHI): Could add mitochondrial stress to any other chemical affecting mitochondria or antioxidant capacity

- Combined stress on soil microbes likely given multiple fungicides

PMRA has not assessed cumulative or mixture toxicity for this five-active formulation.

6. PFAS Cumulative Exposure

Most critically, PMRA has not assessed cumulative PFAS exposure from:

- Other PFAS pesticides (fluralaner, broflanilide, fluxametamide, etc.)

- Non-pesticide PFAS in food (from food packaging, processing equipment, environmental contamination)

- Drinking water PFAS

- Consumer product PFAS

- Environmental PFAS

All PFAS share the property of environmental persistence and bioaccumulation. Assessing dietary risk from isocycloseram in isolation fails to account for Canadians' total PFAS exposure and body burden.

7. Lack of Transparency

PMRA does not explain how the cumulative assessment was conducted. The assessment did not set out:

- Specific data sources

- Models used

- Assumptions made

- Quantitative results

SPN2018-02 emphasizes the importance of transparency to ensure credibility and reproducibility. Without transparency, the validity of the cumulative assessment cannot be verified.

IV. TOXIC SUBSTANCES MANAGEMENT POLICY VIOLATIONS

TSMP Framework and Track 1 Criteria

The Toxic Substances Management Policy (TSMP) was established to provide a framework for managing toxic substances in Canada. DIR99-03 outlines PMRA's approach to implementing TSMP for pesticides.

A substance is classified as TSMP Track 1 if it meets ALL four criteria:

- Persistent: Environmental half-life exceeds specified thresholds
- Bioaccumulative: Bioconcentration factor (BCF) or bioaccumulation factor (BAF) exceeds thresholds

- Toxic: Harmful to organisms or human health
- Anthropogenic: Primarily human-made

The persistence criteria under CEPA Persistence and Bioaccumulation Regulations specify half-lives:

- Water: >182 days
- Sediment: >365 days
- Soil: >182 days
- Air: >2 days

PMRA's Incorrect Assessment

PMRA's Table 29 in PRD2025-11 concludes that isocycloseram and its transformation products are NOT TSMP Track 1 substances. Safe Food Matters contends this conclusion contains critical errors.

SYN549107 Meets Three of Four Track 1 Criteria and PMRA's BCF Assessment Is Flawed

According to Table 29:

Persistence - MEETS CRITERION

- Soil aerobic DT50: 18.9-402.7 days (range based on 4 values)
- Maximum value of 402.7 days EXCEEDS the 182-day threshold for soil persistence under CEPA Persistence and Bioaccumulation Regulations Section 3(d)
- CLEARLY MEETS PERSISTENCE CRITERION

Bioaccumulation - FAILS CRITERION BUT ASSESSMENT IS FLAWED

- Log Kow = 6.29 (EXCEEDS threshold of 5.0, indicating high bioaccumulation potential)
- BCF = 1,140 L/kg (modeled in EAS-E Suite) - below 5,000 L/kg threshold
- HOWEVER: PMRA's footnote 4 to Table 29 acknowledges the BCF was modeled using "Arnot-Gobas BCF (including biotransformation) for lower trophic (96 g; 5.98% lipid content) fish"
- Arnot and Gobas (2006) explicitly state this model is inappropriate for higher trophic level fish
- A proper BCF assessment using an appropriate model for the relevant trophic level would likely show bioaccumulation potential given the high Log Kow of 6.29
- PMRA's use of an admittedly inappropriate model to conclude the bioaccumulation criterion is not met is scientifically invalid

Toxic - MEETS CRITERION

- All pesticides are considered CEPA-toxic or CEPA toxic equivalent (Table 29, footnote 1)
- As a degradation product of isocycloseram (which is toxic to aquatic organisms, bees, mammals), SYN549107 retains toxic properties
- MEETS TOXIC CRITERION

Anthropogenic - MEETS CRITERION

- SYN549107 is a breakdown product of the synthetic pesticide isocycloseram
- Does not occur naturally
- Concentration in environment is entirely due to human activity (pesticide application)
- MEETS ANTHROPOGENIC CRITERION

CONCLUSION: SYN549107 definitively meets THREE of four TSMP Track 1 criteria (persistent, toxic, anthropogenic). The fourth criterion (bioaccumulation) was assessed using an admittedly inappropriate model. With an appropriate assessment method, SYN549107 would likely meet all four criteria and qualify as Track 1.

At minimum, PMRA must:

- Conduct proper BCF assessment using appropriate model for relevant trophic levels
- Apply precautionary principle given Log Kow of 6.29 indicating high bioaccumulation potential
- Classify SYN549107 as Track 1 pending proper bioaccumulation assessment

SYN550738 Assessment Also Flawed

According to Table 29:

Persistence - FAILS CRITERION IN SOIL

- Soil aerobic DT50: 12.1-23.1 days (range based on 5 values)
- Does NOT exceed 182-day threshold for soil
- HOWEVER: No data provided for sediment, water, or air persistence
- Data gaps treated as "criterion not met" rather than "unknown"
- FAILS SOIL PERSISTENCE BUT OTHER MEDIA NOT ASSESSED

Bioaccumulation - HIGH POTENTIAL

- Log Kow = 6.78 (SUBSTANTIALLY EXCEEDS threshold of 5.0)
- BCF = 2,510 L/kg (modeled in EAS-E Suite) - below 5,000 threshold but still indicates moderate bioaccumulation
- High Log Kow suggests strong bioaccumulation potential
- FAILS BCF THRESHOLD BUT LOG KOW INDICATES HIGH POTENTIAL

Toxic - MEETS CRITERION

- CEPA-toxic equivalent
- MEETS TOXIC CRITERION

Anthropogenic - MEETS CRITERION

- Synthetic breakdown product
- MEETS ANTHROPOGENIC CRITERION

CONCLUSION: SYN550738 meets two criteria definitively (toxic, anthropogenic) and shows very high bioaccumulation potential (Log Kow = 6.78). Persistence in media other than soil was not assessed - data gaps should not be treated as negative findings.

Data Gaps Improperly Treated as Negatives

For both transformation products, PMRA's Table 29 shows:

- "Not available" for sediment half-lives
- "Not available" for water half-lives (SYN550738)
- "Not determined" for air persistence

PMRA appears to have treated these data gaps as evidence that criteria are NOT met, rather than acknowledging uncertainty. This is scientifically inappropriate. For substances where data are insufficient, the precautionary approach requires either:

- Generating the necessary data, or
- Treating the substance as if it meets the criterion pending data generation

PMRA cannot conclude a substance does NOT meet Track 1 criteria based on absence of data.

Parent Compound Classification

DIR99-03 states: "if a Track 1 substance results from degradation of a parent substance, the parent may also be considered Track 1."

Since SYN549107 meets or likely meets all four Track 1 criteria (pending proper BCF assessment), isocycloseram itself should be classified as Track 1 under this provision.

Moreover, as a PFAS with perfluorinated moieties, isocycloseram meets the persistence criterion independently. PFAS are by definition persistent - this is their defining characteristic as "forever chemicals."

Consequences of Track 1 Classification

If isocycloseram and its transformation products are properly classified as TSMP Track 1 substances, significant regulatory consequences follow:

Virtual Elimination Goal

TSMP Track 1 substances are subject to a goal of "virtual elimination" from the environment. The policy states:

"Track 1 substances are those that meet all four criteria... The goal for Track 1 substances is to achieve the lowest achievable level, which could ultimately result in virtual elimination of these substances from the environment."

Registering a new TSMP Track 1 pesticide is fundamentally incompatible with the virtual elimination goal.

Enhanced Scrutiny and Restrictions

Track 1 substances receive enhanced regulatory scrutiny, including:

- Stricter use restrictions
- Requirements for additional environmental monitoring
- Consideration of alternatives
- Provisions for future regulatory action if releases cannot be minimized

International Obligations

Track 1 substances may be candidates for international action under:

- Stockholm Convention on Persistent Organic Pollutants
- Other international chemicals management frameworks

Cannot Establish "Reasonable Certainty of No Harm"

For a Track 1 substance that is persistent, bioaccumulative, toxic, and subject to a virtual elimination goal, PMRA cannot establish "reasonable certainty that no harm to... future generations or the environment will result from exposure to or use of the product."

The very classification as Track 1 indicates that harm is expected and that the policy goal is elimination, not management through mitigation measures.

PMRA's Errors Are Not Harmless

PMRA's misclassification of isocycloseram and its transformation products under TSMP is not a minor technical error. It has profound implications:

- It allowed PMRA to avoid applying TSMP Track 1 requirements and scrutiny
- It enabled PMRA to proceed with registration without addressing virtual elimination goals
- It resulted in inadequate assessment of persistence and bioaccumulation
- It facilitated an incorrect conclusion that environmental risks are "acceptable"

Safe Food Matters requests that PMRA:

- Correct Table 29 to properly classify SYN549107 as meeting three of four Track 1 criteria with the fourth (bioaccumulation) requiring proper assessment using an appropriate model
- Acknowledge that SYN550738 has very high bioaccumulation potential (Log Kow = 6.78) and that persistence in media other than soil was not assessed
- Classify isocycloseram itself as Track 1 given that SYN549107 likely meets all four criteria and given isocycloseram's PFAS nature
- Apply TSMP Track 1 requirements to the registration decision
- Acknowledge that registration of a new Track 1 substance is incompatible with TSMP virtual elimination goals
- Deny registration on the basis of Track 1 classification

V. JURISDICTIONAL VIOLATIONS

A. Seed Coatings Are Not Pest Control Products

The Pest Control Products Act defines "pest control product" in Section 2(1):

"pest control product means a product, an organism or a substance, including any thing generated by the product, organism or substance, that consists of its active ingredient, formulants and contaminants and that is manufactured, represented, distributed or used as a means for directly or indirectly controlling, destroying, attracting or repelling a pest or for mitigating or preventing its injurious, noxious or troublesome effects."

The key phrases are:

- "controlling, destroying, attracting or repelling a pest"

- "as a means for directly or indirectly" performing these functions

Seed coatings containing isocycloseram do not meet this definition because they are PROPHYLACTIC, not remedial.

1. Prophylactic vs. Pest Control

Prophylactic: "serving to prevent disease; preventive" (medical definition)

Applied to pesticides: serving to prevent pest establishment before pest is present

Pest Control: responding to existing pest presence or damage; controlling/destroying pests that are present or expected based on pest pressure

Isocycloseram seed treatments are applied:

- Before planting

- Before any pest is present

- Without regard to actual pest pressure

- As insurance against potential future pest occurrence

This is prevention, not control. The treatment aims to prevent pests from establishing, not to control or destroy existing pests.

2. PCPA Definition Requires Active Pest Management

The PCPA definition requires that the product be "used as a means for... controlling, destroying, attracting or repelling" a pest. These are active verbs requiring interaction with an actual pest:

- Control: manage a pest population

- Destroy: kill pests

- Attract: lure pests (e.g., for monitoring or trapping)

- Repel: drive pests away

Prophylactic seed coatings do none of these because no pest is present at the time of application or during early plant development.

3. Analogy to Human Medicine

In human medicine, the distinction between prevention and treatment is well-established:

- Vaccines PREVENT disease before exposure (prophylactic)

- Antibiotics TREAT disease after infection (therapeutic)

Regulatory frameworks distinguish these categories. Health Canada regulates vaccines differently from therapeutics, recognizing that preventive interventions require different assessment frameworks.

Similarly, prophylactic seed treatments should not be regulated under PCPA, which is designed for pest CONTROL products, not pest PREVENTION products.

4. Environmental Consequences of Prophylactic Use

Prophylactic seed coating has distinct and more severe environmental consequences than responsive pest control:

- 100% of planted acres receive pesticide, regardless of whether pests appear

- No targeting based on pest pressure, threshold levels, or integrated pest management

- Inevitable and widespread environmental contamination

- Promotes pesticide resistance by exposing pest populations to continuous selection pressure

- Violates integrated pest management principles

B. Appropriate Regulatory Authority

If seed coatings are not pest control products under PCPA, what is the appropriate regulatory framework?

1. Environment and Climate Change Canada

Seed coatings that prevent pest establishment may be more appropriately regulated under environmental protection legislation:

- Canadian Environmental Protection Act (CEPA)

- Provisions for substances that may enter the environment

- Assessment of environmental risks and fate

- Management of persistent substances

2. Seed Regulations

Seed coatings might be regulated as seed treatments under seed legislation:

- Seeds Act and regulations

- Focus on seed quality, germination, contamination

- Less emphasis on environmental fate

3. Provincial Jurisdiction

Prophylactic agricultural amendments might fall under provincial jurisdiction over:

- Agricultural practices

- Soil amendments

- Farm inputs

C. PMRA's Jurisdictional Overreach

By asserting jurisdiction over prophylactic seed coatings, PMRA:

- Exceeds its statutory authority under PCPA

- Applies a regulatory framework designed for active pest control to preventive pest management

- Inappropriately expands PCPA's scope beyond its intended purpose

This jurisdictional overreach has several consequences:

1. Seed coating uses are ultra vires (beyond PMRA's legal authority)

2. Registration of seed treatment products may be invalid

3. MRLs predicated on seed treatment uses lack legal foundation

D. International Precedent

Other jurisdictions have recognized the distinct nature of prophylactic pesticide uses:

- European Union REACH regulation treats prophylactic uses differently from responsive uses

- Some EU member states restrict prophylactic seed treatments

- Integrated Pest Management (IPM) requirements in EU emphasize responsive rather than prophylactic approaches

E. Implications for PMRL2025-21

If PMRA lacks jurisdiction over isocycloseram seed coating uses, then:

- Applications 2021-3038, 2021-3045, 2021-3048 should be referred to the appropriate regulatory authority

- Registration cannot be granted under PCPA

- MRLs cannot be established under PCPA for uses that fall outside PMRA's jurisdiction

Safe Food Matters requests that PMRA:

- Acknowledge that seed coatings are prophylactic, not pest control products

- Decline jurisdiction over seed coating applications

- Refer applications to Environment and Climate Change Canada or other appropriate authority

- Withdraw proposed MRLs for seed treatment uses

VI. FAILURE TO MEET PCPA SECTION 7(2) STANDARD

A. The "Reasonable Certainty of No Harm" Standard

PCPA Section 7(2) requires "reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product."

This is an extraordinarily high standard:

- "Reasonable certainty" - not probability, not likelihood, but certainty

- "No harm" - not acceptable harm, not managed harm, but no harm

- To "human health, future generations or the environment" - comprehensive scope

- From "exposure to or use" - all exposure pathways and use scenarios

B. PMRA's Burden of Proof

PMRA bears the burden of establishing reasonable certainty of no harm. The applicant must provide data, but PMRA must evaluate that data and reach a conclusion.

If the data are insufficient, contradictory, or raise unresolved safety concerns, PMRA cannot reach a conclusion of reasonable certainty of no harm.

In such cases, the PCPA requires denial of registration. There is no provision for:

- Conditional registration pending additional data

- Registration with extensive mitigation measures to compensate for failure to establish no harm

- Registration based on assumptions rather than data

C. PMRA Cannot Establish Reasonable Certainty for Isocycloseram

Based on the evidence and deficiencies documented in these comments, PMRA cannot establish reasonable certainty that no harm to human health, future generations, or the environment will result from isocycloseram use:

1. PFAS Nature Precludes "No Harm to Future Generations"

- Isocycloseram will persist indefinitely

- Environmental contamination is irreversible

- Future generations will inevitably be exposed

- Harm to future generations is certain, not uncertain

2. Inadequate Toxicity Database

- Critical studies waived without justification

- Cancer and developmental toxicity studies underdosed

- 35 of 36 metabolites untested

- Equivocal cancer evidence dismissed without scientific basis

- Evidence of developmental toxicity (bifid sternum) not adequately addressed

- Immunotoxicity concerns not investigated

Without adequate toxicity data, PMRA cannot establish what exposures would cause harm and therefore cannot establish reasonable certainty that proposed uses will not cause harm.

3. Flawed Exposure Assessment

- Wrong consumption data (U.S., not Canadian)

- Outdated consumption data (2005-2010)

- Insufficient field trials creating high MRL uncertainty

- Metabolite exposure not quantified

- Aggregate PFAS exposure not assessed

- Cumulative exposure inadequately assessed

Without accurate exposure assessment, PMRA cannot establish reasonable certainty that exposures will remain below levels that might cause harm.

4. Environmental Persistence and Toxicity

- Very highly toxic to aquatic invertebrates (RQs up to 413)

- Highly toxic to bees (RQs up to 1,537)

- Persistent in soil (half-lives up to 293 days)

- Degradates more persistent than parent (up to several years)

- High bioaccumulation in fish (BCF 823-982)

- Binds to soil, making soil unavailable for crop development

These environmental characteristics make harm to the environment certain, not preventable through mitigation.

5. TSMP Track 1 Classification

- Transformation products meet Track 1 criteria

- Parent should be classified as Track 1

- Track 1 substances subject to virtual elimination goal

- Registration incompatible with virtual elimination

6. Jurisdictional Issues

- Seed coatings prophylactic, not pest control

- Uses may fall outside PCPA authority

- Registration may be ultra vires

D. Mitigation Measures Cannot Cure Fundamental Deficiencies

PMRA has proposed various mitigation measures:

- Protective equipment for workers

- Label restrictions on use

- Buffer zones

- Best management practices

These mitigation measures cannot establish reasonable certainty of no harm because:

1. The PCPA standard must be met at the assessment stage, before considering mitigation

2. Mitigation addresses use conditions, not fundamental pesticide properties

3. No amount of mitigation can:

- Make a PFAS non-persistent

- Fill data gaps in the toxicity database

- Correct flawed exposure assessments

- Change the inherent toxicity to aquatic organisms and bees

4. Mitigation assumes perfect compliance, which is unrealistic given human nature, financial constraints, and potential for error

5. PMRA provides no evidence that labels are complied with in practice

E. Precautionary Approach

When scientific uncertainty exists about the nature or magnitude of harm, the precautionary approach requires that lack of full scientific certainty not be used as a reason to postpone measures to prevent harm.

For isocycloseram, the precautionary approach supports denial of registration because:

- Significant scientific uncertainties exist (untested metabolites, underdosed studies, equivocal cancer evidence)

- The potential for serious harm is evident (PFAS persistence, toxicity to non-target organisms, cancer concerns)

- The harm would be irreversible (PFAS contamination cannot be remediated)

- Alternatives exist (other pest management approaches, non-PFAS pesticides)

F. Conclusion on PCPA Section 7(2)

Safe Food Matters concludes that PMRA cannot meet the PCPA Section 7(2) standard for isocycloseram. The evidence demonstrates that harm to human health, future generations, and the environment is probable if not certain.

The appropriate regulatory response is to deny registration and refuse to establish MRLs.

VII. INADEQUATE VALUE ASSESSMENT

A. PCPA Section 2(1) Value Definition

The PCPA defines "value" in Section 2(1) as:

"(a) the efficacy of the pest control product for its intended use,

(b) any of its effects on host organisms in connection with which it is intended to be used, and

(c) its health, safety, environmental, social and economic impacts."

PMRA must assess value under all three criteria before registration.

B. No Demonstrated Need

PMRL2025-21 and PRD2025-11 provide no rationale for the need for isocycloseram. Questions that should be addressed include:

1. Are existing pest management tools inadequate?

2. What specific pest pressure or agricultural problem does isocycloseram address that cannot be addressed by existing tools?

3. What is the magnitude of crop loss prevented by isocycloseram?

4. Are there non-chemical alternatives?

5. Are there alternative chemical tools with lower environmental and health risks?

Without justification based on need, PMRA cannot properly weigh the value against the risks.

C. Effects on Host Organisms

PMRL2025-21 and PRD2025-11 provide no information on effects of isocycloseram on host organisms (barley, oats, rye, triticale, wheat).

Relevant questions include:

1. Does isocycloseram affect germination rates?

2. Does it affect plant vigor, growth, or development?

3. Are there effects on grain quality, protein content, or other characteristics?

4. Does it affect subsequent crop rotations?

More importantly, what are the effects on the environment and conditions required for the host:

1. Effects on soil microbiota essential for nutrient cycling

2. Effects on beneficial insects (pollinators, natural pest enemies)

3. Effects on soil structure and long-term fertility

4. Effects from soil binding of persistent compound

These effects on the agricultural ecosystem should be part of the value assessment.

D. Negative Social and Economic Impacts

The proposed registration has significant negative social and economic impacts:

1. Worker Health and Safety

- Extensive protective equipment required (chemical resistant socks, N95 masks)

- Closed cab tractors required for planting

- These requirements:

* Impose costs on farmers

* May not be consistently followed due to cost, discomfort, or human error

* Create worker health risks if not followed

2. Agricultural Land Contamination

- PFAS contamination of agricultural land will:

* Reduce land value

* Threaten future agricultural use

* Impact farmers' livelihoods

* Create liability concerns

3. Market Access

- Growing consumer and retailer concern about PFAS

- Potential for trade barriers if trading partners restrict PFAS pesticides

- Organic and sustainable agriculture markets exclude PFAS pesticides

- Farmers using isocycloseram may lose market access

4. Future Generations

- Irreversible contamination imposes costs on future generations:

* Environmental remediation (if even possible)

* Health care costs from PFAS-related diseases

* Loss of productive agricultural land

* Reduced environmental quality

These social and economic impacts are substantial and negative. PMRA must weigh them against any claimed benefits.

E. Information Requested

Safe Food Matters requested from PMRA an integrated value assessment.

This information has not been provided. Without a comprehensive value assessment, PMRA cannot properly make a registration decision.

F. Minimal Value Does Not Justify Risk

Even if isocycloseram provides some efficacy benefit (which is not demonstrated), that minimal value does not justify:

- Adding another PFAS "forever chemical" to the environment

- Irreversible contamination of agricultural land

- Risks to human health from inadequately tested pesticide

- Impacts to non-target organisms including bees and aquatic life

- Harm to future generations

The precautionary approach and the PCPA standard require that PMRA not approve products where risks outweigh benefits, especially when the risks include irreversible environmental contamination.

VIII. PROCEDURAL VIOLATIONS AND UNLAWFUL SPLIT ASSESSMENT

PMRA's Consultation Process Violates Procedural Requirements

PMRL2025-21 and PRD2025-11 represent an unlawful splitting of what should be a unified assessment process. This bifurcated consultation violates both the letter and spirit of the Pest Control Products Act and denies stakeholders their statutory rights to meaningful participation in the regulatory process.

Statutory Requirement for Integrated Assessment

The PCPA requires integrated assessment of health risks, environmental risks, and value before registration decisions. Section 7(3) mandates that the Minister "conduct any evaluations that the Minister considers necessary with respect to the health or environmental risks or the value of the pest control product" and "carry out any consultation required by section 28."

Section 28(1) specifies when consultation is required, including for decisions "to grant or deny an application to register a pest control product that is or contains an unregistered active ingredient."

The consultation statement under Section 28(2) "shall include 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."

This statutory framework requires a unified consultation on the complete registration decision - health risks, environmental risks, value, and MRLs - all integrated into a single evaluation and consultation process.

MRLs Are Integral to Registration Decision

MRLs should not be set independently of the registration decision. Section 9 states: "When making a decision regarding the registration of a pest control product, the Minister shall, if necessary, specify any maximum residue limits."

The use of "when making a decision" makes clear that MRL specification occurs as part of the registration decision, not as a separate subsequent process. PMRA cannot make a registration decision without simultaneously determining appropriate MRLs.

Dietary Risk Assessment Is Fundamental to Health Risk Determination

PMRL2025-21 relies entirely on the dietary risk assessment. However, dietary risk is a core component of the health risk assessment required under Section 7(3).

Section 7(7)(b) specifically requires the Minister to "in relation to health risks... consider available information on aggregate exposure to the pest control product, namely dietary exposure and exposure from other non-occupational sources."

Dietary exposure and MRLs are not separate issues to be consulted on independently - they are essential elements of the health risk assessment that must be evaluated as part of the unified registration decision.

Value Assessment Requires Consideration of MRLs

Section 2(1) defines "value" to include "health, safety and environmental benefits and social and economic impact."

MRLs directly affect value because they:

- Determine which foods can contain residues and at what levels
- Impact international trade (MRL harmonization with trading partners)
- Affect farmer practices and costs
- Influence consumer acceptance and market access

A value assessment conducted without knowing the proposed MRLs is incomplete and meaningless.

Single Consultation Required

Section 28(2) requires "a consultation statement" (singular) and Section 28(5) requires "a decision statement" (singular) for each decision subject to consultation.

PMRA's creation of two separate consultations - one for registration (PRD2025-11) and one for MRLs (PMRL2025-21) - violates this requirement. There should be one integrated consultation statement covering all aspects of the registration decision including MRLs.

Prejudiced Decision-Making

The bifurcated process reveals that PMRA has prejudged the registration decision before completing consultation on MRLs.

PMRL2025-21 states: "The evaluation of these isocycloseram applications indicated that the end-use products have value, and the human health and environmental risks associated with their proposed uses are acceptable."

This conclusory statement appears in the MRL consultation document, indicating PMRA has already decided to approve registration before stakeholders have had opportunity to comment on the dietary risk assessment and proposed MRLs.

Section 28(4) requires: "The Minister shall consider any comments received pursuant to subsection (2) before making a decision."

By announcing in PMRL2025-21 that risks are "acceptable" and the product "has value," PMRA demonstrates it has made the registration decision before the MRL consultation period has even closed - a clear violation of Section 28(4).

Information Not Provided Despite Requests

Safe Food Matters has requested essential information from PMRA that is necessary to provide meaningful comments on both PRD2025-11 and PMRL2025-21. This was:

- any integrated assessments, including exposure assessments and evaluations of value

- if not in the integrated assessment - any assessments of exposure and evaluations of value

- the details of PMRA's calculations of the maximum residue limits, including any OECD calculator output pages.

- any review of public literature conducted by PMRA for the pesticide

OECD MRL Calculator Outputs

Safe Food Matters requested the complete OECD Calculator output pages, if any, showing how the proposed MRLs were derived. This information is essential to verify that:

- MRLs are not inflated by insufficient trial data
- Statistical treatment is appropriate
- No algorithmic artifacts distort the MRL values

PMRA has not provided this information, preventing stakeholders from verifying the scientific validity of the proposed MRLs.

Integrated Assessments

Safe Food Matters requested integrated assessments that connect the various evaluation components for risk and value. PMRA has not provided these integrated assessments, making it impossible to verify that PMRA properly considered "aggregate exposure" as required by Section 7(7)(b)(i).

Value Assessment Documentation

Safe Food Matters requested documentation of the value assessment required under Section 2(1) and Section 4(2)(d):

- Efficacy data supporting claimed benefits
- Analysis of alternatives (chemical and non-chemical)
- Assessment of effects on host organisms
- Analysis of social and economic impacts (positive and negative)
- Weighing of benefits against risks

PMRA has not provided this documentation. Without it, stakeholders cannot verify that PMRA properly determined the product to be "of acceptable value" as required for registration.

Cumulative Risk Assessment Details

Safe Food Matters requested details of the cumulative risk assessment:

- Which pesticides were included in the assessment
- Quantitative exposure and risk estimates for each pesticide, rather than qualitative statements
- How cumulative risks were calculated
- Why certain pesticides or exposure pathways were excluded

PMRA's PRD2025-11 contains only conclusory statements about cumulative risk, without the underlying data and analysis. This prevents verification that the assessment was conducted properly.

Scientific Literature Review

Safe Food Matters requested information about what review of public scientific literature PMRA conducted on isocycloseram. PMRA is required by law to assess the current science when proposing MRLs. Without this information, stakeholders cannot verify that PMRA considered all available scientific information as required

Denial of Procedural Rights

The failure to provide requested information and the unlawful split assessment violate stakeholders' procedural rights under the PCPA.

Right to Meaningful Participation

The PCPA Preamble states: "the provinces and territories and those persons whose interests and concerns are affected by the federal regulatory system be accorded a reasonable opportunity to participate in the regulatory system."

Participation cannot be "reasonable" or meaningful if:

- Essential information is withheld
- The assessment is artificially split so stakeholders cannot comment on the complete picture
- Comments are solicited after PMRA has already announced its decision

These procedural violations deny affected persons their statutory right to participate in the regulatory process.

Right to Informed Comment

Section 28(2) requires that the consultation statement "include 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."

By not providing the requested information, PMRA has failed to provide summaries of key evaluation reports, violating Section 28(2) and preventing informed comment.

Right to Pre-Decision Consultation

Section 28(4) requires: "The Minister shall consider any comments received pursuant to subsection (2) before making a decision."

PMRL2025-21's statement that "human health and environmental risks associated with their proposed uses are acceptable" indicates the registration decision has already been made, before the MRL consultation has closed and before comments can be considered.

This is a clear violation of Section 28(4) and transforms the consultation from a genuine pre-decision process into a post-decision formality..

Precedential Concerns

PMRA's procedural violations set a dangerous precedent. If PMRA can split registration decisions into multiple consultations, it can prevent stakeholders from seeing the complete picture and manipulate information availability. If PMRA can withhold requested information, it can shield poor quality assessments from scrutiny. If PMRA can announce decisions before consultation closes, it transforms consultation from meaningful process to post-decision formality.

Legal Authorities Supporting Procedural Requirements

Section 2(1) defines "value" to include efficacy, effect on host organisms, and "health, safety and environmental benefits and social and economic impact."

Section 7(3) requires the Minister to "conduct any evaluations that the Minister considers necessary with respect to the health or environmental risks or the value of the pest control product."

Section 7(7)(b)(i) requires the Minister to "consider available information on aggregate exposure to the pest control product, namely dietary exposure and exposure from other non-occupational sources."

Section 9 states: "When making a decision regarding the registration of a pest control product, the Minister shall, if necessary, specify any maximum residue limits."

Section 28(3) requires the consultation statement to "include (a) 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; (b) the proposed decision and the reasons for it."

Section 28(4) requires: "The Minister shall consider any comments received pursuant to subsection (2) before making a decision."

Conclusion on Procedural Violations

PMRA's bifurcation of the isocycloseram assessment, refusal to provide requested information, and premature announcement of conclusions constitute serious procedural violations of the PCPA. These violations deny stakeholders their statutory right to meaningful participation, violate pre-decision consultation requirements, and undermine transparency. The procedural violations are independently sufficient grounds to deny registration and withdraw the proposed MRLs.

IX. CONCLUSION

Safe Food Matters Inc. submits that PMRA cannot and should not establish Maximum Residue Limits for isocycloseram or register isocycloseram products for use in Canada.

The classification of isocycloseram as a PFAS "forever chemical" that will persist indefinitely in the environment and human bodies fundamentally precludes any finding of "reasonable certainty that no harm to human health, future generations or the environment will result."

APPENDIX A: SCIENTIFIC REFERENCES

Scientific Literature

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