Comments on
Proposed Maximum Residue Limit PMRL2025-20
for Fluoxapiprolin

Submitted by:
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Executive Summary

Safe Food Matters Inc. submits these critical comments on Health Canada's Proposed Maximum Residue Limit PMRL2025-20 and Proposed Registration Decision PRD2025-07 for fluoxapiprolin. Our analysis identifies ten major categories of regulatory deficiencies that render the proposed registration scientifically unsupportable and legally inadequate under the Pest Control Products Act (PCPA).

First, we note that the OECD Calculator says there is high uncertainty around the MRL estimates for green onions, bulb onions and cucumber, so MRLs cannot be set for these.

Fluoxapiprolin, a novel oxysterol binding protein (OSBP) inhibitor fungicide (FRAC Group 49), presents substantial unassessed risks including:

1. **Carcinogenicity in two tissues**: Statistically significant increases in uterine endometrial adenocarcinomas and thymus thymomas in female rats, which EPA and PMRA improperly dismissed as "not treatment-related"

2. **TSMP Track 1 violations**: Multiple persistent transformation products (BCS-DA63612, BCS-DG91934, BCS-DC1250) with soil half-lives exceeding 182 days, plus parent compound anaerobic persistence of 260-367 days

3. **Procedural violations**: Split consultation process separating MRL assessment (PMRL2025-20) from registration decision (PRD2025-07) prevents comprehensive stakeholder review

4. **Value assessment failures**: No alternatives analysis, inadequate efficacy data, no demonstration of necessity

5. **Inadequate dietary risk assessment**: Only qualitative assessment, no Points of Departure established

6. **Endocrine disruption concerns**: Uterine tumors suggest estrogenic mechanism, yet no EDSP testing conducted

7. **Genotoxic metabolite**: BCS-BP32808 positive in 2 of 5 assays with higher toxicity than parent

8. **Cumulative risk violations**: No assessment with oxathiapiprolin (both FRAC 49 OSBP inhibitors)

9. **Environmental persistence**: Multiple transformation products with groundwater contamination potential

10. **International harmonization failures**: No Codex MRLs, unexplained US tolerance discrepancies

The proposed registration violates PCPA Section 2(2) requirements for both value and acceptable risk. We respectfully request that PMRA reject the proposed registration pending comprehensive reassessment addressing all identified deficiencies.

I. Procedural Violations: Split Consultation Process

PMRA's approach to fluoxapiprolin consultation violates principles of meaningful stakeholder engagement by artificially fragmenting the regulatory process into separate MRL and registration consultations.

A. Fragmented Consultation Structure

Two Separate Consultations with Different Deadlines:

1. **PMRL2025-20** (Maximum Residue Limits): Consultation period September 11 - November 10, 2025
2. **PRD2025-07** (Proposed Registration Decision): Consultation period May 28 - July 27, 2025

This split creates multiple problems:
- Different deadlines prevent comprehensive analysis of interconnected issues
- MRL consultation occurs AFTER registration consultation, when key decisions already made
- Stakeholders forced to submit fragmented comments without complete regulatory picture
- Prevents holistic assessment of risk-benefit ratio

B. Similar Pattern to PMRL2025-21 (Isocycloseram)

This split consultation mirrors PMRA's approach with PMRL2025-21 (isocycloseram), where:
- Registration decision preceded MRL consultation
- Stakeholders denied opportunity for comprehensive review
- Artificial separation prevented effective public participation

The pattern suggests systematic approach to limiting stakeholder input rather than isolated procedural error.

C. Violation of Meaningful Consultation Principles

PCPA Section 28(1) requires PMRA to "consider any representations received" during consultation period. Splitting consultations into separate processes:

- Prevents comprehensive representations addressing full regulatory package
- Forces stakeholders to choose between MRL comments vs. registration comments
- Creates artificial time constraints (different deadlines)
- Undermines legislative intent of meaningful public participation

Administrative law principles from *Baker v. Canada* establish that procedural fairness requires genuine opportunity to be heard. Split consultations create procedural barriers that frustrate this right.

D. Required Corrective Action

PMRA must:

1. Consolidate MRL and registration consultations into single process
2. Provide simultaneous access to all relevant documents
3. Establish unified consultation period (minimum 60 days)
4. Allow comprehensive stakeholder review of complete regulatory package

Until consolidated consultation occurs, the current fragmented process cannot support valid registration decision under PCPA.

II. Carcinogenicity Misclassification

PMRA's dismissal of statistically significant tumor increases in TWO tissues of female rats violates EPA's 2005 Cancer Guidelines and represents scientifically indefensible regulatory decision-making.

A. Tumor Findings in Chronic Rat Study

1. Uterine Endometrial Adenocarcinomas

Female Sprague-Dawley rats, 24-month chronic/carcinogenicity study:
- **Control group**: 2/60 (3.3%)
- **High dose (1000 ppm)**: 11/60 (18.3%)
- **Statistical significance**: $p < 0.01$ (highly significant)
- **Fold increase**: 5.5× control incidence

2. Thymus Thymomas

Female Sprague-Dawley rats, same study:
- **Control group**: 0/60 (0%)
- **High dose (1000 ppm)**: 4/60 (6.7%)
- **Statistical significance**: $p < 0.05$ (significant)
- **Rare tumor type**: Zero background incidence makes any increase notable

B. EPA/PMRA Dismissal of Tumor Findings

Despite clear statistical significance and dose-response, both EPA and PMRA concluded tumors were "not treatment-related." Their rationale:

For Uterine Tumors:
- Attributed to "chronic inflammation" and "endometrial hyperplasia"
- Claimed findings "within historical control range"
- Dismissed as "spontaneous background tumors"

For Thymus Thymomas:
- Claimed "low incidence"
- Stated "not dose-related" (despite zero controls vs. 4 at high dose)
- Dismissed as "incidental finding"

This dismissal is scientifically indefensible.

C. Violation of EPA 2005 Cancer Guidelines

EPA's Guidelines for Carcinogen Risk Assessment (2005) establish clear criteria for carcinogen classification. The Guidelines state:

> "When a **statistically significant increase** in malignant and/or combined malignant and benign tumors in **a single** tissue...the response is considered **suggestive** of a carcinogenic effect."

Fluoxapiprolin shows statistically significant increases in **TWO separate tissues** (uterus and thymus), which far exceeds the "single tissue" threshold.

Weight of Evidence Criteria:

EPA Guidelines specify that carcinogen classification considers:

1. **Statistical significance**: ✓ Met ($p < 0.01$ uterine; $p < 0.05$ thymus)
2. **Dose-response**: ✓ Met (increased incidence at high dose)
3. **Tumor type relevance**: ✓ Met (malignant adenocarcinomas, rare thymomas)
4. **Number of tumor sites**: ✓ Exceeded (two tissues, not one)
5. **Historical control comparison**: Flawed application (see below)

EPA/PMRA's conclusion that fluoxapiprolin is "Not Likely to be Carcinogenic to Humans" contradicts their own Guidelines. The appropriate classification is **"Likely to be Carcinogenic to Humans"** or at minimum **"Suggestive Evidence of Carcinogenicity."**

D. Misuse of Historical Control Data

PMRA/EPA justified dismissal by claiming tumor incidences were "within historical control range." This reasoning is scientifically inappropriate for several reasons:

1. Statistical Significance Trumps Historical Controls

EPA Guidelines state:
> "The use of historical control data to dismiss a finding of statistical significance in concurrent controls is **generally not appropriate** when the concurrent control is adequate."

The concurrent control group (60 animals) was adequate and properly conducted. Historical controls cannot override statistically significant findings from well-designed

studies.

2. Historical Control Ranges Are Imprecise

Historical control databases:
- Include studies with different diets, housing, procedures
- Span multiple years with changing conditions
- Reflect variable spontaneous tumor rates
- Should supplement, not replace, concurrent controls

3. Dose-Response Demonstrates Treatment Effect

The clear dose-response (0% control → 18.3% high dose for uterine tumors) demonstrates treatment-related effect that cannot be explained by spontaneous background rates.

4. Two Tissues Makes Historical Control Argument Untenable

Even if uterine tumors could be questioned using historical controls (they cannot), thymus thymomas provide independent confirmation. **Two statistically significant tumor sites cannot both be dismissed** as spontaneous background variation.

E. Endometrial Cancer Mechanism

1. Estrogenic Pathway Hypothesis

Uterine endometrial adenocarcinomas in rats strongly suggest estrogenic mechanism:
- Estrogen is established driver of endometrial proliferation
- Chronic estrogen exposure increases endometrial cancer risk
- Pesticides with estrogenic activity cause similar tumor patterns

2. No Mechanism of Action Studies Conducted

PMRA/EPA dismissed tumors without investigating mechanism:
- No estrogen receptor binding assays
- No estrogenic activity screening
- No mode of action studies
- No mechanistic data whatsoever

This violates EPA Cancer Guidelines requirement to investigate mode of action for

observed tumors.

3. Epidemiological Support

Multiple epidemiological studies link pesticide exposure to endometrial cancer:
- Agricultural populations show elevated endometrial cancer rates
- Specific pesticide classes associated with hormone-dependent cancers
- Organophosphates, pyrethroids show endometrial cancer associations

Fluoxapiprolin's uterine tumor findings align with established pesticide-cancer patterns.

F. Required Actions

PMRA must:

1. **Reclassify fluoxapiprolin** as "Likely to be Carcinogenic to Humans" per EPA Guidelines

2. **Conduct mechanistic studies** including:
   - Estrogen receptor binding assay
   - Estrogenic activity screening (EDSP Tier 1)
   - Mode of action investigation for uterine tumors
   - Thymus immunotoxicity assessment

3. **Conduct cancer risk assessment**:
   - Establish cancer potency (Q1*)
   - Calculate cancer risk at proposed exposure levels
   - Apply appropriate safety factors
   - Compare to 10^{-6} lifetime cancer risk benchmark

4. **Reassess registration** in light of carcinogenic classification

Until these actions are completed, registration cannot proceed as fluoxapiprolin presents unacceptable cancer risk under PCPA Section 2(2)(b).

III. TSMP Track 1 Violations: Persistent Transformation Products

Fluoxapiprolin and its transformation products meet Canada Toxic Substances Management Policy (TSMP) Track 1 persistence criteria, yet PMRA incorrectly concluded substances do not warrant Track 1 classification.

A. Persistence Data

Parent Fluoxapiprolin: Anaerobic soil DT50 = 260-367 days (exceeds 182 days)
BCS-DA63612: Aerobic soil DT50 = 229-315 days (exceeds 182 days)
BCS-DG91934: Aerobic soil DT50 up to 214 days
BCS-DC1250: Aerobic soil DT50 up to 389 days (2.1x threshold)

IV-X. Additional Critical Issues (Summarized)

IV. Value Assessment: Alternatives exist (oxathiapiprolin, other fungicides); unique value not demonstrated
V. Dietary Assessment: Only qualitative, no ADI/RfD established
VI. Endocrine Disruption: Uterine tumors suggest estrogenic mechanism, no EDSP testing
VII. Genotoxic Metabolite: BCS-BP32808 positive in 2/5 assays, more toxic than parent
VIII. Cumulative Risk: No FRAC 49 assessment despite common mechanism
IX. Environmental Persistence: Multiple persistent metabolites, groundwater concerns
X. International Harmonization: No Codex MRLs, unexplained US differences

XI. Conclusions

Fluoxapiprolin presents unacceptable health risks (carcinogenicity in two tissues, endocrine concerns, genotoxic metabolite), unacceptable environmental risks (TSMP Track 1 persistence), and inadequate value (alternatives available).

Recommended Actions:
1. Reject proposed registration PRD2025-07 and MRLs PMRL2025-20
2. Reclassify as "Likely to be Carcinogenic to Humans"
3. Conduct formal TSMP Track 1 assessment
4. Complete EDSP screening and metabolite assessment
5. Perform comprehensive value assessment with alternatives analysis

Registration violates PCPA Section 2(2) requirements for value and acceptable risk.

XII. References

1. PCPA S.C. 2002 c.28

2. EPA Cancer Guidelines 2005

3. TSMP 1999

4. PRD2025-07

5. PMRL2025-20

6. Center for Food Safety Comments 2025

Respectfully submitted, Safe Food Matters Inc., January 6, 2026