COMMENTS ON PROPOSED REGISTRATION DECISION FOR ISOCYCLOSESRAM and end-use products VANECTO Cockroach Gel Bait, EQUENTO and A23128 ST

Contents

Introduction

We herein provide comments to PRD 2025-11 concerning Isocycloseram (the “Active” or “IS”) and end-use products VANECTO Cockroach Gel Bait (“EP Bait”), EQUENTO and A23128 ST.

EP Bait is proposed for the control of cockroaches in commercial, industrial and residential buildings and other listed structures.

Seed Tr 1 is a seed treatment product for the control of insect pests on wheat, oat, barley, rye and triticale.

Seed Tr 2 is a seed treatment product for the control of insect pests and the control or suppression of seed-borne and soil-borne diseases on wheat, oat, barley, rye and triticale. It also contains active ingredients difenoconazole, sedaxane, metalaxyl-M (and S-isomer) and fludioxonil.

Additional Information Requested

We have requested and are awaiting information PMRA Info and Access to Information on this PRD. We may have additional comments following our receipt of such information:

- 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 pesticides in issue

PMRA Approach requires proof of no harm with reasonable scientific certainty

The scientific approach under the PCPA requires the registrant to establish a 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 (PCP), taking into account its conditions or proposed conditions of registration (Section 1(2), 4 and 7(6) of the PCPA). PMRA cannot rely upon mitigation measures to establish a reasonable certainty of no harm. At the stage of assessment, if no such reasonable certainty can be established, there no recourse to mitigation measures is permitted.

The PMRA, on behalf of the Minister of Health, must apply a scientifically based approach when evaluating the risks of the PCP. A scientifically based approach uses scientific evidence, which consists of information gathered through rigorous, repeatable procedures that confirm or disconfirm scientific hypotheses. This evidence must be empirical, interpretable according to the scientific method, and capable of being verified or falsified through observation and experimentation.

General

- PFA. The Active is a PFAs. It forms part of class of chemicals known as per- and polyfluoroalkyl substances (PFAS). (“National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 87323565.”) (Wang et al.) It also contains a dichloro-fluorophenyl group which raises risk concerns.

PFA contamination is ubiquitous and very pervasive in our world. This point was presented to the EPA in a submission on the Active, as set out below. It applies to the Canadian context as well, under the auspices of the PMRA under the Pest Control Products Act 9the “Act”):

"It is evident that EPA and other federal regulators are well behind the curve in protecting against the threats posed by PFAS compounds, including PFAS pesticides. Despite evidence on the dangers of PFAS stretching as far back as the 1950s, federal agencies sat on the sidelines, as the plastics industry continued adding the material to new products. The detection of any level of PFAS is cause for concern. As drinking water health advisories issued by EPA show, PFAS levels as low as .02 parts per trillion (ppt) have the potential to cause adverse health effects.16 (Lasee et al.)

From widespread presence in farm fields and sewage sludge (biosolids) to contaminated water bodies throughout the U.S., PFAS have made their way into the environment and human bodies. Given the recent problems with widespread contamination of agricultural land with PFAS, EPA should not register a new PFAS pesticide, which would further disperse a persistent compound in the environment and could further threaten farmers' livelihoods and lives. PFAS are even present in remote environments like the Arctic, Antarctica, and Eastern European Tibetan Plateau. The U.S. Centers for Disease Control and Prevention (CDC) determined that almost all Americans have some level of PFAS in their bloodstream which highlights PFAS as a chronic danger to people that demands urgent regulatory restrictions, rather than an expansion of the market.17 (United States Environmental Protection Agency (2025). Drinking Water Health Advisories (HAs). Available at: https://www.epa.gov/sdwa/drinking-water-health-advisories-has.)

PFAS contamination is much more pervasive than previously thought, polluting storage and transportation containers, food and water resources, and other chemical products. Not only is the public exposed to such chemicals, but those who work in factories that create products that include PFAS, or workers who use them regularly, have higher cumulative exposures as well. This PFAS contamination problem calls for a comprehensive policy rather than the "whack-a-mole" approach to chasing individual contamination crises after they have occurred and inflicted serious harm to people's health. Given EPA's mandatory duty under the *Food Quality Protection Act* (FQPA) to consider aggregate risk from dietary and non-dietary exposure, the addition of a new PFAS-classified pesticide (isocycloseram) 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."

Waivers. Despite a finding of a serious developmental effect, the PRMA allowed a waiver for a developmental neurotoxicity evidence. PMRA also waived an immunotoxicity study, without legitimate grounds. The toxicological data on isocycloseram suggested a possible immune system toxicity, this requires further study. Findings on different pesticides are not relevant to this issue.

Toxic Substances Management Policy Considerations: The PRD in Table 29 sets out the considerations. On persistence, information was **not available** on the criteria for 2 transformation product endpoints and all other major transformation products. For IS itself and all transformation products, **no determination** was made on persistence in air. The conclusion was that the products were not TSMP Track 1 substances because all of the TSMP Track 1 criteria were not met.

This is not a valid conclusion. It is not clear whether or not some of the criteria were met, given that information was not available or a determination was not made. The answer should not have been "no" for the last row of the table, given this uncertainty – an absence of data or an inability to make a determination is not a finding of "no". The answer should also not have been "no" for SYN 549107 because all 4 considerations WERE indeed met. The answer should also not have been no for SYN550738 on persistence, because Table 20 only measured the DT 50 in aerobic soils, but did not measure its half-life in soil. The *Bioaccumulation and Persistence Regulations* under CEPA in section 3(d) consider a

substance persistent when "in soil, its half-life is greater than 182 days", and SYM550738 meets this test, as evidenced in Table 13 Biotransformation in soil where the T 1/2rep was 230. The OECD Test Guideline 307 supports this half-life test. Since SYN550738 is persistent, and is also assessed as toxic, bioaccumulative and anthropogenic, it qualifies as a TSMP Track 1 Substance. Thus the two transformation products meet the TSMP criteria, and, based on DIR99-03 (which PMRA indicated it followed in making the assessment), if a Track 1 substance results from degradation of a parent substance, the parent may also be considered Track 1. As such, the active should be considered a Track 1 substance as well.

Moreover, the second transformation product endpoint, SYN549107 met all the TSMP criteria but for one. The one it did not meet was BCF, but this was based on a model relating to lower tropic fish. This model is in appropriate for the current purposes. (Arnot and Gobas)

Seed Coatings: Seed coating are not pesticides. A pest control product is defined in the Act as a product designed to control, destroy, attract or repel a pest, and a pest is an organism that is injurious, noxious or troublesome. Seed coatings are prophylactic – they act to prevent pests, not control, destroy, attract or repel them. As such, the PMRA does not have jurisdiction over seed coatings. Environment Canada likely does.

There are various concerns with seed coatings. First, allowing them to be used in the environment can lead to resistance and escalating use, both of which are potentially harmful to the environment. Also the seed coating will end up in and contaminate surface waters, causing toxic harm to aquatic species. Seeds also represent a hazardous waste and lead to disposal problems if they are not planted, and their hazardous nature subsists in soil once placed there.

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

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

It is possible for nanomaterial-based agrochemicals can seep into water bodies and enter the food chain (bioaccumulation). {0.Murali M, Gowtham HG, Singh SB, Shilpa N, Aiyaz M, et al. Fate, bioaccumulation and toxicity of engineered nanomaterials in plants: current challenges and future prospects. Sci. Total Environ. 2022;811:152249. doi: 10.1016/j.scitotenv.2021.152249. [DOI] [PubMed] [Google Scholar](Murali et al.)

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

Health Harms and Risk Assessment

Cancer. The cancer risk assessment for the Active is based on equivocal evidence. As such, there is no reasonable certainty that it does not cause cancer.

In a mouse study, an increase in the incidence of ovarian luteomas in female mice was observed. Yet PMRA considered this equivocal based on the weight of evidence. It indicated the findings were not statistically significant, there was no progression to malignant tumors, and the effects were observed only in one sex and one species.

A slight increase in the incidence of Leydig cell tumors in male rats was also observed. PMRA also considered these equivocal and of low concern to humans based on the weight of evidence.

However, with respect to the studies, a finding is a finding, and the significance of it cannot be diminished with recourse to irrelevant factors brought in through a weight of evidence approach. PMRA did not provide scientific authority to justify its dismissal of the findings as treatment related.

With respect to the mouse study, the fact that the findings were observed in only sex and species does not detract from the finding. The sex and species were included in the test requirements. Moreover, in cancer assessments, regulatory agencies often emphasize biological relevance over strict statistical significance, meaning that even if a finding is not statistically significant, it may still be considered relevant if it aligns with other evidence of carcinogenicity or if the observed effect is biologically plausible. There is alignment between the mouse and rat study here, in that both had tumors. A progression to malignancy is also not a requirement of guidelines to cancer assessment.

Given that the potential for cancer is unknown, it was not appropriate for PMRA to rely on non-cancer risk assessment values to address concerns of tumorigenicity in animal studies. No justification was provided for this statement, which is required particularly since toxicity employs dose-response analysis and carcinogenicity does not. Moreover, no evidence was provided to show that values for toxicity address the concerns of tumorigenicity.

It is evident PMRA does not understand the mechanics or mode of action (MOA) of the potential carcinogenic effects. However, Cancer Guidelines emphasize the importance of understanding the MOA to determine whether observed effects in animals are relevant to humans. The lack of clarity on the MOA limits the cancer assessment.

Genotoxicity. With respect to genotoxicity, there was a positive in vitro result for the metabolite SYN548569. PMRA does not provide a detailed explanation of scientific justification for how this result can be discounted.

Reproductive and Developmental Toxicity. In the reproductive and developmental toxicity studies, there were findings of **reproductive toxicity** in the parents. In the young, there was the **serious endpoints** in the form of decreased survival. The fact that there was no finding of increased sensitivity in the young does not obviate from the serious endpoint, because there two criteria are distinct, as outlined in SPN2008-01. In the rat developmental toxicity study, there were serious effects in the young which attracts a high level of concern in accordance with SPN2008-01 and justifies retention of the 100 fold PCPA Factor.

With respect to the dietary 2-generation reproductive toxicity study in rats, there appears to have been qualitative sensitivity, in that the types of effects on the young differed from the parent. This attracts a high level of concern.

The conclusion that serious endpoints in young can be tempered by the presences of paternal toxicity is not adequately justified.

Metabolites. It appears that toxicity assessment for all metabolites was not conducted, meaning a science based approach was not applied to the pesticides.

Dietary Risk Assessment

Uncertainties and problems with the dietary risk assessment include the following. The consumption data is based on National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005–2010, which measures what Americans, not Canadians consume. As such it is not relevant. Also, the data is outdated so not in keeping with a scientifically based approach.

OECD MRL Calculator

The OECD MRL Calculator is a statistical tool that can yield misleadingly high values when limited or heterogeneous residue trials are used. Without transparency about input data (n, mean, and range), there is no assurance the calculate ppm value is technically justified. The output and other related pages regarding the OECD calculations have been requested so we may have additional comments on health risk assessment. PMRA must disclose these data and demonstrate the MRL was not inflated by the calculator's algorithmic rounding or statistical treatment of small datasets. We have requested, and are waiting for, the output page for the OECD calculations, and may update these comments once the data is received.

However it appears from the PRD that there were 5 field trials conducted for each of oats, barley, rye and triticole. The OECD Calculator White Paper warns that for trials numbered between 3 and 7, there is a

"High uncertainty of MRL estimate. [Small dataset]"

Accordingly, based on the PRD, it appears that the MRL estimate use for the dietary risk assessment is highly uncertain.

Occupational Harms and Risk Assessment

The dermal absorption values used in the occupational risk assessment are based on in vitro studies, which may not fully represent real-world conditions. Certain dose groups were not assessed, which presents further uncertainty in the dermal absorption values for these groups.

There is also potential for co-occurrence of exposure for the Active and Broflanilide, but the cumulative risk of these 2 was not assessed.

The target margin of exposure (MOE) is set at 1000 for occupational scenarios, but PMRA document does not provide a clear justification for this value. SPN2018-02 emphasizes the importance of transparency in setting MOEs based on scientific evidence, but this principle was not followed.

The recommended PPE, clothing and vehicles shows a high degree of concern for workers. Engineering controls like a closed cab tractors are recommended for planting. Chemical resistant socks are required, as are N95 face masks. It is unreasonable to dictate what type of vehicle a grower must use and to expect people to be completely protected from all potential bodily exposure as described. These requirements would detract markedly from the **value** of these products.

It is evident that the potential harm to occupational workers is marked. The label requirements cannot reasonably be expected to be followed at all times, given human nature, financial constraints and the potential for error. No argument or evidence was provided to show that labels are complied with. There can be no reasonable certainty of no harm to human health to the extent such certainty is premised on label compliance.

Environmental Harms and Risk Assessment

The assessment of environmental risks associated with IS and the end products shows the risks are unacceptable. The assessment is clear it causes toxic effects in some species. In being environmentally toxic, the pesticide crosses the assessment threshold for "acceptable risk" in the risk assessment, rendering the risk unacceptable. It must be shown that an unacceptable risk has been rendered acceptable by the conditions of registration before registration, amendment or approval can occur. This has not been shown using a scientifically based approach, and therefore the onus for considering the risks acceptable has not been met.

Persistence in Soil. Isocycloseram is *moderately persistent to persistent* in aerobic soil. The EPA's assessment reports its soil half-life (DT_{50}) ranges from **56 to 293 days.** Because of this persistence, residues may remain in soil for a long time, potentially exposing soil organisms repeatedly or over extended periods.

Some of the transformation products are also of concern. They vary in mobility and persistence, and some are mobile enough that they could move, for example, by runoff, into adjacent water bodies, as noted by the EPA in its assessment. However data is not sufficient on this point so the EPA had to resort to modelling to all other degradates. Appropriate data should be requested.

Potential for Runoff and Off-Site Movement**.** Although PMRA indicates Isocycloseram has "limited ability to move downward" in soil in some scenarios, the risk assessment highlights the potential for **runoff** or **erosion** to transport residues into adjacent aquatic systems. This means that even if it's relatively immobile in some soils, wind or water erosion could carry contaminated soil particles (with bound pesticide) off-site presenting potential harm.

Toxicity to Some Soil Organisms, Aquatic Life, Birds, Mammals, Bees

Aquatic Toxicity. Freshwater and marine invertebrates, such as Daphnia magna, Chironomus riparius, and Mysid shrimp, exhibit very high sensitivity to isocycloseram and its transformation products. Chronic NOECs for these species are extremely low, and RQs often exceed LOC, indicating significant ecological risks. Effects at LOEC for Chironomus riparius include reduced dry weight, development rate, and adult emergence, while Mysid shrimp show reduced offspring per female, survival, and hatchling survival.

The transformation products SYNS50918 and SYNS49431 also present risks, as the RQs exceed the level of concern.

Anthropods. The Australian risk assessment reported some sub-lethal / reproductive toxicity for certain soil arthropods (mites). Long-term exposure inhibited reproduction (e.g., lowest EC10 ~ 0.11 mg active/kg dry soil) in one test species (Hypoaspis acuifer).

Birds and Mammals. PRD is clear that the LOC is exceeded for birds and mammals. According to the Canadian registration decision, when used as seed treatment (e.g., in A23128 ST) and with required risk mitigation (e.g., incorporation of spilled seed), the environmental risk to soil organisms is considered acceptable.

Bees. The pesticide IS is highly toxic to bees. PRMA does not see a problem if seeds are not dusty, which is not reasonable. But it does see that dusty seeds present a problem. PMRA in the PRD does not solve the assessment conclusion of toxicity, but rather proposes a mitigation of a "best management practices" on the label. A mitigation

measure cannot ensure a reasonable certainty of no harm and as such the pesticide should not proceed to approval. Any such approval would be unlawful.

Bioaccumulation and Concerns with Soil Bound Residues**.** Table 29 of the PRD shows Isocycloseram has a relatively high log K_ow (≈ 4.89), which suggests potential for bioaccumulation in some systems.

In soil, some portion of the radio-labeled residue in degradation studies was "unextractable" (i.e., bound to soil), which suggests that there may be long-term non-bioavailable (or slowly available) residues. While bound residues may be less bioavailable, they represent a "reservoir" that could potentially be remobilized or affect soil over time, depending on environmental conditions. This presents the risk of exposure.

Moreover, by binding the soil, the soil itself is not available as it would otherwise be for supporting crop development. Given that IS is a forever chemical, this runs afoul of sustainability for future generations which is a requirement of the "no harm" standard under the Act.

Risk of Leaching / Groundwater Contamination**.** Some degradation products are mobile and can leach. According to the EPA assessment, certain "residues of concern" (including degradates) are mobile enough to pose risks to groundwater under some scenarios. This is important because even though the parent compound may be less likely to leach strongly in some soils, its metabolites might.

Secondary Ecological Effects. Because isocycloseram is very toxic to aquatic invertebrates, any movement from soil to water (via runoff or erosion) could pose ecological risk off-site. (Santa Clara Valley et al.) There may also be indirect soil ecosystem effects if non-target soil organisms (e.g., arthropods) are impacted. For example, reduction in soil arthropods could disrupt soil food-webs, nutrient cycling, or predator-prey dynamics.

Unrealistic Mitigation Measures and Uncertainties**.**

The *risk-reduction measures* required on the label for seed treatment products (like A23128 ST), e.g., spilled treated seeds must be incorporated into the soil or cleaned up are very problematic.

- If incorporated into soil, their environmental effects and binding in soil will be amplified.

- Methods for incorporating into soil are unrealistic. Growers use pesticides in many instances to save time, so to the extent this is the motivation for the seed treatments, it cannot reasonably be expected that growers will perform this step. It is also not realistic to expect that they will wear PPE – the fields of the crops in question are massive in the prairie provinces and elsewhere.

- The mitigation measure of providing "best practices" and precautionary statements on labels will have no effect, and will not mitigate risks. Best management practice label statements such as minimizing bee exposure to dust during planting of treated seed and precautionary label statements to indicate leaching to groundwater is possible do nothing.

- There are data gaps and uncertainties. Only some soil-organism tests were done; however real-world complexity (microbial communities, interactions between species) would not be fully captured in lab tests. Uncertainties also remain regarding pore water concentrations for sediment-dwelling organisms and the effectiveness of mitigation measures for transformation products.

Specific Considerations for the Listed Products

When seeds treated with isocycloseram (and in the case of A23128 ST, together with fungicides) are planted, isocycloseram is introduced into soil more directly. For A23128 ST, because it also contains fungicides, there might be combined stress on soil microbes or invertebrates, and interactions with fungicides might add complexity. See also the section below on cumulative risks.

Value Assessment

Under section 2(1) of the Pest Control Products Act, "value" includes:
(a) efficacy,
(b) effects on host organisms, and
(c) health, safety, environmental, social, and economic impacts.

No rationale for the need for this pesticide has been provided, and justification based on need would fit with the objective of reducing exposures to harmful pesticides. PMRA must demonstrate that an evaluation under at least these 3 criteria was conducted before accepting the new use pattern on hops. We have requested and are waiting for an integrated value assessment, and may add to these comments once it is received.

With respect to the effect on the host organism, no effect was presented in the PRD that we saw. No effect on the surrounding environment and conditions required for the host, such as healthy soil, was provided, and should be.

With respect to the health, safety, environmental, social and economic impacts, it is evident from the labels, discussed above, that if workers and growers are not excessively protected, their health could be compromised. The social and economic impacts of complying with the labels are negative and significant (e.g. buy specific PPE and closed tractors).

The impacts to future generations of adding another persistent PFA to the environment and human settings could be enormous, and the minimal (if any) value presented in no way justifies taking on this risk.

Cumulative Effects Assessment

The cumulative effects assessment in the PRD evaluates the Active alongside other pesticides in the same mode of action group (Group 30: GABA-gated chloride channel allosteric modulators). However, there are several problems with the approach employed by PMRA, based on framework set out in SPN2018-02.

First, the assessment was limited in scope. The cumulative assessment only considered isocycloseram, broflanilide, and fluxametamide, excluding cyproflanilide due to its lack of registered uses in Canada or the US. However, SPN2018-02 indicates it is important to consider all pesticides with a common mechanism of toxicity, regardless of their registration status. As such, excluding cyproflanilide may lead to an incomplete understanding of the cumulative risks posed by this group of pesticides.

In addition, the PMRA used a qualitative rather than a quantitative approach. A qualitative approach may not accurately capture the actual cumulative exposure levels or risks. A quantitative approach is important, as set out in SPN2018-02, especially when multiple pesticides share a common mechanism of toxicity.

The assessment was also to narrow, in that it focused only on dietary exposure and excluded residential exposure, saying there is negligible residential exposure for isocycloseram and no residential uses for broflanilide. However SPN2018-02 indicates **all relevant exposure pathways**, including occupational and residential exposure, should be considered. Moreover, the assessment did not speak to sensitive subpopulations.

PMRA also did not include acute exposure in cumulative assessment; however SPN2018-02 says that cumulative assessments should consider both acute and chronic exposures when applicable.

With respect to mammals, the mode of action was not set out. However, until this MOA is understood, the cumulative assessment may fail to fully capture potential risks from combined exposure to the group of pesticides.

PRMA does not explain how the cumulative assessment was conducted. It did not set out the specific data sources, models, or assumptions used. SPN2018-02 emphasizes the importance of transparency in cumulative risk assessments to ensure credibility and reproducibility. As such, the validity of the assessment cannot be verified.

Assessment of other Cumulative Potentials Required

Apart from the discussion on common mechanism of toxicity, other potentials for cumulative risk exist. If two compounds independently cause the same cellular outcome (e.g., mitochondrial dysfunction, oxidative stress, endocrine disruption), their effects can add. SDHIs (sedaxane) cause mitochondrial dysfunction — another chemical that causes oxidative or mitochondrial stress (or impairs antioxidant defences) could produce additive or synergistic effects: (Duarte Hospital et al.; Bouillaud).

Interactions that are toxicokinetic can also occur among different substances:

- Azoles (difenoconazole) frequently inhibit mammalian CYP enzymes and can therefore **raise internal exposures** (blood/tissue concentrations) of co-exposed chemicals that are CYP substrates — producing apparent synergy. Azoles are repeatedly implicated in drug/pesticide interaction cases for this reason. (Pan et al., “The Fungicide Difenoconazole Alters MRNA Expression Levels of Human CYP3A4 in HepG2 Cells”; Draskau and Svingen; Cedergreen, “Quantifying Synergy”)

- SDHIs (sedaxane) have also been predicted/observed to affect human drug transporters (e.g., OAT3) and might change elimination of co-exposures. That creates another plausible kinetic interaction route. (Bouillaud)

In addition, there are potential interactions arising from mixture-level stress and indirect synergy. Pesticides that independently cause cellular stress (mitochondrial inhibition, oxidative stress, ER stress, endocrine disruption) often produce **greater-than-additive effects** in some endpoints or species because defence pathways are overwhelmed. Meta-reviews show synergy is uncommon but documented, and particular classes (azoles, cholinesterase inhibitors) feature in many reported synergistic. (Verbruggen; Cedergreen, “Quantifying Synergy”)

The implications arising for these chemicals include:

- Difenoconazole (azole) is a potential interaction «hotspot» because of CYP inhibition — it could increase internal levels and toxicity of any of the other four if those are metabolized by CYPs. (Draskau and Svingen; Draskau and Svingen; Pan et al., “The Fungicide Difenoconazole Alters MRNA Expression Levels of Human CYP3A4 in HepG2 Cells”)

- Sedaxane (SDHI) could add mitochondrial stress to any other chemical that affects mitochondria or antioxidant capacity (fludioxonil’s metabolic stress/HOG effects could plausibly interact). Also look out for transporter inhibition (OAT3) as a kinetic route. (Kerhoas et al.) (Bouillaud) (Brandhorst et al.)

- Fludioxonil and metalaxyl-M act by different fungal mechanisms; their combined effect on non-target organisms would depend on whether those organisms share the vulnerable pathway and on dose/timing. (Bersching and Jacob) (Randall et al.)

- Isocycloseram (neuroactive insecticide) is mechanistically distinct from the fungicides — direct neuro-additivity with the fungicides is unlikely, but if a fungicide changed isocycloseram metabolism (via CYP/transporter effects), systemic isocycloseram levels could change. (Blythe et al.)

Conclusion

Safe Food Matters forcefully call on PMRA to not register these products. Registration in the face of the facts that the products are PFA, that they present the potential for cancer and are clearly toxic, and they harm the environment, can in no way be justified under the framework of the PCPA or of scientific risk assessments in general.

REFERENCES

Arnot, Jon A, and Frank APC Gobas. “A Review of Bioconcentration Factor (BCF) and Bioaccumulation Factor (BAF) Assessments for Organic Chemicals in Aquatic Organisms.” *Environmental Reviews*, vol. 14, no. 4, Dec. 2006, pp. 257–97. *DOI.org (Crossref)*, https://doi.org/10.1139/a06-005.

Bersching, Katharina, and Stefan Jacob. “The Molecular Mechanism of Fludioxonil Action Is Different to Osmotic Stress Sensing.” *Journal of Fungi*, vol. 7, no. 5, May 2021, p. 393. *DOI.org (Crossref)*, https://doi.org/10.3390/jof7050393.

Blythe, Judith, et al. “The Mode of Action of Isocycloseram: A Novel Isoxazoline Insecticide.” *Pesticide Biochemistry and Physiology*, vol. 187, Oct. 2022, p. 105217. *DOI.org (Crossref)*, https://doi.org/10.1016/j.pestbp.2022.105217.

Bouillaud, Frederic. “Inhibition of Succinate Dehydrogenase by Pesticides (SDHIs) and Energy Metabolism.” *International Journal of Molecular Sciences*, vol. 24, no. 4, Feb. 2023, p. 4045. *DOI.org (Crossref)*, https://doi.org/10.3390/ijms24044045.

Brandhorst, T. Tristan, et al. “Phenylpyrrole Fungicides Act on Triosephosphate Isomerase to Induce Methylglyoxal Stress and Alter Hybrid Histidine Kinase Activity.” *Scientific Reports*, vol. 9, no. 1, Mar. 2019, p. 5047. *DOI.org (Crossref)*, https://doi.org/10.1038/s41598-019-41564-9.

Cedergreen, Nina. “Quantifying Synergy: A Systematic Review of Mixture Toxicity Studies within Environmental Toxicology.” *PLoS ONE*, edited by Aamir Nazir, vol. 9, no. 5, May 2014, p. e96580. *DOI.org (Crossref)*, https://doi.org/10.1371/journal.pone.0096580.

“Quantifying Synergy: A Systematic Review of Mixture Toxicity Studies within Environmental Toxicology.” *PloS One*, vol. 9, no. 5, 2014, p. e96580. *PubMed*, https://doi.org/10.1371/journal.pone.0096580.

Draskau, Monica Kam, and Terje Svingen. “Azole Fungicides and Their Endocrine Disrupting Properties: Perspectives on Sex Hormone-Dependent Reproductive Development.” *Frontiers in Toxicology*, vol. 4, Apr. 2022, p. 883254. *DOI.org (Crossref)*, https://doi.org/10.3389/ftox.2022.883254.

Duarte Hospital, Carolina, et al. “Triggering Tumorigenic Signaling: Succinate Dehydrogenase Inhibitor (SDHi) Fungicides Induce Oncometabolite Accumulation and Metabolic Shift in Human Colon Cells.” *Environment International*, vol. 199, May 2025, p. 109503. *DOI.org (Crossref)*, https://doi.org/10.1016/j.envint.2025.109503.

Kerhoas, Marie, et al. “Inhibition of Human Drug Transporter Activities by Succinate Dehydrogenase Inhibitors.” *Chemosphere*, vol. 358, Jun. 2024, p. 142122. *DOI.org (Crossref)*, https://doi.org/10.1016/j.chemosphere.2024.142122.

Lasee, Steven, et al. “Targeted Analysis and Total Oxidizable Precursor Assay of Several Insecticides for PFAS.” *Journal of Hazardous Materials Letters*, vol. 3, Nov. 2022, p. 100067. *DOI.org (Crossref)*, https://doi.org/10.1016/j.hazl.2022.100067.

Murali, M., et al. “Fate, Bioaccumulation and Toxicity of Engineered Nanomaterials in Plants: Current Challenges and Future Prospects.” *Science of The Total Environment*, vol. 811, Mar. 2022, p. 152249. *DOI.org (Crossref)*, https://doi.org/10.1016/j.scitotenv.2021.152249.

“National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 87323565.” https://pubchem.ncbi.nlm.nih.gov/compound/87323565.

Pan, Liumeng, et al. “The Fungicide Difenoconazole Alters MRNA Expression Levels of Human CYP3A4 in HepG2 Cells.” *Environmental Chemistry Letters*, vol. 15, no. 4, Dec. 2017, pp. 673–78. *DOI.org (Crossref)*, https://doi.org/10.1007/s10311-017-0636-0.

“The Fungicide Difenoconazole Alters MRNA Expression Levels of Human CYP3A4 in HepG2 Cells.” *Environmental Chemistry Letters*, vol. 15, no. 4, Dec. 2017, pp. 673–78. *DOI.org (Crossref)*, https://doi.org/10.1007/s10311-017-0636-0.

Patisaul, Heather B. “Endocrine Disruption by Dietary Phyto-Oestrogens: Impact on Dimorphic Sexual Systems and Behaviours.” *Proceedings of the Nutrition Society*, vol. 76, no. 2, May 2017, pp. 130–44. *DOI.org (Crossref)*, https://doi.org/10.1017/S0029665116000677.

Randall, Eva, et al. “Sequence Diversity in the Large Subunit of RNA Polymerase I Contributes to M Efenoxam Insensitivity in *P Hytophthora Infestans* .” *Molecular Plant Pathology*, vol. 15, no. 7, Sep. 2014, pp. 664–76. *DOI.org (Crossref)*, https://doi.org/10.1111/mpp.12124.

Santa Clara Valley, et al. “Materials for Information.” 23 Jun. 2025, https://scvurppp.org/wp-content/uploads/2025/06/MC-Information-Packet_June-2025.pdf.

Shelar, Amruta, et al. “Recent Advances in Nano-Enabled Seed Treatment Strategies for Sustainable Agriculture: Challenges, Risk Assessment, and Future Perspectives.” *Nano-Micro Letters*, vol. 15, no. 1, Feb. 2023, p. 54. *PubMed*, https://doi.org/10.1007/s40820-023-01025-5.

Verbruggen, E.M.J. *Review of Recent Literature Concerning Mixture Toxicity of Pesticides to Aquatic Organisms*. https://edepot.wur.nl/155269.

Wang, Zhanyun, et al. “A New OECD Definition for Per- and Polyfluoroalkyl Substances.” *Environmental Science & Technology*, vol. 55, no. 23, Dec. 2021, pp. 15575–78. *DOI.org (Crossref)*, https://doi.org/10.1021/acs.est.1c06896.