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EPN Comments on Proposed Registration of Pesticides Containing Isocycloseram
EPA-HQ-OPP-2021-0641
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The Environmental Protection Network (EPN) harnesses the expertise of more than 650 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

On May 9, 2025, EPA announced its proposed decision to register pesticide products containing the new active ingredient isocycloseram. The agency placed a number of documents in public docket EPA-HQ-OPP-2021-0641 at www.regulations.gov and invited public comment on the proposed decisions. Isocycloseram is formulated as a technical product and nine end-use products, including a ready-to-use (RTU) gel bait and various liquid concentrates (i.e., dispersible, suspension, and flowable), with uses on treated seeds, agricultural field crops, indoor/outdoor residential areas, residential/commercial turf, greenhouse, commercial/industrial areas, industrial structures, and agricultural structures. Applications of the end-use products are made by aerial, airblast, groundboom, chemigation, fogger (greenhouse only), electrostatic sprayer (greenhouse only), backpack sprayer, manually-pressurized handwand, mechanically-pressurized handgun, wood injection, crack and crevice treatment, spot treatment, residential/commercial perimeter treatment, and seed treatment equipment. EPA concluded that the proposed registrations meet the statutory standards in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and, by reference, the Federal Food, Drug, and Cosmetic Act (FFDCA).

As explained more fully below, EPN believes that EPA's assessment of the potential risks to humans is deficient and that the proposed labeling does not meet the statutory standard that the use directions are likely to be read and understood and thus adequate to protect health and the environment. Therefore, we recommend that EPA clarify several ambiguous or incomplete aspects of its Human Health Risk Assessment and further analyze the potential of isocycloseram to cause cumulative risks. We also recommend that EPA require the applicant to develop labeling for end-use products that will increase the likelihood that users will obtain and follow the many restrictions relating to controlling spray drift and the protection of endangered and threatened species and their designated critical habitats.

A. EPA's Human Health Risk Assessment is Deficient

1. On page 21, Section 4.3, the last sentence, if supported by the data, should be clarified. A suggestion is to write that "…the available studies provide protective points of departure for all the isomers of isocycloseram." Otherwise, it is unclear what this statement actually means for toxicity of the chemical.

2. Under section 2.2.4, International Harmonization, it is stated that the Pest Management Regulatory Agency (PMRA) of Canada is reviewing the same petition as the agency, but it also states that there are no formal joint review partners for this petition. EPN thinks that it would be prudent for EPA and PMRA to exchange information about their respective

databases, risk assessments, and regulatory conclusions, if the two agencies have not already done so. Such an exchange may be beneficial in several ways – identifying regulatory issues that might have been overlooked or misinterpreted by one of the agencies, promoting harmonization of regulatory standards, and building connections that would support more efficient joint reviews.

3. On page 73 of the assessment is a summary of a 28-day oral toxicity study in the rat with the isomers of isocycloseram. The statement is made at the end of the summary that "Bioanalytical evaluation showed that treated rats were exposed to measurable concentrations of SYN547407 at all dose levels and the concentrations of SYN547407, generally increased with increasing dose." There is no explanation for the terms "bioanalytical evaluation" and "measurable concentration." These need to be defined and explained.

4. On page 76 of the risk assessment, a 28-day oral toxicity study for SYN548285 is summarized. The executive summary for this study states that epithelial vacuolation of the duodenum was observed, but that no adverse effect on function of the intestine was noted. Where is the support for this statement of no alteration in intestinal function? The duodenum performs many essential physiological functions in the mammalian organism, so support for this statement needs to be included.

5. Starting on page 77 of the assessment, executive summaries of the 28-day, 90-day, and developmental toxicity studies and two-generation reproductive toxicity study are presented. The classification of these studies as acceptable/non-guideline is not supported. There was no Lowest Observed Adverse Effect Level (LOAEL) achieved in any of these studies, and the reasoning that the non-guideline classification is applied due to not testing to a limit dose is incorrect. Doses should have been tested where a clear LOAEL was observed in these studies. EPN thinks these studies themselves are not acceptable and should be re-classified as unacceptable. EPA needs either to explain why the studies are acceptable and thus satisfy the data requirements or why acceptable data are not needed to complete the risk assessment.

6. Several of the executive summaries for the toxicity studies state that the test material was "well tolerated." The meaning of this statement is not explained. What criteria are used that support this statement?

7. More information on the acute toxicity profile of this chemical needs to be included in this risk assessment, particularly the dermal sensitization potential of the chemical. The agency has used results of quantitative dermal sensitization studies for determination of points of departure and risk (as in the isothiazolinone chemical cases risk assessment). Although this chemical does have labeling that would include statements regarding dermal sensitization potential, it should be made clear that if there was no risk from dermal exposure as stated in the assessment, that the results of the dermal sensitization study cited were not a driver of risk from dermal exposure. At a very minimum, the EC3 value from the Local Lymph Node Assay (LLNA) study should be included in the summary table for this study.

8. In Appendix A, Section A.2, the method/route of administration of the chemical is not shown consistently in the summary table. The 28-day toxicity studies, for example, are missing the information on method of administration and whether dietary or gavage. Also, the test material is not stated for several of the summaries in the table. Was it the mixture? Individual isomers? This requires clarification.

9. EPA has not adequately explained its decision not to conduct a cumulative risk assessment for isocycloseram.

The FFDCA authorizes EPA to establish a tolerance for a pesticide chemical residue in food or feed only if the agency determines that "the tolerance is safe." FFDCA sec. 408(b)(2)(A)(1). The FFDCA defines "safe" to mean there is a "reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."[1] The FFDCA further provides that "In establishing . . . a tolerance for a pesticide chemical residue, the Administrator shall consider . . . available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity."[2] EPA's Decision Document and other supporting documents do not demonstrate that EPA has adequately considered available, reliable information about potential cumulative effects of isocycloseram and other substances. Before accepting registrations of products containing isocycloseram, either EPA needs to provide better support for its conclusion that the agency does not need to perform a cumulative risk assessment for products containing isocycloseram, or it must assess the cumulative effects of the chemicals belonging to a common mechanism group.[3]

The cursory explanation for EPA's conclusion that the agency does not need to conduct a cumulative risk assessment is inconsistent with the statute, the available scientific information, and EPA's guidance. EPA's Decision Document states:

> Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to isocycloseram and any other substances. For the purposes of this action, therefore, EPA has not assumed that isocycloseram has a common mechanism of toxicity with other substances.[4]

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[1] FFDCA sec. 408(b)(2)(A)(2).

[2] FFDCA sec. 408(b)(2)(D)(v).

[3] While EPA has already closed the comment period on the proposed tolerances for isocycloseram in food, it still must address the safety of those residues as part of its decision to register products containing isocycloseram. Specifically, FIFRA sec. 3(c)(5) requires the agency to find that a pesticide does not cause "unreasonable adverse effects on the environment" – a term which FIFRA defines to mean, among other things, ". . . (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard in [FFDCA sec. 408(b)(2)(A)(1)]." See FIFRA sec. 3(c)(5)(C) and sec. 2(bb)(2).

[4] Decision Document at 25. The language in the Decision Document repeats verbatim the wording that appears in the "Memorandum – Isocycloseram. Human Health Risk Assessment for the Section 3 Registration of the New Active Ingredient Isocycloseram on Treated Seeds, Agricultural Field Crops, Indoor/Outdoor Residential Areas, Residential/Commercial Turf, Greenhouse, Commercial/Industrial Areas, Industrial Structures, and Agricultural Structures" from A. M. Mohammed, et al. to D. Drawbaugh, et al. (April 29, 2025) p. 43, available at: https://www.regulations.gov/document/EPA-HQ-OPP-2021-0641-0015

The statute requires that EPA "shall consider . . . available information" relating to potential cumulative effects, but no document in the administrative record shows that EPA has done so. Instead, EPA describes only what it has not done – "make a common mechanism of toxicity finding." Nor has EPA "assumed that isocycloseram has a common mechanism of toxicity with other substances." What the statute requires EPA to do—and what the agency has failed to do—is to identify relevant available information and determine whether that information is sufficient to warrant further analysis. If, as EPA contends, there is sufficient information to indicate isocycloseram shares a common mechanism of toxicity with other substances, EPA must conduct additional analysis to determine whether cumulative exposure to those chemicals raises a concern about the safety of the residues of isocycloseram in food.

Even simple and quick research by EPA should have identified information that would warrant further examination of the possibility that isocycloseram shares a common mechanism of toxicity with other substances. The Decision Document provides information about isocycloseram that shows this chemical belongs to the same chemical class as four veterinary drugs to which the general population is exposed. Specifically, the Decision Document states:

> Isocycloseram (4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-N-(2-ethyl-3-oxo-1,2-oxazolidin-4-yl)-2-methylbenzamide, containing 80–100% of the (5S,4R)-isomer) is a new broad-spectrum insecticide. It belongs to the isoxazolines chemical class, which have an insecticidal mode of action based on allosteric modulation of the gamma aminobutyric acid (GABA) receptor.[5]

According to the Food and Drug Administration (FDA), the isoxazoline chemical class includes a variety of substances approved for use as veterinary drugs in the United States, including fluralaner, lotilaner, afoxolaner, and sarolaner.[6] EPA should follow its own guidance documents to decide whether these veterinary drugs and isocycloseram share a common mechanism of toxicity and thus, whether further analysis of the potential for cumulative effects is necessary.

EPA has issued three relevant guidance documents addressing how it will determine whether it needs to conduct a cumulative risk assessment:

- "Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity" (USEPA, 1999), available at: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework ;
- "Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity" (USEPA, 2002) available at: https://www.epa.gov/sites/default/files/2015-07/documents/guidance_on_common_mechanism.pdf ; and

[5] Id. at 3

[6] See "**Fact Sheet for Pet Owners and Veterinarians about Potential Adverse Events Associated with Isoxazoline Flea and Tick Products**," (FDA Fact Sheet) available at: https://www.fda.gov/animal-veterinary/animal-health-literacy/fact-sheet-pet-owners-and-veterinarians-about-potential-adverse-events-associated-isoxazoline-flea

- "Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose" (USEPA, 2016) available at: https://www.regulations.gov/document/EPA-HQ-OPP-2015-0422-0019 .

The 1999 Guidance document states that the first step in implementing FFDCA sec. 408(b)(2))(D)(v) is to identify a Candidate Common Mechanism Group. Under the guidance the agency uses a weight-of-evidence approach to identifying chemicals that may share a common mechanism of toxicity by looking at similarities in four types of information – chemical structure, mechanism of pesticidal action, general mechanism of mammalian toxicity, and a particular toxic effect.

EPN thinks that there is enough information in the FDA Fact Sheet to justify designating isocycloseram and the four veterinary drugs as a Candidate Common Mechanism Group. First, the Fact Sheet indicates that the four veterinary compounds belong to the same chemical class as EPA has identified for isocycloseram, meaning the five substances have similar chemical structures. In addition, it appears that all five compounds cause the same kinds of toxic effects in mammals, also suggesting these four compounds share a common mechanism of toxicity. The FDA Fact Sheet indicates that the four veterinary drugs have been associated with adverse neurological effects in dogs and cats. EPA's toxicity review notes that in "the 28-day dog study, slight body tremors were noted in males and accompanied by vomiting."[7] Finally, the chemicals are all used to control insect pests, and thus, it is reasonable to infer that isocycloseram probably shares a common mechanism of pesticidal activity with the isoxazoline veterinary drugs.[8] Thus, at least preliminarily, EPN thinks that these different isoxazoline chemicals need further analysis to determine whether they have cumulative effects that could alter the agency's proposed safety determination respecting tolerances for isocycloseram.

Under the 2016 Guidance, if EPA finds that any of the four veterinary drugs and isocycloseram belong to a Candidate Common Mechanism Group, that determination would, in turn, trigger a screening level analysis. EPN recommends that EPA work with FDA to obtain information that may shed further light on whether isocycloseram shares a common mechanism of toxicity with any of the isoxazoline veterinary drugs. Specifically, EPA should make further inquiry into the available information about the mode of action of each substance, the adverse outcome pathway for common toxic effects in mammals, and ultimately the existence of a common mechanism of toxicity.

The screening level analysis may also take exposures to the different chemicals into account. Several of the FDA-approved products are formulated and applied as topical treatments for dogs and cats.[9] Additional information from FDA would help in assessing the potential exposure to the veterinary products. Based on EPA's own experience with pesticides in registered flea and tick control products, e.g. tetrachlorvinphos, it is reasonable to expect the use of the isoxazoline veterinary products could lead to significant exposures of members of the general public. Thus, EPN thinks that there is potential for meaningful, concurrent exposure of the general population, including children, to both isocycloseram residues in food and other isoxazoline substances that have been applied to family pets.

[7] EPA Human Health Risk Assessment at 23

[8] The legal classification of products as either a veterinary drug vs. a pesticide does not depend on the biological mechanism by which they control insects, but rather on the method of administration and the target pest's life cycle.

[9] FDA Fact Sheet

If the agency determines that a pesticide chemical shares a common mechanism of toxicity with different pesticides or other substances and that there is sufficient potential for meaningful, concurrent exposure to those chemicals, the 2002 Guidance directs EPA to designate those chemicals as a Cumulative Assessment Group and to proceed with additional assessments to characterize the potential cumulative risk.

In sum, the documents in the administrative docket for the proposed registrations and tolerance for isocycloseram fall short of the analysis of potential cumulative risks required by the FFDCA and FIFRA. EPA's 1999, 2016, and 2002 guidance documents lay out how such an analysis should be performed. Applying this guidance, EPN thinks the available information strongly indicates that there is a sound basis for concluding isocycloseram and four veterinary drug products belong in a Candidate Common Mechanism Group.[10] EPA must address this issue before it can make a decision to register isocycloseram for food use and establish tolerances for its residues in food and feed.

B. EPA should require Syngenta to improve the labeling of its end-use products.

EPA's determination that isocycloseram products meet the statutory standards for an unconditional registration under FIFRA sec. 3(c)(5) fails to consider the criterion in FIFRA sec. 3(c)(5)(B). In addition to finding that the use of the pesticide will not cause "unreasonable adverse effects on the environment" as specified in FIFRA sec. 3(c)(5)(C) and (D), FIFRA sec. 3(c)(5)(B) requires the agency to determine that "its labeling and other material required to be submitted comply with the requirements of [FIFRA]." Among other FIFRA requirements pertaining to pesticide labeling, it is unlawful to sell or distribute a pesticide that is "misbranded."[11] FIFRA defines "misbranded" to mean that:

> A pesticide is misbranded if– . . .
> (E) any word, statement, or other information required by or under the authority of [FIFRA] to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or graphic matter in the the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.
> (F) the labeling accompanying it does not contain directions for use which are necessary . . . and if complied with, . . . are adequate to protect public health and the environment.[12]

(Note: FIFRA sec. 2(p)(2) defines the term, "labeling," to include any source of information to which reference is made. Thus, if the labeling refers to the Bulletins Live! Two website (BLT,) the Bulletins found on EPA's website become labeling. Likewise, reference to the Worker Protection Standard in 40 CFR part 156 makes the content of the rule "labeling.") Together, these provisions require EPA to examine closely whether the labeling of an applicant's pesticide is "likely to be read and understood," such that following the use directions is "adequate to protect public health and the environment." If not, the agency cannot make the finding required by FIFRA sec.3(c)(5)(B) that is a prerequisite for an unconditional registration.

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[10] It is also asserted that, because of the fluorine bonds in the isocycloseram molecule, the new active ingredient belongs to the PFAS chemical class. Consequently, EPA should explain how it views the chemical structure of isocycloseram vis-a-vis its definition of the PFAS chemical class and should specifically address whether there is a potential for cumulative effects from exposure to isocycloseram and other PFAS compounds.

[11] FIFRA sec. 12(a)(1)(E)

[12] FIFRA sec. 2(q)(1)(E), (F)

As discussed in more detail below, EPN thinks that the proposed labeling for end-use isocycloseram products should be deemed "misbranded." In the case of labeling designed to protect threatened and endangered species and their critical habitats, the labeling is not "likely to be read and understood." In the case of labeling text designed to tell users how to control spray drift, the labeling is not "adequate to protect public health and the environment."

1. EPA should require Syngenta to offer more user-friendly labeling to protect listed species.

In light of EPA's ecological risk assessment showing the proposed registrations of isocycloseram products would entail very significant risks to threatened and endangered species (listed species) and to their designated critical habitats, the agency needs to do more to protect listed species and their habitats. The agency concluded that the use of Syngenta's products was likely to adversely affect (LAA) multiple species and, despite proposed risk mitigation measures, to cause jeopardy and/or adverse modification of listed species' critical habitats (J/AM). Under the Endangered Species Act, federal agencies like EPA are required to ensure that their actions do not cause J/AM and to take reasonable and prudent measures to minimize "take," i.e., adverse effects on listed species. To address the potential of isocycloseram products to cause J/AM and to minimize take, EPA's proposed registration decisions rely on labeling that would require users to follow certain practices to avoid harming listed species and their critical habitats. To access such requirements, users would need to repeatedly check multiple websites for applicable restrictions. Reliance on such labeling to secure compliance is unrealistic and likely to fail. Given the magnitude of the risks identified, EPA must do better; EPN proposes that EPA use a different approach to labeling.

The Decision Document supporting EPA's proposal to register isocycloseram products states that the products intended for agriculture use must bear a label statement reading:

> Endangered and Threated [sic] Species Protection Requirements
>
> Before using this product, you must obtain any applicable Endangered Species Protection Bulletins (Bulletins) within six months prior to or on the day of application. To obtain Bulletins, go to Bulletins Live! Two (BLT) at https://www.epa.gov/pesticides/bulletins. When using this product, you must follow all label directions and restrictions contained in any applicable Bulletin(s) for the area where you are applying the product, including any restrictions on application timing if applicable. It is a violation of Federal law to use this product in a manner inconsistent with its labeling, including this labeling instruction to follow all directions and restrictions contained in any applicable Bulletin(s). For general questions or technical help, call 1-844-447-3813, or email ESPP@epa.gov.[13]

[13] "End-Use Products: 100-RTRE (A21377 CP), 100-RTRG (A21708 CP), and 100- RTRR (A21550 CP)" Decision Document pp. 44, 50. Similar (but not identical) text is required for "End-Use Product: 100-RTNG (Atexzo)," "End-Use Product: 100-RTRN (A22466 CP)," and "End-Use Products: 100-RTNL (A22241 ST) and 100-RTNI (A22725 ST)." Id. at 55, 57. EPA should consider whether to use identical wording for all of the isocycloseram end-use products. Similar (but not identical) text is required for "End-Use Product: 100-RTNG (Atexzo)," "End-Use Product: 100-RTRN (A22466 CP)," and "End-Use Products: 100-RTNL (A22241 ST) and 100-RTNI (A22725 ST)." Id. at 55, 57. EPA should consider whether to use identical wording for all of the isocycloseram end-use products.

The result of including this labeling text is to require a user to consult an EPA website, "Bulletins Live! Two," – a website that EPN considers not user-friendly. (EPA's tutorial on using BLT contains eight modules covering five distinct steps a user needs to follow to identify relevant restrictions.) To locate any additional restrictions on the use of the product., the user must first go through multiple steps – entering information on the location of intended use, the month of intended use, and the product registration number. (EPN thinks there is potential for user error when entering the product registration number, because of the presence on labels of multiple, potentially confusing identifiers, such as establishment numbers and batch codes.) Assuming the user goes to the website and enters correct information, the website brings up one or more Bulletins for the intended use site(s). The user must then search the bulletin(s) to locate the restrictions that pertain to the specific product he intends to use. As detailed in the Decision Document, the restrictions for isocycloseram products will require the user to employ measures designed to reduce runoff of the product. To mitigate runoff risks, the Bulletin will require the user to accumulate a certain number of "points" depending on the intended use of the product. (The different mitigation measures are assigned points depending on how well the measure limits runoff.) The Bulletin, however, will not contain a menu of the acceptable measures and their assigned points. For that information, the user must consult yet another website:

> The Spray Drift and Runoff Mitigation Calculator and Mitigation Calculator User Guide can help you calculate the number of points earned for practices already in place on the field. The Runoff Mitigation worksheet April 2025 v2 can also be printed out and used as an alternative to the runoff points calculator.

EPA's instructions for using the so-called "Mitigation Menu" cover seven steps, and encourage the user to plan months ahead of the date when he intends to apply the product. The instructions also warn the user that the product labeling itself may contain more stringent restrictions than those produced by consulting the Mitigation Calculator or Runoff Mitigation worksheet. Thus, after checking two different websites and going through the fifteen steps set forth in EPA's instructions, the user must compare what he has gleaned from that work with the labeling that started him on this path.

EPA is being totally unrealistic if the agency thinks that the vast majority of users will follow all of these steps and will correctly understand what they are (and are not) allowed to do. A large body of anecdotal information indicates that many pesticide users do not even read pesticide products' labeling before each use. EPN thinks many may read the labeling when they first use a product but thereafter, many rely on their memory or other sources (crop advisors, agriculture products dealers, friends) to supply whatever information is deemed essential. Such an approach, however, would not comply with the labeling requirement to check BLT during the six months before every use. Making the user go through so many additional steps, at least annually if not more often, only would make it less likely that the user will not even attempt to get the required information.

To simplify the steps and improve the chances that users will obtain accurate information, EPA should require Syngenta to develop and place in the labeling of the affected end-use isocycloseram products a simplified way to obtain requirements relating to the protection of listed species and their habitat. EPN thinks that this would involve the use of a QR code on each product's label that would take the user to a website where the user would enter (ideally by selecting values from a drop-down menu) the relevant information for the product – location of intended use, type of site treated, date(s) of intended application, and application method. It would capture not only the information in any relevant Bulletin but also display

the information about the number of required points and the options for achieving the required points, and then tally the points for measures the user selects. The website would also reconcile the website's restrictions with any more stringent restrictions in the labeling. Such a feature should make it possible for users to access in many fewer steps the information that otherwise would spread across multiple websites.

2. EPA should reconsider the labeling directed at controlling spray drift.

EPN recommends adding the following text to the spray drift labeling section: "Do not apply this product in a manner that results in spray drift which causes harm." EPN thinks this restriction is objective, measurable, and appropriate. Drift which causes any type of harm beyond the treated site is a problem, and it is appropriate to prevent such drift. "Harm" is also an objective, measurable concept. Drift which damages property or non-target animals, plants, or people is harmful. Property damage could include causing a neighbor's crop to violate a tolerance requirement or organic status or reducing the crop's quality or yield. It could also include damaging ornamental plants or causing illness in pets or livestock. Drift that contaminates water at levels unsafe for consumption or recreational use is also harmful. EPN notes that the state of Indiana has long had a regulation applicable to drift of pesticide sprays that is effectively comparable to our recommended labeling requirement.

Including EPN's suggested language would provide an additional backstop to use restrictions that are critical to the protection of listed species.[14] Moreover, EPN's proposed labeling text would be easier to enforce. The Decision Document proposes to require extensive instructions describing how to apply the pesticide, e.g., restrictions on release height, wind speed, and droplet size. To determine whether a user complied with the labeling, an official would have to observe the actual application to determine whether the spray boom was too high, the droplets too fine, or the wind too strong. If EPN's proposed labeling is added, a violation could be found by collecting information on the impacts of an application after the application was over.

Even if EPA elects not to add a "no harm" performance standard for spray drift, EPA should reexamine the content and organization of the spray drift labeling in the Decision Document. That document would require that the printed labeling of non-residential end-use products include detailed instructions related to spray drift mitigation. Id. at 45 - 49 (copied in Appendix A). EPN thinks that users will find the instructions confusing due to their excessive length, their poor organization, and the repeated cross-references to other information that may contradict or supplement what is immediately available on the printed labeling. Thus, EPN questions whether the portions of the labeling dealing with spray drift mitigation meet the standard in FIFRA sec. 2(q)(1)(E) for making labeling statements "likely to be read and understood."

The spray drift labeling that the Decision Document proposes to require is overly and unnecessarily long; as copied into Appendix A, it covers nearly six pages of single-spaced directions. Because it adds little or no value, the agency should consider whether to retain the text appearing after the heading "**ADDITIONAL SPRAY DRIFT INFORMATION**." All of the language that follows that heading uses unenforceable wording, e.g., users "should" take specific actions or "consider" certain factors. Moreover, this text adds little or no value. Much of this language provides advice about factors that affect the extent of drift, e.g.,

[14] EPN's comments on the proposed registration of pesticide products containing cyclobutrifluram made a similar suggestion. Refer to those comments for a more extensive discussion of the reasons for this recommendation: https://www.environmentalprotectionnetwork.org/wp-content/uploads/2025/05/EPN-Comments-on-PFAS-Pesticide-Registration-Cyclobutrifluram.pdf

droplet size, wind speed, release height, temperature and humidity conditions, and temperature inversions. The earlier portion of the required spray drift labeling, however, already contains mandatory restrictions addressing almost all of the same factors. This redundancy seems unnecessary and potentially confusing. Finally, removing the material in the "**ADDITIONAL SPRAY DRIFT INFORMATION**" section would shorten the spray drift section by about a third.

EPN also recommends that EPA consider a different organization for the spray drift mitigation labeling to make the restrictions easier to find and understand. EPN agrees with EPA that the restrictions which apply to all applications should appear first. Therefore, EPN finds it confusing that there are wind speed and boom length restrictions on aerial applications listed under the heading "For all applications." EPN also thinks that buffer restrictions that cannot be modified, i.e., the requirements for buffers around water bodies, should appear before buffer restrictions that can be adjusted, i.e., wind-directional ecological spray drift buffers. Further, because users will refer to Table A for the wind-directional ecological spray drift buffers, we think it makes sense to include the chemigation restrictions in Table A. In Appendix B, EPN offers a reorganized and lightly edited and reformatted version of the Spray Drift Management labeling text that we think would be easier for users to follow.

Finally, because the proposed spray drift labeling would direct users to documents beyond the printed labeling, EPA should look for additional ways to consolidate the instructions. The spray drift labeling set forth in the Decision Document would recommend or require users to consult, for example,

- the most current versions of two sets of American Society of Agricultural & Biological Engineers standards (ASABE S641) and (ASABE S572);
- limitations affecting eligibility for the Conservation Reserve Program (CRP);
- the Bulletins Live! Two (BLT) website;
- ecological drift buffer reduction options on EPA's Mitigation Menu Website (https://www.epa.gov/pesticides/mitigation-menu);
- Application Exclusion Zone drift requirements in EPA's Worker Protection Standard rule; and
- when tank mixing isocycloseram with other pesticides, the restrictions on other products' labels and bulletins.

If the agency adopts EPN's recommendation relating to the inclusion of a QR code on end-use products' labeling, EPA should also direct the applicant to merge the spray drift labeling with endangered species restrictions, to the extent possible.

In sum, given the complexity and length of the spray drift labeling, EPN questions whether it is reasonable to expect the ordinary user will read and understand what restrictions apply. EPN thinks the agency should reexamine the organization, content, and format of the spray drift restrictions to make it more likely users will comply with them.

Conclusion

EPN respectfully requests that EPA not finalize the registration of isocycloseram products as proposed. As explained in more detail in these comments, both the human health risk assessment and the draft labeling have significant deficiencies that should be reevaluated. While EPA may eventually conclude the isocycloseram products do meet the statutory standards for registration, the information in the record accompanying the proposal does not currently support such a conclusion. EPA will not have an adequate record until EPA has more comprehensively analyzed and fully explained its analysis of the potential risks to

human health and has examined whether the labeling, including references to multiple websites, meets the standards in FIFRA sec.2(q)(1)(E) and (F).

Appendix A – EPA's Proposed Spray Drift Labeling

"SPRAY DRIFT MANAGEMENT:

For All Applications:

- During application, the Sustained Wind Speed, as defined by the National Weather Service (standard averaging period of 2 minutes), must register between 3 and 15 miles per hour.
- Do not apply when wind speeds exceed 15 miles per hour at the application site.
- Wind speed and direction must be measured on location using a windsock, an anemometer (including systems to measure wind speed or velocity on an aircraft), or an aircraft smoke system.
- Wind speed must be measured at the release height or higher, in an area free from obstructions such as trees that are not the target crop, buildings, and farm equipment.
- Do not apply during temperature inversions.
- **For Aerial Application**: Select nozzle and pressure that deliver medium or coarser spray droplets as indicated in nozzle manufacturer's catalogues and in accordance with the most current American Society of Agricultural & Biological Engineers standards (ASABE S641). When applying to crops via aerial application equipment, the spray boom must be mounted on the aircraft to minimize drift caused by wing tip or rotor blade vortices.
- When the wind speed is between 11-15 miles per hour, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters.
- When the wind speed is between 11-15 miles per hour, applicators must use a minimum of ¾ swath displacement upwind at the downwind edge of the field. Otherwise, applicators must use a minimum of ½ swath displacement upwind at the downwind edge of the field.
- Do not release spray at a height greater than 10 feet above the crop canopy unless a greater application height is required for pilot safety.

For Ground Boom Application:

- Select nozzle and pressure that deliver medium or coarser spray droplets as indicated in nozzle manufacturer's catalogues and in accordance with the most current American Society of Agricultural & Biological Engineers standards (ASABE S572).
- Spray at the appropriate boom height based on nozzle selection and nozzle spacing, but do not exceed a boom height of 4 feet above ground or crop canopy. Set boom to lowest effective height over the target pest or crop canopy based on equipment manufacturer's directions.

For Airblast Application:

- Sprays must be directed into the canopy.
- User must turn off outward pointing nozzles at row ends and when spraying outer row.

For ground, aerial, and airblast applications, always maintain a no-application area (buffer) from the downwind edge of the last spray row and any non-managed area (i.e., the protection area).

Downwind managed areas that can represent spray drift buffers

When spray drift buffers are identified as mitigation, the following managed areas can be included in the buffer if they are immediately adjacent/contiguous to the treated field in the downwind direction and people are not present in those areas (including inside closed buildings/structures). If the pesticide product label or bulletin, or the state or local government in which the application area is located has a requirement that prohibits or restricts spray drift in any area, including these specific managed areas, that prohibition/restriction must be followed.

a. Agricultural fields, pastures, forage fields, and private rangelands, including untreated portions of the treated field;
b. Roads, paved or gravel surfaces, mowed grassy/fallowed areas adjacent to field, and areas of bare ground from recent plowing or grading that are contiguous with the treated area;
c. Buildings and their perimeters, silos, or other man-made structures with walls and/or roof;
d. Areas present and/or maintained as a runoff/erosion measure as listed on EPA's Mitigation Menu website. Examples include vegetative filter strips (VFS), field borders, grassed waterways, vegetated ditches, riparian areas, managed/constructed wetlands, or other areas of intentional habitat improvement;
e. Areas present and/or maintained as a drift buffer reduction measure as listed on EPA's Mitigation Menu website. Examples include vegetative windbreaks, hedgerows, shelterbelts, riparian areas, private forests, woodlots, and shrublands;
f. Conservation Reserve Program (CRP)1 and Agricultural Conservation Easement Program (ACEP) lands;
g. On-farm contained irrigation water resources that are not connected to adjacent water bodies, including on farm irrigation canals and ditches, water conveyances, managed irrigation/runoff retention basins, farm ponds, and tailwater collection ponds.

Applicators may need to ensure that pesticide use does not cause degradation of CRP habitat.

For Spray Drift Buffers for Broadcast Applications

Applicators must access and search Bulletins Live! Two (BLT) at https://www.epa.gov/pesticides/bulletins within six months of the application to determine whether the application site falls within a Pesticide Use Limitation Area (PULA) that has a Bulletin in BLT.

Wind-directional ecological spray drift buffers are required for applications as follows in Table A:

Table A. Wind-directional Ecological Spray Drift Buffers

Application Method	Droplet Size Distribution (DSD)	Minimum Buffer Distance
Aerial	Medium or coarser	300 ft.
Ground (2 - 4 foot boom height)	Medium or coarser	25 ft.
Airblast	NA	85 ft.

Buffers to Aquatic Areas
In addition to the wind-directional buffers described in Table A, buffers are required to aquatic areas regardless of the wind direction. These buffers cannot be reduced using buffer reduction mitigation options. When buffering to a waterbody, always use the larger buffer distance (either wind-directional ecological or buffer to aquatic areas).

Buffer zone for ground applications
Regardless of buffer mitigations, DO NOT make ground applications within 25 ft of lakes, rivers, reservoirs, permanent streams, marshes, natural ponds, estuaries, or coastal areas.

Buffer zone for non-ULV aerial applications
Regardless of buffer mitigations, DO NOT make aerial applications within 150 ft of lakes, rivers, reservoirs, permanent streams, marshes, natural ponds, estuaries, or coastal areas.

Reduction Options for All Ecological Wind-Directional Drift Buffers:

The applicator may choose among the ecological drift buffer reduction options on EPA's Mitigation Menu Website (https://www.epa.gov/pesticides/mitigation-menu) to reduce the wind-directional ecological buffer distance before applying this product. All buffer reduction options selected must align with the minimum droplet size and release height requirements on this label.

To reduce the buffer distance for the application, the buffer reduction options must be employed in accordance with the instructions and descriptions on EPA's Mitigation Menu Website. These buffer reduction options do not apply to areas occupied by humans for residential or commercial purposes (such as lawns, sidewalks, outdoor recreational areas, athletic fields, buildings/homes, farmworker housing, schools, daycare centers, nursing homes, and hospitals).
Buffer reduction options also cannot reduce distances to aquatic areas.

When using more than one option during the application, the percent reduction in the buffer distances may be added together. The maximum buffer reduction that can be achieved by a combination of buffer reduction options is 100% (i.e., no drift buffer required).

The website includes the full menu of wind-directional ecological drift buffer reduction options for each application method. The following are examples, but may not be applicable for all application methods:

- Reduce single application rate [all]
- Increase in droplet size above the minimum size required [ground and aerial]
- Use hooded sprayer, layby application, or drop nozzles [ground only]
- Lower release boom height [ground only]
- Reduce the number of passes across the field [all]
- Install a downwind windbreak, hedgerow, or artificial screen [all]
- Apply when the relative humidity > 60% [all]

EPA may periodically update the Mitigation Menu Website, for example, by adding new drift buffer reduction options or updating an option's description.

When tank mixing, the most restrictive of the products' label or bulletin requirements must be followed (e.g., drift buffers that are not wind-directional, Application Exclusion Zone drift requirements, drift buffers to residences, schools, and parks where bystanders could be present, use prohibitions, timing restrictions, and application method prohibitions)."

For Chemigation Applications

If using overhead chemigation equipment, choose one of the following two options:
1) 25 ft buffer, or;
2) Choose two of the following additional mitigations

- Use a pressure of 20 psi or less.
- Use a release height of 5 feet or less.
- Include a windbreak downwind of the application site. This can include a downwind windbreak, hedgerow,
  riparian zone, forest, shrubland, or woodlots.

If using non-end gun impact sprinkler chemigation equipment, choose one of the following two options:
1) 25 ft buffer, or;
2) Limit throw distance to edge of field (treated area) plus include a downwind windbreak (this can include a downwind windbreak, hedgerow, riparian zone, forest, shrubland, or woodlots).

ADDITIONAL SPRAY DRIFT INFORMATION:
THE APPLICATOR IS RESPONSIBLE FOR AVOIDING OFF-SITE SPRAY DRIFT. Be aware of nearby non-target sites and environmental conditions.

IMPORTANCE OF DROPLET SIZE

An effective way to reduce spray drift is to apply large droplets. Consider the largest droplets that provide target pest control. While applying larger droplets will reduce spray drift, the potential for drift will be greater if applications are made improperly or under unfavorable environmental conditions.

Controlling Droplet Size – Ground Application

- Volume – Increasing the spray volume so that larger droplets are produced will reduce spray drift. Consider using the highest practical spray volume for the application. If a greater spray volume is needed, consider using a nozzle with a higher flow rate.
- Pressure – Using the lowest spray pressure recommended for the nozzle will produce the target spray volume and droplet size.
- Spray Nozzle – Consider using a spray nozzle that is designed for the intended application, as well as using nozzles designed to reduce drift.

Controlling Droplet Size – Aerial Application

Adjust Nozzles – Applicators should follow nozzle manufacturers' recommendations for setting up nozzles. Generally, to reduce fine droplets, nozzles should be oriented parallel with the airflow in flight.

RELEASE HEIGHT – Ground Application

For ground equipment, the boom should remain level with the crop and have minimal bounce. Automated boom height controllers are recommended with large booms to better maintain optimum nozzle-to-canopy height. Excessive boom height will increase the potential for spray drift.

RELEASE HEIGHT – Aerial Application

Higher release heights increase the potential for spray drift.

HOODED (OR SHIELDED) SPRAYERS

Shielding the boom or individual nozzles can reduce spray drift. Consider using hooded sprayers. Applicators should verify that the shields are not interfering with the uniform deposition of the spray on the target area.

TEMPERATURE AND HUMIDITY

When making applications in hot and dry conditions, consider using larger droplets to reduce effects of evaporation.

TEMPERATURE INVERSIONS

Drift potential is high during a temperature inversion. Temperature inversions are characterized by increasing temperature with altitude and are common on nights with limited cloud cover and light to no wind. The presence of an inversion can be indicated by ground fog or by the movement of smoke from a ground source or an aircraft smoke generator. Smoke that layers and moves laterally in a concentrated cloud

(under low wind conditions) indicates an inversion, while smoke that moves upward and rapidly dissipates indicates good vertical air mixing. Avoid applications during temperature inversions.

WIND

Drift potential generally increases with wind speed.
Applicators need to be familiar with local wind patterns and terrain that could affect spray drift.

MEASURING WIND SPEED AND WIND DIRECTION

Applicators should check and acquire the predicted wind speed and direction for the application site within 12 hours prior to conducting applications to determine the time periods wind speed is likely to fall outside the applicable thresholds.

- Applicators should reassess wind speed and direction at the application site every 15 minutes while applications are in progress.
- Measuring wind speed and direction can be done by:
- Relying on equipment on the application equipment that measures wind speed (e.g., aerial equipment).
- Using a tower anemometer with telemetry or handheld anemometer. Users should read user manual on how to calibrate, operate and interpret the output from an anemometer. Ground applicators should stop every 15 minutes to take a reading with a tower anemometer with telemetry or handheld anemometer. Some anemometers may have software that would allow users to view wind measurements in real time while making an application, and, those cases, applicators would not have to stop to take measurements.
- Using a windsock. Wind can be estimated with a windsock using the strips on a windsock. The applicator should consult the user manual for the windsock on wind speed estimation and direction of wind. Applicators should look at the sock at least every 15 minutes to estimate wind speed and direction. The windsock should be pointed in the opposite direction of the windbreak and the non-managed area.
- Using an aircraft smoke system. Laying down several puffs of smoke along different lines using an aircraft smoke system can provide an accurate view of what the wind speed and direction for the application.
- Checking behind the spray rig at least every 15 minutes to see if the spray has changed direction from when the application started."

Appendix B – EPN's Recommended Revision of Required Spray Drift Labeling

"SPRAY DRIFT MANAGEMENT:

For All Types of Application:

Do not apply this product in a manner that results in spray drift which causes harm.

- During application, the Sustained Wind Speed, as defined by the National Weather Service (standard averaging period of 2 minutes), must register between 3 and 15 miles per hour.
- Do not apply when wind speeds exceed 15 miles per hour at the application site.
- Wind speed and direction must be measured on location using a windsock, an anemometer (including systems to measure wind speed or velocity on an aircraft), or an aircraft smoke system.
- Wind speed must be measured at the release height or higher, in an area free from obstructions such as trees that are not the target crop, buildings, and farm equipment.
- Do not apply during temperature inversions.

For Aerial Application:

- Select nozzle and pressure that deliver medium or coarser spray droplets as indicated in nozzle manufacturer's catalogues and in accordance with the most current American Society of Agricultural & Biological Engineers standards (ASABE S641). When applying to crops via aerial application equipment, the spray boom must be mounted on the aircraft to minimize drift caused by wing tip or rotor blade vortices.
- When the wind speed is between 11-15 miles per hour, the boom length must be 65% or less of the wingspan for fixed wing aircraft and 75% or less of the rotor diameter for helicopters. Otherwise, the boom length must be 75% or less of the wingspan for fixed-wing aircraft and 90% or less of the rotor diameter for helicopters.
- When the wind speed is between 11-15 miles per hour, applicators must use a minimum of ¾ swath displacement upwind at the downwind edge of the field. Otherwise, applicators must use a minimum of ½ swath displacement upwind at the downwind edge of the field.
- Do not release spray at a height greater than 10 feet above the crop canopy unless a greater application height is required for pilot safety.

For Ground Boom Application:

- Select nozzle and pressure that deliver medium or coarser spray droplets as indicated in nozzle manufacturer's catalogues and in accordance with the most current American Society of Agricultural & Biological Engineers standards (ASABE S572).
- Spray at the appropriate boom height based on nozzle selection and nozzle spacing, but do not exceed a boom height of 4 feet above ground or crop canopy. Set boom to lowest effective height over the target pest or crop canopy based on equipment manufacturer's directions.

For Airblast Application:

- Sprays must be directed into the canopy.
- User must turn off outward pointing nozzles at row ends and when spraying outer row.

NO-APPLICATION BUFFER AREAS

Users must maintain two types of no-application areas – buffers to protect water bodies and wind-directional ecological spray drift buffers.

NOTE: If the pesticide product label or bulletin, or the state or local government in which the application area is located has a requirement that prohibits or restricts spray drift in any area, including specific managed areas, that prohibition/restriction must be followed.

When tank mixing, the most restrictive of the products' label or bulletin requirements must be followed (e.g., drift buffers that are not wind-directional, Application Exclusion Zone drift requirements, drift buffers to residences, schools, and parks where bystanders could be present, use prohibitions, timing restrictions, and application method prohibitions).

Buffers Around Aquatic Areas

Buffers are required to aquatic areas regardless of the wind direction. When buffering to a waterbody, always use the larger buffer distance (either wind-directional ecological or buffer to aquatic areas). Buffers to water bodies cannot be reduced using buffer reduction mitigation options.

Buffer zone for ground applications

DO NOT make ground applications within 25 ft of lakes, rivers, reservoirs, permanent streams, marshes, natural ponds, estuaries, or coastal areas.

Buffer zone for non-ULV aerial applications

Regardless of buffer mitigations, DO NOT make aerial applications within 150 ft of lakes, rivers, reservoirs, permanent streams, marshes, natural ponds, estuaries, or coastal areas.

Wind-directional Ecological Spray Drift buffers are required for applications as follows in Table A:

Table A. Wind-directional Ecological Spray Drift Buffers

Application Method	Droplet Size Distribution (DSD)	Minimum Buffer Distance
Aerial	Medium or coarser	300 ft.

Ground (2 - 4 foot boom height)	Medium or coarser	25 ft.
Airblast	NA	85 ft.
Overhead Chemigation		25 ft.[note 1]
Non-end gun impact sprinkler chemigation		25 ft.[note 2]

For ground, aerial, and airblast applications, always maintain a no-application area (buffer) between the downwind edge of the last spray row and the protected area.

1. Choose two of the following additional mitigations

- Use a pressure of 20 psi or less.
- Use a release height of 5 feet or less.
- Include a windbreak downwind of the application site. This can include a downwind windbreak, hedgerow,

riparian zone, forest, shrubland, or woodlots.

2. Limit throw distance to edge of field (treated area) plus include a downwind windbreak (this can include a downwind windbreak, hedgerow, riparian zone, forest, shrubland, or woodlots).

Downwind areas that can represent spray drift buffers

When spray drift buffers are identified as mitigation, only the following types of areas can be included in the buffer and only if they are immediately adjacent/contiguous to the last treated row of the field in the downwind direction and people are not present in those areas (including inside closed buildings/structures).

a. Agricultural fields, pastures, forage fields, and private rangelands, including untreated portions of the treated field;

b. Roads, paved or gravel surfaces, mowed grassy/fallowed areas adjacent to field, and areas of bare ground from recent plowing or grading that are contiguous with the treated area;

c. Buildings and their perimeters, silos, or other man-made structures with walls and/or roof;

d. Areas present and/or maintained as a runoff/erosion measure as listed on EPA's Mitigation Menu website. Examples include vegetative filter strips (VFS), field borders, grassed waterways, vegetated ditches, riparian areas, managed/constructed wetlands, or other areas of intentional habitat improvement;

e. Areas present and/or maintained as a drift buffer reduction measure as listed on EPA's Mitigation Menu website. Examples include vegetative windbreaks, hedgerows, shelterbelts, riparian areas, private forests, woodlots, and shrublands;

f. Agricultural Conservation Easement Program (ACEP) and Conservation Reserve Program (CRP) lands - Note: Applicators may need to ensure that pesticide use does not cause degradation of CRP habitat;

g. On-farm contained irrigation water resources that are not connected to adjacent water bodies, including on farm irrigation canals and ditches, water conveyances, managed irrigation/runoff retention basins, farm ponds, and tailwater collection ponds.

Reduction Options for All Ecological Wind-Directional Drift Buffers:

The applicator may choose among the ecological drift buffer reduction options on EPA's Mitigation Menu Website (https://www.epa.gov/pesticides/mitigation-menu) to reduce the wind-directional ecological buffer distance before applying this product. All buffer reduction options selected must align with the minimum droplet size and release height requirements on this label.

To reduce the buffer distance for the application, the buffer reduction options must be employed in accordance with the instructions and descriptions on EPA's Mitigation Menu Website. These buffer reduction options do not apply to areas occupied by humans for residential or commercial purposes (such as lawns, sidewalks, outdoor recreational areas, athletic fields, buildings/homes, farmworker housing, schools, daycare centers, nursing homes, and hospitals).
Buffer reduction options also cannot reduce distances to aquatic areas.
When using more than one option during the application, the percent reduction in the buffer distances may be added together. The maximum buffer reduction that can be achieved by a combination of buffer reduction options is 100% (i.e., no drift buffer required).

The website includes the full menu of wind-directional ecological drift buffer reduction options for each application method. The following are examples, but may not be applicable for all application methods:

- Reduce single application rate [all]
- Increase in droplet size above the minimum size required [ground and aerial]
- Use hooded sprayer, layby application, or drop nozzles [ground only]
- Lower release boom height [ground only]
- Reduce the number of passes across the field [all]
- Install a downwind windbreak, hedgerow, or artificial screen [all]
- Apply when the relative humidity > 60% [all]

EPA may periodically update the Mitigation Menu Website, for example, by adding new drift buffer reduction options or updating an option's description.