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CENTER FOR FOOD SAFETY

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OPP Docket
Environmental Protection Agency Docket Center (EPA/ DC), (28221T)
1200 Pennsylvania Ave. NW
Washington, DC 20460–0001.

RE: EPA Registration No. 7969-433; PP 9F8818
Docket EPA-HQ-OPP-2020-0202

Center for Food Safety (CFS) appreciates the opportunity to comment on the application for new use of isoxaflutole on HPPD inhibitor-resistant cotton, and the related petition to establish isoxaflutole tolerances in or on cottonseed and cotton gin byproducts, identified above.

CFS was informed that if EPA proposes a registration for the new use and associated tolerances, the proposed registration decision will be made available to the public for comment (personal communication with Debra Rate, Registration Division, EPA, 9/11/20). Because CFS plans to comment on any proposed registration decision, the following comments are brief, intended only to suggest areas of concern that the Agency should address.

CFS also incorporates by reference comments on these actions being submitted by Center for Biological Diversity.

Background on Isoxaflutole

Isoxaflutole is an inhibitor of the 4-hydroxyphenylpyruvate dioxygenase enzyme (4-HPPD) found in both plants and animals. 4-HPPD catalyzes a step in the biosynthesis of the carotenoid pigments that protect chlorophyll from decomposition by sunlight. Isoxaflutole blocks this step, leading to breakdown of chlorophyll, bleaching, reduced growth at sublethal doses, and plant death at higher doses. In mammals, 4-HPPD is present mainly in the liver, where it catabolizes the amino acid tyrosine; by blocking its action, isoxaflutole leads to a buildup of tyrosine levels in plasma.

Isoxaflutole is degraded in plants and in the environment into a number of compounds, some of which have been characterized. These include a diketonitrile degradate known as RPA 202248, which is persistent and toxic to plants and many animals; RPA 205834, a diketo degradate for which there is little or no toxicity data but which appears in aqueous metabolism studies; IFT-amide, for which no toxicity data are reported; RPA 207048, about

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which little information is available; RPA 203328, the terminal degradate of RPA 202248 in soil metabolism studies; and several uncharacterized compounds. Full toxicity data is required for these breakdown products before registration can be considered. Parent isoxaflutole and RPA 202248 are quite soluble and mobile in water, and have been frequently found in surface waters and ground water as a result of runoff and leaching where the herbicide is used.

Isoxaflutole was first registered for use on corn in 1999, its use tripling from an initial 200,000 lbs./year to about 600,000 lbs./year from 2014 to 2017, based on application to 8 to 12% of corn acres. EPA recently approved isoxaflutole for over-the-top use on HPPD inhibitor-resistant soybeans in certain counties of 25 states, counties with roughly 11 million acres of soybeans (2017 Census figure). This OTT soybean use could result in 500,000 to 1 million lbs. of annual use, assuming from 50% to 100% of eligible acres are planted to resistant soybeans, and sprayed with isoxaflutole at the maximum annual (and single) application rate of 0.09375 lbs./acre. Usage on HPPD inhibitor-resistant cotton with the proposed new use is uncertain, but could be as much as the projected use on soybeans if isoxaflutole were sprayed on resistant cotton planted to 5 to 10 million acres. Thus, registration of OTT use on cotton – combined with existing use on corn and projected OTT use on soybeans – could lead to several million pounds of this persistent, highly toxic herbicide being sprayed on a national basis.

Human Health Risks

Unlike many herbicides, isoxaflutole's target is an enzyme that is present in animals as well as plants. As noted above, isoxaflutole inhibits the 4-HPPD enzyme and blocks catabolism of tyrosine, and thereby leads to a buildup of tyrosine in the bloodstream. Effects consistent with this mode of action are found in animal experiments, specifically ocular toxicity (corneal opacity) in rats and hepatic toxicity in rats and mice. Isoxaflutole exerts other non-cancer effects as well, including hematotoxicity in dogs and mice; neurotoxicity in acute and subchronic rat studies, including potential delay in brain development; and adverse developmental effects that include growth retardation and various skeletal anomalies in rats and rabbits.

In establishing reference doses, the greater sensitivity of offspring vs. maternal animals in developmental studies demands application of the full 10x Food Quality Protection Act safety factor. Uncertainty factors must also be applied as needed to account for study and database deficiencies.

Isoxaflutole is a probable human carcinogen based on induction of liver tumors in rats and mice and thyroid tumors in male rats. Estimated dietary exposure from food and water results in an additional risk of cancer at EPA's threshold of concern of 1 in 1 million. Occupational workers are at an even greater risk, with an estimated 1 in 100,000 additional cases of cancer from handling isoxaflutole. EPA's reliance solely on mitigation measures to ameliorate this risk is improper and unreasonable. EPA has failed to analyze

the efficacy and effectiveness of those measures or account for the substantial evidence of non-compliance with label-prescribed use of personal protection equipment.

In addition, EPA must require all necessary studies to establish the true mammalian toxicity of not only isoxaflutole, but also isoxaflutole in combination with the plethora of isoxaflutole metabolites referenced above.

EPA should also further evaluate the aggregate risk posed by the proposed isoxaflutole use on cotton, including its degradates, from all routes of exposure, including dermal and inhalational.

Isoxaflutole is one of at least 14 members of the HPPD inhibitor class of herbicides, which includes at least seven (besides isoxaflutole) that are registered in the U.S. Usage data for five of these are readily available, and all show rising trends: bicyclopyrone, mesotrione, pyrasulfatole, tembotrione and topramezone. Benzobicyclon and tolpyralate are two other EPA-registered HPPD inhibitors for which usage information is not readily available. Other members of the class include benzofenap, fenquinotrione, pyrazolynate, pyrazoxyfen, sulcotrione and tefuryltrione.

EPA concedes that HPPD inhibiting herbicides cause a number of characteristic toxicities in animal studies, including effects on the eye, liver, kidney and organismal development (including delays in skeletal ossification). Yet the Agency has thus far refrained from conducting the cumulative risk assessment demanded by the Food Quality Protection Act for pesticides that share a common mechanism of toxicity.

EPA should formally designate HPPD inhibitors as possessing a common mechanism of toxicity. Then a cumulative risk assessment must be conducted accounting for exposure to all EPA-registered members of the class, including degradates, and all manner of toxicity, including developmental, reproductive and carcinogenic effects. Cumulative reference doses should be developed for the class.

<u>Environmental Risks</u>

The mobility, persistence and potency of isoxaflutole and its phytotoxic degradates (e.g. the diketonitrile compound, RPA 202248 (DKN)) make this herbicide a serious threat to plant life and the biotic communities they support far beyond the bounds of treated fields. If post-emergence use is permitted, past experience with herbicides applied POST to herbicide-resistant crops demonstrates clearly a heightened risk of off-target injury due to later-season application, when other crops and plants are more vulnerable to injury, than is possible in the pre-plant or pre-emergence context.

Isoxaflutole is persistent in soil, particularly in dry conditions, and degrades in water to DKN. DKN exhibits a long half-life in water and soil, is highly phytotoxic, and eventually degrades to RPA 203328, a benzoic acid derivative designated the terminal degradate.

Other degradates are also formed. Isoxaflutole and DKN are moderately to highly soluble and mobile in many soil types; DKN in particular leaches readily into shallow groundwater, and is carried into bodies of water via runoff. The US Geological Survey has detected DKN and RPA 203328 at unexpectedly high frequencies in surface waters of Iowa relative to its modest use in corn, and DKN is detected not only during spring when applied, but into the summer and year-round. EPA also required extensive monitoring of surface and groundwater that uncovered frequent detections of isoxaflutole residues in the 1990s and early 2000s. Based on available data, isoxaflutole and/or its degradates can not only persist, but actually accumulate, in areas of intensive use.

Isoxaflutole is among the most potent of herbicides, inhibiting the growth of sensitive dicot plants like turnip and navy beans in vegetative vigor tests at the vanishingly low rate of 0.00001 lb., or just 4.5 milligrams, per acre. Seedling emergence and germination endpoints are less sensitive than vegetative vigor. Thus, it is critical that EPA utilize vegetative vigor endpoints in its ecological risk assessments to properly gauge the risks posed by isoxaflutole to off-field crops and wild plants.

Isoxaflutole's potency makes spray drift a serious threat to sensitive crops and plants hundreds to over a thousand feet beyond the bounds of a sprayed field. Recent experience with massive dicamba damage to off-field soybeans and many other plant species should alert EPA to the similar threat posed by isoxaflutole drift. Spray droplets can move considerable distances, especially in temperature inversion conditions that occur frequently in the Midwest and other regions.

Another key concern that requires thorough assessment is the risk of off-field plant damage from transport of isoxaflutole and DKN-bearing soil particles via wind. Isoxaflutole is notable for its ability to reactivate after rainfall events, touted as an attractive feature of this herbicide, since it enables control of on-field weeds for an extended period after application. This same property, however, enhances risks to off-field crops and wild plants that receive wind-blown soil particles bearing isoxaflutole and its degradates, since reactivation by rainfall can also harm these crops and plants for extended periods after the application. This risk is especially pronounced under dry conditions, which dramatically increase the half-life of parent isoxaflutole.

EPA must also thoroughly assess the risks associated with irrigation of non-target crops with water contaminated with isoxaflutole/DKN. Once again, the extreme potency of this herbicide and its phytotoxic degradates means that even extremely low contamination levels could lead to serious growth-suppressive effects on irrigated crops. The persistence of isoxaflutole/DKN in soil and water, and the potential for accumulation, further enhances this risk. Drift emanating from such irrigation systems could also cause damage to off-field plants, and must also be assessed. Likewise, EPA must assess the risks posed by water containing isoxaflutole and its degradates to off-field non-crop plants.

Coupled with pre-existing registrations for corn and soybeans, the proposed use on cotton would increase levels of isoxaflutole and its degradates in soil and in water resources in areas where these crops are grown and particularly rotated. The potential for accumulation would be enhanced with additional use on a third crop. EPA showed great concern for the risks outlined above when considering the initial registration for corn alone, and they would all be amplified with the proposed use on cotton.

EPA must also investigate the effects of isoxaflutole on cotton and on off-field plants that receive drift with respect to plant pathogens and plant physiological processes. Drift-level doses of herbicides have been shown to stimulate plant pathogens in off-target plants. Herbicide exposure can also induce higher levels of root exudates, and disrupt rhizosphere microbial communities involved in nutrient provisioning and other processes critical to plant health, among other impacts.

EPA must assess the effects of isoxaflutole use on biodiversity within cotton fields, as well as in off-field areas impacted by drift and runoff.

Effects on aquatic organisms must also be carefully assessed, especially in light of the persistence and potential accumulation of isoxaflutole and its degradates in aqueous systems.

EPA must ensure it has full toxicity data on the formulation of isoxaflutole that BASF is seeking registration of, since the toxicity and other properties of an herbicide active ingredient (especially as regards plants) can vary substantially by formulation due to differences among formulations in secondary (so-called "inert") ingredients like surfactants and safeners that modulate the a.i.'s effects.

Costs and Benefits

EPA typically performs a "benefits" assessment of a new pesticide use, but rarely considers economic or social costs as required by federal pesticide law. The result is an assessment biased in favor of putative benefits.

Frequently cited benefits of herbicides applied to herbicide-resistant crops are a reduction in yield loss due to weeds, increased simplicity of weed control, and an improvement in herbicide-resistant weed management due to availability of a new active ingredient. Yet there is little to no evidence to suggest that post-emergence use of an herbicide on a resistant crop improves yields, especially in light of alternatives that involve either other herbicides or changes in cultural practices (e.g. off-season cover crops managed to suppress weeds in the follow-on cash crop). Increased simplicity of weed control generally means reduced labor needs for weed management, which is a contributing factor to increased consolidation of farmland in fewer hands, since the "saved labor" is often deployed to expand farm size, which should be accounted a cost rather than a benefit. Moreover, the increased simplicity consists in increased reliance on post-emergence use of

the HR crop-associated herbicide(s), which has been demonstrated to foster more rapid emergence of weeds resistant to the herbicide(s), another impact that is more properly considered a cost.

In the case of HPPD inhibitors, a relatively new class of herbicides, resistant populations have emerged quite rapidly, with 11 populations of two impactful weeds – Palmer amaranth and waterhemp – documented since just 2009. Disturbingly, eight of these populations are resistant to one to four additional modes of action, consistent with a general trend of dramatically increasing emergence of multiple herbicide-resistant weeds coincident with the herbicide-resistant crop era. Resistance to multiple HPPD inhibitors in most of these populations indicates a high potential for cross-resistance among members of this class, a common occurrence observed with resistance to other classes of herbicide.

Because most cotton is grown continuously on the same fields, every-year post-emergence use of isoxaflutole on HPPD-inhibitor cotton is possible and would likely promote rapid evolution of resistance to isoxaflutole. Because corn and soybean uses are already registered, there is a potential for every-year use of isoxaflutole and rapid evolution of resistance even if HPPD inhibitor-resistant cotton is rotated with resistant soybeans and corn to which isoxaflutole is applied.

An additional cost that has been previously ignored by EPA in this context is off-target herbicidal crop injury, which is exacerbated with the post-emergence use pattern characteristic of herbicide-resistant crop systems.

Mitigations

EPA has traditionally relied heavily on mitigation measures to reduce the impacts of a pesticide use that would otherwise be ineligible for registration due to unreasonable adverse impacts on the environment. For other pesticides as with this one, EPA has failed to assess the efficacy or feasibility of label-prescribed mitigation measures. As a result, unreasonable adverse impacts often occur because: 1) mitigation measures, even when followed, do not mitigate the harms they are intended to ameliorate; 2) the mitigations, even if effective when followed, are difficult or impossible to comply with in real-world farming practice; and/or 3) there is substantial non-compliance with mitigation measures.

This is improper. In assessing the new use of isoxaflutole on HPPD inhibitor-resistant cotton, EPA must provide assessments of the efficacy and feasibility of any mitigation measures it might propose, as well as the degree of compliance to be expected.

For example, the proclivity of isoxaflutole and degradates like DKN to leach into groundwater and run off into surface waters might prompt EPA to impose site-specific mitigation measures or prohibitions intended to reduce such impacts. EPA must assess the efficacy of any such measures, assess the feasibility of applicators making correct technical assessments in this regard, and estimate the degree of compliance and non-compliance.

Similarly, would label prescriptions that hinge on average precipitation levels or forecasts of future weather conditions be effective and enforceable?

Likewise, EPA must assess the efficacy and feasibility of, and expected compliance with, any herbicide resistance management plan it might choose to impose for the new use of isoxaflutole on cotton.

Without such assessments, EPA has no way of knowing to what extent mitigation measures will achieve their intended purpose of preventing unreasonable adverse effects. EPA should consult the past performance of similar mitigations with other herbicides to inform its assessments. To take one example, EPA has for several years now required herbicide-resistant management plans for other herbicide resistant crop-associated herbicide uses. To what extent have they been effective? Have resistant weeds emerged despite the plans? Can they be improved to achieve their intended purpose? Or to what extent have past mitigations targeting drift, runoff and leaching been feasible and effective, with high compliance levels?

Conclusion

Isoxaflutole is an incredibly potent herbicide whose persistence and mobility amplify its risks to human health and the environment. EPA must obtain all necessary data to thoroughly assess these risks prior to its proposed decision on this new use. CFS will comment further on any proposed registration the Agency issues, during the comment period the agency has confirmed it will have.