CENTER FOR FOOD SAFETY

October 4, 2021

Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460–0001

RE: Docket EPA-HQ-OPP-2010-0979
Comments on proposed interim registration decision for isoxaflutole

Center for Food Safety appreciates the opportunity to comment on EPA's proposed interim registration decision (PID) for the herbicide isoxaflutole, on behalf of itself and its 970,000 members and supporters. Center for Food Safety (CFS) is a public interest, nonprofit membership organization with offices in Washington, D.C., San Francisco, California, and Portland, Oregon. CFS's mission is to empower people, support farmers, and protect the earth from the harmful impacts of industrial agriculture. Through groundbreaking legal, scientific, and grassroots action, CFS protects and promotes the public's right to safe food and the environment. CFS has consistently supported comprehensive EPA review of registered pesticides and individual inert ingredients.

Isoxaflutole is an herbicide which inhibits the 4-hydroxyphenylpyruvate dioxygenase enzyme (4-HPPD). Isoxaflutole is a pigment inhibitor, and works by preventing the biosynthesis of carotenoid pigments, which protect chlorophyll from decomposition by sunlight. Without carotenoid pigments, chlorophyll pigments are photo-oxidized and chloroplast degradation occurs. Without the energy collecting action of the chlorophyll, the entire plant eventually perishes.

Isoxaflutole was first registered for use on corn in 1999, and in 2020 was registered for use on genetically engineered, herbicide-resistant soybean. EPA is presently considering an application to register isoxaflutole use on herbicide-resistant cotton. Since its registration in 1999, usage has increased from ~200,000 lbs. to 600,000 lbs. in 2017,[1] an overall increase of 200%. Isoxaflutole-containing formulations are Restricted Use Pesticides (RUPs) and can only be applied by certified applicators. EPA estimated the annual average application of isoxaflutole at ~550,000 pounds (lbs.) of active ingredient (AI) to ~8,790,000 total acres treated of corn between 2015 and 2019, representing about 10% of U.S. field corn acres. The recent approval for over-the-top (OTT) soybean use could result in additional use of 500,000 to 1 million lbs. of additional annual use, assuming 50% to 100% of eligible acres are planted to resistant soybeans

[1] US Geological Survey, Pesticide Use Maps – Isoxaflutole, Epest-Low. https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2017&map=ISOXAFLUTOLE&hilo=L&disp=Isoxaflutole

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and sprayed with isoxaflutole at the maximum annual (and single) application rate of 0.09375 lbs/acre. If approved, use on herbicide-resistant cotton could approach that projected on soybeans. Thus, several million pounds of this persistent, highly toxic biocide could be sprayed annually on a national basis in the near future.

Relevant Legal Standard

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

FIFRA authorizes EPA to regulate the registration, use, sale, and distribution of pesticides in the United States. Pursuant to FIFIRA, EPA oversees both initial registration of an active ingredient as well as any new uses of the registered active ingredient.

Section 3(c) of FIFRA states that a manufacturer must submit an application to register the use of a pesticide.[2] Under Section 3(c)(5) of FIFRA, EPA shall register a pesticide only if the agency determines that the pesticide "will perform its intended function without unreasonable adverse effects on the environment" and that "when used in accordance with widespread and commonly recognized practice[,] it will not generally cause unreasonable adverse effects on the environment."[3] FIFRA defines "unreasonable adverse effects on the environment" as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide."[4] Alternatively, where there are data gaps and missing information, EPA can register a pesticide with conditions (conditional registration) under Section 3(c)(7) of FIFRA "for a period reasonably sufficient for the generation and submission of required data," but only if EPA also determines that the conditional registration of the pesticide during that time period "will not cause any unreasonable adverse effect on the environment, and that use of the pesticide is in the public interest."[5]

The culmination of the registration process is EPA's approval of a label for the pesticide, including use directions and appropriate warnings on safety and environmental risks. It is a violation of the FIFRA for any person to sell or distribute a "misbranded" pesticide.[6] A pesticide is misbranded if the "labeling accompanying it does not contain directions for use which...if complied with …are adequate to protect health and the environment."[7]

Endangered Species Act

As recognized by the Supreme Court, the Endangered Species Act (ESA) is "the most comprehensive legislation for the preservation of endangered species ever enacted by any

[2] 7 U.S.C. § 136a(c)(1); 40 C.F.R. § 152.42.
[3] 7 U.S.C. § 136a(c)(5).
[4] 7 U.S.C. §136(bb).
[5] 7 U.S.C. §136a(c)(7)(C).
[6] 7 U.S.C. § 136j(a)(1)(E).
[7] 7 U.S.C. § 136(q)(1)(F).

nation."[8] The ESA's statutory scheme "reveals a conscious decision by Congress to give endangered species priority over the 'primary missions' of federal agencies."[9] Federal agencies are obliged "to afford first priority to the declared national policy of saving endangered species."[10]

Section 7(a)(2) of the ESA requires every federal agency to consult the appropriate federal fish and wildlife agency—the U.S. Fish and Wildlife Service (FWS), in the case of land and freshwater species and the National Marine Fisheries Service (NMFS) in the case of marine species—to "insure" that the agency's actions are not likely "to jeopardize the continued existence" of any listed species or "result in the destruction or adverse modification" of critical habitat.[11] The ESA's implementing regulations broadly define agency action to include "all activities or programs of any kind authorized, funded or carried out … by federal agencies," including the granting of permits and "actions directly or indirectly causing modifications to the land, water or air."[12] A species' "critical habitat" includes those areas identified as "essential to the conservation of the species" and "which may require special management considerations or protection."[13]

EPA is required to review its actions "at the earliest possible time" to determine whether the action may affect listed species or critical habitat.[14] To facilitate compliance with Section 7(a)(2)'s prohibitions on jeopardy and adverse modification, the ESA requires each federal agency that plans to undertake an action to request information from the expert agency "whether any species which is listed or proposed to be listed [as an endangered species or a threatened species] may be present in the area of such proposed action."[15] If FWS/NMFS advises the agency that listed species or species proposed to be listed may be present, the agency must then prepare a biological assessment for the purpose of identifying any such species that are likely to be affected by the proposed agency action.[16]

If, based on a biological assessment, an agency determines that its proposed action may affect any listed species and/or their critical habitat, the agency generally must engage in formal consultation with FWS/NMFS.[17] At the end of the formal consultation, FWS/NMFS must provide the agency with a "biological opinion" detailing how the proposed action will affect the threatened and endangered species and/or critical habitats.[18] If FWS/NMFS concludes that the proposed action will jeopardize the continued existence of a listed species or result in the destruction or adverse modification of critical habitat, the biological opinion must outline

[8] *Tenn. Valley Authority v. Hill*, 437 U.S. 153, 180 (1978).
[9] *Id*. at 185.
[10] *Id.*
[11] 16 U.S.C. § 1536(a)(2); *see also* 50 C.F.R. § 402.01(b).
[12] 50 C.F.R. § 402.02 (emphasis added).
[13] 16 U.S.C. § 1532(5)(A).
[14] 50 C.F.R. § 402.14(a).
[15] 16 U.S.C. § 1536(c)(1); *see also* 50 C.F.R. § 402.12(c).
[16] *Id.*
[17] 50 C.F.R. § 402.14.
[18] 16 U.S.C. § 1536(b); 50 C.F.R. § 402.14.

"reasonable and prudent alternatives" to the proposed action that would avoid violating ESA section 7(a)(2).[19]

Pending the completion of formal consultation with the expert agency, an agency is prohibited from making any "irreversible or irretrievable commitment of resources with respect to the agency action which has the effect of foreclosing the formulation or implementation of any reasonable and prudent alternative measures."[20]

Human Health Concerns

EPA's human health risk assessment for the registration review has been radically and unjustifiably overhauled from the assessment it conducted just over a year ago, for registration of isoxaflutole for use on herbicide-resistant soybeans (EPA 3/25/20). As detailed below, what EPA has done is essentially replaced most of its former, isoxaflutole-specific health assessments with one based on other HPPD inhibitor herbicides.

EPA dismissed rat and rabbit studies

As with most pesticides, a large proportion of the toxicology database for isoxaflutole is comprised of studies on rats, and to a lesser extent rabbits. For over a decade through last year, EPA relied upon these studies as appropriate for assessing isoxaflutole's toxicity, and as the basis for critical exposure thresholds. For instance, the former chronic reference dose of 0.02 mg/kg/day was derived from a chronic toxicity/carcinogenicity rat study with an Lowest Observed Adverse Effect Level (LOAEL)/No Observed Adverse Effect Level (NOAEL) of 20/2 mg/kg/day, based on toxicity to the liver and other organs, and the usual 100x uncertainty factor applied to the NOAEL (EPA 9/9/11, p. 13; EPA 3/25/20).

For registration review, EPA has decided the rat and rabbit are inappropriate species for assessing isoxaflutole. This decision was made in the context of the Agency's cumulative assessment of HPPD inhibitors, which share a mode of action/adverse outcome pathway (MOA/AOP) initiated by blockage of tyrosine catabolism, leading to a harmful buildup of tyrosine in plasma and subsequent liver damage and other adverse effects. Based on studies of other HPPD inhibitors, EPA came to the conclusion that rats (as well as rabbits) are more susceptible to the adverse effects of these compounds because they are not able to clear tyrosine from their systems as effectively as mice and humans, which are more similar in this regard. As a result, EPA now regards the low-dose effects of isoxaflutole (and other HPPD inhibitors) in rats and rabbits to be inapplicable to humans, and regards mouse studies as most appropriate for assessing the toxicity of isoxaflutole.

Whatever the case for other HPPD inhibitors, isoxaflutole has similar effects at similar doses on rats and mice, casting doubt on EPA's decision to ignore rat studies as inappropriate for this particular chemical. For instance, isoxaflutole causes quite similar changes in liver enzyme levels, at similar doses, in rats and mice (compare EPA 4/1/97 and EPA 4/7/97). Two carcinogenicity studies, one with mice and one with rats, show that isoxaflutole causes liver

[19] 16 U.S.C. § 1536(b)(3)(A).
[20] 16 U.S.C. § 1536(d).

tumors – again at similar doses. Finally, a comparative metabolism study on isoxaflutole, which was designed to compare how mice and rats process tyrosine in the presence of isoxaflutole, was deemed unacceptable by EPA scientific reviewers due to serious methodological flaws (EPA 11/13/96, the review of a study designated MRID 43904815; note that this same study is still designated unacceptable in EPA's latest human health evaluation, see EPA 9/18/20, Table A.2.2, p. 35).

Thus, EPA's dismissal of rat and rabbit studies is unjustified, and has two consequences. First, a number of critical safety thresholds based on studies with those animals have been illegitimately replaced by others, which permit much higher levels of "safe" exposure to this compound (discussed further below). Second, because rat studies in particular comprised the bulk of isoxaflutole's toxicology database, it also leaves us ignorant of important aspects of this compound's harmful effects.

Acute Endpoint Eliminated

EPA now finds that isoxaflutole poses no hazard upon acute (one-time) exposure, and thus conducted no acute exposure or risk assessment. This is because the acute reference dose (aka safety threshold) was previously based on a prenatal developmental toxicity study in rabbits, and as explained above EPA has rejected rabbits for assessing isoxaflutole's toxicity (EPA 9/18/20). The rabbit study's acute reference dose of 0.02 mg/kg/day was derived from ann LOAEL of 5 mg/kg/day based on skeletal abnormalities, the usual 100x uncertainty factor, and an additional 3x factor to account for lack of an NOAEL (EPA 9/9/11, p. 13; EPA 3/25/20).

Missing Studies

However, even if one accepts EPA's dismissal of rat and rabbit studies as appropriate, the resulting huge gaps in the toxicology database render EPA's interim registration decision contrary to FIFRA. EPA's contention that the toxicological database for isoxaflutole is adequate is wrong (EPA 9/18/20). The problem here is that only two of the many required toxicity studies were conducted with mice (EPA 9/18/20, Table A.2.2, pp. 33-35[21]). These two are the mouse carcinogenicity study and the *in vivo* mammalian cytogenetics (mouse micronucleus) assay. EPA regulations at 40 C.F.R. Part 158.500 require a host of animal feeding trials and other tests to assess various aspects of a pesticide's toxicity. Two required studies are those for prenatal developmental toxicity (in two species) and reproductive toxicity. The former involves feeding a pregnant animal the pesticide to determine whether it can cause birth defects or other adverse effects on the offspring (or maternal animal). The latter is a multi-generational trial to assess the pesticide's effects on various aspects of fertility and reproduction. Neither study is optional; both are required. Yet because EPA has rejected the two prenatal

[21] In a departure from EPA's usual reporting practices, many of the entries in Table A.2.2 under "Study Type" do not specify the test animal's species. As can be confirmed by comparison with an earlier EPA human health assessment of isoxaflutole (EPA 9/9/11, Table A.2, pp. 27-30), the following studies (identified by MRID [Master Record Identification] No.) for which the species is not identified in the 9/18/20 document were all conducted on rats: MRID 43904809, 43904804, 43904805, 45215701 and 43573224. As stated above, this leaves practically no studies on species EPA now deems acceptable.

developmental studies (rats and rabbits) and the reproduction study (rats), it has no animal data to assess these two critical aspects of isoxaflutole's toxicity: developmental malformations and reproductive impairment.

Rather than follow its regulations and issue a data call-in for the appropriate studies in mice, EPA pretends that developmental and reproductive studies ***on different pesticides*** can be plugged in to fill these huge data gaps. The fact that these other pesticides (e.g. mesotrione) are of the same HPPD inhibitor class as isoxaflutole in no way justifies this "bridging" exercise, for the simple reason that each pesticide will have its own unique suite of toxic effects; the fact that a group may share a certain MOA/AOP does not mean that individual members of the group do not exert toxic effects via other modes of action.

<u>Critical safety thresholds based on study of another pesticide</u>

EPA has based three safety thresholds – incidental oral short-term, non-occupational inhalation short- and intermediate-term, and occupational inhalation short- and intermediate-term) for isoxaflutole on a mouse reproduction study with a different pesticide – mesotrione (EPA 9/18/20, Table 4.6.3.1, pp. 19-20). As discussed above, only studies on isoxaflutole suffice to meet the registration standard for this pesticide, and use of a study on another pesticide to establish safety thresholds is particularly egregious.

Cancer

Isoxaflutole is "likely to be a human carcinogen" based on liver tumors in mice and liver and thyroid tumors in rats, and EPA quantified the cancer risk based on liver tumors in male mice: a unit risk or Q_1* = 1.14 x 10^{-2} mg/kg/day in human equivalents (EPA 9/18/20, p. 4). EPA calculated the additional risk of cancer attributable to isoxaflutole in different exposure scenarios based on this unit risk, expressed as the fraction of an exposed group (of 1 million or 100,000) that would contract cancer:

- Dietary (food and water) exposure only: 3 x 10^{-6} or 3 cancers among 1 million exposed (20-49 year-olds)
- Commercial handlers (occupational, wearing baseline attire and chemical-resistant gloves): up to 9 x 10^{-6} or 9 cancers among 1 million exposed
- Post-Application Exposure (occupational, wearing baseline attire and chemical-resistant gloves): up to 1 x 10^{-5} or 1 cancer among 100,000 exposed (equivalent to 10 cancers among 1 million exposed).

None of these cancer risks are "of concern" to EPA, but the Agency fails to explain the criteria by which it distinguishes cancer risks that are acceptable and those that are "of concern" or unacceptable. In the 1970s, the FDA originally set the threshold of concern at anything more than 1 additional cancer among 100 million exposed to a carcinogenic agent, then later in the decade relaxed that standard by 100-fold, to 1 additional cancer among 1 million exposed

(Calabrese 2018). This 1 in 1 million standard is EPA's level of concern for cancer today. Yet all of the above estimates exceed the 1 in 1 million threshold – by from 3 to 10 times.

What this means in practical terms is that there is no cancer safety threshold. The figures calculated by EPA according to established procedures have essentially no meaning, when even a 10-fold exceedance of the 1 in 1 million "level of concern" is not of concern.

Dermal Exposure with Occupational Use

As recently as EPA's 2011 human health assessment for registration of isoxaflutole for use on herbicide-resistant soybeans, EPA assessed both dermal absorption and inhalation as part of its occupational risk assessment, for both cancer and non-cancer outcomes (EPA 9/9/11, p. 12). This is only fitting, since a worker who mixes, loads and/or applies a pesticide generally takes in far more than a consumer (in food and water); and absorption through the skin and inhalation are the major occupational exposure routes. However, in the human health assessment for the proposed interim decision (PID), EPA ignores dermal absorption in the context of assessing workers for non-cancer outcomes, considering only inhalation (EPA 9/18/20). Yet dermal absorption is considered in the cancer assessment. The discrepancy is illogical. EPA should assess both dermal and inhalational absorption for its non-cancer occupational risk assessments as well.

Endocrine Disruption Screening

EPA maintains the toxicology database on isoxaflutole is complete, but this is not the case. Besides the huge gaps resulting from EPA's last minute dismissal of rat and rabbit studies, isoxaflutole has not been tested for its potential to disrupt hormonal function, and is not currently scheduled for EPA's Endocrine Disruptor Screening Program (EDSP): isoxaflutole does not appear on either List 1 or List 2.

Environmental Impacts of Isoxaflutole

Registration Review Ecological Assessment Incomplete and Biased

In registration review, EPA is supposed to conduct comprehensive analyses of the pesticide, including any changes in use patterns, new science, regulatory changes, etc., since the last registration review, re-registration, or original registration. A full assessment of all uses and risks to all taxa is called for. The goal is to determine if the pesticide meets registration standards and/or whether changes to the registration are needed.

The ecological risk assessment for the proposed interim decision is procedurally inadequate, in that it considers only one registered use of isoxaflutole (corn), and explicitly excludes a recently registered use on isoxaflutole-resistant soybeans.[22] The failure to consider both corn and soybean uses together in the ecological risk assessment, and potential use on cotton, undermines the proposed interim decision in substantive ways, as discussed further below. Moreover, EPA assesses only risks to terrestrial plants, providing mere summaries of

[22] The assessment is also silent on a pending request for use on isoxaflutole-resistant cotton.

much older risk assessments for other taxa. While EPA points to a number of prior ecological assessments for use on a single crop, isoxaflutole-resistant soybean, where risks to taxa other than terrestrial plants are discussed, the failure to collect and synthesize this information in a single document is a major flaw that hampers comprehensive review and defeats the purpose of registration review.

In addition, the proposed interim decision is extremely biased in important respects, such that a reader otherwise unfamiliar with isoxaflutole would come away with the false impression that it poses far less risk than it does. For instance, the assessment recounts the environmental fate data for parent isoxaflutole at length, and practically ignores the much more persistent and equally phytotoxic major diketonitrile degradates, RPA 202248 and RPA 205834.

Residues of Concern

EPA must assume all of isoxaflutole's many degradates, particular the diketo degradates RPA 202248 and RPA 205834, are equally toxic to the parent compound in all relevant human health and ecological assessments, given the complete lack of data for RPA 205834 and spotty data on RPA 202248 and other degradates. Moreover, it appears that one major degradate remains unknown (EPA 11/6/19). EPA must identify this metabolite and characterize its environmental fate and toxicity for inclusion, as appropriate, in the human health and ecological assessment.

Test Material in Ecological Toxicity Tests

The ecological toxicity testing upon which EPA's assessment is based has involved diverse forms of isoxaflutole: the technical grade active ingredient (TGAI) as well as various formulations. Because different formulations can have differing toxicity due to compositional differences (e.g. identify and amounts of surfactants), it is critical that the toxicity tests EPA relies upon in its assessments include full datasets with registered formulations. Because registrants frequently change the composition of their formulations, EPA should always employ data for toxicity endpoints from the most potent of the formulations/TGAI for which data are available. EPA needs to require full toxicity datasets for each formulation of isoxaflutole.

Isoxaflutole Use Every Year in Rotations Involving Corn, Soybean and Cotton

The 2020 registration of isoxaflutole for use on soybeans engineered to withstand it opens up far greater opportunities for every-year use of this potent herbicide in the many counties of 33 states where it is registered for use on isoxaflutole-resistant soybeans as well as corn, given the common practice of rotating the two crops in the Midwest. Every-year use on the same fields increases the potential for accumulation of isoxaflutole and particularly its persistent DKN degradates in soils, surface water, and shallow groundwater. EPA is currently considering an application to register isoxaflutole for use on resistant cotton. If approved, this would open up substantial new geographic areas in Texas, the Mid-South, and the Southeast for potential every-year use of isoxaflutole on cotton and corn and/or soybeans.

EPA must fully assess the consequences of every-year use of isoxaflutole use on all three crops. All models used to estimate environmental concentrations in soils, in runoff and irrigation waters, in streams and ponds, and in groundwaters must assume carryover from year-to-year using the most conservative environmental fate data (e.g. maximum half-lives, field dissipation rates, etc.) for parent isoxaflutole and the DKN degradates. EECs that account for carryover with every year use must then be used to assess risks to all relevant taxa.

Terrestrial Plants

Isoxaflutole is among the most potent of herbicides, effective on both monocot and especially dicot plants, inhibiting the growth of sensitive dicots 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. This potency makes spray drift a serious threat to sensitive crops and plants. EPA's analyses show that spray drift damage exceeds the Agency's level of concern (25% inhibition of growth) for sensitive plants from 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. Because spray droplets can move considerable distances under temperature inversion conditions that occur frequently in the Midwest and other regions, EPA must assess drift damage and distances it can occur under this common weather condition.

Isoxaflutole and its DKN degradates also run off fields after rainfall or irrigation. EPA must fully assess the threats posed by runoff, including in small bodies of water such as vernal ponds where environmental concentrations can reach higher levels than in the larger bodies of water that EPA uses in its modeling. Risk assessments of combined damage from spray drift and runoff should utilize the more sensitive vegetative vigor rather than the seedling emergence endpoint.

A key concern that EPA has not assessed is the risk of off-field plant damage from transport of isoxaflutole and DKN-bearing soil particles via wind. Isoxaflutole is stable to soil photolysis, and thus could persist in soils for the duration of rainless periods after application. To the extent it does break down, the RPA 202248 degradate is also very phytotoxic. Under such dry conditions, soil particles bearing isoxaflutole and its degradates could be blown great distances on the wind to land on fields of crops and wild plants. With rain comes reactivation and injury to the distant crops and wild plants. EPA must assess this important mode of off-field crop and plant damage.

EPA must assess damage to off-field plants that ensues from multiple isoxaflutole drift and runoff episodes in the course of a season. This could occur when one field is sprayed more than one time in a season, and/or when crops and wild plants in the vicinity of several fields treated with isoxaflutole (once or multiple times) suffer multiple damage episodes due to drift or runoff originating from the different fields. The latter scenario is more likely considering the long distances at which drift damage can occur. While one application per season to corn may be typical at present, we see no proposed restriction on the number of applications to corn. Isoxaflutole will likely be used more than once per season on isoxaflutole-resistant soybeans,

because labels permit use from 21 days prior to planting up to first bloom, and we see no application number restriction on soybean labels.

EPA must also assess the elevated risk of off-field plant damage associated with the timing of isoxaflutole applications. The Agency appears convinced that isoxaflutole will be used only or practically only early in the season, as it repeatedly emphasizes the pre-plant or pre-emergence use pattern throughout the proposed interim decision and underlying assessments. However, post-emergence use has long been allowed on corn; and post-emergence soybean applications are also permitted and will occur much later in the season than isoxaflutole has ever been sprayed before, for several reasons: 1) Soybeans are planted several weeks later in the season than corn; 2) Isoxaflutole-resistant soybeans can be sprayed up to first bloom, which is also later in the crop's growth cycle than early post-emergence application to corn, which together with later calendar planting pushes the application window a month or later than with corn, into the summer; and 3) Double-crop isoxaflutole soybeans would be planted in summer and also mean application during the heat of summer. Similarly, dicamba is a largely pre-emergence and early post-emergence corn herbicide that caused immeasurably more drift damage when approved for later-season use on dicamba-resistant soybeans and cotton. EPA must not permit anything close to the dicamba debacle to occur with isoxaflutole.

Trees and Other Perennial Plants

EPA's terrestrial plant risk assessment is based on toxicity tests on annual crops involving a single exposure. The real world, however, is populated by trees and other perennial plants that can and are damaged multiple times per season, and over years, by herbicide drift (particle and volatile drift, wind-blown dust) and runoff. Such damage can and does take a cumulative toll that EPA must assess. The dicamba drift debacle has raised awareness of tree and perennial plant damage from off-target movement of herbicides, and EPA must assess this issue with respect to isoxaflutole.

Terrestrial Invertebrates

After a registration review process that began a decade ago in 2011, EPA is still "uncertain" about the risks isoxaflutole poses to bees (EPA 5/30/19, p. 6). The uncertainty stems from EPA's failure to collect adequate data on isoxaflutole's toxicity to terrestrial invertebrates, particularly the surrogate species for this group, the honey bee. In fact, EPA lacks basic data in this regard: "no chronic data are available for adult honey bees and no chronic or acute data are available for larval honey bees" (EPA 6/30/21, p. 16).

EPA's excuse is that its initial data call-in for pollinator data in 2011 came before a 2014 guidance that demanded additional tests (Ibid., p. 18). But clearly there has been sufficient time for EPA to have collected needed studies. Instead, seven years after release of the guidance, the Agency has yet to ***even decide whether*** to require any particular studies, much less specify the sort of data needed, or to propose a schedule for collection of said data.

Neither has EPA collected data on other terrestrial invertebrates potentially at risk from exposure to isoxaflutole. For instance, the persistence of isoxaflutole and/or its degradates in

soil makes it necessary for EPA to assess potential harm to ground-dwelling bees and other invertebrates that reside in the soil. CFS urges EPA to collect the full suite of honey bee data and corresponding toxicity tests on other invertebrates.

Aquatic invertebrates

EPA must collect data on the chronic toxicity of isoxaflutole degradates to mysid shrimps, since it is currently relying on extrapolation from acute and chronic toxicity of the parent chemical to mysids, and the acute endpoint for the degradates, which may not reflect the actual toxicity of the degradates to this sensitive species.

Costs and Putative Benefits of Isoxaflutole

Frequently cited benefits of herbicides applied to herbicide-resistant (HR) 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 consists in increased reliance on the HR crop-associated herbicide(s), to the exclusion of other weed management methods, which fosters more rapid emergence of weeds resistant to the herbicide(s), an impact that is more properly considered a cost (Mortensen et al. 2012). Moreover, HR crop systems mean 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, another "benefit" that is more properly considered a cost (MacDonald et al. 2013).

EPA has included a two-paragraph "Benefits Assessment" in the proposed interim decision (EPA 6/30/21, pp. 18-19), but failed to provide any estimates of the costs of isoxaflutole, beyond admitting that it puts off-field terrestrial plants and animals that depend upon them at risk. EPA has thus failed to weigh costs against putative benefits of this herbicide.

The benefits of isoxaflutole cited by EPA are the ability to mix it with other herbicides and to kill problematic weeds like Palmer amaranth and waterhemp that are resistant to glyphosate, photosystem II inhibitors (e.g. atrazine), protophyrinogen oxidase (PPO) inhibitors, acetolactate synthase (ALS) inhibitors, and synthetic auxin herbicides. The 11 confirmed populations of weeds resistant to HPPD inhibitors in the U.S. have arisen since just 2009, which is fairly rapid emergence, when one considers how limited the use of isoxaflutole has been (HRAC 10/1/21). All of these resistant populations are either Palmer amaranth or waterhemp, the very "problematic weeds" isoxaflutole is intended to control. Eight of the 11 populations are also resistant to multiple (up to five) modes of action, including all of the herbicide modes of action cited above, resistance to which isoxaflutole is said to overcome (Ibid.).

Cultivation of isoxaflutole-resistant soybean and cotton, together with continued use on corn, will dramatically expand acreage sprayed every year with this herbicide, greatly

accelerating emergence of resistance, as occurred with glyphosate-resistant weeds with Roundup Ready crops.

EPA must estimate costs of isoxaflutole drifting to damage neighboring crops and wild plants, based on reasonable scenarios of increased use with introduction of isoxaflutole-resistant soybeans and potential cotton. In addition, EPA must estimate the costs of isoxaflutole-resistant weeds in terms of additional expense from use of additional herbicides and tillage. EPA must also assess the costs involved in extensive isoxaflutole monitoring efforts that have already been undertaken by the U.S. Geological Survey (Scribner et al. 2006) and some state governments,[23] costs only made necessary by the registration of this herbicide. EPA must also estimate the costs of removing isoxaflutole and its degradates from ground water and surface water that will be borne by water and sewer authorities – similar to atrazine – as use of this herbicide increases.

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; 3) The mitigations call for technical judgements many applicators do not have the expertise to make; and/or 4) There is substantial non-compliance with mitigation measures.

As noted above, EPA fails to provide even the roughest estimate of isoxaflutole's costs. Neither does the Agency demonstrate that its four "proposed label mitigations" will do anything to reduce those costs (EPA 6/30/21, pp. 21-24).

The first "mitigation" does not mitigate anything. It consists entirely in updating the "glove statements" on isoxaflutole labels, and "does not fundamentally change the personal protective equipment that workers need to use…."

The second mitigation is a "nontarget organism advisory statement" that is not enforceable, and merely advises the applicator to follow label directions (Ibid., pp. 21, 29). EPA cites no evidence that it will provide any mitigation of isoxaflutole's harms to nontarget organisms.

With the third mitigation – resistance management language on the label – EPA purports only to provide "easy access" to information and recommendations on this topic, yet provides no evidence to suggest the recommendations are effective, or even if they are, that they will be followed, or can be followed given the realities of commercial farming.

The fourth proposed label mitigation involves spray drift management, and mainly involves standardizing language on this topic across different isoxaflutole labels, and advisory

[23] For isoxaflutole monitoring in Wisconsin, see https://www.usgs.gov/centers/umid-water/science/isoxaflutole-monitoring?qt-science_center_objects=0#qt-science_center_objects.

language. EPA intends to prohibit spraying during temperature inversions, but does not discuss how frequently these conditions occur in major use areas, or given that reality how likely it is that applicators will be able or willing to comply; reduced weed control associated with application delays, or the feasibility or costs of switching to a different herbicide or herbicides that do(es) not have this restriction, or to tillage. EPA proposes to prohibit applications at wind speeds above 15 mph, which will lead to more drift episodes at greater distances for those isoxaflutole products for which applications are currently prohibited above 10 mph. Finally, EPA proposes a minimum droplet size of medium, which will permit drift at greater distances than a droplet size that is coarse or larger.

Some label mitigation measures are conditional, based on the depth of groundwater below a field, the organic matter content of the field's soil, or whether certain meteorological conditions are present or not. The right call will often depend on technical knowledge an applicator might well not possess. EPA fails to provide any evidence that these sorts of technical mitigations are effectively followed. Indeed, EPA itself concedes that advisory label statements are at best educational and have no impact on risks of concern.

Endangered Species Assessment

EPA has not completed an assessment of isoxaflutole for its impact on threatened and endangered species. EPA must comply with its duties under Section 7 of the ESA prior to finalizing its interim registration decision, as it is a separate, discretionary action that may affect species listed as threatened or endangered under the ESA. Because imperiled species listed under the ESA are highly susceptive to additional threats, it is clear that listed species would be at increased risk from an approval. Yet EPA has postponed such an assessment indefinitely to the future, contingent upon developing a Revised Method (EPA 6/30/21, pp. 33-34).

Without consulting the expert wildlife agencies, however, EPA has made unilateral "no effect" determinations for one registered use of isoxaflutole – application to isoxaflutole-resistant soybeans (EPA 11/6/19). First, EPA determined that there would be no direct effects on listed taxa other than terrestrial plants. Second, the Agency relied entirely upon its own spray drift and runoff analyses to inform its "may affect" determinations for 352 listed species based on concerns of direct effects on 96 listed species of plants and indirect effects on 256 listed species of animals that depend for food and habitat on plants threatened by isoxaflutole drift and runoff damage (EPA 7/15/16). Finally, the Agency accepted a proposal by the registrant to register isoxaflutole only in those counties of 33 states that either do not contain a listed terrestrial plant species or designated critical habitat, or that are not adjacent to such counties (EPA 11/6/19, p. 2, Appendix 4). In accepting this proposal to limit registration to said counties, EPA made a "no effects" determination for all listed terrestrial plant species and designated critical habitats for all species (Ibid.).

EPA's unilateral actions with respect to one use of isoxaflutole violate the Agency's obligations under the ESA to consult with the relevant expert wildlife agencies. Without a full analysis and ESA consultation EPA cannot determine the full impacts of isoxaflutole on ESA-listed species and their critical habitats and ensure that it will not jeopardize any of those

species. In addition, EPA's action is inconsistent. Isoxaflutole remains registered for use on corn in many of the same counties where its use is prohibited on soybeans, despite the fact that use on corn will have similar detrimental, direct and indirect impacts, on listed species as the soybean use. EPA provides no explanation of the inconsistent assessments of the two uses. No timetable is presented for completion of a valid endangered species assessment.

Endocrine Disruptor Screening Program

EPA has not made a determination as to whether isoxaflutole is an endocrine disruptor (ED), and isoxaflutole is not on either List 1 or List 2 of chemicals for which ED screening has been conducted or is imminent. Thus, the potential adverse impacts of isoxaflutole on human or ecological health via endocrine disruption are unknown, and EPA provides no timetable for completion of endocrine disruptor screening, which will likely take years.

Final Registration Review Decision May be Postponed for Years

EPA states that it will not issue a final registration review decision until it completes both endangered species and endocrine disruptor screening program determinations (PID at 26). As noted above, this will likely stretch out the registration review of isoxaflutole from its current 10 years (begun in 2011) to 15 or more, given in particular the slow pace of EDSP screening, EPA's failure to issue determinations even for many List 1 and List 2 chemicals, and the fact that isoxaflutole is not on either list.

Conclusion

Isoxaflutole is far too hazardous a biocide to permit continued use as recommended in this proposed interim decision. The persistence of its toxic degradates in soil and water resources, its proclivity to leach into surface and ground water like atrazine, the cancer risks to both consumers and occupational users, and the harms of drift and runoff to plant species from hundreds to over 1,000 feet from treated fields, resembling dicamba, all make it unsuitable for continued registration. The harms to threatened and endangered species, already acknowledged by EPA, make continued registration illegal under the Endangered Species Act as well.

Center for Food Safety urges EPA to reject the proposed interim registration review decision and cancel all registrations of this toxic biocide.

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References

Calabrese EJ (2018). The additive to background assumption in cancer risk assessment: A reappraisal. Environmental Research 166: 175-204.

EPA (6/30/21). Isoxaflutole: Proposed Interim Registration Review Decision – Case Number 7242. EPA, June 30, 2021.

EPA (6/28/21). Oxyfluorfen: Proposed Interim Registration Review Decision, Case Number 2490. EPA, June 28, 2021.

EPA (3/25/20). Final Registration of Isoxaflutole on Isoxaflutole-Resistant Soybeans, EPA, March 25, 2020.

EPA (9/18/20). Isoxaflutole – Draft Human Health Risk Assessment for Registration Review, EPA, September 18, 2020.

EPA (11/6/19). Addendum to the 2016 Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Isoxaflutole-Tolerant Soybeans to Consider Proposed Label Restrictions and to Make an Effects Determination for Listed Species, EPA, November 6, 2019. EPA-HQ-OPP-2019-0398-0010.

EPA (5/30/19). Isoxaflutole: Draft Ecological Risk Assessment for Registration Review. EPA, May 30, 2019.

EPA (7/15/16). Revised Addendum to Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Soybeans, EPA, July 15, 2016. EPA-HQ-OPP-2019-0398-0004.

EPA (9/9/11). Isoxaflutole. Section 3 Registration for Use on Soybeans: Human Health Risk Assessment. EPA, September 9, 2011.

EPA (4/7/97). EPA review of mouse liver enzyme study with isoxaflutole. EPA, April 7, 1997.

EPA (4/1/97). EPA review of rat liver enzyme study with isoxaflutole. EPA, April 1, 1997.

EPA (11/13/96). EPA review of comparative metabolism study (rat and mouse) with isoxaflutole. EPA, November 13, 1996.

HRAC (10/1/21). HPPD Inhibitor Resistant Weeds in the U.S. International Herbicide-Reistant Weed Database. Herbicide Resistance Action Committee. www.weedscience.com.

MacDonald JM et al. (2013). Farm Size and the Organization of US Crop Farming. USDA Economic Research Service, August 2013.

Mortensen DA et al. (2012). Navigating a Critical Juncture for Sustainable Weed Management. BioScience 62(1): 75-84.

Scribner EA, Meyer, MT and Kalkhoff SJ (2006). Occurrence of Isoxaflutole, Acetamide, and Triazine Herbicides and Their Degradation Products in 10 Iowa Rivers Draining to the Mississippi and Missouri Rivers, 2004. U.S. Geological Survey, Report 2006-5169.