CENTER FOR FOOD SAFETY

January 11, 2020

US Environmental Protection Agency
EPA Docket Center, Mail Cod 2822IT
1200 Pennsylvania Ave., NW
Washington, DC 20460

Submitted electronically to www.regulations.gov

RE: Comments on EPA-HQ-OPP-2018-0762, registration of new active ingredient, trifludimoxazin

Center for Food Safety (CFS) appreciates the opportunity to comment on EPA's proposed unconditional registration decision for the new active ingredient, trifludimoxazin. The proposed decision covers one technical product, Tirexor Herbicide (99.2% trifludimoxazin) and one end-use formulation, Tirexor soluble concentrate (41.53% trifludimoxazin), which contains 4.17 pounds active ingredient per gallon. CFS incorporates by reference comments to this same docket by the Center for Biological Diversity.

RELEVANT LEGAL STANDARDS

The 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.[1] 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."[2] FIFRA defines "unreasonable adverse effects on the environment" as "any unreasonable risk to man or the environment, taking into account the economic, social, and

[1] 7 U.S.C. § 136a(c)(1); 40 C.F.R. § 152.42.
[2] 7 U.S.C. § 136a(c)(5).

environmental costs and benefits of the use of any pesticide."[3] 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."[4]

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.[5] 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."[6]

INTRODUCTION

Trifludimoxazin is a potent herbicide proposed for extremely broad-scale use to control weeds in corn and other cereal grain crops (excluding rice), soybeans and other leguminous crops, nut trees, fruit trees (pome and citrus) and peanuts, as well as for post-harvest and fallow uses. Proposed non-agricultural uses include tree plantations and industrial landscaping.

The proposed maximum single application rates range from 0.034 to 0.134 lbs a.i./acre, with from two to four applications permitted per year, with maximum annual rates equal to the single application rates. Tri is proposed for ground and/or aerial application for all uses except fruit and nut trees, for which only ground applications are proposed.

Trifludimoxazin kills plants by inhibiting the protoporphyrinogen oxidase (PPO) enzyme, which catalyzes a step in the biosynthesis of chlorophyll in plants and heme in animals. Inhibition of PPO leads to buildup of protoporphyrinogen IX, which is then oxidized in the presence of light to form protoporphyrin IX, which destroys plant cell membranes via generation of oxygen free radicals, leading to plant death (Smith and Foster 2018). Trifludimoxazin is an extremely potent killer of both monocot and dicot plants, with dicots particularly sensitive.

Trifludimoxazin is broken down in environmental media to form seven major degradates: M850H001, M850H002, M850H003, M850H004, M850H033, M850H035, M850H042 (EPA Eco, p. 14). EPA has received extremely limited data on the ecotoxicity of several of these degradates, and none on most of them. In the absence of empirical data from tests, EPA attempted to estimate the toxicity of trifludimoxazin and its degradates via ECOSAR modeling, which predicts a novel compound's toxic effects based on its chemical structure, and what is known about the toxicity of chemicals with similar structures (i.e. quantitative structure

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

activity relationships, or QSARs). However, this exercise failed, since the limited empirical data on degradate toxicity that was available to EPA diverged dramatically from model estimates. For this reason, EPA was unable to use ECOSAR modeling estimates (EPA Eco, pp. 5-6, 14-16). Thus, given the paucity of empirical data, the human and ecotoxicity of trifludimoxazin's degradates remains largely unknown.

EPA states that the database of studies to support its assessment of risks to human health, ecological effects and environmental fate is adequate (EPA 10/10/20, p. 6). However, elsewhere EPA concedes that it has not assessed potential health risks from inhalation of volatilized trifludimoxazin, from exposure to spray drift, or from the cumulative toxicity of trifludimoxazin and other substances that share a common mechanism of toxicity (EPA HHRA at 29-30). In each case, EPA postponed such assessments to registration review (Ibid). Because trifludimoxazin in a new active ingredient, and registration review is conducted at 15-year intervals, such assessments will apparently be postponed 15 years or more. Neither has EPA conducted "a specific endangered species analysis for any taxa," and thus it "has not made effects determinations for specific listed species or designated critical habitat" (EPA 10/10/20, p. 12). Finally, CFS finds no evidence that EPA has conducted any assessment of trifludimoxazin's potential to disrupt endocrine (i.e. hormonal) systems, which is critical for both human health and environmental assessments. This includes lack of any Tier 1 screening test results for endocrine disruption potential in the context of EPA's Endocrine Disruption Screening Program (EDSP). EPA does not even propose a timetable for collection of endocrine disruption data.[7] Despite these data and assessment gaps, EPA has proposed unconditional registration of trifludimoxazin.

HUMAN HEALTH RISKS

Non-Cancer Effects

Trifludimoxazin inhibits the protophyrinogen oxidase (PPO) enzyme, which is present in animals as well as plants. Studies have shown that other PPO-inhibiting herbicides inhibit the action of PPO in animals, for instance in mouse liver mitochondria (Kawamura et al 2014). PPO participates in biosynthesis of heme, the iron-containing component of the protein (hemoglobin) in red blood cells that carries oxygen from the lungs to the body's tissues. Thus, the unspecified hematological effects EPA observed in registrant animal tests are likely a result of trifludimoxazin's PPO inhibition (EPA HHRA, p. 5).

Registrant animal testing shows that trifludimoxazin causes numerous non-cancer adverse impacts to the thyroid and the liver, effects which are fairly consistent across trials. Thyroid effects include follicular cell hypertrophy/hyperplasia, altered colloid, increased relative thyroid weights in rats. Chronic effects in the liver include increased liver weight, foci of (eosinophilic) cellular alteration, centrilobular hypertrophy, macro vesicular fatty change and centrilobular pigment storage in male mice, and oval cell hyperplasia and (multi)focal necrosis

[7] A search of the human health and ecological assessments and the proposed registration decision turned up 0 hits for the terms "endocrine" and "EDSP."

in female mice. Chronic exposure in rats also impacted the liver, with major effects including increased pigment, multinucleated hepatocytes, and bile duct hyperplasia" (EPA 10/10/20, p. 6).

Reproductive effects testing revealed increased abnormal sperm in male rats, while chronic and subchronic tests showed adverse effects to the epididymis (the long, coiled tube in the scrotum where sperm mature and are stored) (Ibid., p. 6).

Trifludimoxazin also elicited serious neurotoxic effects in dogs exposed to it for just 90 days. Functional deficits included insecure gait, hind limbs buckling under pressure, little or no resistance when moving limbs, and hopping movements in females. Damage was also observed to the spinal cord (degeneration of myelin sheaths, axons and oligodendrocytes) and nerve fibers, including white matter, in the brain. These effects occurred at the lowest dose tested (Ibid., p. 6).

Finally, when pregnant rabbits were dosed with trifludimoxazin, there was an increased incidence of late abortions, while fetuses that survived had depressed body weight at lower doses than the late-term abortions, as well as skeletal malformations (Ibid., p. 7; EPA HHRA, p. 47).

EPA based its chronic exposure safety threshold (reference dose) on a rat study in which the test animals exhibited most of the effects discussed above (to the thyroid, liver and male reproductive system) at the relatively low dose of 33 mg/kg bw/day (EPA HHRA, p. 20, Table 4.5.3.1, chronic dietary study). Virtually the same thyroid effects were observed in parental rats of the extended one-generation reproductive toxicity study, but at a lower dose of 22 mg/kg bw/day that should thus serve as the point of departure for the chronic reference dose for ***non-cancer*** effects (EPA HHRA, p. 48). The severe nervous system effects occurred at the lowest dose administered to dogs in the 90-day subchronic study (50 mg/kg bw/day, the LOAEL), thus a no observed effects level (NOAEL) could not be determined (EPA HHRA, pp. 44-45). Given that the highest dose tested in the chronic dog study was just 15 mg/kg bw/day, three-fold lower than the subchronic LOAEL, EPA may well have missed serious chronic neurological effects in the 15 to 50 mg/kg bw/day dose range (EPA HHRA, p. 16), a concern heightened by trifludimoxazin's mode of action, discussed further below.

Trifludimoxazin Merits "Likely to be Carcinogenic" Hazard Classification

Two animal studies submitted by registrants demonstrate the carcinogenic potential of trifludimoxazin, which induced thyroid follicular cell tumors in male and female rats, as well as liver tumors in male mice. EPA misinterpreted the evidence, finding treatment-related tumors only in one group (fed 750 ppm trifludimoxazin in diet) of male rats, but not in female rats; and no treatment-related tumors in mice. As a result, trifludimoxazin was classified as having only suggestive evidence of carcinogenicity rather than being likely carcinogenic, the correct descriptor according to a balanced weight-of-the-evidence assessment (EPA 4/24/20).

Four doses were administered in the rat study (50, 250, 750 and 1500 ppm in diet, equivalent to 2/3, 11/16, 33/47 and 68/95 mg/kg bw/day [M/F]) for up to 24 months. 12% of

females in ***each of two*** treatment groups (250 and 1500 ppm) exhibited thyroid follicular cell adenomas, versus just 2% of the controls, a result that statistical analysis suggests is almost certainly due to trifludimoxazin treatment rather than chance ($p = 0.0590$ for 250 ppm and 0.0557 for 1500 ppm), but which EPA mechanically rejects because the statistical test results are just a hair above the arbitrary $p < 0.05$ significance cutoff. Elevated tumor incidence in two (rather than just one) female treatment groups; the borderline significant dose-response trend of increasing adenoma incidence ($p = 0.0541$); the treatment-related appearance of the ***same tumor type*** in male rats; and finally, supporting evidence of adverse non-neoplastic (altered colloid) and pre-neoplastic (hyperplasia) in female as well as male rats, in both the cancer and the extended one-generation reproduction toxicity study, all argue for trifludimoxazin as a thyroid carcinogen in females as well as male rats.[8]

The situation is similar for liver tumors in male mice (female data not shown), which were fed three doses for 18 months: 37.5, 375 and 750 ppm in diet, equivalent to 5.5, 55.4 and 109.1 mg/kg bw/day (EPA 4/24/20, pp. 14-16). While zero tumors were observed in the control group, and just one adenoma in the low-dose group, the mid- and high-dose groups exhibited 4 and 3 tumors, respectively, with two of the three tumors in the high-dose group being carcinomas. The trend for combined adenoma/carcinoma incidence ($p = 0.0588$), the pairwise comparison of mid-dose group incidence (9%) to control ($p = 0.0560$),[9] as well as the trend for carcinomas alone ($p = 0.0635$), with the only two carcinomas appearing in the high-dose group, all argue for trifludimoxazin as a liver carcinogen in mice, with multiple measures of statistical significance right at the arbitrary statistical significance cut-off of $p < 0.05$. As we argue below, trifludiomoxazin's inhibition of PPO provides a possible biological rationale for these liver tumor results.

Treatment-related induction of tumors at two sites (thyroid follicular cells, liver), in two species, with both male and female thyroids affected in rats, provides more than sufficient evidence for classification of trifludimoxazin as likely to be carcinogenic to humans (EPA 2005, 2-54 to 2-55). With proper hazard classification as likely to be carcinogenic, EPA policy requires a dose-response assessment to quantify the cancer risk posed by trifludimoxazin (EPA 2005).

Carcinogenic Risk Assessment of Trifludimoxazin

According to EPA science policy on assessment of thyroid follicular cell tumors, evaluation of human cancer risk based on this tumor type in experimental rodents can involve linear dose extrapolation, a margin-of-exposure approach, or both, depending upon the chemical's carcinogenic mode of action. A linear approach is used when the mode of action is mutagenic or unknown (EPA 1998, pp. 1-3). Here, it is unknown, since EPA does not identify a mode of action; and because the non-mutagenic mode of action proposed by BASF – disruption

[8] Elsewhere, EPA appears to agree with this assessment: "However, follicular cell adenomas outside of historical control were observed in females treated with 250 and 1500 ppm, and therefore, a treatment-related effect cannot be excluded at 250 ppm for females despite the lack of a dose-response or accompanying increases in hyperplasia." (EPA HHRA, p. 51)

[9] As discussed in the next section, EPA Guidelines for Carcinogen Assessment provide for evaluation of combined incidences of adenomas/carcinoma "when scientifically defensible." McConnell et al (1986) find this to be the case for hepatic adenomas and carcinomas.

of thyroid-pituitary homeostasis – is rejected by EPA as unconfirmed for lack of evidence (EPA 4/24/20, pp. 26-35).

In assessing cancer risk, EPA must use existing data to model a *dose point of departure*, which is generally the "dose producing 10% thyroid tumor incidence," and employ "a straight-line extrapolation of tumor incidence [] from the dose point of departure … to the origin" (Ibid, p. 4). The 10% tumor incidence threshold dose will lie somewhere below 250 ppm in feed in both male and female rats, since incidences in that dosage group as well as higher dosage groups exceed 10% (EPA 4/24/20, pp. 10-11, Tables 3 & 4). Because 250 ppm in feed corresponds to 11/16 mg/kg bw/day (M/F), the dose point of departure will lie somewhere below 11 mg/kg bw/day. EPA's objections to treatment-related tumors at this dose are specious, contradicted by its own guidelines.

First, EPA objects that the separate incidences of adenomas and carcinomas at 250 ppm in male rats were "within historical control ranges" (EPA 4/24/20, p. 14). Yet they were actually identical to the upper limits of those ranges (8% and 6%, respectively) (Ibid., p. 10, Table 3).[10] Moreover, the 14% combined incidence of adenomas/carcinomas at this dose exceeds both the corresponding historical control mean (5.5%) and upper bound (10%) values (Ibid). That consideration of the ***combined incidence*** is valid here is supported by EPA's Guidelines for Carcinogen Risk Assessment, which provide for statistical assessment of combined incidence of benign and malignant lesions of the same cell type, tissue or organ "when scientifically defensible," citing McConnell et al. 1986 (EPA 2005, p. 2-19). McConnell and colleagues, who assess this very "combination" question for a broad range of tumor types based on empirical evidence, affirm that combined assessment of thyroid follicular cell adenomas and carcinomas is scientifically justified (McConnell et al. 1986, p. 287, Table 1). Finally, EPA Guidelines make it clear that historical control data are to be used only with extreme caution, in a subsidiary capacity, not to drive decision-making.

More importantly, EPA entirely ignores the fact that malignant tumors in the 250 ppm group lend greater weight to carcinogenicity at this dose. As per Guidelines, a high "proportion of malignant tumors" adds significance to tumor findings (EPA 2005 at 2-21- to 2-22), and "a greater proportion of malignancy is weighed more heavily than is a response with a greater proportion of benign tumors" (Ibid., p. A-5). Clearly, the evidence for treatment-related carcinogenic effects is as strong or stronger at 250 ppm versus 750 ppm (11 versus 33 mg/kg bw/day).

Porphyria and Neuropathy

Porphyria refers to a group of disorders that result from a buildup of porphyrin-forming compounds. It is best known as a hereditary disease in people with defects in enzymes, such as PPO, that catalyze reactions in the biosynthesis of heme. In acute forms of porphyria, inhibition of the heme pathway in the liver leads to accumulation of porphyrins and their precursors, which are then distributed throughout the body via the blood stream. Acute porphyrias, which

[10] In addition, the 250 ppm group tumor incidences were 2- to 3-fold higher than the ***mean*** historical control incidences (3.5% for adenomas and 2% for carcinomas) (Ibid.), which is the proper standard of comparison.

are triggered by various environmental agents, affect both the central and peripheral nervous systems, resulting in cramps, vomiting, severe pain in the extremities, and muscle numbness, weakness or paralysis. Muscular effects result from impairment of the nerves controlling their action. Severe attacks can lead to nerve damage (MayoClinic undated, APF undated).

A number of registrant animal studies demonstrate that trifludimoxazin treatment induced porphyrin accumulation, almost certainly the result of PPO enzyme inhibition in the liver and perhaps other tissues (EPA HHRA, pp. 44-45, 50; EPA 4/24/20, pp. 11-12), though EPA gives only scanty information about this (e.g. porphyrin levels measured, but not reported, in the rabbit developmental study, see EPA HHRA, p. 47).

In the subchronic dog study, severe nervous system effects closely resembling those seen in acute porphyrias were observed, including vomiting and a range of neurobehavioral deficits (unsteady gait, tremors, paralysis of fore- and/or hindlimbs and impaired reflexes). Severe adverse lesions to the cervical cord, thoracic and lumbar cords and brain (white matter) were also observed (EPA HHRA, pp. 16, 45). Elevated porphyrin levels in the mid and high dose animals (tissue unspecified) provide further support for trifludiomoxazin's inhibition of PPO as the mode of action for these severe nervous system effects, which occurred at the lowest dose tested (EPA HHRA, p. 45).

Independent studies on other PPO-inhibiting herbicides also corroborate this mode of action. Krijt et al. (1997) generated most of the features of variegate porphyria in mice by dosing them with either of two PPO inhibiting herbicides: oxadiazinon and oxyflurofen. Among the effects they observed were a ten-fold increase in porphyrin levels in the mouse trigeminal nerve (suggestive of the nervous system impairment and nerve damage in the subchronic dog study on trifludimoxazin), and a condition of "latent porphyria" that rendered the mice more susceptible to porphyrogenic agents such as phenobarbital.

Liver Impacts and Hepatic Cancer

Acute porphrias are caused by accumulation of toxic porphyrins and porphyrin precursors in the liver, thus it is not surprising that PPO inhibitors also have adverse liver impacts. As we have seen, trifludimoxazin induces liver tumors in mice and many other adverse hepatic effects in both rats and mice. Chronic effects in the liver included increased liver weight, foci of (eosinophilic) cellular alteration, centrilobular hypertrophy, macro vesicular fatty change and centrilobular pigment storage in male mice, and oval cell hyperplasia and (multi)focal necrosis in female mice. Chronic exposure in rats also impacted the liver, with major effects including increased pigment, multinucleated hepatocytes, and bile duct hyperplasia. (EPA 10/10/20, p. 6).

Independent studies also suggest adverse liver impacts from administration of other PPO-inhibiting substances. Krijt et al. (1999) report precancerous changes in the livers of mice treated with high doses of fomesafen. Smith and Foster (2018) review evidence pointing to an association between chemical-induced porphyria and hepatic cancer. Interestingly, patients with a wide range of porphyrias have an elevated risk (up to 100x in some studies) of hepatocellular carcinoma (HCC), the most common type of primary liver cancer. It is possible

that exposure to porphyria-inducing compounds such as trifludimoxazin could also predispose to a higher risk of HCC (Smith and Foster 2018). This highlights the need for an assessment of trifludimoxazin and other substances that share with it a common mechanism of toxicity.

Developmental Impacts

In the rabbit developmental study, fetuses of trifludimoxazin-treated pregnant does had depressed weights and also three skeletal malformations – misshapen interparietal, severely malformed vertebral column and/or rib, and small interparietal (EPA HHRA, p. 47). The findings are poorly reported, but EPA appears to dismiss them even when their incidence exceeds the upper limit of the historical control range or does not exhibit "strict dose-dependency," both excessively stringent criteria of significance.

Other PPO-inhibiting herbicides of the same chemical class as trifludimoxazin (N-phenylimides) also reveal developmental impacts. In a series of studies, Kawamura and colleagues 2014) have investigated the developmental toxicity of flumioxazin, flumipropyn and flumiclorac-pentyl, also designated S-53482, S-23121 and S-23031, respectively. They find both test animal and compound-specific differences in developmental toxicity. Further investigation of trifludimoxazin's potential developmental impacts are called for.

ENVIRONMENTAL RISKS

Terrestrial plants

Trifludimoxazin is an incredibly potent herbicide, and poses severe risks to terrestrial plants from runoff and spray drift.[11] The end use product suppresses both seedling emergence and vegetative vigor of a broad range of plants at extremely low exposure levels (for following discussion, see EPA Eco, p. 38, Tables 6-8 and 6-9). For instance, the concentrations of trifludimoxazin that reduce survival of lettuce and cabbage seedlings by 25% (IC_{25} values)[12] are just 0.00127 and 0.000857 lbs a.i./acre, respectively.

Trifludimoxazin is a still more potent inhibitor of plant growth (vegetative vigor). The concentrations that reduce growth of corn and soybeans by 25% (based on weight reduction) are vanishingly small: just 0.000193 and 0.0000438 lbs a.i./acre, respectively. The concentrations that cause 5% growth inhibition (IC_{05}) in the most sensitive monocot and dicot species are still lower: 0.0000005 (corn) and 0.0000045 lb a.i./acre (soybeans).

[11] While trifludimoxazin is not expected to exhibit much volatility based on its physical properties, EPA nevertheless plans to conduct a volatilization assessment for registration review, as noted above. Volatilization is highly dependent on environmental conditions, thus a full assessment is needed now, and should not be postponed to registration review. For instance, EPA discovered only belatedly that dicamba's volatility increases dramatically as pH declines.

[12] IC = inhibitory concentration, with the subscript denoting the percentage reduction in the designated "endpoint" or effect, which can include survival, weight, or height of the affected plants.

To put these numbers into perspective, the IC_{25} value for soybeans represents just 2 one-hundredths of a gram of trifludimoxazin distributed across an acre. The corresponding value for 5% growth inhibition is just 2 one-thousandths of a gram per acre. A second comparison is equally illuminating. Trifludimoxazin is roughly ten-fold more potent on soybeans than dicamba,[13] the herbicide whose spray and vapor drift and runoff has caused unprecedented damage across many millions of acres of soybeans the past several years. And while dicamba affects primarily broadleaf plants like soybeans, with cereal crops like corn being relatively insensitive, trifludimoxazin is extremely toxic to both plant groups.

Moreover, at least one degradate, 001, is still more toxic to certain plant species than trifludimoxazin, based on suppression of seedling emergence. Yet EPA collected no data on the ability of degradates to suppress vegetative growth, the more sensitive endpoint. Thus, even the figures above may underestimate damage to certain plant species from use of this herbicide.

EPA's estimates of the environmental concentrations of trifludimoxazin resulting from drift and runoff are one to three orders of magnitude higher than the exposure levels that cause severe injury (as discussed above) to sensitive plants (EPA Eco, p. 55, Table 11-1). Thus, it is not surprising that the Agency anticipates non-target plant damage that far exceeds its safety threshold (level of concern, or LOC) to "potentially large areas off of the field due to spray drift and runoff exposure" (EPA Eco, p. 59). Although the tests EPA reviewed involved only crops, the Agency's scientists anticipate damage to "a wide variety of other [e.g. wild] plant species both on and off the field" (Ibid., p. 60).

When a field is sprayed, spray droplets move off-field. Field edge plants receive the highest exposures, which tail off with distance. EPA provides estimates of the distances that spray drift travels at concentrations that are still sufficient to cause damage under various scenarios (e.g. application rate, ground vs. aerial application, fine vs. coarse droplet size). Aerial application generates more drift than ground application, and drift distance also increases with the amount applied. Even at the lowest modeled application rate of 0.034 lbs a.i./acre, EPA estimates that ground applications will generate spray drift that causes at least 25% growth inhibition (IC_{25}) at distances up to 468 to 643 feet from the sprayed field (EPA Eco, p. 59). Aerial applications, which generate more drift, will cause damage at distances over 1,000 feet (Ibid.). At the highest proposed label rate of 0.134 lbs a.i./acre, both ground and aerial applications result in unacceptable damage to sensitive plants at unspecified distances of more than 1,000 feet from the treated field (Ibid.).

Aquatic Plants

Trifldimoxazn also poses serious risks to aquatic plants from runoff and spray drift that reach bodies of water. At estimated environmental concentrations in surface water, the risk

[13] Dicamba's IC_{25} for soybeans (based on plant height reduction) is 0.000513 lbs a.e./acre (EPA 10/26/20, p. 49). This is an order of magnitude higher than trifludimoxazin's IC_{25}. Note that dicamba's ten-fold higher value means it takes ten-fold more to cause a 25% reduction in the pertinent endpoint relative to the more potent trifludimoxazin.

quotients for trifludimoxazin exceeded the level of concern (LOC) of 1.0 for both vascular and non-vascular aquatic plants "for all proposed uses" (EPA Eco, pp. 47-48). These findings are based on the aquatic concentrations that suppress growth of duckweed, the surrogate for aquatic vascular plants, and freshwater diatom, a surrogate species for non-vascular plants, by 50% (EPA Eco, pp. 30-32). Freshwater algae species would also be at risk (Ibid., p. 47). Finally, one of just three degradates that were tested for aquatic toxicity (M850H002) was also projected to pose risks of concern to aquatic plants in certain use scenarios (Ibid.).

Other Aquatic Organisms

Trifludimoxazin has two properties that increase the risk it poses to aquatic organisms. First, as a light-dependent peroxidizing herbicide (LDPH), its toxicity to fish and other aquatic life increases dramatically upon exposure to UV light (EPA Eco, pp. 11-12). Second, it has a moderate potential for bioaccumulation (Ibid., p. 7).

Fish exposed to trifludimoxazin for just over 30 days at low parts per billion levels exhibited reductions in weight, length and number of live larvae (EPA Eco, p. 26). Based on trifludimoxazin's status as an LDPH, EPA estimated a safety threshold of less than 1 part per billion (0.82 ug a.i./liter) for fish exposed to it in the presence of UV light, compared to subchronic toxicity thresholds (NOAECs) of just 12 and 2.7 ug a.i./liter for freshwater and saltwater fish, respectively, in the absence of UV light (EPA Eco, pp. 26-27, and Table 6-1). This suggests UV light increases the toxicity of trifludimoxazin to fish by 3 to 15-fold. As a result, EPA found that the maximum estimated 60-day concentrations of trifludimoxazin in water exceed its level of concern for fish in all exposure scenarios (EPA Eco, pp. 45-46). EPA did not collect any laboratory studies on the toxicity of the seven major degradates to fish or aquatic invertebrates, and merely assumed they would be no more toxic than the parent compound (EPA Eco, pp. 6, 15). In general, the degradates are more persistent than the parent compound, with long degradation half-lives in both soils and water, particularly under low pH (acidic) conditions (EPA Eco, p. 23). One degradate, M850H003, had a half-life of 488 days in low pH soil (EPA Eco, p. 23).

The second property that increases risk to fish is trifludimoxazin's affinity for lipids, as indicated by an octanol-water partition coefficient (K_{ow}) of 2,138 (equivalent to log K_{ow} = 3.33), which confers on it a moderate potential for bioaccumulation (EPA Eco, p. 7). In a single study on rainbow trout submitted by BASF, a bioconcentration factor of 28 to 44 L/kg lipid was determined, which means the concentration of trifludimoxazin in the lipid of rainbow trout exceeded the concentration in water by 28 to 44 times (EPA Eco, pp. 19-20). In bioconcentration tests, it is important to expose the organism to the test compound for a sufficient length of time to achieve a steady-state or equilibrium level of the compound in the organism's tissue. While the trout in BASF's study were exposed for just 14 days (EPA Eco, p. 20, ft. 4), even a 3 to 4-week exposure period is often too short to reach a steady state (Gobas 2001). In fact, for large organisms like fish, equilibrium may not be reached even over their lifetime (Wang 2016). This suggests fish exposed in real-world conditions exceeding two weeks may well accumulate more trifludimoxazin from the surrounding water than indicated by BASF's test. Another consideration is that the bioconcentration factor only accounts for uptake of trifludimoxazin from water, not from any contaminated food the fish consumes, which

requires a fuller assessment of bioaccumulation that encompasses both water and food source contamination (Wang 2016). EPA did not collect such bioaccumulation data.

MITIGATIONS

The proposed registration decision and label contain very little in the way of mandatory mitigation measures. We find no assessment of the efficacy of the few mandatory measures that are imposed, or of the advisory language, in the trifludimoxazin docket. Below we discuss mandatory measures to mitigate harm to terrestrial plants and aquatic plants, followed by an assessment of EPA's resistance management assessment and recommendations.

Drift damage to non-target plants

EPA's proposed mitigation involves label language barring ground and aerial applications when wind speeds exceed 10 mph, a maximum nozzle height of 3 feet above ground or crop canopy, and a requirement that applicators use spray nozzles that emit medium to ultra-coarse spray droplets (EPA 10/10/20, pp. 18-19, Tirexor Proposed Label). EPA provides no assessment of the efficacy of these measures, or the degree to which they will actually be followed (Ibid.). Given the long-distance drift damage threats that EPA itself concedes (discussed above), these mitigations will be entirely inadequate.

Spray drift distance increases with wind speed, nozzle height, and aerial vs. ground application. It also increases as droplet size becomes finer, since bigger droplets fall to earth more quickly, while smaller, lighter droplets are carried farther on the wind. The drift distances to damage discussed above involved, confusingly, "fine to medium/coarse" droplets for ground application (EPA Eco, p. 59, Table 11-4). Because the proposed label permits droplets as small as "medium" sized, one can expect damaging drift to occur to sensitive plants even with legal applications from hundreds to thousands of feet beyond a sprayed field. Because trifludimoxazin is largely a "contact herbicide" for which thorough coverage of target weed surfaces is critical to efficacy, growers are likely to use the smallest permissible droplet size (medium), rather than coarse or ultra-coarse droplets. As for the wind speed restriction, EPA has long known that numerous pesticide applications are made under conditions that are too windy (AAPCO 2002), yet has never to our knowledge assessed compliance with or efficacy of wind-speed restrictions at mitigating drift. Likewise, EPA permits aerial application despite drift distances to damage that are considerably greater than for ground applications at corresponding rates (EPA Eco, p. 59, Table 11-4). The 3-foot nozzle height requirement is unlikely to provide much mitigation; at least, it is a foot greater than the maximum 2-foot (24") boom height restriction on over-the-top dicamba labels, which has demonstrably failed to mitigate massive spray and vapor drift from use of these herbicides.

Regulators in other countries have appreciated the extreme plant toxicity of trifludimoxazin and in response have imposed much stronger usage restrictions to mitigate off-target terrestrial plant damage. For instance, the Australian Pesticides and Veterinary Medicines Authority (APVMA) has established the following mandatory restrictions for use of the trifludimoxazin-containing herbicide, Voraxor (APVMA 2020):

1) DO NOT apply by aircraft (permitted by EPA)

2) Spray droplets are not smaller than a COARSE spray droplet size category (EPA permits more drift-prone "medium" size droplets)

3) Mandatory downwind buffer zones of 70 to 220 meters, depending on application rate and boom height, and a downwind buffer of 325 meters when mixed with glyphosate. EPA has proposed no mandatory buffer zones whatsoever, or for specific tank mixes that might increase drift distance/damage.

Drift and runoff damage to aquatic organisms

EPA proposes next to no mandatory measures to mitigate acknowledged risks to aquatic flora and fauna from runoff and drift of trifludimoxazin to surface waters. Unlike EPA, Australian authorities have established several restrictions on use of Voraxor to mitigate harms to aquatic organisms:

4) DO NOT apply if heavy rains or storms are forecast within 3 days. (EPA has no rainfall-related restriction, despite conceding that trifludiomoxazin has a "high potential for reaching surface water via runoff for several weeks after application," and noting that runoff would be reduced if applications are avoided when rainfall is forecast within the next 48 hours. However, even this toothless advisory is undercut by a contradictory statement elsewhere on the proposed label: "Tirexor is rainfast 1 hour after application." Rainfast means not able to be washed off by rain, an incorrect and misleading statement given the clear runoff risks presented by this herbicide.)

5) DO NOT irrigate to the point of runoff for at least 3 days after application. (EPA has no irrigation-related restrictions on use of Tireoxor, aside from a prohibition against applying it to irrigation channels.)

6) DO NOT apply unless zero-till or no-till farming is practiced. (EPA has no comparable restriction, which is presumably imposed by AVPMA to reduce runoff of Voraxor associated with soil when applied to tilled fields.)

Resistance Management

Weeds resistant to PPO inhibiting herbicides have evolved very rapidly since the turn of the century, shortly after they began being introduced. Most such resistant populations have emerged in the United States since 2010 (IHRWD 2020), and are attributable to intensive use of PPO inhibitors to control glyphosate-resistant (GR) weeds. GR weeds evolved across over 120 million acres (Pucci 2018) in response to intensive use of glyphosate on glyphosate-resistant, Roundup Ready crops. The Roundup Ready crop system, in turn, was hailed in its day as the solution to weeds that had evolved resistance to ALS inhibitor herbicides in the 1980s and early 1990s. Clearly, the successive introduction of new herbicides to "solve" resistance problems generated by yesterday's "solutions," followed by additional resistance and still newer herbicides, has generated an ever-quickening treadmill of herbicide use and resistance.

Interestingly, this treadmill has been accelerated dramatically with herbicide-resistant crops systems, since the post-emergence use pattern typical of these systems promotes more rapid evolution of resistance (, giving rise to the the "transgenic treadmill." Yesterday's resistance generally does not go away, replaced by today's. Instead, resistance to different modes of action builds over time in an additive manner, explaining the explosion of weed populations resistant to three, four, five and more herbicidal modes of action.

The proposed registration of trifludimoxazin must be seen in this broader context of dramatically escalating herbicide resistance and use. While this proposed registration does not involve application to a genetically engineered crop, BASF clearly anticipates this, stating "trifludimoxazin will be an important tool or future PPO herbicide tolerant crops" (Armel et al. 2017a).

EPA, following BASF, proposes trifludimoxazin, confusedly, as a "solution" to PPO-resistant weeds as well as non-PPO-resistant weeds. The claim that trifludimoxazin will kill weeds resistant to already-approved PPO inhibitor herbicides is attributable to an unpublished presentation made by no fewer than eight BASF officers at a weed science society meeting (Armel et al. 2017a), and unpublished, un-peer-reviewed data that BASF kindly shared with EPA (Baldwin et al 2018, cited in EPA Benefits document).

We strongly urge EPA to remove from the proposed label the claim that "because of unique binding properties of Tirexor to the PPO enzyme, it still ***may*** remain an effective herbicide to control biotypes resistant to other Group 14/E herbicides." This claim has not been substantiated by independent scientists,[14] the inclusion of "may" testifies to the claim's uncertain basis, and it directly contradicts the sentence that precedes it, a fundamental principle of herbicide-resistant weed management: "Weeds resistant to Group 14/E herbicides may be effectively managed using herbicide(s) ***from a different group***" (emphasis added). Growers who read these two sentences will likely conclude that label language on herbicide-resistant weed management is worthless. Apparently, the idea of using an herbicide with mode of action B to control, or prevent evolution of resistance to, herbicide A, is not true after all, if the PPO inhibitor trifludimoxazin is a control tool for PPO inhibitor-resistant weeds. Compliance with HR weed management directions is already low; such contradictory label language in this case can only further farmers' skepticism and lead to lesser compliance.

Trifludimoxazin is not "from a different group." In fact, it belongs to the largest sub-class of PPO inhibitors, the "N-phenyl-imides," as per the recent formal classification of it by the Herbicide Resistance Action Committee (HRAC 2/12/19). Accordingly, trifludimoxazin appears together with eight other N-phenylimide PPO inhibitors in HRAC's 2020 Mode of Classification Chart (HRAC 2020), which displays structural formulas for each, revealing the close similarity in structure between members of the group (e.g. see especially flumioxazin). Structural similarity between herbicides makes it more likely that they will bind to the same target enzyme in the same way, though of course this is not an absolute law. PPO inhibitor-resistant weed populations include several that are resistant to the N-phenylimides flumiclorac-pentyl and flumioxazin (common ragweed, DE, 2005); fluthiacet-methyl (Palmer amaranth, AR, 2016); and

14

saflufenacil (Sumatran fleabane and wild poinsettia in Brazil). Label language that in any way encourages growers to treat trifludimoxazin as a solution to PPO-inhibitor resistant weeds may well serve BASF's interests in maximizing sales, but it is entirely unjustified and hazardous given the apparent lack of independent data on its precise mode of action.

And whatever the case now, new resistance mechanisms evolve very rapidly. Recent weed science literature reports a novel mutation in Palmer amaranth conferring resistance to several PPO inhibitors (Rangel et al. 2019), and waterhemp with novel resistance to the PPO inhibitor carfentrazone-ethyl that is also resistant to HPPD inhibitors (Obenland et al. 2019). The resistance in the latter population is metabolism-based, highlighting the hazard, with increasing use of multi-herbicide tank mixes, of weeds evolving resistance to several herbicides at once.

COSTS AND BENEFITS

EPA failed entirely to assess in any way the costs of the proposed registration of trifludimoxazin, in particular the environmental and economic costs of damage to plants, including crops, and to aquatic organisms due to spray drift. Instead, the Agency conducted a "benefits" assessment based entirely on a submission by BASF, the registrant, and uncritically accepts most of the claimed benefits. This is far short of the Agency's obligations under FIFRA.

REFERENCES

AAPCO (2002).

APF (undated). Variegate Porphyria (VP), American Porphyria Foundation, https://porphyriafoundation.org/for-patients/types-of-porphyria/vp/.

APVMA (2020). Evaluation of the new active trifludimoxazin in the product Voraxor herbicide. Australian Pesticides and Veterinary Medicines Authority. April 2020.

EPA (10/10/20). Proposed Registration Decision for the New Active Ingredient, Trifludimoxazin, EPA, Dec. 10, 2020. EPA-HQ-OPP-2018-0762-0017.

EPA Eco (11/30/20). Trifludimoxazin: Ecological Risk Assessment for the Proposed Section 3 New Chemical Registration. EPA, November 30, 2020. EPA-HQ-OPP-2018-0762-0013.

EPA HHRA (11/30/20). Amended: Trifludimoxazin: New Active Ingredient Human Health Risk Assessment for Registrations on Legume Vegetable Group 6, Foliage of Legume Vegetable Group 7, Citius Frnit Group 10-10, Pome Frnit Group 11-10, Tree Nut Group 14-12, Cereal Grain Group 15 (except Rice), Forage Fodder and Sti·aw of Cereal Grain Group 16 (except Rice), Peanut and Peanut Hay. EPA, Nov. 30, 2020. EPA-HQ-OPP-2018-0762-0009.

EPA 10/26/20

EPA (4/24/20). Trifludimoxazin: Report of the Cancer Assessment Review Committee, EPA, April 24, 2020. EPA-HQ-OPP-2018-0762-0008.

EPA (2005). Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F, Risk Assessment Forum, EPA, March 2005.

EPA (1998). Assessment of Thyroid Follicular Cell Tumors. EPA/630/R-97/002, EPA, March 1998.

HRAC (2020).

HRAC (2/12/19). Global HRAC MOA Classification Working Group Draft Report Version. Herbicide Resistance Action Committee, February 12, 2019.

IHRWD (2020). PPO Inhibitor Resistant Weeds

Kawamura S et al. (2014). Close Link between Protoporphyrin IX Accumulation and Developmental Toxicity Induced by N-Phenylimide Herbicides in Rats. Birth Defects Research (Part B) 101: 429-37.

Krijt J et al. (1999). Liver preneoplastic changes in mice treated with the herbicide fomesafen. Human & Experimental Toxicology 18: 338-344.

Krijt J et al. (1997). Herbicide-induced experimental variegate porphyria in mice: tissue porphyrinogen accumulation and response to porphyrogenic drugs. Can. J. Physiol. Pharmacol. 75: 1181-87.

MayoClinic (undated). Porphyria. https://www.mayoclinic.org/diseases-conditions/porphyria/symptoms-causes/syc-20356066.

McConnell EE et al. (1986). Guidelines ofr combining neoplasms for evaluation of rodent carcinogenesis studies. J. Nat'l Cancer Institute 76(2): 283-289.

Smith AG and Foster JR (2018). The association between chemical-induced porphyria and hepatic cancer. Toxicology Research 7: 647.

Wang WX (2016). Bioaccumulation and Biomonitoring. Marine Ecotoxicology 2016.