CENTER FOR FOOD SAFETY

September 13, 2021

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

RE: Docket EPA–HQ–OPP–2021–0191
Application to register new uses of difenoconazole on caneberry subgroup 13-07A, corn and peanut

Center for Food Safety appreciates the opportunity to comment on the application received by EPA to register the following new uses of the fungicide difenoconazole:

- Caneberry subgroups 13-07A (foliar)
- Corn (foliar)
- Peanut (seed treatment and foliar)

We urge EPA to deny Syngenta's application to approve these new uses, as discussed below. EPA should at least postpone any action on this application until completion of the ongoing registration review of difenoconazole, with correction of assessment deficiencies, and completion of an endangered species assessment. This is particularly advisable because granting a new use registration on America's most widely planted crop, corn, could lead to dramatic increases in the use of this fungicide – on top of already skyrocketing usage – with serious adverse impacts to human health and the environment.

While we recognize that EPA has not yet assessed these new uses, below we discuss past and current EPA assessments of difenoconazole and other information to inform this decision. We call on EPA to publish a proposed decision on this application, notify the public of the same in the Federal Register, and provide full opportunity for public comment.

Introduction

First registered by EPA in 1994, difenoconazole is a broad-spectrum fungicide registered for use on many fruits, vegetables, cereals (seed treatment), field crops as well as on golf course turf grass and ornamental plants. Difenoconazole kills fungi by blocking the synthesis of sterols, which are key components of fungal cell walls. It belongs to the demethylase inhibitor

(DMI) class of fungicides, also known as triazoles, because members of this group block sterol synthesis by inhibiting a specific enzyme – C14 demethylase.

Difenoconazole was little used for a dozen years after it was first registered. Agricultural use first registers in 2008, and has increased by 20-fold over the decade from 2008 to 2017: from 25,000 to over 500,000 lbs. per year.[1] Because the US Geological Survey data upon which these estimates are based have excluded seed treatment uses since 2015, and seed treatment of wheat is a major use of difenoconazole, actual use is likely at least 100,000 lbs/year greater.

In assessing Syngenta's application, we urge EPA to keep several facts in mind. First, because difenoconazole is one of many DMI/triazole fungicides with the same mode of action in fungi, and broadly similar effects on non-target organisms, its putative benefits and impacts must be viewed in the broader context of its class. Second, triazole use overall is dramatically increasing, and the new use on corn in particular has the potential to accelerate this rising trend. Finally, difenoconazole in particular and other members of its class are quite persistent in the environment.

Human Health Concerns and Assessment Deficiencies

Liver Endpoint and Chronic Reference Dose

The major target organ of difenoconazole and other triazoles is the liver. EPA originally classified difenoconazole as a Group C Possible Human Carcinogen in 1994, based on clear inducement of hepatic adenomas and carcinomas in a mouse study (EPA 7/27/94), then subsequently re-classified it under the descriptor Suggestive Evidence of Carcinogenicity.

In 1994, EPA established a chronic reference dose of 0.01 mg/kg/day based on hepatic hypertrophy in males in a chronic rat study (NOAEL = 0.96 mg/kg/day) (EPA 7/27/94). By 2015, EPA had retained the same chronic reference dose, based on the same rat study, but changed the endpoint from hepatic hypertrophy to cumulative decreases in body weight gains in both sexes (EPA 2/24/15). In EPA's latest human health assessment, the proposed chronic reference dose has been increased five-fold, and based on liver lesions in male mice and hepatocyte hypertrophy in both sexes of mice, with an NOAEL of 4.7 mg/kg/day (EPA 9/18/20). EPA's dismissal of hepatocyte hypertrophy in male rats and the associated NOAEL and reference dose (0.96 and 0.01 mg/kg/day, respectively) in favor of the five-fold higher mouse study endpoints is incorrect and should be reversed (see also EFSA 2011).

[1] US Geological Survey, Pesticide National Synthesis Project, Difenoconazole, Epest-High. https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2017&map=DIFENOCONAZOLE&hilo=L&disp=Difenoconazole.

Toxicity of Metabolite Unknown

EPA has identified a major metabolite of difenoconazole that is present in humans, livestock and fish – CGA-205375 – yet has practically no toxicological information on it (EPA 9/18/20). EPA should demand toxicity studies on this and other metabolites rather than rely on guesstimates based on unreliable, *in silica* structure-activity modeling.

Dermal Absorption

An *in vivo* dermal absorption study in rats found dermal absorption of 48% of the applied dose after 24 hours in rats exposed to 0.5 ug/cm^2 of difenoconazole for 6 hours (EPA 9/18/20, p. 18). Rather than use this value as the dermal absorption factor, EPA reduced it to 6% based on two *in vitro* dermal absorption tests, one with human and one with rat skin. EPA multiplied the ratio of the *in vitro* absorption results (human/rat = 0.12) by the *in vivo* rat result of 48% to arrive at a dermal absorption factor of 6%. The flaws with this approach are, first, that the relevant EPA Guidelines for the dermal penetration assay prescribe an *in vivo* rat study, and provide no support for EPA's manipulation of this figure by applying *in vitro* results (EPA 1998). Second, the in vitro human/rat ratio was derived from tests employing far higher doses than the *in vivo* study, rendering them incompatible given the large differences in absorption that were observed as a function of dermal dose (EPA 9/18/20, pp. 49-50). Finally, the test substance used in these assays was not specified, and if it is the technical active ingredient, this would likely lead to an underestimate of dermal absorption relative to use of real-world formulations with absorption-enhancing surfactants. Even use of a particular difenoconazole formulation in this test would not be predictive of absorption with other formulations.

EPA should demand full dermal absorption data for various formulations. Until then, it should conduct residential and occupational exposure assessments that incorporate dermal absorption based on a dermal absorption factor of 48% as found in EPA (1998).

Cumulative Exposure and Risk Assessment

EPA dances around the obvious necessity of a cumulative assessment of the triazole/DMI group of fungicides. Contrary to the EPA, the liver is the target organ for a large number of triazole fungicides, and many also cause adverse ocular effects. EPA should not demand that every single triazole exerts the same effect in the same way as a precondition to conducting a cumulative exposure and risk assessment. It is enough that many of them share common targets and cause similar effects (see e.g. EFSA 2009).

EPA itself recognized this in 1994, when difenoconazole was first registered. The Agency's Carcinogenicity Peer Review Committee described multiple (eight) conazoles that are both structurally related to difenoconazole ***and*** have been found to induce hepatocellular tumors, like difenoconazole (EPA 7/27/94). Clearly, there is no excuse for EPA not to perform a cumulative exposure and risk assessment of the triazole group of fungicides.

Agricultural Triazole Use Likely Breeds Resistance to Triazole Antifungal Drugs in Human Pathogens

Invasive aspergillosis is a serious and frequently fatal lung disease that mainly affects people who are immunocompromised: for instance, those recovering from tuberculosis, with pulmonary disease, or in conjunction with organ transplantation (for this discussion, see Toda et al. 2021 unless otherwise cited). The major pathogen of this disease is *Aspergillus fumigatus*, which is commonly found in the environment (e.g. decaying plant matter), has unusually high tolerance to heat, and is not known to cause plant disease. The major medications (and only ones available in oral form) used to treat this disease are triazole fungicides like itraconazole, voriconazole and posoconazole.

Over the past several decades, there has been an extremely concerning rise in invasive aspergillosis caused by *A. fumigatus* that is resistant to triazole antifungals; in such virtually untreatable infections, the mortality rate rises to 42-88%. There is a large and growing body of scientific literature demonstrating that agricultural use of triazole fungicides is one source of this growing resistance, with resistant *A. fumigatus* spores dispersed in the air from sites where triazole-treated decaying plant matter and harboring residues of the same, containing considerable populations of *A. fumigatus*, some selected for resistance.

Agricultural triazoles that most resemble, structurally, their medical counterparts are difenoconazole, bromuconazole, epoxiconazole, propiconazole and tebuconazole.

EPA must assess the potential for greatly expanded use of difenoconazole enabled by new uses on corn and other crops in this application to exacerbate the growing suffering and death toll taken by antifungal triazole-resistant *A. fumigatus.*

Environmental Concerns and Assessment Deficiencies

The new uses of difenoconazole proposed by Syngenta would also have unacceptable environmental impacts, including but not limited to threatened and endangered species. A key aspect of this fungicide's threat is its extreme persistence in the environment, which as described below EPA has not sufficiently accounted for in its environmental assessments to date. Unless otherwise noted, the following discussion is based on EPA (9/16/20).

Difenoconazole's Environmental Persistence

Difenoconazole is extremely persistent in multiple laboratory and field tests, in soil and water. It is stable to abiotic hydrolysis at pH values of 5, 7 or 9; it has a half-life of 228 days in an aqueous photolysis test; and half-lives ranging from 349-823 days in soil photolysis tests. Aerobic soil metabolism half-lives range from over 100 days to over 500 days, depending on soil type, while the anaerobic soil metabolism half-life is nearly three years (947 days). Aerobic aquatic metabolism half-lives are 300-565 days; anaerobic 433 days (EPA 9/16/20, p. 26).

Terrestrial field dissipation data also show considerable persistence, with most half-lives in various soil types, bare plot vs. vegetative cover, ranging from over 100 to 535 days (Ibid, p. 28).

It is no wonder that EPA scientists warn repeatedly of the potential for difenoconazole to accumulate in soils and water with repeat applications:

"The overall stability/persistence profile for difenoconazole suggests that it has potential to accumulate in soil and aquatic environments with each successive application" (Ibid, pp. 25-26).

Critically, EPA's exposure and risk assessments do not appear to account for the accumulation of difenoconazole over years. This is a huge data gap that in itself invalidates EPA's latest risk assessments and argues strongly against approving ANY new uses – particularly on a crop so widely grown as corn – until the Agency revisits its ecological assessments and corrects this glaring deficiency.

Risks to Terrestrial Organisms

Risk quotients exceed levels of concern for a host of different taxa. For instance, chronic risks to mammals reach risk quotients up to 5.2 from consumption of grass and other forage with difenoconazole residues. Similarly, birds are chronically threatened by both foliar applications (risk quotients up to 10.99) and via consumption of treated seeds (risk quotients up to 16.13). These risks are exacerbated by difenoconazole's persistence. EPA has identified chronic risk LOC exceedances for birds for up to 150 days after application in some scenarios, and after 56 days for mammals. Risks in some scenarios persist even when mean rather than maximum Kenaga difenoconazole residues are used in the assessment.

Honeybees are also likely threatened by difenoconazole, particularly its formulations, which are more toxic than the active ingredient alone. Acute and chronic risk quotients for larval bees, 0.99 and 1.35, exceed the respective levels of concern, 0.4 and 1.0, for one difenoconazole formulation that was tested. Additionally, difenoconazole's extreme persistence and potential for build-up in soil over a single season or years pose potential risks to ground-dwelling bees and a host of other soil-borne invertebrates that are not well-represented by the honeybee. This points up the importance of EPA expanding its required testing to include effects on soil organisms.

Risks to Aquatic Organisms

Difenoconazole also threatens aquatic organisms. EPA scientists identified risk quotients up to 22 for chronic risks to aquatic vertebrates, and noted that: "Overall, chronic LOC exceedances included crops that have some of the highest poundage of difenoconazole applied annually. ***Due to the persistence of difenoconazole, repeated use can considerably increase these risks over time."*** (EPA 9/16/20, pp. 6-7, 9, emphasis added).

Nearly all usage scenarios posed chronic risks to fish, but even so, risks are still greater than represented by these risk quotients – due to difenoconazole's persistence. EPA scientists stated this clearly: "Due to the persistence of difenoconazole in terrestrial and aquatic environments, repeated use can ***considerably increase these chronic risks*** over time." (emphasis added).

Fish and other aquatic organisms are also threatened by bioaccumulation of difenoconazole and its metabolites. EPA documented a 330x bioconcentration factor for whole fish. Over half of the applied dose was detected in the fish in the form of the metabolite, CGA-205375, for which EPA has next to no toxicity data (setting aside unreliable ECOSAR structure-activity guesstimates).

Aquatic invertebrates are likewise at risk, with chronic risk quotients up to 6.3, far exceeding the LOC of 1. As with fish, EPA's risk assessment methodologies do not appear to encompass risks arising from accumulating levels of difenoconazole over years:

"Crops for which chronic risks to aquatic invertebrates were identified included rice, ornamentals, soybeans, sugar beets, tree nuts, small vine fruits (e.g., grapes), potatoes, cabbage, tomato, apples and cucurbits. These crops encompass some of the highest difenoconazole use rates in terms of lbs a.i. applied annually (Section 3-2). ***Like fish, due to the persistence of difenoconazole, repeated use can considerably increase these risks over time***." (EPA 9/16/20, p. 55, emphasis added).

In short, it would be foolhardy and irresponsible in the extreme of EPA to consider approving new uses of difenoconazole – particularly one with potential for such an extreme increase in usage as corn – prior to correcting the deficiencies in its ecological risk assessment and completing its registration review. This requires exposure and risk assessments that account for year-on-year accumulation of difenoconazole residues, animal toxicity data on CGA-205375 (beyond a single LD_{50} assay), and cumulative assessment of the impact of multiple triazoles on non-target organisms.

<u>Threatened and Endangered Species</u>

EPA has not completed an assessment of difenoconazole for its impact on threatened and endangered species. Because there are many risks of concern to non-listed taxa, and levels of concern are in many cases lower for listed species, it is clear that listed species would be at increased risk from an approval of Syngenta's application, particularly for foliar use on corn.

Costs and Benefits

Putative benefits

Agronomists are disturbed by the dramatically increasing use of fungicides of all sorts on field crops like corn and soybeans, which began around 2007 (see Hershman et al. 2011 and Wise and Mueller 2011 for the following discussion). They note that foliar fungicide applications were extremely rare on corn and soybeans until this time; to the small extent fungicides were used, it was for seed production or specialty corn varieties, where quality demanded and higher prices justified the expenditures.

Agronomists attribute the rise in fungicide use on corn and soybeans largely to marketing drives by fungicide manufacturers, who have had success selling farmers on fungicides for dubious "plant health" reasons rather than disease; to higher corn prices beginning in 2007; and to growers' prioritization of yield potential over disease-resistance in selection of corn hybrids. There is also a troubling "insurance treatment" approach to fungicide spraying that goes fundamentally against IPM principles to use a pesticide only when needed, and only when the expenditure delivers more benefit in yield than the cost of the pesticide.

There are already a number of other fungicides, including DMI/triazole fungicides, already approved for use on corn. To the very limited circumstances in which their use might be justified, there are already sufficient control options available to growers, and no need for still another foliar fungicide for corn.

Costs

Resistance to triazole/DMI fungicides has been building steadily over years, and together with widespread resistance to strobilurin and other fungicides is a serious problem.

"For decades, scientists have watched as fungi all over the world have become incrementally more and more resistant to DMI fungicides. The use of any fungicide for 'plant health' reasons increases the risk of developing resistance." (Hershman et al. 2011).

Clearly, superfluous use of fungicides like difenoconazole – as for "plant health" reasons – must be avoided at all costs to stem or at least slow resistance development. In this respect, too, one must recall how difenoconazole and other triazoles are also likely fostering increased resistance to critical antifungal triazole medications and the associated costs in terms of human health and deaths (discussed above).

Difenoconazole's use on soybeans has risen dramatically since 2012 (essentially zero) to 2017 (about 200,000 lbs./year). This soybean use represents about half of (non-seed treatment) uses of difenoconazole, even though only roughly 2% of soybean acres are, at present, being sprayed. This usage will likely continue to rise, usually for no good reason.

The expansion of difenoconazole to corn would exacerbate an unhealthy trend of excessive and largely unnecessary triazole use in corn and soybeans (Toda et al. 2021, Toda et al. 2021 Supplemental). Critically, it would expand those acres that are sprayed with a triazole every year in corn-soybean rotations, intensifying selection pressure for resistant plant and human fungal pathogens across the Corn Belt, where just 15-20 years ago hardly anyone saw any need fungicide use on these crops. Cross-resistance among triazole herbicides is common. For instance, even the fungicide manufacturers' group Fungicide Resistance Action Committee has stated: "Generally wise to accept that cross resistance is present between DMI fungicides active against the same fungus." (FRAC 2021, p. 11).

Potential Mitigations

Currently proposed mitigations consist largely of toothless hazard advisory statements for difenoconazole labels, and are entirely inadequate to the task of reducing any of the risks of concern it poses to humans and non-human organisms, or the risks of resistance in agricultural or human pathogens.

Clearly, the costs of approving these new uses of difenoconazole (particularly on corn) far outweigh any putative and highly dubious benefits.

Conclusion

CFS urges EPA to deny Syngenta's application for new uses, particularly foliar use of difenoconazole on corn. At the very least, any decision should be postponed until correction of its assessments and completion of the registration review. It should also be postponed until EPA completes an assessment of difenoconazole's risks to listed species. Any proposed decision on these new uses should be published in the Federal Register and made available for public comment.

Sincerely,

Bill Freese, Science Director
Center for Food Safety

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