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Difenoconazole

Interim Registration Review Decision
Case Number 7014

March 2022

Approved by: _____
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Table of Contents

I. INTRODUCTION 3
A. Updates to the Proposed Interim Decision 4
B. Summary of Public Comments on the Draft Risk Assessments and Agency Responses 4
II. USE AND USAGE 12
III. SCIENTIFIC ASSESSMENTS 13
A. Human Health Risks 13
1. Risk Summary and Characterization 13
2. Human Incidents and Epidemiology 17
3. Tolerances 17
4. Human Health Data Needs 18
B. Ecological Risks 18
1. Risk Summary and Characterization 18
2. Ecological Incidents 23
3. Ecological and Environmental Fate Data Needs 24
C. Benefits Assessment 24
IV. INTERIM REGISTRATION REVIEW DECISION 25
A. Risk Mitigation and Regulatory Rationale 25
4. Updated Glove Label Language 25
5. Soil Incorporation of Treated Seed 26
6. Seed Container Label Instructions 26
7. Use Restrictions for Foliar Rice Application 28
8. Standardize Environmental Hazard Language 29
9. Fungicide Resistance Management 29
10. Advisory Spray Drift Management 30
B. Environmental Justice 31
C. Tolerance Actions 31
D. Interim Registration Review Decision 33
E. Data Requirements 35
V. NEXT STEPS AND TIMELINE 35
A. Interim Registration Review Decision 35
Implementation of Label Changes 35
VI. REFERENCES 36
Appendix A: Summary of Labeling Actions for Difenoconazole 39
Appendix B: Labeling Changes for Difenoconazole Products 40
Appendix C: Listed-Species Assessment 46
Appendix D: Endocrine Disruptor Screening Program 47

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I. INTRODUCTION

This document is the Environmental Protection Agency's (EPA or the Agency) Interim Registration Review Decision (ID) for difenoconazole (PC Code 128847, case 7014). In a registration review decision under the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA), the Agency determines whether a pesticide continues to meet FIFRA's registration standard.[1] Where appropriate, the Agency may issue an interim registration review decision before completing a registration review.[2] Among other things, the interim registration review decision may determine that new risk mitigation measures are necessary, lay out interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review.[3] For more information on difenoconazole, see EPA's public docket (EPA-HQ-OPP-2015-0401) at www.regulations.gov.

FIFRA[4] mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. In 2006, the Agency began implementing the registration review program. EPA will review each registered pesticide every 15 years. Through the registration review program, the Agency intends to verify that all registered pesticides continue to meet the registration standard as the ability to assess and reduce risk evolves and as policies and practices change. By periodically re-evaluating pesticides as science, public policy, and pesticide-use practices change, the Agency ensures that the public can continue to use products in the marketplace that do not present unreasonable adverse effects. For more information on the registration review program, see http://www.epa.gov/pesticide-reevaluation.

The EPA is issuing an ID for difenoconazole so that it can (1) move forward with aspects of the registration review that are complete and (2) implement interim risk mitigation (see Appendices A and B). EPA is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (the Services) to improve the consultation process for national threatened and endangered (listed) species for pesticides under the Endangered Species Act (ESA).[5] The Agency has not yet fully evaluated difenoconazole's risks to federally listed species. However, EPA will complete its federally listed-species assessment and any necessary consultation with the Services before completing the difenoconazole registration review. Before completing registration review, EPA will also complete endocrine screening for difenoconazole under the Federal Food, Drug, and Cosmetic Act (FFDCA).[6]

Difenoconazole is a systemic triazole fungicide registered for foliar applications to numerous field crops, landscape ornamentals, golf course turf, and as a seed treatment for cereal crops, canola, cotton, and potato seed pieces. It is also registered for post-harvest use on various

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[1] Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) § 3(g), 7 U.S.C. § 136a(g); 40 C.F.R. § 155.57.
[2] 40 C.F.R. §§ 155.56, 155.58.
[3] 40 C.F.R. § 155.56.
[4] As amended by the Food Quality Protection Act (FQPA) of 1996, Pub. L. No. 104-170, 110 Stat. 1489.
[5] Endangered Species Act (ESA) § 7, 16 U.S.C. § 1536.
[6] Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), 21 U.S.C. § 346a(p).

tuberous and corm vegetables and pome fruits. Because it was registered after November 1984, difenoconazole was not subject to reregistration under FIFRA § 4(a).

This document is organized into five sections: *Introduction*, which includes this summary and a summary of public comments and EPA's responses; *Use and Usage*, which describes how and where difenoconazole is used and summarizes data on its use; *Scientific Assessments*, which summarizes EPA's risk and benefits assessments, and provides broader context with a discussion of risk characterization; *Interim Registration Review Decision*, which describes the mitigation measures to address risks of concern and the regulatory rationale for EPA's ID; and, lastly, *Next Steps and Timeline* for completion of this registration review.

A. Updates to the Proposed Interim Decision

In July 2021, EPA published the PID for difenoconazole. The Agency has made several changes to the PID in this ID. These changes include updating the water advisory to be more consistent with environmental hazard language in the Label Review Manual[7] as well as updating the labeling for seed treatments for clarity to be consistent with current fungicide seed treatment labeling. The PID proposed a dye statement for difenoconazole products that allow commercial seed treatment. The Agency has determined that a dye statement is not necessary because tolerances exist for residues of difenoconazole on treated seeds. According to 40 CFR 153.155(a) and explained the Label Review Manual,[8] the dye requirement does not apply if appropriate tolerances have been established under FFDCA for residues. The Agency has also streamlined the Personal Protective Equipment (PPE) labeling for seed treatment products to add clarity.

The revised labeling does not materially impact the instructions for users and should have no impacts on users. The Agency is also streamlining the personal protective equipment labeling proposed in the PID. See Section IV and Appendix B of this document for the revised labeling.

EPA has not updated the draft Human Health Risk Assessment and the draft Ecological Risk Assessment. This ID finalizes the Agency's draft supporting documents *Difenoconazole: Draft Human Health Risk Assessment for Registration Review* and the *Difenoconazole: Draft Ecological Risk Assessment for Registration Review*, which are available in EPA's public docket (EPA-HQ-OPP-2015-0401).

B. Summary of Difenoconazole Registration Review

On January 11, 2016, the Agency formally initiated registration review for difenoconazole with the opening of the registration review docket for the case.[9] The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of difenoconazole:

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[7] See Chapter 8: Environmental Hazards section of the Label Review Manual at: https://www.epa.gov/sites/default/files/2015-03/documents/chap-08-sep-2012.pdf
[8] See Chapter 18: Unique Product Labeling section of the Label Review Manual at: https://www.epa.gov/sites/production/files/2014-06/documents/chap-18_0.pdf
[9] 40 CFR § 155.50

- January 2016 – EPA posted the *Difenoconazole Preliminary Work Plan Registration Review: Initial Docket Case Number 7014* (PWP) (December 21, 2015),the *Difenoconazole: Human Health Risk Scoping Document in Support of Registration Review* (October 1, 2015), the *Difenoconazole: Preliminary Problem Formulation for Environmental Fate, Ecological Risk, Endangered Species, and Drinking Water Exposure Assessments in Support of Registration Review* (November 5, 2015), and other supporting documents to the public docket for a 60-day public comment period.

- June 2016 – EPA posted the *Difenoconazole Final Work Plan* (FWP) (June 13, 2016) to the public docket. The Agency received five comments on the PWP. The comments did not result in changes to the registration review timeline or data needs as described in the FWP.

- January 2017 – EPA issued a generic data call-in (GDCI) for difenoconazole to obtain data needed to conduct the registration review risk assessments (GDCI-128847-1602). All data were submitted and reviewed. All data requirements have been fulfilled and the DCI is satisfied.

- November 2020 – EPA posted *Difenoconazole. Draft Human Health Risk Assessment for Registration Review* (September 18, 2020) and *Difenoconazole: Draft Ecological Risk Assessment for Registration Review* (September 16, 2020) for a 60-day public comment period. The Agency received comments from 6 commenters. The comments did not change the risk assessments or registration review timeline for difenoconazole.

- June 2021 – EPA completed the PID for difenoconazole and posted it to the public docket for a 60-day public comment period. The Agency received comments from 6 commenters. The comments did not change the risk assessments or registration review timeline for difenoconazole. However, comments did result in minor clarification changes to the labeling. Comments and responses to comments are summarized in section I.C below.

- March 2022 – EPA has completed the ID for difenoconazole and will post it to the public docket. Along with the ID, EPA will post the following documents to the public docket:
    - *Difenoconazole: EFED Response to Comments on the Proposed Interim Registration Review Decision (PID)* (November 30, 2021)
    - *Difenoconazole. Response to Comments on the Proposed Interim Decision* (March 10, 2022)

C. Summary of Public Comments on the Proposed Interim Registration Review Decision and Agency Responses

During the 60-day public-comment period for the difenoconazole Proposed Interim Registration Review Decision (which opened on August 3, 2021 and closed on October 2, 2021), the Agency

received six public comments. Comments were submitted by the United States Department of Agriculture (USDA), the Center for Food Safety (CFS), Syngenta Crop Protection, LLC (Syngenta), the Northwest Horticultural Council (NHC), the National Potato Council, and the American Soybean Association (ASA). The Agency has summarized and responded to all substantive comments and comments of a broader regulatory nature below. More detailed responses to comments can be found in the *Difenoconazole: EFED Response to Comments on the Proposed Interim Registration Review Decision (PID)* and the *Difenoconazole. Response to Comments on the Proposed Interim Decision*, which responds to comments relating to the human health risk assessment. Both are available on the public docket. The Agency thanks all commenters for participating and has considered all comments in developing this ID.

Comments Submitted by the Center for Food Safety (Docket ID: EPA-HQ-OPP-2015-0401-0053 to 0057)

Comments pertaining to the ecological risk assessment:

Center for Food Safety (CFS) submitted several comments related to environmental fate and ecological effects outlined in the Agency's ecological risk assessment. CFS mentioned that difenoconazole is extremely persistent in laboratory and field tests and is found in both water and soil. There is concern that EPA's exposure and risk assessments do not account for the accumulation of difenoconazole over a single season, or years.

CFS noted concern that the presented risks to terrestrial organisms do not capture the potential effect of difenoconazole on different taxa, specifically related to risk quotient (RQ) exceedances and difenoconazole's propensity to persist in the environment. It was stated that there are likely effects on ground-dwelling bees which was not adequately described in the Agency's risk assessment.

CFS stated that given the persistence of difenoconazole in terrestrial and aquatic environments repeated use can increase risks to aquatic organisms and increase the risks over time. CFS commented that difenoconazole can lead to bioaccumulation in fish and other aquatic organisms.

EPA Response: EPA considered the comment related to the persistence of difenoconazole in soil and water. The exposure modeling of aquatic environments is based on a collection of environmental fate properties as well as site-related input parameters. Additionally, variations in meteorological measurements were used to probabilistically estimate concentrations of difenoconazole in aquatic environments. These three things accounted for the accumulation of difenoconazole over a year and over multiple years.

The Agency's assessments rely on a surrogate species approach where a few tested species are used to represent sensitivity for all species. It is assumed that if honey bee data suggest level of concern (LOC) exceedances, then there is a risk concern for other bees, including ground-dwelling bees. When additional data are available for other terrestrial invertebrates, such as non-*Apis* bees, earthworms, and other soil dwelling invertebrates, that information is included in risk assessment as an additional line of evidence. For difenoconazole, no soil dwelling terrestrial invertebrate toxicity data are available, so refinement is not possible.

EPA acknowledges the risk for aquatic organisms and identified LOC exceedances for fish and aquatic invertebrates and disagrees with the comment that the Agency is not considering accumulation of difenoconazole over a year, or over multiple years. See the *Difenoconazole: EFED Response to Comments on the Proposed Interim Registration Review Decision (PID)* for more information.

Comments pertaining to the human health risk assessment:

CFS also submitted several comments related to the human health risk conclusions outlined in the Agency's human health risk assessment.

In 1994, the chronic reference dose EPA used was 0.01 mg/kg/day based on hepatocellular hypertrophy in male rats (MRID 42090019). In 2015, the chronic reference dose was retained, but the endpoint was changed to cumulative decreases in body weight gains. In the most recent 2020 human health risk assessment, the chronic reference dose was increased five-fold to 0.05 mg/kg/day and was based on a mouse instead of a rat study (MRID 42090015). CFS stated that EPA dismissed hepatocellular hypertrophy in male rats and that the current chronic reference dose value used for human health risk assessment is incorrect and should be reversed.

CFS noted that EPA originally classified difenoconazole as a Group C "Possible Human Carcinogen" in 1994, based on inducement of hepatocellular adenomas and carcinomas in a mouse study. In the 2020 human health risk assessment, EPA re-classified difenoconazole under the descriptor "Suggestive Evidence of Carcinogenicity." CFS suggested that the cancer classification should be reversed.

CFS asserted that a major metabolite of difenoconazole has been identified (CGA-205375) as present in humans, fish, and livestock. No toxicity data exists for the metabolite and CFS requested that EPA require that toxicity data be submitted.

Additionally, CFS asked EPA to require full dermal absorption data for various difenoconazole formulations and requested that the Agency conduct exposure assessments that incorporate a dermal absorption factor of 48% based on an older risk assessments, rather than the 6% dermal absorption factor derived from the dermal triple-pack approach.

CFS stated that triazole fungicides meet the criteria for designation as a common mechanism group and should have a cumulative assessment completed. CFS asserted that there are two endpoints, shared by most triazoles, that should be the focus of a cumulative risk assessment: fatty changes and carcinogenicity.

EPA Response: CFS correctly stated that the 2020 difenoconazole draft human health risk assessment used the no-observed adverse-effect level (NOAEL) from the mouse carcinogenicity study (4.7 mg/kg/day, from MRID 42090015) to derive a chronic population-adjusted dose (cPAD). That NOAEL is based on increased incidence of liver lesions (individual cell necrosis and bile stasis in males, hepatocyte hypertrophy in both sexes), and increased serum levels of serum sorbitol dehydrogenase (SDH) in males at a lowest-observed adverse-effect level

(LOAEL) of 46 mg/kg/day. Older risk assessments used a NOAEL from a combined rat chronic toxicity/carcinogenicity study (0.96 mg/kg/day, from MRID 42090019) to derive the cPAD, based on cumulative decreases in body weight gains. However, the difenoconazole toxicology database underwent extensive review for registration review in late 2020, and most studies were updated to reflect current toxicology evaluation practices. Changes in study LOAELs at that time prompted changes to the points of departure (PODs) selected for risk assessment. During the 2020 review, it was established that the rat combined chronic toxicity/carcinogenicity study determined the lowest-observed effect level (LOEL), not the lowest-observed adverse-effect level (LOAEL). Current Agency policy is to use only adverse effects, which are indicated by a LOAEL, not a LOEL, as a basis for risk assessment. The mouse study had a lower LOAEL than the rat study and was, therefore, selected to derive the cPAD.

EPA originally classified difenoconazole as a Group C Possible Human Carcinogen in 1994, based on clear inducement of hepatocellular adenomas and carcinomas in a mouse study. In 2007, in accordance with EPA's 2005 *Guidelines for Carcinogen Risk Assessment*,[10] the Agency subsequently re-classified it under the descriptor Suggestive Evidence of Carcinogenicity based on liver tumors in male and female mice. This classification is consistent with current Agency guidelines. The reference dose would address the concern for chronic toxicity, including carcinogenicity, likely to result in exposure to difenoconazole.

EPA has reviewed the data that indicated a major metabolite of difenoconazole that has been identified (CGA-205375) as a residue of concern in humans, fish, and livestock. EPA uses structure-activity-relationship (SAR) analyses, as appropriate, to support decisions on residues of concern in situations where empirical data are lacking, and/or, to trigger the need for additional toxicology studies. In the case of difenoconazole, the SAR analysis of the metabolites using DEREK v.12 did not indicate any concerns for toxic effects that were not observed in the available difenoconazole toxicity database.

A dermal penetration study is conditionally required in the Code of Federal Regulations (CFR) Title 40 – Part §158.500, however, EPA has the flexibility to establish or modify data needs for individual pesticides and may require submission of additional data beyond what is specified. The dermal penetration study (guideline 870.7600) must be followed for *in vivo* studies in rodents, but it does not preclude use of other kinds of studies to derive a dermal absorption factor (DAF), such as *in vitro* skin absorption studies, or studies from the public scientific literature, or studies conducted under special protocols. Use of the triple pack approach is supported by EPA to refine dermal penetration results by accounting for differences between *in vitro* and *in vivo* absorption within a test species as well as species differences between animal and human skin. For registration review, the Agency used a DAF of 6% for human health risk assessment. The highest *in vivo* rat absorption from the available *in vivo* rat study was multiplied by the highest ratio of human vs. rat absorption from the available *in vitro* studies using technical difenoconazole.

The resulting DAF was considered a conservative estimate of absorption by human skin for difenoconazole at the time it was derived; however, the triple pack should be applied when

[10] https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

similar protocols are utilized across the *in vitro* and *in vivo* studies, including the same test substance and similar dosing. Therefore, the DAF for difenoconazole has been reevaluated and based on all the available data and current practices, EPA has concluded that a DAF of 8% should be applied for difenoconazole moving forward. The updated DAF of 8% is similar to the previous DAF of 6% that was applied in the 2020 human health risk assessment and, therefore, this change does not materially impact the human health risk assessment.

The triazole fungicides share the following common metabolites: 1,2,4-Triazole (1,2,4-T), triazole alanine (TA), and triazole acetic acid (TAA). In 2006, the Agency issued aggregate human health risk assessments for 1,2,4-T and the conjugated metabolites of 1,2,4-T, TA and TAA. The assessment was based on sufficient data to support a risk assessment for these metabolites. The Agency conducted two assessments: one for 1,2,4-T and one for combined exposure to TA and TAA. Both assessments are highly conservative, using the maximum combination of uncertainty factors and high-end estimates of both dietary and non-dietary exposures. In addition, the 2006 aggregate assessments retained a 10X database uncertainty factor to account for the data gaps associated with the toxicological database and were designed to be extremely conservative so that the assumptions will remain valid for anticipated registrations. The Agency has not received any new data following the 2006 assessments, however; several requests for new uses of triazole fungicides have been submitted to the Agency and have been evaluated with the same conservatisms that were in place for the 2006 aggregate risk assessments. EPA does not believe that exposure or risk has been underestimated through these risk assessment approaches. The Agency will continue to employ a protective screening approach for all actions involving the triazoles and will continue to evaluate the need for additional data.

The Agency has not assumed that difenoconazole has a common mechanism of toxicity with other substances at this time. The Agency will use the *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis*[11] to determine if the available toxicological data for difenoconazole suggest that a candidate common mechanism group may be established with other pesticides. If a common mechanism group is established, a screening-level analysis may be conducted to provide an initial screen for multiple pesticide exposure.

See the *Difenoconazole. Response to Comments on the Proposed Interim Decision* for more information.

Comments pertaining to fungicide resistance:

CFS noted that the triazole fungicides are the dominant compounds used to treat crops, animals, and humans and are the only class used in both medicine and agriculture. Triazoles used in human medicine include compounds such as itraconazole, voriconazole, and posoconazole. CFS noted concern regarding the development of resistance because the drivers of resistance in plant and human pathogens share some similarities. CFS expresses concern that the widespread use of triazole fungicides in agriculture may contribute to the development of fungal resistance to

[11] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework

medical-use triazole drugs. CFS requested that the Agency assess the public health threats posed by continued and expanding use of difenoconazole and other agricultural triazoles in terms of increasing resistance of human fungal pathogens such as *A. fumigatus* and *C. auris* to medical antifungal compounds.

EPA Response: EPA is aware of increases in the total agricultural usage of both difenoconazole between 2015-2019 and triazoles more generally. EPA is also aware of increased global incidence of triazole-resistant human fungal pathogens. The extent to which the continued use of triazole fungicides to control plant pathogens in agricultural production may contribute to the emergence of antifungal resistant human pathogens is unclear and a direct association between the quantity of U.S. agricultural triazole fungicide use and human fungal infections has not been established.[12] EPA is working with federal partners to assess the potential impact of increased plant agriculture fungicide (e.g., difenoconazole) use in the U.S. on the development of triazole-resistance in medical settings. The Agency considers it critical that a variety of mode of action (MOA) groups remain available for use in the interest of suppressing resistance development to both agricultural and public health pathogens. For more information, see Section IV of this document and PRN 2017-1 and PRN 2017-2, available at https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year.

Comments Submitted by the United States Department of Agriculture (Docket ID: EPA-HQ-OPP-2015-0401

Comment: The United States Department of Agriculture (USDA) emphasized the importance of difenoconazole as a tool in specialty crop production, particularly to control certain fungal pests in almond, ginseng, guava, papaya, and parsley production. USDA noted that another key benefit of difenoconazole is its compatibility with other fungicides, which can broaden the spectrum of disease control and manage the development of resistance. USDA supports the re-registration of difenoconazole but is concerned about the withdrawal of EPA's previous recommendations to harmonize U.S. tolerances with Codex maximum residue limits (MRLs) for green onion, rapeseed, and wild rice. USDA stressed the importance of international harmonization and has requested that EPA reconsider this proposal.

EPA Response: The EPA thanks the USDA for its comments and will take them into consideration. Regarding the potential for additional harmonization with Codex MRLs, EPA attempts to harmonize existing U.S. tolerances with Codex MRLs where feasible. However, harmonization is not possible in some cases due to a difference in tolerance expression (*e.g.*, a difference in metabolites covered), a difference in commodity definition (*e.g.*, livestock meat versus livestock fat), or a difference in use pattern (*e.g.*, in season versus post-harvest). In addition, EPA does not routinely harmonize U.S. tolerances for pesticide residues in/on livestock feed commodities with Codex MRLs.

For green onion, rapeseed, and wild rice, the Agency originally proposed to harmonize with Codex, however Syngenta subsequently submitted confidential business information (CBI) with rationales for retaining the green onion/rapeseed tolerances and a preference for the wild rice

[12] https://www.cdc.gov/fungal/diseases/aspergillosis/antifungal-resistant.htm

tolerance. The human health risk assessment tolerance table contained an error: there is no Codex MRL for wild rice but there a Canadian MRL for wild rice. Anticipated tolerance revisions for difenoconazole are detailed in Section IV.C of this document. Tolerance amendments follow a notice and comment process separate from registration review and the Agency will consider any relevant comments submitted at that time, including USDA's comment. Any proposed tolerance changes will be announced in the *Federal Register* and will be subject to public comment prior to being finalized.

Comments Submitted by Syngenta (Docket ID: EPA-HQ-OPP-2015-0401)

Comment: Syngenta noted that the proposed drift/runoff, surface water advisory, and terrestrial use hazard statement should not be under the Directions for Use section of the label, but rather be placed under the Environmental Hazards section. Syngenta proposes that the drift and runoff statement ("Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas") and the surface water advisory should not be added to the seed treatment labels because the advisory is intended for applications made to crops and not seed. Seed treatment product labels already have this text, which Syngenta argues is adequate: "This product is toxic to fish, shrimp, and other aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present, or to intertidal areas below the mean high-water mark. Do not contaminate water when disposing of equipment washwater or rinsate."

Furthermore, Syngenta suggested using a streamlined personal protective equipment (PPE) statement on the seed tag and in the Directions of Use section of the seed treatment product labels: "Wear long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves when loading or otherwise handling treated seed and when covering or collecting treated seeds spilled during loading and planting."

EPA Response: EPA thanks Syngenta for their comments on the difenoconazole PID and agrees that the noted advisory and hazard statements belong under the Environmental Hazards section of the label. Commercial seed treatments are likely to occur indoors, and environmental hazard statements intended for outdoor terrestrial uses would not apply. However, on-farm seed treatments can occur outdoors with portable treaters that can be used in the field, and on-farm seed treatment labels need to reflect any drift/runoff, surface water advisory, and terrestrial use environmental hazard statements specified for outdoor terrestrial uses as noted in Chapter 8 of the Label Review Manual. The Agency has clarified the label table (Appendix B) to note the types of uses affected for the drift/runoff, surface water advisory, and terrestrial use environmental hazard statements.

The Agency does not object to the proposed PPE statement, however, the gloves text needs to be updated to reflect the appropriate chemical-resistant glove types to use (*e.g.*, barrier laminate, butyl rubber, nitrile rubber, neoprene rubber, polyvinyl chloride, or viton) in accordance with Chapter 10 of the Label Review Manual. The revised PPE statement is as follows:

"When loading/pouring the treated seed/seed-pieces or covering/collecting spilled seed during loading and planting, wear long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves [list specific glove types].

See Appendix B for the revised labeling, clarification on affected uses, and revised label placement.

Comments Submitted by Northwest Horticultural Council, National Potato Council, and American Soybean Association (Docket IDs: EPA-HQ-OPP-2015-0401-0051, -0052, and -003)

Comment: The Northwest Horticultural Council (NHC), the National Potato Council (NPC), and the American Soybean Council (ASC) submitted comments in support of the re-registration of difenoconazole. They stressed the importance of difenoconazole as an integral component of several fungicide combination products to control fungal diseases on specialty crops and promote effective resistance management. In addition, NHC and NPC indicated that adopting the label changes for difenoconazole are reasonable.

EPA Response: EPA thanks the Northwest Horticultural Council, the National Potato Council, and the American Soybean Association for their comments. The benefits of difenoconazole have been considered in developing this Interim Decision, see Section III.C of this document for a summary of the Agency's benefits analysis.

II. USE AND USAGE

Difenoconazole is a broad-spectrum systemic triazole fungicide first registered for use in the United States in 1994. Difenoconazole is registered for use as a foliar application to various fruit, nut, vegetable, and field crops as well as a seed treatment for a number of crops. Commodity postharvest applications including dip treatments and spray drenches registered for pome fruits (apple and pears) and tuberous and corm vegetables (such as arracacha, arrowroot, cassava, sweet potato, and yam). Seed treatment uses are also registered for barley, canola, sweet corn, cotton, oats, potatoes, rye, triticale, and wheat.[13]

Agricultural Usage

Seed treatment uses of difenoconazole have been registered for almost 30 years, but foliar uses were first registered in 2008. Usage for foliar uses is still increasing in some cases. For years 2015-2019, the annual average of foliar difenoconazole usage was 400,000 pounds of active ingredient (lbs. a.i.) on 3.7 million total acres treated.[14] Recent usage data for seed treatments and postharvest applications are not available; these usage estimates are not provided because reliable data sources are not available at present.

In terms of total acres treated and pounds of active ingredient applied, between 2015-2019 difenoconazole foliar usage was largely driven by soybeans with an annual average of 1,800,000

[13] United States Environmental Protection Agency (EPA). Biological and Economic Analysis Branch (BEAD). Science Information and Analysis Branch (SIAB). 2019. Difenoconazole (PC Code: 128847) Pesticide Label Use Summary (PLUS) Line by Line Report dated: 30/09/2019.
[14] Kynetec USA, Inc. 2020. "The AgroTrak® Study from Kynetec USA, Inc." Microsoft Access Database. Database Subset: 2015-2019. [Accessed April 2021].

total acres treated with an average of 200,000 lbs difenoconazole applied to soybeans, although this represents only 2 percent of the crop treated (PCT) for soybean. The leading crops in terms of PCT were tomatoes (45%), almonds (30%), sugar beets (30%), apples (30%), wine grapes (25%), and potatoes (15%). Although a significant percent crop treated of table grapes (30%) and watermelon (20%) were treated with difenoconazole, the total acres treated, and total pounds applied were relatively small in comparison to other sites. The average application rate across all crops was 0.1 lbs. ai/acre.[15]

Non-agricultural Usage

Difenoconazole is also registered for non-agricultural use on established ornamentals in landscaped areas, including recreational parks, institutional sites, roses, golf courses and residential properties treated by commercial and non-professional (*i.e.,* homeowner) applicators. These uses are surveyed but no recent usage has been reported, implying low or infrequent usage of difenoconazole.[16]

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

A summary of the Agency's human health risk assessment is presented below. The Agency used the most current science policies and risk assessment methodologies available at the time to prepare a risk assessment in support of the registration review of difenoconazole. For additional details on the human health and drinking water assessments for difenoconazole, see the *Difenoconazole: Draft Human Health Risk Assessment for Registration Review,* and other supporting documents, which are available in the public docket.

1. Risk Summary and Characterization

Dietary Assessment

The Agency assessed exposure to difenoconazole in food and drinking water from the registered uses, since it may be applied directly to growing crops and application may result in difenoconazole reaching surface and ground water sources of drinking water. The acute dietary analysis assumed tolerance-level residues and 100% crop treated values for all registered crops. The chronic dietary analysis assumed tolerance-level residues and average percent crop treated information for some commodities.

Acute dietary risk estimates are not of concern at the 95th percentile of the exposure distribution for all population subgroups. Acute risk estimates for the general U.S. population equaled 17% of the acute population adjusted dose (aPAD), where risk estimates below 100% are not of

[15] Kynetec USA, Inc. 2020. "The AgroTrak® Study from Kynetec USA, Inc." iMap Software. Database Subset: 2015-2019. [Accessed April 2021].
[16] United States Environmental Protection Agency (EPA). Biological and Economic Analysis Branch (BEAD). Science Information and Analysis Branch (SIAB). 2019. Difenoconazole (PC Code: 128847) Summary Use and Usage Matrix dated: 28/08/2019.

concern. The most highly exposed population subgroup was all infants <1 year old which equaled 53% of the aPAD and not of concern.

Similarly, chronic risk estimates are not of concern. Chronic dietary risk estimates equaled 11% of the chronic population adjusted dose (cPAD) for the general U.S. population, where risk estimates below 100% are not of concern. The most highly exposed population subgroup was all infants less than 1 years old at 38% of the cPAD and not of concern.

Dietary Assessment—Triazole Metabolites

Difenoconazole belongs in the triazole group of fungicides, and triazole metabolites common to the group, 1,2,4-triazole (1,2,4-T), triazolylalanine (TA), and triazolylacetic acid (TAA) are residues of concern which are considered toxicologically different from difenoconazole and were assessed separately from the parent compound. Acute dietary risk estimates for the triazole metabolites ranged from 20% to 70% of the aPAD and were not of concern (where risk estimates below 100% are not of concern). Chronic dietary risk estimates for the metabolites ranged from 11% to 86% of the cPAD and were also not of concern.

Cancer Classification

In accordance with EPA's 2005 Guidelines for Carcinogenic Risk Assessment, difenoconazole was re-classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors in male and female mice. Difenoconazole is not genotoxic and there is no evidence of carcinogenicity in rats. Quantification of cancer risk was not required. The current reference dose (RfD) for chronic dietary exposure assessment would address the concern for chronic toxicity, including carcinogenicity, likely to result from exposure to difenoconazole.

Residential Assessment

There are registered uses on commercial and residential landscapes and interior plantscapes, as well as turf applications to golf courses, that would result in residential handler and post-application exposures.

There are no residential handler inhalation risks of concern. Inhalation exposures result in margins of exposures (MOEs) ranging from 3,200,000 to 340,000,000, where the LOC is 100 and risk estimates below 100 are of concern.

A quantitative residential post-application assessment was not performed because a dermal endpoint was not identified due to the lack of adverse effects attributable to a single dose. Because the use around the home is limited to ornamentals (not turf), the Agency has concluded that homeowner use of difenoconazole would not result in incidental oral exposure to children.

Aggregate Assessment

There are no aggregate (dietary + residential) risks of concern. The Agency evaluated acute, short-term, and chronic aggregate exposure. Because no acute or chronic dietary risks of concern were identified, there are no risks of concern for acute and chronic aggregate exposures.

Short-term aggregate risk was estimated by combining chronic dietary exposure (food + water) with the residential handler inhalation exposures from applications to gardens/ornamentals via hose-end sprayer. The resulting risk estimate is an MOE of 5,000 which is not of concern (LOC=100, risk estimates below 100 are potentially of concern).

No intermediate-term aggregate exposure scenarios were identified; therefore, a quantitative intermediate-term aggregate assessment was not required.

A separate cancer aggregate assessment was not required because the chronic dietary exposure assessment is adequately protective of carcinogenicity from exposure to difenoconazole.

Aggregate Assessment of Free Triazole & its Conjugates

Application of triazole-containing pesticides, such as difenoconazole, also result in exposure to free triazole and its conjugates, which are considered toxicologically different from difenoconazole and are assessed separately from the parent compound. The aggregate MOE's range from 1,700 – 12,000 (LOC = 1,000) and, therefore, are not of concern.

Non-occupational Spray Drift Assessment

A quantitative spray drift assessment for difenoconazole was performed for incidental oral exposure to children 1 to 2 years old, the highest exposed population subgroup. Risk estimates were not of concern using difenoconazole-specific turf transferable residue (TTR) data and the highest registered application rates (0.126 lb ai/A - 0.427 lb ai/A) from the assessed occupational handler scenarios and equipment combinations. MOEs ranged from 94,000 to 420,000 at the field edge and were not of concern (LOC=100, MOEs below 100 are potentially of concern).

A dermal point of departure (POD) was not selected due to the lack of an adverse effect attributable to a single dose, so a quantitative dermal assessment was not performed.

Non-occupational Bystander Post-Application Assessment

The Agency considered volatilization as a source of post-application inhalation exposure to individual near application sites. The Agency sought expert advice on issues related to volatilization of pesticides in a FIFRA Science Advisory Panel meeting in December 2009 and received the SAP's final report in March 2010.[17] The Agency developed a volatilization screening tool and a subsequent volatilization screening analysis.[18] EPA will utilize this analysis during registration review to determine if data or further analysis is required for difenoconazole.

[17] https://www.regulations.gov/document/EPA-HQ-OPP-2009-0687-0037
[18] https://www.regulations.gov/docket/EPA-HQ-OPP-2014-0219

Cumulative Assessment

EPA has not made a common mechanism of toxicity finding as to difenoconazole and any other substances. Although the triazole fungicides produce common metabolites, these metabolites do not contribute to the toxicity of the parent difenoconazole. The Agency assessed aggregate risk from the metabolites separately and did not find risks of concern. Difenoconazole does not appear to produce any other toxic metabolite produced by other substances.

Occupational Handler Assessment

The Agency assessed risk to occupational handlers who may be exposed while mixing, loading, and applying difenoconazole. No dermal endpoint was selected because the database does not show systemic effects after exposure from the dermal route at doses that would be relevant to risk assessment, so occupational handler dermal risk assessments were not conducted. Occupational handler inhalation risk estimates range from 4,300 to 45,000,000 for agricultural crop uses and were not of concern (LOC=100, MOEs below 100 are potentially of concern). For seed treatment use, risk estimates range from 11,000 to 1,100,000 and were not of concern (LOC=100, MOEs below 100 are potentially of concern). For post-harvest use, MOEs range from 77,000 to 320,000 and were not of concern (LOC=100, MOEs below 100 are potentially of concern).

Occupational Post-Application Assessment

Dermal Post-Application Risk

A quantitative post-application dermal assessment was not completed because a dermal endpoint was not identified due to the lack of adverse effects attributable to dermal exposure. The potential for post-application exposure following the planting of treated seeds was considered unlikely because sustained levels of contact with treated seed after planting would not be expected.

Restricted Entry Interval

Difenoconazole is classified as Toxicity Category III for acute dermal and oral exposures, inhalation exposures, and acute dermal toxicity and eye irritation. It is classified as Toxicity Category IV for skin irritation potential, and it is not a skin sensitizer. Under 40 CFR 156.208(c)(2) (iii), active ingredients classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour restricted-entry interval (REI). This REI is adequate to protect agricultural workers where post-application exposures to difenoconazole are expected to occur. For products that contain difenoconazole and inert ingredients or other active ingredients, longer REIs may be required.

Inhalation Post-Application Risk

A quantitative inhalation post-application exposure assessment was not performed for workers re-entering treated fields. Handler exposure resulting from application of pesticides outdoors is

likely to result in higher exposure than post-application exposure. Since occupational handler inhalation risk estimates were not of concern for field applications, occupational post-application inhalation risk estimates are also not of concern.

A post-application inhalation exposure assessment was not required for the seed treatment uses of difenoconazole, as exposure is expected to be negligible. A post-application inhalation exposure assessment for the post-harvest uses of difenoconazole was conducted to assess risk from activities such as sorting and packing treated commodities and MOEs ranged from 990,000 to 22,000,000, which are not of concern with baseline attire composed of long-sleeved shirt, long pants, shoes, and socks (LOC=100, MOEs below 100 are potentially of concern).

2. Human Incidents and Epidemiology

On July 15, 2020, EPA reviewed difenoconazole incidents reported to both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases. For the Main IDS from January 1, 2015 to June 9, 2020, there were seven incidents reported that involved difenoconazole. All difenoconazole incidents reported involved multiple active ingredients. One incident was classified as minor severity and six incidents were classified as moderate severity. For Aggregate IDS for the same time period, there were three minor severity incidents reported that involved difenoconazole. A query of SENSOR-Pesticides from 1998-2015 identified nine cases that involved difenoconazole. Of these difenoconazole cases, eight involved multiple active ingredients and one case involved difenoconazole as a single active ingredient. All nine cases were occupational and were classified as low severity. Difenoconazole is not included in the Agricultural Health Study (AHS), a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes, and represents a collaborative effort between the U.S. National Cancer Institute, the National Institute of Environmental Health Sciences, the Centers for Disease Control's National Institute of Occupational Safety and Health, and the U.S. EPA.

For more detail on incidents, please refer to *Difenoconazole: Tier I Update Review of Human Incidents and Epidemiology for Draft Risk Assessment*, available on the docket at https://www.regulations.gov/document/EPA-HQ-OPP-2015-0401-0020. The frequency and severity of the difenoconazole incidents are consistent with the conclusions drawn from the empirical data. The Agency intends to conduct ongoing human incident monitoring for difenoconazole and will conduct additional analyses if necessary.

3. Tolerances

Tolerances for difenoconazole are established in 40 CFR §180.475. EPA is anticipating several commodity definition revisions and some tolerance level changes consistent with OECD rounding class practice or to harmonize with established Codex and Canadian MRLs. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes. For more detail, see Section 2.C., below.

4. Human Health Data Needs

The human health database for difenoconazole is complete. The Agency does not anticipate any further human health data needs for difenoconazole.

B. Ecological Risks

The Agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of difenoconazole.[19] For additional details on the 2020 ERA, see *Difenoconazole: Draft Ecological Risk Assessment for Registration Review* in EPA's public docket (EPA-HQ-OPP-2015-0401).

The EPA is currently working with its federal partners and other stakeholders to improve the consultation process for federally-listed species and their designated critical habitats. The Agency has not yet fully evaluated difenoconazole's risks to listed species. However, EPA will complete its listed-species assessment and any necessary consultation with the Services before completing the difenoconazole registration review. See Appendix C for more details. As such, potential risks for non-listed species only are described below.

1. Risk Summary and Characterization

The Agency uses a deterministic approach/risk quotient method to estimate risk to non-target taxa based on the current registered uses of difenoconazole, the available ecotoxicity data, and the environmental fate properties. The risk estimates (Risk Quotients, or RQs) are compared to the EPA's Levels of Concern (LOC). Potential risk was identified when RQs are greater than the LOC. For scenarios in which RQs could not be calculated (*e.g.,* when endpoints are nondefinitive), EPA compared the estimated environmental concentrations (EECs) of difenoconazole with the appropriate toxicological endpoint. For birds and mammals, the acute and chronic LOCs are 0.5 and 1.0 respectively; for plants the LOC is 1.0. For bees, the acute and chronic LOCs are 0.4 and 1.0, respectively.

As established in the Overview document[20], the Agency's risk assessments for all taxa rely on a surrogate species approach where one or a few tested species are used to represent the potential sensitivity for all species of a taxon. For example, fish serve as the surrogates for aquatic-phase amphibians and reptiles, daphnia and mysids serve as surrogates for aquatic invertebrates, birds as surrogates for terrestrial phase amphibians and reptiles, the laboratory rat is a surrogate for mammals, and honey bees may serve as surrogates for terrestrial invertebrates. If toxicity data

[19] The 2020 ERA only addresses potential risks to species not listed under the Endangered Species Act. EPA is working with its federal partners and other stakeholders to implement a Revised Method (EPA-HQ-OPP-2019-0185-0054) for assessing potential risk to listed species and their designated critical habitats. The Agency will complete difenoconazole's listed-species assessment once EPA has fully implemented the scientific methods necessary to complete listed species' risk assessments. For more details, see Appendix C.

[20] USEPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs; January 23, 2004. Environmental Fate and Effects Division. Office of Pesticide Programs. U.S. Environmental Protection Agency. Available at https://www.epa.gov/sites/production/files/2014-11/documents/ecorisk-overview.pdf)

are available in the open literature (*i.e.,* on amphibians), these data may be used instead of data on the surrogate species.

Given the uses of difenoconazole, the available ecotoxicity data, and environmental fate properties, there are potential risks of concern for fish (from chronic exposure), aquatic invertebrates (from acute and/or chronic exposure), birds (from chronic exposure), and mammals (from chronic exposure). Risks are considered low for honey bees, aquatic plants, and terrestrial plants, despite minor LOC exceedances for honey bees and aquatic plants.

Terrestrial Risks

Mammals

Foliar Applications

No acute risks of concern were identified for mammals for any registered uses of difenoconazole. Acute dose-based endpoints did not exceed mammalian non-listed species LOCs at the maximum single application rate of difenoconazole (RQs < 0.07). Subacute dietary toxicity data were not available for mammals; therefore, risks from this route of exposure could not be evaluated.

Chronic risks of concern for mammals were identified from foliar applications and seed treatment uses. The chronic endpoint for mammals was derived from a 2-generation reproduction study in rats. The most sensitive endpoint (no observable adverse effect concentration [NOAEC]=250 mg a.i./kg-diet; lowest observable adverse effect concentration [LOAEC]=2,500 mg a.i./kg-diet) was based on a decrease (≥ 10%) in body weight observed in parental females and first-generation males and females and decreased pup weight that progressed over time (6-8% at birth to 29-33% at weaning).

On a chronic basis, no dietary-based risks of concern were identified (RQs ranged from 0.004-0.96). Risks of concern were identified on a dose-basis only. Dose-based risk estimates account for the fact that different sized animals need to consume different proportions of food relative to body size. For a single application, there were risks of concern at the maximum single application rate for non-agricultural uses (turf, 0.43 lbs a.i./A) for small mammals consuming short and tall grass and broadleaf plants/small insects, and medium and large mammals consuming short grass (RQs ranged from 0.01-2.2, LOC=1). No chronic LOC exceedances were reported for single applications on agricultural use sites.

For multiple applications, at the lowest single application rate (pome fruit, 0.0684 lbs a.i./A x 3 applications x 14-day application interval), risks of concern were identified for small and medium-sized mammals consuming short grass only (RQs ranged from <0.01-1.4, LOC=1). For multiple applications at the maximum agricultural application rate (citrus, 0.125 lbs a.i./A x 4 applications x 7-day application interval), risks of concern were identified for small and medium mammals consuming short grass and broadleaf plants/small insects (RQs ranged from 0.01-2.1, LOC=1). For multiple applications at the maximum overall application rate for non-agricultural applications (turf, 0.43 lbs a.i./A x 3 applications x 14-day application interval), there were risks

of concern for small, medium and large mammals consuming short grass, tall grass, broadleaf plants/small insects and arthropods (RQs ranged from 0.03-5.2, LOC=1). Additional lines of evidence for chronic risks to mammals include: 1) LOC exceedances using mean estimates of dietary consumption for multiple applications, and 2) for single applications, dose-based LOC exceedances occurred 0-41 days after application and, for multiple applications, 0 to >56 days after application.

Seed Treatments

Chronic risks of concern were identified for mammals ingesting difenoconazole-treated seeds (all seed treatment application rates except seed potato) (RQs up to 1.7, LOC=1). The number of seeds (except seed potato) required to reach the mammalian chronic LOC for seed treatment uses based on the NOAEC ranged from 11 (small mammals consuming corn seed) to 12,893 seeds (large mammals consuming rapeseeds). Chronic exposure from difenoconazole seed treatment has some inherit uncertainties in that actual ingestion depends on the number of seeds available at the ground surface and how closely they are planted to each other. Once seeds are planted at depth (*e.g.,* potato chunks), the main exposure route would be limited to spillage. The actual difenoconazole exposure is additionally dependent on foraging behavior, seed size, and timing of consumption.

Off-Field Risks

Risks of concern to mammals from spray drift extends up to 3.3 feet from the edge of the field from the use site (the "effects distance," based on applications to turf at 0.43 lbs a.i./A x 3 applications x 14-day application interval: using fine to medium droplet sizes for aerial and ground applications). In general, applications with larger droplet sizes and lower boom heights have lower effects distances; aerial applications generally have greater drift potential than ground applications.

Birds (Surrogates for Reptiles, and Terrestrial-Phase Amphibians)

No acute risks of concern were identified for birds for the any registered use of difenoconazole. Acute oral dose-based exposure RQs were not calculated for birds, since definitive endpoints are not available. No avian mortalities were reported at concentrations tested in acute oral studies in canary and mallard ducks; LD_{50} values (lethal dose which caused death in 50% of the test animals) were greater than 2,000 mg a.i./kg body weight (bw). Based on EECs for a single application at the maximum application rate, there was no evidence that residues exceeded the tested concentrations. On a subacute dietary basis, RQs (<0.01-0.06) did not exceed the acute risk LOC (0.5). Overall, there were no risks of concern on a subacute dietary and acute dose basis for birds.

Chronic risks of concern were identified for birds from foliar application and seed treatment uses. The most sensitive chronic endpoint (NOAEC=21.8 mg a.i./kg-diet; LOAEC=108 mg a.i./kg-diet) for birds was selected from a study with bobwhite quail, in which a 4% reduction in hatchling body weight was observed.

On-field Chronic Risks from Foliar Applications

Overall, chronic dietary risks of concern were identified for birds for both single and multiple applications of difenoconazole. For single applications, chronic dietary-based RQs (0.09-4.7) exceeded the LOC of 1.0 for birds for applications to turf (birds foraging on short grass, tall grass, broadleaf plants/small insects and arthropods) and citrus (short grass only). There were no LOC exceedances for single applications to pome fruits (minimum application rate). For multiple applications, chronic dietary-based RQs (0.18-11) exceeded the LOC for applications to pome fruits, citrus and turf for all foraging groups (with the exception of fruits/pods and seeds). Additional evidence for potential chronic risk to birds included: 1) exceedances at the mean estimates of dietary consumption (RQs up to 3.9), 2) exceedances at the LOAEC for multiple applications to turf resulted in exceedances of the LOC (chronic RQs up to 2.2), and 3) exposure estimates exceeded the LOC for up to 80 days for single applications and up to 150 days for multiple applications.

Chronic Risks from Seed Treatments

Chronic risks of concern to birds from difenoconazole-treated seeds were identified for all seed treatment uses (RQs 1.1-16). The number of seeds required to reach the avian chronic LOC for seed treatment uses based on the NOAEC ranged from 4 (small birds consuming barley seed) to 2,166 seeds (large birds consuming rapeseeds). Despite an estimated consumption of only 1-3 potato seeds necessary to exceed the LOC (large birds), potatoes are planted at depth (4-8 inches) and any surface-available seed pieces would most likely be due to potential spillage. RQs also exceeded chronic LOCs at the avian LOAEC (108 mg a.i./kg-diet) for all labeled uses except potatoes.

Off-Field Risks

Risks of concern to birds from spray drift extends up to 29.5 feet from the application site (single application at 0.125 lbs a.i./A to turf; assuming fine to medium droplets with aerial application).

Terrestrial Invertebrates

Difenoconazole is registered for foliar application use on a suite of crops that are pollinator-attractive (*e.g.*, tree nuts, ornamentals, citrus, and fruiting vegetables) including several that require the use of managed pollinators. To understand the risks posed by pesticides, EPA relies on data about honey bees as a surrogate for terrestrial invertebrate species. Despite its use on pollinator-attractive crops, based on the available data and representative exposure scenarios, EPA has concluded that difenoconazole uses do not present risks of concern to honey bees.

Difenoconazole is absorbed by leaves and is then distributed within plant tissue by translaminar movement. Acute and chronic Tier I data on technical grade active ingredient (TGAI) difenoconazole are available for adult honey bees; however, for larval honey bees only chronic toxicity data are available. Two additional chronic toxicity studies were conducted on honey bee adults and larvae using a typical end-use product (TEP) of difenoconazole. For adult honey bees, there were no acute or chronic risks of concern at both the minimum and maximum

difenoconazole application rates for TEP- and TGAI-based endpoints. No larval acute toxicity data are available for TGAI; however, the 8-day LD_{50} from the 22-day larval chronic study is approximately 10 times greater than the estimated maximum dietary dose and, therefore, results in an RQ which is below the acute risk LOC of 0.4 and is not of concern. For the TEP data, acute RQs for larvae are of concern (RQs up to 0.99; LOC=0.4). On a chronic exposure basis for larval bees, there are no risks of concern for the TGAI-based NOAEC; however, for TEP-based endpoints, there are LOC exceedances (RQ=1.35; LOC=0.4) at the maximum difenoconazole application rate.

Honey bee larvae may be exposed to the TEP following applications made during bloom and when pollen and nectar resources are collected soon after application and fed directly to larvae. It is assumed that this is not a common exposure scenario, when considering the likely timing of difenoconazole applications relative to bloom and that adult bees are likely to process nectar and pollen prior to feeding to bees. Since the proportion of the components of the formulation are expected to change by the time difenoconazole reaches larvae, it is assumed that the TGAI toxicity data are more representative of the exposure larvae will encounter. Therefore, risks to honey bee larvae are considered low. Given the lack of acute or chronic risks of concern for difenoconazole based on Tier I data and current registered uses, additional higher-tier toxicity and/or exposure data are not needed at this time.

Terrestrial Plants

There are no risks of concern for terrestrial plants.

Aquatic Risks

Difenoconazole is persistent in terrestrial and aquatic environments. The Agency has concluded that repeated use of difenoconazole can increase chronic risks significantly over time.

Freshwater and Estuarine/Marine Fish (Surrogates for Aquatic-Phase Amphibians)

Difenoconazole has similar acute toxicity to both freshwater and estuarine/marine fish. There were no acute risk concerns identified for fish (RQs $\leq$ 0.14, acute LOC=0.5). Due to the lack of available chronic toxicity studies on the most acutely sensitive freshwater fish species (rainbow trout), chronic fish endpoints were estimated using an ACR (acute to chronic ratio). Chronic risks to freshwater fish were identified at the ACR-based NOAEC (0.86 µg a.i./L; (RQs ranged from 0.7-22.2, chronic LOC=1). Additional evidence for potential chronic risks of concern included LOC exceedances based on empirical data for the less sensitive fish species (fathead minnow; NOAEC=1.9 µg a.i./L and LOAEC=3.7 µg a.i./L based on a 5% reduction in male length in F0 generation post-hatch) at both the NOAEC (RQs ranged from 0.4 to 16) and LOAEC (RQs ranged from 0.2-8.1). No empirical data were available for estuarine/marine fish; however, the ACR estimated-NOAEC for estuarine/marine fish was identical to freshwater fish; therefore, both RQs and risk conclusions were the same.

Freshwater and Estuarine/Marine Invertebrates

Risks of concern for water column invertebrates were estimated using the most sensitive acute and chronic endpoints for freshwater invertebrates (daphnid acute LC_{50}=770 µg a.i./L; chronic daphnid NOAEC = 5.6 µg a.i./L) and estuarine/marine invertebrates (acute mysid LC_{50} = 150 µg a.i./L and chronic mysid NOAEC= 4.8 µg a.i./L) respectively. There are no acute risks of concern associated with the terrestrial uses of difenoconazole for freshwater water-column aquatic invertebrates (RQs ranged from <0.01-0.14; acute LOC =0.5). However, for estuarine/marine water-column invertebrates there was an acute risk LOC exceedance identified for rice applications (RQ=0.74; acute LOC = 0.5).

Chronic risks of concern were identified for aquatic invertebrates. Chronic RQs based on the NOAEC for both freshwater and estuarine/marine invertebrates exceeded the LOC of 1.0 Chronic RQs for freshwater invertebrates ranged from 0.12-5.4, with the rice use at the high-end of that range. In addition, chronic risks of concern were identified for freshwater invertebrates for a suite of uses including potatoes, cabbage, peppers, cucumbers, citrus, tomatoes, melon, grapes, nurseries and turf. There were chronic risk LOC exceedances for the scenarios with the highest EECs (*i.e.,* potatoes, rice and grapes). For estuarine/marine invertebrates in the water column, RQs followed the same pattern, with rice at the high-end (RQs ranged from 0.12-6.3, chronic LOC=1). Chronic risks of concern were identified for estuarine/marine invertebrates for the aforementioned crop groups and apples. There were limited LOC exceedances at the LOAECs for aquatic invertebrates in the water column for those scenarios with the highest EECs (including rice, potatoes, grapes, and cherries) with RQs ranging up to 3.0.

Chronic endpoints for benthic invertebrates were based on reductions in the number of offspring (up to a 47% reduction). For benthic invertebrates, there were no sediment-based exposures resulting in risks of concern (RQs ranged from <0.01- 0.8; LOC = 1.0). Risks of concern for freshwater benthic invertebrates from pore water exposure were identified for a subset of uses including potatoes, tomatoes, cherries, grapes, and rice (RQs ranged from 0.08-1.9; LOC=1). There were no risks of concern identified for estuarine/marine benthic invertebrates.

Aquatic Vascular and Non-Vascular Plants

No risks of concern were identified for aquatic non-vascular plants for terrestrial agricultural and non-agricultural uses (RQs ranged from < 0.01-0.15; LOC=1.0). However, RQs for the semi-aquatic agricultural use on rice (with the exception of rice in Mississippi) exceeded the LOC (rice RQs ranged from 0.78-1.1). Overall, risk to non-vascular plants is considered low.

No toxicity studies were available for vascular aquatic plants with difenoconazole TGAI. Therefore, risks to vascular aquatic plants remain uncertain. Given the generally low risks for non-vascular aquatic plants and terrestrial plants, it is likely that there is a low-risk potential to aquatic vascular plants.

2. Ecological Incidents

The Incident Data System (IDS) and the Agency's Aggregated Incidents Reports database were reviewed for difenoconazole incidents on May 19, 2020. The search excluded incidents classified as "unlikely" or "unrelated" and only included incidents with the certainty categories of

"possible" and "probable." Overall, there were 4 possible incidents, 4 unlikely incidents, and one that was unclassified. Three incidents are reported in IDS for damage (necrotic browning and death) to wine grapes in New York, all with a certainty of "possible" for difenoconazole as a causal agent. Two of the three incidents involved application of a fungicide containing both mandipropamid and difenoconazole and the other incident involved a fungicide containing difenoconazole and cyprodinil.

In addition to the incidents recorded in IDS, additional incidents are reported to the Agency in aggregated form. For difenoconazole, there were 10 minor plant incidents associated with a fungicide containing mandipropamid and difenoconazole and one minor plant incident associated with a fungicide containing azoxystrobin and difenoconazole. A single aggregate minor wildlife incident was reported and was associated with a formulation containing sedaxane, difenoconazole, fludioxonil, mefenoxam, and thiamethoxam. The frequency and severity of the difenoconazole incidents are consistent with the conclusions drawn from the laboratory data. The Agency intends to conduct ongoing ecological incident monitoring for difenoconazole.

3. Ecological and Environmental Fate Data Needs

Both the environmental fate and ecological effects datasets are considered complete. Given the lack of acute or chronic risks of concern to honey bees from difenoconazole based on Tier I data and current registered uses, the Agency does not plan to require additional honey bee higher-tier toxicity and/or exposure data at this time.

C. Benefits Assessment

Difenoconazole is a systemic fungicide with protective, curative, and eradicative properties against plant diseases (FRAC, 2021). Preventative properties inhibit fungal spore germination and establishment of fungal pest infection whereas curative and eradicative properties kill fungal pathogens that have already infected plant tissues.

Foliar Applications to Agricultural Crops

Difenoconazole foliar applications on soybean control leaf frogeye spot and *Cercospora* spot (Kynetec, 2020). On almonds, difenoconazole is used for controlling brown blossom rot, blossom blight, shot hole, anthracnose (Kynetec, 2020, Gemperle *et al.*, 2018; Adaskaveg *et al.*, 2017); and on sugar beet, difenoconazole co-formulated with propiconazole has excellent activity against *Cercospora* leaf spot and powdery mildew (Kynetec, 2020; Tedford *et al.*, 2011).

Difenoconazole also is used for controlling early blight disease on potato, scab disease and powdery mildew on apple, and various fungal pests on crops such as cucumber, grapes, pumpkin, squash, tomato, and watermelon.

Post-Harvest Use

Difenoconazole is used for post-harvest treatments of apples and pears for fungal pests such as blue mold caused and gray mold causing fruit rot during storage (Amiri, 2021). Infected fruits

may cause reductions in marketable yields of apple and pears if fruits are not treated with difenoconazole.

Seed Treatment

Difenoconazole provides broad-spectrum and systemic control of important seed and soil-borne diseases of many crops. Prior to planting, small grain seeds (barley, oats, rye, triticale and wheat) and other crop seeds (such as cotton, potato, canola, corn) are treated with difenoconazole to control seed and soil-borne fungal pests (such as *Fusarium* spp., *Tilletia tritici*, *Ustilago* spp., *Urocystis* spp.) (Smiley *et al.*, 2002). Seed potatoes also are treated with difenoconazole for controlling soil-borne fungal diseases (Johnson, 2019).

Ornamentals and Turf

On roses and other ornamentals (such as gerbera, ranunculus, petunia, and hydrangea), difenoconazole is used to control powdery mildew (Minuto *et al.*, 2018; Kumar, 2018). On turf, difenoconazole is used against multiple fungal pests (such as *Rhizoctonia* spp., *Sclerotinia homoeocarpa*, *Bipolaris* spp., *Lycoperdon* spp., *Agrocybe pediades*, *Bovistra plumbea*, *Puccinia* spp., *Erysiphe graminis*) (Clarke, 2020; Syngenta, 2018). Fungal pests can reduce yields and quality and decrease aesthetic value of ornamentals and turf.

IV. INTERIM REGISTRATION REVIEW DECISION

A. Risk Mitigation and Regulatory Rationale

The Agency has reviewed the risks, benefits, and uses of difenoconazole in formulating its decision. As discussed in Section II of this document, no human health risks of concern have been identified for difenoconazole when used as directed on current labels. Difenoconazole poses potential ecological risks of concern from its labeled uses. EPA identified potential risks of concern to mammals, birds, terrestrial invertebrates, freshwater and estuarine/marine fish, and aquatic invertebrates.

While no risks of concern have been identified for occupational handlers, the Agency is requiring that labels of difenoconazole products that already require the use of gloves be amended to specify the appropriate glove type. The Agency is adding soil incorporation instructions for treated seeds and new labeling for treated seed containers to prevent the ingestion of treated seeds by nontarget organisms. The Agency is also adding use restrictions for foliar rice applications in order to prevent potential exposure to aquatic organisms. Additionally, the Agency is also implementing consistent advisory spray drift management and pesticide resistance management labeling and updated advisory and environmental hazard language aimed at reducing the potential exposure of difenoconazole in the environment.

4. Updated Glove Label Language

The Agency is updating the glove statements currently on labels that already require the use of gloves by handlers, to be consistent with the Label Review Manual. In particular, EPA is removing any references to specific categories in EPA's chemical-resistance category selection chart and specifying the appropriate types of gloves.[21] This clarification does not fundamentally change the personal protective equipment (PPE) that workers currently must use, and therefore should impose no impacts on users.

5. Soil Incorporation of Treated Seed

The Agency identified potential chronic avian and mammalian risks of concern from ingestion of difenoconazole-treated seeds. Birds and mammals may have increased access to treated seeds on the soil surface relative to seed that is covered or incorporated into the soil. Most seed treatment products containing difenoconazole are co-formulated with other pesticides that require that seeds be planted at depth. Currently, some labels of seed treatment products for barley, canola, cotton, oats, potato, rye, sweet corn, wheat, and triticale in which difenoconazole is the only active ingredient do not require soil incorporation of treated seeds. The Agency is adding soil-incorporation instructions for all difenoconazole-treated seed products, and other measures to reduce access to spilled seed.

The Agency has determined it is necessary that difenoconazole-treated seed be planted to specific depths depending on seed type to remove the need for workers to follow the default REI after treated seeds are planted and to reduce potential exposure to non-target birds and mammals. The depth of planting for each seed type is consistent with established agronomic practice and is not expected to impose new impacts on users. The REI and the WPS exceptions will remain on the product labels.

- For canola and rapeseed crop subgroup 20A (borage, crambe, cuphea, echium, flax seed, gold of pleasure, hare's ear mustard, lesquerella, lunaria, meadowfoam, milkweed, mustard seed, oil radish, poppy seed, rapeseed, sesame, and sweet rocket): Treated seed must be planted into the soil at a depth of at least ½ inch.
- For cotton, small grain cereals (barley, oats, rye, triticale, and wheat), and sweet corn: Treated seed must be planted into the soil at a depth of at least 1 inch.
- For potato: Treated seed must be planted into the soil at a depth of at least 2 inches.

6. Seed Treatment Label Instructions

In addition to the soil incorporation instructions above, the Agency is standardizing seed treatment label instructions to include a number of elements designed to:

- identify the pesticide used to treat the seed and clarify the rate at which the seed has been treated,
- limit access to or potential contamination from the treated seed,
- implement PPE when handling treated seed, and
- address the disposition of spilled and excess seed and waste from the planting process.

[21] For specific label language, see Appendix B.

The new seed treatment labeling is consistent with good management practices and is not expected to impart economic impacts on users.

On-Farm Treated Seed that are Not Sold or Distributed

The new seed treatment labeling is as follows for pesticide products intended to be used on-farm to treat seeds:

- "Store treated seed away from food and feedstuffs.
- Do not allow children, pets, or livestock to have access to treated seeds.
- When loading/pouring the treated seed/seed-pieces or covering/collecting spilled seed during loading and planting, wear long-sleeved shirt, long pants, shoes, socks, and chemical resistant gloves [list specific glove types].
- Treated seeds exposed on the soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting (such as in row ends).
- Dispose of all excess treated seed by burying seed away from bodies of water.
- Do not contaminate bodies of water when disposing of planting equipment wash water.
- Plant treated seed into the soil to the recommended minimum depth or greater to minimize exposure.
- DO NOT plant treated seed by broadcasting to the soil surface. Ensure that all planted seeds are thoroughly incorporated by the planter during planting, additional incorporation may be required to thoroughly cover exposed seeds.
- Dispose of seed packaging or containers in accordance with local requirements."

Commercial Seed Treatments and On-Farm Treated Seeds that are Distributed or Sold

The Agency has determined it is necessary that labels of products containing difenoconazole that are registered for commercial seed treatment or on-farm treated seeds that are distributed or sold are required to add comporting statements directing seed treatment facilities to include the following language on containers of treated seed:

"Seed treated with [PRODUCT NAME] must be labeled in accordance with all applicable requirements of the Federal Seed Act. All bags containing treated seed must be labeled or tagged as follows. Any seed treated with difenoconazole that is sold or distributed without these statements is an unregistered pesticide, in violation of FIFRA section 12."

"The Federal Seed Act requires that bags containing treated seeds shall be labeled with the following statement(s):

- This seed has been treated with (insert name of active ingredient of pesticide).
- Do not use for food, feed or oil purposes."

"The U.S. Environmental Protection Agency requires that bags containing treated seeds shall be labeled with the following statements:

- This seed has been treated with [INSERT PRODUCT NAME(s), EPA REG. NO(s)), a [INSERT CHEMICAL TYPE(S)] containing [INSERT ACTIVE INGREDIENT(S)].
- This seed is treated with [number] lbs of difenoconazole per 100 lbs of seed.
- Do not use treated seed for feed, food, or oil purposes.
- Store treated seed away from food and feedstuffs.
- Do not allow children, pets, or livestock to have access to treated seeds.
- When loading/pouring the treated seed/seed-pieces or covering/collecting spilled seed during loading and planting, wear long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves [list specific glove types].
- Treated seeds exposed on the soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting (such as in row ends).
- Dispose of all excess treated seed by burying seed away from bodies of water.
- Do not contaminate bodies of water when disposing of planting equipment wash water.
- Plant treated seed into the soil to the recommended minimum depth or greater to minimize exposure.
- Do not plant treated seed by broadcasting to the soil surface. Ensure that all planted seeds are thoroughly incorporated by the planter during planting, additional incorporation may be required to thoroughly cover exposed seeds.
- Dispose of seed packaging or containers in accordance with local requirements.
- Excess treated seed may be used for ethanol production it (1) by-products are not used for livestock feed and (2) no measurable residues of pesticide remain in ethanol by-products that are used in agronomic practice."

"All other requirements regarding the use of the treated seed, which include, but are not limited to, instructions relating to endangered species protection, environmental hazard statements, maximum use rates, plant back intervals, personal protective equipment, and storage and disposal statements, remain and must be listed on the bag tag."

7. Use Restrictions for Foliar Rice Application

In order to address potential chronic risks to aquatic organisms, the Agency is adding use restrictions for foliar rice applications to flooded fields by adding the following instructions on product labels:

- "Do not treat fields simultaneously used for aquaculture of fish or crustaceans.
- Do not drain water from treated rice fields into ponds used for aquaculture of fish and crustaceans.
- Do not use water drained from treated fields to irrigate other crops.
- Do not allow release of irrigation or flood water for at least 7 days after the last application.
- Do not apply when weather conditions favor drift from treated areas to non-target aquatic habitat."

These restrictions are consistent with good management practices and are not expected to impose economic impacts on users.

8. Standardize Environmental Hazard Language

The Agency is updating and standardizing existing environmental hazard warnings to be consistent across all product labels and to warn users of potential exposure and risk to aquatic organisms. The Agency is requiring that the following statements be included on all product labels under the Environmental Hazard section:

> *Drift and Runoff Warning:*
> "Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas."
>
> *Terrestrial Use Environmental Hazard Statement:*
> "Do not apply directly to water or to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when disposing of equipment washwater or rinsate."

The Agency is adding the following surface water advisory on all agricultural product labels under the Environmental Hazard section:

> "This product may impact surface water quality due to runoff of rain water. This is especially true for poorly draining soils and soils with shallow groundwater. This product is classified as having a high potential for reaching surface water via runoff for several months or more after application.
>
> A level, well-maintained vegetative buffer strip between areas to which this product is applied and surface water features such as ponds, streams, and springs will reduce the potential loading of difenoconazole from runoff water and sediment. Runoff of this product will be reduced by avoiding applications when rainfall or irrigation is expected to occur within 48 hours. Sound erosion control practices will reduce this product's potential to reach aquatic sediment via runoff."

The Agency is adding the following statement on all non-agricultural product labels under the Environmental Hazard section:

> "This product may impact surface water quality due to runoff of rain water. This is especially true for poorly draining soils and soils with shallow groundwater. This product is classified as having a high potential for reaching surface water via runoff for several months or more after application."

These updates are advisory and are not expected to impose economic impacts on users.

9. Fungicide Resistance Management

The Agency is implementing resistance-management language to difenoconazole labels[22] to address fungicide resistance.[23] Fungicide resistance occurs when genetic or behavioral changes enable a portion of a pest population to tolerate or survive what would otherwise be lethal doses of a given pesticide. The development of such resistance is influenced by a number of factors. One important factor is the repeated use of pesticides with the same mode (or mechanism) of action. This practice kills sensitive pest individuals but allows less susceptible ones in the targeted population to survive and reproduce, thus increasing in numbers. These individuals will eventually be unaffected by the repeated pesticide applications and may become a substantial portion of the pest population. An alternative approach, recommended by resistance management experts as part of integrated pest management (IPM) programs, is to use pesticides with different chemical modes (or mechanisms) of action against the same target pest population. This approach may delay and/or prevent the development of resistance to a particular mode (or mechanism) of action without resorting to increased rates and frequency of application, possibly prolonging the useful life of pesticides. EPA is adding resistance-management labeling, as listed in Appendix B, for products containing difenoconazole, in order to provide pesticide users with easy access to important information to help maintain the effectiveness of useful pesticides. Additional information on EPA's guidance for resistance management can be found at the following website: https://www.epa.gov/pesticide-registration/prn-2017-1-guidance-pesticide-registrants-pesticide-resistance-management. Adding this language will provide pesticide users with easy access to important information on maintaining the effectiveness of pesticides—including difenoconazole—thereby preserving the benefits of difenoconazole and other useful pesticides.[24]

The measures are consistent with best management practices and are not expected to impose economic impacts on users.

10. Advisory Spray Drift Management

The Agency is adding advisory spray drift management labeling to reduce off-target spray drift and establish a baseline level of protection against spray drift that is consistent across all difenoconazole products.[25] Reducing spray drift will reduce the extent of environmental exposure and risk to non-target plants and animals.

These updates are advisory and are not expected to impose economic impacts on users.

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[22] For specific label language, see Appendix B.

[23] Pesticide resistance is the ability of portions of a pest population to tolerate or survive otherwise lethal doses of a pesticide through genetic or behavioral changes. EPA considers increased pesticide resistance an adverse effect that can drive increased use of pesticides. For more details, see PRN 2017-1 and PRN 2017-2, available at https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year.

[24] For a detailed discussion of difenoconazole's benefits, see Section III.C, above.

[25] Reducing spray drift will decrease environmental exposure and risk to nontarget organisms. Although EPA is not making a listed species finding at this time, these label changes are expected to reduce the extent of exposure and may reduce risk to listed species whose range and/or critical habitat co-occur with the use of difenoconazole. For specific label language, see Appendix B.

B. Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. Throughout the registration review process, EPA has sought to include all communities and persons across the Nation, including minority, low-income, and indigenous populations who may be disproportionately overburdened by the use of difenoconazole.

One community which may experience disproportionate exposure to pesticides is agricultural farmworkers. EPA has conducted assessments of risks to farmworkers who handle difenoconazole or may be exposed to difenoconazole when working in treated fields and have found no risks of concern. EPA has also evaluated the risks to people living adjacent to treated fields, which may include many farmworker families, and found no risks of concern for difenoconazole. EPA has also evaluated risk to residential handlers (such as homeowners) and adults/children that may be exposed to residues after pesticide application and has not found risks of concern.

The Agency sought information during the public comment periods throughout registration review on any other groups or segments of the population who, as a result of their proximity and exposure to pesticides, unique exposure pathway (e.g., as a result of cultural practices), location relative to physical infrastructure, exposure to multiple stressors and cumulative impacts, lower capacity to participate in decision making, or other factors, may have unusually high exposure to difenoconazole compared to the general population or who may otherwise be disproportionately affected by the use of difenoconazole as a pesticide. EPA requested but did not receive any comments concerning environmental justice.

C. Tolerance Actions

As outlined in the ID, the Agency anticipates making several commodity definition revisions, removing trailing zeros to be consistent with OECD rounding class practice, and making changes to harmonize with established Canadian and Codex MRLs. Only the anticipated commodity definition and tolerance level revisions are presented below.

Summary of Anticipated Tolerance Revisions for Difenoconazole (40 CFR §180.475).			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Anticipated Revised Tolerance (ppm)	Comments
40 CFR §180.475(a)(1)			
Almond, hulls	7.0	7	Correct level to be consistent with OECD Rounding Class Practice.
Apple, wet pomace	--	30	Tolerance level increase to correct level to be consistent with OECD Rounding Class Practice.
Apple, wet pomace	25	Remove	
Beet, sugar, dried pulp	--	2	
Beet, sugar, dried pulp	1.9	Remove	
Bushberry subgroup 13-07B	4.0	4	Correct level to be consistent with OECD Rounding Class Practice.
Cottonseed subgroup 20C	0.40	0.4	

Summary of Anticipated Tolerance Revisions for Difenoconazole (40 CFR §180.475).			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Anticipated Revised Tolerance (ppm)	Comments
Cranberry	0.60	0.6	
Fruit, citrus, group 10-10	0.60	0.6	
Fruit, citrus, group 10-10, dried pulp	--	2	Commodity definition revision. Correct level to be consistent with OECD Rounding Class Practice.
Citrus, dried pulp	2.0	remove	
Fruit, citrus, group 10-10, oil	--	25	Commodity definition revision. Level not consistent with OECD Rounding Class Practice; however, retained due to harmonization with Canadian MRL.
Citrus, oil	25	remove	
Fruit, pome, group 11-10	5.0	5	Correct level to be consistent with OECD Rounding Class Practice.
Fruit, small, vine climbing, except fuzzy kiwifruit, subgroup 13-07F	3.0	3	
Grain, aspirated fractions	--	100	Commodity definition revision. Tolerance level increase to correct level to be consistent with OECD Rounding Class Practice.
Aspirated grain fractions	95	remove	
Grape, raisin	6.0	6	Correct level to be consistent with OECD Rounding Class Practice.
Guava	3.0	3	
Kohlrabi	2.0	2	
Onion, bulb, subgroup 3-07A	0.20	0.2	
Onion, green, subgroup 3-07B	6.0	6	
Papaya	0.60	0.6	
Pea and bean, dried shelled, except soybean, subgroup 6C	0.20	0.2	
Pea, field, forage	--	10	Commodity definition revision.
Pea, field, vines	10	remove	
Potato, wet peel	--	8	Tolerance level increase to correct level to be consistent with OECD Rounding Class Practice.
Potato, wet peel	7.3	remove	
Rapeseed subgroup 20A	0.10	0.1	Correct level to be consistent with OECD Rounding Class Practice.
Rice, grain	--	8	Tolerance level increase to harmonize with Codex MRL which is based on same data used for U.S. tolerance.
Rice, grain	7.0	remove	
Rice, wild, grain	7.0	7	Correct level to be consistent with OECD Rounding Class Practice.
Soybean, hulls	0.20	0.2	
Vegetable, *Brassica*, head and stem, group 5-16	2.0	2	
Vegetable, cucurbit, group 9	0.70	0.7	
Vegetable, fruiting, group 8-10	0.60	0.6	
Vegetable, tuberous and corm, subgroup 1C	4.0	4	
40 CFR §180.475(a)(2)			
Cattle, fat	0.10	0.1	Correct level to be consistent with OECD Rounding Class Practice.
Cattle, meat byproduct	--	1.5	Commodity definition revision.

Summary of Anticipated Tolerance Revisions for Difenoconazole (40 CFR §180.475).			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Anticipated Revised Tolerance (ppm)	Comments
Cattle, liver	0.7	remove	Tolerance level increase to harmonize with Codex MRL for edible offal (mammalian).
Cattle, meat byproduct (except liver)	0.10	remove	
Egg	0.02	0.03	Tolerance level increase to harmonize with Codex MRL
Goat, fat	0.10	0.1	Correct level to be consistent with OECD Rounding Class Practice.
Goat, meat byproduct	--	1.5	Commodity definition revision. Tolerance level increase to harmonize with Codex MRL for edible offal (mammalian).
Goat, liver	0.7	remove	
Goat, meat byproduct (except liver)	0.10	remove	
Hog, fat	0.10	0.1	Correct level to be consistent with OECD Rounding Class Practice.
Hog, meat byproduct	--	1.5	Commodity definition revision. Tolerance level increase to harmonize with Codex MRL for edible offal (mammalian).
Hog, liver	0.40	remove	
Hog, meat byproduct (except liver)	0.10	remove	
Horse, fat	0.10	0.1	Correct level to be consistent with OECD Rounding Class Practice.
Horse, meat byproduct	--	1.5	Commodity definition revision. Tolerance level increase to harmonize with Codex MRL for edible offal (mammalian).
Horse, liver	0.7	remove	
Horse, meat byproduct (except liver)	0.10	remove	
Sheep, fat	0.10	0.1	Correct level to be consistent with OECD Rounding Class Practice.
Sheep, meat byproduct	--	1.5	Commodity definition revision. Tolerance level increase to harmonize with Codex MRL for edible offal (mammalian).
Sheep, liver	0.7	Remove	
Sheep, meat byproduct (except liver)	0.10	Remove	

D. Interim Registration Review Decision

The Agency is issuing this ID in accordance with 40 C.F.R. §§ 155.56 and 155.58. The Agency has made the following interim decision: (1) no additional data are required at this time; and (2) EPA has determined that difenoconazole does not meet the registration standard without changes to the affected registrations and their labeling. EPA has determined that the mitigation specified in Sections IV.A-C and Appendices A and B are sufficient to address certain concerns.

The Agency conducted detailed human health and ecological risk assessments. EPA did not identify any human health risks of concern from use of difenoconazole. EPA identified potential risk to fish, aquatic invertebrates, mammals, birds, and terrestrial invertebrates from use of difenoconazole. To address potential risks to birds and mammals from ingestion of treated seed, the Agency is adding soil incorporation labeling and directions to limit access to spilled seed and address the disposition of spilled seed for seed treatment products. To warn users of potential risk to aquatic animals, the Agency is adding water advisories on product labels. Additional label updates include pesticide resistance management labeling and updated environmental hazard

statements aimed at educating the user of potential exposure of difenoconazole to the environment.

EPA also determined that continuing to register difenoconazole provides benefits when used as a foliar application to agricultural crops, ornamentals, and turf, during post-harvest processing, as a seed treatment. As a foliar application, difenoconazole is used for controlling various fungal pests on soybean, almonds, sugar beets, potato, apple, and other crops. Use of difenoconazole on roses and other ornamentals, as well as turf, controls fungal pests that can otherwise reduce yields, quality, and decrease aesthetic value. Difenoconazole is used for post-harvest treatments of apples and pears to avoid fruit rot during storage. Infected fruit may cause a reduction in marketable yields. As a seed treatment, difenoconazole prevents fungal seed decay and seedling infections that may result in yield loss for crops such as barley, oats, rye, cotton, potato, corn.

During registration review, EPA considers whether a pesticide registration "continues to satisfy the FIFRA standard for registration."[26] Here, EPA has determined that difenoconazole does not meet the FIFRA registration standard without the changes to the affected registrations and their labeling described in Section IV.A and Appendices A and B.

EPA has determined that there is no human health dietary risk from registered uses of difenoconazole that is inconsistent with the FFDCA safety standard. Taking into consideration the available information on toxicity and exposure, EPA assessed difenoconazole's potential aggregate risks, including dietary (food and water) and non-occupational residential exposures, and found no risks exceeding the Agency's levels of concern.[2]

EPA has determined that there is a reasonable certainty that no harm will result from aggregate exposure to difenoconazole, including all anticipated dietary exposures and all other exposures for which there is reliable information. Therefore, difenoconazole residues do not present human dietary risk. EPA intends to revise certain commodity definitions, remove trailing zeros to be consistent with current rounding class practices, and modify certain tolerances to harmonize with established Canadian and Codex MRLs, as EPA's analysis indicates that such modifications would also be safe.

In this Interim Registration Review Decision, the Agency is making no human health or environmental safety findings associated with the EDSP screening of difenoconazole, nor is it making a complete endangered species finding. Although the Agency is not making a complete endangered species finding at this time, the mitigation described in this document is expected to reduce the extent of environmental exposure and may reduce risk to listed species whose range and/or designated critical habitat co-occur with the use of difenoconazole. The Agency's final registration review decision for difenoconazole will be dependent upon the result of the

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[26] 40 C.F.R. § 155.40(a); 7 U.S.C. § 136a(c)(5); *see also* 7 U.S.C. §§ 136(bb) (defining "unreasonable adverse effects on the environment" as encompassing both "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" [FIFRA's risk-benefit standard] **and** "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the [FFDCA safety standard]").

[2] *Difenoconazole: Human Health Risk Assessment for Registration Review.* Can be found in the public docket (EPA-HQ-OPP-2015-0401).

Agency's ESA assessment and any needed § 7 consultation with the Services and an EDSP FFDCA § 408(p) determination. For more information, see Appendices C and D.

E. Data Requirements

A Generic Data Call-In (GDCI-128847-1602) was issued for difenoconazole for data needed to conduct the registration review risk assessments. All data requirements from the registration review DCI have been satisfied and no additional data are required at this time.

V. NEXT STEPS AND TIMELINE

A. Interim Registration Review Decision

A Federal Register Notice will announce the availability of this Interim Registration Review Decision for difenoconazole. A final decision on the difenoconazole registration review case will occur after: (1) an EDSP FFDCA § 408(p) determination, and (2) an endangered species determination under the ESA and any needed § 7 consultation with the Services.

Implementation of Label Changes

Registrants must submit a cover letter, a completed Application for Registration (EPA form 8570-1) and electronic copies of the amended product labels within 60 days after the announcement of this ID in the *Federal Register*. Two copies for each label must be submitted, a clean copy and an annotated copy with changes. In order for the application to be processed, registrants must include the following statement on the Application for Registration (EPA form 8570-1):

"I certify that this amendment satisfies the requirements of the *Difenoconazole Interim Registration Review Decision* and EPA regulations at 40 CFR Section 152.44, and no other changes have been made to the labeling of this product. I understand that it is a violation of 18 U.S.C. Section 1001 to willfully make any false statement to EPA. I further understand that if this amendment is found not to satisfy the requirements of the *Difenoconazole Interim Registration Review Decision* and 40 CFR Section 152.44, this product may be in violation of FIFRA and may be subject to regulatory and/or enforcement action and penalties under FIFRA."

Within the required timeframe, registrants must submit the required documents to the Registration Review section of the EPA's Pesticide Submission Portal (PSP), which can be accessed through the EPA's Central Data Exchange (CDX) using the following link: https://cdx.epa.gov/. Registrants may instead send paper copies of their amended product labels, with an application for a fast-track, Agency-initiated non-PRIA label amendment to Lauren Weissenborn at the following address, so long as the labels and application are submitted within the required timeframe:

VIA US Mail

USEPA Office of Pesticide Programs
Pesticide Re-evaluation Division
Mail Code: 7508 M
1200 Pennsylvania Ave NW
Washington, DC 20460-0001

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Appendix A: Summary of Labeling Actions for Difenoconazole

Registration Review Case #: 7014 PC Code: 128847 Chemical Type: Fungicide Chemical Family: Triazoles Mode of Action: Sterol demethylation inhibitor; disrupts cell membrane ergosterol biosynthesis					
Affected Population(s)	Source of Exposure	Route of Exposure	Duration of Exposure	Potential Risk(s) of Concern	Labeling Actions
• Fish	• Runoff • Drift • Aquatic residues	• Ingestion • Respiration	• Chronic	• Body length reduction	• Drift and Runoff Environmental Hazards • Advisory Spray Drift Language • Rice (flooded field) Use Restrictions
• Aquatic Invertebrates	• Runoff • Drift • Aquatic residues	• Ingestion • Respiration	• Chronic	• Reduced # of young • Growth reduction • Survival reduction	
• Mammals	• Dietary	• Ingestion	• Chronic	• Effects on weight	• Terrestrial Outdoor Use Environmental Hazards • Advisory Spray Drift Language • Treated Seed Soil Incorporation • Management of wastes from treated seed
• Birds	• Dietary	• Ingestion	• Chronic	• Hatchling weight reduction	

Appendix B: Labeling Changes for Difenoconazole Products

Description	Label Language for Difenoconazole Products	Placement on Label
	End Use Products	
Mode of Action Group Number	**Note to registrant:** • Include the name of the **ACTIVE INGREDIENT** in the first column • Include the word "**GROUP**" in the second column • Include the **MODE/MECHANISM/SITE OF ACTION CODE** in the third column (for fungicides this is the FRAC Code, and for insecticides this is the Primary Site of Action; for Herbicides this is **SITE OF ACTION)** • Include the type of pesticide (**FUNGICIDE)** in the fourth column. **DIFENOCONAZOLE** | **GROUP** | **3** | **FUNGICIDE**	Front Panel, upper right quadrant. All text should be black, bold face and all caps on a white background, except the mode of action code, which should be white, bold face and all caps on a black background; all text and columns should be surrounded by a black rectangle.
Updated Gloves Statement	Update the gloves statements to be consistent with Chapter 10 of the Label Review Manual. In particular, remove reference to specific categories in EPA's chemical-resistance category selection chart and list the appropriate chemical-resistant glove types to use.	In Personal Protective Equipment (PPE) within Precautionary Statements and Agricultural Use Requirements, if applicable
Resistance-management for fungicides and bactericides	Include resistance management label language for fungicides/bactericides from PRN 2017-1 (https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year)	Directions for Use, prior to directions for specific crops
Drift and Runoff Warning	"Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas."	Environmental Hazards

Description	Label Language for Difenoconazole Products	Placement on Label
(for products with outdoor, terrestrial uses)		
Surface Water Advisory (outdoor agricultural use products only, such as fruits, nuts, vegetables, cereal grains, and other crops, and for products labeled for seed treatment)	"This product may impact surface water quality due to runoff of rain water. This is especially true for poorly draining soils and soils with shallow groundwater. This product is classified as having a high potential for reaching surface water via runoff for several months or more after application. A level, well-maintained vegetative buffer strip between areas to which this product is applied and surface water features such as ponds, streams, and springs will reduce the potential loading of difenoconazole from runoff water and sediment. Runoff of this product will be reduced by avoiding applications when rainfall or irrigation is expected to occur within 48 hours. Sound erosion control practices will reduce this product's potential to reach aquatic sediment via runoff."	Environmental Hazards (for difenoconazole products and for the seed container/bag tag)
Surface Water Advisory (outdoor non-agricultural use products only, such as ornamental turf, golf course turf, and nursery/greenhouse ornamentals)	"This product may impact surface water quality due to runoff of rain water. This is especially true for poorly draining soils and soils with shallow groundwater. This product is classified as having a high potential for reaching surface water via runoff for several months or more after application."	Environmental Hazards
Terrestrial Use Environmental Hazard (for products with outdoor, terrestrial uses, including products labeled for seed treatment)	"Do not apply directly to water or to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water when disposing of equipment washwater or rinsate."	Environmental Hazards (for difenoconazole products and for the seed container/bag tag)
Additional Required Labelling Action **Applies to all products delivered**	Remove information about volumetric mean diameter from all labels where such information currently appears.	Directions for Use

Description	Label Language for Difenoconazole Products	Placement on Label
via liquid spray applications		
Treated Seed Soil Incorporation	**Note to registrant**: include the following soil incorporation instructions, based on seed type: • For Canola and Rapeseed Crop Subgroup 20A (borage, crambe, cuphea, echium, flax seed, gold of pleasure, hare's ear mustard, lesquerella, lunaria, meadowfoam, milkweed, mustard seed, oil radish, poppy seed, rapeseed, sesame, sweet rocket): "Treated seed must be planted into the soil at a depth of at least ½ inch." • For Cotton, Small Grain Cereals (Barley, Oats, Rye, Triticale, and Wheat), and Sweet Corn: "Treated seed must be planted into the soil at a depth of at least 1 inch." • For Potato: "Treated seed pieces must be planted into the soil at a depth of at least 2 inches."	Directions for Use, for specific crops Directions for Use on Seed Container/Bag
Seed Treatment – For products allowed for on-farm seed treatment (not for distribution or sale of the seed)	• "Store treated seed away from food and feedstuffs. • Do not allow children, pets, or livestock to have access to treated seeds. • When loading/pouring the treated seed/seed-pieces, or covering/collecting spilled seed during loading and planting, wear long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves [list specific glove types]. • Treated seeds exposed on the soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting (such as in row ends). • Dispose of all excess treated seed by burying seed away from bodies of water. • Do not contaminate bodies of water when disposing of planting equipment wash water. • Plant treated seed into the soil to the recommended minimum depth or greater to minimize exposure. • DO NOT plant treated seed by broadcasting to the soil surface. Ensure that all planted seeds are thoroughly incorporated by the planter during planting, additional incorporation may be required to thoroughly cover exposed seeds. • Dispose of seed packaging or containers in accordance with local requirements."	Directions for Use, prior to directions for specific crops under the heading "On-farm Seed Treatment Directions"
Seed Bag/Container Labeling—for Products that Allow Commercial Seed Treatment and On-Farm Treated Seeds that are Distributed or Sold	"Seed Bag Labeling Requirements" "Seed treated with [PRODUCT NAME] must be labeled in accordance with all applicable requirements of the Federal Seed Act. All bags containing treated seed must be labeled or tagged as follows. Any seed treated with difenoconazole that is sold or distributed without these statements is an unregistered pesticide, in violation of FIFRA section 12."	In Directions for Use under the heading "Commercial Seed Container Labeling Requirements"

Description	Label Language for Difenoconazole Products	Placement on Label
(to Appear on Bag Tags for Treated Seed when Seed is to be Distributed)	**"The Federal Seed Act requires that bags containing treated seeds shall be labeled with the following statements:** • This seed has been treated with (insert name of active ingredient of pesticide). • Do not use for food, feed or oil purposes." **"The U.S. Environmental Protection Agency requires that bags containing treated seeds shall be labeled with the following statements:** • "This seed has been treated with [INSERT PRODUCT NAME(s), EPA REG. NO(s)), a [INSERT CHEMICAL TYPE(S)] containing [INSERT ACTIVE INGREDIENT(S)]. • This seed is treated with [number] lbs of difenoconazole per 100 lbs of seed. • Do not use treated seed for feed, food, or oil purposes. • Store treated seed away from food and feedstuffs. • Do not allow children, pets, or livestock to have access to treated seeds. • When loading/pouring the treated seed/seed-pieces or covering/collecting spilled seed during loading and planting, wear long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves [list specific glove types]. • Treated seeds exposed on the soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting (such as in row ends). • Dispose of all excess treated seed by burying seed away from bodies of water. • Do not contaminate bodies of water when disposing of planting equipment wash water. • Plant treated seed into the soil to the recommended minimum depth or greater to minimize exposure. • Do not plant treated seed by broadcasting to the soil surface. Ensure that all planted seeds are thoroughly incorporated by the planter during planting, additional incorporation may be required to thoroughly cover exposed seeds. • Dispose of seed packaging or containers in accordance with local requirements. • Excess treated seed may be used for ethanol production if (1) by-products are not used for livestock feed and (2) no measurable residues of pesticide remain in ethanol by-products that are used in agronomic practice." "All other requirements regarding the use of the treated seed, which include, but are not limited to, instructions relating to endangered species protection, environmental hazard statements, maximum use rates, plant back intervals, personal protective equipment, and storage and disposal statements, remain and must be listed on the bag tag."	

Description	Label Language for Difenoconazole Products	Placement on Label
Advisory Spray Drift Management Language for all products delivered via liquid spray application	**"SPRAY DRIFT ADVISORIES** THE APPLICATOR IS RESPONSIBLE FOR AVOIDING OFF-SITE SPRAY DRIFT. BE AWARE OF NEARBY NON-TARGET SITES AND ENVIRONMENTAL CONDITIONS. **IMPORTANCE OF DROPLET SIZE** An effective way to reduce spray drift is to apply large droplets. Use the largest droplets that provide target pest control. While applying larger droplets will reduce spray drift, the potential for drift will be greater if applications are made improperly or under unfavorable environmental conditions. **Controlling Droplet Size – Ground Boom** ***(note to registrants:*** *remove if ground boom is prohibited on product labels)* • Volume - Increasing the spray volume so that larger droplets are produced will reduce spray drift. Use the highest practical spray volume for the application. If a greater spray volume is needed, consider using a nozzle with a higher flow rate. • Pressure - Use the lowest spray pressure recommended for the nozzle to produce the target spray volume and droplet size. • Spray Nozzle - Use a spray nozzle that is designed for the intended application. Consider using nozzles designed to reduce drift. **Controlling Droplet Size – Aircraft** ***(note to registrants:*** *remove if aerial application is prohibited on product labels)* • Adjust Nozzles - Follow nozzle manufacturers' recommendations for setting up nozzles. Generally, to reduce fine droplets, nozzles should be oriented parallel with the airflow in flight. **BOOM HEIGHT – Ground Boom** ***(note to registrants:*** *remove if ground boom is prohibited on product labels)* For ground equipment, the boom should remain level with the crop and have minimal bounce. **RELEASE HEIGHT - Aircraft** ***(note to registrants:*** *remove if aerial application is prohibited on product labels)* Higher release heights increase the potential for spray drift. **SHIELDED SPRAYERS** Shielding the boom or individual nozzles can reduce spray drift. Consider using shielded sprayers. Verify that the shields are not interfering with the uniform deposition of the spray on the target area. **TEMPERATURE AND HUMIDITY** When making applications in hot and dry conditions, use larger droplets to reduce effects of evaporation.	Directions for Use, just below the Spray Drift box, under the heading "Spray Drift Advisories"

Description	Label Language for Difenoconazole Products	Placement on Label
	TEMPERATURE INVERSIONS Drift potential is high during a temperature inversion. Temperature inversions are characterized by increasing temperature with altitude and are common on nights with limited cloud cover and light to no wind. The presence of an inversion can be indicated by ground fog or by the movement of smoke from a ground source or an aircraft smoke generator. Smoke that layers and moves laterally in a concentrated cloud (under low wind conditions) indicates an inversion, while smoke that moves upward and rapidly dissipates indicates good vertical air mixing. Avoid applications during temperature inversions. **WIND** Drift potential generally increases with wind speed. o Applicators need to be familiar with local wind patterns and terrain that could affect spray drift."	
Advisory Spray Drift Management Language for products that are applied as liquids and allow boom-less ground sprayer applications	**"SPRAY DRIFT ADVISORIES** **Boomless Ground Applications:** o Setting nozzles at the lowest effective height will help to reduce the potential for spray drift."	Directions for Use, just below the Spray Drift box, under the heading "Spray Drift Advisories"
Advisory Spray Drift Management Language for all products that allow liquid applications with handheld technologies	**"SPRAY DRIFT ADVISORIES** **Handheld Technology Applications:** • Take precautions to minimize spray drift."	Directions for Use, just below the Spray Drift box, under the heading "Spray Drift Advisories"

Appendix C: Listed-Species Assessment

In 2015, EPA, along with the Services—the Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS)—and the United States Department of Agriculture (USDA) released their joint Interim Approaches for assessing risks to listed species from pesticides. The agencies jointly developed these Interim Approaches in response to the 2013 National Academy of Sciences' recommendations that discussed specific scientific and technical issues related to the development of pesticide risk assessments conducted on listed species. Since that time, the agencies have been continuing to work to improve the consultation process.

EPA initially conducted biological evaluations (BEs) using the interim method on three pilot chemicals representing the first nationwide pesticide consultations (final pilot BEs for chlorpyrifos, malathion, and diazinon were completed in January 2017). These initial pilot consultations were envisioned as the start of an iterative process. Later that year, NMFS issued a final biological opinion for these three pesticides. In 2019, EPA requested to reinitiate formal consultation with NMFS on malathion, chlorpyrifos and diazinon to consider new information that was not available when NMFS issued its 2017 biological opinion. EPA recently received a draft revised biological opinion on these pesticides from NMFS and posted it for public comment.[27] In February 2022, EPA also received a final malathion biological opinion[28] from FWS, which the Agency plans to implement according to the 18-month timeframe specified in the opinion.

After receiving input from the Services and USDA on proposed revisions to the pilot interim method and after consideration of public comments received, EPA released an updated *Revised Method for National Level Listed Species Biological Evaluations of Conventional Pesticides* ("Revised Method") in March 2020.[29] During the same timeframe, EPA also released draft BEs for carbaryl and methomyl, which were the first to be conducted using the Revised Method. To date, EPA has used the Revised Method to complete final BEs for carbaryl, methomyl, atrazine, simazine, and glyphosate.

The 2018 Farm Bill established a FIFRA Interagency Working Group (IWG) to recommend improvements to the ESA section 7 consultation process for FIFRA actions and to increase opportunities for stakeholder input. This group is led by EPA and includes representatives from NMFS, FWS, USDA, and the Council on Environmental Quality (CEQ). The IWG outlines its recommendations and progress on implementing those recommendations in reports to Congress.[30] The agencies continue to work collaboratively, consistent with Congress's intent in creating the IWG.

In January 2022, EPA announced a policy[31] to evaluate potential effects of new conventional pesticide active ingredients to listed species and their designated critical habitat and initiate consultation with the Services, as appropriate, before registering these new pesticides. Before the Agency registers new uses of pesticides for use on pesticide-tolerant crops, EPA will also continue to make effects determinations.

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[27] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions
[28] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions
[29] https://www.regulations.gov/document?D=EPA-HQ-OPP-2019-0185-0084
[30] https://www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act
[31] https://www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides

If these determinations are likely to adversely affect determinations, the Agency will not register the use unless it can predict that registering the new use will not jeopardize listed species or adversely modify their designated critical habitats. EPA will also initiate consultation with the Services as appropriate.

Appendix D: Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for difenoconazole, the EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA § 408(p), difenoconazole is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA § 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The Agency has reviewed all of the assay data received for the List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. A second list of chemicals identified for EDSP screening was published on June 14, 2013,32 and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. Difenoconazole is not on either list. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, visit EPA website.33

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[32] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[33] https://www.epa.gov/endocrine-disruption

EPA's EDSP is actively pursuing the application of new approach methods (NAMs) to create a more efficient and robust screening program. In October 2020, EPA underwent a reorganization and the EDSP was moved to the Office of Pesticide Programs. This reorganization provides better alignment of the EDSP with the procedures and methods used by the program offices. On July 28, 2021, the Office of Inspector General (OIG) released its new report on the EDSP and made ten recommendations. EPA is also developing a strategic planning document for EDSP which will be available for public comment in 2022. EPA expects additional documents for public release in 2021-2023 that address aspects of EDSP chemical determinations. EPA looks forward to working with stakeholders and the scientific community to accelerate the implementation of this important program into pesticide risk assessments and decision making.

In this ID, EPA is making no human health or environmental safety findings associated with the EDSP screening of difenoconazole. Before completing this registration review, the Agency will make an EDSP FFDCA § 408(p) determination."