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Fluopyram Final Work Plan

Registration Review: Initial Docket
Case Number 5092

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Approved by: _____

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Table of Contents

OVERVIEW 3
UPDATES SINCE THE PWP WAS ISSUED 4
SUMMARY OF THE COMMENTS AND AGENCY RESPONSES 4
PLANNED DATA NEEDS 5
RISK ASSESSMENTS FOR REGISTRATION REVIEW 6
TIMELINE 9
NEXT STEPS 10
APPENDIX – ADDITIONAL AREAS CONSIDERED IN THE FLUOPYRAM REGISTRATION REVIEW **11**

OVERVIEW

This is the Environmental Protection Agency's (EPA or the Agency) Final Work Plan (FWP) for registration review of fluopyram (CAS 658066-35-4, PC Code 080302). This FWP addresses public comments received concerning the Preliminary Work Plan (PWP), which was posted in the fluopyram registration review docket (EPA-HQ-OPP- 2021-0350).

Fluopyram, (N-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2(trifluoromethyl)benzamide; fluopyram) represents a group of fungicide chemistry, pyridinyl-ethyl benzamides. Fluopyram is a succinate dehydrogenase inhibitor (SDHIs; Group 7, C2); the biochemical mode of action of this chemical involves the inhibition of the enzyme succinate dehydrogenase within the fungal mitochondrial respiratory chain, thus blocking electron transport, according to the Food Research and Action Center (FRAC).

Fluopyram was first registered in 2012, with additional uses registered in 2014 and 2016, including its use as a nematicide. Products containing fluopyram are registered for use on a wide variety of crops including tree nuts, fruits, tree fruits, and berries, root tuberous and corm, legumes, and leafy vegetables and includes non-agricultural uses on Christmas tree plantations, ornamentals, and turf. Fluopyram is formulated as liquid (flowable suspension, liquid suspension, suspension concentrate, and soluble concentrate) and is applied as foliar/soil spray and seed treatment.

This Final Work Plan (FWP) explains what the United States Environmental Protection Agency (hereafter, EPA or the Agency) knows about fluopyram, highlights data and risk assessment needs, and provides an anticipated timeline for completing the registration review of fluopyram.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended by the Food Quality Protection Act (FQPA) of 1996, 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. The registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically re-evaluates pesticides to make sure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided at http://www.epa.gov/pesticide-reevaluation. In 2006, the Agency implemented the registration review program pursuant to FIFRA § 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The initial registration review covered all pesticide products registered prior to October 1, 2007, which included over 1,100 pesticide active ingredients. Subsequent registration reviews begin on a revolving basis, with chemicals going through the process no later than 15 years after either the date on which the initial registration review is completed or the date products containing the active ingredient were first registered.

The FWP begins with any updates since the PWP was issued. Next is a summary of substantive comments received during the public comment period for the PWP concerning anticipated data needs, expected risk assessments, the estimated timeline identified in the PWP, and a summary of the Agency's responses to those comments. This section is followed by sections on planned data needs, risk assessments expected to be conducted, and the projected registration review timeline for fluopyram. Lastly, there is a discussion of next steps.

UPDATES SINCE THE PWP WAS ISSUED

Since the PWP was issued, the occupational post-application dermal assessment is no longer anticipated. The case number in the title of this document has been corrected to 5092; it was incorrectly listed in the title of the PWP as 7067.

SUMMARY OF THE COMMENTS AND AGENCY RESPONSES

During the 60-day public comment period on the fluopyram Preliminary Work Plan (PWP), which opened in February 2022 and closed on April 4, 2022, the Agency received three public comments. The comments were submitted by the FIFRA Endangered Species Task Force (FESTF) LLC, Washington State Potato Commission, and Bayer, the technical registrant. The comments do not affect the planned ecological risk assessments or data requirements, but the occupational post-application dermal assessment is not anticipated. In the PWP, the EPA also solicited comments on the specific topics of environmental justice and water quality concerns, but no specific comments or information were received on those issues.

This section summarizes the public comments. Public comments are located in the fluopyram docket, EPA-HQ-OPP-2021-0350.

Comment submitted by Robin Charlton, on behalf of the FIFRA Endangered Species Task Force (FESTF), LLC in EPA-HQ-OPP-2021-0350-0006.

Comment: Bayer U.S. CropScience is the technical registrant for fluopyram, as identified in the PWP. Bayer U.S. CropScience is a FESTF member and is entitled to rely on FESTF data for endangered species risk assessment.

Response: EPA thanks FESTF for its comment and will consider all appropriate information during registration review.

Comment submitted by Bayer in EPA-HQ-OPP-2021-0350-0007.

Comment: Bayer provided comments on the fluopyram PWP, gave information on the existing labels, and commented on the Problem Formulation and Scoping Document. Bayer requested clarification for the intent of the occupational post-application dermal risk assessment that was included in the PWP and Scoping Document. Additionally, Bayer included the correct values that should replace missing or incorrect values in Table 1 of the Problem Formulation. Bayer clarified that MRID 49859339 (referenced in Table C-4 of the PF) is a colony feeding study in which bees were exposed to fluopyram-fortified sugar and pollen diet under confined conditions

followed by an extended observation period in unconfined conditions. MRID 49859324 is incorrectly listed in Table C-4 and should be corrected to MRID 49859323 as reference for a bumble bee acute contact study. A second colony feeding study (MRID 49859325) performed with fluopyram technical has been submitted to EPA but is not included in the list of available studies in the PWP. Bayer commented that three of the anticipated studies (fish early life stage toxicity test with marine/estuarine species, mysid chronic toxicity test, and chronic freshwater amphipod (Hyalella) toxicity test) are not necessary and stated their plan to submit the Honeybee larval chronic toxicity test for EPA review concurrently with this comment.

Response:
EPA thanks Bayer for their comment and will ensure the errors will be fixed in the future draft human health and ecological risk assessments. The toxicity endpoint and dermal points of departure have been updated since the dermal risk was assessed in the 2020 Human Health risk assessment. After review of the current toxicity profile, EPA has determined that a dermal point of departure and toxicity endpoint were not selected as no systemic effects were observed in the dermal toxicity studies. Therefore, a dermal assessment for fluopyram will not be conducted for registration review unless the toxicity database is updated again with studies that identify adverse effects. EPA encourages the formal submission of data waiver requests for the individual studies (fish early life stage toxicity test with marine/estuarine species, mysid chronic toxicity test, and chronic freshwater amphipod (Hyalella) toxicity test). The corrected label use information will be considered in future human health and ecological risk assessments. EPA acknowledges the receipt of the Honeybee larval chronic toxicity test for review (MRID 51925101).

Comment submitted by Matthew J. Blua, on behalf of Washington State Potato Commission in EPA-HQ-OPP-2021-0350-0008.

Comment: Washington State Potato Commission outlined the importance of fluopyram as an agrichemical for WA growers and provided information on the use and usage of fluopyram. The comment discussed how fluopyram is applied on 75% of WA potato fields alone or in combination with pyrimethanil as a fungicide resistance management strategy. Washington State Potato Commission stated that 90% of Washington's potatoes are grown in the Columbia Basin, which is arid and with low rainfall and low surface water runoff. Additionally, the importance of the Washington potatoes for food security was emphasized.

Response: EPA thanks Washington State Potato Commission for the fluopyram benefits and use/usage information provided in this comment and will consider this information during registration review.

PLANNED DATA NEEDS

The Agency plans to call in data in support of the fluopyram registration review case. These data are needed to assess the potential risks to and the environment. The EPA anticipates issuing a data call-in (DCI) to obtain these data. The anticipated data needs are outlined in Table 1 below.

The Agency has determined that additional pollinator exposure and effects data are necessary to fully evaluate the risks of fluopyram to non-target terrestrial invertebrates, especially pollinators,

based on the June 2014 *Guidance for Assessing Pesticide Risks to Bees*. EPA will issue a data call-in (DCI) to obtain these data.

For additional discussion of the anticipated data needs, see the *Fluopyram: Problem Formulation for the Registration Review Assessment* and *Fluopyram. Registration Review Scoping Document. Recommendations for Anticipated Data and Risk Assessments for Registration Review*, available in the fluopyram docket (EPA-HQ-OPP-2021-0350).

Table 1: Anticipated Data Needs for the Fluopyram Registration Review

Guideline Number[1]	Study Title	Test Material	Estimated Timeframe (Months from receipt of DCI)
Anticipated Data Needs for Fluopyram			
850.1350	Mysid chronic toxicity test	TGAI	12
850.1400	Fish Early Life Stage Toxicity Test	TGAI	12
Non-guideline	Chronic freshwater amphipod toxicity	TGAI	12
Pollinator Data Requirements[2]			
Non-guideline (OECD 239)	Honeybee larvae chronic toxicity (Tier 1)	TGAI	12

TGAI = technical grade active ingredient.

RISK ASSESSMENTS FOR REGISTRATION REVIEW

The most recent comprehensive human health risk assessment for fluopyram was completed in 2020 in *Support of Tolerances without U.S. Registration on Lentils, Dry Peas, and Cranberries* for import-only tolerances. The most recent ecological and environmental fate risk assessment was completed in 2019 for the *Proposed New Uses of Fluopyram as a Seed Treatment for Canola and Oriental Mustard Seed*. Findings and conclusions from these risk assessments are summarized in the *Fluopyram: Problem Formulation for the Registration Review Assessment* and *Fluopyram and Registration Review Scoping Document. Recommendations for Anticipated Data and Risk Assessments for Registration Review,* which are available in the fluopyram registration review docket (EPA-HQ-OPP-2021-0350) at www.regulations.gov.

During registration review, the Agency anticipates the need to conduct new assessments and/or update elements of existing recently conducted risk assessments for fluopyram. If toxicological endpoints or points of departure are revised based on the data that are anticipated to be required

[2] The need for higher tier tests for pollinators will be determined based upon the results of lower tiered tests and/or other lines of evidence and the need for a refined pollinator risk assessment.

for registration review, they will be considered in the new assessments, as well as any changes to the standard operating procedures or default exposure assumptions.

The Agency may need to reevaluate existing databases as well as any new data that may be submitted and any new routes of exposure will be considered. As EPA policies and models develop, assessment approaches may also change. Additionally, teams plan to review and update labels as some labels/use sites may be lacking use parameters critical to risk assessment. Table 2 presents a summary of the anticipated risk assessments for the fluopyram registration review based on the EFED Problem Formulation and HED Scoping Document.

Table 2: Anticipated Risk Assessments for the Fluopyram Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Ecological and Environmental Fate		
Non-listed species	Yes	Chronic data are not available for estuarine/marine fish; an acute-to-chronic ratio could not be calculated for based on a lack of definitive acute toxicity endpoints, chronic data is not available for estuarine/marine invertebrates; an acute-to-chronic ratio could not be calculated for based on a lack of definitive acute toxicity endpoints, and chronic data are not available for freshwater amphipods.
Pollinators	Yes	Chronic data using TGAI is not available for honeybee larvae.
Drinking Water	Yes	A new drinking water assessment will be conducted based on fate data that will result in updated input parameters for the metabolism studies.
Incidents	Will check for updates	For a discussion of reported ecological incidents for fluopyram, see Section 6 of the *Fluopyram Problem Formulation for Registration Review Assessment*.
Human Health		
Dietary		
Food	Yes	Acute and chronic dietary exposure assessments will be conducted based on new points of departure (PODs) and updated drinking water estimates (if conducted). The chronic dietary endpoint has been updated since the last risk assessment, and the acute dietary endpoint did not require updating and remains the same.
Residential		
Handlers	No	All registered labels specify commercial applicators only; therefore, residential handler uses are not anticipated.
Post-application	Yes	Inhalation and incidental oral exposures will need to be assessed. During initial review of the hazard database for fluopyram, a dermal endpoint was not identified, and therefore dermal exposure assessments are not warranted.
Occupational		
Handlers (mixers, loaders, applicators)	Yes	Inhalation
Post-application	Yes	Inhalation
Non- occupational Exposure		
Spray drift	Yes	Non-occupational spray drift exposures from application to agricultural use sites may result from the registered uses and will also need to be assessed.

Bystander	No	During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for fluopyram.
Other Human Health		
Aggregate	Yes	A new aggregate risk assessment will be conducted based on using the latest dietary and residential assessments.
Cumulative	No	Fluopyram has not been identified as a member of a cumulative group that shares a common mechanism of toxicity.
Tolerance changes required	Yes	Updated as needed.
Incident analysis, literature review	Yes	For a discussion of reported human incidents for fluopyram, see page 7 of the Scoping Document and the *Incident and Epidemiological Data Review for Fluopyram.*
Other Considerations		
Domestic Animal Incidents	No residential pet uses	

TIMELINE

The EPA has created an estimated timeline for the completion of the fluopyram registration review in Table 3.

Table 3: Projected Fluopyram Registration Review Timeline

Activities	Estimated Date
Opening the Docket	
Open Docket and 60-day Public Comment Period	January 2022- *Completed*
Close Public Comment	March 2022- *Completed*
Case Development	
Final Work Plan	July 2022- *Completed*
Issue Data Call-In (DCI)	January 2023
Data Submission	January 2025
60-day Public Comment Period for Draft Risk Assessments[3]	February- April 2026
Registration Review Interim Decision	
60-day Public Comment Period for Proposed Interim Registration Review Decision	November 2026- January 2027

[3] The regulations governing registration review generally require the Agency to provide a public comment period of at least 30 calendar days for draft risk assessments; see 40 CFR § 155.53(c). For conventional pesticides, the Agency plans to provide a 60-calendar day public comment period generally for draft risk assessments.

Table 3: Projected Fluopyram Registration Review Timeline	
Activities	**Estimated Date**
Interim Registration Review Decision and Begin Post-Decision Follow-up	July 2027
Total (years)	5

NEXT STEPS

As noted previously, the Agency plans to require a comprehensive ecological assessment and to conduct dietary, residential, and occupational risk assessments for fluopyram through a Data Call-In Notice, expected to be issued in January 2023. Based on the findings of risk and benefit assessments, the Agency intends to issue a Proposed Interim Registration Review Decision in 2026.

Appendix – Additional Areas Considered in the Fluopyram Registration Review

FEDERALLY-THREATENED/ENDANGERED (LISTED) SPECIES ASSESSMENT:

The Agency has not yet fully evaluated fluopyram's risks to listed species. However, EPA will complete its listed-species effects determination and any necessary consultation with the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS) (the Services) before completing the fluopyram registration review.

In 2015, EPA, along with the Services and the United States Department of Agriculture (USDA) released their joint Interim Approaches for assessing risks to federally-listed endangered and threatened (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. In February 2022, EPA also received a final malathion biological opinion 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. 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, glyphosate, clothianidin, imidacloprid and thiamethoxam.

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. The agencies continue to work collaboratively, consistent with Congress's intent in creating the IWG.

In January 2022, EPA announced a policy 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. 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.

ENDOCRINE DISRUPTOR SCREENING PROGRAM:

As required by FIFRA and FFDCA, the 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, the 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 fluopyram, 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), fluopyram is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

The 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 is intended to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. 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. For further information on the status of the EDSP, please visit the EPA website.[4]

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

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

forward to working with stakeholders and the scientific community to accelerate the implementation of this important program into pesticide risk assessments and decision