Docket Number EPA-HQ-OPP-2006-0114
www.regulations.gov

Hexythiazox Updated Final Work Plan

Registration Review: Initial Docket
Case Number 7404

July 2024

Approved by: Jean Overstreet

Jean Overstreet
Director
Pesticide Re-evaluation Division

Date: 7/5/2024

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References:

This Updated Final Work Plan summarizes the Environmental Protection Agency's current position based on the following documents:

1. *Hexythiazox: Tier I (Scoping) Review of Human Incidents and Epidemiology*. Shanna Recore, *et al*. November 15, 2022.

2. *Hexythiazox: Scoping Document for Registration Review*. Adrian Britt, *et al*. March 14, 2023.

3. *Hexythiazox: Problem formulation for Registration Review*. Kristin Jones, *et al*. March 30, 2023.

4. *Hexythiazox. Updated Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review.* Adrian Britt, *et al.* April 24, 2024.

These and other supporting documents for the hexythiazox registration review case may be found in the docket EPA-HQ-OPP-2006-0114 at www.regulations.gov.

OVERVIEW

This is the Environmental Protection Agency's (EPA or the Agency) Updated Final Work Plan (UFWP) for registration review of hexythiazox (CAS 78587-05-0, PC Code 128849). This UFWP addresses public comments received concerning the Continuing Work Plan (CWP), which was posted on April 6, 2023, in the hexythiazox registration review docket (EPA-HQ-OPP-2006-0114).

Hexythiazox is a mite growth inhibitor/ovicide categorized as a Group 10 insecticide by the Insecticide Resistance Action Committee (IRAC)[1]. First registered in 1989, hexythiazox is formulated as a wettable powder, water dispersible granule, or emulsifiable concentrate and can be applied as a broadcast foliar spray by aerial equipment, ground equipment, or chemigation.

Hexythiazox is used to control spider mites on a variety of crops and outdoor residential settings (i.e., ornamental landscaping, ornamental lawns and turf, residential gardens). Hexythiazox is a contact pesticide which achieves control of eggs and immature mites via direct contact or contact with treated surfaces.

This UFWP explains what EPA knows about hexythiazox, highlights anticipated data and risk assessment needs, identifies the types of information that would be especially useful to the Agency in conducting registration review, and provides an anticipated timeline for completing the registration review of hexythiazox.

The UFWP begins with any updates since the CWP was issued. Next is a summary of substantive comments received during the public comment period for the CWP concerning anticipated data needs, expected risk assessments, the estimated timeline identified in the CWP, and a summary of the Agency's responses to those comments. Subsequently, the UFWP details the planned data needs, planned risk assessments, and the projected registration review timeline for hexythiazox. Lastly, there is a discussion of next steps.

STATUTORY AND REGULATORY AUTHORITY

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-

[1] Insecticide Resistance Action Committee (IRAC). 2022. Mode of Action Classification Scheme: Version 10.4. https://irac-online.org/documents/moa-classification/

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 publication of this UFWP is part of the ongoing registration review of hexythiazox.

The regulations governing registration review begin at 40 CFR § 155.40. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision.

Before completing registration review, EPA will also address its Federal Food, Drug, and Cosmetic Act (FFDCA) section 408(p)(6)-related commitments and obligations to ensure the protection of public health for hexythiazox.[2] For more information on EPA's review of hexythiazox under this FFDCA provision, see the Appendix section titled *Endocrine Disruptor Screening Program*.

UPDATES SINCE THE CWP WAS ISSUED

The Agency has updated the information in the Appendix, which includes information regarding the Endocrine Disruptor Screening Program (EDSP) for hexythiazox, and updated Table 3 with additional studies.

SUMMARY OF THE COMMENTS AND AGENCY RESPONSES

During the 60-day public comment period on the hexythiazox Continuing Work Plan (CWP), which opened on April 6, 2023, and closed on June 5, 2023, the Agency received one public comment. The comment was submitted by Gowan Company, LLC. The comment does not affect the planned ecological or human health risk assessments. In the CWP, 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 comment. The public comment is located in the hexythiazox docket, EPA-HQ-OPP-2006-0114.

Comment submitted by Gowan Company, LLC in EPA-HQ-OPP-2006-0114-0042.

Comment: *Gowan indicated how they intend to address each identified data gap, including generating new studies and citing existing data while also questioning the utility of several environmental fate and ecotoxicity studies that were identified as data needs in the CWP. In*

[2] Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), 21 U.S.C. § 346a(p).

particular, Gowan suggested that additional aquatic studies are unlikely to result in data that would be more useful in the risk assessment than the already available data given the labeled use sites and low aqueous solubility of hexythiazox.

Response: The Agency appreciates Gowan's comment and will consider their concerns before selecting the final set of data requirements and issuing a Generic Data Call-In (GDCI).

CHEMICAL AND REGULATORY INFORMATION

Table 1 provides a summary of the chemical identification and pesticide registration for hexythiazox.

Table 1: Chemical Facts for Hexythiazox	
PC code(s)	128849
Case Number	7404
CAS Number	78587-05-0
Year first registered	1989
Pesticide Type	Acaracide
Chemical class	Thiazolidine
Mode of Action Group Number	Mite growth inhibitor/ovicide in IRAC Group 10
Date of last Registration Review Decision	The Interim Decision was completed on December 5, 2014. EPA-HQ-OPP-2006-0114-0034
Cumulative group	Not applicable. Hexythiazox has not been identified as a member of a cumulative group that shares a common mechanism of toxicity.
Tolerances	Tolerances for hexythiazox are established in 40 CFR §180.448(a)(1) and (c)(1).
Dual-use	Products containing hexythiazox are registered for conventional pesticidal uses only and have no registered antimicrobial or biopesticidal uses.
Non-pesticidal uses	There are no identified non-pesticidal uses of hexythiazox.
Pesticide Re-evaluation Division, Chemical Review Manager	Alex Hazlehurst Hazlehurst.alexander@epa.gov
Registration Division, Product Manager	Tamica Cain cain.tamica@epa.gov

USE AND USAGE INFORMATION

Hexythiazox is registered for use on the following food/feed use sites: alfalfa, alfalfa grown for seed[4], beans (dry and succulent)[2] low growing berries (Crop Subgroup 13-07G), caneberries (Crop Subgroup 13-07A)[3], carrots grown for seed[4], citrus (Crop Group 10-10)[3], field corn, sweet

[3] Sites have geographic restrictions limiting use to all or part of the western U.S.

corn[2], dates, hops, mint[4], pepper/eggplant (Crop Subgroup 8-10B), pistachios[4], pome fruits (Crop Group 11-10)[3], potatoes, small fruit vine climbing subgroup except fuzzy kiwifruit (Croup Subgroup 13-07F), sorghum[2], stone fruits (Crop Group 12)[3], sugar beets[2], greenhouse tomatoes, tree nuts (Crop Group 14)[3], and wheat[2]. Hexythiazox is also registered on the following non-food use sites: bermudagrass[2], Christmas trees, clover grown for seed[5], cotton, grasses grown for seed[4], non-bearing fruit trees, non-bearing nut trees, non-bearing fruit vines, ornamentals[3], timothy[2], and turf[3].

According to recent national surveys of pesticide usage (2017-2021), on average, approximately 120,000 pounds of hexythiazox were applied to about 830,000 acres of agricultural crops annually[6]. Almond, walnuts, and corn were the highest usage crops both in terms of the average annual total acres treated and pounds of active ingredient applied[5]. Approximately 42,000 pounds of hexythiazox were applied annually to 258,000 acres of almonds with 20 percent crop treated (PCT)[7]. Comparatively, 10,000 pounds of hexythiazox were applied annually to 60,0000 acres of walnuts (14 PCT)[6]. Additionally, 49,000 pounds of hexythiazox were applied annually to 375,000 acres of corn; however, given the large number of acres annually planted with corn, this amounts to <1 PCT. Apricots exhibited the highest average annual PCT of surveyed crops (27 PCT)[6]. Caneberries, peaches, plum/prunes, and strawberries, were also significant use sites, with PCT in the 10-20% range[6]. Lower levels of usage (<5 PCT annual average) were reported on the following crops: alfalfa, apples, cherries, cotton, dry beans, grapefruit, grapes (table, raisin and wine), lemons, lima beans, oranges, pears, peppers, pistachios, potatoes, sorghum, sugar beets, sweet corn, and winter wheat.

In recent national surveys of turf and ornamental use sites, there was no reported usage of hexythiazox[8]. The lack of reported usage for hexythiazox as a miticide does not imply a lack of usage but does indicate that usage of this active ingredient on turf and ornamental sites is likely minimal.

Table 2 summarizes the use and usage information for hexythiazox.

Table 2: Hexythiazox Use and Usage Information

Summary of Use	Insecticide; mite growth inhibitor/ovicide
Use Sites	Numerous agricultural crops; Food/feed and Non-food use sites
Summary of Usage	Between 2017 and 2021, an average of approximately 120,000 pounds of hexythiazox were applied to about 830,000 acres of agricultural crops annually.

[4] Use on these sites allowed in both commercial and residential areas
[5] Only on special local needs (SLN) registrations.
[6] Kynetec USA, Inc. 2022a. "The AgroTrak® Study from Kynetec USA, Inc." iMap Software. Database Subset: 2017-2021. [Accessed January 2023].
[7] Kynetec USA, Inc. 2022b. "The AgroTrak® Study from Kynetec USA, Inc." Microsoft Access Database. Database Subset: 2017-2021. [Accessed January 2023].
[8] Nonagricultural Market Research Data (NMRD). 2022. Professional Turf and Ornamental 2021: United States Market for Pesticides and Fertilizers. [Accessed January 2023].

Table 2: Hexythiazox Use and Usage Information	
	Almond, walnuts, and corn were the highest usage crops both in terms of the average annual total acres treated and pounds of active ingredient applied. Apricots exhibited the highest average annual PCT (about 27%). Caneberries, peaches, plum/prunes, and strawberries PCT ranged from 10-20%. Lower levels of usage (<5 PCT annual average) were reported on the following crops: alfalfa, apples, cherries, cotton, dry beans, grapefruit, grapes (table, raisin and wine), lemons, lima beans, oranges, pears, peppers, pistachios, potatoes, sorghum, sugar beets, sweet corn, and winter wheat. In recent national surveys of turf and ornamental use sites, there was no reported usage of hexythiazox.
Formulation Type(s)	Wettable powder, water dispersible granule, or emulsifiable concentrate
Application Method(s)	Broadcast foliar spray by aerial equipment, ground equipment, or chemigation
Technical Registrant(s)	Argite, LLC., Gowan Company, LLC., and Albaugh, LLC.
No. of Registrations	4 FIFRA Section 3 technical registrations; 25 FIFRA Section 3 end-use registrations; 18 FIFRA Section 24(c) (special local needs—SLN) registrations
Restricted Use	Hexythiazox has no products that are classified as restricted use.

RECENT ACTIONS

The *Hexythiazox Interim Registration Review Decision* was completed in December 2014. The *Hexythiazox: Streamlined Environmental Fate and Ecological Risk Assessment and Drinking Water Assessment for Proposed Increased Application Rate on Caneberry Subgroup 13-07A and Dates* was completed in February 2020. The *Hexythiazox: Human Health Risk Assessment for Amended Tolerances on Caneberry Subgroup 13-07 A and Dates, Dried Fruit and Establishment of a Tolerance Without U.S. Registration for Residues in Tea* was completed in July 2020. The *Hexythiazox Continuing Work Plan* was completed in April 2023. The *Hexythiazox. Updated Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review* was completed in April 2024. These and other supporting documents for the hexythiazox registration review case may be found in the docket EPA-HQ-OPP-2006-0114 at www.regulations.gov.

DATA NEEDS

The anticipated data needs have been expanded since the CWP to confirm EPA's assessment of estrogen and androgen effects as further explained in the Appendix on EDSP.

The Agency anticipates calling-in data in support of the hexythiazox registration review case. These data are needed to assess the potential risks to human health and the environment, including anticipated pollinator studies to fully evaluate risks to nontarget terrestrial invertebrates based on the June 2014 Guidance for Assessing Pesticide Risks to Bees. The anticipated data requirements are outlined in Table 3 below. EPA will issue a DCI to obtain these data.

The National Pesticide Standards for hexythiazox is current with a new expiration of August 16, 2028; however, metabolite PT-1-3 moiety has not been submitted to the Repository.[9] Gowan Company, LLC. informed the Agency that they will be shipping metabolite PT-1-3 (CAS No. 78587-59-4) to the National Pesticide Standards Repository on July 10, 2024.[10] EPA requests that the standard be forwarded to the address below (full 9-digit ZIP Code is required). Three grams should be submitted in 30 aliquot vials of 100 mg each; the vials should be sealed and labeled with percent purity, lot number, and expiration date.

USEPA
National Pesticide Standards Repository
Analytical Chemistry Branch/BEAD/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

For additional discussion of the anticipated data needs, see the *Hexythiazox: Problem formulation for Registration Review* and *Hexythiazox. Updated Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review*, available in the hexythiazox docket (EPA-HQ-OPP-2006-0114). Additionally, see the Appendix for information on EDSP for hexythiazox.

Table 3: Data Needs for the Hexythiazox Registration Review

Guideline Number	Study Title	Test Material	Estimated Timeframe (Months from receipt of DCI)
835.4100	Aerobic soil metabolism (4 soils)	TGAI	24
835.4300	Aerobic aquatic metabolism (2 sediment systems)	TGAI	24
835.4400	Anaerobic aquatic metabolism (2 sediment systems)	TGAI	24
835.6100	Environmental chemistry methods and independent laboratory validation (soil and water)	TGAI	24
835.6200	Aquatic field dissipation	TGAI	24

[9] Based on communication with Craig Vigo (Analytical Chemistry Branch - Biological and Economic Analysis Division; 06/05/20240)
[10] Based on communication with Gowan Company, LLC. on 6/17/2024

Table 3: Data Needs for the Hexythiazox Registration Review			
Guideline Number	**Study Title**	**Test Material**	**Estimated Timeframe (Months from receipt of DCI)**
850.1010	Acute toxicity freshwater invertebrates	TGAI	12-24
850.1075	Freshwater fish acute toxicity test	TGAI, TEP	12-18
850.1075	Saltwater fish acute toxicity test	TGAI, TEP	12-18
850.1010	Acute toxicity freshwater invertebrates	TGAI, TEP	12-24
850.1025	Estuarine/marine invertebrate acute toxicity mollusk	TGAI	12
850.1400	Fish early-life stage (freshwater and saltwater)	TGAI	12
850.1735	Sub-chronic whole sediment toxicity freshwater invertebrates	TGAI	12
850.1740	Sub-chronic whole sediment toxicity estuarine/marine invertebrates	TGAI	12
850.4100	Terrestrial plant seedling emergence	TEP	12
850.4159	Terrestrial plant vegetative vigor	TEP	12
870.3200	21/28 Day dermal toxicity	TGAI	24
Non-guideline	Chronic whole sediment toxicity freshwater invertebrates (EPA 600/R-99/064)	TGAI	12-24
Non-guideline	Chronic whole sediment toxicity estuarine/marine invertebrates (EPA Test Method 600/R-01/020)	TGAI	12-24
850.4400	Aquatic Plant Toxicity Test with *Lemna* spp	TGAI or TEP	12
850.4500	Algal toxicity	TGAI	12
850.4550	Cyanobacteria (*Anabena flos-aquae*) toxicity	TGAI	12
850.2100	Avian oral toxicity with a passerine species	TGAI	12
870.3800	Reproduction and Fertility Effects (Rat)[11]	TGAI	48
890.1200	Aromatase (Human Recombinant)	TGAI	6
890.1400	Hershberger (Rat)	TGAI	9
890.1450	Pubertal Development and Thyroid Function in Intact Juvenile Female Rats	TGAI	15

[11] This is an EDSP Tier 2 study if conducted according to the current (1998) 870.3800 test guideline. The need for this study will be determined based on the results of the five EDSP Tier 1 studies (i.e., 890 guideline studies) submitted to comply with this DCI. Alternatively, this Tier 2 study may be conducted in lieu of the five Tier 1 studies required in this DCI to address the estrogen and androgen pathways.

This study requirement may also be fulfilled by conducting an extended one-generation reproductive toxicity study according to OECD (2018), Test No. 443: Extended One-Generation Reproductive Toxicity Study, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, available at the following link: https://doi.org/10.1787/9789264185371-en.

Table 3: Data Needs for the Hexythiazox Registration Review			
Guideline Number	**Study Title**	**Test Material**	**Estimated Timeframe (Months from receipt of DCI)**
890.1500	Pubertal Development and Thyroid Function in Intact Juvenile Male Rats	TGAI	15
890.1550	Steroidogenesis (Human Cell Line – H295R)	TGAI	6
Pollinator Data Requirements[12]			
Non-guideline (OECD TG 213)	Honey bee adult acute oral toxicity (Tier 1)	TGAI	12
Non-guideline (OECD TG 237)	Honey bee larvae acute toxicity (Tier 1)	TGAI	12
Non-guideline (OECD 239)	Honey bee larvae chronic toxicity (Tier 1)	TGAI	12
Non-guideline (OECD TG 245)	Honey bee adult chronic oral toxicity (Tier 1)	TGAI	12
Non-guideline	Semi-field testing for pollinators (Tier 2)	TEP	24
Non-guideline	Field fielding study for pollinators (tunnel or colony feeding studies) (Tier 2)	TEP	24
Non-guideline	Field trial of residues in pollen and nectar (Tier 2)	TEP	24
850.3030	Honey bee toxicity of residues on foliage (Tier 2)	TEP	12
850.3040	Full Field Testing for Pollinators (Tier 3)	TEP	24

TGAI = technical grade active ingredient; TEP = typical end-use product

PLANNED RISK ASSESSMENTS FOR REGISTRATION REVIEW

The most recent comprehensive human health risk assessment for hexythiazox was completed on July 8, 2020 for assessing proposed label amendments for use on caneberry subgroup 13-07A and dates, and establishment of a tolerance without U.S. registration for residues in tea. The most recent ecological and environmental fate risk assessment was completed on February 12, 2020 to assess proposed increased application rates on caneberry subgroup 13-07A and dates. Findings and conclusions from these risk assessments are summarized in the *Hexythiazox: Problem formulation for Registration Review* and *Hexythiazox: Scoping Document for Registration Review*.

[12] 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.

During registration review, the Agency does anticipate the need to conduct new assessments or update elements of existing risk assessments for hexythiazox (Table 4). If toxicological endpoints or points of departure are revised based on the data that are anticipated to be required 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 4: Planned Risk Assessments for the Hexythiazox Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Ecological and Environmental Fate		
Non-listed species	Yes	Neither the environmental fate nor the ecological effects database is complete for hexythiazox. Data expected during registration review could change previous conclusions.
Drinking Water	Yes	The most recent estimated drinking water concentrations (EDWCs) assessed for hexythiazox are from currently labeled uses representing the potential maximum exposure sorghum estimated with the Pesticide Root Zone Model-Exposure Analysis Modeling System (PRZM-EXAMS; PE5) model. Model updates since the completion of the last drinking water assessment could result in changes in recommended EDWCs. If a change in EDWCs results in different risk conclusions, an update to the drinking water assessment may be necessary
Incidents	Yes	The Agency will continue to monitor for ecological incidents and will conduct an incidents search as part of the planned risk assessment.
Human Health		
Dietary		

Table 4: Planned Risk Assessments for the Hexythiazox Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Food	Yes	In the most recent hexythiazox chronic dietary risk assessments resulted in risk estimates below the Health Effects Division's (HED) level of concern (LOC). An acute dietary risk assessment is not required since no endpoint attributable to a single oral exposure was identified from the available toxicity database. However, a new dietary risk assessment may be required which utilizes the most current version of the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID; version 4.02). Any revisions to the dietary assessment will incorporate up to date percent crop treated (PCT) data, monitoring data, any updated Estimated Drinking Water Concentration estimates from the Ecological Fate and Effects Division (EFED), and any revised toxicological PODs, as appropriate.
Residential		
Handlers	No	HED has made the assumption that hexythiazox products are not for homeowner use, and, for all current and future assessments, a quantitative residential handler assessment will not be conducted unless PPE is removed from labels with residential use sites.
Post-application	Yes	Any updates to policies or practices for residential exposure and risk assessment will be incorporated at the time of the draft risk assessment for registration review including: updated PODs, exposure data (i.e., DFR, TTR), and the consideration of spray drift and volatilization for non-occupational bystanders.

Table 4: Planned Risk Assessments for the Hexythiazox Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Occupational		
Handlers (mixers, loaders, applicators)	Yes	Any updates to policies or practices for occupational or residential exposure and risk assessment will be incorporated at the time of the draft risk assessment for registration review including: updated PODs, exposure data (i.e., DFR, TTR), and the consideration of spray drift and volatilization for non-occupational bystanders.
Post-application	Yes	Any updates to policies or practices for occupational or residential exposure and risk assessment will be incorporated at the time of the draft risk assessment for registration review including: updated PODs, exposure data (i.e., DFR, TTR), and the consideration of spray drift and volatilization for non-occupational bystanders.
Non- occupational Exposure		
Spray drift	Yes	Previous assessment may need to be updated.
Bystander	Yes	Volatilization assessment needed.
Other Human Health		
Aggregate	Yes	Dictated by changes to dietary and exposure assessments.
Cumulative	No	EPA has not made a common mechanism of toxicity finding as to hexythiazox and any other substances, and hexythiazox does not appear to produce a toxic metabolite produced by other substances.
Tolerance changes required	Yes	HED will consider the need to update tolerances, such as to reflect updated policies or harmonization, including consideration of any comments from stakeholders.

Table 4: Planned Risk Assessments for the Hexythiazox Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Incident analysis, literature review	Yes	For a discussion of reported human incidents for hexythiazox, see page 4 of the Scoping Document and the *Hexythiazox: Tier I (Scoping) Review of Human Incidents and Epidemiology*.
Other Considerations		
Domestic Animal Incidents	No	There are no residential pet uses.

TIMELINE

The EPA created an estimated timeline for the completion of the hexythiazox registration review in Table 5.

Table 5: Projected Hexythiazox Registration Review Timeline

Activities	Estimated Date
Opening the Docket	
Open 60-day Public Comment Period	April 2023 - *completed*
Close Public Comment	June 2023 - *completed*
Case Development	
Updated Final Work Plan	July 2024
Issue DCI	February 2025
Data Submission	February 2027
60-day Public Comment Period for Draft Risk Assessments[13]	May – July 2028

NEXT STEPS

As noted previously, the Agency plans to require certain human health and/or ecological fate and effects data for hexythiazox through a Generic Data Call-In Notice, expected to be issued in January 2025. The data will be used to conduct updated human health and ecological risk assessments, which are planned for 2028. Based on the findings of risk assessments and consideration of benefits, the Agency may decide to issue an Updated Proposed Interim Registration Review Decision after completion of the updated risk assessments.

[13] 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.

Appendix – Additional Areas Considered in the Hexythiazox Registration Review

LISTED SPECIES ASSESSMENT:

This Appendix provides general background about the Agency's assessment of the effects of pesticides on listed species and designated critical habitats under the Endangered Species Act (ESA).

Developing Approaches for ESA Assessments and Consultation for FIFRA Actions

In 2015, EPA, along with the Services—the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS)—and the United States Department of Agriculture (USDA) (referred to as "the agencies") released their joint Interim Approaches[14] for assessing the effects of pesticides to listed species. 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 assessments of pesticides' effects to listed species. Since that time, the agencies have been continuing to work to improve the approaches for assessing effects to listed species. After receiving input from the Services and USDA on proposed revisions to the 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.[15]

The agencies also continue to work collaboratively through a FIFRA Interagency Working Group (IWG). The IWG was created under the 2018 Farm Bill 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.[16]

Consultation on Chemicals in Registration Review

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 received a final

[14] https://www.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report.
[15] https://www.epa.gov/endangered-species/revised-method-national-level-listed-species-biological-evaluations-conventional.
[16] https://www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act.

malathion biological opinion[17] from FWS in February 2022 and a final biological opinion from NMFS on malathion, chlorpyrifos and diazinon in June 2022.[18] The Agency plans to implement both biological opinions according to the 18-month timeframes specified in the biological opinions.

In 2020, EPA released draft BEs for the first two chemicals conducted using the 2020 Revised Method—carbaryl and methomyl. Subsequently, EPA has used the Revised Method to complete final BEs for carbaryl, methomyl, atrazine, simazine, glyphosate, clothianidin, imidacloprid, and thiamethoxam. EPA is currently in consultation with the Services on these active ingredients.

EPA's New Actives Policy and the 2022 Workplan

In January 2022, EPA announced a policy[19] 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 would not have a likelihood of jeopardizing listed species or adversely modifying their designated critical habitats. EPA will also initiate consultation with the Services as appropriate.

In April 2022, EPA released a comprehensive, long-term approach to meeting its ESA obligations, which is outlined in *Balancing Wildlife Protections and Responsible Pesticide Use*.[20] This workplan reflects the Agency's most comprehensive thinking to date on how to create a sustainable ESA-FIFRA program that focuses on meeting EPA's ESA obligations and improving protection for listed species while minimizing regulatory impacts to pesticide users and collaborating with other agencies and stakeholders on implementing the plan.

On November 16, 2022, EPA released the *ESA Workplan Update: Nontarget Species Mitigation for Registration Review and Other FIFRA Actions*.[21] As part of this update, EPA announced its plan to consider and include, as appropriate, a menu of FIFRA Interim Ecological Risk Mitigation intended to reduce off-target movement of pesticides through spray drift and runoff in its registration review and other FIFRA actions. These measures are intended to reduce risks to nontarget organisms efficiently and consistently across pesticides with similar levels of risks and benefits. EPA expects that these mitigation measures may also reduce pesticide exposures to listed species.

ENDOCRINE DISRUPTOR SCREENING PROGRAM:

The Federal Food Drug and Cosmetic Act (FFDCA) §408(p) requires EPA to develop a screening program to determine whether certain substances (including pesticide active and other

[17] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[18] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[19] https://www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.
[20] https://www.epa.gov/endangered-species.
[21] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf.

ingredients) may have an effect in humans similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." (21 U.S.C. 346a(p)). In carrying out the Endocrine Disruptor Screening Program (EDSP), FFDCA section 408(p)(3) requires that EPA "provide for the testing of all pesticide chemicals," which includes "any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), including all active and pesticide inert ingredients of such pesticide." (21 U.S.C. 231(q)(1) and 346a(p)(3)). However, FFDCA section 408(p)(4) authorizes EPA to, by order, exempt a substance from the EDSP if the EPA "determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen." (21 U.S.C. 346a(p)(4)).

The EDSP initiatives developed by EPA in 1998 includes human and wildlife testing for estrogen, androgen, and thyroid pathway activity and employs a two-tiered approach. 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 pathways. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship for any adverse estrogen, androgen, or thyroid effect. If EPA finds, based on that data, that the pesticide has an adverse endocrine effect on humans, FFDCA § 408(p)(6) also requires EPA, "… as appropriate, [to] take action under such statutory authority as is available to the Administrator … as is necessary to ensure the protection of public health." (21 U.S.C. 346a(p)(6)).[22]

Between October 2009 and February 2010, EPA issued Tier 1 test orders/data call-ins (DCIs) for its first list of chemicals ("List 1 chemicals") for EDSP screening and subsequently required submission of EDSP Tier 1 data for a refined list of these chemicals. EPA received data for 52 List 1 chemicals (50 pesticide active ingredients and 2 inert ingredients). EPA scientists performed weight-of-evidence (WoE) analyses of the submitted EDSP Tier 1 data and other scientifically relevant information (OSRI) for potential interaction with the estrogen, androgen, and/or thyroid signaling pathways for humans and wildlife.[23]

In addition, for FIFRA registration, registration review, and tolerance-related purposes, EPA collects and reviews numerous studies to assess potential adverse outcomes, including potential outcomes to endocrine systems, from exposure to pesticide active ingredients. Although EPA has been collecting and reviewing such data, EPA has not been explicit about how its review of required and submitted data for these purposes also informs EPA's obligations and commitments under FFDCA section 408(p). Consequently, on October 27, 2023, EPA issued a Federal Register Notice (FRN) providing clarity on the applicability of these data to FFDCA section 408(p) requirements and near-term strategies for EPA to further its compliance with FFDCA section 408(p). This FRN, entitled *Endocrine Disruptor Screening Program (EDSP): Near-Term Strategies for Implementation' Notice of Availability and Request for Comment* (88 FR 73841) is

[22] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.

[23] Summarized in *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions*;

EPA-HQ-OPP-2023-0474-0001; https://www.regulations.gov/document/EPA-HQ-OPP-2023-0474-0001

referred to here as EPA's EDSP Strategies Notice. EPA also published three documents supporting the strategies described in the Notice:

- *Use of Existing Mammalian Data to Address Data Needs and Decisions for Endocrine Disruptor Screening Program (EDSP) for Humans under FFDCA Section 408(p)*;
- *List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed;* and,
- *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions* (referred to here as List 1 Screening Conclusions).

The EDSP Strategies Notice and the support documents are available on www.regulations.gov in docket number EPA-HQ-OPP-2023-0474. As explained in these documents, EPA is prioritizing its screening for potential impacts to the estrogen, androgen, and thyroid systems in humans, focusing first on conventional active ingredients. Although EPA voluntarily expanded the scope of the EDSP to screening for potential impacts to the estrogen, androgen, and thyroid systems in wildlife, EPA announced that it is not addressing this discretionary component of the EDSP at this time, considering its current focus on developing a comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[24] and November 2022 ESA Workplan Update[25]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[26] indicate that available data were sufficient for FFDCA section 408(p) assessment and review for potential adverse effects to the estrogen, androgen, or thyroid pathways for wildlife. For the remaining 17 List 1 chemicals, Tier 1 WoE memoranda made recommendations for additional testing. EPA expects to further address these issues taking into account additional work being done in concert with researchers within the EPA's Office of Research and Development (ORD).

As discussed in EPA's EDSP Strategies Notice and supporting documents, EPA will be using all available data to determine whether additional data are needed to meet EPA's obligations and discretionary commitments under FFDCA section 408(p). For some conventional pesticide active ingredients, the toxicological databases may already provide sufficient evaluation of endocrine potential for estrogen, androgen, and/or thyroid pathways and EPA will generally not need to obtain any additional data to reevaluate those pathways, if in registration review, or to provide an initial evaluation for new active ingredient applications. For instance, EPA has endocrine-related data for numerous conventional pesticide active ingredients through either a two-generation reproduction toxicity study performed in accordance with the current guideline (referred to here as the updated two-generation reproduction toxicity study; OCSPP 870.3800 - Reproduction and Fertility Effects) or an extended one-generation reproductive toxicity (EOGRT) study (OECD Test Guideline 443 - Extended One-Generation Reproductive Toxicity Study). In these cases, EPA expects to make FFDCA 408(p)(6) decisions for humans without seeking further estrogen or androgen data. However, as also explained in the EPA's EDSP Strategies Notice, where these data do not exist, EPA will reevaluate the available data for the

[24] https://www.epa.gov/system/files/documents/2022-04/balancing-wildlife-protection-and-responsible-pesticide-use_final.pdf
[25] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf
[26] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and

conventional active ingredient during registration review to determine what additional data, if any, might be needed to confirm EPA's assessment of the potential for impacts to estrogen, androgen, and/or thyroid pathways in humans. For more details on EPA's approach for assessing these endpoints, see EPA's EDSP Strategies Notice and related support documents.

Also described in the EPA's EDSP Strategies Notice is a framework that represents an initial approach by EPA to organize and prioritize the large number of conventional pesticides in registration review. For conventional pesticides with a two-generation reproduction toxicity study performed under a previous guideline (i.e., an updated two-generation reproduction toxicity study or an EOGRT is not available), EPA has used data from the Estrogen Receptor Pathway and/or Androgen Receptor Pathway Models to identify a group of chemicals with the highest priority for potential data collection (described in EPA's EDSP Strategies Notice as Group 1 active ingredients). For these cases, although EPA has not reevaluated the existing endocrine-related data, EPA has sought additional data and information in response to the issuance of EPA's EDSP Strategies Notice to better understand the positive findings in the ToxCast™ data for the Pathway Models and committed to issuing DCIs to require additional EDSP Tier 1 data to confirm the sufficiency of data to support EPA's assessment of potential adverse effects to the estrogen, androgen, and/or thyroid pathways in humans and to inform FFDCA 408(p) data decisions. For the remaining conventional pesticides (described in EPA's EDSP Strategies Notice as Group 2 and 3 conventional active ingredients), EPA committed to reevaluating the available data to determine what additional studies, if any, might be needed to confirm EPA's assessment of the potential for impacts to endocrine pathways in humans.

As stated in the EPA's EDSP Strategies Notice, two-generation reproduction toxicity studies conducted prior to the guideline updates in 1998 may not have evaluated all of the same endocrine-related endpoints now included in the guideline. As a result, for these pesticides, EPA stated that it would need to re-evaluate the results of the two-generation reproduction toxicity studies along with any OSRI to confirm the sufficiency of data to support EPA's assessment of potential adverse effects to the estrogen, androgen, and/or thyroid pathways in humans. What constitutes additional data would depend on the extent of the available information. As appropriate to the circumstances, EPA indicated it might seek Tier 1 data or OSRI to augment the data obtained from these studies.

The two-generation reproduction toxicity study for hexythiazox was performed under a previous guideline. EPA has searched the toxicological database and public literature for endocrine-related data for hexythiazox. Although there are some endocrine-related data available, EPA has concluded that additional data are needed at this time to confirm its assessment of the estrogen and androgen pathways. The additional data is listed in Table 3.

Several studies are available in the database for hexythiazox that evaluated thyroid toxicity and there were no adverse thyroid effects observed related to thyroid hormone perturbations. No additional thyroid data are needed at this time. Therefore, EPA has concluded at this time that the points of departure for human health risk assessment to evaluate the EPA-registered uses and established tolerances of hexythiazox are protective of potential adverse thyroid effects in humans. EPA will further address its FFDCA section 408(p)(6) commitments and obligations as part of registration review.