Docket Number EPA-HQ-OPP-2023-0094
www.regulations.gov

Tolclofos-Methyl Final Work Plan

Registration Review: Initial Docket
Case Number 7072

July 2024

Approved by: Jean Overstreet

Jean Overstreet
Director
Pesticide Re-evaluation Division

Date: July 5, 2024

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References:

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

1. *Tolclofos Methyl. Updated Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review*. Adrian Britt, Sheila Piper, and Victoria Kurker. April 22, 2024.

2. *Tolclofos-methyl: Problem Formulation for Registration Review*. Mohammed Ruhman and Hannah Yingling. March 2, 2023.

3. *Tolclofos Methyl. Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review*. Adrian Britt, Sheila Piper, and Victoria Kurker. January 11, 2023.

4. *Tolclofos-Methyl: Summary of Hazard and Science Policy Council (HASPOC) Meeting on September 1st, 2022: Recommendations on the Need for a Multi-Generation Reproduction Study, 90-Day Inhalation Toxicity, 90-Day Dermal Toxicity Studies, a Developmental Neurotoxicity Study, a Developmental Toxicity Study in the Rabbit, and an In-Vivo Cytogenetics Study*. Zachary Staley. September 8, 2022.

5. *Tolclofos-Methyl: Tier I Scoping Review of Human Incidents and Epidemiology*. Shanna Recore, Elizabeth Evans, and Erin Jones. March 16, 2022.

These and other supporting documents for the tolclofos-methyl registration review case may be found in the docket EPA-HQ-OPP-2023-0094 at www.regulations.gov.

OVERVIEW

This is the Environmental Protection Agency's (EPA or the Agency) Final Work Plan (FWP) for registration review of tolclofos-methyl (CAS 57018-04-9, PC Code 128905). This FWP addresses public comments received concerning the Preliminary Work Plan (PWP), which was posted in the tolclofos-methyl registration review docket (EPA-HQ-OPP-2023-0094).

Tolclofos-methyl is a fungicide, first registered in 2013, used as a seed treatment to protect against soil-borne and seed-borne fungal pathogens that cause seed decay and seedling blights. The mode of pesticidal action as a fungicide is via oxidative deterioration of fungal lipids. Tolclofos-methyl is a member of the FRAC[1] 14 mode-of-action group.

Tolclofos-methyl is registered for seed treatment use on various crops, grasses and non-grasses (for forage, fodder, straw, and hay), ornamental flowers, and conifers. Tolclofos-methyl is not registered for any residential use sites. There are eight active Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3 end-use product registrations and one technical registration for tolclofos-methyl. The end-use product registrations are for both commercial and on-farm seed treatment. The end-use products are formulated as a liquid with tolclofos-methyl alone or combined with other pesticides (*e.g.,* difenoconazole, fludioxonil, imidacloprid, ipconazole, mefenoxam, metalaxyl, thiabendazole).

This Final Work Plan (FWP) explains what EPA knows about tolclofos-methyl, 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 the registration review of tolclofos-methyl.

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. Subsequently, the FWP details the planned data needs, planned risk assessments, and the projected registration review timeline for tolclofos-methyl. Lastly, there is a discussion of next steps.

STATUTORY AND REGULATORY AUTHORITY

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

[1] The fungicide resistance action committee (FRAC) assigns fungicides a code to group active ingredients which demonstrate potential for cross resistance because they have the same target site.

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. This is the first round of registration review of tolclofos-methyl.

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. After reviewing comments received in the docket during this initial comment period, the Agency developed this Final Work Plan (FWP) and anticipated schedule for the registration review of tolclofos-methyl.

UPDATES SINCE THE PWP WAS ISSUED

The Agency has made three minor corrections to clarify text in the document. The Agency corrected a typo on the case number for tolclofos-methyl on the cover page and in Table 1 from '7069' to 7072.' In the overview section, EPA corrected 'turf grass' to read 'grasses and non-grasses (for forage, fodder, straw, and hay)' since none of the tolclofos-methyl products are currently labeled for use on turf grass. In addition, the Agency corrected the test material for the Algal toxicity study using marine diatom (850.4500) in Table 3. The preferred test material for the study is typical end-use product (TEP). The Agency also updated the information in the Appendix, which includes information regarding the Endocrine Disruptor Screening Program (EDSP) for tolclofos-methyl, and additional studies in Table 3.

SUMMARY OF THE COMMENTS AND AGENCY RESPONSES

During the 60-day public comment period on the tolclofos-methyl Preliminary Work Plan (PWP), which opened in April 2023 and closed on June 5, 2023, the Agency received one public comment. The comment was submitted by Valent U.S.A. LLC (Valent). The comment does not affect the planned ecological and or/ human health risk assessments or data requirements. 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 comment. It is located in the tolclofos-methyl docket, EPA-HQ-OPP-2023-0094.

Comment submitted by Valent in EPA-HQ-OPP-2023-0094-0008.

Comment 1: For each environmental fate and ecotoxicology study anticipated to be required for the registration review of tolclofos-methyl, Valent noted whether they anticipate providing additional data, requesting a waiver, submitting an existing study, or conducting a new study. Valent also requested clarification of the test material for the Cyanobacteria (*Anabaena flos-aquae*) toxicity study (850.4550).

EPA Response 1: Per the guideline, the preferred test material for the Cyanobacteria (*Anabaena flos-aquae*) toxicity study (850.4550), is TEP. This also applies to the Algal toxicity study using marine diatom (850.4500). Table 3 has been updated accordingly.

For the fate study, anaerobic aquatic metabolism (835.4400), EPA prefers that the study be conducted. However, the registrant can submit a waiver request which will be reviewed by the Agency.

For the various ecotoxicology studies, EPA acknowledges the registrant's intention for fulfilling each data recommendation and looks forward to further information.

Comment 2: For the anticipated human health data requirement, 90-day inhalation toxicity study (870.3465), Valent stated they will evaluate adding PF-10 respirator language to the label for the commercial loading/planting of potato seed. They also noted that the respirator requirement does not apply to on-farm treating/planting of potato seed, according to the HASPOC document, since the MOE for this operation is greater than 1,000.

EPA Response 2: The Agency acknowledges that Valent will look into the feasibility of adding a PF-10 respirator to the label and agrees with Valent's assertion that a respirator is only needed for commercial seed treatment and does not apply to on-farm treating/planting of potato seed.

Comment 3: Valent agreed with the results of the Agency's incident review for tolclofos-methyl.

EPA Response 3: The Agency thanks Valent for their comment on the *Tolclofos-Methyl: Tier I Scoping Review of Human Incidents and Epidemiology.*

CHEMICAL AND REGULATORY INFORMATION

Table 1 provides a summary of the chemical identification and pesticide registration for tolclofos-methyl.

Table 1: Chemical Facts for Tolclofos-Methyl	
PC code(s)	128905
Case Number	7072
CAS Number	57018-04-9
Year first registered	2013
Pesticide Type	Fungicide
Chemical class	Organophosphorous compound
Mode of Action Group Number	FRAC 14
Date of last Registration Review Decision	N/A
Cumulative group	Not applicable. Tolclofos-methyl is an organophosphorus fungicide but is not included in the organophosphate (OP) chemical class due to differences in the mode of action, toxicity, and chemical structure relative to other registered OPs. As a result, EPA concludes that tolclofos-methyl does not have a common mechanism of toxicity with other substances.
Tolerances	Tolerances are not required for the registered seed treatment uses of tolclofos-methyl as they are determined to be non-food uses.
Dual-use	Products containing tolclofos-methyl 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 tolclofos-methyl.
Pesticide Re-evaluation Division, Chemical Review Manager	Susan Bartow bartow.susan@epa.gov 202-566-2280
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USE AND USAGE INFORMATION

Tolclofos-methyl is a fungicide that was first registered for use in 2013. There are eight FIFRA Section 3 end-use registrations and one technical registration. Tolclofos-methyl is registered for use solely as a seed treatment for the control and suppression of various soil-borne and seed-borne fungal pathogens for the following crops: crop group 1A root vegetables (excluding burdock, turnip-rooted chervil, ginseng, horseradish, salsify, black salsify, Spanish salsify and skirret); crop group 3-07 bulb vegetables (such as pearl or green onions but excluding daylily bulb, Elegans Hosta, fritillaria bulb and leaves, garlic bulb, great-headed garlic bulb, serpent

garlic bulb, lily bulb, Chinese onion bulb, macrostem onion bulb, potato onion bulb, tree onion tops, Welsh onion tops, and shallot bulb and fresh shallot leaves); crop group 4 leafy vegetables (except brassica vegetables); crop group 5 brassica (cole) leafy vegetables; crop group 6 succulent or dried legume vegetables; crop group 8-10 fruiting vegetables; crop group 9 cucurbit vegetables; crop group 15 cereal grains (except rice and wild rice); crop group 17 grass forage, fodder, and hay; crop group 18 non-grass animal feeds (forage, fodder, straw and hay); crop group 19 herbs and spices; crop group 20 oilseeds (except cotton); cotton; ornamental flowers; and conifers. Tolclofos-methyl may be applied to the seed in commercial facilities as well as on-farm.

Since the publication of the PWP for tolclofos-methyl, seed treatment data for some use sites have been acquired by the Agency which can be utilized qualitatively as an indicator of positive usage. However, at this time, it is not possible to estimate the geographic extent of the seed treatment usage or provide robust quantitative estimates of usage. Rather, the Agency provides a qualitative description of seed treatment usage using these datasets. An understanding of how usage of tolclofos-methyl ranks among other fungicide seed treatments may indicate its relative importance for crops for which data is available.

From 2017 to 2021, tolclofos-methyl usage was reported on cereals (barley, wheat, oats, rye), soybeans, sugarbeets, and pulses (edible dried legume seeds such as chickpeas, peas, lentils, beans (navy, kidney, black, pinto and great northern))[2]. Kline and Co., an additional survey data source, reported tolclofos-methyl usage on wheat, soybeans and sugarbeets in 2018[3]. In both surveys, tolclofos-methyl was not among the top three most widely used fungicide seed treatments in terms of sales, in dollars, nor in pounds of total volume sold for cereals, soybeans, sugarbeets or pulses[4].

Seed treatment fungicide use on alfalfa, corn, cotton, canola, peanut, rice, sorghum, and sunflower were surveyed for usage and sales from 2017-2021, however, no tolclofos-methyl usage or sales were reported, suggesting tolclofos-methyl was not likely to be widely used as a seed treatment on these crops[5].

The Agency does not have available sources of seed treatment data on the remaining registered agricultural and non-agricultural use sites of tolclofos-methyl. The absence of such seed treatment data should not be interpreted as lack of usage. Table 2 summarizes the use and usage information for tolclofos-methyl.

[2] Ben Kirk. 2022. United States Seed Treatment Product and Brand Historical Database. Database Subset: 2017-2021. Accessed May 2023.
[3] Kline and Company. 2019. Global Seed Treatment 2018: United States Market Analysis and Opportunities. Accessed May 2023.
[4] Kirk 2022 and Kline 2019.
[5] Kirk 2022.

Table 2: Tolclofos-Methyl Use and Usage Information	
Summary of Use	Fungicide member of FRAC 14.
Use Sites	Registered for seed treatment use only on cereal grains; conifers; cotton; grass/non-grass (forage, fodder, straw, and hay); herbs and spices; oilseeds; ornamental flowers; and vegetables (brassica, bulb, cucurbit, fruiting, leafy, legume, and root).
Summary of Usage	Tolclofos-methyl usage was reported on cereals, soybeans, sugarbeets, and pulses, though, tolclofos-methyl was not among the top three most widely used fungicide seed treatments in terms of dollar amount nor volume of sales from 2017 to 2021. The Agency does not have available sources of seed treatment data on the remaining registered agricultural and non-agricultural use sites of tolclofos-methyl. The absence of seed treatment usage analysis for these use sites should not be interpreted as lack of seed treatment usage.
Formulation Type(s)	Liquid
Application Method(s)	Commercial and on-farm seed treatment seed treatment
Technical Registrant(s)	Valent U.S.A. LLC
No. of Registrations	1 FIFRA Section 3 technical registration; 8 FIFRA Section 3 end-use registrations; 0 FIFRA Section 24(c) (special local needs—SLN) registrations
Restricted Use	Tolclofos-methyl has no products that are classified as restricted use.

RECENT ACTIONS

There are no recent actions for tolclofos-methyl since the publication of the PWP. Products containing tolclofos-methyl were first registered in 2013. Additional end-use products were registered in 2018 and 2020. In 2022, four more end use products containing tolclofos-methyl were registered. There are now eight end-use product registrations and one technical registration for tolclofos-methyl.

DATA NEEDS

The Agency anticipates calling in data in support of the tolclofos-methyl registration review case. The planned data needs have been expanded from what was included in the PWP to confirm EPA's assessment of estrogen and androgen effects as further explained in the Appendix on EDSP. 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. EPA anticipates issuing a data call-in (DCI) to obtain these data. The anticipated data needs are outlined in Table 3.

For additional discussion of the anticipated data needs, see the *Tolclofos-methyl: Problem Formulation for Registration Review* (Environmental Fate and Effects Division (EFED) Problem

Formulation) and *Tolclofos Methyl - Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review* (Health Effects Division (HED) Scoping Document), available in the tolclofos-methyl docket (EPA-HQ-OPP-2023-0094). Additionally, see the Appendix for information on EDSP for tolclofos-methyl.

Table 3: Anticipated Data Needs for the Tolclofos-Methyl Registration Review

Guideline Number	Study Title	Test Material	Estimated Timeframe (Months from receipt of DCI)
835.4400	Anaerobic aquatic metabolism (using two systems - river and pond)	TGAI or PAIRA	24
850.1400	Fish early-life stage toxicity test (using freshwater fish)	TGAI	12
850.4400	Aquatic plant toxicity test (using *Lemna spp*.)	TEP or TGAI	12
850.4550	Cyanobacteria (*Anabaena flos-aquae*) toxicity	TEP	12
850.4500[6]	Algal toxicity (using marine diatom)	TEP	12
870.3465	90-day inhalation toxicity[7]	TGAI	24
890.1150	Androgen receptor binding (Rat Prostate)	TGAI	6
890.1200	Aromatase (Human Recombinant)	TGAI	6
890.1250	Estrogen receptor binding (Rat Uterine)	TGAI	6
890.1300	Estrogen receptor transcriptional activation (Human Cell Line HeLa-9903)	TGAI	6
890.1400	Hershberger (Rat)	TGAI	9
890.1450	Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Female Rats	TGAI	15
890.1500	Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Male Rats	TGAI	15
890.1550	Steroidogenesis (Human Cell Line – H295R)	TGAI	6
890.1600	Uterotrophic (Rat)	TGAI	9
Pollinator Data Requirements[8]			
Non-guideline (OECD TG 213)	Honey bee adult acute oral toxicity (Tier 1)	TGAI	12

[6] OCSPP 850.4500 (Algal toxicity using marine diatom) was formerly OPPTS 850.5400 (Algal toxicity).

[7] The Hazard Science and Policy Council (HASPOC) recommended that the subchronic inhalation toxicity study not be waived for tolclofos-methyl. However, if a PF10 respirator is added to the commercial seed treatment label directions for loading/planting of potato seed, the estimated inhalation margin of exposure (MOE) would increase to > 10 times the level of concern (LOC). In that case, an inhalation study would not be needed, and the HASPOC would recommend waiving the inhalation study, pending finalization of modified labels. The HASPOC memo is available in the public docket (EPA-HQ-OPP-2023-0094-0005) on regulations.gov.

[8] 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.

Table 3: Anticipated Data Needs for the Tolclofos-Methyl Registration Review			
Guideline Number	**Study Title**	**Test Material**	**Estimated Timeframe (Months from receipt of DCI)**
Non-guideline (OECD TG 237)	Honey bee larvae acute toxicity (Tier 1)	TGAI	12
Non-guideline (OECD TG 245)	Honey bee adult chronic oral toxicity (Tier 1)	TGAI	12
Non-guideline (OECD TG 239)	Honey bee larvae chronic toxicity (Tier 1)	TGAI	12
Non-guideline	Semi-field testing for pollinators (Tier 2)	TEP	24
Non-guideline	Field feeding study for pollinators (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	Field Testing for Pollinators (Tier 3)	TEP	24
TGAI = technical grade active ingredient; PAIRA = Pure active ingredient radio-labeled; TEP = typical end-use product			

As discussed in the PWP, the Agency also needs the amount of tolclofos-methyl added to 100 pounds of seed for each crop to provide further clarity for what is already provided on the label. This information will allow the Agency to model tolclofos-methyl exposure accurately and avoid making assumptions that may not align with actual use. In addition, usage data for tolclofos-methyl by use site is of interest. These data include application rate per seed, maximum seeding rate, and percent of seed treated with tolclofos-methyl by registered crop and geographic unit (e.g., national, region, state).

PLANNED RISK ASSESSMENTS FOR REGISTRATION REVIEW

The most recent comprehensive human health risk assessment for tolclofos-methyl was completed on November 20, 2012, when tolclofos-methyl was initially registered with EPA. The most recent ecological and environmental fate risk assessment was completed August 3, 2012, for the same purpose. Findings and conclusions from these risk assessments are summarized in the EFED Problem Formulation and HED Scoping Document, which are available in the tolclofos-methyl registration review docket (EPA-HQ-OPP-2023-0094) at www.regulations.gov.

During registration review, the Agency does anticipate the need to conduct new assessments or update elements of existing risk assessments for tolclofos-methyl. 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, EPA plans to review and update labels as some labels/use sites may be lacking use parameters critical to risk assessment. Table 4 presents a summary of the anticipated risk assessments for the tolclofos-methyl registration review based on the EFED Problem Formulation and HED Scoping Document.

Table 4: Planned Risk Assessments for the Tolclofos-Methyl Registration Review

Type of Risk Assessment	Conduct?	Notes
Ecological and Environmental Fate		
Non-listed species	Yes	The Agency will use data expected during registration review to update risk assessments for estuarine/marine fish on a chronic basis, vascular aquatic plants, nonvascular marine diatom, and honeybees on an acute and chronic basis.
Drinking Water	No	Given the limited pattern of use (*i.e.,* seed treatment), the Agency does not expect exposure from drinking water; hence, a drinking water assessment is not needed at this time.
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		
Food	No	Given the limited uses, non-food use determination, and low rates of application a dietary assessment is not needed at this time.
Residential		
Handlers	No	Products are not registered for residential use sites and therefore not used by residential handlers.
Post-application	No	Products are not registered for use on residential sites or golf courses.
Occupational		
Handlers (mixers, loaders, applicators)	Yes	The Agency will complete an updated occupational exposure assessment to reflect the updated seed treatment assessment.
Post-application	Yes	The Agency will complete an updated occupational exposure assessment to reflect the updated seed treatment assessment.

Table 4: Planned Risk Assessments for the Tolclofos-Methyl Registration Review		
Type of Risk Assessment	**Conduct?**	**Notes**
Non-occupational Exposure		
Spray drift	No	The Agency does not expect exposure in residential and non-occupational settings.
Bystander	No	The Agency does not expect exposure in residential and non-occupational settings.
Other Human Health		
Aggregate	No	An aggregate assessment combines pesticide exposures and risks from three major sources: food, drinking water, and residential/non-occupational exposures. The Agency does not expect exposure from food, drinking water, or in residential/non-occupational settings.
Cumulative	No	Tolclofos-methyl does not have a common mechanism of toxicity with other substances.
Tolerance changes required	No	No tolerances are required for the registered seed treatment uses of tolclofos-methyl as they are non-food uses.
Incident analysis, literature review	Yes	For a discussion of reported human incidents for tolclofos-methyl, see page 5 of the Scoping Document and the *Tolclofos-Methyl: Tier I Scoping Review of Human Incidents and Epidemiology.*
Other Considerations		
Domestic Animal Incidents	No	There are no residential pet uses.

TIMELINE

EPA has created the estimated timeline for the next steps of the tolclofos-methyl registration review in Table 5.

Table 5: Projected Tolclofos-Methyl Registration Review Timeline	
Activities	**Estimated Date**
Opening the Docket	
Open Docket and 60-day Public Comment Period	April 2023 - *completed*
Close Public Comment	June 2023 - *completed*
Case Development	
Final Work Plan	July 2024 - *completed*
Issue DCI	January 2025
Data Submission	January 2026

Table 5: Projected Tolclofos-Methyl Registration Review Timeline	
Activities	**Estimated Date**
60-day Public Comment Period for Draft Risk Assessments[9]	April – June 2028

NEXT STEPS

As noted previously, the Agency plans to require certain human health and ecological fate and effects data for tolclofos-methyl through a Generic Data Call-In Notice, expected to be issued in January 2025. The data will be used to conduct human health and ecological risk assessments, which are planned in April 2028.

[9] 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 Tolclofos-Methyl Registration Review

FEDERALLY THREATENED/ENDANGERED (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[10] 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.[11]

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.[12]

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

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

consultation with NMFS on malathion, chlorpyrifos and diazinon to consider new information that was not available when NMFS issued its 2017 biological opinion.

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.

In February 2022, EPA received a final malathion biological opinion[13] from FWS in February 2022 and a final biological opinion from NMFS on malathion, chlorpyrifos and diazinon in June 2022.[14] In August 2023, the Agency implemented the FWS malathion biological opinion by issuing Endangered Species Protection Bulletins[15] and approving malathion label amendments[16] to incorporate measures to protect listed species. In March 2024, EPA implemented the NMFS biological opinion for malathion, chlorpyrifos (for non-food uses), and diazinon.[17]

EPA's New Actives Policy and the 2022 Workplan

In January 2022, EPA announced a policy[18] 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*.[19] 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.

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[13] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[14] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[15] https://www.epa.gov/endangered-species/endangered-species-protection-bulletins.
[16] https://www.regulations.gov/document/EPA-HQ-OPP-2009-0317-0154.
[17] https://www.epa.gov/pesticides/epa-announces-implementation-mitigation-measures-insecticides-chlorpyrifos-diazinon-and#:~:text=For%20chlorpyrifos%2C%20diazinon%2C%20and%20malathion,one%20or%20more%20listed%20species.
[18] https://www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.
[19] https://www.epa.gov/endangered-species.

On November 16, 2022, EPA released the *ESA Workplan Update: Nontarget Species Mitigation for Registration Review and Other FIFRA Actions*.[20] 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.

The *ESA Workplan Update* also discussed additional efforts to expedite and streamline ESA consultation, including the Vulnerable Species Pilot, regional strategies (i.e., a Hawaii strategy), approaches for specific niche pesticide uses (e.g., mosquito adulticide applications), and programmatic approaches to consultation (e.g., the Herbicide Strategy).

In June 2023, EPA announced proposed mitigation for the Vulnerable Species Pilot, an implementation plan, and information on potential expansion of the pilot.[21] EPA also published interactive maps (StoryMaps) for the 27 pilot species to convey geospatial information about the location of the affected species and the location of draft pesticide application minimization and avoidance zones to protect these species.[22] Visit the public docket for more information about the Vulnerable Species Pilot (docket EPA-HQ-OPP-2023-0327 at www.regulations.gov).

In July 2023, EPA published the framework of the Draft Herbicide Strategy[23] for public comment along with various supporting documents. For more information about the Herbicide Strategy, visit the public docket (docket EPA-HQ-OPP-2023-0365 at www.regulations.gov).

EPA continues to work on these pilot efforts and once finalized, expects to implement these through registration review and new active ingredient registration.

[20] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf.
[21] https://www.regulations.gov/document/EPA-HQ-OPP-2023-0327-0002.
[22] View the StoryMaps for the 27 pilot species here: https://storymaps.arcgis.com/collections/896d140363174c9d8ee78e4c471bd7fd.
[23] https://www.regulations.gov/document/EPA-HQ-OPP-2023-0365-0009.

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 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))[24].

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.[25]

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

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

[25] 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

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 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[26] and November 2022 ESA Workplan Update[27]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[28] 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

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

(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 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 tolclofos-methyl was performed under a previous guideline. EPA has searched the toxicological database and public literature for endocrine-related data for tolclofos-methyl. 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 need for additional thyroid data for tolclofos-methyl has been considered by EPA's Hazard and Science Policy Council (HASPOC) using a WoE approach. The HASPOC recommended that additional thyroid data are not needed at this time (Pope-Varsalona, TXR# 0057878, 12-June-2019). Therefore, EPA has concluded at this time that the points of departure for human health risk assessment to evaluate the EPA-registered uses of tolclofos-methyl 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.