OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION
WASHINGTON, D.C. 20460

MEMORANDUM

DATE: 4/22/2024

SUBJECT: **Tolclofos Methyl. Updated Scoping Document:** Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review

PC Code: 128905
CAS No.: 57018-04-9
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Risk Assessment Type: Single Chemical Aggregate
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40 CFR: NA

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The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

The Pesticide Re-evaluation Division (PRD) has requested that the Health Effects Division (HED) complete a scoping document for the registration review of tolclofos-methyl. HED considered the most recent human-health risk assessments with respect to its toxicity, exposure, and usage databases, the most updated HED science policy and risk assessment methodologies, incident databases, and conducted a screening-level literature search to determine the scope of work necessary to support the registration review of tolclofos-methyl. This is the first time the Agency will conduct the registration review of tolclofos-methyl.

INTRODUCTION

Consistent with the Food Quality Protection Act of 1996, under FIFRA, HED is providing a scoping document for tolclofos-methyl in support of registration review. This updated scoping document provides a summary of the current risks associated with tolclofos-methyl and identifies data needs as well as anticipated risk assessments needed to support the registration review. Since the initial scoping document was completed in 2023 (D464839, A. Britt *et. al.*, 11-JAN-2023), the final data needs for satisfying the Endocrine Disruptor Screening Program (EDSP) were determined and incorporated into this updated scoping document.

Tolclofos-methyl (*O*-(2,6-dichloro-4-methylphenyl) *O,O*-dimethyl phosphorothioate) is an organophosphorus fungicide used to protect plants from soil borne and seed borne fungal pathogens. The mode of pesticidal action as a fungicide is via oxidative deterioration of fungal lipids. Tolclofos-methyl is registered for seed treatment use on various crops, turf grass, ornamental flower, and conifers. There are seven active liquid formulation end-use product labels (EPA Reg. Nos. 42750-327 [6.95% a.i.], 42750-334 [3.6% a.i.], 42750-381 [4.61% a.i.], 45002-30 [9.82% a.i.], 59639-178 [42% a.i.]), 45002-28 [13.90% a.i.], 45002-46 [13.9% a.i.], and one technical label (EPA Reg. No. 59639-177 [97% a.i.]) for tolclofos-methyl. The registered labels are for both commercial and on-farm seed treatment. The registered labels also state that the product is only to be applied to "true seeds" and is not to be applied on other propagation parts. The application rates range from 0.00000977 to 0.000489 lb ai/lb seed. Tolerances are not required for the registered seed treatment uses of tolclofos-methyl as they are determined to be non-food uses. There are no residential uses.

EXPOSURE PROFILE

Humans are not expected to be exposed to tolclofos-methyl in their diet as these registered seed treatment uses of tolclofos-methyl have been determined to be non-food uses. Tolclofos-methyl may transport to nearby surface water through runoff and erosion, especially if tolclofos-methyl treated

seeds are planted coinciding with or closely followed by a rain event. However, based on the very low proposed seed treatment application rates, environmental fate data, and modeling estimates; HED does not expect the proposed seed treatment uses of tolclofos-methyl to adversely impact ground water or surface water. There are also no residential uses of tolclofos-methyl, so exposure in residential and non-occupational settings is not expected. In an occupational setting, applicators may be exposed while handling the pesticide prior to and during the application to the seed. Additionally, there is potential for exposure to workers who handle previously treated seed during planting activities. Handler exposure is expected to be short- (1 to 30 days) or intermediate-term (1 to 6 months) in duration and can result in both dermal and inhalation exposures.

ANTICIPATED DATA NEEDS

HED has reviewed the most recent risk assessments (D387242, C. Smith, 22-MAR-2012; D406797, E. Reaves *et. al.,* 20-NOV-2012) and the existing database for tolclofos-methyl to determine the need for additional data and any updates to the human health risk assessment to support the forthcoming registration review decision. The Hazard Science and Policy Council (HASPOC) recommended that the subchronic inhalation toxicity study not be waived for tolclofos-methyl (TXR 0058302, Z. Staley, 08-SEP-2022). 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.

Toxicology

The existing toxicology database is not complete but is adequate for characterizing tolclofos-methyl toxicity and quantification of risk for a non-food seed treatment use. In accordance with the revised 40 CFR Part 158 Toxicity Data Requirements, the tolclofos-methyl database lacks a multi-generation reproduction toxicity study in rats, a 90-day dermal toxicity study in rats, a developmental neurotoxicity study, a developmental toxicity study in rabbits, an adequate *in vivo* genotoxicity mammalian cell assay, and a subchronic inhalation toxicity study.

Based on a weight of evidence (WOE) approach, considering all the available hazard and exposure data for tolclofos-methyl, the HASPOC recommended that the multi-generation reproduction study, 90-day dermal study, developmental neurotoxicity study, developmental toxicity study in the rabbit, and *in-vivo* mammalian genotoxicity study be waived (TXR 0058302, Z. Staley, 08-SEP-2022).

Based on a WOE approach, the HASPOC also recommended that the subchronic inhalation toxicity study not be waived for tolclofos-methyl (TXR 0058302, Z. Staley, 08-SEP-2022). In the absence of this study, a 10X database uncertainty factor would be applied (LOC = 1,000) for assessing inhalation risks for the exposure scenario that results in an MOE that is not 10 times greater than the LOC for inhalation exposure. This uncertainty factor would remain applicable until either an inhalation study is submitted, or other information is provided to support a data waiver. However, if a PF10 respirator is added to the commercial seed treatment label directions for loading/planting of potato seed, the estimated inhalation MOE would increase to > 10 times the 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. These recommendations may be revised if the use or exposure patterns for tolclofos-methyl change in the future.

It is noted that additional toxicity studies would be required to fulfill the Revised Part 158 guidelines for any other use than the seed treatment use, especially for a food use, and the registrant should consult with the Agency about any of the outstanding studies before requesting any additional uses.

Please see Appendix B for a discussion of the endocrine disruptor screening program as it relates to tolclofos-methyl.

Occupational and Residential Exposure

HED notes that two labels (EPA Reg. No. 42750-327, EPA Reg. No. 59639-178) have maximum seeding rate limitations of 200 lbs seed/A for all crops except cotton, which has a 40 lbs seed/A seeding rate limitation. The remaining tolclofos-methyl labels do not contain this seeding rate limitation. Due to differences in the labeled seeding rates and HED standard assumptions concerning seeding rates, registration review may require the seeding rate information on the registered labels to be revised.

In accordance with the updated Part 158 data requirements (2007), one or more dislodgeable foliar residue (DFR) studies are required when a pesticide has residential or occupational uses that could result in post-application dermal exposure. Since there is no hazard via the dermal route of exposure, DFR studies are not needed for tolclofos-methyl at this time. If the dermal hazard determination were to change, the need for DFR studies may be re-evaluated in the future to refine the post-application assessment.

Chemistry/Dietary

The residue chemistry database for tolclofos-methyl is complete to support current data requirements. Adequate metabolism, storage stability, magnitude of the residue, and processing data are available to support the registered uses. An adequate data collection method is available for tolclofos-methyl. No additional residue chemistry data are required to support the current registrations. ChemSAC concluded if all total radioactive residue (TRR) results are less than 5 ppb (Reduced Residue Chemistry Data Requirements for Seed Treatment Uses and Guidance Document, D. Vogel, 1/26/2018), then the proposed seed treatment uses of tolclofos-methyl on various crops can be classified as non-food. The radiotracer study for the seed treatment use of tolclofos-methyl on corn, lettuce, soybean, cucumber, radish, and cotton seeds supports the seed treatment uses being classified as non-food uses ($\leq$5 ppb). The results showed that plants grown for seeds treated with [phenyl-^{14}C]tolclofos-methyl did not take up the radiolabeled test substance residue. HED would not recommend conducting a dietary assessment for tolclofos-methyl given its limited uses, non-food use determination, and low rates of application.

ANTICIPATED RISK ASSESSMENTS FOR REGISTRATION REVIEW

As part of Registration Review, the toxicological endpoints, doses and uncertainty/safety factors used in the most recent risk assessment will be re-evaluated according to current HED policy. An updated

occupational and residential exposure assessment will be completed to reflect the updated seed treatment assessment.

Unlike other pesticides, for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to tolclofos-methyl and any other substances. For the purposes of this action, therefore, EPA has not assumed that tolclofos-methyl has a common mechanism of toxicity with other substances.

In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis.[1] This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[2] and conducting cumulative risk assessments (CRA).[3]

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. At this time, EPA does not expect any exposures from other pesticides or substances that would warrant screening tolclofos-methyl with the framework. As a result, EPA concludes that tolclofos-methyl does not have a common mechanism of toxicity with other substances. If other pesticides are registered that have the potential to be screened with tolclofos-methyl, EPA will use the framework to examine the potential for a common mechanism of toxicity and the potential for cumulative risk as part of the ongoing registration review process.

INCIDENT REPORT SUMMARY

A Tier I Incident Report has been completed for tolclofos-methyl. HED has reviewed the available incident data and the Agricultural Health Study (AHS) publications listed on the AHS publication website for tolclofos-methyl. For this evaluation, both OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR-Pesticides) databases were consulted for pesticide incident data on the active ingredient tolclofos-methyl (PC Code: 128905). The purpose of the database search is to identify the frequency and severity of incidents attributed to tolclofos-methyl exposure reported to IDS and SENSOR-Pesticides. In addition, a search for available epidemiological publications was also conducted.

For the Main IDS for the five years from January 1, 2017, to March 8, 2022, there were no incidents reported that involved the active ingredient tolclofos-methyl. For Aggregate IDS for the five years from January 1, 2017, to March 8, 2022, there was one incident reported involving tolclofos-methyl. This incident was classified as having no or unknown effects

[1] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
[2] Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)
[3] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

A query of SENSOR-Pesticides 1998-2017 identified no cases involving tolclofos-methyl.

EPA reviewed the AHS publications listed on the AHS publication website. As of March 1, 2022, no epidemiological studies were identified that evaluated exposure to tolclofos-methyl and adverse health effects.

HED conducted a review of the open literature for Registration Review. In creating the Tier I Scoping memorandum, a search of the available peer-reviewed literature on March 1, 2022, returned 6, 1, and 10 publications from PubMed, PubMed Central, and Science Direct, respectively. None of the 17 publications were epidemiologic studies that evaluated exposure to tolclofos-methyl and adverse health effects.

HED will continue to monitor the incident and epidemiology information and, if a concern is triggered, then additional analysis will be included in the registration review risk assessment.

REFERENCES

Tolclofos-methyl. Human Health Risk Assessment for Proposed New Seed Treatment Uses. D387242, C. Smith, 22-MAR-2012.

Tolclofos-methyl. REVISED Human Health Risk Assessment for Proposed New Seed Treatment Uses. D406797, E. Reaves *et. al.,* 20-NOV-2012.

Tolclofos-Methyl: Tier I Scoping Review of Human Incidents and Epidemiology, D464849, S. Recore *et. al.,* 16-MAR-2022.

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; TXR 0058302, Z. Staley, 8-SEP-2022.

Reduced Residue Chemistry Data Requirements for Seed Treatment Uses and Seed-Treatment Focus Group (STFG) Guidance Document, D. Vogel, January 26, 2018.

Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999).

Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002).

Tolclofos Methyl. Scoping Document: Recommendation for Anticipated Data and Human Health Risk Assessments for Registration Review. D464839, A. Britt *et. al.*, 11-JAN-2023.

APPENDIX A. Seeding and Use Rates

Below are the maximum seeding rate conversions from fl oz/lb seed to lb ai/A based on EPA's assumptions. Of note, two labels (EPA Reg. No. 42750-327, EPA Reg. No. 59639-178) have maximum seeding rate limitations of 200 lbs seed/A for all crops except cotton and root vegetables (crop group 1A exclude burdock, chervil, turnip-rooted; ginseng; horseradish; salsify; salsify, black; salsify, Spanish; skirret), which has a 40 lb/A seeding rate limitation.

Tolclofos-methyl Calculations for Seeds:

Cotton
(1.5 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.00049 lb ai/lb seed
= (0.0093 lb ai/lb seed) (19 lb seed/A[2]) = **0.0093 lb ai/A**

Corn
(0.3 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.000098 lb ai/lb seed
= (0.000098 lb ai/lb seed) (30 lb seed/A[2]) = **0.0029 lb ai/A**

Soybean
(0.3 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.000098 lb ai/lb seed
= (0.000098 lb ai/lb seed) (167 lb seed/A[2]) = **0.016 lb ai/A**

Cucumber
(0.3 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.000098 lb ai/lb seed
= (0.000098 lb ai/lb seed) (12 lb seed/A[2]) = **0.0012 lb ai/A**

Radish
(1.5 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.00049 lb ai/lb seed
= (0.0049 lb ai/lb seed) (33lb seed/A[2]) = **0.0162 lb ai/A**

Lettuce
(0.3 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.000098 lb ai/lb seed
= (0.000098 lb ai/lb seed) (0.39 lb seed/A[2]) = **0.00004 lb ai/A lettuce leaf**

[1] RizolexTM Flowable Fungicide label (EPA Reg. No. 59639-178)

[2] SOP ExpoSAC Standard Values for the Amount of Seed Treated and/or Planted Per Day; Table 3.1 Maximum Seedling Rate (Jan 2022) and Tolclofos-methyl. REVISED Human Health Risk Assessment for Proposed New Seed Treatment Uses. D406797, E. Reaves *et. al.,* 20-NOV-2012.

Tolclofos-methyl use rates as shown below were calculated using BEAD seeding rates as calculated above.

Table A.1. Tolclofos-methyl Use Rates

Raw Agricultural Commodities (RACs)	fl oz/100 lb seed[1]	lbs ai/lb seed[2]	Maximum Seedling Rate lb seed/A[3] (Label rates)	lb ai/A[4] (Label rates)	Maximum Seedling Rate lb seed/A[5] (EPA rates)	lb ai/A[6] (EPA rates)	g ai/100 kg seed[7]
Cotton	1.5	0.00049	40	0.02	19	0.0093	50
Corn	0.3	0.000098	200	0.02	30	0.0029	10
Soybean	0.3	0.000098	200	0.02	167	0.016	10
Cucumber	0.3	0.000098	200	0.02	12	0.0012	10
Radish	1.5	0.00049	40	0.02	33	0.01617	50
Lettuce	0.3	0.000098	200	0.02	0.39	0.00004 (leaf)	10

[1,3] Tolclofos-methyl labels (Rizolex Flowable Fungicide EPA Reg. No. 59639-178)

[2] Example of calculations for lb ai/A- Cotton (1.5 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.00049 lb ai/lb seed

[4] Example of calculations for lb ai/A- Cotton (1.5 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.00049 lb ai/lb seed = (0.00049 lb ai/lb seed) (40 lb seed/A[2]) = 0.02 lb ai/A

[5] Maximum seedling rate from SOP ExpoSAC Standard Values for the Amount of Seed Treated and/or Planted Per Day; Table 3.1 Maximum Seedling Rate (Jan 2022) and Tolclofos-methyl. REVISED Human Health Risk Assessment for Proposed New Seed Treatment Uses. D406797, E. Reaves *et. al.,* 20-NOV-2012

[6] Example of calculations for lb ai/A- Cotton (1.5 fl oz/100 lb seed[1]) (1 gal/128 fl oz) (4.17 lb ai/gal) = 0.00049 lb ai/lb seed = (0.00049 lb ai/lb seed) (19 lb seed/A[2]) = 0.0093 lb ai/A (SOP ExpoSAC Standard Values for the Amount of Seed Treated and/or Planted Per Day; Table 3.1 Maximum Seedling Rate (Jan 2022)

[7] The target tolclofos-methyl seed treatment application rate for cotton (50 g ai/100 kg seed) and CG 1,2 and 3 (10 g ai/100kg seed). D362358, S. Piper, 27-FEB-2009

APPENDIX B. Endocrine Disruptor Screening Program (EDSP)

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))[4].

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.[5]

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*

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

[5] 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

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[6] and November 2022 ESA Workplan Update[7]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[8] 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 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,

[6] https://www.epa.gov/system/files/documents/2022-04/balancing-wildlife-protection-and-responsible-pesticide-use_final.pdf

[7] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf

[8] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and

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 (TXR 0057878, Pope-Varsalona, 12-JUN-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 address its FFDCA section 408(p)(6) commitments and obligations as part of registration review.