Demiditraz

Proposed Final Registration Review Decision
Case Number 7482

February 2024

Approved by: _____

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Date: February 27, 2024

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I. INTRODUCTION

This document is the Environmental Protection Agency's (EPA or the Agency) Proposed Final Registration Review Decision (PFD) for demiditraz (PC Code 577501, case 7482). In a registration review decision under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Agency determines whether a pesticide continues to meet FIFRA's registration standard.[1] A final registration review decision addresses all aspects of the registration review, as necessary, including considerations under the Endangered Species Act (ESA) and for the Endocrine Disruptor Screening Program (EDSP) under the Federal Food, Drug and Cosmetic Act (FFDCA)[2] as amended by the Food Quality Protection Act (FQPA). For more information on demiditraz see EPA's public docket (EPA-HQ-OPP-2021-0407) at www.regulations.gov.

FIFRA[3] mandates the continuous review of existing pesticides. Pesticides distributed or sold in the United States must be registered by EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. In 2006, the Agency began implementing the registration review program in which EPA reviews each registered pesticide every 15 years. Through the registration review program, the Agency intends to verify that all registered pesticides continue to meet the registration standard as the ability to assess and mitigate risks evolves and as policies and practices change. By periodically re-evaluating pesticides as science, public policy, and pesticide-use practices change, the Agency ensures that the public can continue to use products in the marketplace that do not present unreasonable adverse effects on human health or the environment. For more information on the registration review program, see http://www.epa.gov/pesticide-reevaluation. The Agency is issuing a PFD for demiditraz before issuing a final decision in registration review, as required under 40 CFR 155.58.

Demiditraz was first registered with EPA as an active ingredient in 2013. EPA has registered one product containing demiditraz as a spot-on product to kill blood-feeding invertebrates (ticks and fleas) on dogs. The registered end-use product (EPA Reg. No. 1007-97, LA Combo for Dogs) contains two active ingredients: demiditraz (14.4%) and fipronil (4.8%). The directions for use instruct the applicator to reapply the product to the skin of dogs every 30 days to control fleas and ticks and to prevent reinfestation.

A. Historical Context

1. The Registration Decision for Demiditraz

A registration decision for demiditraz was issued in 2013. During the decision-making process, EPA did not identify any potential ecological risks of concern. Furthermore, EPA determined

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

that the use of the compound will result in no effect (NE) on federally listed threatened or endangered species and its use will not adversely modify designated critical habitat of federally listed species. EPA also did not identify potential human health risks of concern. For more detail on how the potential risks and benefits were determined, see the Combined Work Plan and Proposed Interim Registration Review Decision for demiditraz, available in the public docket.

At the PID stage, EPA had not made a determination on whether it had met its obligations for demiditraz under the endocrine screening program at section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Since then, EPA has evaluated the studies available in the database for demiditraz and determined that there were no adverse thyroid effects observed, allowing it to make a determination.

B. Organization of this Document

This document is organized in five sections:

- *Introduction* (summarizing the registration review milestones and responding to public comments);
- *Use and Usage* (discussing how and where demiditraz is used);
- *Scientific Assessments* (summarizing EPA's risk and benefits assessments, updating or revising previous risk assessments, and discussing risk characterization);
- *Proposed Final Registration Review Decision* (presenting EPA's proposed decision, regulatory rationale, and any mitigation measures to address risks of concern); and
- *Next Steps and Timeline* (discussing how and when EPA intends to complete registration review).

C. Summary of Demiditraz Registration Review

In March 2023, EPA published the Combined Work Plan and Proposed Interim Registration Review Decision (PID) for demiditraz. The Following summary highlights other significant milestones that occurred during the registration review of demiditraz:

- March 2023 – EPA posted the Combined Work Plan and PID for demiditraz for a 60-day public comment period. The Agency received no comments. Along with the Combined Work Plan and PID, the following documents were also posted to the demiditraz docket:
    - *Demiditraz: Combined Human Health Scoping Document and Human Health Draft Risk Assessment in Support of Registration Review,* dated January 25, 2023.
    - *Demiditraz: Preliminary Problem Formulation and Ecological Risk Assessment in Support of Registration Review*, dated June 15, 2022.

- February 2024 – EPA is issuing this PFD for demiditraz in the public docket for a 60-day public comment period.

D. Summary of Public Comments on the Draft Risk Assessments and Agency Responses

During the 60-day public-comment period for the Demiditraz Combined Work Plan and PID and Draft Risk Assessments (April 1, 2023 to June 5, 2023), the Agency received no public comments.

II. USE AND USAGE

Demiditraz (PC # 577501) is a spot-on acaricide first registered in 2013 for use on domesticated dogs and puppies nine weeks and older. This active ingredient has one technical grade registration and one end-use registration. The end-use registration is co-formulated with fipronil and is labeled for control and prevention of flea infestations as well as control and prevention of brown dog ticks (*Rhipicephalus sanguineus*) and American dog ticks (*Dermacentor variabilis*). There are no registered food/feed uses for demiditraz.

Data characterizing national usage of insecticidal products are limited. Available data (*i.e.*, calendar years 2016 and 2019) indicate that there was no reported usage of demiditraz for flea and tick control on dogs in 2016 or 2019.[4,5] The absence of reported usage available for demiditraz does not demonstrate that these products are not used but does suggest that usage of demiditraz is likely low.

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

The Agency has summarized the 2023 HH DRA below. The Agency used the most current science policies and risk assessment methodologies to prepare this risk assessment in support of the registration review of demiditraz. For additional details on the 2023 HH DRA, see *Demiditraz: Combined Human Health Scoping Document and Human Health Draft Risk Assessment in Support of Registration* in EPA's public docket (EPA-HQ-OPP-2021-0407).

1. <u>Risk Summary and Characterization</u>

a. Dietary (Food + Water) Risks

There are no existing food uses for demiditraz, therefore, the Agency did not identify any dietary or drinking water exposure risks.

[4] Kline and Company. 2017. Consumer Markets for Pesticides and Fertilizers 2016: U.S. Market Analysis and Opportunities – Volume 1. [Accessed July 2022]
[5] Nonagricultural Market Research Data (NMRD). 2020. Study on consumer markets for pesticides and fertilizers. [Accessed July 2022]

b. Residential Handler and Residential Post-Application Risks

Evidence of neurotoxicity was observed in an acute neurotoxicity (ACN); subchronic neurotoxicity (SCN); developmental neurotoxicity (DNT); subchronic dermal in rats; subchronic oral in dogs; two-generation reproduction in rats; and developmental toxicity in rats and rabbits. The oral subchronic neurotoxicity study in the rats was selected to assess incidental oral exposures. The lowest observed adverse effect level (LOAEL) of 25 mg/kg bw/day, was based on clinical signs (subdued appearance, rocking, lurching/swaying when walking, hunched posture, hypoactivity, etc. in both sexes and decreased body weight, increased motor activity in males), the no observed adverse effect level (NOAEL) = 5 mg/kg bw/day, making it the point of departure (POD) for short-term oral toxicity. The route-specific subchronic dermal toxicity study in the rat was selected to assess dermal exposures. For dermal toxicity, the LOAEL of 100 mg/kg bw/day was based on decreased motor activity in both sexes and a NOAEL could not be established, because adverse effects were observed at the lowest dose tested (100 mg/kg/day) making the LOAEL the POD for dermal toxicity.

There is potential for residential exposures from the registered spot-on use of demiditraz on dogs. Residential handler exposure is assumed to be short-term only due to the intermittent nature of homeowner spot-on applications (*i.e*., one monthly treatment). In addition, residential post-application dermal exposures are expected for adults and children that may be transferred from a dog's hair coat by petting as well as incidental oral exposures from hand to mouth for children. The POD selected for both incidental oral and dermal scenarios are appropriate for all durations, so assessment of short-term exposure is protective of both intermediate and long-term exposures. Inhalation exposures from residential handler and from post application exposures to the registered spot-on products are assumed to be negligible since the products are in a liquid formulation; therefore, an inhalation assessment was not conducted.

Short-term residential handler dermal risk was assessed and is not of concern (i.e., margins of exposure (MOEs) are above the level of concern (LOC) of 300). Residential post-application exposures to adults (dermal only) resulted in no risk of concern. Residential post-application exposures to children 1 < 2 years old assessed dermal and incidental oral exposures from spot-on treatment on dogs resulted in no risk estimates of concern. For children 1 to < 2 years of age, dermal and incidental oral exposures were combined using the aggregate risk index (ARI) approach. This approach was required to assess combined post-application exposure and risks for children 1 to < 2 years old, because the LOCs are different for dermal and oral routes of exposure (i.e., dermal LOC = 300 and incidental oral LOC = 100). For children 1 to < 2 years old, combined dermal and incidental oral post-application risk estimates ranged from 3.9 to 5.7 (ARI = 1) and were not of concern.

c. Aggregate Risks

In an aggregate assessment, EPA considers the combined pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. Since there are no

registered outdoor or food uses for demiditraz, only residential exposures are considered. As a result, aggregate exposures and risk estimates from demiditraz are not of concern.

d. Cumulative Risks

EPA has not made a common-mechanism-of-toxicity-to-humans finding for demiditraz and any other substance. Demiditraz does not appear to produce a toxic metabolite produced by other substances. Therefore, EPA has premised this PFD and the underlying risk assessments on the understanding that demiditraz does not have a common mechanism of toxicity with other substances.

e. Occupational Handler and Post-Application Risks

Occupational dermal exposures to veterinarians, veterinary assistants, and groomers may occur from the application of the registered spot-on product to dogs. No risks of concern were identified for any of the durations assessed (i.e., MOEs are ≥ 300 for short, intermediate, and long-term exposures). Occupational handler inhalation exposure is expected to be negligible and was not quantitatively assessed. Occupational post-application activities are not anticipated as dogs are expected to be treated and returned to their owners resulting in negligible potential for exposure, so a quantitative assessment of these occupational post-application exposure was not conducted, and risk is not expected.

2. Human Incidents and Epidemiology

EPA reviewed demiditraz incidents reported to both the Incident Data System (IDS) and the Sentinel Event Notification System for Occupational Risk (SENSOR). As of EPA's latest search on August 16, 2022, IDS and SENSOR showed no incidents reported from January 1, 2017 to June 8, 2022. The Agency intends to monitor human incidents for demiditraz and will conduct additional analyses if necessary.

3. Tolerances

No tolerances under the FFDCA are necessary because demiditraz is not registered for any uses that result in residues in or on food.

4. Human Health Data Needs

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

B. Ecological Risks

The Agency has summarized the 2022 ecological risk assessment (Eco DRA) below. The Agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of demiditraz. For additional details on the

2022 Eco DRA, see *Demiditraz: Preliminary Problem Formulation and Ecological Risk Assessment in Support of Registration Review* in EPA's public docket (EPA-HQ-OPP-2021-0407).

1. Risk Summary and Characterization

The Agency concluded that the likelihood of exposure to non-target organisms is considered negligible due to demiditraz, as formulated into a domesticated pet spot-on product, adhering to the animal's fur and skin and therefore is not expected to enter into the environment. Therefore, the likelihood of adverse effects to non-target organisms from exposure as a result of the registered use of demiditraz is low. Consequently, the Agency did not conduct a quantitative assessment.

2. Ecological Incidents

EPA reviewed demiditraz incidents reported to the Incident Data System (IDS). As of EPA's latest search on April 20, 2022, IDS showed no incidents reported. The Agency will conduct additional analyses if necessary.

3. Pet Incidents

As of EPA's latest search on April 20, 2022, IDS showed no domestic animal incidents reported. The Agency will continue to monitor domestic animal incident data as it is reported to the Agency.

In its efforts to protect pets under FIFRA, EPA intends to request enhanced incident reporting and sales data for pet products akin to what is already submitted for spot-on products.[6] These data would allow the Agency to conduct a comparative assessment of pet incidents across registered pet products based on sales data to better determine whether any changes to the pet product registrations and labels are necessary. EPA is interested in feedback from stakeholders on the most efficient way these data can be provided to the Agency and types of analyses that could be submitted to expedite the Agency's assessment. EPA is also considering additional measures that could enhance its oversight of pet products, such as additional targeted studies and monitoring, and welcomes public comments on these and other potential measures.

4. Ecological and Environmental Fate Data Needs

The ecological and environmental fate database for demiditraz is considered complete. The Agency does not anticipate any further data needs for demiditraz.

[6] https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects

C. Benefits Assessment

In its role as an active ingredient that protects dogs from fleas and ticks, demiditraz can potentially provide important public health benefits. Fleas that feed on dogs can easily spread to humans, and while largely a nuisance pest, they can infest homes and transmit diseases and parasites that affect humans as well as their pets.[7] Ticks carry pathogens that can lead to at least sixteen human diseases, including Lyme disease, which is particularly widespread.[8] There are several other registered and widely marketed products (*e.g*., collars, topical treatments, and ingestibles containing many different active ingredients such as organophosphates, neonicotinoids, pyrethroids and isoxozalines) that also offer simultaneous protection from fleas and ticks. Given the serious public health concerns posed by fleas and ticks and diversity in consumer preference for a particular formulation, demiditraz products could add pest management benefit by potentially adding to the choices available to consumers who need to protect their dogs from these pests. Because there are several alternatives that are widely marketed, including other topical spot-on treatments, and given the lack of reported use of demiditraz, the current benefits of demiditraz appear to be low. However, this could change in the future if demiditraz products are increasingly used by consumers.

IV. PROPOSED FINAL REGISTRATION REVIEW DECISION

A. Proposed Regulatory Rationale

In evaluating potential risk mitigation for demiditraz, the EPA considered the risks, the benefits, and the use pattern of this compound. Given EPA's assessments and there are no human health or ecological risks, the Agency is not proposing any label mitigation. As described in Section III. B., the Agency has made a no effect determination from the use of demiditraz for federally listed threatened or endangered species and the use will not adversely modify designated critical habitat of federally listed species.

B. Environmental Justice

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

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[7] Centers for Disease Control and Prevention. 2020a. Flea-borne Diseases of the United States. Factsheet prepared by the Centers for Disease Control (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-borne Diseases (DVBD). Available at https://www.cdc.gov/fleas/diseaseshtml.
[8] Centers for Disease Control and Prevention. 2020b. Diseases Transmitted by Ticks. Factsheet prepared by the Centers for Disease Control (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-borne Diseases (DVBD). Available at https://www.cdc.gov/ticks/diseases/indexhtml

EPA has also evaluated risk to residential handlers (such as homeowners) and adults/children that may be exposed to residues after pesticide application and has not found risks of concern.

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

C. Proposed Final Registration Review Decision

The Agency is issuing this PFD in accordance with 40 C.F.R. §§ 155.56 and 155.58. The Agency has made the following proposed decision: (1) EPA proposes that no additional data are required; and (2) EPA has determined that demiditraz meets the registration standard without any additional mitigation.

The Agency conducted Human Health DRA and an Ecological DRA. In these risk assessments, EPA did not identify any risks of concern to registering demiditraz.

During registration review, EPA considers whether a pesticide registration "continues to satisfy the FIFRA standard for registration." Here, EPA proposes that demiditraz meets the FIFRA registration standard without changes to the registrations.

No clearances under the FFDCA are necessary because demiditraz is not registered for any uses that result in residues in or on food.

The Agency made a no effect determination for all federally listed endangered and threatened species, as well as their designated critical habitat, for the currently registered uses of demiditraz (see Appendix A).

D. Data Requirements

EPA does not anticipate calling-in additional data for demiditraz's registration review at this time.

V. NEXT STEPS AND TIMELINE

A. Proposed Final Registration Review Decision

A Federal Register Notice will announce the availability of the demiditraz PFD and open a 60-day comment period. After considering public comments on this PFD, the Agency may issue a final registration review decision for this case.

Appendix A: Listed-species Assessment

There is no reasonable expectation for any registered use of demiditraz to cause direct or indirect adverse effects to threatened and endangered species. No adverse modification of critical habitat is expected from the use of demiditraz. This is because demiditraz, as formulated into a domesticated pet spot-on product, adhering to the animal's fur and skin and therefore is not expected to enter into the environment. EPA has made a "no effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required.

Appendix B: 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 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 estrogen, androgen, or thyroid effect. If EPA finds, based on that data, that the pesticide has an 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))[9].

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.[10]

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

[9] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[10] 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

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, taking into account its current focus on its comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[11] and November 2022 ESA Workplan Update[12]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[13] indicate that available data were sufficient for FFDCA section 408(p) assessment and review for potential 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 or what 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 evaluate those pathways. For instance, EPA has data for numerous conventional pesticide active ingredients on mammalian estrogen and androgen effects through either an acceptable two-generation reproductive study in accordance with the current guideline (referred to here as the updated two-generation reproduction study; OCSPP 870.3800 - Reproduction and Fertility Effects) or an extended one-generation reproductive toxicity (EOGRT) study (OECD Test Guideline 443 - Extended One-

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

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 assess available data for the conventional active ingredient to determine what additional data, if any, might be needed to assess 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 that lack an updated two-generation reproduction study or an EOGRT study, 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, EPA sought in the FRN data and information in response to 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. For the remaining conventional pesticides (described in EPA's EDSP Strategies Notice as Group 2 and 3 conventional active ingredients), EPA committed to assessing the available data to determine what additional studies, if any, might be needed to assess the potential for impacts to endocrine pathways in humans.

As noted in EPA's EDSP Strategies Notice and summarized above, where EPA has received data on mammalian estrogen and androgen effects through an acceptable updated two-generation reproduction study or EOGRT study, EPA will generally not need to obtain any additional data, including EDSP Tier 1 data or other data, to assess effects to the estrogen and androgen pathways in humans for FIFRA registration or FFDCA tolerance-related purposes or to make the requisite FFDCA section 408(p)(6) finding. In the case of demiditraz, an acceptable updated two-generation reproductive study has been submitted and no additional data are needed to assess effects to the estrogen and androgen pathways in humans at this time.

Additionally, several studies are available in the database for demiditraz that evaluated thyroid toxicity and there were no adverse thyroid effects observed.

For the above reasons, EPA has concluded at this time that the points of departure used for human health risk assessment to evaluate current registrations of demiditraz are protective of potential adverse estrogen, androgen, and thyroid effects in humans, as required by FFDCA section 408(p)(6).