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

d-Allethrin

Proposed Final Registration Review Decision
Case Number 0437

September 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 *d*-cis/trans-allethrin or pynamin forte (hereto known as *d*-allethrin, PC Code 004005, case 0437). 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] The PFD is being issued pursuant to 40 CFR §§155.57 and 155.58. For more information on *d*-allethrin, see EPA's public docket (EPA-HQ-OPP-2010-0022) at www.regulations.gov.

FIFRA[2] mandates the continuous review of existing pesticides. Pesticides distributed or sold in the United States must be registered. EPA evaluates pesticides, taking into consideration scientific data, to determine whether 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. EPA will review 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 reduce risk evolves, and as policies and practices change. *d*-Allethrin was first registered on November 12, 1968, and had a Registration Review Interim Decision signed in November 2014. 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. For more information on the registration review program, see http://www.epa.gov/pesticide-reevaluation.

d-Allethrin belongs to the pyrethroid insecticide class. *d*-Allethrin acts as a sodium channel modulator (*i.e.,* mode of action group 3A, according to the Insecticide Resistance Action Committee [IRAC])[3] resulting in hyperexcitation and in some cases nerve block. *d*-Allethrin is registered for small-scale, outdoor residential use as an ambient air repellent against mosquitoes. The four FIFRA Section 3 registered end-use *d*-allethrin products are formulated and sold as active ingredient-impregnated mats. These mats volatize the active ingredient into the air for between 4-12 hours (depending on the size of the mat) across a 15-foot diameter area when heated by a candle or butane cartridge. This use is not intended for use in enclosed areas.

The Agency is issuing a PFD for *d*-allethrin so that it can move forward with the registration review. Under the Endangered Species Act (ESA), the Agency made a no effect (NE) determination for direct and indirect effects to all federally listed endangered and threatened species, as well as their designated critical habitat, for the FIFRA use pattern of *d*-allethrin as an

[1] Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) § 3(g), 7 U.S.C. § 136a(g); 40 C.F.R. § 155.57.
[2] As amended by the Food Quality Protection Act (FQPA) of 1996, Pub. L. No. 104-170, 110 Stat. 1489.
[3] IRAC (Insecticide Resistance Action Committee). 2022. Mode of Action Classification Scheme, Version 10.4, December 2022. Accessed 01/2023. See online at https://irac-online.org/documents/moa-classification/.

ambient air mosquito repellent. During this registration review, EPA completed endocrine screening for malathion under the Federal Food, Drug, and Cosmetic Act (FFDCA).[4] For more information on the listed-species assessment and the endocrine screening for *d*-allethrin registration review, see Appendices B and C.

This document is organized in five sections:

- *Introduction* (summarizing the registration review milestones and responding to public comments);
- *Use and Usage* (describing how and where *d*-allethrin can legally be used and how it is typically used);
- *Scientific Assessments* (summarizing EPA's risk and benefits assessments);
- *Proposed Final Registration Review Decision* (presenting EPA's proposed final decision and regulatory rationale); and,
- *Next Steps* (discussing completion of registration review).

A. Updates Since the Interim Decision was Issued

In December 2014, EPA published *Allethrins Interim Registration Review Decision* (ID). In the ID, the Agency found no human health or ecological risks of concern and made a "no effects" determination under the Endangered Species Act (ESA) for all listed species. EPA did not require any changes to product labels or registrations. All allethrin products, except three end-use products containing d-allethrin, were voluntarily cancelled in September 2015 (technical products) and December 2016 (end-use products). Another end use product with *d*-allethrin was registered in May 2017, so currently there are four end-use products registered. No registrations remain for other allethrins.

EPA has concluded at this time that the points of departure for human health risk assessment to evaluate the EPA-registered uses of the allethrins are protective of potential adverse estrogen, androgen, and thyroid effects in humans. Therefore, EPA has completed its FFDCA section 408(p)(6)-related commitments and obligations "to ensure the protection of public health" at this time. For additional information, please see Appendix C.

Beyond the conclusion on the EDSP, EPA has updated the human incidents memo and proposed label clarification in this PFD. There are no updates to the draft risk assessments (DRAs) in this Proposed Final Decision. The Agency's draft supporting documents *Allethrins. Registration Review Preliminary Risk Assessment* and *EFED Registration Review: Draft Ecological Risk Assessment and Endangered Species Effects Determination for d-Allethrin* (published September 2014), are available in the allethrins docket (EPA-HQ-OPP-2010-0022).

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

B. Summary of *d*-Allethrin Registration Review

Pursuant to 40 CFR § 155.50, EPA initiated the registration review for *d*-allethrin in March 2010. The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of *d*-allethrin:

- March 2010 - Publication of the Allethrins Summary Document, including the Preliminary Work Plan (PWP), for a 60-day comment period. The Summary Document was accompanied by the Scoping Document and the Problem Formulation.

- August 2010 - Publication of the Final Work Plan (FWP) and EPA's response to the single public comment received. The FWP did not modify the anticipated risk assessment, data needs, or registration review timeline described in the PWP.

- October 2011 – The Allethrins Registration Review Generic Data Call-In (GDCI) was issued.

- 2014 – In several Federal Register Notices, all allethrin products except three end-use products were voluntarily cancelled. The effective cancellation dates were September 30, 2015 (for technical products) and December 31, 2016 (for end-use products).

- September 2014 - EPA published qualitative human health and environmental fate and ecological risk assessments for allethrins in the allethrins registration review docket for a 60-day comment period. No comments were received on the documents: *Allethrins. Registration Review Preliminary Risk Assessment and EFED Registration Review: Draft Ecological Risk Assessment and Endangered Species Effects Determination for d-allethrin.*

- September 2014 - EPA published the *Allethrins Proposed Interim Registration Review Decision* (PID) for allethrins in the Federal Register (79 FR 57084; FRL–9916–39). No comments were received.

- November 2014 – EPA published the *Revised Allethrins Proposed Interim Registration Review Decision*. This document corrected an error (i.e. incorrect docket number) in the September 2014 PID.

- December 2014 – EPA published the *Allethrins Interim Registration Review Decision*.

- September 2024 – The Agency is announcing the availability of the PFD in the d-allethrin public docket for a 60-day public comment period. The following documents are also posted to the *d*-allethrin docket for a 60-day public comment period:
    - *d-Allethrin: Tier I Review of Human Incidents and Epidemiology for Draft Risk Assessment.* Elizabeth Evans, *et al.*, November 30, 2022

II. USE AND USAGE

d-Allethrin is a contact, non-systemic, pyrethroid insecticide classified by the Insecticide Resistance Action Committee[5] as a Group 3, Subgroup 3A chemical (sodium channel modulator). *d*-Allethrin has four FIFRA Section 3 registrations, all of which are registered for use as mosquito repellents for small-scale, outdoor, residential use. The registered products are formulated as impregnated mats that use a heating source (via candle or butane cartridge) to volatilize the repellent. All registrations claim an approximate 15-foot diameter "protection zone" and a duration of 4 or 12 hours per mat, depending on the size of the mat.

Available mosquito repellent usage data in U.S. consumer markets are limited. In a one-year study of 2019, household usage of *d*-allethrin was reported as part of the larger description of pyrethroid household usage. Quantitative usage data specific to *d*-allethrin are not available, but the absence of such data should not be interpreted as a lack of usage.[6]

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

A summary of the Agency's human health risk assessment is presented 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 *d*-allethrin. For additional details on the human health assessment for *d*-allethrin, see the *Allethrins. Revised Registration Review Preliminary Risk Assessment. 0422619* and *Allethrins Interim Registration Review Decision,* which is available in the public docket (EPA-HQ-OPP-2010-0022) at www.regulations.gov.

1. Risk Summary and Characterization

The Agency concluded that there are no outstanding data requirements and/or data deficiencies identified at this time for the registration review of *d*-allethrin. The data available to support the currently registered uses assumes that *d*-allethrin use will not occur near uncovered food or water.

Dietary (Food + Water) Risks, Aggregate, Residential, and Occupational Risks

d-Allethrin is only registered as impregnated mats that are used outdoors and are heated by either a candle or butane cartridge; therefore, there is no potential for exposure to *d*-allethrin in food and drinking water. Based on the registered use, exposure is not anticipated in an

[5] IRAC (Insecticide Resistance Action Committee). 2022. Mode of Action Classification Scheme, Version 10.4, December 2022. Accessed 01/2023. See online at https://irac-online.org/documents/moa-classification/.
[6] NMRD (Nonagricultural Market Research Data). 2020. Study on Consumer Markets for Pesticides and Fertilizers. Accessed 01/2023.

occupational setting. In a residential setting, residential adult handler exposure is expected to be negligible; however, adults and children may have inhalation exposure following use of *d*-allethrin-registered end-use products outdoors. These potential inhalation exposures do not result in risks of concern. Dermal and incidental oral exposures following use of the registered products are not expected. Non-occupational exposures resulting from spray drift from agricultural applications onto residential areas are not expected.

Cumulative Risks

The Agency has determined that the pyrethroids and pyrethrins share a common mechanism of toxicity with respect to human health (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). A 2011 cumulative risk assessment for the pyrethroids and pyrethrins did not identify cumulative risks of concern. Since that time, additional uses have been registered for several pyrethroids/pyrethrins, but these new uses have not impacted the cumulative conclusions.

2. Human Incidents and Epidemiology

EPA reviewed *d*-allethrin incidents reported to the Incident Data System (IDS). As of EPA's latest search on November 2022, Main IDS and Aggregate IDS showed one high-severity incident and 30 minor-severity incidents, respectively, reported from January 1, 2017, to October 21, 2022. In 2018, a 4-year-old male was given melatonin, sprayed with the product (Reg. No. 4822-513; 0.1% *d*-allethrin co-formulated with 0.34% tetramethrin and 0.1% permethrin; now cancelled) and fell from a slide at day care. He was outside in the heat and experienced vomiting and diarrhea. He was taken to the hospital by ambulance after he had a seizure. Pharmacologists that his mother consulted said that the child's symptoms were due to a combination of events in one day. A query of National Institute for Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides from 2010-2017 identified 24 cases involving *d*-allethrin. All 24 cases involving *d*-allethrin reported exposures to d-allethrin products that are now cancelled. As of November 2022, no epidemiological studies pertaining to the Agricultural Health Study (AHS) were listed for the prospective cohort population of *d*-allethrin exposure and both carcinogenic and non-carcinogenic effects. The Agency intends to monitor human incidents for *d*-allethrin and will conduct additional analyses if necessary.

3. Tolerances

There are no U.S. tolerances established for *d*-allethrin because *d*-allethrin is not registered for any food/feed uses.

4. Human Health Data Needs

The human health database for *d*-allethrin is considered complete. The Agency does not anticipate any further human health data needs for the registration review of *d*-allethrin.

B. Ecological Risks

A summary of the Agency's ecological risk assessment is presented 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 *d*-allethrin. EPA considered potential *d*-allethrin exposure for non-target organisms, available information on the toxicity of *d*-allethrin, and the registered use of *d*-allethrin in the assessment. For additional details on the ecological assessment for *d*-allethrin, see the *EFED Registration Review: Draft Ecological Risk Assessment and Endangered Species Effects Determination for d-Allethrin*, which is available in the public docket.

1. Risk Summary and Characterization

Earlier evaluations of *d*-allethrin conducted to support the Reregistration Eligibility Decision (RED) for allethrins indicated that *d*-allethrin, classified as a type 1 pyrethroid (*i.e*., lacking a cyano group at the α carbon position of the alcohol moiety), is highly toxic to aquatic animals, is moderately toxic to mammals and terrestrial invertebrates, and is practically non-toxic to birds (which serve as surrogates for reptiles and aquatic-phase amphibians) on an acute exposure basis. No guideline chronic toxicity data are available for aquatic organisms, birds or terrestrial invertebrates and no guideline toxicity data are available for either aquatic or terrestrial plants. However, based on the low likelihood of exposure for non-target organisms from the registered uses, EFED considered the need for these data as low.

EPA considered potential *d*-allethrin exposure of non-target organisms based on the chemical's registered use and determined that no acute risk levels of concern (LOCs) were exceeded for fish, aquatic invertebrates, birds, or mammals. In addition, the likelihood of adversely affecting non-target insects was expected to be low given the relatively limited "repellency effect area" (~15 feet in diameter) around the dispensing device, the likely setting of use (*e.g.*, residential backyards), and the short half-life of *d*-allethrin in air (less than one hour). While the Agency did not have terrestrial plant toxicity data nor chronic toxicity data for *d*-allethrin, risks are not expected due to the low exposure potential. Therefore, given the types and extent of the registered uses of *d*-allethrin, the low potential for exposure (*i.e*., *de minimis*), and the diffuse nature of use, the Agency believed that registered uses of *d*-allethrin should not adversely affect non-target organisms.

2. Endangered Species Assessment

EPA determined that for the currently registered use of *d*-allethrin, no direct or indirect effects are reasonably likely to occur to federally listed threatened or endangered species. Additionally, no adverse modification of designated critical habitat is reasonably likely to occur from the currently registered uses of *d*-allethrin. Therefore, EPA made a "no effect" (NE) determination

under the Endangered Species Act (ESA) for all federally listed threatened or endangered species. EPA also determined that "no adverse modification" was likely for designated critical habitat for such species. Given the NE determination and no adverse modification of designated critical habitat based on the registered use of *d*-allethrin, consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA section 7(a)(2) is not required.

3. Ecological Incidents

The 2010 *Registration Review: Preliminary Problem Formulation for Environmental Fate, Ecological Risk, and Endangered Species Assessments for the Allethrins* [7] identified 13 "minor" incidents involving terrestrial plants. Those 13 incidents involved the use of pressurized liquid spray or ready-to-use solution formulations (containing additional active ingredients and/or inerts) which are no longer registered. Reviews of the Ecological Incident Information System (EIIS, version 2.1), the Avian Incident Monitoring System (AIMS), and the Incident Data System (IDS) conducted in 2014 yielded (in addition to the plant incidents noted previously) two additional minor wildlife incidents which involved the use of an impregnated material (*i.e.*, mosquito coil) or pressurized liquid formulation; details are not available on the specific species affected. None of the incidents involved the lantern use (which is the use pattern assessed in this document). With respect to *d*-allethrin (PC Code 004005) specifically, a search of the IDS on January 9, 2023, did not identify any incidents. A similar search of the aggregate data base resulted in five incidents associated with phenothrin/*d*-allethrin. Three of the incidents were associated with minor effects on humans, one was associated with a moderate effect on a domestic animal, and one was associated with a minor effect on wildlife; however, none of the aggregated incidents indicate the nature of the effect.

4. Ecological and Environmental Fate Data Needs

The Agency does not anticipate that any further ecological and environmental fate data, including pollinator data, will be needed for the registration review of *d*-allethrin due to negligible environmental exposure to *d*-allethrin.

C. Benefits Assessment

The presence of mosquitos can diminish the enjoyment of recreational activities, mosquito bites can cause itching, discomfort, and inflammation at the site of the bite, and some mosquito species can vector human pathogens that cause disease including, but not limited to, dengue fever, chikungunya, Zika virus, and West Nile virus.[8] *D*-allethrin is used to reduce the

[7] *Registration Review: Preliminary Problem Formulation for Environmental Fate, Ecological Risk, and Endangered Species Assessments for the Allethrins*, March 2010, see online at https://www.regulations.gov/document/EPA-HQ-OPP-2010-0022-0002.

[8] CDC (Center for Disease Control and Prevention). 2020. Mosquitos in the United States. Accessed 01/2023.

incidence of nuisance encounters between humans and mosquitos. Since only female mosquitos take blood meals (*i.e*., bite), mosquito repellents work by modulating the female mosquito's odorant receptor activity so that their host seeking and feeding behaviors are altered.[9] [10] [11] [12]

Mosquito repellants can be grouped as topical (*e.g*., picaridin, N, N-diethyl-meta-toluamide [aka, DEET], 2-undecanone, and IR3535[13]) or spatial. Spatial repellents, such as *d*-allethrin, are active ingredients that are applied such that the chemical fills a three-dimensional space, providing protection to people within the treated space[9] [12] while topical protection only protects the one person wearing the active ingredient. Chemicals identified to have spatial repellency include volatile pyrethroids (*e.g*., *d*-allethrin, metofluthrin, and transfluthrin) and volatile botanicals (*e.g*., cinnamon, lemongrass, and citronella oils).[12] However, the volatile pyrethroids, unlike the botanicals, have the ability to repel, disorientate, and kill mosquitos that are not successfully repelled or that cannot leave the treated area. *D*-allethrin also provides mosquito control for approximately 4 to 12 hours, in contrast with other competing products such as botanical that last for a shorter period.

IV. PROPOSED FINAL REGISTRATION REVIEW DECISION

A. Proposed Risk Mitigation and Regulatory Rationale

In evaluating potential risk mitigation for *d*-allethrin, EPA considered the risks, the benefits, and the use pattern of this compound. With limited human health and environmental exposure and no risks of concern, the Agency is proposing label clarification for three products. This label clarification is consistent with the data on file which include adding a restriction to cover or remove food (*i.e.*, EPA Reg. No. 71910-8) and removing any claims of usage of the products

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See online at https://www.cdc.gov/mosquitoes/about/mosquitoes-in-the-us.html#:~:text=Some%20Mosquitoes%20Spread%20Germs&text=Dengue%2C%20chikungunya%2C%20and%20Zika%20virus,into%20the%2020th%20century.

[9] Bibbs, C.S., Fulcher, A., and Xue, R. 2015. Allethrin-Based Mosquito Control Device Causing Knockdown, Morbidity, and Mortality in Four Species of Field-Caught Mosquitoes (Diptera: Culicidae). J. Med. Ento.2015.1-4. DOI:10.1093/jme/tjv065. Accessed 01/2023. See online at https://academic.oup.com/jme/article/52/4/739/2459742.

[10] Bohbot, J.D. and J.C. Dickens. 2010. Insect Repellents: Modulators of Mosquito Odorant Receptor Activity. Accessed 01/2023. See online at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0012138.

[11] Grieco, J.P., Achee, N.L., Chareonviriyaphap, T., Suwonkerd, W., Chauhan, K., Sardelis, M.R., and D.R. Roberts. 2007. New Classification System for the Actions of IRS Chemicals Typically Used for Malaria Control. PLOS ONE, August 2007. Accessed 01/2023. See online at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0000716.

[12] Logan, J., Chen-Hussey, V., O'Halloran, L, Greaves, C., Due, C., and M. Macdonald. 2020. An Expert Review of Spatial Repellents for Mosquito Control. Accessed 01/2023. See online at https://www.ivcc.com/wp-content/uploads/2020/08/An-Expert-Review-of-Spatial-Repellents-for-Mosquito-Control.pdf.

[13] EPA (Environmental Protection Agency). 2022. Find the Repellent That is Right for You. Accessed 01/2023. See online at https://www.epa.gov/insect-repellents/find-repellent-right-you.

near water bodies (*i.e.*, EPA Reg. Nos. 71910-2, 71910-3, and 71910-8). The data available to support the currently registered uses assumes use will not happen near uncovered food or drinking water. To make a determination that the registrations meet the FIFRA standard, these label restrictions are necessary to ensure those assumptions can be relied upon.

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 sought to include all communities and persons, including minority, low-income, and indigenous populations who may be disproportionately overburdened by the exposure to *d*-allethrin.

The Agency quantitatively evaluated the *d*-allethrin use and did not find any risk of concern to humans, and therefore not to any sub-populations either.

The Agency requests information 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 *d*-allethrin compared to the general population or who may otherwise be disproportionately affected by the use of *d*-allethrin as a pesticide.

C. Proposed Final Registration Review Decision

The Agency is issuing this PFD in accordance with 40 CFR §§ 155.50, 155.56 and 155.58. The Agency has made the following proposed final decision: (1) that no additional data are required; and (2) that *d*-allethrin products would meet the registration standard with the label amendments below.

The Agency conducted a draft human health risk assessment and a draft ecological risk assessment. In these risk assessments, EPA did not identify risks from the registrations of *d*-allethrin.

EPA also determined that *d*-allethrin provides a low-risk alternative for repelling mosquitoes, which are often vectors for public health diseases.

During registration review, EPA considers whether a pesticide registration "continues to satisfy the FIFRA standard for registration."[14] Here, EPA proposes that *d*-allethrin would meet the FIFRA registration standard with the proposed label changes to the registrations.

No clearances under the Federal Food Drug and Cosmetic Act (FFDCA) are necessary because *d*-allethrin is not registered for any uses that result in residues in or on food.

D. Data Requirements

The Agency does not anticipate calling-in additional data for the registration review of *d*-allethrin.

V. NEXT STEPS

A. Proposed Final Registration Review Decision

A Federal Register Notice will announce the availability of the *d*-allethrin PFD and open a 60-day comment period. The Agency may issue a Registration Review Final Decision for *d*-allethrin after the close of this comment period if commenters do not submit significant comments or additional information that lead the Agency to change the proposed decision in Section IV.A, above.

[14] 40 C.F.R. § 155.40(a); 7 U.S.C. § 136a(c)(5); see also 7 U.S.C. §§ 136(bb) (defining "unreasonable adverse effects on the environment" as encompassing both "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide" [FIFRA's risk-benefit standard] and "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the [FFDCA safety standard]"). In a PID, EPA sets out a proposed interim decision that includes EPA's "proposed findings with respect to the FIFRA standard for registration and describe the basis for such proposed findings." 40 C.F.R. §§ 155.56, 155.58(b)(1).

Appendix A: Proposed Labeling Changes for *d*-Allethrin Products

Description	Proposed Label Language for *d*-Allethrin Products	Placement on Label
	End-Use Products	
For EPA Reg. No. 71910-2, 71910-3, and 71910-8		
Label clarification	Remove the following wording (all wording and graphics) from the label: • Fishing • Swimming • Beaches • Poolside • Docks • All Around Outdoor Use	Entire label
For EPA Reg. No. 71910-8		
Add Restriction	Add the following statement: Cover or remove all exposed food.	Use Restrictions Section Under Directions for Use
All end-use product labels		
Add Restriction	Add the following statement: Do not use around water bodies.	Use Restrictions Section Under Directions for Use

Appendix B: Listed-Species Assessment

EPA has determined that direct or indirect effects to federally listed species is not reasonably likely to occur from the single registered use of *d*-allethrin. Additionally, no adverse modification of designated critical habitat is reasonably expected from the use of *d*-allethrin. EPA found no risks to any taxa for the one registered use as a mosquito repellent based *on de minimus* exposure. Therefore, EPA made a "no effect" determination under the ESA for all listed species and "no adverse modification" of 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 C: 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-related 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))[15].

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.[16]

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

[15] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[16] 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

its review of required and submitted data for these purposes also informs EPA's obligations and commitments under FFDCA section 408(p). Consequently, on October 27, 2023, EPA issued a Federal Register Notice (FRN) providing clarity on the applicability of these data to FFDCA section 408(p) requirements and near-term strategies for EPA to further its compliance with FFDCA section 408(p). This FRN, entitled *Endocrine Disruptor Screening Program (EDSP): Near-Term Strategies for Implementation' Notice of Availability and Request for Comment* (88 FR 73841) is 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).

Since the release of the EDSP Strategies Notice, EPA has updated these groups for conventional pesticides.[17]

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[18] and November 2022 ESA Workplan Update[19]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[20] 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).

[17] Updated List of Conventional Pesticide Active Ingredients with Adequate Estrogen and Androgen Data for Humans to Inform FFDCA Section 408(p)(6) Determinations: https://www.regulations.gov/document/EPA-HQ-OPP-2023-0474-0066

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

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

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

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 the chemical's potential to interact with 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, 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 noted in EPA's EDSP Strategies Notice and summarized above, where EPA has received endocrine-related data through an updated two-generation reproduction toxicity study or EOGRT study, EPA will generally not need to obtain any additional data, including EDSP Tier 1 data, to confirm its assessment of the potential for adverse effects to the estrogen and

androgen pathways in humans. In the case of the allethrins, an updated two-generation reproduction toxicity study has been submitted and no additional data are needed, at this time, to support EPA's assessment of the potential for adverse estrogen and androgen effects in humans.

The need for additional thyroid data for the allethrins 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 (J. Fredericks; 24-June-2024; TXR 0058690).

EPA has concluded at this time that the points of departure (PODs) for human health risk assessment to evaluate the EPA-registered uses of the allethrins are protective of potential adverse estrogen, androgen, and thyroid effects in humans. Therefore, EPA has completed its FFDCA section 408(p)(6)-related commitments and obligations "to ensure the protection of public health" at this time.