Capsaicin and Related Capsaicinoids

PC Codes 070701, 070703, and 070704

Preliminary Work Plan
Case Number 4018

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I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) *Preliminary Work Plan* (PWP) for Capsaicin and Related Capsaicinoids Case 4018 and is being issued pursuant to 40 CFR § 155.50. This case includes the active ingredients capsaicin[1] (PC Code 070701) and related capsaicinoids, red pepper (PC Code 070703), and oleoresin of capsicum (PC Code 070704), hereafter referred to as capsaicin and related capsaicinoids (Case 4018). These active ingredients were grouped into one registration review case pursuant to 40 CFR § 155.42(a). This document explains what EPA's Office of Pesticide Programs (OPP) knows about capsaicin and related capsaicinoids, highlights anticipated data and assessment needs, identifies types of information that would be especially useful to the Agency in conducting the review, and provides an anticipated timeline for completing the registration review process for capsaicin and related capsaicinoids. As stated in 40 CFR § 155.50, the opening of this docket initiates the current cycle of registration review for capsaicin and related capsaicinoids.

A registration review decision is the Agency's determination of whether a pesticide meets, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States generally must be registered by the Agency based on scientific data showing that they will not cause unreasonable adverse effects to human health or to the environment when used as directed on product labeling. The registration review program is intended to ensure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically re-evaluates pesticides to ensure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided at www.epa.gov/pesticide-reevaluation.

In 2006, the Agency implemented the registration review program pursuant to FIFRA § 3(g). The Agency will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The Agency published an interim registration review decision in 2009 for the first cycle of registration review of capsaicin and related capsaicinoids; the second cycle marks the next 15 years of the Agency's periodic review of pesticide registrations in the capsaicin and related capsaicinoids case to ensure that each pesticide continues to satisfy the statutory standard for registration; that is, that the pesticide can perform its intended function without causing unreasonable adverse effects on human heath or the environment. The regulations governing registration review are provided in 40 CFR part 155, subpart C. The public phase of registration review begins when the initial docket is opened for the case. The docket is the Agency's opportunity to inform the public what it knows about capsaicin and related capsaicinoids and what additional risk analyses and data or information it believes are needed to make a registration review decision on capsaicin and related capsaicinoids.

[1] Based upon the current review of previously submitted data, the Agency has determined there are no biochemical products that consist solely of capsaicin. Instead, registered products consist of either capsicum oleoresin or a mixture of capsaicin and related capsaicinoids. The Agency is currently working to clarify the nomenclature and composition of the active ingredients by modifying the active ingredient name of PC Code 070701.

The Agency encourages all interested stakeholders to review the PWP and to provide comments and additional information that will help the Agency's decision-making process for capsaicin and related capsaicinoids. Interested stakeholders could include the following: environmental nonprofit or interest groups; pesticide manufacturers; agricultural labor or commodity groups; commercial, institutional, residential, and other users of pesticides; or the general public. In addition to general areas on which persons may wish to comment, there are some areas identified in the PWP about which the Agency specifically seeks comments and information.

After reviewing and responding to comments and data received in the docket during this initial comment period, the Agency will develop and commit to a Final Work Plan (FWP) and anticipated schedule for the registration review of the capsaicin and related capsaicinoids case. Additional information on capsaicin and related capsaicinoids can be found in the Agency's public docket (EPA-HQ-OPP-2024-0396) at www.regulations.gov.

This document is organized into five sections: the *Introduction*, which includes this summary and capsaicin and related capsaicinoids case overview; *Use Information*, which describes how and why capsaicin and related capsaicinoids are used and summarizes data on its use, and associated pesticide products; *Scientific Assessments*, which summarizes the Agency's risk assessments, any revisions, risk conclusions, and any anticipated data needs that will help the Agency's decision-making process for capsaicin and related capsaicinoids; *Guidance for Commentors*, which highlights topics of special interest, additional information and data the Agency should consider prior to issuing a FWP; and, lastly, the *Next Steps* and *Timeline* which provides an anticipated timeline for the registration review process for capsaicin and related capsaicinoids.

Capsaicin and Related Capsaicinoids Registration Review Case Overview

Pursuant to 40 CFR § 155.50, the Agency will initiate a pesticide's registration review by establishing a docket for registration review of Capsaicin and Related Capsaicinoids Case 4018 and opening it for public review. Documents from the first cycle of registration review for the Capsaicin and Related Capsaicinoids registration review case can be found in docket ID EPA-HQ-OPP-2009-0121 available at www.regulations.gov.

This PWP marks the beginning of the current cycle of registration review for capsaicin and related capsaicinoids, with the opening of public docket EPA-HQ-OPP-2024-0396 available at www.regulations.gov. The following list highlights significant events that have occurred during the current cycle of registration review for this case:

- September 2024 – The Agency is now publishing the Capsaicin and Related Capsaicinoids *Preliminary Work Plan* for a 60-day public comment period.

II. Use Information

The first pesticide product containing capsaicin as an active ingredient was registered by the U.S. Department of Agriculture in 1962. Capsaicin is the primary active component of chili peppers, plants that belong to the genus *Capsicum*. Capsaicin is one of six natural capsaicinoids typically found in capsicum peppers, all of which have pesticidal active properties. Capsaicin is generally obtained through extraction and comprises approximately 70% of the typical capsaicinoid mix. The physical form resulting from extraction may be either a powder that is reconstituted or more commonly an oleoresin. While capsaicin may be isolated from the other capsaicinoids, it generally is not. Thus, the

active ingredient typically bears the qualifying statement: capsaicin and related capsaicinoids. The liquid oleoresin is reddish-brown, only mildly odorous, but extremely pungent to the taste.

The sole antimicrobial product, Barnacle-Stop (EPA Reg. No. 89825-1), containing capsaicin at 0.075%, is used to prevent marine invertebrate organisms from attaching to and growing on underwater surfaces. The product is applied to boat hulls, propellers, and other boat running gear either in or out of the water. It may also be applied to other underwater structures such as water intake grates or screens. The product is supplied as a waxy solid and applied to surfaces as a 'crayon', or by heating the solid product and applying the product with a brush. Table 1 includes the use information for antimicrobial use related to capsaicin and capsaicinoids.

Biochemical pesticide products containing capsaicin are registered for a wide variety of use patterns—vertebrate repellent, insect repellent (including termites), bactericide, and fungicide. Currently, there are 38 registered products containing capsaicin registered for biochemical uses; all are end-use products (EPs) containing 0.00001125 – 2.50% active ingredient, and none are manufacturing-use products (MPs). In addition, there are 6 registered products containing oleoresin of capsicum (containing 1.73 - 7.6% active ingredient) registered for biochemical uses; five EPs and one MP. The last product containing red pepper for biochemical use was cancelled in July 2014. Therefore, red pepper was neither assessed nor discussed further in this document. There are no Special Local Need (SLN) products. Table 1 summarizes the use information for biochemical uses related to capsaicin and capsaicinoids.

Antimicrobial Use Label Recommendations

The label for the antimicrobial product, Barnacle-Stop (EPA Reg. No. 89825-1, dated 12/21/2018), states that it can be applied to "other underwater structures" and specifies one example as water intake grates or screens. This language suggests that other unspecified underwater structures are intended for product use. Based on correspondence with the registrant, other use sites that may be intended include underwater structures in both freshwater and marine environments that may have potential drinking water exposure, which results in dietary exposure. The Agency therefore recommends that the label clearly state all intended underwater structures and use sites for this product. In the absence of these clarifications, the Agency will assume the product can be used on all underwater structures.

The Agency also recommends the label for Barnacle-Stop (EPA Reg. No. 89825-1) clearly state the weight of one bar. According to the label, one bar covers approximately 12 square feet of surface area, but the weight of the bar is not specified. In the absence of this information, the Agency will assume the most conservative maximum application rate; that is, a 120-gram container covers approximately 12 square feet of surface area in one coat.

Biochemical Use Label Recommendations

In biochemical pesticide products, the active ingredients are generally identified on all biochemical pesticide product labels as "capsaicin", "capsaicin and related capsaicinoids", and "capsicum oleoresin extract". Based upon the current review of previously submitted data, the Agency has determined there are no biochemical products that consist solely of capsaicin. Instead, registered products consist of either capsicum oleoresin or a mixture of capsaicin and related capsaicinoids. The Agency is currently working to clarify the nomenclature and composition of the active ingredients by modifying the active ingredient name of PC Code 070701. Additionally, the nomenclature of the active

ingredients on labels and Confidential Statements of Formula (CSFs) should be revised accordingly. The percent of capsaicin and related capsaicinoids or oleoresin capsicum should be included in the ingredient statement, rather than the amount of capsaicin. Should registrants wish to quantify the amount of capsaicin on product labels, this could be done via asterisk in the ingredient statement. Please see Appendix A for additional information on the Agency's clarification on product characterization of capsaicin and related capsaicinoids.

Table 1. Capsaicin and Related Capsaicinoids Use Information		
Ingredient Name	Capsaicin[1]	Oleoresin of capsicum
PC Code	070701	070704
CAS Number	404-86-4	8023-77-6
Pesticide Classification	Vertebrate Repellent, Insect Repellent, Bactericide, Fungicide, Aquatic Invertebrate Repellent	Insect Repellent
Use Site Locations	Agricultural (Indoor and Outdoor); Recreational/Schools/Institutional/Retail/ Occupational/Manufacturing/Processing/ Industrial (Indoor and Outdoor); Underwater surfaces and structures	Agricultural (Indoor and Outdoor); Greenhouse (Indoor); Hemp; Recreational/Schools/Institutional (Indoor and Outdoor)
Application Types	Broadcast; Directed; Wax application	Directed
No. of Registrations[2]	38 FIFRA Section 3 products 0 FIFRA Section 24c products	6 FIFRA Section 3 products 0 FIFRA Section 24c products
Physical Forms	Emulsion, Gas, Granule, Liquid, Pellet/Tablet, Wax	Emulsion, Liquid, Solution
New Uses since Last Registration Review Decision	Non-food use; antifoulant for use on underwater vessels and structures (EPA Reg. No. 89825-1; U.S. EPA, 2016)	None

III. Scientific Assessments

A summary of the Agency's human health and ecological risk assessments for capsaicin and related capsaicinoids is presented below. Refer to the Appendices for a detailed listing of product analysis, human health assessment, and nontarget organism data that support the scientific assessments for this registration review. For further information on the human health and environmental risk assessments, including a summary of data and literature search findings, please see Appendices B and C.

A. Human Health Assessment

Summary of Hazard Characterization

There are no anticipated human health risks of concern from the sole antimicrobial use of capsaicin. The human health data set is considered complete for the antimicrobial use of capsaicin, and an updated human health risk assessment will not be conducted for this use. A new use risk assessment for the antimicrobial use of capsaicin was conducted in 2016 (U.S. EPA, 2016). Since then, the label has been updated to clarify the use pattern. These updates did not result in exposures higher than what was previously assessed in the 2016 assessment. Because of this, an updated risk assessment is not warranted. If, in the future, the use is expanded or a new use is added, a new risk assessment may be

[2] FIFRA labels can be obtained from the Pesticide Product Label System (ordspub.epa.gov/ords/pesticides/f?p=PPLS:1)

required. See Appendix B for additional information regarding hazard characterization for the antimicrobial use of capsaicin.

For biochemical uses of capsaicin and related capsaicinoids the current hazard characterization is based on the toxicology data in the Agency's database as well as the results of a cursory review of the open scientific literature. The Agency concludes that the toxicological database is considered incomplete for characterizing hazard and assessing risk from the active ingredients in this case due to the potential for adverse effects noted in the recent open literature search, the lack of developmental toxicity data on the active ingredients, and the lack of adequate data to substantiate rapid degradation in the environment. In order to complete the hazard characterization, a comprehensive review of the available repeat-dose oral toxicity, acute inhalation toxicity, genotoxicity, and carcinogenicity data is needed. The Agency has determined that additional data and an updated risk assessment are needed in order to reliably support a safety finding for the existing use patterns and to evaluate whether the current exemption from the requirement of a tolerance is still justified for the active ingredients in this case (Table 2).

Some data requirements, per 40 CFR § 158.2050, have been fulfilled for the current registered biochemical pesticide uses. With respect to acute toxicity, the active ingredients are classified into Toxicity Category II[3] for acute oral toxicity and acute dermal toxicity, Toxicity Category III for primary eye irritation and Toxicity Category III for primary dermal irritation. Based on the available data, these active ingredients are not considered to be skin sensitizers. A Toxicity Category for acute inhalation toxicity will be assigned once the Agency has completed its review. The 90-day dermal data requirement has been satisfied with rationale. Please see Appendix B for additional information regarding hazard characterization for the biochemical uses of capsicum oleoresin/capsaicin and related capsaicinoids.

Summary of Dietary Exposure and Risk Characterization

There are no anticipated dietary (food) risks of concern from the antimicrobial use of capsaicin. While the 2016 new use risk assessment (U.S. EPA, 2016) did not assess dietary exposures, there is potential for drinking water exposure. However, exposure to capsaicin is not expected to result in any adverse health effects via the drinking water exposure pathway, due to the amount of capsaicin in the antifoulant product (0.075%; 750 ppm) being lower than concentrations found in some natural peppers (e.g., 4,249 ppm in hot chili; Al Othman *et al.*, 2011), the expectation that not all of the capsaicin will leach from the product, and that dilution in a water treatment plant will occur. Based on the current antimicrobial label and 40 CFR §158.2290, indirect food contact uses may also be assumed for product application on underwater structures that capture food, which could result in indirect food contact. However, for many of the same reasons listed above, dietary risks are not anticipated from these uses. See Appendix B for additional information regarding dietary exposure from the antimicrobial use of capsaicin.

For biochemical pesticide products containing capsicum oleoresin/capsaicin and related capsaicinoids, there is anticipated dietary exposure due to registered use on food. Previously, these active ingredients were qualitatively assessed based on expected rapid degradation in the environment, existing presence in the human diet, low acute toxicity, and lack of reported adverse effects (U.S. EPA, 2010). Due to the potential for adverse effects noted in the recent open literature search, the lack of

[3] See Section III of Chapter 7 of the Label Review Manual for a complete description of the Toxicity Categories.

developmental toxicity data on the active ingredients, and the lack of reliable environmental fate data to support the previous conclusion that these substances degrade rapidly in the environment, the Agency has determined that an updated assessment is necessary to evaluate the potential for dietary risk for uses of capsaicin and related capsaicinoids that may result in residues on food. This includes reevaluating the current exemption from the requirement of a tolerance and whether residue data will be needed. Please see Appendix B for additional information regarding dietary exposure from the biochemical use of capsicum oleoresin/capsaicin and related capsaicinoids.

Food Tolerances

The Agency has found the current available database and information on capsaicin and related capsaicinoids from the available repeat dose oral data are inadequate based on adverse effects at doses relevant for risk assessment to characterize potential hazard to the general population to residues on food. Therefore, as part of this registration review, the Agency is determining whether the current exemption from the requirement of a tolerance is still justified. Residue data will be needed should it be determined that a tolerance(s) is more appropriate for the active ingredients. Additionally, if appropriate, the Agency anticipates updating the current tolerance exemption 40 CFR § 180.1165 to be consistent with any future modifications to the active ingredient name for PC Code 070701. As described earlier in the PWP, the Agency is working to modify the active ingredient name for PC Code 070701 to accurately describe the composition of the active ingredient for all registered uses. The current tolerance exemption is stated as follows:

> **40 CFR § 180.1165 Capsaicin**; capsaicin is exempt from the requirement of a tolerance in or on all food commodities when used in accordance with approved label rates and good agricultural practice. [63 FR 39521, July 23, 1998]

Summary of Residential and Non-Occupational Exposure and Risk Characterization

A qualitative assessment for inhalation exposures to the antimicrobial use of capsaicin is included in Appendix B. Based on the low volatility of capsaicin, and minimal exposure for both inhalation and dermal routes, no exposures of concern for residential handlers are anticipated as was concluded in the 2016 new use risk assessment for the antimicrobial use of capsaicin (U.S. EPA, 2016). For residential post-application exposures, there is no anticipated exposure of concern. See Appendix B for additional information on residential and non-occupational exposure from the antimicrobial use of capsaicin.

A qualitative assessment was conducted for residential (non-occupational) and post-application exposure via various application methods for biochemical uses of capsicum oleoresin/capsaicin and related capsaicinoids. Due to the potential for adverse effects noted in the recent open literature search, the lack of developmental toxicity data on the active ingredients, and the lack of reliable environmental fate data to support the previous conclusion that these substances degrade rapidly in the environment, the Agency has determined that an updated assessment is necessary to evaluate the potential for residential risk and exposure for all registered biochemical uses, with the exception of the defensive animal repellents for dogs and bears since this product use is transient (e.g., in emergency situations) and significant residential exposure is not expected. Please see Appendix B for additional information on residential and non-occupational exposure from the biochemical uses of capsicum oleoresin/capsaicin and related capsaicinoids.

Summary of Occupational Exposure and Risk Characterization

There are no anticipated occupational handler or occupational post-application exposures of concern from the antimicrobial use of capsaicin, as was concluded in the 2016 risk assessment (U.S. EPA, 2016). See Appendix B for additional information on occupational handler and occupational post-application exposure from the antimicrobial use of capsaicin.

A qualitative assessment was conducted for occupational handler and post-application exposure via various application methods for biochemical uses of the active ingredients in this case. Due to the potential for adverse effects noted in the recent open literature search, the lack of developmental toxicity data on the active ingredients, and the lack of reliable environmental fate data to support the previous conclusion that these substances degrade rapidly in the environment, the Agency has determined that an updated assessment is necessary to evaluate the potential for occupational risk and exposure for all registered biochemical uses. Please see Appendix B for additional information on occupational exposure from the biochemical uses of capsicum oleoresin/capsaicin and related capsaicinoids.

Human Incidents

A search of the OPP Incident Data System conducted on May 14, 2024, revealed 5 reported incidents associated with biochemical use of capsaicin since September 2010. Most of the incidents are described as minor to moderate human incidents predominantly due to mishandling of the products containing capsaicin (*i.e*., did not follow label directions, incorrect reinstalment, *etc*.). There are no incidents associated with the antimicrobial use of capsaicin. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

B. Summary of Environmental Risk Assessment

The 2016 new use risk assessment for the antimicrobial use of capsaicin determined there were no risks of concern to aquatic nontarget organisms based on preliminary review of freshwater invertebrate, estuarine/marine invertebrate, and freshwater fish toxicity data, which suggested low toxicity. However, after review conducted during reevaluation, these toxicity studies were found to be unacceptable. The Agency has determined that all environmental fate and nontarget ecotoxicity data requirements for the *Antifoulant Coatings and Paints* use pattern under 40 CFR part 158 subpart W are required to determine risks to nontarget organisms from the antimicrobial use of capsaicin. See Appendix C and Anticipated Data Needs Section III. C. for additional information on the Agency's rationale for requiring these data and the specific environmental fate and nontarget ecotoxicity studies that will be called in for the antimicrobial use of capsaicin during registration review.

Currently, there are no nontarget organism toxicity data available for the biochemical uses of capsaicin and related capsaicinoids in the Agency's database. Scientific rationale was previously submitted for various products to satisfy Tier I nontarget organism toxicity data requirements for biochemical uses. Upon reevaluation, the Agency concludes the rationale is considered adequate for the indoor use of capsaicin in agricultural settings, as well as for use as a defensive animal repellent (i.e. for dogs or bears) since these expected environmental exposures and risks from these uses are negligible. Thus, no additional data and no updated ecological risk assessments are needed for these use patterns. However, upon further review, the Agency determined that the submitted scientific rationales for outdoor uses of capsaicin are inadequate based on the lack of adequate data to substantiate rapid degradation of capsaicin in the environment. Due the lack of nontarget organism toxicity data in the

Agency's database and the potential for exposure to both terrestrial and aquatic organisms following capsaicin applications (e.g., foliar, aerial, or granular) and post-application via spray drift or runoff, ecological toxicity data are required to assess the risk of capsaicin as a pesticide when it is applied outdoors. Please see Appendix C and Anticipated Data Needs Section III. C. for additional information on why the Agency is requiring ecotoxicological and environmental fate data for the biochemical pesticide outdoor uses of capsicum oleoresin/capsaicin and related capsaicinoids (Table 2). Upon review of the data, the Agency anticipates updating its ecological risk assessment.

Ecological Incidents

A search of OPP's Incident Data System conducted on May 14, 2024 revealed two reported incidents associated with the biochemical uses of capsaicin. All incidents were reported by Woodstream Corporation in 2009 and involved damage to plants (e.g., turning yellow or brown, wilting, and/or dying) following registered spray applications to plants using two products called Deer Off (067356-00002) and Ready-to-use Deer Off (Reg. No. 067356-00007). These incidents reported the product as being the probable cause of plant damage. However, because both products contain multiple active ingredients and no terrestrial plant data are available for capsaicin at the applied quantity, it is uncertain if the plant damage can be attributable to capsaicin. No incidents were reported for the antimicrobial use of capsaicin.

No incidents were reported for the other two PC Codes (070703 and 070704) in this case. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

Endangered Species Assessment

This section provides general background about the Agency's assessment of the effects of pesticides on federally threatened and endangered (listed) species and designated critical habitats under the Endangered Species Act (ESA). Additional background specific to capsaicin and related capsaicinoids appears at the conclusion of Appendix C.

Developing Approaches for ESA Assessments and Consultation for FIFRA Actions

In 2015, EPA, along with the Services—the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS)—and the United States Department of Agriculture (USDA) (referred to as "the agencies") released their joint Interim Approaches[4] for assessing the effects of pesticides to listed species. The agencies jointly developed these Interim Approaches in response to the 2013 National Academy of Sciences' recommendations that discussed specific scientific and technical issues related to the development of assessments of pesticides' effects to listed species. Since that time, the agencies have been continuing to work to improve the approaches for assessing effects to listed species. After receiving input from the Services and USDA on proposed revisions to the interim method and after consideration of public comments received, EPA released an updated *Revised Method for National Level Listed Species Biological Evaluations of Conventional Pesticides* ("Revised Method") in March 2020.[5]

[4] www.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report.
[5] https://www.epa.gov/endangered-species/revised-method-national-level-listed-species-biological-evaluations-conventional.

The agencies also continue to work collaboratively through a FIFRA Interagency Working Group (IWG). The IWG was created under the 2018 Farm Bill to recommend improvements to the ESA section 7 consultation process for FIFRA actions and to increase opportunities for stakeholder input. This group is led by EPA and includes representatives from NMFS, FWS, USDA, and the Council on Environmental Quality (CEQ). The IWG outlines its recommendations and progress on implementing those recommendations in reports to Congress.[6]

Consultation on Chemicals in Registration Review

EPA initially conducted biological evaluations (BEs) using the interim method on three pilot chemicals representing the first nationwide pesticide consultations (final pilot BEs for chlorpyrifos, malathion, and diazinon were completed in January 2017). These initial pilot consultations were envisioned as the start of an iterative process. Later that year, NMFS issued a final biological opinion for these three pesticides. In 2019, EPA requested to reinitiate formal consultation with NMFS on malathion, chlorpyrifos and diazinon to consider new information that was not available when NMFS issued its 2017 biological opinion. EPA received a final malathion biological opinion[7] from FWS in February 2022 and a final biological opinion from NMFS on malathion, chlorpyrifos and diazinon in June 2022.[8] The Agency plans to implement both biological opinions according to the 18-month timeframes specified in the biological opinions.

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

EPA's New Actives Policy and the 2022 Workplan

In January 2022, EPA announced a policy[9] to evaluate potential effects of new conventional pesticide active ingredients to listed species and their designated critical habitat and initiate consultation with the Services, as appropriate, before registering these new pesticides. Before the Agency registers new uses of pesticides for use on pesticide-tolerant crops, EPA will also continue to make effects determinations. If these determinations are likely to adversely affect determinations, the Agency will not register the use unless it can predict that registering the new use would not have a likelihood of jeopardizing listed species or adversely modifying their designated critical habitats. EPA will also initiate consultation with the Services as appropriate.

In April 2022, EPA released a comprehensive, long-term approach to meeting its ESA obligations, which is outlined in *Balancing Wildlife Protections and Responsible Pesticide Use*.[10] This workplan reflects the Agency's most comprehensive thinking to date on how to create a sustainable ESA-FIFRA program that focuses on meeting EPA's ESA obligations and improving protection for listed species while minimizing regulatory impacts to pesticide users and collaborating with other agencies and stakeholders on implementing the plan.

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[6] https://www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act.

[7] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.

[8] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.

[9] https://www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.

[10] https://www.epa.gov/endangered-species.

On November 16, 2022, EPA released the *ESA Workplan Update: Nontarget Species Mitigation for Registration Review and Other FIFRA Actions*.[11] As part of this update, EPA announced its plan to consider and include, as appropriate, a menu of FIFRA Interim Ecological Risk Mitigation intended to reduce off-target movement of pesticides through spray drift and runoff in its registration review and other FIFRA actions. These measures are intended to reduce risks to nontarget organisms efficiently and consistently across pesticides with similar levels of risks and benefits. EPA expects that these mitigation measures may also reduce pesticide exposures to listed species.

For the currently registered biochemical and antimicrobial uses, acceptable ecotoxicology and environmental fate studies are needed to assess environmental risks and conduct an assessment of effects to threatened and endangered (listed) species and their designated critical habitats. The Agency has indicated a need for these data in Section III. C. 2 and 4. Additionally, after these data are submitted and reviewed, the Agency will determine whether the biochemical and antimicrobial uses of capsaicin affect listed species or their designated critical habitats and, as appropriate, will consult with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service pursuant to ESA § 7(a)(2).

C. Anticipated Data Needs

Summary of Registration Review Data Needs

Antimicrobial Data Needs:

Upon reevaluation of the scientific rationales previously submitted in support of outdoor uses of capsaicin, the ecotoxicity rationales are considered inadequate. To assess the risk of capsaicin as an antimicrobial for antifoulant uses, both environmental fate and ecological toxicity data will be required under 40 CFR part 158 subpart W and these data requirements are summarized in Table 2.

No human health data are needed currently for the antimicrobial antifoulant uses of capsaicin.

Biochemical Pesticide Data Needs

Based on reevaluation of the submitted data, the Agency has determined that developmental toxicity data are inadequate, and this data is required to assess the risk of capsaicin oleoresin/capsaicin and related capsaicinoids, as summarized in Table 2. An oral developmental toxicity study is preferred since the active ingredients are not well-absorbed systemically via the dermal route, based on the Agency's understanding. Currently, the available developmental toxicity data are via the dermal route and are considered supplemental and limited due to reporting deficiencies and because they only represent a purified form of capsaicin. As stated in Appendix B, it has been suggested that the oleoresin could be more toxic than purified or synthetic capsaicin. Therefore, developmental toxicity data is required for both active ingredients.

The Agency will utilize the developmental toxicity data and the results of the comprehensive review of the literature to update the hazard characterization, and the human health risk assessments for biochemical uses. This includes determining whether the current exemption from the requirement of a tolerance is still justified. Residue data may be needed should it be determined that a tolerance(s) is more appropriate for the active ingredients. Therefore, a residue chemistry data requirement is also shown in Table 2.

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

Upon re-evaluation of the scientific rationales previously submitted in support of outdoor uses of capsaicin, the ecotoxicity rationales are considered inadequate. Therefore, ecological toxicity data or updated rationales are required in order to assess the risk of capsaicin as a biochemical pesticide applied in outdoor use settings. These data requirements for both capsicum oleoresin and capsaicin and related capsaicinoids are summarized in Table 2. No additional ecological data are needed in support of the biochemical use as a defensive animal repellent (for dogs and bears) or for indoor use patterns (e.g., greenhouses).

Table 2. Summary of All Data Requirements for Antimicrobial and Biochemical Uses (40 CFR sections 158.2050, 158.2060, 158.2240, 158.2250, 158.2280)						
OCSPP Guideline No.	**Data Requirement[12]**	**Active Ingredient**	**Test Substance**	**Time Needed to complete (months)**	**Use Site(s) Triggering Data Requirement**	**Applicable Exposure Scenario**
870.3700	Prenatal Developmental Toxicity (rat)	Capsicum Oleoresin & Capsaicin[13,14]	TGAI	24	All biochemical uses except for defensive animal repellents (e.g., bear sprays)	Dietary, residential and occupational exposures
Series 860	Residue Chemistry[15]	Capsicum Oleoresin & Capsaicin	TGAI or ROC	24-36	Food uses	Dietary exposure
835.1230	Leaching and adsorption/desorption	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
835.2120	Hydrolysis	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
835.2240	Photodegradation in water	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
835.4300	Aerobic aquatic metabolism	Capsaicin	TGAI	24	Antifoulant use on underwater structures	Ecological
835.4400	Anaerobic aquatic metabolism	Capsaicin	TGAI	24	Antifoulant use on underwater structures	Ecological
835.6200	Aquatic (sediment) field dissipation	Capsaicin	TEP	12	Antifoulant use on underwater structures	Ecological

TGAI = Technical Grade Active Ingredient; TEP = Typical End-use Product; ROC = Residue of Concern; EP = end-use product

[12] Conservative assumptions and risk may be assumed if data are not provided

[13] Due to the uncertainty regarding the differences between the toxicity profile of capsicum oleoresin & capsaicin and related capsaicinoids (Bley et al., 2012; Luo, et al., 2011, Watanabe et al., 2008a and 2008b), data for both substances should be submitted for all biochemical uses.

[14] Currently the Agency is working on modifying the active ingredient name for PC Code 070701 to accurately describe the composition of the active ingredient for all registered uses.

[15] Should dietary endpoints be selected once the hazard characterization is completed, residue data will be needed as a tolerance may be considered more appropriate for the active ingredients. It should be noted that based on the Agency's preliminary review, the available repeat dose oral data show adverse effects at doses relevant for risk assessment, so a tolerance exemption may no longer be justified. However, these conclusions are not yet definitive since the hazard characterization has not been finalized due to the need for reassessment of the toxicology database and the need for developmental toxicity data. Should it be determined that the current tolerance exemption is still justified, it is unlikely that residue data will be needed.

Table 2. Summary of All Data Requirements for Antimicrobial and Biochemical Uses (40 CFR sections 158.2050, 158.2060, 158.2240, 158.2250, 158.2280)						
OCSPP Guideline No.	**Data Requirement[12]**	**Active Ingredient**	**Test Substance**	**Time Needed to complete (months)**	**Use Site(s) Triggering Data Requirement**	**Applicable Exposure Scenario**
Special Study	Monitoring of representative U.S. waters[16,17]	Capsaicin	ROC	12	Antifoulant use on underwater structures	Ecological
Special Study	Special leaching	Capsaicin	TEP	12	Antifoulant use on underwater structures	Ecological
850.1010	Acute freshwater invertebrate toxicity	Capsaicin	TGAI	12-24	Antifoulant use on underwater structures	Ecological
850.1025	Oyster acute toxicity test (shell deposition)	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.1035 or 850.1045	Acute estuarine/marine invertebrate toxicity test	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.1055	Bivalve acute toxicity test (embyro-larval)	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.1075[18]	Acute freshwater and estuarine/marine fish toxicity test	Capsaicin	TGAI	12-18	Antifoulant use on underwater structures	Ecological
850.1300[19]	Aquatic invertebrate lifecycle toxicity test	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.1400[16]	Fish early life stage toxicity test	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological

[16] Per 40 CFR section 158.2280, environmental chemistry methods used to generate data associated with this study must include results of a successful confirmatory method trial by an independent laboratory.
[17] Per 40 CFR section 158.2280, data are required if the weight-of-evidence indicates that the active ingredient or principal transformation products are likely to occur in nontarget freshwater, estuarine, or marine waters such that human or environmental exposures are likely to occur. In making that determination, the Agency takes into account other factors such as the toxicity of the chemical(s), available monitoring data and the vulnerability of the freshwater, estuarine, or marine water resources in the antimicrobial use area.
[18] Study results for two freshwater (one cold-water and one warm-water) and one estuarine/marine fish species must be submitted to satisfy this requirement.
[19] Testing must be conducted with the most sensitive organism (either freshwater or estuarine marine) as determined from the results of the acute toxicity tests.

Table 2. Summary of All Data Requirements for Antimicrobial and Biochemical Uses (40 CFR sections 158.2050, 158.2060, 158.2240, 158.2250, 158.2280)						
OCSPP Guideline No.	**Data Requirement[12]**	**Active Ingredient**	**Test Substance**	**Time Needed to complete (months)**	**Use Site(s) Triggering Data Requirement**	**Applicable Exposure Scenario**
850.2100[20]	Acute avian oral toxicity test	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.4400[21]	Aquatic vascular plant toxicity test using *Lemna spp.*	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.4550	Cyanobacteria (*Anabaena flos-aquae*) toxicity test	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.4500[22]	Algal toxicity test	Capsaicin	TGAI	12	Antifoulant use on underwater structures	Ecological
850.2100	Avian acute oral toxicity	Capsicum Oleoresin & Capsaicin[11]	TGAI	12	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological
850.2200	Avian dietary toxicity[23]	Capsicum Oleoresin & Capsaicin[11]	TGAI	12	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological
850.1075	Fish acute toxicity, freshwater	Capsicum Oleoresin & Capsaicin[11]	TGAI	12-18	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological
850.1010	Aquatic invertebrate acute toxicity, freshwater	Capsicum Oleoresin & Capsaicin[11]	TGAI	12-24	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological

[20] For antifoulant uses, the OECD TG 233 using the "LD_{50}- slope test" or "limit dose test" can be used instead of OCSPP 850.2100 for certain species and conditions (e.g., causes no delayed effects, causes no regurgitation). Details on the species and conditions under which TG 233 would not fulfill the data requirement are described at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-classifying-studies-conducted-using-oecd

[21] For antifoulant paints, one definitive test is required for duckweed (*Lemna gibba* or *L. minor*)

[22] For antifoulant uses, studies are required on three species of algae, *Navicula pelliculosa*, *Skeletonema costatum*, and *Pseudokirchneriella subcapitata*

[23] A scientific rationale may be accepted in lieu of toxicity data submitted for the biochemical uses based on the results of the avian acute oral toxicity (OCSPP 850.2100) test and citation of the Agency guidance (U.S. EPA, 2020). A link to the guidance can be found here: https://www.epa.gov/sites/default/files/2020-02/documents/final-waiver-guidance-avian-sub-acute-dietary.pdf

Table 2. Summary of All Data Requirements for Antimicrobial and Biochemical Uses (40 CFR sections 158.2050, 158.2060, 158.2240, 158.2250, 158.2280)						
OCSPP Guideline No.	**Data Requirement[12]**	**Active Ingredient**	**Test Substance**	**Time Needed to complete (months)**	**Use Site(s) Triggering Data Requirement**	**Applicable Exposure Scenario**
850.4100	Terrestrial plant toxicity, seedling emergence	Capsicum Oleoresin & Capsaicin[11]	EP	12	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological
850.4150	Terrestrial plant toxicity, vegetative vigor	Capsicum Oleoresin & Capsaicin[11]	EP	12	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological
880.4350	Nontarget Insect Testing	Capsicum Oleoresin & Capsaicin[11]	TGAI	12	Outdoor use sites (excluding antifoulant use on underwater structures)	Ecological

IV. Guidance for Commentors

Preliminary Work Plan

During the comment period, anyone may submit relevant data or information for the Agency's consideration. The public is invited to comment on the Agency's PWP. The areas below highlight topics of special interest to the Agency where comments, information and data, or reference to sources of additional information could be of particular use. The Agency will carefully consider all comments, as well as any additional information or data provided in a timely manner, prior to issuing a FWP for this case.

Additional Information

Stakeholders are also specifically asked to provide information and data that will assist the Agency in refining the risk assessments as well as the ESA assessment. The Agency is interested in obtaining the following information regarding capsaicin and related capsaicinoids:

i. Confirmation on the following label information:
   - Sites of application
   - Formulations
   - Application methods and equipment
   - Maximum application rates
   - Frequency of application, application intervals, and maximum number of applications
   - Geographic limitations on use

ii. Use or potential use distribution (e.g., acreage and geographical distribution of relevant use sites)

iii. Median and 90th percentile reported use rates from usage data – national, state, and county

iv. Application timing (date of first application and application intervals) – national, state, and county

v. Usage/use information for agricultural and nonagricultural uses

vi. Typical application interval (days)

vii. State or local use restrictions

viii. Monitoring data

ix. Foreign technical registrants not listed above who supply pesticide products containing capsaicin and related capsaicinoids to the U.S. market

x. The Agency welcomes any information on the effects of capsaicin and related capsaicinoids, including biodegradability of the active ingredient and ecotoxicology and environmental fate data/information that would help refine the ESA assessment

xi. Product identity data/information that would help inform the Agency's need to modify PC Code 070701 to accurately describe the active ingredient composition of registered products

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. To help address potential environmental justice issues related to registration review decisions, the Agency seeks information on any groups or

segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to capsaicin and related capsaicinoids compared to the general population or who may otherwise be disproportionately affected by the use of capsaicin and related capsaicinoids as a pesticide. Please comment if you are aware of any such issues and can provide information to help the Agency to more fully consider and address potential environmental justice issues.

V. Next Steps and Timeline

A Federal Register Notice will announce the docket opening for the current cycle of registration review for capsaicin and related capsaicinoids and a 60-day comment period for this *Preliminary Work Plan* to provide comments and additional information that will help the Agency's decision-making process for capsaicin and related capsaicinoids. After the 60-day comment period closes, the Agency will review and respond to any comments received in a timely manner, then issue a Final Work Plan for capsaicin and related capsaicinoids. The Agency's final decision on the capsaicin and related capsaicinoids registration review case will include a determination on the Endocrine Disruptor Screening Program (EDSP) obligations under FFDCA § 408(p) and completion of an endangered species determination and any necessary consultation with the Services.

Table 3. Anticipated Registration Review Schedule for Capsaicin and Related Capsaicinoids

Anticipated Activity	Estimated Month/ Year
Opening the Docket	
Open Docket and 60-Day Public Comment Period for Preliminary Work Plan	September 2024
Close Public Comment Period	November 2024
Case Development	
Final Work Plan	December 2024
Issue Data Call-In	March 2025
Data Submission	March 2028
Open 60-Day Public Comment Period for Draft Risk Assessments	March 2029
Close Public Comment Period	May 2029
Registration Review Decision and Implementation	
Open 60-Day Public Comment Period for Proposed Registration Review Decision	July 2029
Close Public Comment Period	September 2029
Final Decision*	TBD

*The anticipated schedule will be revised as necessary (e.g., need arising under the Endocrine Disruptor Screening Program with respect to the active ingredients in this case).

Appendix A – Product Characterization

The product chemistry database is acceptable and complete for biochemical uses. Table 4 summarizes the current product chemistry data requirements and results supporting registration review of the active ingredients. After review of the available data, labels, and Confidential Statements of Formula (CSFs) for the registered products, it has been determined that there should be clarification regarding the nomenclature of the active ingredients and their classification under the existing PC Codes.

Capsicum oleoresin is an oily organic resin derived from the fruit of *Capsicum* plants, such as chili peppers. It is rich in a variety of compounds (capsaicinoids, carotenoids, flavonoids, triglycerides, terpenes, vitamins, etc.). The oleoresin is formed from finely ground plants via different extraction processes. It can be further processed to produce more concentrated capsaicin and related capsaicinoids. Capsaicin is one of the six common natural capsaicinoids, namely capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, and nonivamide, found in chili peppers. Capsaicin is usually not separated from other capsaicinoids. It should be noted that in the literature and industry, the term “capsaicin” is often used as an umbrella term that references capsaicin, capsaicinoids, capsicum oleoresin, capsicum extracts, etc. It also should be noted that capsaicinoids must not be confused with capsinoids (e.g., capsiate, dihydrocapsiate, nordihydrocapsiate, etc.), which are capsaicinoid-like and can also be found in some chili peppers; however, they contain an ester bond instead of an amide bond between the vanillyl moiety and fatty acid chain, and they lack the characteristic pungency and do not produce an intense burning sensation.

In pesticide products, the active ingredients are generally identified on product labels as “capsaicin”, “capsaicin and related capsaicinoids”, and “capsicum oleoresin extract”. There are two CAS numbers and two PC Codes for these substances: CAS No. 404-86-4 and PC Code 070701 for capsaicin and CAS No. 8023-77-6 and PC Code 070704 for capsicum oleoresin. According to the data on file with the Agency, there are no biochemical products that consist solely of capsaicin. Registered biochemical products either contain capsicum oleoresin or the more purified derivative, capsaicin and related capsaicinoids. Based on the data available to the Agency, capsaicin and related capsaicinoids is described as a powder and capsicum oleoresin is described as a liquid or slurry. Therefore, it is recommended that biochemical products containing capsaicin and related capsaicinoids are grouped under PC Code 070701 and biochemical products containing capsicum oleoresin are grouped under PC Code 070704. The Agency is currently working to modify the PC Code 070701 to accurately describe the composition of the active ingredient for all registered uses. Additionally, the nomenclature of the active ingredients on labels and CSFs should be revised accordingly. The percent of capsaicin and related capsaicinoids or oleoresin capsicum should be included in the ingredient statement, rather than the amount of capsaicin. While capsaicin is the primary constituent of the oleoresin, it is not the only ingredient responsible for pesticidal activity. Should registrants wish to quantify the amount of capsaicin on product labels, this could be done via asterisk in the ingredient statement. It is worth noting that the aforementioned conclusions are based on the data submitted to the Agency; in some cases, the manufacturing processes and analyses for these substances are not available, detailed and/or clear. For example, some sources of active ingredients are food-grade, and the manufacturing process data requirement was waived. Additionally, the substances can be produced via different means (e.g., water extraction, solvent extraction, supercritical fluid extraction, etc.). Substances derived using different extraction methods can vary somewhat in composition. Capsaicin can be

manufactured synthetically as a distinct chemical; however, based on the existing data, synthetic capsaicin is not used as an active ingredient in registered biopesticide products.

Table 4. Summary of Product Chemistry Data (40 CFR sections 158.2030 and 158.2210)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Product Identity and Composition	880.1100 830.1550	Confidential Business Information (CBI)	--
Description of Starting Materials, Production and Formulation Process	880.1200 830.1600 830.1620 830.1650	CBI	--
Discussion of Formation of Impurities	880.1400 830.1670	CBI	--
Preliminary Analysis	830.1700	CBI	--
Color	830.6302	Reddish brown (capsicum oleoresin) Off-white (capsaicin and related capsaicinoids)	42802204 50899502 NCBI, 2023
Physical State	830.6303	Viscous liquid (capsicum oleoresin) Crystalline powder (capsaicin and related capsaicinoids)	42802204 50899502 NCBI, 2023
Odor	830.6304	Pungent/chili-like (capsicum oleoresin) Odorless (capsaicin and related capsaicinoids)	42802204 50899502
Stability to Normal and Elevated Temperatures, Metals, and Metal Ions	830.6313	Stable to normal and elevated temperatures, and to metals and metal ions (both TGAIs)	42802204 50899502
pH	830.7000	N/A; TGAIs are insoluble in water	--

Table 4. Summary of Product Chemistry Data (40 CFR sections 158.2030 and 158.2210)									
Data Requirement	**Guideline No.**	**Results / Findings**							**MRIDs**
UV/Visible Light Absorption	830.7050	**UV-VIS absorption spectra**	**Neutral**		**Acidic**		**Alkaline**		50899502
		Wavelength of maximum (nm)	228.561	279.937	227.966	279.661	216.842	246.715	293.283
		Absorbance observed at maximum (nm)	1.523	0.646	1.661	0.727	1.697	1.727	0.757
		E value calculated	82.77	35.11	90.27	39.51	92.23	93.86	41.14
		Satisfies the requirement for both TGAIs							
Melting Point/Melting Range	830.7200	N/A for capsicum oleoresin: TGAI is a liquid 65°C (capsaicin and related capsaicinoids)							NCBI, 2023
Boiling Point/Boiling Range	830.7220	123°C (capsicum oleoresin) 199.9°C (decomposition point) (capsicum oleoresin) 210-220°C (capsaicin and related capsaicinoids)							U.S. EPA, 2009 50899502 NCBI, 2023
Density/Relative Density/Bulk Density	830.7300	1.082 (specific gravity) (capsicum oleoresin) 1.012 g/mL @ 20°C (density) (capsicum oleoresin) 1.05 g/cm^3 (predicted density) (capsaicin and related capsaicinoids)							42802204 50899502 U.S. EPA, 2023
Particle Size, Fiber Length, and Diameter Distribution	830.7520	N/A: TGAIs are a liquid or are not fibrous							--
Partition Coefficient (n-octanol/water)	830.7550 830.7560 830.7570	Log P_{ow} (constituents of capsicum oleoresin): Nordihydrocapsaicin: 3.38 Capsaicin: 3.47 Dihydrocapsaicin: 3.90							50899502
Water Solubility	830.7840 830.7860	2.2 mg/L; practically insoluble (both TGAIs)							42802204

Table 4. Summary of Product Chemistry Data (40 CFR sections 158.2030 and 158.2210)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Vapor Pressure	830.7950	4.90×10^{-6} mmHg @ 20°C (capsicum oleoresin) 1.30×10^{-8} mmHg @ 20°C (capsaicin)	50899504 U.S. EPA, 2017 (based on bond method in EPI-Suite, v4.11)

N/A = not applicable; TGAI = Technical Grade Active Ingredient

Appendix B – Human Health Risk Assessment

Summary of Mammalian Toxicology Data

Antimicrobial Use

New human health risk assessments are not needed for the antimicrobial use of capsaicin. The previous new use risk assessment concluded that adverse effects to humans and nontarget organisms are not expected to occur with labeled uses of capsaicin (U.S. EPA, 2016). All data requirements have been met and the database is complete, and no additional information has been found in the literature or incident database that would alter the Agency's risk conclusions. Therefore, previous risk conclusions are still applicable for the antimicrobial use of capsaicin (U.S. EPA, 2016). No additional human health data are needed at this time for the antimicrobial use of capsaicin.

Biochemical Uses

The mammalian toxicology database is incomplete as a data gap has been identified for developmental toxicity. Additionally, a comprehensive review of the available repeat-dose oral toxicity, acute inhalation toxicity, genotoxicity, and carcinogenicity data is needed. This includes studies from the open scientific literature that have been published since the previous registration review. Some of the data show potential for adverse effects, and exposure is anticipated from use of pesticide products containing these active ingredients. Products are for occupational and residential use, are applied via a wide variety of application methods, and are applied to food commodities. It should be noted that at this time, the Agency does not have a serious concern regarding exposure to pesticide products containing these active ingredients given the widespread exposure to the substances in food, but it has been determined that additional data and an updated risk assessment are needed in order to reliably support a safety finding for the existing use patterns. This includes determining whether the current exemption from the requirement of a tolerance is still justified. Residue data will be needed, should it be determined that a tolerance(s) is more appropriate for the active ingredients. Table 5 summarizes the current mammalian toxicology data requirements and results supporting registration review of the active ingredients.

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Acute Oral Toxicity	870.1100	LD_{50} = 200 (95% confidence limit: 11–3501 mg/kg (trans-capsaicin) (mouse). LD_{50} = 285 (95% confidence limit: 134–605) mg/kg (cis-capsaicin) (mouse) LD_{50} = 800 (95% confidence limit: 437–1463) mg/kg (capsicum oleoresin[1] containing 20% capsaicinoids) (mouse) LD_{50} = 283 (95% confidence limit: 71–1130) mg/kg (capsicum oleoresin[1] containing 40% capsaicinoids) (mouse) LD_{50} = 283 (95% confidence limit: 70–1141) mg/kg (capsicum oleoresin[1] containing 80% capsaicinoids) (mouse) LD_{50} = 50 (95% confidence limit: 16–157) mg/kg (isolated capsaicinoids from oleoresin[1]) (mouse) Acceptable/Non-guideline/Toxicity Category II	Kumar et al., 2012
		LD_{50} = 60-75 mg/kg (capsaicin[2]) (mouse) LD_{50} = 190 mg/kg (capsaicin[2]) (mouse) Acceptable/Non-guideline/Toxicity Category II	Glinsukon et al. 1980
		LD_{50} = 97-119 mg/kg (capsaicin[2]) (mouse) LD_{50} = 148-161 mg/kg (capsaicin[2]) (rat) Acceptable/Non-guideline/Toxicity Category II	Saito and Yamamoto, 1996
Acute Dermal Toxicity	870.1200	LD_{50} > 512 mg/kg (capsaicin[2]) (mouse) Acceptable/Non-guideline/Toxicity Category II	Glinsukon et al. 1980

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Acute Inhalation Toxicity	870.1300	Numerous published non-guideline studies measuring acute inhalation effects and lethality are available in laboratory animals. Although each study is considered limited due to various reporting deficiencies, collectively they show that capsaicin and capsicum oleoresin are of relatively low acute toxicity. However, these substances can be respiratory irritants. Studies measuring acute inhalation effects in humans are also available. During registration review, the Agency will conduct a comprehensive review of the database for these active ingredients. The studies conducted using humans are likely subject to the Agency's Human Studies rule (40 CFR Part 26) and have not yet undergone ethics review or review by the Human Studies Review Board (HSRB).	Selection of animal study references: Kumar et al., 2012; Reilly et al., 2003; Karmouty-Quintana et al., 2007; Mozsik et al., 2009; Pesonen et al., 2010
Primary Eye Irritation	870.2400	<u>Primary Eye Irritation Test:</u> After test substance instillation (27 mg; 0.1 mL weight equivalent), there were observations of corneal opacity (1/6 animals at 1 hour), iritis (3/6 animals at 1-hour) and slight to moderate positive conjunctival irritation (6/6 animals at 1 hour, 4/6 animals at 24 hours and 4/6 animals a 48 hours). All ocular irritation was clear by 96 hours. (ground capsicum) (rabbit) Acceptable/Guideline/Toxicity Category III	44189202

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
		Primary Eye Irritation Test: Immediately after test substance instillation (50 mg/mL), erythema, corneal and conjunctival abrasion and corneal opacity were observed (6/6 animals). Effects diminished over time and resolved within 7 days. (The test material was identified as capsaicin; however, the CAS number provided was for capsicum oleoresin.) (rabbit) Acceptable/Non-guideline/Toxicity Category III Primary Eye Irritation Test: Doses between 50 and 100 µg/mL caused severe irritation and animals were euthanized due to indications of pain and distress. A dose of 25 µg/mL resulted in positive corneal and iridal effects (based on mean grades) at 1-hour after test substance instillation with clearance by 24 hours. (The test material was identified as capsaicin; however, the CAS number provided was for capsicum oleoresin.) (rat) Acceptable/Non-guideline/Toxicity Category Undetermined Bovine Corneal Opacity and Permeability Test: *In Vitro* Irritancy Score (IVIS; scores rounded): IVIS = 19 (dose: 5 mg/mL) IVIS = 19 (dose: 25 mg/mL) IVIS = 20 (dose: 50 mg/mL) (The test material was identified as capsaicin; however, the CAS number provided was for capsicum oleoresin.) Acceptable/Non-guideline/Toxicity Category III	Krishnatreyya et al., 2018

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Primary Dermal Irritation	870.2500	Primary Dermal Irritation Test: Very slight to well-defined erythema and very slight to slight edema were observed in all animals with clearance by day 7. Slight irritation was observed at 72 hours. (ground capsaicin) (rabbit) Acceptable/Guideline/Toxicity Category III Capsaicin and capsicum oleoresin can cause a sensation of burning pain as well as irritation and erythema of the skin.	44146709 NCBI, 2023
Dermal Sensitization	870.2600	No data are available on the active ingredients. However, results of a guideline dermal sensitization study on a product containing 10% capsicum oleoresin were negative. Furthermore, the results of another guideline dermal sensitization study on a product containing 2.5% capsaicin were negative as well. Additionally, capsaicin is used in topical ointments as an analgesic. The Agency is not aware of any data or information indicative of the potential for allergic contact dermatitis from exposure to the active ingredients. Acceptable	50899522 NCBI, 2023 42817704
Hypersensitivity Incidents	N/A	None reported	N/A

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
90-Day Oral – Rodent	870.3100	Gavage: 0, 30, 100, 250 mg/kg/day NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day based on liver effects: increased liver weights, periportal vacuolation associated with hepatocellular hypertrophy and increased liver enzyme levels. Localized gastric effects were noted at 100 mg/kg/day and were attributed to irritation. (phenylcapsaicin- 98.8%) (rat) Supplemental/Non-guideline	Paulsen et al., 2018
		Dietary: 0, 0.0625, 0.125, 0.25, 0.5, 1% Renal toxicity and reduced body weights were observed in males at a dose level of 1% in the diet, and reduced body weights were observed in females at all dose levels. (mixture of 64.5% capsaicin and 32.6% dihydrocapsaicin and other natural capsaicinoids) (mice) Supplemental/Non-guideline	Akagi et al., 1998
		A few additional studies that are considered supplemental/non-guideline at this time are available in the literature. This section will be updated once the Agency's assessment is completed.	
90-Day Oral – Nonrodent	870.3150	NR	N/A
21/28-Day Dermal Toxicity	870.3200	NR	N/A

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
90-Day Dermal – Rat	870.3250	Based on a review of the open scientific literature, while capsaicin and capsicum oleoresin can be dermal irritants and can be absorbed by the skin, they do not appear to be well-absorbed systemically. Additionally, humans are already exposed dermally to these ingredients, as they are used in over-the-counter and prescription topical analgesics. Lastly, pesticide products containing these active ingredients are not purposefully applied to the skin. Acceptable	NCBI, 2023 U.S. EPA, 2016
90-Day Inhalation – Rat	870.3465	No subchronic inhalation toxicity data are available. In the absence of these data, and because the active ingredients are known irritants, at this time the Agency believes the existing acute inhalation toxicity data can be used for assessing risk. Portal-of-entry effects are anticipated, are expected to occur at doses lower than systemic effects (if any) and have been observed in the acute inhalation toxicity data; therefore, the Agency believes these data are appropriate for risk assessment. This section will be updated once the Agency's assessment is completed.	N/A
Developmental Toxicity	870.3700	<u>Dermal (3-hour treatment/day):</u> Dermal irritation was noted in dams at all doses tested. No treatment related systemic maternal or developmental effects were noted up to the highest dose tested (1.3 mg/cm^2). (trans-capsaicin) (rabbit) Supplemental/Non-guideline Additional data are needed.	Chanda, et al., 2006
Reproduction and Fertility Effects	870.3800	NR	N/A

Table 5. Summary of Toxicology Data (40 CFR sections 158.2050 and 158.2230)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Chronic Oral Toxicity – Rodent	870.4100	NR	N/A
Carcinogenicity	870.4200	There are studies in the open scientific literature indicative of the potential for carcinogenic effects. This section will be updated once the Agency's assessment is completed.	--
Bacterial Reverse Mutation Test	870.5100	There are several studies in the open scientific literature showing positive and negative results. This section will be updated once the Agency's assessment is completed.	--
In vitro Mammalian Cell Assay	870.5300 870.5375	There are several studies in the open scientific literature showing positive and negative results. This section will be updated once the Agency's assessment is completed.	--
In vivo Cytogenetics	870.5385 870.5395	There are studies in the open scientific literature showing variable results. This section will be updated once the Agency's assessment is completed.	--
90-Day Neurotoxicity – Rat	870.6200	NR	N/A
Developmental Neurotoxicity	870.6300	NR	N/A

LD_{50} = median lethal dose; LC_{50} = median lethal concentration; NOAEL = no-observed-adverse-effect-level;
LOAEL = lowest-observed-adverse-effect-level
N/A = not applicable
NR = Not required for the current use patterns. If, in the future, the use of capsaicin is expanded or a new use is added, new data may be required.
[1] Extracted from *Capsicum frutescence var. Nagahari*
[2] Synthetic

Hazard Characterization

Antimicrobial Uses

In the 2016 new use risk assessment (U.S. EPA, 2016) for capsaicin, no points of departure (POD) (endpoints) were established due to minimal exposure. The registrants submitted a review article of the open scientific literature (MRID 49410905) at the time of registration (U.S. EPA, 2016). The individual citations included in this MRID are referenced throughout the discussion below. In the submitted information (Johnson, 2007), chronic toxicity, carcinogenicity, and metabolism and pharmacokinetics data were also cited but are not required for the current use of capsaicin. No additional human health data are needed for the antimicrobial use at this time.

The National Pesticide Information Center (NPIC) summary shows capsaicin to be moderately toxic by the oral route, with LD_{50} values of 60-75 mg/kg in one experiment (Glinsukon et al. 1980), and of 95-119 mg/kg in another experiment using mice (Saito and Yamamoto, 1996). Acute dermal toxicity of capsaicin was reported as > 512 mg/kg in one experiment using mice (Glinsukon et al. 1980). Results of the acute oral and dermal experiments therefore place capsaicin in Toxicity Category II.

In a publication by Kasting et al. (1997), the *in vivo* absorption of vanillylnonanamide, a close structural analog of capsaicin, was shown to be approximately 5% after 24 hours and 12% after 72 hours. A dermal metabolism study showed the presence of vanillylamine, a hydrolysis product, and that over 72 hours, 7.5% of the applied dose was excreted in urine, and 3.4% in feces, with 68% of the applied dose unabsorbed (Kasting et al., 1997). There are no data on the inhalation LC_{50} of capsaicin. No data were cited for primary skin or eye irritation in the NPIC summary, however other data in the database show that Capsaicin is Toxicity Category III for primary skin and eye irritation. An older dermal sensitization guideline study submitted to the Agency and cited in the capsaicin Reregistration Eligibility Decision [RED] document (MRID 42817704) reported no sensitization reactions in guinea pigs treated with the product containing 2.5% capsaicin.

Summary information on the non-acute toxicity of capsaicin in experimental animals was provided in an article from the open scientific literature (Johnson, 2007). There are numerous studies cited, and only general statements are made here as no dose information was provided in the open literature review. Immune effects of capsaicin were cited in data from both adult and neonatal animals. Dose-dependent gastric vascular damage was observed in Wistar rats from oral administration of capsaicin. Neurotoxicity of capsaicin is observed from studies using the subcutaneous injection route of exposure. Positive responses in mutagenicity tests are also observed. Carcinogenicity studies with capsaicin indicate that capsaicin induces tumors of the gastrointestinal tract. Studies of developmental and reproductive toxicity of capsaicin from the review article were screened and appeared to indicate no significant effects.

Biochemical Uses

The toxicological database is considered incomplete for characterizing hazard and assessing risk from the active ingredients in this case, and the Agency has determined that additional data are needed for biochemical uses of capsaicin. When capsicum oleoresin and its derivatives were last assessed during registration review (U.S. EPA, 2010), the data requirements were considered satisfied based on a long history of dietary exposure, acute toxicity data on registered end-use products, rapid degradation in the environment, and lack of reported toxicity in the public literature according to the Agency's 1992 Reregistration Eligibility Decision (RED). During the current registration review, the Agency has

determined that additional data are needed to sufficiently assess the potential for risk from exposure to pesticide products containing these active ingredients. This conclusion is based on a cursory review of the open scientific literature in which information was identified that indicated the potential for adverse effects. It was also determined that there is a lack of adequate data to substantiate a rapid degradation argument.

With respect to acute toxicity, the active ingredients are classified into Toxicity Category II for acute oral toxicity and acute dermal toxicity, Toxicity Category III for primary eye irritation and Toxicity Category III for primary dermal irritation. Based on the available data, these active ingredients are not considered to be skin sensitizers. A Toxicity Category for acute inhalation toxicity will be assigned once the Agency has completed its review.

Repeat-dose oral toxicity data are available in the open scientific literature. In a 13-week non-guideline dietary toxicity study, mice were exposed to a mixture of 64.5% capsaicin and 32.6% dihydrocapsaicin and other natural capsaicinoids. The study authors noted renal toxicity and reduced body weights in males in the highest dose group (1% in the diet), and reduced body weights in females in all dose groups (0.0625%-1% in the diet) (Akagi et al., 1998). The study is considered supplemental as it was conducted as a dose range finding study for a carcinogenicity study and lacks sufficient reporting of methodology and results.

There is also a 90-day oral gavage toxicity study in rats for phenylcapsaicin, a synthetically produced analog of capsaicin. The NOAEL in this study was 100 mg/kg/day and the LOAEL was 250 mg/kg/day based on liver effects. Localized gastric effects were noted at 100 mg/kg/day and were attributed to irritation, as capsaicin is considered to be a strong gastric irritant. In a 28-day dose range finding study summarized in the 90-day study, all animals in the 500 mg/kg/day and 1000 mg/kg/day dosing groups were either found dead or were euthanized for humane reasons by day four of the study (Paulsen et al., 2018). Summaries of two other oral repeat-dose studies were included by the study authors and showed similar effects to those seen in the 90-day study, but definitive conclusions cannot be drawn as the original sources of the data are unavailable to the Agency. A few additional studies that are considered supplemental/non-guideline at this time are available in the literature.

During registration review, the Agency will conduct a comprehensive review of the available data and update the oral/dietary hazard characterization. The remainder of the available repeat-dose oral toxicity data in the open scientific literature are for capsinoids, and as stated in the product characterization section, products contain capsaicinoids, rather than capsinoids.

The Agency does not consider data on capsinoids to be bridgeable to capsaicinoids because capsinoids are thought to be of lower toxicity. The existing acute oral toxicity data, for example, provide evidence supporting these conclusions. The acute oral LD_{50} values for dihydrocapsiate and capsinoid-containing CH-19 Sweet extract (a cultivar of *Capsicum annuum L.)* are greater than 5,000 mg/kg and 1,425 mg/kg, respectively, whereas the acute oral LD_{50} values for capsaicin and capsicum oleoresin range from 60-800 mg/kg (Watanabe et al., 2008a and 2008b; Saito and Yamamoto, 1996; Glinsukon et al. 1980 and Kumar et al., 2012).

Additionally, it has been suggested that the toxicity profile of pure and/or synthetic capsaicin and capsinoids may differ from the extracts (e.g., capsicum oleoresin) (Bley et al., 2012; Luo, et al., 2011, Watanabe et al., 2008). For example, in two non-guideline 13-week oral gavage studies and one non-guideline 26-week oral gavage study, the NOAELs for dihydrocapsiate in rats were at the limit dose of

1,000 mg/kg/day. In a non-guideline 26-week oral gavage study in rats with capsinoid-containing CH-19 Sweet extract, the NOAEL for female rats was the highest dose tested (361.0 mg capsinoid/kg/day) and the NOAEL for male rats was 180.5 mg/kg/day and the LOAEL was 361.0 mg/kg/day based on liver effects (Kodama et al., 2008a; Watanabe et al., 2008b; Kodama et al., 2008b and Kodama et al., 2010).

The 90-day dermal data requirement has been satisfied with rationale. While the active ingredients can be dermal irritants and can be absorbed by the skin, they are not well-absorbed systemically (NCBI, 2023; U.S. EPA, 2016). Additionally, humans are already dermally exposed to capsaicin as it is used in over-the-counter and prescription topical analgesics. Pesticide products are not purposefully applied to the skin.

No subchronic inhalation toxicity data are available for the active ingredients. In the absence of these data, and because the active ingredients are known irritants, at this time the Agency believes the existing acute inhalation toxicity data can be used for assessing risk. Portal-of-entry effects are anticipated, are expected to occur at doses lower than systemic effects (if any) and have been observed in the acute inhalation toxicity data; therefore, the Agency believes these data are appropriate for risk assessment. During registration review, a comprehensive review of the database will be conducted, and the hazard characterization will be completed. The studies conducted using humans are likely subject to the Agency's Human Studies rule (40 CFR part 26) and have not yet undergone ethics review or review by the Human Studies Review Board (HSRB).

Regarding developmental toxicity, there is one non-guideline study for trans-capsaicin in the open literature that is considered supplemental due to reporting deficiencies. In the study, the test substance was administered topically to time-mated rabbits for three hours (hrs.) per day from gestation day (GD) 7 through 19. No treatment related systemic maternal or developmental effects were noted up to the highest dose tested, 1.3 mg/cm^2. Dermal irritation was noted in dams at all doses tested (Chanda, et al., 2006). The remainder of the studies found in the initial search of the literature were conducted using capsinoids, which, as stated previously, are anticipated to be less toxic than the capsaicinoids.

There are several *in vitro and in vivo* genotoxicity studies, as well as carcinogenicity studies in the open scientific literature for capsaicin, capsaicinoids and capsinoids that show variable results. In fact, these substances have been studied as potential carcinogens, co-carcinogens and anti-cancer agents. Some epidemiological studies have suggested a positive correlation between the incidence of cancer in humans, particularly gastric and gallbladder cancers, and consumption of capsaicin-rich or chili pepper-rich diets. (Bernard et al., 2008; Bley et al., 2012; Chanda et al., 2007; Georgescu et al., 2017; Hwang, et al., 2010; Luo et al., 2021). Consensus about cancer prevention or causation has not been reached in the scientific community. The Agency has determined that these data will need to be thoroughly reviewed and the risk assessment will need to be updated during registration review.

The current hazard characterization is based on the toxicology data in the Agency's database as well as the results of a cursory review of the open scientific literature. In order to complete the hazard characterization, a comprehensive review of the available repeat-dose oral toxicity, acute inhalation toxicity, genotoxicity, and carcinogenicity data is needed. This will occur during registration review. Additionally, data are needed to adequately assess the potential for developmental toxicity from exposure to capsicum oleoresin/capsaicin and related capsaicinoids. Further, exposure is anticipated from the biopesticide uses of pesticide products containing these active ingredients. Biopesticide

products are for occupational and residential use, are applied via a wide variety of application methods, and are applied to food commodities. Additionally, there are no reliable environmental fate data available to support the previous conclusion that the substances rapidly degrade in the environment. Lastly, there are multiple articles in the open literature involving the intentional exposure of human subjects that show potential for adverse effects from exposure to capsicum oleoresin/capsaicin and related capsaicinoids. These studies are likely subject to the Agency's Human Studies rule (40 CFR part 26) and have not yet undergone ethics review or review by the HSRB.

Dietary Exposure and Risk Characterization

Antimicrobial Uses

There are no anticipated dietary risks of concern for the routine application of capsaicin from antimicrobial products. In the 2016 assessment, no food uses were identified (U.S. EPA, 2016). Based on the current antimicrobial label, indirect food contact uses may be assumed for product application on underwater structures that could have indirect food contact.

Based on the current antimicrobial labeled use, there is a potential for drinking water exposure. The current label does not restrict the application of the product on water intake grates for drinking water treatment systems. Exposure to capsaicin is not expected to result in any adverse health effects via the drinking water exposure pathway for a few reasons. These reasons include that the amount of capsaicin found in some natural peppers (e.g., 4,249 ppm in hot chili; Al Othman *et al*., 2011) is higher than the maximum amount of capsaicin in the registered antifoulant product (0.075% capsaicin; 750 ppm). In addition, the current registered product's leachable capsaicin is expected to be at a lower level than the final concentration of the applied product. Leached capsaicin would also be diluted into the water flowing past the grate. This dilution would further lower the expected concentration of capsaicin in water entering the water treatment plant, where treatment may reduce capsaicin concentrations further. Based on the current antimicrobial label and 40 CFR §158.2290, indirect food contact uses may also be assumed for product application on underwater structures that capture food that could have indirect food contact. However, for many of the same reasons listed above, risks are not anticipated from these uses.

Biochemical Uses

Dietary exposure is anticipated as biochemical products containing capsicum oleoresin/capsaicin and related capsaicinoids are registered for use on food. These active ingredients were previously assessed qualitatively based on expected rapid degradation in the environment, existing presence in the human diet, low acute toxicity and lack of reported adverse effects (U.S. EPA, 2010). The exemption from the requirement of a tolerance was also based on these conclusions. Due to the potential for adverse effects noted in the recent open literature search, the lack of developmental toxicity data on the active ingredients, and the lack of reliable environmental fate data to support the previous conclusion that these substances degrade rapidly in the environment, the Agency has determined that an updated assessment is necessary to evaluate the potential for dietary risk for uses that may result in residues on food. This includes determining whether the current exemption from the requirement of a tolerance is still justified. Residue data will be needed should it be determined that a tolerance(s) is more appropriate for the active ingredients.

It is noted that capsaicin is approved as a flavoring agent or adjuvant by the Food and Drug Administration (FDA; 21 CFR designation not available[24]) and the oleoresin (from *Capsicum frutescens L*. and *Capsicum annuum L*.) is approved as a color additive and a food additive and is Generally Recognized As Safe (GRAS; 21 CFR 73.345 and 182.20). It is also acknowledged that capsaicin and capsaicinoids are consumed naturally in food (i.e., pungent peppers); however, it is unknown if dietary exposure from pesticidal use will significantly increase overall dietary exposure.

Residential and Non-Occupational Exposure and Risk Characterization

Antimicrobial Uses

While the 2016 Human Health and Ecological Risk Assessments for the New Antifoulant Use of Capsaicin (U.S. EPA, 2016) qualitatively evaluated risks for residential handlers from dermal exposures, it did not address potential for inhalation exposure to capsaicin from the antifoulant use. There is a low potential for inhalation exposure given the low volatility of capsaicin (vapor pressure = 1.3×10^{-8} mmHg, based on bond method in EPI-Suite, v4.11; U.S. EPA, 2017). In addition, the antifoulant product is formulated as a wax which, according to label directions, should only be heated to 135°F (57.2°C) (boiling point of capsaicin = 210-220°C; NCBI, 2023). While capsaicin is a known dermal irritant, potential effects are mitigated by Personal Protective Equipment (PPE) required on the label, including gloves and long-sleeve shirt. Based on the minimal exposure for both inhalation and dermal routes, no exposures of concern for residential handlers are anticipated as was concluded in the 2016 risk assessment (U.S. EPA, 2016).

For residential post-application exposures, there is a low potential for inhalation exposure based on the low volatility of capsaicin as discussed above. Based on the use pattern, applicators are not expected to touch the hull of the boat, where the product is applied, frequently or long enough to elicit dermal irritation. Even if extended contact with a treated surface occurs, the amount of active ingredient in the antifoulant product (750 ppm) is relatively low (Marshall et al., 1981); thus, concern from dermal exposure is not anticipated. Based on the use pattern, there is no potential for incidental oral exposure as it is not a vertical surface a child would be on or an object to be mouthed. Taken together, there is no anticipated exposure of concerns for residential post-application exposure.

Biochemical Uses

Residential (non-occupational) handler and post-application exposure may occur from use of biochemical pesticide products containing capsicum oleoresin/capsaicin and related capsaicinoids. Products are applied via a variety of application equipment, including trigger spray bottles, manually pressurized hand sprayers, hose-end sprayers, etc., and are applied as broadcast, perimeter and direct sprays and treatments, as well as spot treatments. These active ingredients were previously assessed qualitatively based on expected rapid degradation in the environment, dilute applications, low acute toxicity, and lack of reported adverse effects (U.S. EPA, 2010). Due to the potential for adverse effects noted in the recent open literature search, the lack of developmental toxicity data on the active ingredients, and the lack of reliable environmental fate data to support the previous conclusion that these substances degrade rapidly in the environment, the Agency has determined that an updated assessment is necessary to evaluate the potential for residential risk for all products with these uses,

[24]https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances&sort=Sortterm_ID&order=ASC&startrow=1&type=basic&search=capsaicin

with the exception of the defensive animal repellents for dogs and bears which are sprayed directly at animals deemed to be dangerous. These products are used transiently (e.g., in emergency situations) and significant residential exposure is not anticipated.

Occupational Exposure and Risk Characterization

Antimicrobial Uses

There are no anticipated exposures of concern to capsaicin for occupational handler exposures. As with the residential handler exposures, dermal or inhalation exposure for occupational handlers will be assessed qualitatively as was previously done in the 2016 risk assessment (U.S. EPA, 2016). As with residential handlers, based on the label, PPE will be required to apply the active ingredient, and the potential for inhalation exposure to the volatilized active ingredient is low. Based on the minimal exposure for both inhalation and dermal exposure, no exposures of concern for occupational handlers are anticipated as was concluded in the 2016 risk assessment (U.S. EPA, 2016).

As with post-application for residential exposures, dermal and inhalation exposures will not result in exposures of concern for occupational post-application exposures given the low volatility of capsaicin and limited contact with treated surfaces. Taken together, there is no anticipated exposure of concern for occupational post-application exposures.

Biochemical Uses

Occupational handler and post-application exposure may occur from use of biochemical pesticide products containing the active ingredients. Products are applied via a variety of application equipment, including airplanes, manually pressurized hand sprayers, groundboom sprayers, backpack sprayers, etc., and are applied as broadcast, perimeter and direct sprays and treatments, spray drenches, dip treatments, and spot treatments. The active ingredients were previously assessed qualitatively based on expected rapid degradation in the environment, dilute applications, low acute toxicity, and lack of reported adverse effects and personal protective equipment (PPE) requirements on product labels (U.S. EPA, 2010). Due to the potential for adverse effects noted in the recent open literature search, the lack of developmental toxicity data on the active ingredients, and the lack of reliable environmental fate data to support the previous conclusion that these substances degrade rapidly in the environment, the Agency has determined that an updated assessment is necessary to evaluate the potential for occupational risk for all products resulting in occupational exposure.

Overall Human Health Risk Characterization and Conclusion

Antimicrobial Uses

There are no anticipated human health risks of concern from the sole antimicrobial use of capsaicin. The human health data set is considered complete for the antimicrobial use of capsaicin. A new use risk assessment for the antimicrobial use of capsaicin was conducted in 2016 (U.S. EPA, 2016) using current methods. An updated human health risk assessment will not be conducted for the antimicrobial use of capsaicin.

Biochemical Uses

While the Agency does not have a serious concern regarding exposure to biochemical pesticide products containing these active ingredients given the widespread exposure to the substances in food, it has been determined that additional data and an updated risk assessment are needed in order to

reliably support a safety finding for the existing use patterns. This includes determining whether the current exemption from the requirement of a tolerance is still justified.

Literature and Incident Search Findings

To support registration review, the Antimicrobials Division and the Biopesticides and Pollution Prevention Division conduct searches of the literature and incident databases to determine if there are any reports of adverse effects that might change risk conclusions or change knowledge of the state of the science for an active ingredient. Searches conducted for the active ingredients in this case are described below.

Human Health Results:

A literature search was conducted using Google Scholar, the PubChem search engine, the European Food Safety Authority Journal, and the Agency's CompTox Chemicals Dashboard. The following search terms were used: "capsaicin" or "capsicum" with "toxicity", "safety", "effects", "oral", "developmental", "dermal", "eye", "irritation", "reproduction", "inhalation", "carcinogenicity" and "cancer". These terms yielded numerous results, many of which are considered relevant to the human health risk assessment. For example, several oral and inhalation toxicity studies were identified, as well as carcinogenicity studies. The relevant studies will be thoroughly reviewed and are likely to be utilized in the updated assessment which will be completed during registration review.

Appendix C – Environmental Risk Assessment

Summary of Environmental Fate and Nontarget Organism Data

Antimicrobial Uses

One environmental fate study was submitted to the Agency but was found to be unacceptable. While it provides modeled estimates of various environmental fate parameters and public literature data on the persistence of capsicum oleoresin in soils, it does not provide empirical or definitive data on how rapidly capsaicin degrades (*e.g.*, half-lives) in the environment. Degradation data are needed to support the rationale that capsaicin degrades rapidly in the environment. In addition, nontarget ecotoxicity studies were submitted to account for several required nontarget OCSPP toxicity tests (OCSPP 850.1010, 850.1075, 850.1035); however, all were found to be unacceptable. There are no other nontarget toxicity data available to assess the risk of capsaicin from use as an antifoulant on underwater structures.

Because the antimicrobial use of capsaicin in Barnacle-Stop is as an antifoulant for underwater structures (*e.g.*, boat hulls), data requirements for the *Antifoulant Coatings and Paints* use pattern under 40 CFR 158 subpart W will be required to determine risks to nontarget organisms from this use.

Biochemical Uses

Scientific rationale[25] was previously submitted for various biochemical products to satisfy Tier I nontarget organism toxicity testing requirements and cited lines of evidence including the mode of action to the target pest, use patterns, mammalian acute toxicity profile, and environmental degradation. After re-evaluation, the rationale is considered adequate for indoor use patterns and defensive animal repellents, but inadequate for outdoor uses. There are currently no data available to assess the risk of capsaicin for use outdoors as a biochemical pesticide. Some uses of capsaicin involve outdoor foliar spray, aerial, or granular applications on agricultural crops and ornamental plants. These applications trigger nontarget organism toxicity data requirements due to the potential exposure to nontarget species from these uses (per 40 CFR Part 158 Subpart U)

Risk Characterization

Antimicrobial Uses

While several Agency memoranda (U.S. EPA, 1985, 1991 & 1992a) discussed concerns about risks to aquatic nontarget organisms from capsaicin uses, the Agency ultimately waived all environmental fate and ecotoxicological data in the 1992 Registration Eligibility Document (RED). The data were waived based on the assumption that the environmental hazard language would limit aquatic exposure for the registered uses (U.S. EPA, 1985 & 1992b).

The 2016 new antifoulant use risk assessment (U.S. EPA, 2016) for capsaicin concluded no risks to aquatic organisms based on preliminary reviews of freshwater invertebrate, estuarine/marine invertebrate, and freshwater fish data which suggested low toxicity. However, after review conducted during reevaluation, these studies were found to be unacceptable.

Nontarget aquatic plant ecotoxicological data were waived in the 2016 new use risk assessment (U.S. EPA, 2016) based on the following rationale: 1) the product's limited use pattern; 2) a label that does

[25] MRIDs included: 47192005, 47381103, 47402201, 48128002, 48152312, 49517505, 50179413, 51445105, and 51796105.

not state the product controls algal growth; and 3) that capsaicin insect repellents have been applied to plants without adverse effect. The Agency has since revised these conclusions and found these rationales were insufficient. The reasons are: 1) the antifoulant use pattern of the product on underwater structures would not exclude the exposure of aquatic plants; 2) statements or lack of statements regarding the control or prevention of algal growth on the label cannot be used as a substitute for toxicity data on algae; 3) capsaicin's use as an insect repellent does not provide proof that the antifoulant product will not harm vascular plants; and 4) ecological incidents reported in 2009 by the Woodstream Corporation found that two registered products with capsaicin caused harm to plants (see Ecological Incidents), though it is unclear whether capsaicin or another active ingredient contributed to the harm. One study was also submitted to provide environmental fate data on capsaicin, though after formal review was found to be unacceptable as well (see the section on *Biochemical Uses* below for more details). Consequently, there are currently no environmental fate or ecotoxicological data to assess the risk of the antifoulant use of capsaicin.

Because the antimicrobial product use of capsaicin in Barnacle-Stop is as an antifoulant for underwater structures (e.g., boat hulls), all environmental fate and nontarget ecotoxicity data requirements for the *Antifoulant Coatings and Paints* use pattern under 40 CFR part 158 subpart W are required to determine risks to nontarget organisms from product use. The environmental fate and nontarget ecotoxicity data requirements for this antimicrobial use are listed in Section III. C. (Table 2).

Biochemical Uses

There are currently no nontarget organism toxicity data available for capsaicin in the Agency's database. Scientific rationale was previously submitted for various products to satisfy nontarget organism toxicity testing requirements for biochemical uses. The rationale stated that significant risks to nontarget organisms, including threatened and endangered species, are not anticipated due to capsaicin's non-toxic mode of action as a repellent and control agent, its use patterns, and its biodegradability. The rationale also states that mammalian toxicology data affirm that capsaicin is not acutely toxic to mammals through the acute inhalation, dermal, and dietary routes of exposure, and strongly indicate that capsaicin should be non-toxic to terrestrial wildlife.

After re-evaluation, the rationale is considered adequate for the use of capsaicin in indoor agriculture settings (e.g., in greenhouses), as well as for use as a defensive animal repellents (*i.e.,* for dogs or bears) where the products are sprayed directly at animals deemed to be dangerous and products are used transiently (e.g., in emergency situations). For these uses, environmental exposure and risks are anticipated to be negligible. Therefore, no additional data and no updated ecological risk assessments are needed for these use patterns.

However, upon further review, the submitted scientific rationale are considered inadequate for the outdoor uses of capsaicin. Insufficient data are provided to support the claim that capsaicin rapidly degrades to a degree that will result in minimal exposure to nontarget organisms, and mammalian toxicity cannot be expected to be representative of other taxa given the potential for differences in species sensitivities to toxicants. An environmental fate study was identified in the Agency's database (MRID 47901902). However, the study provides modeled estimates of environmental fate parameters including vapor pressure, Henry's Law constant, soil adsorption (log K_{OC}), and lipid partitioning (log K_{OW}), but does not provide any empirical data on how rapidly capsaicin degrades in the environment (e.g., environmental half-lives). These degradation data are needed in order to support the rationale

that capsaicin degrades rapidly in the environment. The study also includes two research articles from the scientific literature. Both articles discuss the persistence of capsicum oleoresin in soils, but the studies do not provide definitive soil half-lives. Therefore, the articles cannot be used in support of the scientific rationale that capsaicin is rapidly degradable and thus exposure to nontarget organisms cannot be ruled out.

Capsaicin uses as a biochemical involve foliar spray, aerial, and granular applications in outdoor use settings. When the pesticide is applied in these outdoor settings, there is potential for exposure to terrestrial taxa including birds, amphibians, reptiles, invertebrates, and plants. There is also potential for exposure to aquatic organisms as capsaicin can enter aquatic habitats through spray drift or runoff. Due the lack of nontarget organism toxicity data in the Agency's database and the potential for exposure to both terrestrial and aquatic taxa following capsaicin applications, ecological toxicity data are required to assess the risk of capsaicin as a pesticide when it is applied outdoors. These data requirements include avian acute oral toxicity (OCSPP 850.2100), avian dietary toxicity (OCSPP 850.2200), fish acute toxicity (OCSPP 850.1075), aquatic invertebrate acute toxicity (OCSPP 850.1010), terrestrial plant toxicity (OCSPP 850.4100 and OCSPP 850.4150), and nontarget insect testing (OCSPP 880.4350). Based on the results of the ecotoxicity studies, the Agency anticipates updating its ecological risk assessments for biochemical pesticide outdoor use patterns.

Literature and Incident Search Findings

Ecological Results:

To support registration review, the Antimicrobials Division (AD) and the Biopesticides and Pollution Prevention Division (BPPD) conduct searches of the literature and incident databases to determine if there are any reports of adverse effects that might change risk conclusions or change knowledge of the state of the science for capsaicin. Searches conducted for capsaicin are described below.

A literature search was conducted using Google Scholar with the terms "capsaicin" and "avian toxicity", "terrestrial mammal toxicity", "plant toxicity", "insect toxicity", "fish toxicity", "aquatic invertebrate toxicity", "aquatic organism toxicity", and "ecotoxicity". A literature search was also conducted for "oleoresin of capsaicin" using the same taxa search times as described for capsaicin. The search returned seven results, four of which were for terrestrial species. The remaining three studies were for aquatic taxa.

Three of the terrestrial organism toxicity studies were with plants and one study was with insects. In one of the plant studies, seeds of two no-heat cultivars of pepper (Keystone Resistant Giant and Pimiento L) treated with capsaicin at 500 ppm or higher for 20 days exhibited reduced and delayed seed germination (Barchenger and Bosland, 2016). A study by Gosling and Baker (2004) treated seeds of European ash (*Fraxinus excelsior*), silver birch (*Betula pendula*), Corsican pine (*Pinus nigra* ssp. *laricio*) and sycamore (*Acer pseudoplatanus*) with capsaicin at a concentration of 1 mL per 75 g of seed. No significant effects on germination capacity or seed viability were noted in any of the treated species after 28 (birch and pine seeds) and 42 (ash and sycamore seeds) days of exposure. A study by Cloyd (2002) was conducted to determine the potential phytotoxic effects of selected insecticides on Spanish lavender (*Lavandula stoechas*), oregano (*Origanum vulgare*), rosemary (*Rosmarinus officinalis*), St. Johnswort (*Hypericum perforatum*), wolly thyme (*Thymus vulgaris*), and nutmeg thyme (*Thymus vulgaris*). Capsaicin treatments at a concentration of 62.25 mL/L resulted in no visible injury after three applications at 7-day intervals. The study authors only noted light injury (phytotoxicity rating of 0.11) in

plants in a second study conducted following the same study design but during a different growing season. In a 24-hr acute oral toxicity test with honeybees, the study authors concluded that capsaicin was virtually non-toxic based on an LD_{50} of >100 µg/bee (Flesar et al., 2010).

The studies identified for aquatic taxa included capsaicin toxicity experiments with zebrafish, algae, daphnids, marine mussels, sea urchins, and copepods. In acute toxicity studies with zebrafish (*Danio rerio*) and algae (*Selenastrum capricornutum*), Wang et al. (2014) identified a 96-hr LC_{50} value of 5.98 mg/L in zebrafish. For algae, a 72-hr EC_{50} of 114 mg/L was determined. Research by Olivera et al. (2017) conducted toxicity studies with zebrafish (*Danio rerio*), water fleas (*Daphnia magna*), and algae (*Chlamydomonas reinhardtii*). In the zebrafish toxicity experiment, no mortality was observed up to the highest dose tested (1 mg/L) in zebrafish larvae exposed for 5 days to capsaicin. Results of the daphnid acute immobilization test indicated that capsaicin demonstrated no toxic effects in *D. magna* after 48 hours of exposure to the highest dose (1 mg/L) tested. In algae, capsaicin did not cause significant alterations in algal growth, adenosine triphosphate (ATP) content, or effective quantum yield after 24 hours of exposure to doses of capsaicin up to 0.25 mg/L. In marine species, capsaicin toxicity tests have been conducted with marine mussels (*Mytilus galloprovincialis*), sea urchin (*Paracentrotus lividus*), and copepods (*Tisbe battagliai*). The 48-hr EC_{50} for which capsaicin altered development in marine mussel D-veligar larvae and impaired growth of sea urchin was 3.87 and 5.25 mg/L, respectively. In the marine copepod, the 48-hr LC_{50} was 1.25 mg/L (Oliver et al., 2014).

The EPA database is currently lacking nontarget organism data, so data provided in the scientific literature provides insight into potential capsaicin toxicity. However, the data as a whole are insufficient for evaluating the risk of capsaicin to nontarget species due to issues with the study methodologies and/or certain deficiencies identified in the studies. For instance, the plant studies by Barchenger and Bosland (2016) as well as Gosling and Baker (2004) are non-guideline studies that apply capsaicin directly to incubated seeds as opposed to applying the test substance to planted seeds using equipment designed to simulate conventional farm equipment as outlined in EPA test guidelines. Furthermore, these plant studies provide data on seed germination, but do not measure other endpoints, including shoot length and weight inhibition and phytotoxicity, which are necessary to evaluate plant toxicity. Similarly, the plant study by Cloyd (2002) only measures phytotoxicity, but is missing all the other guideline endpoints. The honeybee toxicity (Flesar et al., 2010) study was conducted over a 24-hour period as opposed to a 48-hour period as outlined in the EPA/OECD test guidelines. Furthermore, the report does not provide the doses used or the number of replicates and bees used for each dose. Toxicity experiments by Olivera et al. (2017) did not dose high enough to establish a definitive EC_{50}/LC_{50} for any of the test organisms including zebrafish, daphnids, and algae. Experiments by Olivera et al. (2014) were performed with non-guideline marine test organisms, and therefore, cannot be used to address toxicity requirements for biochemical pesticide toxicity testing. Research by Wang et al. (2014) identifies a capsaicin LC_{50} value of 5.98 mg/L in zebrafish. However, the study does not report mortality data for the control fish, so it cannot be determined if the test passes acceptability criteria.

Appendix D – 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-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))[26].

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.[27]

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

[26] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[27] 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

- *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[28] and November 2022 ESA Workplan Update[29]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[30] 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 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.

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

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.

Although EPA has prioritized conventional active ingredients as presented in EPA's EDSP Strategies Notice, EPA is planning to develop similar strategies for biopesticide and antimicrobial pesticide (*i.e.*, nonconventional) active ingredients and will provide public updates on these strategies, when appropriate. At this time, EPA is making no findings associated with the implementation of EDSP screening of capsaicin oleoresin/capsaicin and related capsaicinoids. Such issues will be addressed in future updates by EPA on its strategies for implementing FFDCA section 408(p).

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