Streptomyces strain K61

PC Code 129069

Amended Preliminary Work Plan
Case Number 6066

Approved by: Le, Madison

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I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) Amended Preliminary Work Plan (PWP) for *Streptomyces* strain K61 and is being issued pursuant to 40 CFR §155.50. This document explains what EPA's Office of Pesticide Programs (OPP) knows about *Streptomyces* strain K61, 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 *Streptomyces* strain K61. As stated in 40 CFR §155.50, the opening of this docket initiates the second cycle of registration review for *Streptomyces* strain K61.

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), as amended by the Food Quality Protection Act (FQPA) of 1996, which 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 2011 for the first cycle of registration review of *Streptomyces* strain K61; the second cycle marks the next 15 years of the Agency's periodic review of pesticide registrations in the *Streptomyces* strain K61 case to ensure that each pesticide continues to satisfy the statutory standard for registration; that is, the pesticide can perform its intended function without causing unreasonable adverse effects on human health 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 *Streptomyces* strain K61 and what additional risk analyses and data or information it believes are needed to make a registration review decision on *Streptomyces* strain K61.

The Agency encourages all interested stakeholders to review the Amended PWP and to provide comments and additional information that will help the Agency's decision-making process for *Streptomyces* strain K61. 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 Amended 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 for the Amended PWP, the Agency will develop and commit to a Final Work Plan (FWP) and anticipated schedule for the second cycle of registration review of the *Streptomyces* strain

K61 case. Additional information on *Streptomyces* strain K61 can be found in the Agency's public docket (EPA-HQ-OPP-2021-0832) at www.regulations.gov.

This document is organized into six sections: *Response to Comments,* which explains the Agency's response to comments received on the PWP that was published on July 25, 2023; the *Introduction*, which includes this summary and *Streptomyces* strain K61 case overview; *Use Information*, which describes how and why *Streptomyces* strain K61 is used and summarizes data on its use, and associated pesticide products; *Scientific Assessments and Anticipated Data Needs*, 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 *Streptomyces* strain K61; *Guidance for Commentors*, which highlights topics, additional information and data of special interest to the Agency and are considered prior to issuing a FWP; and, lastly, the *Next Steps* and *Timeline* provides an anticipated timeline for the registration review process for *Streptomyces* strain K61.

***Streptomyces* strain K61 (Case 6066) Registration Review Case Overview**

Pursuant to 40 CFR section §155.50, the Agency will initiate a pesticide's registration review by establishing a docket for registration review of *Streptomyces* strain K61 (Case 6066) and opening it for public review. Documents from the first cycle of registration review for the *Streptomyces* strain K61 registration review case can be found in docket ID EPA-HQ-OPP-2009-0509 available at www.regulations.gov.

This Amended PWP continues the second cycle of registration review for *Streptomyces* strain K61, under public docket EPA-HQ-OPP-2021-0832 available at www.regulations.gov. The following list highlights significant events that have occurred during the second cycle of registration review for this case.

- July 25, 2023 – The Agency published the *Streptomyces* strain K61 *Preliminary Work Plan* for a 60-day public comment period. On September 25, 2023, the Agency received a comment from Danstar Ferment AG/ LALLEMAND PLANT CARE. Please see the Response to Comments section and the Anticipated Data Needs section for further information.
- June 2024- The Agency is publishing the Amended *Streptomyces* strain K61 *Preliminary Work Plan* for a 60-day public comment period.

II. Response to Comments

In response to the Agency's PWP, published July 25, 2023, Danstar Ferment AG / LALLEMAND PLANT CARE, provided a comment requesting clarification on the anticipated data needs and supporting science reviews and rationales included in the PWP. This comment can be found in docket ID EPA-HQ-OPP-2021-0832 available at www.regulations.gov.

EPA Response: The Agency thanks the commenter. After reviewing the information provided by Danstar Ferment AG / LALLEMAND PLANT CARE, the Agency has amended the PWP, including the anticipated data needs section of the document. The acceptability of product analysis and mammalian toxicology data for *Streptomyces* strain K61 has been updated and clarifications have been added. Additionally, the data needs were updated to reflect pertinent current EPA assessment records. For further information, please see the Anticipated Data Needs section of this document.

III. Use Information

The first pesticide product containing *Streptomyces* strain K61 as an active ingredient was registered by the Agency in 1993. Currently, there are three registered pesticide products containing *Streptomyces* strain K61, one manufacturing-use product and two end-use products, ranging from 35%-100% active ingredient.

Streptomyces strain K61 (formerly *Streptomyces griseoviridis*) is a naturally occurring soil bacterium initially isolated from peat in Finland. It is believed to act against disease-causing fungi in at least two ways: by colonizing plant roots to deprive disease organisms of space and nourishment; and by producing antifungal compounds. As a microbial active ingredient, products containing *Streptomyces* strain K61 are registered for control of seed, root and stem rot, and to prevent wilt of ornamentals, vegetables and tree and forest seedlings caused by Fusarium, Alternaria, and Phomopsis. *Streptomyces strain* K61 also suppresses root rots of Pythium, Phytophthora and Rhizoctonia in greenhouse plants and is used as a seed treatment for seed or soil borne damping off and early root rot. *Streptomyces* strain K61 is approved for use on all raw agricultural commodities and can be applied to seeds, soil, roots and transplants, or as a dip or spray (U.S. EPA, 2011).

Table 1. *Streptomyces* strain K61 Use Information

Ingredient Name	*Streptomyces* strain K61
PC Code	129069
Pesticide Classification	Fungicide
Use Site Locations	Agricultural (Indoor, Outdoor)
Application Types	Chemigation, Dip Treatment, Foliar Spray, Hydroponic Water Treatment, Seed Treatment
No. of Registrations	3 FIFRA Section 3 products[1]
Physical Form	Solid

IV. Scientific Assessments

A summary of the Agency's human health and ecological risk assessments for *Streptomyces* strain K61 is presented below. Refer to the Appendices for a 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

When the initial registration was issued in the 1990s, the guideline test data that was submitted was based on microbial pesticide data requirements and test guidelines that were still in draft form. After that time, the data requirements were updated, and as explained below, the current database and original human health assessments do not include all the data currently required for assessing human health, including to support the current food tolerance exemption at 40 CFR §180.1120. The initial food tolerance exemption read: "The biological pesticide *Streptomyces sp.* strain K61 is exempted from the requirement of a tolerance in or on all raw agricultural commodities when used as a fungicide for the treatment of seeds, cuttings, transplants, and plants of agricultural crops in accordance with good

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

agricultural practices" [58 FR 21403, Apr. 21, 1993], and currently reads: "An exemption from the requirement of a tolerance is established for residues of *Streptomyces sp.* strain K61 in or on all food commodities when used in accordance with label directions and good agricultural practices" [87 FR 51914, Aug. 24, 2022].

During the previous registration review it was noted that an initial risk assessment and summary of data was not on hand, so in 2011 a Biopesticide Registration Action Document [Docket EPA-HQ-OPP-2009-0509] and Fact Sheet containing summaries of test data cited above, were prepared. However, as noted, not all original guideline tests were performed and characterized according to current data requirements, and significant toxicity was demonstrated in the acute pulmonary and injection toxicity/pathogenicity studies (see Table 5). Also, no routes of administration except for acute dermal toxicity and eye irritation were assigned an EPA toxicity category corresponding to the latest EPA label review manual endpoints. As a result, additional test data is warranted and, therefore, acute oral, acute inhalation and subchronic oral data are needed to properly characterize the toxicity of this active ingredient and support the development of an updated human health risk assessment. This updated assessment will include a review of the tolerance exemption, the current use patterns and the label PPE. Depending on the results of this new toxicity testing, residue analysis data may be necessary to evaluate potential dietary risks. In addition, new product identity data is needed to verify the taxonomic classification of this active ingredient based on current evaluation methods.

Summary of Hazard Characterization

The toxicological database is considered incomplete for characterizing hazard and assessing human health risk associated with *Streptomyces* strain K61. In this case, the active ingredient can be classified as toxicity category III for dermal irritation and Toxicity Category IV for eye irritation, according to EPA toxicity categories. However, due to the level of toxicity demonstrated in the toxicity/pathogenicity studies, the current database is not adequate to assess potential risks resulting from the use of products containing *Streptomyces* strain K61. Thus, the Agency anticipates the need for additional studies during registration review to fully assess potential risks to human health (see Table 6).

Summary of Dietary Exposure and Risk Characterization

Several of the current labeled uses are expected to result in insignificant dietary exposures, namely: seed treatments; soil-sprays or drenches for small seedlings; transplanted, and production crops; banded in-furrow or side-dress applications; greenhouse or field irrigation; chemigation; hydroponic; NFT (nutrient film technique); irrigation, growing medium soil incorporation; mushroom substrate sprays or drenches; and turfgrass sprays or drenches. Furthermore, most crops have limitations to not use foliar sprays, except for cucurbit vegetables, trees with edible products (except pome and stone fruit trees, which have this limitation), root, tuber, and bulb vegetables. These uses are expected to have a higher likelihood of significant dietary exposure. Additionally, for root, tuber, and bulb vegetables, there is no limitation on pesticide application during the pre-harvest interval. Testing showed no potential for infectivity or pathogenicity. However, assessment of toxicity by the oral route of administration is incomplete. Exposures and risk characterizations cannot be readily made for some labeled uses to edible crops and applications to production crops, without more focused oral toxicity data. Potential risk concerns related to dietary exposure will be addressed in the updated human health risk assessment for *Streptomyces* strain K61.

Food Tolerances

Considering the available toxicity and exposure data discussed above, EPA concluded that there was a reasonable certainty that no harm would result to the U.S. population from aggregate exposure to residues of *Streptomyces* strain K61when used according to label directions. Therefore, EPA established a tolerance exemption for residues of the active ingredient. The current tolerance exemption is stated as follows:

> **§ 180.1120 Streptomyces sp. strain K61; exemption from the requirement of a tolerance.** An exemption from the requirement of a tolerance is established for residues of *Streptomyces* sp. strain K61 in or on all food commodities when used in accordance with label directions and good agricultural practices. [87 FR 51914, Aug. 24, 2022]

Summary of Residential and Non-Occupational Exposure and Risk Characterization

Although products containing this active ingredient do not have homeowner uses, use on turfgrass by professional applicators could result in exposures to residential sites. In addition, agricultural spray applications could result in spray-drift and lead to low-level exposures outside of treated areas which could result in respiratory and dermal sensitization issues. A comprehensive assessment of these potential risks related to residential and non-occupational exposure will be addressed in the updated human health risk assessment for *Streptomyces* strain K61.

Summary of Occupational Exposure and Risk Characterization

All uses of this agricultural pesticide would likely result in occupational exposure. A prior risk assessment (U.S. EPA, 2002) supporting a 4-hour restricted entry interval, and rejecting a 0-hour interval, is valid and on the current label. Use of PPE for eye, dermal, and inhalation protection currently on the label is considered appropriate. Additional data is needed, however, to allow an assessment of potential risk concerns related to occupational exposure. This will be performed in the updated human health risk assessment for this active ingredient.

Human Incidents

A search of the OPP Incident Data System conducted on May 7, 2024, revealed no reported incidents associated with *Streptomyces* strain K61. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

B. Summary of Environmental Risk Assessment

All nontarget organism and environmental fate data necessary to meet the standard for *Streptomyces* strain K61 were satisfied by either data submissions or the acceptance of scientific rationales. The available data (including guideline studies and rationale) indicated that effects on nontarget organisms, including pollinators, are not expected as a result of the currently registered uses for *Streptomyces* strain K61. The LD_{50} for both Northern Bobwhite and mallard ducks was greater than 2.45 x 10^9 CFU/kg bw per day (MRIDs 41821119 and 41821120), and the LC_{50} for honeybees were more than 1000 times greater than the estimated environmental concentration (EEC) that would result from the registered uses for *Streptomyces* strain K61. It should be noted that the honeybee study was cited to satisfy the data requirement for nontarget insect testing. This is generally not considered acceptable under current standards, especially without rationale to justify the citation. However, the literature search that was conducted during this round of registration review did not return any articles indicating that

Streptomyces species adversely affect insects. In fact, many of the articles indicated that many insects have symbiotic associations with *Streptomyces* species that protect them from pathogens (Kaltenpoth et al. 2006; Kaltenpoth et al. 2012; Kim et al. 2021; Matarrita-Carranza et al. 2017). As a result, the nontarget insect data requirement is considered satisfied for the currently registered uses and no additional data is needed at this time. However, if additional uses are proposed for *Streptomyces* strain K61 in the future, additional rationale or nontarget insect testing will likely be required. In addition, although it is clear from the public literature search that some species of *Streptomyces* are plant pathogens, there is sufficient evidence to support the claim that *Streptomyces* strain K61 is not taxonomically related to known plant pathogens. This active ingredient was previously classified as *Streptomyces griseoviridis* (EPA, 2011A) and a literature search on *Streptomyces griseoviridis* indicated that *Streptomyces griseoviridis* and closely related species are not pathogenic to plants. An article by Labeda, et al. (2012) illustrated that *Streptomyces griseoviridis* is in a separate clade from the phytotoxin-producing *Streptomyces* species, and these clades are not closely related. Finally, there have not been any reports of adverse effects to plants in the 30 years since this strain was originally registered for use in pesticide products.

Adverse effects to the environment are also not expected as a result of the currently registered uses of *Streptomyces* strain K61. This active ingredient is registered for use in a variety of application methods, including seed treatment, foliar, and applications to the soil surface. As a result, exposure to aquatic ecosystems likely does occur due to both spray drift and/or runoff. However, studies on freshwater fish and *Daphnia*, and/or rationale is available for *Streptomyces* strain K61. This information indicated that adverse effects to aquatic species are not expected as a result of possible exposures. The LC_{50} values for freshwater fish and the EC_{50} value for *Daphnia* were all more than 75 times greater than the concentration that would result from applying the currently registered end use products containing *Streptomyces* strain K61 to a 6-inch layer of water.

Ecological Incidents

A search of OPP's Environmental Incident Information System conducted on May 7, 2024, revealed no reported incidents associated with *Streptomyces* strain K61. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

Endangered Species Assessment

The Agency believes there is no reasonable expectation for any registered use of *Streptomyces* strain K61 to cause direct or indirect discernible adverse effects to threatened and endangered species or their designated critical habitat potential based on the lack of toxicity, pathogenicity, and effects to birds, honeybees, and aquatic organisms, and the lack of studies in the scientific literature indicating the potential for effects to insects or plants. This section provides general background about the Agency's assessment of the effects of pesticides on listed species and designated critical habitats under the Endangered Species Act (ESA).

Developing Approaches for ESA Assessments and Consultation for FIFRA Actions

In 2015, EPA, along with the Services—the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS)—and the United States Department of Agriculture (USDA) (referred to as "the

agencies") released their joint Interim Approaches[2] 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.[3]

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.[4]

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[5] from FWS in February 2022 and a final biological opinion from NMFS on malathion, chlorpyrifos and diazinon in June 2022.[6] 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[7] 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

[2] www.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report.
[3] www.epa.gov/endangered-species/revised-method-national-level-listed-species-biological-evaluations-conventional.
[4] www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act.
[5] www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[6] www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[7] www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.

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*.[8] 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.

On November 16, 2022, EPA released the *ESA Workplan Update: Nontarget Species Mitigation for Registration Review and Other FIFRA Actions*.[9] 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.

C. Anticipated Data Needs

Certain product analysis and mammalian toxicology data are needed to support an updated human health risk assessment for this active ingredient. The need for an updated human health risk assessment is based on the Agency's concern that the mortality seen in the pulmonary and injection toxicity/pathogenicity studies supporting this registration may be due to the presence of cytotoxic metabolites. The guideline studies being required are necessary to verify the taxonomic classification of the active microbe, identify any metabolites of toxicological concern produced by the active microbe, and characterize the potential mammalian toxicity of any such metabolites. The specific data requirements will be determined using the stepwise approach described below. Note that this stepwise testing approach is consistent with testing schemes described in the OPPTS 885.3000 guideline (Background -Mammalian Toxicity/ Pathogenicity/Infectivity). Further, per OPPTS test guidelines 885.3000 and 885.3550, such an approach may include the requirement of chemical (or biochemical) pesticide tests, such as those described in OPPTS series 870.

Step 1 - required data: Product Identity (885.1100), acute oral toxicity (870.1100), acute inhalation toxicity (870.1300)

The 885.1100 testing should include an updated taxonomic classification and the identification of the pesticidal active metabolites in the final product. Metabolites identified should be characterized with regard to their mammalian toxicity potential. The acute oral toxicity (870.1100) and acute inhalation toxicity (870.1300) studies should be performed with the manufacturing use product. The results of the 885.1100, 870.1100, and 870.1300 testing will determine the need for step 2 testing.

[8] www.epa.gov/endangered-species.
[9] www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf.

Step 2 - conditionally required data: Acute Toxicity, Tier II (885.3550)

This testing is needed if the results of the acute oral toxicity (870.1100) and acute inhalation toxicity (870.1300) testing performed under step 1 indicate mammalian toxicity concerns or if metabolites of toxicological concern are identified (as determined by the Agency). The acute toxicity, Tier II (885.3550) study is to be performed on metabolites of toxicological concern identified in the 885.1100 metabolite analysis. The results of the 885.3550 testing will determine the need for step 3 testing.

Step 3 - conditionally required data: 90-Day Oral (870.3100)

This testing is needed if the results of the acute toxicity, Tier II (885.3550) testing performed under step 2 indicate mammalian toxicity concerns (as determined by the Agency). This study is to be performed on metabolites of toxicological concern evaluated in step 2 testing. The results of the 870.3100 testing will determine the need for step 4 testing.

Step 4 - conditionally required data: Chemical Identity (885.2100), Analytical Methods, plants (885.2300), Storage Stability (885.2400)

This residue analysis testing is to be performed on metabolites of toxicological concern evaluated in step 3 testing.

Table 2. Data needs for *Streptomyces* strain K61

OCSPP Guideline No.	Data Requirement	Test Substance	Time Needed to complete (months)	Use Site(s) Triggering Data Needs	Applicable Exposure Scenario
Step 1 Testing					
885.1100	Product Identity	TGAI	8	All	All
870.1100	Acute Oral Toxicity	MP	12	All	All
870.1300	Acute Inhalation Toxicity	MP	12	All spray applications	All spray applications
Step 2 Testing (conditionally required)					
885.3550	Acute Toxicity, Tier II (oral route)	TBD	12		
Step 3 Testing (conditionally required)					
870.3100	90-Day Oral (one species)	TBD	18	All	All
Step 4 Testing (conditionally required)					
885.2100	Chemical Identity	TBD	24	Food uses	Food uses
885.2300	Analytical methods - plants	TBD	24	Food uses	Food uses
885.2400	Storage Stability	TBD	24	Food uses	Food uses

V. Guidance for Commentors

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 Amended PWP for *Streptomyces* strain K61. 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. The Agency is interested in obtaining the following information regarding *Streptomyces* strain K61:

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 *Streptomyces* strain K61 to the U.S. market

x. The Agency welcomes any information on the effects of *Streptomyces* strain K61 that would help refine the ESA assessment

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 *Streptomyces* strain K61 compared to the general population or who may otherwise be disproportionately affected by the use of *Streptomyces* strain K61 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.

VI. Next Steps and Timeline

A Federal Register Notice will announce a 60-day comment period for this *Amended Preliminary Work Plan*. 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 *Streptomyces* strain K61. The Agency's final decision on the *Streptomyces* strain K61 registration review case will occur following satisfaction of the Endocrine Disruptor Screening Program (EDSP) obligations under FFDCA § 408(p).

Table 3. Anticipated Registration Review Schedule for *Streptomyces* strain K61	
Anticipated Activity	**Estimated Month/ Year**
Opening the Docket	
Open Docket and 60-Day Public Comment Period for Preliminary Work Plan	July 25, 2023
Close Public Comment Period	September 25, 2023
Open Docket and 60-Day Public Comment Period for Amended Preliminary Work Plan	September 2024
Close Public Comment Period	November 2024
Case Development	
Final Work Plan	March 2025
Issue DCI	June 2025
Data Submission	June 2026
Open 60-Day Public Comment Period for Draft Risk Assessments	TBD
Close Public Comment Period	TBD
Registration Review Decision and Implementation	
Open 60-Day Public Comment Period for Proposed Registration Review Decision	TBD
Close Public Comment Period	TBD
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

Table 4 summarizes the current product analysis data requirements and results supporting registration review of *Streptomyces sp.* strain K61 (previously *S. griseoviridis*). All product analysis data are considered adequate except the product identity data (885.1100).

Table 4. Summary of Product Analysis Data (40 CFR §158.2120)

Data Requirement	Guideline No.	Results / Findings	MRIDs
Product Identity	885.1100	At registration, original identification using biochemical testing and microscopy to *S. griseoviridis* was made, however, this identification was refuted, and the taxonomy was changed to *Streptomyces sp.* strain K61. Evaluation using modern methods such as MLST (atpD, gyrB, rpoB, recA, trpB), 16s rDNA [employing distance trees alongside known type strain sequences], ANI and dDDH from whole genome sequencing [alongside known type strain sequences], is needed to resolve identification of this active ingredient. The current data is inadequate. Additional data is needed to support an updated human health risk assessment.	418211-01 418211-02 418211-03 418211-04 418211-05 422980-01 422980-02 422980-03 422980-04 422980-05
Manufacturing Process	885.1200	Acceptable to support guideline requirements	415211-06 422980-07 516476-01 518061-01
Deposition of a Sample in a Nationally Recognized Culture Collection	885.1250	Acceptable to support guideline requirements	422980-02 422980-04
Discussion of Formation of Unintentional Ingredients	885.1300	Acceptable to support guideline requirements	418211-02 418211-03 418211-04 418211-05 418211-07 516476-01 518061-01
Analysis of Samples	885.1400	Acceptable to support guideline requirements	418211-08 475768-01 476780-01 477719-01 516476-01 518061-01
Color	830.6302	Acceptable to support guideline requirements	418211-10
Physical State	830.6303	Acceptable to support guideline requirements	418211-10
Odor	830.6304	Acceptable to support guideline requirements	418211-10
Stability to Normal and Elevated Temperatures, Metals, and Metal Ions	830.6313	Acceptable rationale to support guideline requirements	N/A
Storage Stability	830.6317	Acceptable to support guideline requirements	418211-11 422980-07

			514822-01 516476-02
Corrosion Characteristics	830.6320	Acceptable to support guideline requirements	514822-01 516476-02
pH	830.7000	Acceptable to support guideline requirements	418211-10 455114-02
Density/Relative Density/Bulk Density (Specific Gravity)	830.7300	Acceptable to support guideline requirements	418211-10 455114-02

Appendix B – Human Health Risk Assessment

Summary of Mammalian Toxicology Data

Table 5 summarizes the current mammalian toxicology data requirements and results supporting registration review of *Streptomyces sp.* strain K61 (previously *S. griseoviridis*). Certain mammalian toxicity data requirements are not adequately addressed as indicated below.

Table 5. Summary of Toxicology Data (40 CFR §158.2140)

Data Requirement	OCSPP Guideline No.	Results / Findings	MRIDs
Acute Oral Toxicity	870.1100	An acute oral toxicity/pathogenicity study in MRID 418211-12 was cited to assess the potential for oral toxicity and support a food tolerance exemption. The current data does not match our current data requirements. Additional acute oral toxicity data is needed to support an updated human health risk assessment.	418211-12
Acute Dermal Toxicity	870.1200	*S. griseoviridis* was not toxic to rabbits when a single 2,000 mg/Kg dose was administered dermally. One deficiency was noted: the rabbit body weight data was not submitted. A later evaluation noted that: Rabbit body weights were not affected by an exposure of 2 g/Kg of *S. griseoviridis*. Thus, the original study, #89892D/RKY 114/1/AC, was upgraded to acceptable. Classification: ACCEPTABLE – LD_{50} > 2,000 mg/Kg - EPA Toxicity Category III - dermal PPE is required.	418211-13 422980-08
Acute Inhalation Toxicity	870.1300	Due to toxicity noted in the pulmonary toxicity/pathogenicity studies, a Tier II IP injection study was performed in lieu of this Tier I study. Those test results are as follows: *S. griseoviridis* caused death in 54% of treated male and 48% of treated female rats within the first 2 days after intratracheal instillation. Dosage was 0.1 mL of a 3.46 x 10^8 CFU/mL suspension. In MRID 418211-14 it is noted that: Microbial enumeration of the pulmonary challenge indicated that males and females receiving 5,000 mg/Kg body weight were dosed with approximately 1.61 x 10^9 viable fungi/Kg body weight. The current data is inadequate. Additional acute inhalation toxicity data is needed to support an updated human health risk assessment.	418211-14
Acute Eye Irritation	870.2400	A mild conjunctival irritation was elicited due to the administration of *S. griseoviridis* into the rabbits' eyes. No infectivity was noted during the seven-day study. The original review suggested that protective eyewear be worn during application of the product. Classification: ACCEPTABLE - EPA Toxicity Category IV – protective eyewear is recommended.	418211-16
Primary Dermal Irritation	870.2500	Minimal dermal irritation was noted in a skin sensitization study, MRID 418211-17. However, in that study the active ingredient was found to be a moderate irritant. Classification: ACCEPTABLE - EPA Toxicity Category III – dermal PPE is required.	418211-17
Skin Sensitization	870.2600	An overall moderate skin sensitization reaction was noted in the treated guinea pigs 24 and 48-hours post-test challenge.	418211-17

		Classification: ACCEPTABLE – The tested product is a MODERATE skin sensitizer and requires the addition of a label warning statement for this end-use product. The required statement is not currently on the label.	
Acute Oral Toxicity/ Pathogenicity	885.3050	The data show no clinically significant signs in rats. *S. griseoviridis* was detected in kidney, brain, liver, lungs, spleen, mesenteric lymph nodes, blood or urine samples and cleared from the feces and cecum following day 2. Necropsy studies showed no significant signs of abnormalities. There were significant reductions in the weights of dosed males compared to controls at all study times and in the dosed females on day 8 and day 22. Although *S. griseoviridis* was detected in the feces following administration and was cleared from the intestinal tract by day 4, the procedure evaluating organ infectivity was not a quantitative measure of the MPCA infectivity and clearance. However, validation of the detection methods was required to assess the sensitivity of the assay. The need for method validation was addressed via a (resubmitted) pulmonary toxicity/pathogenicity study. No signs of toxicity or disease were present and clearance through the caecum was established in the pulmonary study. Therefore, the Agency concluded that the method of detection for the MPCA clearance in the resubmitted pulmonary toxicity/pathogenicity study (MRIDs 424415-01 and 424415-02) was adequate and that it was not necessary to repeat the acute oral toxicity/pathogenicity study as well (U.S. EPA, 1992). Classification: ACCEPTABLE – not infective or pathogenic –no significant signs of toxicity by the oral route of administration.	418211-12
Acute Pulmonary Toxicity/ Pathogenicity	885.3150	Two separate studies were performed: In MRID 418211-14 *S. griseoviridis* was cleared from the feces by day 21. This organism was found to be somewhat toxic to the test animals at a dose of $3x10^9$ CFU/animal. Although the test organism was not found in any organs 24 hours post dosing, three rats died at dosing and an additional eight rats died by day 5. Clinical signs such as piloerection, hunched posture, abnormal gait and lethargy were noted throughout the 22-day study. The methods used to evaluate this pulmonary challenge were indicative of a qualitative, not quantitative measure of infectivity and clearance. Also, a validation of the organ infectivity protocol was not provided to the Agency. The authors reported that microscopic examination of the dosing preparation showed densely packed inter-meshing mycelia in aggregations with dimensions of 100 to 200 mm, whereas spores normally have dimensions of 1 x 2 mm. It was concluded that the size of the mycelial masses would not penetrate into the peripheral lungs and would be rapidly cleared from the airways by the pulmonary mucociliary escalator system. In MRIDs 424415-01 and 424415-02 *S. griseoviridis* caused death in 54% of treated male and 48% of treated female rats within the first 2 days after intratracheal instillation. This high death rate may partially be due to the large size of the test organism. Dosage was 0.1 mL of a 3.46×10^8 CFU/mL suspension. The initial review concluded that these studies are ACCEPTABLE as performed, and that *S. griseoviridis* caused sufficient mortality to provoke concern about pulmonary exposure to significant amounts of the bacterium. Consultation with the Occupational/Residential	418211-14 424415-01 424415-02

		Exposure Branch in the Health Effects Division was necessary to determine the type of coverings needed during times of potential exposure. OREB/HED advised that a dust/mist filter respirator (MSHA/NIOSH approval number prefix TC-21C) be worn when handling this product. Classification: ACCEPTABLE - However, subchronic data is needed to further characterize the noted toxicity and support an updated human health risk assessment.	
Acute Toxicology, Tier II (IP Injection)	885.3550	Due to toxicity noted in the pulmonary toxicity/pathogenicity studies, a Tier II intraperitoneal (IP) injection study was performed in lieu of the tier I (885.3200) study. The LD_{50} of IP injected *S. griseoviridis* was determined to be 1306 mg/Kg and 870 mg/Kg in male and female mice respectively. There was a high mortality rate: 100% of the mice died when dosed with either 5,000 mg/Kg test material or 5,000 mg/Kg killed test material; 40% of male and female mice died when injected with 1,000 mg/Kg of the test material and 40% of the females died when given 500 mg/Kg test material. There were no apparent signs of infectivity as shown by a lack of clinical signs by day 4. The large size of the organism and quantity of material given to the animals was a strong influence in the toxicity of the MPCA. Classification: ACCEPTABLE - LD_{50} on IP injection is 1,306 mg/Kg in male mice, 870 mg/Kg in female mice, and 1,041 mg/Kg combined. However, subchronic data is needed to further characterize the noted toxicity and support an updated human health risk assessment.	418211-15
Hypersensitivity Incidents	885.4300	Two incidences of hypersensitivity were reported prior to EPA registration. The first incident was reported in 1986, the details of which are included in MRID No. 418211-18. One part-time summer trainee at the Espoo Research Centre in Finland had symptoms of a mild alveolar reaction to a product containing *S. griseoviridis*. The alveolar reaction could have been due to exposure to biological dust from the product, though there were indications that the incident might have been avoided by careful use of the safety equipment that was recommended and provided. In 1991, a research associate in a lab in Fort Collins, CO, experienced dizziness, faintness, difficulty breathing and dilated pupils after treating seed with a product containing *S. griseoviridis*. The individual had a history of allergies and asthma and was not wearing the required face mask when exposed. The symptoms disappeared in approximately one hour, and no medical attention was sought. Both individuals recovered completely, and no other employees working with the product have reported any problems. NOTE: these two FIFRA 6(a)(2) reports may not be hypersensitivity and are possibly related to the toxic effects noted in the pulmonary and IP injection assays performed with this active ingredient.	418211-18
Cell Culture	885.3500	The active ingredient is not a virus, so this testing is not required.	N/A

Overall Human Health Risk Characterization and Conclusion

Very little oral toxicity data exists for this active ingredient; there is demonstrated toxicity via the inhalation (inferred inhalation LD_{50} is 1,075 mg/Kg combined) and injection (LD_{50} on IP injection is

1,306 mg/Kg in male mice, 870 mg/Kg in female mice, and 1,041 mg/Kg combined) routes, but unknown toxicity by the oral route (no lethality noted, though dosing was low at approximately 311 mg/Kg).

The data supporting previous registration review efforts was in some cases miscategorized or unavailable for review. There are FIFRA 6(a)(2) adverse effects reports from the 1980's that do not appear in the current OPP incident tracking database. Generation of an updated human health risk assessment is necessary due to the lack of adequate toxicity data supporting this active ingredient. As a result, additional product analysis and toxicity studies are needed (see Table 6). Once acceptable studies are submitted, an updated human health risk assessment will be developed.

Literature and Incident Search Findings

Actinomycete bacteria are common in soil and water, with *Streptomyces* species often being the majority of those found. Soil smell is from *Streptomyces* species that produce the metabolites geosmin and 2-methylisoborneol (MIB) (Becher et al., 2020). Among other metabolites discovered are a wide range of antibiotics and other drugs (antibacterial, antiviral, antitumor, antiparasitic, anticancer) some of which have been commercialized for use by humans and animals as pharmaceuticals, while others are produced by biopesticides for plant disease control. There are a wide range of industrial enzymes useful in detergents (amylase, lipase), for clarifying foods and drinks (laccase, pectinase) and a wide variety of other common uses such as various proteases. Certain commercialized herbicides are produced by *Streptomyces* species including bialaphos and thaxtomin A. *Streptomyces sp.* strain K61 is for plant pathogenic fungus control and there is ample literature supporting this mode of action for various *Streptomyces* strains (Harir et al., 2018). Most of these compounds are produced in small amounts for local protection and competition for niches in soil and plant environments, also for the acquisition of nutrients, but can be coaxed to produce industrial amounts during fermentations. *Streptomyces* were separated from other Actinomycetes in 1943 as a group with mycelia, spores, and hyphae, though they are Gram-positive bacteria and not related to fungi which share similar traits.

Human Health Results:

To support registration review, the Biopesticides and Pollution Prevention Division (BPPD) conducts 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 *Streptomyces sp.* strain K61. Searches conducted for information pertaining to *Streptomyces sp.* strain K61 are described below.

A literature search was conducted with the Google Scholar search engine using the terms "*Streptomyces*" and "strain K61" in addition to Bergey's Manual. These terms yielded several reports of treatable infections from certain geographically distributed strains of Streptomyces and cases of opportunistic infections in immune compromised hosts. A search was also performed using the genus "*Streptomyces*" and the search terms "pathogen," "disease," "infect," and "toxic." *Streptomyces* species are rarely isolated from clinical specimens except for some cases of progressive skin infections called actinomycetoma in tropical and subtropical regions, caused by *Streptomyces somaliensis* and *Streptomyces sudanensis* (Bergey's Manual, 2012) from accidental inoculation when the skin is compromised; this condition can be treated with antibiotics once identified. A review of treatable clinical cases involving other *Streptomyces* species reported "6 cases of invasive *Streptomyces*

infections and review [of]13 previously reported cases. Our series included 2 cases of lung abscess or pneumonitis, 3 cases of central venous catheter-related bloodstream infection, and 1 case of possible hypersensitivity pneumonitis. Most previous cases also included lung infections and bloodstream infections. Preexisting conditions, such as cancer, AIDS or HIV infection, presence of a central venous catheter, and prosthetic heart valve, were present in all cases since 1985. Diverse *Streptomyces* species were involved, consistent with the highly opportunistic nature of the infections" (Kapadia et al., 2007). These relatively rare opportunistic infections with *Streptomyces* species are largely treatable. As this summary discusses, these cases are often the result of immune system compromise and/or invasive procedures to the human body. No additional information was gained from these searches that would alter BPPD's understanding of the current state of the science for any potential effects of *Streptomyces sp.* strain K61 on humans.

Appendix C – Environmental Risk Assessment

Summary of Nontarget Organism Data

Table 7 summarizes the current nontarget organism data requirements and results supporting registration review of *Streptomyces* strain K61. The nontarget organism data requirements have all been satisfied for *Streptomyces* strain K61.

Table 7. Summary of Nontarget Organism Data (40 CFR §158.2150)

Data Requirement	Guideline No.	Results / Findings	MRIDs
Avian oral toxicity	885.4050	The LD_{50} for both Northern bobwhite and mallard ducks was ≥ 2.45 x 10^9 CFU/kg bw per day. Acceptable	418211-19 and 418211-20
Avian inhalation toxicity/pathogenicity	885.4100	Not required for *Streptomyces* strain K61 because the nature of the active ingredient indicates no potential pathogenicity to birds (Refer to test note #3 of 40 CFR § 158.2150).	N/A
Wild mammal toxicity/pathogenicity	885.4150	Not required for *Streptomyces* strain K61 because the results of the tests required by 40 CFR 158.2140 are adequate and appropriate for assessment of hazards to wild mammals. The Acute Oral Toxicity/Pathogenicity study showed no signs of toxicity or pathogenicity in rats. *Streptomyces* Strain K61 was not detected in the kidney, brain, liver, lungs, spleen, mesenteric lymph nodes, or in blood or urine samples, and was cleared from the feces and cecum following day two.	N/A
Freshwater fish toxicity/ pathogenicity	885.4200	The LD_{50} for rainbow trout was estimated to be > 40.8 mg/L at 21 days and > 10.2 mg/L at 30 days. In a second study the day 1, day 2, day 3, and day 4 LD_{50}[s] for Rainbow trout were 2.8 x 10^5, 1.6 x 10^5, 1.2 x 10^3, and 0.8 x 10^5 CFU/mL, respectively. Acceptable	418211-21 and 430903-01
Freshwater invertebrate toxicity/pathogenicity	885.4240	The 21-day EC_{50} for *Daphnia magna* = 1.9 x 10^5 CFU/mL. Acceptable	418211-22
Estuarine/Marine fish testing Estuarine/Marine invertebrate testing	885.4280	No effects to Estuarine/marine fish and invertebrates are expected due to low expected exposure.	U.S. EPA, 2011a
Nontarget plant testing	885.4300	Not required for *Streptomyces* Strain K61 because this microbial pest control agent is not taxonomically related to known plant pathogens.	U.S. EPA, 2011a
Nontarget insect testing	885.4340	The LC_{50} for honeybees was ≥ 9.8 x 10^8 CFU/g of diet. Citing the honeybee study to satisfy the data requirement for nontarget insect testing is generally not considered acceptable under current standers, but the literature search that was conducted during this round of registration review returned several articles that indicated that many insect species have symbiotic associations with *Streptomyces* spp. that protect the insects from pathogens, and did not return any articles indicating that *Streptomyces* spp. are able to adversely affect insects. Acceptable	418211-23

Literature and Incident Search Findings

To support registration review, BPPD conducts 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 *Streptomyces* strain K61. Searches conducted for *Streptomyces* strain K61 are described below.

Ecological Results:

A literature search was conducted using the Web of Science Core Collection, the default database within the Web of Science system, using the terms "*Streptomyces*" and "avian," "mammals," "plant and pathogen not *scabies*," "insects and pathogen," and "aquatic organisms." This search sequence returned 8, 56, 929, 54, and 28 results respectively. None of the results returned for avian, mammals, "insects and pathogen," or aquatic organisms indicated potential adverse effects of *Streptomyces* on organisms from these taxa. Many of the results returned for "plant and pathogen not *scabies*" discussed the ability of various *Streptomyces* species to protect plants from pathogenic fungi and bacteria. However, a few *Streptomyces* species can cause plant diseases. Out of the over 900 *Streptomyces* species described so far, only about 12 species have been identified as plant pathogens (Bignell et al., 2010). These include *Streptomyces scabies*, *Streptomyces turgidiscabies*, and *Streptomyces acidiscabies*, which can all cause potato common scab, and *Streptomyces ipomoeae*, which is the causative agent of soil rot. This active ingredient was previously classified as *Streptomyces griseoviridis* (U.S. EPA, 2011a), and a literature search on *Streptomyces griseoviridis* indicates that *Streptomyces griseoviridis* and closely related species are not pathogenic to plants.

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))[10].

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.[11]

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:

[10] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[11] 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[12] and November 2022 ESA Workplan Update[13]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[14] 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.

[12] https://www.epa.gov/system/files/documents/2022-04/balancing-wildlife-protection-and-responsible-pesticide-use_final.pdf
[13] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf
[14] 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 *Streptomyces* strain K61. Such issues will be addressed in future updates by EPA on its strategies for implementing FFDCA section 408(p).

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