Natamycin

PC Code 051102

Preliminary Work Plan
Case Number 6316

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I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) *Preliminary Work Plan* (PWP) for natamycin (Case 6316) and is being issued pursuant to 40 CFR § 155.50. This document explains what EPA's Office of Pesticide Programs (OPP) knows about natamycin, 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 natamycin. As stated in 40 CFR § 155.50, the opening of this docket initiates the current cycle of registration review for natamycin.

A registration review decision is the Agency's determination 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. This PWP marks the beginning of registration review for natamycin. 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 natamycin and what additional risk analyses and data or information it believes are needed to make a registration review decision on natamycin.

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 natamycin. 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 natamycin case. Additional information on natamycin can be found in the Agency's public docket (EPA-HQ-OPP-2024-0132) at www.regulations.gov.

This document is organized into five sections: the *Introduction*, which includes this summary and natamycin case overview; *Use Information*, which describes how and why natamycin is 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 natamycin; *Guidance for Commentors*, which highlights topics of special interest, additional information and data to the Agency and are considered prior to issuing a FWP; and, lastly, the *Next Steps* and *Timeline* provides an anticipated timeline for completing the registration review process for natamycin.

Natamycin Registration Review Case Overview

Pursuant to 40 CFR § 155.50, the Agency will initiate a pesticide's registration by establishing a docket for registration review of natamycin (Case 6316) and opening it for public review.

This PWP marks the beginning of the current cycle of registration review for natamycin, with the opening of public docket EPA-HQ-OPP-2024-0132 available at www.regulations.gov. The following list highlights significant events that have occurred during the current cycle of registration review for this case.

- June 2024 – The Agency is now publishing the *Natamycin Preliminary Work Plan* for a 60-day public comment period.

II. Use Information

The first pesticide product containing natamycin as an active ingredient was registered by the Agency in 2012. Currently, there are six registered products containing natamycin, consisting of two manufacturing-use products and four end-use products, ranging from 4.00%-91.02% active ingredient.

Natamycin is a naturally occurring antifungal compound derived from the common soil microorganisms *Streptomyces natalensis, Streptomyces lydicus* (strain CGMCC No. 1653), *Streptomyces chattanoogensis,* and *Streptomyces gilosporeus* (U.S. EPA, 2014a). It was originally discovered in *Streptomyces natalensis* in South Africa in the early 1950s and was later discovered in *Streptomyces lydicus* (strain CGMCC No. 1653) in China and *Streptomyces chattanoogensis* in North America (U.S. EPA, 2014a). Natamycin is commercially produced by a submerged oxygen-based fermentation of *Streptomyces natalensis* cells, which are then lysed by increasing the temperature in the fermentation vessel, thereby causing the release of natamycin from the cell solids (U.S. EPA, 2014a).

Natamycin is used as a food additive and preservative to suppress mold and yeast on the surfaces of cheese, meat, and sausage, as an additive in the feed and drinking water of chickens to slow the growth of specific molds, and as a treatment to suppress fungal eye infections (U.S. EPA, 2014a). As a pesticide, natamycin is used in enclosed mushroom facilities; for postharvest use on citrus, pome, stone fruits, avocados, kiwis, mangos, pineapples, and pomegranates; for seed treatment of soybean, corn, and wheat; and as a preplant, transplant, or at plant dip treatment on all crops to control fungal diseases. It has a non-toxic mode of action and functions as a fungistat, preventing the germination of fungal and yeast spores (U.S. EPA, 2014a).

Table 1. Natamycin Use Information

Ingredient Name	Natamycin
PC Code	051102
CAS Number	7681-93-8
Pesticide Classification	Fungistat

Use Site Locations	Agricultural (indoor and outdoor)
Application Types	Spray drench, flood, dip treatment, seed/seed piece treatment
No. of Registrations	6 FIFRA Section 3 products[1]
Physical Forms	Suspension, dust/powder

III. Scientific Assessments

A summary of the Agency's human health and ecological risk assessments for natamycin is presented below. Refer to the Appendices for a detailed listing of product analysis, human health assessment, and non-target 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

Natamycin is classified as Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, and primary dermal irritation, and Toxicity Category III for acute oral toxicity and primary eye irritation. Additionally, natamycin is not mutagenic or a dermal sensitizer (U.S. EPA, 2014a).

Previous dietary assessments of natamycin were based on the Agency's previous expectation, that when ingested, dietary administered natamycin and its related degradants and metabolites are poorly absorbed and short-lived in the gastrointestinal tract. However, this presumption was not further assessed by the Agency because absorption, distribution, metabolism, and excretion (ADME) data are not part of the human health assessment data requirements for biochemical pesticides. An Agency-conducted literature search for the active ingredient in this case indicated that since the time of the original assessment, the United Nations Food and Agriculture Organization Joint Meeting on Pesticide Residues (JMPR) determined that insufficient details were reported to allow for independent findings on natamycin's ADME profile. The Agency agrees with these findings and cannot validate the previous expectations regarding dietary administered natamycin. This conclusion has prompted the need for the reexamination of the available information for natamycin during this registration review case (JECFA, 2002; EFSA, 2009; U.S. EPA, 2012a, 2012b, 2014a).

Additionally, the Agency finds the prenatal developmental toxicity data (OSCPP 870.3700) does not confirm the previous presumptions supporting the original natamycin registrations, nor does it address concern over the active ingredient's potential adverse postnatal development effects on study test subjects. Therefore, the Agency finds the current available database on dietary natamycin inadequate to characterize its potential hazards to the general population, including fetuses, infants, and children. Consequently, a guideline metabolism and pharmacokinetics study (OCSPP 870.7485), prenatal developmental study (OCSPP 870.3700), and reproduction and fertility effects study (OCSPP 870.3800) are needed to adequately characterize natamycin's hazard profile. Hazard and exposure data, Agency risk assessments, and other information on the active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies. Please see Appendix B for additional information.

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

Summary of Dietary Exposure and Risk Characterization

Run-off into water bodies is not expected for natamycin's contained use patterns and limited application sites in enclosed facilities. Further, according to available data, natamycin is expected to degrade and rapidly inactivate in water and in the presence of common environmental elements. Dietary exposure to natamycin from registered uses at preplant, transplant, at-plant root, dip, and seed treatment is not known due to lack of crop field data (OCSPP 860.1500) and residue data. However, dietary exposure to natamycin in treated postharvest food commodities can be expected due to the enclosed nature of processing and storage of these treated food commodities, and lack of degradation due to a lack of exposure to common environmental elements. Further, natamycin's degradant and metabolite toxicity profile and mode of actions following ingestion are unknown. The Agency considers the current available data and information on orally administrated or dietary natamycin inadequate to characterize potential hazard to general population, including fetuses, infants, and children. Therefore, risk due to dietary exposure must be re-assessed following additional product chemistry, human health, and residue data/information. Please see Appendix B for additional information.

Food Tolerances

The Agency has found the current available database and information on orally administrated or dietary natamycin inadequate to characterize potential hazard to the general population, including fetuses, infants, and children. Therefore, as part of this registration review case, the Agency is requiring submission of additional data and information on orally administrated or dietary natamycin in order to adequately reassess and determine if the current tolerance exemption for natamycin remains valid. Please see Appendix B for additional information regarding anticipated data needs to adequately characterize risk due to dietary exposure to natamycin.

The current tolerance exemption is stated as follows:

> **40 CFR § 180.1315 Natamycin; exemption from the requirement of a tolerance.** An exemption from the requirement of a tolerance is established for the residues of natamycin in or on mushrooms, pineapples, citrus, pome, stone fruit crop groups, avocado, kiwi, mango, and pomegranates when used in accordance with label directions and good agricultural practices. [81 FR 58410, Aug. 25, 2016]

Summary of Residential and Non-Occupational Exposure and Risk Characterization

Direct residential and non-occupational exposure from natamycin is not expected since there are no approved residential uses. Indirect residential and non-occupational exposure from spray drift is not likely based on labeled use patterns and application sites. Therefore, residential handlers (non-occupational) and post-application risks of concern are not expected. Please see Appendix B for additional information.

Summary of Occupational Exposure and Risk Characterization

Based on contained use patterns and limited application sites in enclosed facilities or as a seed treatment or a preplant, plant, and transplant dip treatment, occupational exposure to natamycin is expected to be negligible. Additionally, to further mitigate potential occupational exposure, a combination of PPE (Personal Protective Equipment), and baseline work clothes are required for

applicator and handlers. Additionally, a respirator requirement on product labeling is required due to the potential presence of allergenic microbial proteins. Since natamycin is derived from microbes, the Agency has determined additional data are needed to complete the product chemistry databases for specific products containing natamycin in order to fully characterize and assess the active ingredient in this case. Please see Appendices A and B for additional information.

Human Incidents

A search of the Office of Pesticide Programs' (OPP) Incident Data System conducted on May 23, 2024, revealed no reported incidents associated with natamycin. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

B. Summary of Environmental Risk Assessment

All non-target organism and environmental fate data necessary to meet the standard for natamycin risk assessments were satisfied through acceptable guideline data submissions or scientific rationales.

Although submitted data and rationales indicated that natamycin is slightly toxic to birds, fish, and aquatic invertebrates, exposure of natamycin to non-target species via spray drift and runoff is expected to be minimal due to use patterns according to approved labeling and natamycin's rapid environmental degradation (U.S. EPA, 2014a).

The use and environmental exposure from natamycin have not changed and the Agency's existing risk assessments are sufficient to evaluate the use of the active ingredient in the current registrations. Additionally, the Agency conducted a literature search for the active ingredient in this case, which returned no relevant open literature studies and no incident reports. Hazard and exposure data, Agency risk assessments, and other information on the active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies. Please see Appendix C for additional information.

Ecological Incidents

A search of OPP's Incident Information System conducted on May 23, 2024, revealed no reported incidents associated with natamycin. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

Endangered Species Assessment

EPA has no reasonable expectation for any registered use of natamycin to cause direct or indirect discernable effects to threatened and endangered (listed) species or their designated critical habitat. This is because exposure of natamycin to nontarget organisms is expected to be minimal due to the active ingredient's application methods being off field and in enclosed treatment facilities or seed treatment in which treated seeds are buried directly in field at planting, reducing potential for exposure. Further, preplant and transplant dip treatments occur prior to planting, and there are no outdoor broadcast applications to crops. Any potential exposure is further reduced due to the rapid environmental degradation of natamycin. Therefore, EPA has made a "No Effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required. Please see Appendix C for additional information.

C. Anticipated Data Needs

Please see Appendices A and B for further information and a list of anticipated data needs.

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. The Agency is interested in obtaining the following information regarding natamycin:

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 natamycin to the U.S. market

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 natamycin compared to the general population or who may otherwise be disproportionately affected by the use of natamycin 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 natamycin 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 natamycin. 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 natamycin. The Agency's final decision on the natamycin registration review case will include a determination on the Endocrine Disruptor Screening Program (EDSP) obligations under FFDCA § 408(p).

Table 2. Anticipated Registration Review Schedule for Natamycin

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 DCI	January 2025
Data Submission	January 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	March 2030
Close Public Comment Period	May 2030
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

Registration review is concerned with the active ingredient (for practical purposes, the technical grade active ingredient), not individual end- and manufacturing-use products. Provided in Table 3 are the Biochemical Pesticides Product Chemistry Data Requirements (40 CFR 158.2030) and how they are met. The Agency has determined that there are data gaps in the product chemistry database for specific products containing natamycin (including the manufacturing use products EPA Reg. Nos.: 92311-1, 92311-4 and 87485-1), concerning the product identity, manufacturing process, discussion of the formation of impurities and preliminary analysis data requirements. At the time of the original registrations, all product chemistry data requirements were considered fulfilled considering the Agency's understanding of the active ingredient. Since that time, the Agency has determined that additional data are needed in order to adequately characterize and assess natamycin. Some of these data needs fall under the 40 CFR Subpart V Microbial Pesticide data requirements because natamycin is produced via microbes (specifically, 40 CFR 158.2120, guideline Nos. 885.1100 and 885.1200). The data needs are identified in Table 4.

Table 3. Summary of Product Analysis Data (40 CFR § 158.2030)

Data Requirement	Guideline No.	Results / Findings	MRIDs
Product identity and composition	880.1100	Confidential Business Information. Data are needed under guideline no. 885.1100 for specific products (including EPA Reg. Nos.: 92311-1, 92311-4 and 87485-1).	--
Description of Starting Materials, Production and Formulation Process	880.1200	Confidential Business Information. Data are needed under guideline no. 885.1200 for specific products (including EPA Reg. Nos.: 92311-1, 92311-4 and 87485-1).	--
Discussion of Formation of Impurities	880.1400	Confidential Business Information. Data are needed under guideline no. 880.1400 for specific products (including EPA Reg. Nos.: 92311-1, 92311-4 and 87485-1).	--
Preliminary Analysis	830.1700	Confidential Business Information. Data are needed under guideline no. 830.1700 for specific products (including EPA Reg. Nos.: 92311-1, 92311-4 and 87485-1).	--
Color	830.6302	White to pale cream	48105503
Physical State	830.6303	Powder of flat crystals	48105503
Odor	830.6304	Odorless to lightly acidulous	48105503
Stability to Normal and Elevated Temperatures, Metals, and Metal Ions	830.6313	Natamycin was stable at 54°C for 14 days. Storage stability studies supporting pharmaceutical uses found acceptable stability in tests of 2 to 5 years in duration. Natamycin is degraded by contact with most metals and metal ions. However, the product is never packaged in metal containers.	48105504
Flammability	830.6315	NA. This requirement is product-specific and is "Required if the product contains combustible liquids" (40 CFR 158.2030(e) footnote 9).	--
Storage stability	830.6317	NA. This requirement is product-specific. It is commonly conducted in combination with Corrosion characteristics (830.6320).	--

Table 3. Summary of Product Analysis Data (40 CFR § 158.2030)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Miscibility	830.6319	NA. This requirement is product-specific and is "Required if the product is an emulsifiable liquid and is to be diluted with petroleum solvents."	(40 CFR 158.2030(e) footnote 10).
Corrosion characteristics	830.6320	NA. This requirement is product-specific. It is commonly conducted in combination with Storage stability (830.6317).	--
pH	830.7000	6.5 (1% aqueous solution)	48105503
UV/Visible Light Adsorption	830.7050	A 0.0005 % w/v solution in 1 % methanolic acetic acid solution has absorption maxima at about 290 nm, 303 nm and 318 nm, a shoulder at about 280 nm and exhibits minima at about 250 nm, 295.5 nm and 311 nm.	EU 2012
Viscosity	830.7100	NA. This requirement is product-specific and is "Required if the product is a liquid" (40 CFR 158.2030(e) footnote 12).	--
Melting Point/Melting Range	830.7200	Does not melt; darkens at 200°C; vigorously decomposes at 280 to 300°C	48105503
Boiling Point/Boiling Range	830.7220	NA. This is required "when the technical chemical is a liquid at room temperature." (40 CFR 158.2030(e) footnote 14). The technical is a solid.	--
Density/Relative Density/Bulk Density	830.7300	Loose bulk density < 3,300 ml/kg; tapped bulk density > 1,700 ml/kg	48105503
Particle Size, Fiber Length, and Diameter Distribution	830.7520	NA. "Required for water insoluble test substances (>10-6 g/l) and fibrous test substances with diameter ≥0.1 µm" (40 CFR 158.2030(e) footnote 15). The technical is water soluble.	--
Partition coefficient (n-Octanol/Water)	830.7550	NA. "Required for organic chemicals unless they dissociate in water or are partially or completely soluble in water" (40 CFR 158.2030(e) footnote 16). The technical is water soluble.	--
Water Solubility	830.7840	30 to 50 mg/L at 20 to 25°C and pH 5 to 7.5; very soluble at pH ≥ 10 or pH ≤ 2 but rapidly degrades.	48105503
Vapor Pressure	830.7950	6.31 X 10^{-10} mm Hg	U.S. EPA 2022

Anticipated Product Chemistry Data Needs

In order to adequately characterize and assess natamycin, additional product chemistry data are needed for the sources of natamycin. Natamycin is produced during microbial fermentation using *Streptomyces natalensis, Streptomyces lydicus, Streptomyces chattanoogensis*, or *Streptomyces gilosporeus,* and data are needed to ensure proper microbial identification and absence of live cells in the final product. There is no current accepted taxonomic identification for the microbe(s) used in production of the active ingredient in these products. Therefore, a recognized, published taxonomic classification based on sequencing analysis and comparison to published type strains is needed. Further, this requirement applies separately to the microbe(s) used in each source of natamycin (including EPA Reg. Nos.: 92311-1, 92311-4 and 87485-1) unless the microbe used is from the same source culture. Additionally, since natamycin is produced via microbes, data are needed to ensure the absence of allergenic microbial proteins in the final product. If data are not provided or are insufficient, a respirator requirement is needed on product labels. The data needs are included in Table 4.

Table 4. Anticipated Studies for the Registration Review of Natamycin[1]					
OCSPP Guideline No.	**Data Requirement**	**Active Ingredient/Test Material**	**Time Needed to Complete (Months)**	**Use Site(s) Triggering Data Requirement**	**Applicable Exposure Scenario**
885.1100	Product Identity[2]	TGAI	12	All	All
885.1200	Manufacturing Process[3]	TGAI	12	All	All
880.1400	Discussion of Formation of Impurities[4]	TGAI	12	All	All
830.1700	Preliminary Analysis[4]	TGAI	12	All	All

[1] Data in this section are requested for all sources of natamycin (including EPA Reg. Nos: 92311-1, 92311-4 and 87485-1).

[2] The microbe used in each source needs to have a recognized, published taxonomic classification based on sequencing analysis and comparison to published type strains. Such an analysis typically involves performing 16s rDNA sequence analysis with progression to whole genome sequencing and digital DNA/DNA hybridization.

[3] The manufacturing processes for the sources of natamycin in these products need to include an analysis for viable *Streptomyces* under the quality assurance/quality control process to verify the absence of live cells in the final product.

[4] A detailed chemical analysis should be performed to demonstrate that allergenic microbial proteins are not present in the final products. Alternatively, the registrant can include a respirator requirement on the end-use product label. The Agency recommends submission of a testing protocol prior to definitive testing. If the chemical analysis data are not provided or are insufficient, a respirator requirement is needed on product labels.

Appendix B – Human Health Risk Assessment

Summary of Mammalian Toxicology Data

At the time of the original registrations, the submitted mammalian toxicity database/rationales for natamycin (Table 5) were considered limited but acceptable with a presumption that orally administrated or dietary natamycin and its related degradants/metabolites are poorly absorbed and short-lived in the gastrointestinal tract (JECFA, 2002; EFSA, 2009; and U.S. EPA, 2012a). However, since then, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2017) concluded that although the absorption, distribution, metabolism, and excretion (ADME) of orally administrated radiolabeled (^{14}C) natamycin were studied in rats and dogs, the identities of its related degradants/metabolites in these animals were not investigated and insufficient details were reported to allow for an independent evaluation of the findings. The conclusion prompted a careful reexamination of the available database/information for natamycin in the process of this registration review.

The Agency concurs with JMPR's position on the incomplete ADME profile of natamycin and is therefore unable to validate the previous presumption supporting the original registrations. In addition, the Agency finds the submitted data (MRID 48105512 and 48593401) for the prenatal developmental toxicity data requirement (OCSPP 870.3700) unacceptable due to poorly controlled test environment, lack of characterization of the test substance, lack of sound study design, inadequate details or missing critical data, etc. (U.S. EPA, 2012b). Furthermore, there is a concern over natamycin's potential adverse postnatal development effect. Reduced pup weaning body weights were identified at relatively low doses in an open literature reproduction and lactation study (the lowest-observable-adverse-effect-level (LOAEL) for offspring toxicity was 1000 ppm in the diet (about 50 mg/kg/day), Levinskas, 1966) as well as a three-generation reproduction and fertility study (the LOAEL for offspring toxicity was 300 ppm in the diet (about 15 mg/kg/day), MRID 48593401 and a data review by JMPR, 2017). The Agency finds that the current available database/information on orally administrated or dietary natamycin is inadequate to characterize its potential hazards to the general population, including fetuses, infants, and children.

Table 5. Human Health Toxicological Profile of Natamycin (40 CFR § 158.2050)

Study/ OCSPP Guideline No.	Results	Toxicity Category/ Description	MRIDs/ References
Acute oral toxicity (870.1100)	LD_{50} = 2,730 and 4,670 mg/kg in male and female rats, respectively. ACCEPTABLE/NON-GUIDELINE	III	Levinskas (1966)
Acute dermal toxicity (870.1200)	LD_{50} > 5,050 mg/kg in both male and female rats. ACCEPTABLE/GUIDELINE	IV	48105506
Acute inhalation toxicity (870.1300)	LC_{50} > 2.39 mg/L in both male and female rats. ACCEPTABLE/GUIDELINE	IV	48105507
Primary eye irritation (870.2400)	Severely irritating to male rabbit eyes (the maximum average irritation score of 62 was obtained at 1 hour after treatment), all effects were cleared within 24 hours. ACCEPTABLE/GUIDELINE	III	48105508
Primary dermal irritation (870.2500)	Slightly irritating to male rabbit skin (Primary Irritation Index (PII) = 0.1). ACCEPTABLE/GUIDELINE	IV	48105509

Table 5. Human Health Toxicological Profile of Natamycin (40 CFR § 158.2050)			
Study/ OCSPP Guideline No.	**Results**	**Toxicity Category/ Description**	**MRIDs/ References**
Dermal sensitization (870.2600)	Not a dermal sensitizer (Local Lymph Node Assay in female mice) ACCEPTABLE/GUIDELINE	N/A	48105510
90-day oral toxicity (870.3100)	Dose levels in the 90-day dietary study (rat): 0, 10, 38, and 143 mg/kg/day in males, 0, 11, 43, and 167 mg/kg/day in females. NOAEL = 38 and 43 mg/kg/day in males and females, respectively, LOAEL = 143 and 167 mg/kg/day in males and females, respectively, based on reduced body weights (-22% in males and -17% in females). ACCEPTABLE/GUIDELINE		48105511
90-day dermal toxicity (870.3200)	Addressed with rationale based on its natural origin, highly specific mode of action in its intact form (binds to fungal cell membrane ergosterol, which humans don't have), large molecular size (MW = 665.7 Da) with unlikely dermal penetration/absorption, low (Toxicity Category IV) acute dermal toxicity and primary dermal irritation, and minimal exposure due to the requirement of baseline clothing (long sleeved shirt, long pants, and socks plus shoes) plus personal protective equipment (PPE: protective eyewear and water proof gloves), and/or use of controlled or automated application systems. ACCEPTABLE/NON-GUIDELINE		N/A
90-day inhalation toxicity (870.3465)	Addressed with rationale based on its natural origin, unlikely volatility (solid powder with very low vapor pressure = 6.31×10^{-10} mm Hg), highly specific mode of action in its intact form (binds to fungal cell membrane ergosterol, which humans don't have), low acute inhalation toxicity (Toxicity Category IV), and/or use of controlled or automated application systems. ACCEPTABLE/NON-GUIDELINE		N/A
Prenatal developmental toxicity (870.3700)	Dose levels in the prenatal development study (rabbit): 0, 5.0, 15.0, and 50 mg/kg/day by oral gavage from gestation days (GD) 6-18 UNACCEPTABLE/GUIDELINE Dose levels in the combined three-generation reproductive and developmental dietary study (rat): 0, 100, 300, 1000, or 2000 ppm (equivalent to 0, 5, 15, 50, and 100 mg/kg/day). UNACCEPTABLE/NON-GUIDELINE		48105512 48593401
Bacterial reverse mutation test (870.5100)	3.3 mg/plate (with and without metabolic activation) produced negative results. ACCEPTABLE/GUIDELINE		48105513
In vitro mammalian cell assay (870.5300-5375)	10 µg/ml (with and without metabolic activation) produced negative results. ACCEPTABLE/GUIDELINE		48105514

LD_{50} = median lethal dose. LC_{50} = median lethal concentration. LOAEL=lowest-observed-adverse-effect-level. NOAEL=no-observed-adverse-effect-level. N/A = not applicable.

Hazard Characterization

At the time of the original registrations, the toxicological database/rationales were considered limited but acceptable for characterizing hazard and assessing risk with a presumption that orally administrated or dietary natamycin and its related degradants/metabolites are poorly absorbed and short-lived in the gastrointestinal tract (JECFA, 2002; EFSA, 2009; and U.S. EPA, 2012a). Data requirements (40 CFR §158.2050) were satisfied either through scientific rationales, submitted guideline/nonguideline studies and/or data in the open literature. Natamycin was classified as Toxicity Category III for acute oral toxicity and primary eye irritation, and Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, and primary dermal irritation. The active ingredient was not considered as a skin sensitizer. Natamycin was not considered to be mutagenic or genotoxic. A 90-day dietary guideline study (MRID 48105511) in rats indicated the no-observable-adverse-effect-level (NOAEL) at 38 mg/kg/day and the LOAEL at 143 mg/kg/day based on reduced body weights (-22%). The prenatal developmental toxicity (OCSPP 870.3700) data requirement was considered satisfied by a guideline prenatal developmental study in rabbits (MRID 48105512) and a combined non-guideline three-generation reproductive and developmental study in rats (MRID 48593401). 90-day dermal and 90-day inhalation toxicity data requirements were addressed with rationales based on its natural origin, highly specific mode of action in its intact form (binds to fungal cell membrane ergosterol, which humans don't have), large molecular size (MW = 665.7 Da) with unlikely dermal penetration/absorption (Bos, 2000), unlikely volatility (solid powder with very low vapor pressure = 6.31×10^{-10} mm Hg), low acute dermal toxicity (Toxicity Category IV), low acute inhalation toxicity (Toxicity Category IV), requirement of baseline clothing (long sleeved shirt, long pants, and socks plus shoes) plus personal protective equipment (PPE: protective eyewear and water proof gloves), and/or use of controlled or automated application systems.

However, the argument that orally administrated or dietary natamycin and its related degradants/metabolites are poorly absorbed and short-lived in the gastrointestinal tract was not scrutinized because ADME data is not part of the human health assessment data requirements for biochemical pesticides (40 CFR §158.2050). JMPR concluded in 2017 that although the ADME of orally administrated radiolabeled (^{14}C) natamycin were studied in rats and dogs, the identities of its related degradants/metabolites in these animals were not investigated and insufficient details were reported to allow for an independent evaluation of the findings. The conclusion prompted a careful reexamination of the available database/information for natamycin in the process of this registration review.

The Agency concurs with JMPR's position on the incomplete ADME profile of natamycin and is therefore unable to validate the previous presumption supporting the original registrations. In addition, the Agency finds the submitted data (MRID 48105512 and 48593401) for the prenatal developmental toxicity data requirement (OCSPP 3700) unacceptable due to poorly controlled test environment, lack of characterization of the test substance, lack of sound study design, inadequate details or missing critical data, etc. (U.S. EPA, 2012b). Furthermore, there is a concern over natamycin's potential adverse postnatal development effect after reduced pup weaning body weights were identified at relatively low doses in an open literature reproduction and lactation study (the LOAEL for offspring toxicity was 1000 ppm in the diet (about 50 mg/kg/day), Levinskas, 1966) and a three-generation reproduction and fertility study (the LOAEL for offspring toxicity was 300 ppm in the diet (about 15 mg/kg/day), MRID 48593401 and a data review by JMPR, 2017). The unacceptability of the

prenatal development data and the observed postnatal effect on pup weaning body weights also question the validity of the previous presumption that orally administrated or dietary natamycin and its related degradants/metabolites are poorly absorbed and short-lived in the gastrointestinal tract, as the transfer of natamycin and/or its related degradants/metabolites through placenta or milk cannot be ruled out. The Agency finds the current available database/information on orally administrated or dietary natamycin is inadequate to characterize its potential hazards to the general population, including fetuses, infants, and children.

To help address the uncertainty regarding the absorption and elimination (from the gastrointestinal tract) of orally administrated or dietary natamycin and its related degradants/metabolites, a guideline metabolism and pharmacokinetics study (OCSPP 870.7485) and its corroborative guideline prenatal developmental (OCSPP 870.3700) and reproduction and fertility effects (OCSPP 870.3800) studies are needed. The data will support characterizing natamycin's hazard profile and assessing the human health risk as they will help determine if orally administrated or dietary natamycin and its related degradants/metabolites are indeed poorly absorbed and short-lived in the gastrointestinal tract under more relevant conditions and if their transfer through placenta or milk could be ruled out. The data can also clarify if there is any adverse prenatal or postnatal effect for orally administrated or dietary natamycin and its related degradants/metabolites. Additional details on the guideline metabolism and pharmacokinetics, prenatal developmental and reproduction and fertility effects studies requested for this registration review are listed in Table 6.

Antifungal Effects, Antifungal Resistance, and Effects on Human Mycobiome

Natamycin is a polyene antifungal agent with highly specific mode of action in its intact form. It binds primarily to ergosterol in the fungal cell membrane and disrupts its function. Bacteria are insensitive to natamycin because their membranes lack ergosterol, and therefore natamycin is selectively antifungal. Furthermore, there is no concern for the induction of antifungal resistance (JECFA, 2002 and EFSA, 2009) as induction of natamycin-resistant mutants in yeast was reported to be difficult and there was no evidence of the transfer of resistance (Athar, 1971). Fungal communities can be found in different anatomic sites of the human body, especially the gastrointestinal tract, where they form an important part of the so-called "human mycobiome" (Cui, 2013). There is growing interest in its role in the pathogenesis of various diseases. However, the potential disturbance that natamycin might cause on human mycobiome and its consequence on human health are unknown at this time because of the lack of definitive data.

Dietary Exposure and Risk Characterization

Drinking water exposure due to the current biopesticide use is not expected. Natamycin is often used in enclosed facilities or as a seed treatment or a preplant, plant, and transplant dip treatment, so run-off into ditches, ponds, or other water bodies is expected to be minimal. Natamycin, especially in solutions or suspensions, is susceptible to rapid degradation/inactivation in the presence of common environmental elements such as ultraviolet (UV) light and low concentrations of peroxides, oxidants, chlorine, and heavy metals (Raab, 1972 and Stark, 2004). Natamycin also degrades extremely quickly in water under simulated sunlight: within one hour (the first tested interval) over 99% of natamycin was already degraded (MRID 51908603, data submitted for a pending case on EPA registration 92311-1).

Dietary exposure to natamycin from registered uses as a corn, soybean, and wheat seed-treatment or as a preplant, transplant, and at-plant root or whole plant dip treatment is not known as no crop field trials (OCSPP 860.1500) or residue data were submitted at the original registrations. However, dietary exposure to natamycin in treated postharvest food commodities and mushroom is expected. As these food commodities are often treated/processed, stored, and transported in clean and enclosed equipment/facilities, natamycin is therefore protected from common environmental elements and degradation/inactivation. In addition, although natamycin has a highly specific mode of action in its intact form, the identities of its degradants/metabolites after ingestion and their mode of actions and toxicity profiles remain unknown. And the Agency found the current available database/information on orally administrated or dietary natamycin is inadequate to characterize its potential hazards to the general population, including fetuses, infants, and children. Therefore, risk due to dietary exposure is uncertain and will need to be re-assessed when the requested additional product chemistry, human health, and residue data/information (refer to Anticipated Data Needs sections and Tables 4 and 6 for details) becomes available.

The Agency found the current available database/information on orally administrated or dietary natamycin is inadequate to characterize its potential hazards to the general population, including fetuses, infants, and children. Therefore, whether the current tolerance exemption (40 CFR § 180.1315) for natamycin is still valid remains to be determined.

Residential and Non-Occupational Exposure and Risk Characterization

Based on the requirement of PPE usage, natamycin is only approved for commercial use, thus residential exposure from its pesticidal use is not expected. Natamycin is often used in enclosed facilities or as a seed treatment or a preplant, plant, and transplant dip treatment, therefore, non-occupational exposure to natamycin from spray drift and bystander exposure are expected to be negligible.

Occupational Exposure and Risk Characterization

Based on the requirement of baseline clothing plus PPE usage, and/or use of controlled or automated application systems, occupational exposure to natamycin is expected to be minimal. Natamycin is a naturally occurring substance, and has a highly specific mode of action in its intact form (binds to fungal cell membrane ergosterol, which humans do not have), large molecular size (MW = 665.7 Da) with unlikely dermal penetration/absorption, unlikely volatility (solid powder with very low vapor pressure = 6.31×10^{-10} mm Hg), low (Toxicity Category IV) acute dermal toxicity and primary dermal irritation, and low acute inhalation toxicity (Toxicity Category IV).

Since natamycin is produced via microbes in the registered end-use products, a respirator requirement on product labels is needed due to the likely presence of allergenic microbial proteins. This requirement is not applicable if data are provided showing that these proteins are not present in the products.

When used in accordance with label directions, no risks of concern for occupational handlers during or post application are expected to occur from the current biopesticide use of natamycin.

Anticipated Human Health Data Needs

In order to assess dietary risk and re-evaluate the need for a tolerance or tolerance exemption for natamycin, a guideline metabolism and pharmacokinetics study (OCSPP 870.7485) and its corroborative guideline prenatal developmental (OCSPP 870.3700) and reproduction and fertility effects (OCSPP 870.3800) studies are needed. A study on reproduction and fertility effects (OCSPP 870.3800) is required since a prenatal developmental (OCSPP 870.3700) study is not able to address the concern over natamycin's potential adverse postnatal development effect observed in the database. Additional details on why these studies are requested can be found in Hazard Characterization section. In the absence of these data, the ADME and toxicity profiles of orally administrated or dietary natamycin and its related degradants/metabolites is not clear, adverse effects on prenatal and postnatal development will be assumed, and the tolerance exemption will be reexamined. If the current tolerance exemption (40 CFR § 180.1315) for natamycin is not supported, its covered food commodities without residue data and proposed tolerance levels (OCSPP 860.1500, 860.1520, and 860.1550) will be subject to compliance with these data requirements.

Registered uses as a corn, soybean, and wheat seed-treatment or as a preplant, transplant, and at plant root or whole plant dip treatment were claimed as non-food uses at the original registrations. However, residue data requirements (OCSPP 860.1000 and 860.1500) for a non-food use determination were never fulfilled due to the existing tolerance exemption and the confusion between low hazard/toxicity (therefore tolerance exempt) and low exposure (non-food determination due to no detectable or negligible residue in/on food). Without residue data, these uses do not qualify for a non-food determination. If the residue data do not support a non-food determination and a tolerance exemption is not warranted, a proposed tolerance level (OCSPP 860.1550) is also required.

Additionally, since natamycin is produced via microbes in the registered end-use products, a respirator requirement on product labels is needed due to the likely presence of allergenic microbial proteins in these products. Alternatively, a detailed chemical analysis may be performed to demonstrate that these proteins are not present in these final products (see Table 4).

Table 6. Anticipated Studies for the Registration Review of Natamycin

OCSPP Guideline No.	Data Requirement	Active Ingredient/-Test Material	Time Needed to Complete (Months)	Use Site(s) Triggering Data Requirement	Applicable Exposure Scenario
870.7485	Metabolism and pharmacokinetics	Orally administrated natamycin and its related degradants/metabolites	24	All	Dietary and tolerance exemption
870.3700	Prenatal developmental	Natamycin	24	All	Dietary and tolerance exemption
870.3800	Reproduction and fertility effects	Natamycin	48	All	Dietary and tolerance exemption
860.1000, 860.1500, 860.1550	Background, Crop field trials, Proposed tolerances[#]	Natamycin	24	Seed treatment and preplant, transplant, and at plant root or whole plant dip treatment	Dietary

860.1500, 860.1520, 860.1550	Crop field trials*, Processed food/feed*, Proposed tolerances*	Natamycin	24	Commodities covered under the tolerance exemption (40 CFR § 180.1315)	Dietary

* If the current tolerance exemption (40 CFR § 180.1315) for natamycin is not supported, its covered commodities without residue data and proposed tolerance levels (OCSPP 860.1500, 860.1520, and 860.1550) will be subject to compliance with these data requirements.

[#] If the residue data do not support a non-food determination and a tolerance exemption is not warranted, a proposed tolerance level is also required (OCSPP 860.1550).

Overall Human Health Risk Characterization and Conclusion

When used in accordance with label directions, no residential or non-occupational exposure or risk is expected. Additionally, no risks of concern for occupational handlers during or post application are expected to occur from the current biopesticide use of natamycin. However, since natamycin is produced via microbes in the registered end-use products, in the absence of data showing microbial proteins are not present, a respirator requirement on product labels is needed. Finally, in order to assess dietary risk and re-evaluate the need for a tolerance or tolerance exemption for natamycin additional toxicity and residue studies are needed (Table 6).

Literature and Incident Search Findings

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 natamycin. Searches conducted for natamycin are described below.

Human Health Results:

A literature search was conducted with the PubMed search engine using the terms “natamycin” and “toxicity”. These terms yielded a total of 62 results (accessed on 6/24/2023). An oral LD_{50} (2730 mg/kg) was reported in male rats (Levinskas, 1966). Also in this report, reduced pup weaning body weights were identified at a relatively low dose (the LOAEL for offspring toxicity was 1000 ppm in the diet (about 50 mg/kg/day)). JMPR concluded in 2017 that although the ADME of orally administrated radiolabeled (^{14}C) natamycin were studied in rats and dogs, the identities of its related degradants/metabolites in these animals were not investigated and insufficient details were reported to allow for an independent evaluation of the findings. All the other studies are either not relevant or unacceptable for use in risk assessment (U.S. EPA, 2012b). An incident search performed for natamycin using the Agency’s pesticide incident database system returned no incident reports.

EPA CompTox Chemicals Dashboard (U.S. EPA, 2023) indicates there are no endocrine disruption relevant data available for natamycin. A search was also performed using PubMed with the terms “natamycin” and “endocrine”. The search terms produced no relevant result.

In summary, information gained from these searches warrants the need for additional definitive data on the ADME and toxicity profiles of orally administrated or dietary natamycin and its related degradants/metabolites, an update on the human health risk assessment, and reexamination of the current tolerance exemption (40 CFR § 180.1315) for natamycin.

Appendix C – Environmental Risk Assessment

Summary of Nontarget Organism Data

Guideline toxicity studies were submitted to satisfy data requirements for avian acute oral toxicity, freshwater fish acute toxicity, aquatic invertebrate acute toxicity, and nontarget insect toxicity data requirements. Natamycin is slightly toxic to birds, fish, and aquatic invertebrates, and practically non-toxic to insects. Although some toxicity was observed in studies with birds, fish, and aquatic invertebrates, exposure to wildlife from natamycin applications is anticipated to be minimal due to the pesticides use pattern and environmental fate characteristics. For treatments to mushrooms, natamycin is used in enclosed mushroom facilities. When natamycin is used post-harvest on citrus fruit, pome fruit, stone fruit, avocado, kiwi, mango, pineapples, and pomegranate, there is not treatment in the field, but instead commodities are taken to a packing house for treatment, where there is nominal environmental exposure potential (US EPA, 2015). For treatments to soybean, corn and wheat seeds, there are no on-farm applications. The treated seeds are buried in the soil by direct sowing (shanking, injection) at planting, so there will be minimal potential for exposure to terrestrial wildlife and there will be no run-off into ditches, ponds, or other water bodies. For preplant and transplant dip treatments, applications are made prior to planting the commodities, so there are no outdoor broadcast (e.g., ground spray, arial) applications made to crops through this application method. Therefore, there is no potential exposure to non-target organisms to natamycin via spray drift from pre-plant and transplant applications. While there is potential for natamycin to wash-off of dip treated crops following rainfall, any non-target organism exposure to natamycin via run-off from dip treated crops would be minimal because the a.i. is understood to degrade rapidly. Data from a photolysis study (MRID 51908603) demonstrated over 99% natamycin degraded within one hour in water under simulated light. Given the minimal potential for exposure and natamycin's rapid environmental degradation, avian dietary toxicity and non-target plant toxicity data requirements were satisfied through scientific rationale based on lack of exposure.

Table 7 summarizes the current nontarget organism data requirements and results supporting registration review of natamycin. The ecological database is considered complete.

TABLE 7. Nontarget Organism Toxicity Profile of Natamycin (40 CFR § 158.2060)

Study/OCSPP Guideline No.	Results	Toxicity Category/Description	MRID
Avian acute oral toxicity (850.2100)	LD_{50} = 1405.74 mg/kg-bw NOAEL: 800 mg/kg-bw ACCEPTABLE/GUIDELINE	Slightly toxic	50891801
Avian dietary toxicity (850.2200)	Satisfied through scientific rationale based on minimal potential for exposure. Also, natamycin is considered slightly toxic via the oral route and dietary toxicity is not anticipated to be significantly greater than oral toxicity.	N/A	50891804 49957201
Freshwater fish acute toxicity (850.1075)	96-hour LC_{50} = 11 mg/L (95% C.I.: 8.7 – 15 mg/L) NOAEC = 10 mg/L ACCEPTABLE/GUIDELINE	Slightly toxic	50891806
Aquatic invertebrate acute toxicity (850.1010)	48- hour EC_{50} = 20 mg/L NOAEC = 10.0 mg/L ACCEPTABLE/GUIDELINE	Slightly toxic	50891805

Nontarget plant studies-seedling emergence (850.4100)	Satisfied through scientific rationale based on lack of exposure.	N/A	50891804
Nontarget plant studies-vegetative vigor (850.4150)	Satisfied through scientific rationale based on lack of exposure.	N/A	50891804
Nontarget insect testing (880.4350)	48-hour LD_{50} > 25 µg AI/bee ACCEPTABLE/GUIDELINE	Practically nontoxic	50891802

LD_{50} = median lethal dose; NOAEL= no observed adverse effect level; LC_{50} = median lethal concentration; NOAEC = no observed adverse effect concentration; NOAEC = no observed effect concentration; EC_{50} = median estimated concentration; NOER = no observed effect rate; ER_{25} = estimated effect rate yielding 25% reductions relative to controls; ER_{50} = estimated effect rate yielding 50% reductions relative to controls; LOER = lowest observed effect rate.

Risk Characterization

Natamycin is not expected to cause effects in any non-target organisms, including threatened and endangered species. The active ingredient is practically non-toxic to non-target insects and only slightly toxic to birds, fish, and aquatic invertebrates. Although some toxicity was observed in studies with birds, fish, and aquatic invertebrates, these toxic effects do not trigger any risk concerns because non-target organism exposure to natamycin will be minimal due to the active ingredient's use pattern and its rapid environmental degradation. For post-harvest applications, natamycin is not applied on-field, but instead is used in enclosed treatment facilities or packing houses, where there is minimal environmental exposure potential. When natamycin is used as a seed treatment, the treated seeds are buried in the soil by direct sowing (shanking, injection) at planting, so there will be minimal potential for exposure to terrestrial wildlife and there will be no run-off into ditches, ponds, or other water bodies. For preplant and transplant dip treatments, applications occur before planting the crops, so there are no outdoor broadcast applications to crops. Therefore, non-target organisms cannot be exposed to natamycin via spray drift from dip applications to pre-plant and transplant crops. Although it is possible for natamycin to be washed off of dip-treated crops during rainfall, any non-target organism exposure to natamycin through run-off would be minimal because the active ingredient degrades rapidly in the environment. Data from a photolysis study (MRID 51908603) showed that over 99% of natamycin degraded within one hour in water under simulated light. Given the minimal potential for exposure to natamycin, no risks are expected to listed and non-listed non-target organism when natamycin containing products are applied in accordance with approved labeling.

Literature and Incident Search Findings

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 natamycin. Searches conducted for natamycin 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, with the terms "natamycin" and "avian toxicity," "terrestrial

mammal toxicity," "plant toxicity," "insect toxicity," and "aquatic organism toxicity," which returned 0 relevant results. An ecological incident search was performed for natamycin using the incident data search system and no incident reports were returned.

No additional information was gained from these searches that would alter the BPPD's understanding of the current state of the science for any potential effects of natamycin on nontarget organisms.

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))[2].

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.[3]

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*

[2] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[3] Summarized in *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions*; EPA-HQ-OPP-2023-0474-0001; https://www.regulations.gov/document/EPA-HQ-OPP-2023-0474-0001

Comment (88 FR 73841) is referred to here as EPA's EDSP Strategies Notice. EPA also published three documents supporting the strategies described in the Notice:

- *Use of Existing Mammalian Data to Address Data Needs and Decisions for Endocrine Disruptor Screening Program (EDSP) for Humans under FFDCA Section 408(p)*;
- *List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed;* and,
- *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions* (referred to here as List 1 Screening Conclusions).

The EDSP Strategies Notice and the support documents are available on www.regulations.gov in docket number EPA-HQ-OPP-2023-0474. As explained in these documents, EPA is prioritizing its screening for potential impacts to the estrogen, androgen, and thyroid systems in humans, focusing first on conventional active ingredients. Although EPA voluntarily expanded the scope of the EDSP to screening for potential impacts to the estrogen, androgen, and thyroid systems in wildlife, EPA announced that it is not addressing this discretionary component of the EDSP at this time, considering its current focus on developing a comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[4] and November 2022 ESA Workplan Update[5]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[6] 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,

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

androgen, and/or thyroid pathways in humans. For more details on EPA's approach for assessing these endpoints, see EPA's EDSP Strategies Notice and related support documents.

Also described in the EPA's EDSP Strategies Notice is a framework that represents an initial approach by EPA to organize and prioritize the large number of conventional pesticides in registration review. For conventional pesticides with a two-generation reproduction toxicity study performed under a previous guideline (i.e., an updated two-generation reproduction toxicity study or an EOGRT is not available), EPA has used data from the Estrogen Receptor Pathway and/or Androgen Receptor Pathway Models to identify a group of chemicals with the highest priority for potential data collection (described in EPA's EDSP Strategies Notice as Group 1 active ingredients). For these cases, although EPA has not reevaluated the existing endocrine-related data, EPA has sought additional data and information in response to the issuance of EPA's EDSP Strategies Notice to better understand the positive findings in the ToxCast™ data for the Pathway Models and committed to issuing DCIs to require additional EDSP Tier 1 data to confirm the sufficiency of data to support EPA's assessment of potential adverse effects to the estrogen, androgen, and/or thyroid pathways in humans and to inform FFDCA 408(p) data decisions. For the remaining conventional pesticides (described in EPA's EDSP Strategies Notice as Group 2 and 3 conventional active ingredients), EPA committed to reevaluating the available data to determine what additional studies, if any, might be needed to confirm EPA's assessment of the potential for impacts to endocrine pathways in humans.

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 natamycin. Such issues will be addressed in future updates by EPA on its strategies for implementing FFDCA section 408(p).

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