BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Natamycin

PC Code: 051102

U.S. Environmental Protection Agency
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division

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Table of Contents

BIOPESTICIDES REGISTRATION ACTION DOCUMENT (BRAD) TEAM

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I. EXECUTIVE SUMMARY

Natamycin is a biochemical pesticide active ingredient intended for use as a fungistat to control the germination of mold and yeast spores in the growth media of mushrooms produced in enclosed mushroom production facilities and on pineapples. Natamycin is a naturally-occurring antimycotic compound derived from the common soil microorganisms *Streptomyces natalensis, Streptomyces lydicus,* and *Streptomyces chattanoogensis.* It 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. Natamycin was originally discovered in *Streptomyces natalensis* in South Africa in the early 1950s, and was subsequently discovered to also occur naturally in North America in *Streptomyces lydicus* and *Streptomyces chattanoogensis.* Natamycin has a non-toxic mode of action and functions as a fungistat, preventing the germination of fungal spores. It has no effects on fungal mycelia. Development of antibiotic resistance to Natamycin has not been reported during its entire history of use.

Natamycin has been used as a food preservative worldwide for over 40 years and is approved as a food additive/preservative by the European Union, the World Health Organization and individual countries for use as a fungistat to suppress mold on cheese, meats and sausage. In the United States, natamycin is approved by The Food and Drug Administration (FDA) as a direct food additive/preservative for the inhibition of mold and yeast on the surface of cheeses (21 CFR § 172.155) and as an additive to the feed and drinking water of broiler chickens to retard the growth of specific molds (21 CFR § 573.685). Natamycin is also FDA approved for use as a treatment to suppress fungal eye infections such as blepharitis, conjunctivitis, and keratitis. On August 17, 2007, the EPA's Biochemical Classification Committee classified Natamycin as a Biochemical Pesticide active. *Streptomyces lydicus* (the source of natamycin) is currently registered by the Agency under Registration Nos. 73314-1, -2, and -4 as a microbial pesticide for greenhouse, nursery, turfgrass, agricultural, and seed treatment uses. Natamycin is currently registered by the Agency under Registration Nos. 87485-1 and -2 for use in enclosed mushroom production facilities. The pending product registration for natamycin is EPA File Symbol 87485-G; this product is intended for use post-harvest, indoors, on pineapples.

The Agency has concluded that adequate product chemistry and mammalian toxicology data are available to support natamycin (U.S. EPA, 2010; U.S. EPA, 2011a; U.S. EPA, 2011b; U.S. EPA 2011c; U.S. EPA, 2014). Acute toxicity studies on natamycin (98.17% and 98.27% pure), confirm a low toxicity profile. The acute toxicity data show virtual nontoxicity for all routes of exposure (Toxicity Category III for acute oral toxicity and primary eye irritation; Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, and primary dermal irritation; not a dermal sensitizer). A 90-Day Oral study on natamycin indicated no adverse effects up to the highest dose tested, which was 2,000 milligrams (mg) per kilogram (kg) body weight (bw) per day. No 90-Day Dermal or 90-Day Inhalation studies were submitted and none are required since products containing natamycin will be used indoors only by applicators wearing appropriate Personal Protective Equipment (PPE), as stated on the product labels. A prenatal developmental toxicity study showed no effects up to the highest dose tested, which was 50 mg/kg bw/day. Submitted studies indicate that natamycin is non-mutagenic. Therefore, the Agency concludes that this active ingredient is not likely to result in adverse human health

effects, based upon available reports and information.

Tier I studies were not submitted for non-target organisms and environmental fate data requirements for natamycin and such studies are not required. Based on its use pattern and use instructions as a fungistat intended solely for use indoors (in enclosed mushroom production facilities or in packaging facilities on pineapples), natamycin exposure to non-target organisms is not expected. Further, EPA has determined that natamycin will have "**No Effect**" on any currently listed threatened or endangered species or any designated critical habitat based on its use pattern.

On October 1, 2009, the U.S. Environmental Protection Agency (EPA or the Agency) announced a policy to provide a more meaningful opportunity for the public to participate in major registration decisions before they occur. According to this policy, EPA provides a public comment period prior to making a registration decision for the following types of applications: new active ingredients; first food uses; first outdoor uses; first residential uses; or any other registration actions for which EPA believes there may be significant public interest.

Consistent with the policy of making registration decisions more transparent, the public is provided 15 days in which to submit comments to the Agency regarding its pending decision to register a product containing natamycin for use on pineapples post-harvest, indoors. The following documents are available for comment in the docket, identification number EPA-HQ-OPP-2014-0352: a draft of this Biopesticides Registration Action Document (BRAD) and the draft product label for Zivion P (EPA File Symbol 87485-G).

Altogether, the Agency believes that, based on the existing information in the Agency's database on natamycin and the recent information submitted in support of the registration of a pesticide product containing natamycin for use on pineapples, post-harvest, indoors, it is in the best interest of the public to issue the registration for Zivion P (EPA File Symbol 87485-G). The basis for this decision can be found in the science review memorandums for these products (U.S. EPA, 2010; U.S. EPA, 2011a; U.S. EPA, 2011b; U.S. EPA 2011c; U.S. EPA, 2014) and the existing information in the Agency's database on natamycin, all of which are characterized in this BRAD.

For definitions of scientific terms, please refer to *http://www.epa.gov/pesticides/glossary/*.

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II. ACTIVE INGREDIENT OVERVIEW

Common Name: Natamycin

Chemical Names: IUPAC Chemical Name:
(1*R*,3*S*,5*R*,7*R*,8*E*,12*R*,14*E*,16*E*,18*E*,20*E*,22*R*,24*S*,25*R*,26*S*)-22-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.05,7]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid

Trade & Other Names: Natamycin L
Pimaricin
Tennectin
Delvocid

CAS Registry Number: 7681-93-8

OPP Chemical Code: 051102

Type of Pesticide: Biochemical Pesticide – Fungistat

Biochemical Classification

On August 17, 2007, EPA's Biochemical Classification Committee classified natamycin as a Biochemical Pesticide active ingredient.

III. REGULATORY BACKGROUND

A. Application for Pesticide Registration

On May 20, 2010, EPA received an application filed by Keller and Heckman, 1001 G Street, N.W., Suite 500 West, Washington, D.C.20001 on behalf of DSM Food Specialties B.V. (hereafter referred to as "DSM" or "applicant"), Alexander Fleminglaan 1, Delft, The Netherlands 2613AX to register the products Natamycin TGAI (EPA Reg. No. 87485-1), and Natamycin L (EPA Reg. No. 87485-2) containing the new biochemical active ingredient natamycin. The application was submitted to both EPA and The Health Canada Pest Management Regulatory Agency (PMRA) along with a request for a North American Free Trade Agreement (NAFTA) Joint Review of the applications. Concurrent with these applications, DSM filed a petition for a tolerance exemption for residues of natamycin on mushrooms when used as a fungistat in enclosed mushroom producing facilities. No comments were received following publication of the notice. On November 24, 2010, EPA published in the Federal Register (76 FR 22067) a Notice of Receipt (NOR) announcing receipt of the applications, and on April 20, 2011 EPA published in the Federal Register (76 FR 22067) a Notice of Filing (NOF) announcing receipt of the petition.

On January 6, 2014, Becker Underwood, on behalf of DSM, submitted an application to register a biochemical pesticide product, Zivion P (EPA File Symbol 87485-G), containing natamycin as its active ingredient. Zivion P is intended for use as a fungistat applied to pineapples post-harvest in indoor packages facilities. In the Federal Register of August 1, 2014 (79 FR 44729), a NOF announced the pesticide tolerance petition (PP 4F8233) by DSM. The petition requested that 40 CFR part 180 be amended by establishing an exemption from the requirement of a tolerance for residues of natamycin post-harvest, indoors, on pineapples. There were no comments received in response to this NOF.

B. Food Clearances/Tolerances

Natamycin is exempt from the requirement of a tolerance as stated at 40 CFR § 180.1315:

> **40 CFR § 180.1315 Natamycin; exemption from the requirement of a tolerance.**
>
> An exemption from the requirement of a tolerance is established for residues of natamycin in or on mushrooms when applied as a fungistat to prevent the germination of fungal spores on mushrooms produced in enclosed mushroom production facilities.

The proposed end-use product, Zivion P (EPA File Symbol 87485-G), will be used post-harvest on pineapples inside packaging facilities (indoor use only). With the registration of this product, the Agency will also amend the tolerance exemption at 40 CFR § 180.1315 to read 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 residues of natamycin in or on mushrooms when applied as a fungistat to prevent the germination of fungal spores on mushrooms produced in enclosed mushroom production facilities, and in or on pineapples when applied as a fungistat in accordance with label directions and good agricultural practices

IV. RISK ASSESSMENT

A. Product Analysis Assessment (40 CFR § 158.2030)

Biochemical pesticide product analysis data requirements include product chemistry and composition, analysis and certified limits, and physical and chemical characteristics. Product chemistry and composition data include information about the identity of the active ingredient, the manufacturing process, and discussion of the potential for formation of unintentional ingredients. Analysis and certified limits data include information on analysis of samples and certification of limits. Physical and chemical characteristics data describe basic characteristics of the registered pesticide products, including color, physical state, odor, stability, miscibility, pH, corrosion characteristics, viscosity and density.

All product chemistry data requirements have been satisfied for the active ingredient (natamycin) and the proposed product, Zivion P (EPA File Symbol 87485-G). Refer to Appendix A for a summary of natamycin product chemistry data.

B. Human Health Assessment

1. Tier I Toxicology

All applicable mammalian toxicology data requirements an exemption from the requirement of a tolerance for residues of natamycin when used on mushrooms in enclosed production facilities and on pineapples, indoors, post-harvest have been fulfilled with data submitted by the petitioner. These data indicate that the active ingredient is of low acute toxicity and is not a developmental toxicant, a mutagen, or toxic via repeat oral exposure.

The following is a summary of EPA's review of the toxicity profile of this biochemical:

Acute Toxicity: Acute toxicity studies on natamycin (98.17% and 98.27% pure), confirm a low toxicity profile. The acute toxicity data show virtual nontoxicity for all routes of exposure. Therefore, it can be concluded that any dietary risks associated with this biochemical would be negligible.

1. The acute oral median lethal dose (LD50) in rats was greater than 2,000 milligrams per kilogram (mg/kg) bodyweight. There were no observed toxicological effects on the test subjects in the acute oral study submitted (MRID No. 48105505). Natamycin is classified as Toxicity Category III for acute oral toxicity.

2. The acute dermal LD50 in rats was greater than 5,050 mg/kg body weight (MRID 48105506). Natamycin is classified as Toxicity Category IV for acute dermal toxicity.

3. The acute inhalation median lethal concentration (LC50) was greater than 2.39 milligrams per liter (mg/L) in rats and showed no significant inhalation toxicity (MRID 48105507). Natamycin is classified as Toxicity Category IV for acute inhalation toxicity.

4. A primary eye irritation study on rabbits indicates that natamycin is severely irritating to the eye but with no effects observed at 24 hours after treatment (MRID 48015508). Natamycin is classified as Toxicity Category III for primary eye irritation.

5. A skin irritation study on rabbits indicates that natamycin is slightly irritating (MRID 48105509). Natamycin is classified as Toxicity Category IV for primary skin irritation.

6. Data indicate that natamycin is not a dermal sensitizer (MRID 48105510).

Mutagenicity: Two mutagenicity studies, using natamycin (98.17% and 98.27% pure) as the test substance, were performed. These studies are sufficient to confirm that there are no expected dietary or non-occupational risks of mutagenicity with regard to food use of natamycin.

1. A Bacterial Reverse Gene Mutation Test (MRID No. 48105513) investigating doses of test substance up to those that were cytotoxic, both with and without metabolic S9 activation, found no incidences of a 2-fold or greater increase in the number of revertants compared to the corresponding solvent control in two independently repeated experiments. Therefore, natamycin

is considered to be non-mutagenic under the conditions of this assay.

2. An *in vitro* Mammalian Cell Chromosome Aberration Test (MRID No. 48105514) tested natamycin genotoxicity on cultured peripheral human lymphocytes in the presence and absence of metabolic S9 activation. Natamycin did not induce a statistically significant or biologically relevant increase in the number of cells with chromosome aberrations in the absence and in the presence of S9-mix, in two independently repeated experiments. In addition, all of the negative, solvent, and positive controls gave appropriate responses. Therefore, under the conditions of this assay, natamycin is considered to be non-mutagenic and does not cause chromosome aberrations.

Subchronic Toxicity: In a subchronic oral toxicity study using natamycin (98.17% and 98.27% pure) as the test substance, doses of 125 and 500 mg/kg/day showed no treatment related findings. The highest concentration level, 2,000 mg/kg/day, showed reduced weight for both male and female rats (MRID 48105511). The Agency does not consider the temporary decrease in body weight or food intake observed in the 2,000 mg/kg bw/day test group to be an adverse effect, as this is likely due to the palatability of the food containing this high dose of test substance. Therefore, the Agency establishes the NOAEL (No Observed Adverse Effect Level) for this study as 2,000 mg/kg bw/day. A LOAEL (Lowest Observed Adverse Effect Level) was not identified, suggesting that the test animals could have tolerated a higher dose.

Developmental Toxicity: A developmental toxicity study using natamycin (98.17% and 98.27% pure) as the test substance (MRID 48105512) showed no discernable effects on growth, reproduction, teratological or mutagenic responses, or on gross and microscopic pathology, at concentration levels 0, 5, 15 and 50 mg/kg bw/day.

2. Tier II and Tier III Toxicity Studies

The biochemical pesticide Human Health Assessment data requirements for Tier II and Tier III were not required due to the low toxicity of the active ingredient and the low levels of exposure expected from its intended uses in EP products.

3. Effects on the Endocrine System

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. 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 (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders and data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and nine inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Natamycin is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders and data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4. Dose Response Assessment

No toxicological endpoints have been identified for natamycin; therefore, a dose-response assessment was not required.

5. Drinking Water Exposure and Risk Characterization

Exposure of humans to natamycin in drinking water is not expected because natamycin is approved for application indoors only (enclosed mushroom houses or pineapple packing facilities).

6. Occupational, Residential, School and Day Care Exposure and Risk Characterization

a. Occupational Exposure and Risk Characterization

Occupational exposure to registered pesticide products containing natamycin is not expected due to mitigation through precautionary language and personal protective equipment (PPE) on the label.

b. Residential, School and Day Care Exposure and Risk Characterization

Natamycin is intended for use only in enclosed mushroom houses and in indoor packaging facilities on pineapples. No indoor residential, school, or day care uses are currently approved for products containing natamycin.

7. Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation

There is reasonable certainty of no harm to U.S. populations, including infants and children, from aggregate exposures to residues of natamycin when used as proposed. This includes all anticipated dietary exposures and all other exposures for which there is reliable information.

Moreover, potential non-occupational inhalation and dermal exposure is not likely to pose any adverse effects to exposed populations via aggregate and cumulative exposure.

a. Food Exposure

Dietary exposure to residues of natamycin is expected to be insignificant, even in the event of exposure. The lowest NOEL (No observed effect level) for natamycin is 50 mg/kg/day. The application of natamycin on pineapples produces residues in the edible portions (meat and juice) in the range **< 0.01 – 0.07 ppm**. A human adult exposure threshold was calculated at **30 mg/day** (NOEL/uncertainty factor x 60kg; 50 mg/kg/day/100 x 60 kg = 30 mg/day). Oral exposure to children (1-2 years old, 11.2 kg) was found at **5.6 mg/day** (50 mg/kg/day/100 x 11.2 kg = 5.6 mg/day). Therefore, expected residue levels on natamycin on pineapple meat and juice are about three orders of magnitude below the adult and children exposure threshold (EPA, 2014). Furthermore, the active ingredient is of low acute toxicity and is not a developmental toxicant, a mutagen, or toxic via repeat oral exposure

b. Drinking Water Exposure

Exposure of humans to natamycin in drinking water is not expected because natamycin is approved for application indoors only (enclosed mushroom houses or pineapple packing facilities).

c. Other Non-occupational Exposure

Non-occupational exposure is not expected because natamycin is not approved for residential uses. The active ingredient is applied directly to commodities and degrades rapidly.

8. Cumulative Effects from Substances with a Common Mechanism of Toxicity

The EPA has not found natamycin to share a common mechanism of toxicity with any other substances, and natamycin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, the EPA has assumed that natamycin does not have a common mechanism of toxicity with other substances. Following from this, the EPA concludes that there are no cumulative effects associated with natamycin that need to be considered. For information regarding the EPA's efforts to determine chemicals that have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the EPA's website at http://www.epa.gov/pesticides/cumulative.

9. Determination of Safety for United States Population, Infants and Children

FFDCA section 408(b)(2)(C) provides that, in considering the establishment of a tolerance or tolerance exemption for a pesticide chemical residue, the EPA shall assess the available information about consumption patterns among infants and children, special susceptibility of infants and children to pesticide chemical residues, and the cumulative effects on infants and children of the residues and other substances with a common mechanism of toxicity. In addition,

FFDCA section 408(b)(2)(C) provides that the EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure, unless the EPA determines that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the Food Quality Protection Act Safety Factor. In applying this provision, the EPA either retains the default value of 10X, or uses a different additional or no safety factor when reliable data are available to support a different additional or no safety factor.

Because there are no threshold effects associated with this biochemical, an additional margin of safety for infants and children is not necessary.

EPA has determined that there are no foreseeable dietary risks to the U.S. population, including infants and children, from the use of natamycin as a pesticide (fungicide) on mushrooms in enclosed mushroom facilities and post-harvest, indoors, on pineapples when label instructions and good agricultural practices are followed. The available data and information indicate that the chemical is of low toxicity and not a developmental toxicant. Therefore, EPA concludes that there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to the residues of natamycin when it is used as labeled and in accordance with good agricultural practices. Such exposure includes all anticipated dietary exposures and all other exposures for which there is reliable information. EPA has arrived at this conclusion because the data and information available on natamycin do not demonstrate significant toxic potential to mammals, including infants and children.

10. Risk Characterization

The Agency considered human exposure to natamycin in light of the relevant safety factors in FQPA and FIFRA. A determination has been made that no unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, will result from the use of products containing natamcyin when label instructions are followed.

C. Environmental Assessment

1. Ecological Hazards

Tier I studies were not submitted but are not required. However, based on its use pattern and use instructions as a fungistat intended solely for use in indoors, exposure to non-target organisms is not expected.

2. Environmental Fate and Ground Water Data

Environmental fate and groundwater data are not required at this time because the results of the nontarget organism toxicity assessment (Tier I data requirements) did not trigger these Tier II data requirements.

3. Ecological Exposure and Risk Characterization

Exposure and risk from the registered and proposed uses of natamycin are expected to be minimal for nontarget organisms because all uses are indoors only.

4. Endangered Species Assessment

Based on its use pattern and use instructions, EPA has determined that natamycin will have "**No Effect**" on any currently listed threatened or endangered species or any designated critical habitat.

D. Product Performance Data

Product performance (efficacy) data must be developed for all pesticides to ensure that the products will perform as intended and that unnecessary pesticide exposure to the environment will not occur as a result of the use of ineffective products. The Agency reserves the right to require, on a case-by- case basis, the submission of efficacy data for any pesticide product registered or proposed for registration, but applications to register pesticide products intended to control a pest of significance public health importance, as defined in FIFRA section 28(d) and section 2(nn), must include such data. For further guidance on the product performance data requirement, refer to Pesticide Registration Notice (PR) Notices 96-7, 2002-1 and Explanation of Statutory Framework for Risk-Benefit Balancing for Public Health Pesticides (http://www.epa.gov/PR _Notices/pr1996-7.pdf) (http://www.ea.gov/PR_Notices/pr2002-1.pdf) and (http://www.epa.gov/pesticides/health/risk-benefit.htm).

Natamycin is not intended to be formulated into products to control public health pests as defined in FIFRA section 28(d) and section 2(nn), and product performance (efficacy) was not evaluated by the Agency.

V. RISK MANAGEMENT DECISION

A. Determination of Eligibility for Registration

Section 3(c)(5) of FIFRA provides for pesticide product registration if it is determined that: (A) its composition warrants proposed claims; (B) its labeling and other materials comply with the requirements of FIFRA; (C) it will perform its intended function without unreasonable adverse effects on the environment; and (D) when used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment.

The four eligibility criteria have been satisfied for the proposed pesticide product containing the active ingredient natamycin (and for all previous registered pesticide products containing natamycin).

B. Regulatory Decision

The data submitted fulfill the requirements for the unconditional registration of Zivion P (EPA File Symbol 87485-G) as an EP for use on pineapples, post-harvest, indoors, and EPA believes it is in the best interest of the public to grant this registration. For product-specific labels and

information on other product containing natamycin, please refer to http://www.epa.gov/pesticides/pestlabels.

C. 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—with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies. At this time, EPA does not believe that products containing the active ingredient natamycin, or the use of natamycin on pineapples post-harvest, indoors, will cause harm or a disproportionate impact on at-risk communities. For additional information regarding environmental justice issues, please visit EPA's website at *http://www.epa.gov/compliance/environmentaljustice/index.html*.

VI. ACTIONS REQUIRED BY REGISTRANTS

EPA evaluated all data submitted in connection with the registration of natamycin and determined that these data are sufficient to satisfy current registration data requirements for Zivion P (EPA File Symbol 87485-G). At this time, no additional data must be submitted to EPA. For new uses and/or changes to existing uses, EPA may require additional data.

Notwithstanding the information stated in the previous paragraph, it should be clearly understood that certain specific data are required to be reported to EPA as a requirement for maintaining the federal registration for a pesticide product. A brief summary of these types of data are listed below.

A. Reporting of Adverse Effects

Pursuant to FIFRA section 6(a)(2), reports of all incidents of adverse effects to the environment must be submitted to EPA.

B. Reporting of Hypersensitivity Incidents

Under the provisions of 40 CFR Part 158.2050(d), all incidents of hypersensitivity (including both suspected and confirmed incidents) must be reported to the Agency.

VII. Appendix A: Product Chemistry Data Tables

TABLE 1. Product Chemistry Data Requirements for Natamycin *Technical* (40 CFR § 158.2030)			
OSCPP Guideline No.	**Study**	**Results**	**MRID No.**
880.1100 880.1200 880.1400	Product identity; Manufacturing process; Discussion of formation of impurities	Submitted data satisfy the requirements for product identity, manufacturing process, and discussion of formation of impurities.	48105401 48105501 47206713 47760931
830.1700	Analysis of samples	Submitted data satisfy the requirements for analysis of samples.	48105502
830.1750	Certification of limits	Limits listed in the confidential statement of formula are acceptable	48105402
830.1800	Analytical method	Acceptable	48105403

TABLE 2. Physical and Chemical Properties of Natamycin *Technical* (40 CFR § 158.2030)			
OCSPP Guideline No.	**Property**	**Description of Results**	**MRID**
830.6302	Color	Colourless	48105503
830.6303	Physical State	Viscous liquid	48105503
830.6304	Odor	Odorless	48105503
830.6313	Stability to Normal and Elevated Temperatures, Metals and Metal Ions	Natamycin was found 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
830.6315	Flammability	Does not contain any flammable components. Consists of ~ 80% water.	48105503
830.6317	Storage Stability	The product is stable when stored for 12 and 18 months in HDPE plastic bottles at 25°C.	8105405 48439301 48544501
830.6320	Corrosion Characteristics	The product is not corrosive.	48105405 48439301 48544501
830.7000	pH	6.5 (1% aqueous solution) 6.5 (1% aqueous solution). May vary between 5 to 7.5	48105503?
830.7100	Viscosity	~2200 mPa.s, Brookfield Test Method: RPM-20, Axe=3, T=20°C.	48105503
830.7220	Boiling Point/Range	N/A The product is a solid.	48105503
830.7300	Density	Loose bulk density 0.3 g/mL Tapped bulk density 0.59 g/mL	

TABLE 2. Physical and Chemical Properties of Natamycin *Technical* (40 CFR § 158.2030)			
OCSPP Guideline No.	**Property**	**Description of Results**	**MRID**
830.7560 830.7570	Octanol/water partition coefficient (K_{ow})	Log K_{ow} = – 3.67	48105503
830.7840	Water Solubility	30-50 ppm @ 20-25°C and pH 5-7.5; very soluble at pH ≥ 10 or pH ≤ 2 but rapidly degrades.	8105503
830.7950	Vapor Pressure	NA The product is a solid	48105503
	Formulation Type	Suspension (SU)	48105501
	Container Material and Description	HDPE plastic bucket, jerry can, drum or jumbo container (5 to 1000 Litres)	48105501
830.7000	pH	6.5 (1% aqueous solution) 6.5 (1% aqueous solution). May vary between 5 to 7.5	48105503
830.6314	Oxidizing or Reducing Action	Not applicable. Does not contain oxidizing or reducing chemicals.	48105503
830.6316	Explodability	Not applicable. Does not contain any substance capable of exploding.	48105503
830.6319	Miscibility	Not formulated to be mixed with petroleum solvents.	48105503
830.6321	Dielectric Breakdown Voltage	Not applicable. Not intended to be used around electrical equipment.	48105503

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] For example, "brown" for 830.6302; "1.021" for 830.7300.
[3.] There was a slight shift in the retention time (close to a minute) for the active ingredient based on the chromatograms provided for the 18-month storage stability study. The applicant provided a rationale indicating that there was a change in the column packing material (new batch). The applicant provided additional chromatograms for the controls (standard sample) for the 6- and 18-month to confirm the slight shift in the retention times for the active. The rationale is accepted.

VIII. Appendix B. References

EPA Science Review Memos

U.S. EPA, 2010. Jones, Russell, Ph.D. Science Review in Support of Natamycin Technical, Containing 91.02% Natamycin as Its Active Ingredient. United States Environmental Protection Agency (U.S. EPA) Memorandum dated 10/15/2010.

U.S. EPA, 2011a. Jones, Russell, Ph.D. Science Review in Support of Natamycin Technical, Containing 91.02% Natamycin as Its Active Ingredient. United States Environmental Protection Agency (U.S. EPA) Memorandum dated 04/04/2011.

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IX. GLOSSARY OF ACRONYMS AND ABBREVIATIONS

a.i.	active ingredient
BPPD	Biopesticides and Pollution Prevention Division
BRAD	Biopesticide Registration Action Document
bw	body weight
CBI	Confidential Business Information
CFR	Code of Federal Regulations
cm^3	cubic centimeter
CSF	Confidential Statement of Formula
°C	degrees Celsius
EC_{50}	median effective concentration. A statistically derived single concentration in environmental medium that can be expected to cause an effect in 50% of the test animals when administrated by the route indicated (inhalation). It is expressed as a concentration in air or water (e.g. mg/L).
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Advisory Committee
EP	end-use product
EPA	Environmental Protection Agency (the "Agency")
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
FR	Federal Register
g	gram
ha	hectare
kg	kilogram
Kow	octanol-water partition coefficient
L	liter
LC_{50}	median lethal concentration. A statistically derived single concentration in air or water that can be expected to cause death in 50% of the test animals when administrated by the route indicated (inhalation and environment). It is expressed as a concentration in air or water (e.g. mg/L).
LD_{50}	median lethal dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral and dermal). It is expressed as a weight of substance per unit weight of animal (e.g., mg/kg).
MRID No.	Master Record Identification Number
mg	milligram
mPa	millipascal
mL	milliliter
MP	manufacturing-use product
N/A	not applicable
NE	"No Effect"
NIOSH	National Institute for Occupational Safety and Health

nm	nanometer
NOEL	no-observed-effect-level
NOF	notice of filing
NOR	notice of receipt
OPP	Office of Pesticide Programs
OCSPP	Office of Chemical Safety and Pollution Prevention
pa	pascal
PPE	personal protective equipment
PR Notice	Pesticide Registration Notice
TGAI	technical grade of the active ingredient
ug	microgram
USDA	United States Department of Agriculture
UV	ultra-violet