BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Natamycin

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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 TEAM

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I. EXECUTIVE SUMMARY

Natamycin is a new 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. 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 (WHO TRS 430) 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 (21CFR172.155) and as an additive to the feed and drinking water of broiler chickens to retard the growth of specific molds (21CFR573.685). 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 ingredient, and -*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.

The Biopesticides and Pollution Prevention Division (BPPD) determined that the data/information submitted for product chemistry and Tier I acute toxicity for Natamycin satisfy the current guideline requirements. Acceptable studies were submitted for the subchronic 90-day oral (OCSPP 870.3100) and 90-day inhalation (OCSPP 870.3465) data requirements. Those data showed no biologically significant changes in the hematology or clinical chemistry profiles of the test animals. No 90-Day Dermal (OCSPP 870.3250) or 90-Day Inhalation (OCSPP 870.3465) studies were submitted and none are required since products containing Natamycin will only be applied in irrigation water to mushrooms growing in enclosed facilities. Based on this application method, the Agency does not anticipate any repeated dermal exposure to Natamycin.

In lieu of a Guideline study the applicant developed a science based rationale in support of Prenatal Developmental Toxicity ((OCSPP 870.3700) for Natamycin. The rationale was supported with information and data obtained from the open technical literature. The rationale relies primarily on a comprehensive review of Natamycin by the European Food Safety Authority (EFSA, 2009) and its associated citations. By way of the EFSA review of Natamycin (aka Pimaricin), the rationale demonstrated that Natamycin is poorly absorbed by mammals and

that it does not pose any dietary concerns based on current usage. The Agency concurs with this conclusion based on per capita consumption of all mushroom commodities in the United States (USDA/ERS, 2010), dietary intake from treated, unwashed mushrooms is conservatively estimated to be no more than 0.00030 mg a.i./kg bw/person/day. This value is well below any known acute oral, subchronic and chronic dietary, reproductive, and developmental endpoints for Natamycin by many orders of magnitude. In addition, the estimated dietary intake from unwashed, treated mushrooms also is well below the Acceptable Dietary Intake (ADI) of 0.3 established by Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2001& 2006) and an ADI of 0.1 established European Food Safety Authority (EFSA, 2009). The information submitted by the registrant, along with open technical literature also support the Tolerance Exemption Petition submitted for Natamycin.

Tier I studies were not submitted for non-target organisms and environmental fate data requirements (OCSPP 850.1010 to 850.4450) for Natamycin and such studies are not required. Based on its use pattern and use instructions as a fungistat intended solely for use in indoor, enclosed mushroom production facilities, 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 and use instructions and the fact that Natamycin is intended solely for indoor use in enclosed mushroom production facilities.

Based on the acute toxicity data for Natamycin, the active ingredient is toxicity category III. EPA has not identified any toxic endpoints for nontarget mammals, birds, plants, aquatic, or soil organisms. EPA has no concerns for any nontarget organisms exposed to Natamycin when used in accordance with approved label directions. Given that Natamycin has very low toxicity and presents little, if any, risk to nontarget organisms, EPA has concluded that it is in the best interests of the public to issue the registration for the Natamycin TGAI (EPA File Symbol No. 87485-1) and the end-use product Natamycin L (EPA File Symbol No. 87485-2), which contain this new active ingredient, Natamycin.

The Agency has reviewed the data/information in support of the requirements for granting registration under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and determined that the data/information submitted adequately satisfy current guideline requirements (see 40 CFR Subpart U § 158.2000).

On October 1, 2009, EPA announced a new policy to provide a more meaningful opportunity for the public to participate on 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 use, first outdoor use, first residential use; and any registration decisions for which the Agency believes there may be substantial public interest.

Consistent with the policy of making registration actions more transparent, Natamycin was subject to a 30 day comment period as a “new active ingredient”. The notice for this comment period included the draft Biopesticides Registration Action Document (BRAD) and draft product labels for the technical grade active ingredient, Natamycin TGAI and the EP, Natamycin L.

which contain this new active ingredient, Natamycin. The docket identification (ID) number is EPA-HQ-OPP-2010-0685. The Agency believes that based on the risk assessment and information submitted in support of the registration of the EP containing Natamycin, it is in the best interests of the public to issue the registration for Natamycin L. The basis for this decision can be found in the risk assessment for Natamycin, which is characterized in this BRAD.

II. ACTIVE INGREDIENT OVERVIEW

Common Name: Natamycin

Chemical Name: 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.$0^{5,7}$]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: Fungistat

III. REGULATORY BACKGROUND

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., Alexander Fleminglaan 1, Delft, The Netherlands 2613AX to register the products Natamycin TGAI (EPA File Symbol No. 87485-1), and Natamycin L (EPA File Symbol No. 87485-2) containing the new biochemical active ingredient Natamycin. The application was submitted to both the U.S. Environmental Protection Agency (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[1]. 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.

A. Classification

[1] See *http://www.epa.gov/oppfead1/international/naftatwg/guidance/jointreview-biope.pdf*.

Natamycin was classified as a Biochemical Pesticide by the Agency's Classification Committee on August 17, 2007. The Classification Committee confirmed its nontoxic mode of action, its natural occurrence in the environment, and its history of exposure to humans and the environment without known toxicity.

B**. Food Clearance/Tolerances**

Natamycin is intended for use as a fungistat only on mushrooms grown in enclosed mushroom growing facilities. The Agency considers this use to be a food use. On April 20, 2011 the Agency issued a notice in the federal register (76 FR 22067) of the filing of a petition by DSM for the exemption of residues of on mushrooms.

IV. RISK ASSESSMENT

A. Active Ingredient Characterization

Natamycin is a biochemical active ingredient intended for use as a fungistat to be in enclosed mushroom production facilities for the control of fungi and mold on mushrooms. It is derived from the common soil microorganism, *Streptomyces natalensis* and is commercially produced by submerged aerobic fermentation by *Streptomyces natalensis, Streptomyces lydicus,* and *Streptomyces chattanoogensis.* Fermentation is conducted for several days, and the antibiotic is isolated either by broth extraction or by extraction of the mycelium. Dried Natamycin recovered from the fermentation broth is white to cream-colored and has little or no odor or taste; in the crystalline form it is very stable. During the extraction procedure the Natamycin is dissolved and filtered through a membrane. The membrane is not permeable to the organism and the concentration of the extraction is high enough to kill the organism. None of the microorganism that is used to produce Natamycin is viable at the end of this process.

All product chemistry and composition data requirements for Natamycin have been satisfied. The information submitted to support the product chemistry and composition data requirements for Natamycin are summarized in Tables 1 and 2 in Appendix A.

B. Human Health Assessment

1. Toxicology

For acute toxicity data requirements, toxicity categories are assigned based on the hazard(s) identified from studies and/or information on file with the Agency. The active ingredient is classified into Toxicity Category I, II, III or IV where Toxicity Category I indicates the highest toxicity and Toxicity Category IV indicates the lowest toxicity.

Adequate mammalian toxicology data/information is available to support registration o Natamycin. All toxicology data requirements for Natamycin have been **satisfied.**

a. Acute Toxicity

Acute toxicity testing is required to 1) determine systemic toxicity from acute exposure via the dermal, inhalation and oral routes, 2) determine irritant effects from exposure to the eyes, and 3) determine the potential for skin sensitization (allergic contact dermatitis).

Tier I acute toxicity studies submitted and reviewed showed that Natamycin is Toxicity Category III for acute oral toxicity and Toxicity Category IV for acute dermal toxicity, acute inhalation toxicity, primary eye irritation, and primary dermal irritation. Natamycin is not a sensitizer. Natamycin is not a mutagen and is not cytotoxic.

For more information regarding acute toxicity data requirements, refer to Table 3 in Appendix A.

b. Subchronic Toxicity

Subchronic data are required to determine a no-observed-effect-level (NOEL) and any toxic effects associated with repeated or continuous exposure to a test substance for a period of ninety days. Subchronic (90-day) dermal toxicity and Subchronic inhalation studies were not submitted, but are not required based on a lack of repeated exposure to workers and applicators via these two routes of exposure.

A 90-day oral (OCSPP 870.3100) and 90-day inhalation (OCSPP 870.3465) study was submitted and is acceptable based on the data demonstrating that no biologically significant changes in the hematology or clinical chemistry profiles were observed. The Agency concurs with the findings.

For more information regarding the subchronic data requirements, refer to Table 3 in Appendix A.

c. Developmental Toxicity and Mutagenicity

In lieu of a Guideline study the applicant developed a science based rationale in support of Developmental Toxicity ((OCSPP 870.3700) for Natamycin. The rationale was supported with information and data obtained from the open technical literature. The rationale relies primarily on a comprehensive review of Natamycin by the European Food Safety Authority (EFSA, 2009) and its associated citations. By way of the EFSA review of Natamycin (aka Pimaricin), the rationale demonstrated that Natamycin is poorly absorbed by mammals and that it does not pose any dietary concerns based on current usage. The Agency concurs with this conclusion based on per capita consumption of all mushroom commodities in the United States (USDA/ERS, 2010), dietary intake from treated, unwashed mushrooms is conservatively estimated to be no more than 0.00030 mg a.i./kg bw/person/day. This value is well below any known acute oral, subchronic and chronic dietary, reproductive, and developmental endpoints for Natamycin by many orders of magnitude. In addition, the estimated dietary intake from unwashed, treated mushrooms also is well below the Acceptable Dietary Intake (ADI) of 0.3 established by Joint FAO/WHO Expert

Committee on Food Additives (JECFA, 2001& 2006) and an ADI of 0.1 established European Food Safety Authority (EFSA, 2009). The information submitted by the registrant, along with open technical literature also support the Tolerance Exemption Petition submitted for Natamycin.

For more information regarding developmental toxicity and Mutagenicity data requirements, refer to Table 3 in Appendix A.

d. Tier II and Tier III (40 CFR § 158.2050)

No Tier II and Tier III studies were required, based on a lack of acute toxicity in the Tier I studies and a lack of exposure relative to Natamycin's use pattern as a fungistat to control mold on mushrooms in enclosed mushroom producing facilities.

c. Effects on the Endocrine System

As required under Federal Food, Drug, and Cosmetic Act (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 quantitative relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 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), EPA must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP orders/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/*.

2. Dose Response Assessment

No definitive toxicological endpoints were identified for Natamycin and no effects were observed at maximum hazard doses.

3. Dietary Exposure and Risk Characterization

Dietary exposure to Natamycin is expected to be minimal. Natamycin is a fungistat that has a long history of use in food for the prevention of spoilage. The active ingredient was demonstrated to be minimally toxic in OCSPP Guideline studies using the TGAI (see Appendix A, Table 4). In a review of toxicological literature by the European Food Safety Agency (EFSA, 2009), Natamycin was shown to be poorly absorbed by gastrointestinal systems of mammals and rapidly excreted in the feces (Blankwater and Hespe, 1979; Hespe and Meier, 1980; both reviewed and cited in EFSA, 2009). In addition, Natamycin is rapidly degraded by stomach acids, with a 1-hour half-life in simulated gastric juice (Morgenstern and Muskens, 1976; reviewed and cited in EFSA, 2009).

All inert ingredients used in the end-use product, Natamycin L, are approved for food use under 40 CFR 180.950 and 40 CFR 180.960; and are considered to be Generally Recognized As Safe (GRAS) by FDA.

Acute and Chronic Dietary Exposure and Risks for Sensitive Subpopulations, Particularly Infants and Children

Based on the minimal toxicity of Natamycin demonstrated in laboratory testing of the TGAI (see Table 4), the anticipated minimal dietary exposure, and the mode of action of Natamycin as a fungistat, acute and chronic dietary risks for sensitive subpopulations are not anticipated.

4. Drinking Water Exposure Risk Characterization

Based on the intended use sites (enclosed mushroom production facilities) and use directions (steam sterilization of compost and casing prior to disposal outside of the mushroom growth facility), it is highly unlikely that residues of Natamycin will enter any sources of drinking water. However, in the unlikely event that Natamycin residues escape from its indoor application site (completely enclosed mushroom houses), its concentration in surface waters would never exceed 30-50 ppm due to its low solubility in water; up to 50 ppm @ 20-25°C and pH 5-7.5; and at ~~t~~ <pH2 or >pH 10 it completely degrades (USEPA, 2011). Natamycin is extremely sensitive to UV light and is completely degraded by UV within 24 hours of exposure in aqueous solution (Koontz et. al., 2003). Even assuming that no environmental degradation takes place, should Natamycin be ingested via drinking water, gastric juices typically found in the human stomach will completely degrade Natamycin within 24 hrs (JECFA, 2006). Finally, the non-definitive endpoints for acute oral toxicity (>1820 ppm) and subchronic oral toxicity (>500 ppm in the diet) (USEPA, 2011) are approximately 36X and 10X greater than the highest measured solubility of Natamycin in water. For these reasons, the Agency believes that there are no concerns for exposure of humans to Natamycin in drinking water.

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

Based on use sites (enclosed mushroom production facilities) and use directions (steam sterilization of compost and casing prior to disposal outside of the mushroom growth facility), no Residential, School, or Day-Care exposure is expected.

a. Occupational Exposure and Risk Characterization

Occupational exposure to mixer/loader/applicators is expected to be minimal, but can be mitigated with appropriate Personal Protective Equipment (PPE). **See Discussion of Human Activities below.**

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

A residential, school and day care exposure assessment was not conducted for Natamycin. However, based on use sites of products containing Natamycin (enclosed mushroom production facilities) and use directions (steam sterilization of compost and casing prior to disposal outside of the mushroom growth facility), no Residential, School, or Day-Care exposure is expected.

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

Based on the mode of action of the active ingredient as a fungistat, no aggregate exposure is anticipated.

7. Cumulative Effects

Based on the mode of action of the active ingredient as a fungistat, minimal dietary exposure (see Dietary Exposure and Risk Characterization above) and rapid degradation and excretion from animal systems (EFSA, 2009), no cumulative exposure is anticipated.

Pursuant to FFDCA section 408(b)(2)(D)(v), EPA has considered available information concerning the cumulative effects of Natamycin residues and other substances that have a common mechanism of toxicity. These considerations include the potential for cumulative effects on infants and children of Natamycin residues and other substances with a common mechanism of toxicity. Because Natamycin has a long history of dietary consumption without incident, and because the available data show a lack of acute toxicity in the Tier I studies as well as a lack of exposure relative to Natamycin's use pattern as a fungistat to control mold on mushrooms in enclosed mushroom producing facilities, the Agency concludes that Natamycin does not share a common mechanism of toxicity and that there are no potential cumulative effects arising from incidental exposures to Natamycin residues in or on food commodities.

8. Risk Characterization

The Agency considered human exposure to Natamycin in light of the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the relevant safety factors in FFDCA. 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 Natamycin 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 indoor, enclosed mushroom production facilities, exposure to non-target organisms is not expected. Additionally, 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.

For more information regarding nontarget organism toxicity data requirements, please refer to Table 4 in Appendix A.

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. Endangered Species Assessment

The Agency has not conducted a risk assessment that supports a complete endangered species determination. The ecological risk assessment planned during registration review will allow the Agency to determine whether Natamycin use has “no effect” or “may effect” federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide’s use “may affect” a listed species or its designated critical habitat, the Agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Services (the Services) as appropriate.

D. EFFICACY DATA

Product performance data must be developed for all pesticides to ensure that pesticide 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, submission of efficacy data for any pesticide product registered or proposed for registration that are intended to be used to control a pest of significance public health importance and a public health pest as defined in FIFRA section 28(d) and section 2(nn). For further guidance on product performance 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).

The EPs submitted with this new active ingredient did not list pests of significance public health importance or a public health pest as defined in FIFRA section 28(d) and section 2(nn). Therefore, the Agency does not require product performance for Natamycin under the proposed uses. However, these data are required by Canada/PMRA and was submitted and reviewed by Canada/PMRA as part of the joint review of the active ingredient. We are reporting the results of that review below.

Canada/PMRA Review

Natamycin has proven to be an extremely effective in food preservation because its mode of action is to stop the growth of molds and yeasts before damage begins. Curative fungicidal treatments cannot always negate the harmful effects that a growing mycelium leaves behind. In addition, fungi can produce dangerous mycotoxins, some of which are even carcinogenic, that can cause health problems. Removing the fungi has no effect on mycotoxins once they are embedded. Natamycin is able to protect food products against mold growth for long periods of time due to its stability and crystalline form. It has a low level of solubility in water (~50 ppm) and in organic materials. Specifically, Natamycin can reduce the development of Verticillium disease - a use for which this active ingredient is being registered - of the commercial mushroom. As a fungistat to control Verticillium disease, the best control was noted when 2 mL (form) per sq m were applied. There appears to be little difference between 2 applications (pinning and casing) or 4 applications (pinning, casing, between 1st and 2nd breaks and between 2nd and 3rd breaks). All product performance data required by Canada/PMRA for registration of Natamycin have been **satisfied**.

V. 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, 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. Please comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.

VI. Risk Management and Registration Decision

A. Determination of Eligibility

Section 3(c)(5) of FIFRA provides for the registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted 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 criteria of the Eligibility Determination for Pesticidal Active Ingredients are satisfied by the science assessments supporting products containing Natamycin. Such products are not expected to cause unreasonable adverse effects and are likely to provide protection as claimed when used according to label instructions. Therefore, EPA concludes that Natamycin is eligible for registration for the labeled uses.

B. Regulatory Decision

On October 1, 2009, the EPA announced a new policy to provide a more meaningful opportunity for the public to participate in major registration decisions before they occur. According to this policy, EPA intends to provide a public comment period prior to making a registration decision for, at minimum, 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. Accordingly, this pesticide was subjected to a 30-day comment period as a new active ingredient with outdoor uses.

The Agency believes that the data submitted fulfill the requirements of registration for products containing Natamycin for use as a fungistat for use on mushrooms in enclosed mushroom production facilities. Acute toxicity data for Natamycin demonstrate that it is toxicity category III and IV for all routes of exposure. (No toxicological endpoints were established.) Data confirm that Natamycin does not demonstrate subchronic or developmental toxicity, and it is not mutagenic or genotoxic. EPA has no concerns for any nontarget organisms exposed to Natamycin in accordance with its approved uses. EPA has not identified any toxic endpoints for nontarget mammals, birds, plants, aquatic, or soil organisms. Nor are there any anticipated concerns for any threatened and endangered species. Given the nontoxic character of Natamycin and because all applicable data requirements have been fulfilled, EPA supports its registration under FIFRA section 3(c)(5).

C. Labeling

Before releasing pesticide products containing Natamycin for shipment, the applicant is required to provide appropriate labels. Such labeling for the technical grade active ingredient (TGAI) must include personal protection equipment (PPE) requirements as follows:

“Mixer/loader/applicators are required to wear the following Personal Protection Equipment (PPE):

- **eye protection**
- **long pants**
- **long-sleeved shirt**
- **closed shoes**
- **gloves**

VII. ACTIONS REQUIRED OF THE REGISTRANT

The Agency evaluated the data submitted in connection with the initial registration of Natamycin and determined that these data fulfill current registration guideline requirements. No additional data are required to be submitted to the Agency at this time. Additional data may be required for new uses and/or changes to existing uses.

Notwithstanding the information stated in the previous paragraph, it should be clearly understood that certain, specific data are required to be reported to the Agency 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 and Hypersensitivity Incidents

Reports of all incidents of adverse effects to the environment must be submitted to the Agency under the provisions stated in FIFRA section 6(a)(2).

Additionally, all incidents of hypersensitivity (including both suspected and confirmed incidents) must be reported to the Agency under the provisions of 40 CFR § 158.2050(e).

VIII. GLOSSARY OF ACRONYMS AND ABBREVIATIONS

ADI	average daily intake
BPB	Biochemical Pesticides Branch
BRAD	Biopesticides Registration Action Document
CA	chromosomal aberrations
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
EDSP	Endocrine Disruptor Screening Program
EP	End-use Product
EPA	United States Environmental Protection Agency (Agency)
FDA	United States Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
g	gram
g/mL	gram per milliliter
Hg	mercury
HSDB	Hazardous Substances Data Bank
LC_{50}	median lethal concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed (e.g., mg/L, mg/kg, or ppm).
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, dermal, or inhalation). It is expressed as a weight of substance per unit weight of animal (e.g., mg/kg).
LOC	level of concern
LOEL	lowest observed effect level
µg	microgram
µm	micrometer
MRID No.	Master Record Identification Number
mg/kg	milligram per kilogram
mg/L	milligram per liter
mg/ml	milligram per milliliter
ml	milliliter
mm	millimeter
MP	Manufacturing-use Product
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OCSPP	Office of Chemical Safety and Pollution Prevention
OPP	Office of Pesticide Programs
Pa	pascal
PC Code	Pesticide Chemical Code

ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
RQ	risk quotient
SCE	sister chromatid exchange

IX. Appendix A. Data Requirements (40 CFR Part 158-Subpart U)

*NOTE: Master Record Identification (MRID) numbers listed in the following tables are representative of supporting data/information for the original registration of the product containing this active ingredient. Subsequent to this registration, there may be additional MRIDs that support registration of other products containing this active ingredient.

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	48105504

TABLE 2. Physical and Chemical Properties of Natamycin *Technical* (40 CFR § 158.2030)			
OCSPP Guideline No.	**Property**	**Description of Results**	**MRID**
		containers.	
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	
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	48105503

TABLE 2. Physical and Chemical Properties of Natamycin *Technical* (40 CFR § 158.2030)			
OCSPP Guideline No.	**Property**	**Description of Results**	**MRID**
		exploding.	
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.

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Table 4. Acute Toxicity Data for the Technical Grade Active Ingredient Product, Natamycin TGAI (91.02% a.i.); EPA File Symbol No. 87485-R			
Study Type/OCSPP Guideline	**LD_{50}/LC_{50}/Results**	**Toxicity Category**	**MRID**
Acute Oral Toxicity/OCSPP 870.1100	>2000 mg/kg (>1820 mg a.i./kg) **ACCEPTABLE**	III	48105505
Acute Dermal Toxicity/OCSPP 870.1200	>5050 mg/kg (>4696.5 mg a.i./kg) **ACCEPTABLE**	IV	48105506
Acute Inhalation Toxicity/OCSPP 870.1300	>2.39 mg/L (2.18 mg a.i./L)	IV	48105507

Table 4. Acute Toxicity Data for the Technical Grade Active Ingredient Product, Natamycin TGAI (91.02% a.i.); EPA File Symbol No. 87485-R			
Study Type/OCSPP Guideline	**LD_{50}/LC_{50}/Results**	**Toxicity Category**	**MRID**
	ACCEPTABLE		
Primary Eye Irritation/OCSPP 870.2400	No corneal or positive irritation effects at 24-hr post instillation **ACCEPTABLE**	IV	48105508
Primary Dermal Irritation/OCSPP 870.2500	PII = 0.1 **ACCEPTABLE**	IV	48105509
Skin Sensitization-LLNA/OCSPP 870.2600	LLNA SI <3 **ACCEPTABLE**[1]	Not a sensitizer	48105510

TABLE 3a. Natamycin residues in mushrooms from the first break (MRID 48105408)				
Treatment	**Treatment date**	**Sampling date**	**Tray no.**	**Residue (mg/kg)**
Delvocid 2 mL/m^2	At casing, January 26 At pinning, February 2	February 11	29	0.0590
			29	0.0890
			30	0.0267
			30	0.0285
			31	0.0287
			31	0.0178
			32	0.0180
			32	0.0192
			1	0.0230
			1	0.0221
			2	0.0369
			2	<0.01
			3	0.0271
			3	0.0344
			4	0.0340
			4	0.0274
Untreated control	NA	February 11	9	<0.01
			9	<0.01
			10	<0.01
			10	<0.01

TABLE 3b. Natamycin residues in washed and unwashed mushrooms from the second and third breaks (treated three or four times, respectively) MRID 48105408

Treatment	**Treatment date**	**Sampling date**	**Tray no.**	**Residue (mg/kg)**
Delvocid 2 mL/m^2, **unwashed**	At casing, January 26 At pinning, February 2 Between breaks 1 & 2, February 13	February 17	1	0.2370
			1	0.1420
	At casing, January 26 At pinning, February 2 Between breaks 1 & 2, February 13 Between breaks 2 & 3, February 20	February 25	1	0.0407
			1	0.1452
Delvocid 2 mL/m^2, **washed**	At casing, January 26 At pinning, February 2 Between breaks 1 & 2, February 13	February 17	1	<0.01
			1	0.0755
	At casing, January 26 At pinning, February 2 Between breaks 1 & 2, February 13 Between breaks 2 & 3, February 20	February 25	1	0.0123
			1	0.0220
Untreated control	NA	February 17	10	<0.01
		February 25	10	<0.01

X. BIBLIOGRAPHY

MRID	Citation Reference
59399	American Cyanamid Company (1959) Antibiotic A-5283, Myprozine: Acute Toxicity to Rats; Subacute Toxicity to Rats and Dogs: Re- port No. 59-4. (Unpublished study received on unknown date un- der unknown admin. no.; CDL:223651-A)
59400	American Cyanamid Company (1963) Pimaricin (Myprozine^(R)I): Report on Two-Year Toxicity Studies. Summary of studies 223651-C through 223651-H. (Unpublished study received on unknown date under unknown admin. no.; CDL:223651-B)
59401	American Cyanamid Company (1963) Pimaricin: Two-Year Feeding to Dogs: Report No. 63-6. (Unpublished study received on unknown date under unknown admin. no.; CDL:223651-C)
59402	American Cyanamid Company (1963) Pimaricin: Two-Year Feeding to Rats: Report No. 63-7. (Unpublished study, including report no. 63-8, received on unknown date under unknown admin. no.; CDL: 223651-D)
59403	Levinskas, G.J.; Bushey, C.; Kunde, M.L.; et al. (1963) Pimaricin: Successive Generation Studies: Report No. 63-9. (Unpublished study received on unknown date under unknown admin. no.; submit- ted by American Cyanamid Co., Princeton, N.J.; CDL:223651-E)
59404	Shirk, R.J.; Lovesky, R.L. (1963) A Gross Examination of the Fecal Flora of Rats Sustained for Two Years on Diets Containing from 0 to 1000 ppm. Pimaricin: Report FS 3. Progress rept., Jun 21, 1962 to Aug 1, 1962. (Unpublished study received on unknown date under unknown admin. no.; submitted by American Cyanamid Co., Princeton, N.J.; CDL:223651-F)
59405	Shirk, R.J. (1963) The Fecal Excretion and Non-absorption of Pimaricin in Animals: Report FS 3. Progress rept. (Unpublished study received on unknown date under unknown admin. no.; submit- ted by American Cyanamid Co., Princeton, N.J.; CDL:223651-G)
48105400	DSM Food Specialties B.V. (2010) Submission of Product Chemistry, Residue, Toxicity, and Exposure and Risk Data in Support of the Application for Registration of Natamycin L and the Petition for Tolerance of Natamycin for Use on Mushrooms. Transmittal of 11 Studies.
48105401	van der Lee, J.; Jovanovich, A. (2010) Natamycin L: Product Identity, Composition, and Formulation. Unpublished study prepared by Keller and Heckman LLP. 48 p.
48105402	van der Lee, J.; Jovanovich, A. (2010) Natamycin L: Certified Limits. Unpublished study prepared by Keller and Heckman LLP. 9 p.
48105403	van Hilten, P. (2010) Natamycin L: Enforcement Analytical Method. Unpublished

MRID	Citation Reference
	study prepared by Keller and Heckman LLP. 18 p.
48105404	van der Lee, J.; Jovanovich, A. (2010) Natamycin L: Summary of Physical/Chemical Properties and Self-Certification. Unpublished study prepared by Keller and Heckman LLP. 32 p.
48105405	van der Lee, J.; Jovanovich, A. (2011)(Sic) Natamycin L: Interim Report for Storage Stability and Corrosion Characteristics. Project Number: STAB/SLD/09/008. Unpublished study prepared by DSM Food Specialties B.V. 24 p.
48105406	Jovanovich, A. (2010) Residue Data: Chemical Identity and Directions for Use for Natamycin L. Unpublished study prepared by Keller and Heckman LLP. 9 p.
48105407	Marin, J. (2010) Development and Validation of an Analytical Method for the Determination of Natamycin in Mushrooms and Mushroom Compost, Casing and Casing plus Innoculum. Project Number: 1869W. Unpublished study prepared by PTRL West, Inc. 73 p.
48105408	Marin, J. (2009) Magnitude of the Residue of Natamycin in Mushrooms. Project Number: 1915W. Unpublished study prepared by PTRL West, Inc. 165 p.
48105409	Wilms, L.; Jovanovich, A. (2010) Natamycin L: Request for Waiver of 5 Acute Toxicity Tests. Unpublished study prepared by Keller and Heckman LLP. 16 p.
48105410	Kuhn, J. (2009) Natamycin Liquid Formulation: Acute Eye Irritation Study in Rabbits: Final Report. Project Number: 12753/09. Unpublished study prepared by Stillmeadow, Inc. 20 p.
48105411	Wach, M. (2010) Natamycin L: Descriptions of Human Activity for Natamycin L. Unpublished study prepared by Keller and Heckman LLP. 10 p.
48105500	DSM Food Specialties B. V. (2010) Submission of Product Chemistry and Toxicity Data in Support of the Application for Registration of Natamycin TGAI and the Petition for Tolerance of Natamycin for Use on Mushroom. Transmittal of 14 Studies.
48105501	Zuur, P.; Hee, P.; Roghoenath, D.; et al. (2010) Natamycin TGAI: Product Identity, Composition, and Production. Unpublished study prepared by Keller and Heckman LLP. 252 p.
48105502	Zeeman, M.; Boogers, I.; Van der Lee, J.; et al. (2010) Natamycin TGAI: Preliminary Analysis and Certified Limits. Unpublished study prepared by Keller and Heckman LLP. 140 p.
48105503	Van der Lee, J.; Jovanovich, A. (2010) Natamycin TGAI: Physical and Chemical Properties. Unpublished study prepared by Keller and Heckman LLP. 9 p.
48105504	Van der Lee, J.; Jovanovich, A. (2010) Stability to Normal and Elevated Temperatures, Metals, and Metals Ions. Unpublished study prepared by Keller and Heckman LLP. 27 p.

MRID	Citation Reference
48105505	Kuhn, J. (2008) Natamycin TGAI: Acute Oral Toxicity Study (UDP) in Rats: Final Report. Project Number: 11403/07. Unpublished study prepared by Stillmeadow, Inc. 12 p.
48105506	Kuhn, J. (2008) Natamycin TGAI: Acute Dermal Toxicity Study in Rat: Final Report. Project Number: 11404/07. Unpublished study prepared by Stillmeadow, Inc. 13 p.
48105507	Crutchfield, V. (2008) Natamycin TGAI: Acute Inhalation Toxicity Study in Rats: Final Report. Project Number: 11405/07. Unpublished study prepared by Stillmeadow, Inc. 19 p.
48105508	Kuhn, J. (2008) Natamycin TGAI: Acute Eye Irritation Study in Rabbits: Final Report. Project Number: 11406/07. Unpublished study prepared by Stillmeadow, Inc. 18 p.
48105509	Kuhn, J. (2008) Natamycin TGAI: Acute Dermal Irritation Study in Rabbits: Final Report. Project Number: 11407/07. Unpublished study prepared by Stillmeadow, Inc. 13 p.
48105510	Kuhn, J. (2008) Natamycin TGAI: Skin Sensitization: Local Lymph Node Assay in Mice: Final Report. Project Number: 11408/07. Unpublished study prepared by Stillmeadow, Inc. 13 p.
48105511	Otterdijk, F. (2003) Natamycin TGAI: 90 Day Oral Toxicity Study with Natamycin in the Rat. Project Number: NOTOX/PROJECT/339323, 002019. Unpublished study prepared by Notox B.V. 220 p.
48105512	Knickerbocker, M. (1979) Natamycin TGAI: Teratologic Evaluation of Pimaricin in Dutch-Belted Rabbits. Project Number: 5906. Unpublished study prepared by Food & Drug Research Laboratories, Inc. 290 p.
48105513	Verspeek, C. (2002) Natamycin TGAI: Evaluation of the Mutagenic Activity of Natamycin in the Salmonella typhimurium Reverse Mutation Assay and the Escherichia coli Reverse Mutation Assay (with Independent Rat). Project Number: NOTOX/PROJECT/339345. Unpublished study prepared by Notox B.V. 29 p.
48105514	Meerts, I. (2002) Natamycin TGAI: Evaluation of the Ability of Natamycin to Induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes. Project Number: NOTOX/PROJECT/339356. Unpublished study prepared by Notox B.V. 28 p.
48439300	DSM Food Specialties (2011) Submission of Product Chemistry Data in Support of the Application for Registration of Natamycin L. Transmittal of 1 Study.
48439301	van der Lee, J.; Jovanovich, A. (2011) 12-Month Interim Report for Storage Stability and Corrosion Characteristics: Natamycin L. Project Number: STAB/SLD/09/008. Unpublished study prepared by DSM Food Specialties B.V. 38 p.

MRID	Citation Reference
48544501	van der Lee, J.; Jovanovich, A. (2011) 18-Month Final Report for Storage Stability and Corrosion Characteristics: Natamycin L. Project Number: STAB/SLD/09/008. Unpublished study prepared by DSM Food Specialties B.V. 41p.
48593401	Cox, G.; Bailey, D. (1973) Natamycin TGAI Rat Development Toxicity Study. Project Number: 1052. Unpublished study prepared by Food & Drug Research Laboratories, Inc. 495p.
48613501	Thate, C.; Jovanovich, A. (2011) Natamycin TGAI: Request for Waiver of Teratology Study Data Requirement. Unpublished study prepared by Keller and Heckman LLP and DSM Food Specialities. 177p.

B. EPA Risk Assessment Memoranda

U.S. EPA. 2010- Jones, Russell, Science Review in Support of Natamycin Technical, Containing 91.02% Natamycin as Its Active Ingredient. Memorandum dated 10/15/2010

2011a. Jones, Russell, Science Review in Support of Natamycin Technical, Containing 91.02% Natamycin as Its Active Ingredient. Memorandum dated 04/04/2011

U.S. EPA. 2011b. Jones, Russell, Science Review in Support of Natamycin Technical, Containing 91.02% Natamycin as Its Active Ingredient. Memorandum dated 07/11/2011.

U.S. EPA. 2011c. Jones, Russell, Science Review in Support of Natamycin Technical, Containing 91.02% Natamycin as Its Active Ingredient. Memorandum dated 12/13/2011 06/16/2011.

C. References

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2001. Safety Evaluation of Certain Food Additives and Contaminants. Natamycin (Pimaricin). WHO Food Additives Series: 48 http://www.inchem.org/documents/jecfa/jecmono/v48je06.htm

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2006. Summary and Conclusions. Sixty-Seventh Meeting. Rome, 20-29 June 2006. ftp://ftp.fao.org/ag/agn/jecfa/jecfa67_final.pdf (Accessed 04/04/2011)

European Food Safety Authority (EFSA). 2009. Scientific opinion on the use of Natamycin (E 235) as a food additive. EFSA Panel of Food Additives and Nutrient Sources added to Food (ANS). EFSA Journal 7(12):1412, 25 p. http://www.efsa.europa.eu/en/efsajournal/doc/1412.pdf (Accessed 04/04/2011)

USDA/ERS. 2010. Mushrooms: Supply and Utilization and Per Capita Consumption. February 2010 Update. www.ers.usda.gov/data/food**consumption**/spreadsheets/**mushroom**.xls (Accessed 04/04/2011).

World Health Organization (WHO). 2009. The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1968, 1976, 2002, 2006, and 2007. See EFSA 2009 for specific reference citations.

European Food Safety Authority (EFSA). 2009. Scientific opinion on the use of Natamycin (E 235) as a food additive. EFSA Panel of Food Additives and Nutrient Sources added to Food (ANS). EFSA Journal 7(12):1412, 25 p. http://www.efsa.europa.eu/en/efsajournal/doc/1412.pdf (Accessed 04/04/2011)

USDA/ERS. 2010. Mushrooms: Supply and Utilization and Per Capita Consumption. February 2010 Update. www.ers.usda.gov/data/food**consumption**/spreadsheets/**mushroom**.xls (Accessed 04/04/2011).

REFERENCES CITED BY EFSA (2009).

Blankwater, Y. J. and W. Hespe. 1979. Autoradiographic and bioautographic study of the distribution of oral Natamycin in the rat. Unpublished report No. 20.502, dated 8 May 1979 from Gist-Brocdades NV, Delft.

Cox, G. E., D. E. Bailey, and K. Morgareidge. 1973. Multigeneration studies in rats with Delvocid brand of Pimaricin. Unpublished report No. 1-1052 submitted to WHO by Food and Drug Research Laboratories, Inc.

Hespe, W. and A. M. Meier. 1980. Studies involving in regard to the resorption of radioactivity following the oral administration of 14C-pimaricin, applied on cheese, in comparison to other oral forms of administration. Unpublished report No. 20.532, dated 4 February 1980, submitted to WHO by Gist-Brocades NV, Haarlem.

Hutchinson, E. B., W. E. Ribelin, and G. J. Levinskas. 1966. Report on acid-degraded Pimaricin: Ninety-eight day repeated feeding to rats. Unpublished report submitted to WHO by American Cyanamid Co., Central Medical Department.

Levinskas, G. J., C. B. Shaffer, C. Bushey, M. L. Kunde, D. W. Stackhouse, L. B. Vidone, B. Javier, and E. Monell. 1963. Two year feeding study in rats. Unpublished report from the Central Medical department. Submitted to WHO by American Cyanamid Co.

Levinskas, G. J., W. E. Ribelin, and C. B. Shaffer. 1966. Acute and chronic toxicity of Pimaricin. Toxicology and Applied Pharmacology 8: 97-109.

Morgenstern, A. P. and G. J. A. M. Muskens. 1976. Further data on the toxicity of the decomposition products of Pimaricin. Unpublished report Gist-Brocades NV, Delft, 4 pages.

Pacifici, G. M. and R. Nottoli. 1995. Placental transfer of drugs administered to the mother. Clinical Pharmacokinetics 28(3): 235-269.

Van Ecken, C. J., R. D. R. Birtwhistle, and M. J. e. Aboulwafa-wan Velthoven. 1984. Three months study in dogs of the toxicity of Natamycin by addition to the food. Unpublished report 12.401, 24 October 1984. Submitted to WHO by Gist-Brocades Research and Development.

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