UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLUTION PREVENTION/OFFICE OF PESTICIDE PROGRAMS

MEMORANDUM

DATE: 04 April 2011

SUBJECT: Science Review in Support of the Registration of Natamycin TGAI, a Technical Grade Active Ingredient (TGAI) Product; and Natamycin L, an End-Use Product (EP), Respectively Containing 91.02% and 10.34% Natamycin, a New Active Ingredient. Hazard Assessment for Tier I Toxicity Studies and Waiver Requests, Tier I Non-Target Organism Waiver Requests, and Metabolism/Residue Studies.

Decision Numbers:	434160 & 434161
DP Numbers:	378661 & 378664
EPA File Symbol Numbers:	87485-R & -E
Chemical Class:	Biochemical
PC Code:	051102
CAS Number:	7661-93-8
Tolerance Exemptions:	Pending
MRID Numbers:	481055-01 to -13

FROM: Russell S. Jones, Ph.D., Senior Biologist
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TO: Cheryl Greene, Regulatory Action Leader
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Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

On behalf of DSM Food Specialties B.V. (DSM), A. Jovanovich (Keller & Heckman, LLP) requests registration of Natamycin, a new active ingredient which is intended to be used to control fungal diseases in mushroom production. The registrant has submitted product

chemistry, Tier I toxicity, and Tier I non-target organism information and studies in support of the registration of a Technical Grade Active Ingredient (TGAI), an End-use Product (EP), two Confidential Statements of Formula (CSFs), and a request for an exemption from the requirement of tolerances for the active ingredient. This registration application is conducted under the Joint Review program (US and Canada only). Canada PMRA will conduct primary reviews of Product Chemistry and Product Performance.

RECOMMENDATIONS AND CONCLUSIONS

1a. The submitted Product Chemistry studies, data, and information are **ACCEPTABLE**, **pending** submission of acceptable 1 year storage stability and corrosion characteristics studies for the TGAI and EP. Primary reviews were conducted by Canada PMRA. The Agency concurs with the conclusions made by PMRA

1b. All intentionally added inert (other) ingredients are cleared for food use under 40 CFR 180.950 and/or 40 CFR 180.960. An inert initially questioned by PMRA in their review for the EP has been cleared for food use under 40 CFR 180.910.

2. **ACCEPTABLE** information, studies, and data were submitted in support of Chemical Identity & Use Directions (OCSPP 860.1100 and 860.1200), Residue Analytical Methods (OCSPP 860.1340), and Crop Field Trials (OCSPP 860.1500).

3a. Tier I Toxicity studies, data, and waiver requests for the Natamycin TGAI (91.02% a.i.) are ACCEPTABLE, except for the Skin Sensitization-Modified LLNA Study (OPPTS 870.2600; see Conclusion 2b) and the Prenatal Developmental Toxicity Study (OPPTS 870.3700; see Conclusion 2c).

3b. The Prenatal Developmental study is **UNACCEPTABLE and cannot be upgraded.** A new study must be conducted according to OCSPP 870.3700. The highest dose used in the study (50 mg/kg/day), was substantially below the recommended limit dose (1000 mg a.i./kg/day) for a developmental toxicity study in rabbits; the housing conditions and husbandry were very poor, likely caused considerable stress on the animals; and the study did not comply with any GLP standards (40 CFR part 160) (see Study Summaries for details).

3c. Except for eye irritation, Acute Toxicity Guideline studies were not submitted for the End-use Product (EP), Natamycin L (10.34% a.i.). The primary eye irritation study is **ACCEPTABLE.**

3d. In lieu of Acute Toxicity Guideline studies to support the EP, the registrant submitted waiver requests with supporting information from the technical literature for the remainder of the acute exposure studies (also see Conclusion 7).

3e. The waiver requests are deemed **ACCEPTABLE**, based on the low acute toxicity of the TGAI, the existing tolerance exemptions granted for the intentionally added inert ingredients (see Conclusion 1b), the minimal toxicity of the inert ingredients and that, collectively, the inert ingredients (minus an innocuous diluent) comprise less that 9% of the product by weight (see Confidential Appendix).

4a. Tier I Non-Target Organism studies were not submitted, but are not required. 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.

4b. Based on its use pattern and use instructions, EPA has determined Natamycin will have "**No Effect**" on any currently listed threatened or endangered species or any designated critical habitat.

5. Product Performance (efficacy) studies, data, and information are currently under review by Canada PMRA.

6. The information provided in the Descriptions of Human Activity (OPPTS 875.2800) are **ACCEPTABLE**, pending revision of PPE statements on the EP product label to require **"long pants, long-sleeved shirt, closed shoes, gloves, and eye protection"** to mitigate dermal and ocular exposure in the absence of Guideline Acute toxicity studies.

7. The information submitted by the registrant, together with open technical literature obtained by the BPB reviewer, support the Tolerance Exemption Petition for Natamycin, pending resolution of deficiencies identified in Conclusion 1a and 3b above.

EXECUTIVE SUMMARY

Natamycin is a naturally-occurring biochemical compound originally derived from the common soil microorganism, *Streptomyces natalensis*, in South Africa in the early 1950s. *Streptomyces chattanoogensis* and *Streptomyces lydicus* (other sources of natamycin) were later found in North America and testing determined that they were the same organisms as *Streptomyces natalensis*. Therefore, the microorganism, *Streptomyces natalensis*, as well as its biochemical product, Natamycin, are demonstrated to be naturally-occurring in North American soils. *Streptomyces lydicus* is registered in the United States by U.S. EPA under Registration Nos. 73314-1, -2, and -

4 as a microbial pesticide for greenhouse, nursery, turfgrass, agricultural, and seed treatment uses; and is registered by the Canadian PMRA under Registration Nos. 28672 and 28673.

Natamycin has been used for more than 40 years to prevent food spoilage by molds and yeasts, and as a pharmaceutical to prevent eye infections. It is approved as a direct food additive in more than 70 countries. 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 was classified as a Biochemical Pesticide active ingredient by BPPD's Biochemical Classification Committee in November 2007.

The Natamycin Technical Grade Active Ingredient TGAI is classified in 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. Subchronic (rat) feeding studies demonstrate that the Lowest Observable Adverse Effect Level (LOAEL) was 2000 ppm in the diet (204 mg/kg bw/day for males and 238 mg/kg bw/day for females) based on significantly lower body weight. The No Observable Adverse Effect Level NOAEL was 500 ppm in the diet (42 mg/kg bw/day for males and 48 mg/kg bw/day for females). Natamycin is not a mutagen and is not cytotoxic. 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 review of the literature demonstrates that Natamycin is not a developmental or reproductive toxicant at up to 50 mg/kg bw/day in rats and up to 15 mg/kg bw/day in rabbits.

Crop field trials indicate that maximum residues on button mushrooms following application of Natamycin at the maximum label use rate results in residues up to 0.2370 mg a.i./kg in unwashed mushrooms or up to 0.0755 mg a.i./kg in washed mushrooms. 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. 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 end-use product (EP), Natamycin L is not an eye irritant (Tox IV), indicating that the individual active and inert ingredients are not likely to be eye irritants. Guideline studies were not submitted for the remainder of the EP acute toxicity data requirements. In lieu of Acute Toxicity Guideline studies to support the EP, the registrant submitted waiver requests with supporting information from the technical. An Acceptable waiver rationale was presented for the remainder of the acute toxicity data requirements. The rationale was based upon the

Inert ingredient information may be entitled to confidential treatment

following (see Confidential Appendix for details):

1. The minimal toxicity of the active ingredient (10.34% of the EP by weight) demonstrated by Tier I Guideline toxicity studies (see Table 4 below and Conclusion 2b);
2. All intentionally-added inert ingredients are cleared for food use under 40 CFR 180.950 and 189.960; and all inert ingredients are considered GRAS by FDA (see Table 3 and Appendix Table 3); in addition, and independent literature search by the BPB reviewer determined that all intentionally-added inerts are considered to be minimally toxic to humans (http://toxnet.nlm.nih.gov/); none are known as irritants or sensitizers;
3. The major intentionally-added inert ingredient is an innocuous, well-known and characterized, ubiquitous substance used as a diluent and is present at approximately [redacted] of the EP by weight (see Table 3 and Appendix Table 3);
4. The remaining inert ingredients comprise slightly over [redacted] see Table 3 and Appendix Table 3);
5. Upon dilution of the EP with water prior to use (in accordance with label use directions), the concentrations of intentionally-added inerts will be well below any known toxic endpoints for these ingredients.

Natamycin is intended solely for indoor use in enclosed mushroom production facilities. All compost and casing used in mushroom production will be autoclaved prior to being removed from the mushroom growing facilities to destroy any natamycin residues and preventing them from entering the outdoor environment. Based on its use pattern and use instructions, EPA has determined Natamycin will have "**No Effect**" on any currently listed threatened or endangered species or any designated critical habitat.

STUDY SUMMARIES

Product Chemistry (Primary Review by Canada PMRA; see attached Canada DERs in Confidential Appendix)

Product Identity And Composition (OSCPP 880.1100; MRID).

Natamycin is a polyene macrolide antimycotic biochemical compound (i.e. an anti-fungal agent) originally derived from the common soil microorganism, *Streptomyces natalensis* (see Figure 1).

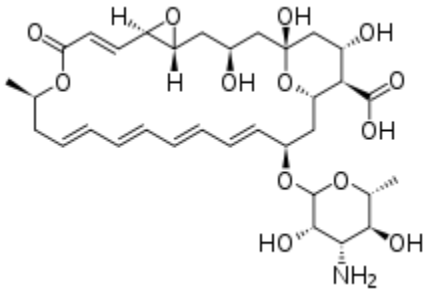

Figure 1. Natamycin

Chemical Identity & Directions for Use (OCSPP 860.1100 & 860.1200; MRID 48105406)

Chemical Identity: Natamycin TGAI (containing 91.02% Natamycin as its active ingredient)

Natamycin L (containing 10.34% Natamycin as its active ingredient) is an end use product to be used to prevent dry bubble disease (*Verticillium fungicola*) on commercially-produced button mushrooms (*Agaricus bisporus*).

Formulated Product Name:	Natamycin L
Active Ingredient (a.i.):	Natamycin
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
CAS Index Name for a.i.:	6,11,28-trioxatricyclo[22.3.1.$0^{5,7}$]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid, 22-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-, (1R,3S,5R,7R,8E,12R,14E,16E,18E,20E,22R,24S,25R,26S)-
CAS Registry No. for a.i.:	7661-93-8
Other a.i. Common Names:	Pimaricin Tennectin Delvocid
Molecular Formula of a.i.:	$C_{33}H_{47}NO_{13}$
Molecular Weight of a.i.:	665.725 g/mol

Nominal conc. a.i. (TGAI): 91.02% w/w

Nominal conc. a.i. (EP): 10.13% w/w (as listed in MRID 48105406; see Note to RAL below).

Directions for Use: The directions for use given on the proposed label are listed in Table 1 below. The four recommended application times are also normal points for irrigation during a crop cycle. Natamycin L is added to the irrigation water in enclosed mushroom production facilities.

Table 1a. Natamycin L Directions for Use

For use in mushroom production	
Target pest	Dry bubble disease caused by *V. fungicola*
Application time	May be applied: 1. immediately after casing 2. at pinning 3. between first and second breaks 4. between second and third breaks Two applications, one at casing and one at pinning, may provide adequate control
Application rate after casing and at pinning	Apply 0.6 to 2.0 mL Natamycin L diluted in 2.5 liters tap water per square meter
Application rate when applied between breaks	Apply 0.6 to 2.0 mL Natamycin L diluted in 2.5 liters tap water per square meter
Maximum number of applications	Four. **NOTE**: Two applications, one at casing and one at pinning, may provide adequate control
Pre-harvest interval	DO NOT apply within less than 4 days of harvest
Disposal of compost and casing	The spent medium must be steamed within the mushroom house at the end of each production run for no less than 24 hours at a temperature of 65°C or greater before disposal outdoors.

Starting Materials, Production Process, Formulation Process (TGAI & EP: OSCPP 880.1200)

ACCEPTABLE. BPB concurs with Canada PMRA reviews for the TGAI and the EP (See PMRA Chemistry data review for the registration of a technical grade of active ingredient (TGAI) or an integrated system product (ISP); & Chemistry data review for the registration of a manufacturing concentrate (MA) or an end-use product (EP) (see CONFIDENTIAL APPENDIX for details).

Discussion of the Formation of Impurities (OSCPP 880.1400)

ACCEPTABLE. BPB concurs with Canada PMRA reviews for the TGAI and the EP (See

PMRA Chemistry data review for the registration of a technical grade of active ingredient (TGAI) or an integrated system product (ISP); & Chemistry data review for the registration of a manufacturing concentrate (MA) or an end-use product (EP) (see CONFIDENTIAL APPENDIX for list of impurities and details).

Preliminary Analysis (OSCPP 830.1700)

ACCEPTABLE. BPB concurs with Canada PMRA reviews for the TGAI (See PMRA Chemistry data review for the registration of a technical grade of active ingredient (TGAI) or an integrated system product (ISP). Preliminary analysis data submitted for the TGAI also fulfill the US EPA data requirements for the EP. (see CONFIDENTIAL APPENDIX for details).

Certified Limits (OSCPP 830.1750)

ACCEPTABLE. BPB concurs with Canada PMRA reviews for the TGAI and the EP [See PMRA Chemistry data review for the registration of a technical grade of active ingredient (TGAI) or an integrated system product (ISP); & Chemistry data review for the registration of a manufacturing concentrate (MA) or an end-use product (EP)] (see CONFIDENTIAL APPENDIX for details).

Enforcement Analytical Method (OSCPP 830.1800)

ACCEPTABLE. BPB concurs with Canada PMRA reviews for the TGAI [See PMRA Chemistry data review for the registration of a technical grade of active ingredient (TGAI) or an integrated system product (ISP)]. Analytical methods information submitted for the TGAI also fulfill the US EPA data requirements for the EP. (see CONFIDENTIAL APPENDIX for details).

Physical and Chemical Properties

Table 2a. Physical and Chemical Properties for Natamycin TGAI.

OSCPP Gln No.	Title	Test substance purity (%)	MRID / Report #	Status[1]	Result[2] or Deficiency
830.6302	Colour	91	Ref 1	A	White to pale cream
830.6303	Physical state	91	Ref 1	A	Powder of flat crystals, >80%<25µm >95% <50µm
830.6304	Odour	91	Ref 1	A	Odourless to lightly acidulous.
830.7200	Melting point/range	91	Ref 1	A	Does not melt; darkens at 200°C; vigorously decomposes at 280-300°C.

Table 2a. Physical and Chemical Properties for Natamycin TGAI.

OSCPP Gln No.	Title	Test substance purity (%)	MRID / Report #	Status[1]	Result[2] or Deficiency
830.7220	Boiling point/range			N/A	The product is a solid.
830.7300	Density or specific gravity at 25°C	91	Ref 1 Ref 3	A	Loose bulk density 0.3 g/mL Tapped bulk density 0.59 g/mL 303 – 588 g/L
830.7840	Water solubility	91	Ref 1	A	30-50 ppm @ 20-25°C and pH 5-7.5; very soluble at pH ≥ 10 or pH ≤ 2 but rapidly degrades.
830.7860	Solvent solubility at 20°C	91	Ref 1	A	Methanol = 0.3%; Ethanol = 40 ppm; Acetone = 10 ppm; Ethyl acetate = 10 ppm; Glacial acetic acid = 25%
830.7950	Vapour pressure			N/A	The product is a solid.
830.7000	pH	91	Ref 1	A	1% suspension in water, pH = 5.0-7.5, generally 6.5.
830.7370	Dissociation constant (pK_a)	91	Ref 1	A	Isoelectric point pH 6.5; pKa 8.35 and 4.6
830.7550 830.7560 830.7570	Octanol/water partition coefficient (K_{ow})	91	Ref 1	A	Log K_{ow} = – 3.67
830.7050	UV/visible absorption spectrum	91	Ref 1	A	Absorption maxima at 292, 305 and 320 nm. No absorption maxima above 350 nm.
830.6313	Stability (temperature, metals, sunlight)	89.1	Ref 1 Ref 2	A	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.
830.6317	Storage stability			N/A	*For ISP only*

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] For example, "brown" for 830.6302; "155°C" for 830.7200.

Table 2b. Physical and Chemical Properties for Natamycin L (EP).

OSCPP Gln No.	Title	MRID / Report #	Status[1]	Result[2] or Deficiency
830.6302	Colour	Ref 1	A	Colourless

Table 2b. Physical and Chemical Properties for Natamycin L (EP).

OSCPP Gln No.	Title	MRID / Report #	Status[1]	Result[2] or Deficiency
830.6303	Physical State	Ref 1	A	Viscous liquid
830.6304	Odour	Ref 1	A	Odourless
PMRA 3.5.4	Formulation Type	Ref 1,3	A	Suspension (SU)
PMRA 3.5.5	Container Material and Description	Ref 4	A	HDPE plastic bucket, jerry can, drum or jumbo container (5 to 1000 Litres) (The draft label has 5 to 125 Litres)
830.7300	Density	Ref 1,3	A	1.08 g/mL
830.7000	pH	Ref 3 Ref 1	A	6.5 (1% aqueous solution) 6.5 (1% aqueous solution). May vary between 5 to 7.5
830.6314	Oxidizing or Reducing Action		N/A	Not applicable. Does not contain oxidizing or reducing chemicals.
830.7100	Viscosity	Ref 1,3	A	~2200 mPa.s, Brookfield Test Method: RPM-20, Axe=3, T=20°C.
830.6317	Storage Stability Data	Ref 1,5	Study in Progress	Based on an interim report for storage stability, the average decrease in active ingredient concentration was ~ 0.28% after 6 months storage in HDPE plastic bottles at 25°C. The 12 month interim report will be ready in a few weeks. The applicant has indicated that the final report for the full 18 months test will be provided before June 30, 2011.
830.6315	Flammability		N/A	Does not contain any flammable. Consists of ~ 80% water.
830.6316	Explodability		N/A	Not applicable. Does not contain any substance capable of exploding
830.6319	Miscibility		N/A	Not formulated to be mixed with petroleum solvents.
830.6320	Corrosion Characteristics	Ref 1,5	Study in Progress	The 9 and 12 month interim report will be ready in a few weeks, while the final report for the full 18 months test will be provided before June 30, 2011.
830.6321	Dielectric Breakdown Voltage		N/A	Not applicable. Not intended to be used around electrical equipment.

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] For example, "brown" for 830.6302; "1.021" for 830.7300.

NOTE to RAL: The Confidential Statement of Formula and the draft product label for Natamycin L list the nominal concentration of Natamycin as 10.34%. BPPD will defer to the CSF and product label as listing the correct amount of active ingredient in the end-use product.

Residue Analytical Method (OCSPP 860.1340; MRID 48105407): The registrant developed and validated a residue analytical method to determine residues of natamycin in mushrooms, mushroom compost, casing, and casing plus inoculum. Samples were extracted in methanol, filtered, then analyzed by liquid chromatography with mass spectrometry/mass spectrometry detection (LC-MS/MS). The analyte was quantified by comparison with external calibration curve using Natamycin (88.7% purity). The analyte in mushroom samples and casing plus inoculum samples were quantified using solvent-based reference standard (88.7% Natamycin), whereas the analyte in compost and casing was quantified relative to matrix-based reference standard. Samples were fortified with 0.1 or 1.0 mg/kg natamycin. Overall recovery for mushrooms was 89 ± 11%. Overall recovery for compost was 84 ± 12%, and for casing was 99 ± 16%. Overall recovery for casing plus inoculum was 66 ± 8%. The limit of quantitation (LOQ) was 0.01 mg/kg (ppm) for mushrooms and 0.1 mg/kg for the other matrices. There were no interfering substances. The limit of detection (LOD) was 0.25 ng/mL for the reference substances. Details of the Residue Analytical Method may be found in MRID 48105407.

Classification: **ACCEPTABLE.**

Crop Field Trials (OPPTS 860.1500; MRID 48105408): A study was conducted to determine the residues of natamycin in white button mushrooms (*Agaricus bisporus*) and their growth substrate following 1 to 4 treatments with the end-use product, Delvocid L 05096 (containing 10% Natamycin as its active ingredient). The field trial was conducted at the Mushroom Research Facility of the University of Guelph (Vineland Station, Ontario, CANADA). Mushrooms were grown on commercially-prepared compost that was conditioned for 5 days prior to inoculation with mushroom spawn. After 14 days the spawn run was cased with a wet mixture of sphagnum peat moss and agricultural limestone (1:1 dry weight; pH ~7.5). Seven days after casing, the environmental conditions were changed to initiate mushroom formation (pinning). Treatments consisted of 2, 3, or 4 applications of product (2 mL/m^2 at casing, and between the second and third breaks, respectively). Each treatment was replicated four times with a negative (water) control and a positive (Bravo EC; a conventional chemical fungicide product) control. Mushrooms were harvested after two, three, or four applications of the test material and analyzed for natamycin residue using the Residue Analytical Method previously described above. Samples of growth substrate (casing and compost) steam-sterilized for 24 hours at study end were also collected and analyzed for natamycin.

Natamycin residues were not detected in the untreated (water) controls. Residues in mushrooms from the first break receiving two applications of the test material ranged from 0.0180 to 0.0890

mg/kg; residues in mushrooms receiving four applications ranged from below detection to 0.0369 mg/kg (Table 3a).

TABLE 3a. Natamycin residues in mushrooms from the first break

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

Data from p. 27, Table III, MRID 48105408; Trays 29-32 = 2 treatments; Trays 1-4 = 4 treatments; Trays 9-10 = Water controls

The maximum residue in mushrooms from the second and third breaks, treated three times and four times, respectively, was 0.2370 mg/kg, and 0.1452 mg/kg (Table 3b). Rinsing treated mushrooms under running water greatly decreased the natamycin residue. Natamycin residue was stable in mushrooms, casing, and compost after three months of frozen storage (~75% initial values) (see Table VII in MRID 48105408, p. 31) .

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

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

Data from p. 28, Table III, MRID 48105408;

Natamycin residues were not detected in compost or casing after steam sterilization (see Tables V and VI in MRID 48105408, pp. 29 -30).

Classification: **ACCEPTABLE**

Tier I Toxicity

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) **ACCEPTABLE**	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
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

TGAI: The Natamycin TGAI product (EPA File Symbol No. 87485-R) is classified in 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. The remainder of the Tier I toxicity data requirements are discussed below:

90-Day Oral (OCSPP 870.3100; MRID 48105511): Natamycin was administered to rats via the diet at concentrations of 0, 125, 500, or 2000 ppm for 13 weeks (equivalent to 0, 11, 42, and 204 mg/kg bw/day for males and 0, 12, 48, and 238 mg/kg bw/day for females). There were to ten rats per dose for each sex. All test animals survived the experimental period. Statistically significant lower body weight was observed at the high dose (2000 ppm) relative to controls (approximately 20% less). Food and water consumption were not significantly affected in any dose group. No biologically significant changes in the hematology or clinical chemistry profiles were observed. Discolored mandibular lymph nodes in 5/10 males at the high dose were observed at necropsy. Two males at the mid dose and two at the high dose had congestion and erythrophagocytosis in the mandibular lymph nodes under microscopic examination. These findings were not treatment related and no other abnormalities were observed. The **LOAEL (rat) = 2000 ppm in the diet** (204 mg/kg bw/day for males and 238 mg/kg bw/day for females) based on significantly lower body weight. The **NOAEL (rat) = 500 ppm in the diet** (42 mg/kg bw/day for males and 48 mg/kg bw/day for females).

Classification: **ACCEPTABLE.**

90-Day Dermal (OCSPP 870.3250): Studies were not submitted, but none are required. The product is applied in irrigation water to mushrooms growing in enclosed facilities. There will be not be any repeated dermal exposure to Natamycin based on the application method.

90-Day Inhalation (OCSPP 870.3465): Studies were not submitted, but none are required. The product is applied in irrigation water to mushrooms growing in enclosed facilities. There will be not be any repeated inhalation exposure to Natamycin based on the application method.

Prenatal Developmental (OCSPP 870.3700; OECD 414; MRID 48105512): A 5% Natamycin product (Pimaricin) was administered to 15 rabbits/dose by gavage in sterile distilled water at 0, 5.0, 15.0, or 50.0 mg/kg/day from gestation days (GD) 6 through 18. The animals were maintained without treatment after GD 18 and sacrificed on GD 29 for evaluation of uterine content and developmental toxicity. There were no treatment-related effects on survival, clinical signs, body weight, or cesarean parameters. **The maternal Lowest Observable Adverse Effects Level (LOAEL) for Pimaricin in rabbits could not be determined; the maternal NOAEL is >50 mg/kg bw/day.** There were no treatment-related effects in developmental parameters (fetal body weight, sex ratio, or external or skeletal abnormalities). **The developmental LOAEL for Pimaricin in rabbits could not be determined; the developmental No Observable Adverse Effects Level (NOAEL) is >50 mg/kg bw/day.**

There were numerous deficiencies that compromised the usefulness of this study: (i) Testing was not conducted at the recommended limit dose of 1000 mg a.i./kg bw/day (see OCSPP 830.3700 for details). The highest dose used in the study (50 mg/kg/day), was substantially below the recommended limit dose for a developmental toxicity study in rabbits; (ii) the housing conditions and husbandry were very poor, numerous maggots were found in the cage trays of the animals indicating an unclean environment. These poor conditions likely caused considerable stress on the animals; and (iii) this study does not comply with any GLP standards (see 40 CFR part 160). A Quality Assurance (QA) Statement was not included in this report indicating that a QA check on the conduct on this study was not performed.

Classification: **UNACCEPTABLE; the study cannot be upgraded.** A new study must be conducted according to OCSPP 870.3700.

In a review of the toxicological literature, the European Food Safety Authority (EFSA, 2009) reported that in a 3-generation reproductive toxicity study (rat) "Natamycin dietary doses of 5, 15, and 50 mg/kg body weight/day for 11 weeks had no effect on growth, reproduction and on Gross and microscopy pathology;" the **LOAEL = 100 mg/kg body weight/day and the NOAEL = 50 mg/kg body weight/day** (Cox et. al., 1973; reviewed and cited in EFSA, 2009). The same study noted that there were no adverse effects on nidation or maternal or fetal survival at dietary doses of 5 to 50 mg/kg body weight/day for the 11-week experimental period. In other developmental studies (Knickerbocker and Re, 1978 & 1979; reviewed and cited in EFSA, 2009), rabbits dosed with Natamycin by gavage with 5-15 mg/kg body weight on days 6 to 18 of gestation, had a **LOAEL = 50 mg/kg body weight/day and a NOAEL = 15 mg/kg body** weight/day, based on maternal toxicity.

Bacterial Reverse Mutation Test (OCSPP 870.5100; MRID 481005513): Strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and *Escherichia coli* strain WP2uvrA were exposed to Natamycin TGAI in a preliminary range finding assay and in definitive studies. In the preliminary range-finding assay, *S. typhimurium* TA100 and *E. coli* WP2uvrA were tested at 0, 3, 10, 33, 100, 333, 1000, 3330, and 5000 µg/plate. Cytotoxicity was not observed, but slight test material precipitation was reported at ≥3330 µg/plate. The two definitive mutagenicity assays tested Natamycin at 0, 33, 100, 333, 1000, and 3330 µg/plate, both with and without S9 activation, for all five bacterial strains (except for the two strains that were assayed as part of the range-finding test).

In the range-finding study, there were no dose-related or two-fold increase in the number of revertants of *E. coli* WP2uvrA compared to the solvent (negative) controls. Treatment of *S. typhimurium* TA100 with 333 µg/plate natamycin caused up to a 2-fold increase in the mean number of revertants in the presence of activation (200±10 vs. 101±19 colonies), but the response was not dose-related and was not observed in the second experiment. In the remaining mutagenicity assays (Experiments 1 and 2), there was no evidence of cytotoxicity or mutagenicity in any strain at any test concentration, with or without S9-mix. Slight precipitation was observed at 3330 µg/plate, but did not interfere with scoring. The vehicle and positive control values were appropriate for the respective strains and within the provided historical control ranges. **Natamycin did not increase the mean number of revertants per plate relative to the corresponding vehicle control in any strain, with or without S9-mix, when tested up to the limit of solubility.**

Classification: **ACCEPTABLE.**

In vitro Mammalian Cell Assay (OCSPP 870.5300 & 870.5375): Human lymphocytes in culture were exposed to Natamycin TGAI (88.5% a.i) in ethanol at concentrations of 0, 1, 3, and 10 µg/mL (0, 0.89, 2.66, and 8.85 µg a.i./mL) for 3 hours with and without S9-mix, and harvested 24 hours after the beginning of exposure. Duplicate cultures were prepared. In a second assay, cells were treated continuously for 24 or 48 hours with immediate harvest without S9 activation, or were treated for 3 hours followed by a 48-hour harvest with S9 activation. Test concentrations were based on a preliminary range-finding test in which cultures were treated with 0, 0.1, 0.3, 1, 3, or 10 µg/mL natamycin for 3, 24, or 48 hours without activation (21, 0, 0 hour recovery, respectively), or for 3 hours with activation (21-hour recovery). At 10 µg/mL (8.85 µg a.i./mL), the test material precipitated in the culture medium under all growth conditions. No treatment-related effects were observed on the mitotic index.

No evidence of treatment-induced mutagenicity or cytotoxicity was observed in either experiment. In both experiments, at 10 µg/mL the test material precipitated under all growth conditions, but the cells could still be scored for chromosome aberrations. There was no evidence of cytotoxicity, as the mitotic index was 59-78% and 80-116% of the solvent control

value in the first and second experiment, respectively. The fraction of metaphase cells with chromosome aberrations was within the historical solvent control range (0-6% without activation and 0-4% with activation, excluding gaps) for the solvent controls, and for all natamycin-treated cultures in both experiments. Treatment did not increase polyploidy or endoreduplication in the presence or absence of metabolic activation. The positive controls (mitomycin C without activation and cyclophosphamide with activation) caused a statistically significant increase ($p<0.001$) in chromosome aberrations. **No evidence of structural chromosomal aberrations induced were observed over background.**

Classification: **ACCEPTABLE.**

Table 5. Acute Toxicity Data for the End-Use Product, Natamycin L (10.34% a.i.); EPA File Symbol No. 87485-E.

Study Type/OCSPP Guideline	LD_{50}/LC_{50}/Results	Toxicity Category	MRID
Acute Oral Toxicity/OCSPP 870.1100	Waiver requested ACCEPTABLE	-	48105409
Acute Dermal Toxicity/OCSPP 870.1200	Waiver requested ACCEPTABLE	-	48105409
Acute Inhalation Toxicity/OCSPP 870.1300	Waiver requested ACCEPTABLE		48105409
Primary Eye Irritation/OCSPP 870.2400	No corneal or positive irritation effects at 24-hr post instillation ACCEPTABLE	IV	48105410
Primary Dermal Irritation/OCSPP 870.2500	Waiver requested ACCEPTABLE	-	48105409
Skin Sensitization/OCSPP 870.2600	Waiver requested ACCEPTABLE	-	48105409

EP: For the end-use product, Natamycin L [EPA File Symbol No. 87485-E (10.34% a.i.), studies were not submitted for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary dermal irritation, and skin sensitization. In lieu of studies, the registrant requested bridging of the acute toxicity studies and data submitted in support of the TGAI [Natamycin TGAI, EPA File Symbol No. 87485-R (91.02% a.i.) to support the registration of the EP, Natamycin L.

In addition, a rationale was provided in regard to the safety of all intentionally added other (inert) ingredients. The other (inert) ingredients in the EP formulation are cleared for food use under 40 CFR 180.950 and/or 40 CFR 180.960. In addition, these other ingredients also have been listed

Inert ingredient information may be entitled to confidential treatment

as Generally Recognized As Safe (GRAS) by the US Food and Drug Agency (FDA) (see Table 5 below; see Confidential Appendix Table 3 for identities and amounts of the other ingredients). Guideline studies for the TGAI, demonstrate that the active ingredient in the EP (Natamycin L).

Table 5. Food clearances for other ingredients in the End-Use Product, Natamycin L (10.34% a.i.); EPA File Symbol No. 87485-E.

[redacted]

[1] Minimal toxicity according to TOXNET HSDB (http://toxnet.nlm.nih.gov); not known irritants or sensitizers

[2] Data sources in MRID 48105409

NOTE: See Confidential Appendix for details relating to the discussion of the following waiver rationale.

With the exception of an innocuous, well-known and characterized, non-toxic diluent [redacted]

Conclusion: Based on the minimal toxicity of Natamycin (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),

Exposure

Dietary Exposure and Risk Characterization: Dietary exposure to Natamycin is expected to be minimal and well below any known toxic endpoints. In crop residue trials, a maximum of 2.0 mL Natamycin L diluted in 2.5 liters tap water per square meter was applied up to 4 times to white button mushrooms as follows:

1. immediately after casing
2. at pinning
3. between first and second breaks
4. between second and third breaks

Residues in mushrooms from the first break receiving two applications of the test material ranged from 0.0180 to 0.0890 mg/kg; residues in mushrooms receiving four applications ranged from below detection to 0.0369 mg/kg (see Table 3a above). The maximum residue in mushrooms from the second and third breaks, treated three times and four times, respectively, was 0.2370 mg/kg, and 0.1452 mg/kg (see Table 3b above). Rinsing treated mushrooms under running water greatly decreased the Natamycin residues from <0.01 to 0.0755 mg/kg.

US mushroom consumption (fresh market and processed) per person in 2008 (the most recent year for which information is available) from farm and retail sources was estimated to be 3.8 lbs and 3.2 lbs (1.72 kg and 1.45 kg), respectively (USDA/ERS, 2010). Based on an average 70 kg human being and the maximum detected residues in the crop field trials (see Tables 3a and 3b above), dietary exposure to Natamycin, conservatively assuming all mushrooms were unwashed, is estimated to be:

0.2370 mg a.i./kg mushroom X 1.720 kg farm mushroom = 0.4076 mg a.i./person/year (farm)

0.2370 mg a.i./kg mushroom X 1.450 kg retail mushroom = 0.3437 mg a.i./person/year (retail)

Therefore, Total Estimated Consumption (farm and retail) = **0.7513 mg a.i./person/year**, or

(0.7513 mg/a.i.) / 70 kg = **0.0107 mg a.i/kg body weight/year**.

Based on the above calculations, the average daily dietary intake is estimated to be:

(0.0107 mg a.i./kg body weight/year) / (352 days/year) = **0.00003 mg Natamycin/day**

To be protective of children and females of childbearing age, the FQPA 10X safety factor is estimated to be:

10 X 0.00003 = **0.00030 mg Natamycin/day**

In laboratory testing, **acute oral toxicity was observed >1820 mg a.i./kg bodyweight**, or

>1820 mg a.i. / 0.00030 mg/day = **>606666X greater** than the maximum estimated daily intake for humans

The maximum estimated average daily intake of Natamycin from treated mushrooms (0.00030 mg a.i./day) is 3 orders of magnitude below the Acceptable Daily Intakes (ADI) estimated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2001 & 2006) and the European Food Safety Authority (EFSA, 2009), which were 0.3 and 0.1 mg/kg body weight, respectively.

The active ingredient, 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 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 US FDA.

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.

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.

Drinking Water 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), it is highly unlikely that residues of Natamycin will enter any sources of drinking water.

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

Estimated daily dietary exposure to infants and children is estimated to be **0.00030 mg a.i./kg** body weight/day (see Dietary Exposure and Risk Characterization discussion above). In laboratory testing, **acute oral toxicity was observed >1820 mg a.i./kg bodyweight**, or

>1820 mg a.i. / 0.00030 mg/day = **>606666X greater** than the maximum estimated daily intake for humans

In subchronic oral toxicity testing (90-day, rat) of Natamycin, the No Observable Adverse Effects Level (NOAEL) for was **42 mg/kg bw/day for males and 48 mg/kg bw/day for females**) (see MRID 48105511), which is approximately 14000-16000X greater than the estimated daily dietary intake from mushrooms and 140-480X greater that the Acceptable Daily Intakes (ADIs) estimated by JECFA (2001 & 2006) and EFSA (2009), which are 0.3 and 0.1 mg a.i./kg body weight/day, respectively.

Similarly, in a review of the toxicological literature, the European Food Safety Authority (EFSA, 2009) reported that Natamycin was not a developmental or reproductive toxicant in rats at levels of **50 mg/kg body weight/day** for up to 11 weeks and in rabbits at **15 mg/kg body weight/day** dosed by gavage on days 6 to 18 of gestation.

The same study noted that there were no adverse effects on nidation or maternal or fetal survival at dietary doses of 5 to 50 mg/kg body weight/day for the 11-week experimental period. In other developmental studies (Knickerbocker and Re, 1978 & 1979; reviewed and cited in EFSA, 2009), rabbits dosed with Natamycin by gavage with 5-15 mg/kg body weight on, had a **LOAEL = 50 mg/kg body weight/day and a NOAEL = 15 mg/kg body** weight/day, based on maternal toxicity.

Based on the minimal toxicity of Natamycin demonstrated in laboratory testing of the TGAI (see Table 4), the anticipated minimal dietary exposure, rapid degradation and excretion from animal systems (EFSA, 2009), and the mode of action of Natamycin as a fungistat, acute and chronic dietary risks for sensitive subpopulations are not anticipated.

Aggregate Exposure: Based on the minimal dietary exposure (see Dietary Exposure and Risk Characterization above) and rapid degradation and excretion from animal systems (EFSA, 2009), no aggregate exposure is anticipated.

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.

Non-Target Organisms and Environmental Fate

Tier I studies were not submitted but are not required. 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. Based on its use pattern and use instructions, EPA has determined Natamycin will have "**No Effect**" on any currently listed threatened or endangered species or any designated critical habitat.

Product Performance

Product performance (Efficacy) studies were reviewed by Canada PMRA. Product performance studies are not required for non-public health use pesticides such as Natamycin.

Descriptions of Human Activity

The product, Natamycin L, is intended for use in enclosed, commercial mushroom production facilities and will be applied in the irrigation water to the surface of a prepared mushroom bed containing a growth medium (compost). The first application is made 1-5 days after the casing, with up to three additional applications made at approximately 7-day intervals. The single application rate will be 1600 mL/8000 ft^2 (up to 6400 mL/crop/growing season). Typical exposure time to a mixer/loader/applicator will be less than one hour. Once the product is diluted with water (in accordance with label use directions), it will be applied using a hose fitted with a hand wand.

Mixer/loader/applicators are required to wear the following PPE according to MRID 48105411:
Long pants, long-sleeved shirt, closed shoes, gloves, and eye protection

The above statement is at variance with the proposed product label which states:
long pants, long-sleeved shirt, and shoes plus socks

Mixer/loader/applicator exposure will be limited to the time of the spray application. Post application exposure may result from harvesting or data collection activities. Harvesting may require up to 8 hours, whereas data collection (e.g. temperature and CO2 monitoring) may require 10-15 min per day. Worker exposure will be mitigated by wearing the required PPE. In addition, Natamycin residues on the treated mushrooms are expected to be extremely low (see Tables 2 and 3).

Classification: **ACCEPTABLE**; pending revision of the product label to reflect the PPE statement expressed in MRID 48105411.

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R. S. Jones, FT, PY-S: 04/04/2011.

NON-CONFIDENTIAL APPENDIX

(HARDCOPIES OF DERs INSERT HERE)

Inert ingredient information may be entitled to confidential treatment

Natamycin
PC Code: 051102
Product chemistry, Tier I Tox, Tier 1 Non-targets

DP Numbers: 378661, 378664
EPA File Symbol Nos.: 87485-R & -E
Hazard Assessment

CONFIDENTIAL APPENDIX

Appendix Table 3. Food clearances for other ingredients in the End-Use Product, Natamycin L (10.34% a.i.); EPA File Symbol No. 87485-E.

[redacted]

[1] Minimal toxicity according to TOXNET HSDB (http://toxnet.nlm.nih.gov); not known irritants or sensitizers

[2] Data sources in MRID 48105409

Justification in Support of Acute Toxicity Study Waivers for the End-use Product, Natamycin L. (see MRID 48105409)

The end-use product (EP), Natamycin L is not an eye irritant (Tox IV), indicating that the individual active and inert ingredients are not likely to be eye irritants. Guideline studies were not submitted for the remainder of the EP acute toxicity data requirements. In lieu of Acute Toxicity Guideline studies to support the EP, the registrant submitted waiver requests with supporting information from the technical. An Acceptable waiver rationale was presented for the remainder of the acute toxicity data requirements. The rationale was based upon the following (see Confidential Appendix for details):

1. The minimal toxicity of the active ingredient (10.34% of the EP by weight) demonstrated by Tier I Guideline toxicity studies (see Table 4 and Conclusion 2b);

2. All intentionally-added inert ingredients are cleared for food use under 40 CFR 180.950 and 189.960; and all inert ingredients are considered GRAS by FDA (see Appendix Table 3); in addition, an independent literature search by the BPB reviewer determined that all intentionally-added inerts are considered to be minimally toxic to humans (http://toxnet.nlm.nih.gov/); none are known as irritants or sensitizers;
3. The major intentionally-added inert ingredient [redacted] is an innocuous, well-known and characterized, ubiquitous substance used as a diluent and is present at approximately [redacted] of the EP by weight (see Appendix Table 3);
4. The remaining inert ingredients comprise slightly over [redacted] (see Appendix Table 3);
5. Upon dilution of the EP with water prior to use (in accordance with label use directions), the concentrations of intentionally-added inerts will be well below any known toxic endpoints for these ingredients.