Natamycin
Handling/Processing

Identification of Petitioned Substance

Chemical Name (IUPAC):
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

Other Names:
Antibiotic A-5283
CL 12625
Delvopos
Natafucin
Pimafucin
Pimaricin
Pimaricine
Synogil
Tennecetin

Trade Names:
Delvocid
Delvolan
Mycophyt
Myprozine
Natamax
Natacyn

CAS Number:
7681-93-8

Other Codes:
235 (INS Number)
231-683-5 (EINECS Number)

Characterization of Petitioned Substance

Composition of the Substance:
Natamycin is a naturally occurring antimicrobial compound that is generally produced by the bacterium *Streptomyces natalensis*. The chemical structure of natamycin is illustrated in Figure 1.

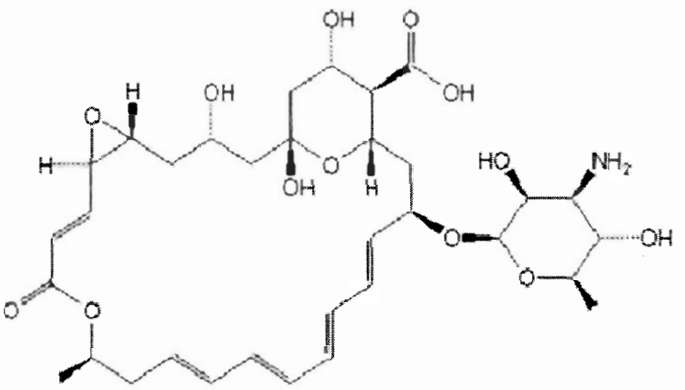

Figure 1. Chemical Structure of Natamycin (ChemIDplus 2006)

Properties of the Substance:
Natamycin is a white, tasteless, and odorless powder. It is practically insoluble in water except at extreme pH levels. Natamycin is soluble in glacial acetic acid and demethylformamide (Thomas and Delves-Broughton 2003).

Specific Uses of the Substance:

Natamycin is being petitioned for use as a post-baking surface treatment of yeast-leavened and non-yeast-leavened baked goods to prevent or delay mold growth and to maintain the wholesomeness of packaged baked goods.

In general, the food industry uses natamycin as a preservative to inhibit fungal growth on cheese; it also is used for other foods like meat and sausages (Mattia et al. 2002).

Natamycin is also used as a medicinal product in both humans and animals (Mattia et al. 2002). In humans, natamycin is currently used as an antifungal medicine to treat fungal infections of the eye (Drugs.com 2006). It was previously used in the treatment of fungal infections of the skin and mucous membranes (Mattia et al. 2002). Although no literature was found detailing why natamycin is no longer used in this way, one source stated that natamycin does not appear to be absorbed to a significant extent from mucous membranes, skin, or from the GI tract (AHFS Drug Information 2004). In animals, natamycin is used to treat ringworm in horses and cattle by applying it topically to the skin or mucous membranes (Mattia et al. 2002).

Natamycin can be used as a pesticide. According to the World Health Organization (WHO), natamycin is a Class III (i.e., slightly toxic) pesticide that is primarily used as a fungicide (WHO 2005).

Approved Legal Uses of the Substance:

Under 21 CFR 172.155, natamycin is an additive permitted by the U.S. Food and Drug Administration (FDA) for direct addition to food intended for human consumption. Specifically, it is approved as a preservative for the inhibition mold and yeast in cheese; levels may not exceed 20 milligrams per kilogram (20 ppm) in the finished product (FDA 2001).

Although the petitioner states that natamycin is a "Generally Recognized as Safe" (GRAS) food additive, it is not listed as such by FDA (FDA 2006a) nor has a GRAS notification been submitted to FDA. The petitioner also refers to self-affirmation of GRAS status by the manufacturer of natamycin, Danisco USA, Inc. A manufacturer may self-affirm that a compound is GRAS by performing all necessary research, including review by qualified experts (FDA 2004b). The manufacturer does not need to get approval from FDA or notify FDA of the results of its investigation, as long as the qualified experts agree that the compound is safe (Ziker 2002). However, the manufacturer may choose to notify FDA of the results of its investigation under the voluntary GRAS notification program.[1] The petitioner provides a letter from the manufacturer describing its self-affirmation process. The letter does not contain sufficient information to determine whether the manufacturer followed the proper procedures for the self-affirmation of GRAS status; there is no mention of an expert panel or its findings.

According to FDA's "Electronic Orange Book," natamycin is approved as the active ingredient for use in Natacyn, an ophthalmic suspension used to treat fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms including *Fusarium solani* keratitis (FDA 2006b).[2] Although it also is effective in the treatment of oral, cutaneous, or vaginal candidiasis, this use is not currently included in the labeling approved by the FDA (AHFS Drug Information 2004).

In 2004, FDA announced that it was amending its regulations for food additives permitted in feed and drinking water of animals to allow the use of natamycin in broiler chicken feeds (FDA 2004a). Under the

[1] The GRAS notification program is a voluntary procedure operating under a proposed rule published by FDA on April 17, 1997 (62 FR 18936).

[2] FDA's "Electronic Orange Book" is a database available on-line that is based on FDA's annual publication of the "Orange Book Annual Edition," which identifies drug products approved on the basis of safety and effectiveness by the FDA under the Federal Food, Drug, and Cosmetic Act. The electronic version enables searching of the approved drug list by active ingredient, proprietary name, applicant holder or applicant number. Data are updated concurrently with the publication of the annual edition or cumulative supplements (FDA 2006c).

amendment, up to 11 parts per million (ppm) of natamycin may be added to broiler chicken feed to retard the growth of *Aspergillus parasiticus* in the feed for up to 14 days.

Action of the Substance:
The mode of action for natamycin is to disrupt the cell membrane by binding to sterols (e.g., ergosterol[3]) and increase the permeability of the fungal cell membrane, which eventually leads to cell death (Myers 2006).

Status

International:
Natamycin is used in the European Union, the United States, much of South America and Eastern Europe, as well as several Middle Eastern countries (Deift 2002). It is listed as an allowed preservative for the European Union. According to WHO Food Additives Series, natamycin is proposed in the Codex draft General Standard for Food Additives (GSFA) for use in the following: cheese at 40 mg/kg; cured and dried non-heat treated processed meats, poultry, and game products at 6 mg/kg; and cured and dried non-heat comminuted meat, poultry, and game products at 20 mg/kg (Mattia et al. 2002). According to the Codex Alimentarius (2001), 2 mg/dm^2 natamycin can be added to the surface during cheese rind treatment, as long as it is not present at a depth of 5 mm. The Codex standard also states that 20 mg/kg of natamycin can be added to the surface of sliced, cut, shredded, and grated cheese as a preservative during the kneading and stretching process. The Food Standards Australia and New Zealand has been petitioned to approve natamycin for the following uses (FSANZ 2004):

- breads and bakery products;
- fruit and vegetable preparations, including pulp;
- dairy and fat based desserts, dips, and snacks; and
- sauces and toppings (including mayonnaises and salad dressings).

The WHO Food Additives Series (Mattia et al. 2002) on natamycin reports that the acceptable daily intake (ADI) is 0-0.3 mg/kg body weight. The expected daily intake (EDI) for internationally approved uses of natamycin in cheese and meats is not expected to exceed the ADI.

Natamycin is not specifically listed for the petitioned use (i.e., as a post-baking surface treatment of yeast-leavened and non-yeast-leavened baked goods to prevent or delay mold growth and to maintain the wholesomeness of packaged baked goods) or other uses in the following international organic standards:

- Canadian General Standards Board
- CODEX Alimentarius Commission
- European Economic Community (EEC) Council Regulation 2092/91
- International Federation of Organic Agriculture Movements
- Japan Agricultural Standard for Organic Production

Evaluation Questions for Substances to be used in Organic Handling

Evaluation Question #1: Is the petitioned substance formulated or manufactured by a chemical process? (From 7 U.S.C. § 6502 (21).)

Natamycin can be isolated from *Streptomyces natalensis* or related *Streptomyces* bacteria by a submerged aerobic fermentation process. It is isolated after several days of fermentation either by broth extraction or extraction of the mycelium (Mattia et al. 2002). When produced for commercial applications, however, the petitioner describes a method by Borden et al. (US Patent No. 5942611, 1999) that recovers natamycin by

[3] Ergosterol is a part of fungal cell membranes and is similar in function to cholesterol in animal cells (Wikipedia 2006).

adjusting the pH of the fermentation broth to above 10. The agent used to bring the fermentation broth above a pH of 10 is not specified in the petition; however, the Borden et al. patent states that the following alkaline compounds are all appropriate: sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, or a combination of these. Isopropanol (or other water-miscible solvent) is then added to dissolve natamycin in the broth. Insoluble solids are removed from the broth and the pH is lowered so that natamycin is precipitated.

Thus, although natamycin is produced by a naturally occurring biological process, a chemical process is used to extract the natamycin from the fermentation medium. However, the extraction steps do not alter the identity of the natamycin produced by the microbial culture.

Evaluation Question #2: Is the petitioned substance formulated or manufactured by a process that chemically changes the substance extracted from naturally occurring plant, animal, or mineral sources? (From 7 U.S.C. § 6502 (21).)

No information was found that indicates that the extraction steps alter the identity of the natamycin produced by the microbial culture.

Evaluation Question #3: Is the petitioned substance created by naturally occurring biological processes? (From 7 U.S.C. § 6502 (21).)

Natamycin can be isolated from the bacterium *Streptomyces natalensis* (Suloff 1999).

Evaluation Question #4: Is there a natural source of the petitioned substance? (From 7 CFR § 205.600 (b) (1).)

As noted in Evaluation Question #1, natamycin can be isolated from the bacterium *Streptomyces natalensis* (Suloff 1999). Natamycin was first isolated from this bacterium in 1955 from a soil sample taken from South Africa (Suloff 1999). Later in 1959, natamycin was isolated from was isolated from *Streptomyces gilvosporus* (Suloff 1999). Natamycin can also be isolated from related *Streptomyces* bacteria. Although natamycin can be isolated from *Streptomyces natalensis* and related *Streptomyces* bacteria that are naturally occurring, there is no information indicating that natural sources produce natamycin in quantities sufficient for commercial uses.

Evaluation Question #5: Is there an organic agricultural product that could be substituted for the petitioned substance? (From 7 CFR § 205.600 (b) (1).)

No other organic agricultural products were identified that could be substituted for the petitioned substance.

Evaluation Question #6: Are there adverse effects on the environment from the petitioned substance's manufacture, use, or disposal? (From 7 CFR § 205.600 (b) (2).)

There is no information available from EPA or FDA to suggest that adverse environmental effects result from the manufacture, use, or disposal of natamycin. When used as a preservative for cheese or in broiler chicken feeds, natamycin does not individually or cumulatively have a significant effect on the environment (FDA 2001, 2004a).

The petitioner intends to obtain natamycin from a supplier that produces the compound in Denmark. According to the petitioner, this facility disposes of no waste to the environment since the extracted fermentation broth is either (1) disposed of in the waste water treatment facility at the factory or (2) used in gas production by a local utility to generate electricity.

In addition, the petitioner states that more than 99 percent of the isopropanol used during manufacture is recovered via distillation and is subsequently reused. Consequently, very little isopropanol would be lost

to the environment. However, a small amount of isopropanol would enter the wastewater treatment facility where, according to the petitioner, it would be readily biodegraded. Isopropanol is readily biodegraded in aerobic aqueous systems; the range of half-lives for aerobic degradation using a sewage sludge inocula is <1 day to 48 days (HSDB 2006). Isopropanol is also biodegraded under anaerobic aqueous conditions (HSDB 2006).

Evaluation Question #7: Does the petitioned substance have an adverse effect on human health as defined by applicable Federal regulations? (From 7 CFR § 205.600 (b) (3).)

The WHO Food Additives Series (Mattia et al. 2002) on natamycin reports the results of two studies where humans showed an adverse effect to oral doses of natamycin. In one study, oral daily doses of 300-400 mg of natamycin caused nausea, vomiting, and diarrhea; there were no changes in peripheral blood cells. In the second study, a group of 10 patients with systemic mycoses received oral daily doses of 50-1000 mg for 13-180 days. At 600-1000 mg, patients experienced nausea, vomiting, and diarrhea. Based on these findings, the ADI of natamycin was determined to be 0-0.3 mg/kg body weight, or up to 2.1 mg for a 70-kg adult.

The WHO Food Additives Series (Mattia et al. 2002) reported that no allergic sensitization was observed among 111 patients that were treated with natamycin for a variety of conditions. In another study, 102 patients with various forms of eczema that underwent repeated exposure to natamycin did not show any allergic sensitization to it. In 73 workers employed for an average of five years in the manufacture of natamycin, there was no history of any allergic reactions; no allergic reactions occurred when 71 of the workers were tested.

Oral animal toxicity testing also has been conducted for natamycin and is summarized in Mattia et al. (2002). These results indicate that natamycin has low toxicity, with the only adverse effect reported in a short-term toxicity study in dogs being diarrhea. This effect occurred most frequently in high-dose animals (equivalent to 25 mg/kg body weight per day); however, as only two dogs were tested, the usefulness of this study is limited.

Evaluation Question #8: Is the nutritional quality of the food maintained when the petitioned substance is used? (From 7 CFR § 205.600 (b) (3).)

No information was identified that states or implies that natamycin changes the nutritional quality of food. Producers of Natamax (a mold and yeast inhibitor made with natamycin) claim that natamycin does not interfere with the nutritional value, taste, or odor of the food product.[4]

Evaluation Question #9: Is the petitioned substance to be used primarily as a preservative? (From 7 CFR § 205.600 (b) (4).)

All information provided in the petition indicates that natamycin would be used as a food preservative. Specifically, the petitioner intends to treat the surface of yeast-leavened and non-yeast-leavened baked goods after baking to prevent or delay mold growth.

Evaluation Question #10: Is the petitioned substance to be used primarily to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law, e.g., vitamin D in milk)? (From 7 CFR § 205.600 (b) (4).)

Natamycin is petitioned for use as a preservative. It is not intended to recreate or improve flavors, colors, textures, or nutritive values lost in processing.

Evaluation Question #11: Is the petitioned substance generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices? (From 7 CFR § 205.600 (b) (5).)

[4] Further information is available at http://www.kelleysupply.com/ext/ext_promo.html.

As noted previously (see "Approved Legal Uses of the Substance"), although the petitioner states that natamycin is a GRAS food additive, it is not listed as such by FDA (FDA 2006a) nor has a GRAS notification been submitted to FDA. The petitioner also refers to self-affirmation of GRAS status by the manufacturer of natamycin, Danisco USA, Inc. In this regard, the petitioner provides a letter from the manufacturer describing its self-affirmation process. However, the letter does not contain sufficient information to determine whether the manufacturer followed the proper procedures for the self-affirmation of GRAS status; there is no mention of an expert panel or its findings.

Evaluation Question #12: Does the petitioned substance contain residues of heavy metals or other contaminants in excess of FDA tolerances? (From 7 CFR § 205.600 (b) (5).)

No information was found that indicates that natamycin contains residues of heavy metals or other contaminants in excess of FDA tolerances. Table 1 illustrates an analysis of natamycin from Penglai Chemical, Inc. that conforms to the Food Chemical Codex (FCC) IV, which is an activity of the Food and Nutrition Board of the Institute of Medicine and is supported by FDA.

Table 1. Analysis of Natamycin (source: http://www.penglaichem.com/OLDPAGE/Natamycin.htm)

Item	Standard Requirement	Result
Appearance	White to yellow crystalline powder	Conform
Purity	≥50%	51.2%
Moisture	6.0-9.0%	6.7%
PH	5.0-7.5	6.0
Specific Rotation	+2760 ~ +2800	+2780
Ash	≤0.5%	0.2%
Heavy metals	< 20 ppm	< 10 ppm
Pb	< 20 ppm	< 5 ppm
Arsenic (As)	< 3 ppm	< 3 ppm
Hg	< 1 ppm	< 1 ppm
Microbiological Count	< 10 colony forming units (cfu)/g	< 10 cfu/g
Pathogen	Absent	Absent
E. coli	Negative/in 25g	Negative/in 25g
Salmonella	Negative/in 25g	Negative/in 25g

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