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Ms. Michelle Arsenault
National Organic Standards Board
USDA-AMS-NOP
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Room 2648-S, Mail Stop 0268
Washington, DC 20250-0268

Re. CS: Natamycin

These comments to the National Organic Standards Board (NOSB) on its Fall 2018 agenda are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

Beyond Pesticides opposes the use of natamycin in organic production. We do not believe that its classification as nonsynthetic can be supported with the available information, and when judged against the criteria for allowing synthetic substances, it fails to meet the criteria for no hazards to human health and the environment, essentiality, and compatibility with organic practices.

Natamycin cannot be classified nonsynthetic based on available information.

Natamycin is produced by fermentation. The Organic Materials Research Institute (OMRI) has classified it as nonsynthetic (and therefore allowed in organic crop production) based on the National Organic Program's (NOP) classification of materials guidance. According to OMRI and the Technical Review (TR), "NOP has stated that this substance is not allowed under the NOP regulations and has instructed OMRI not to list products containing natamycin."[1] Neither the OMRI website nor the TR cites NOP documentation for this statement, so we cannot evaluate it.

[1] TR lines 415-416. OMRI. 2017. *Out of Scope and Beyond Resolution.* https://www.omri.org/suppliers/OMRIscope.

However, there are scientific and review process reasons for challenging the nonsynthetic classification. As stated in the TR, the petition does not give specific information about the medium or technique used for biosynthesis. However, the TR presents information about the components of the growth media in Table 3, reproduced below.

Table 3: Natamycin growth media components

Source	Type	Components
(Struyk, et al. 1957-1958)	Experimental	Soybean meal, glucose, nutrient salts.
(Burns 1959)	Experimental	Peptone, phytone, beef extract, yeast extract, and glycerol. Inositol dextrin, and galactose were satisfactory replacements for glycerol as a carbohydrate source.
(Eisenschink and Olson 1993)	Patent	Difco "Bacto" peptone, Hormel peptone PSR 5, corn steep liquor, sodium chloride, glucose.
(Eisenschink, Millis and Olson 1997)	Patent	Carbon sources such as glucose, polysaccharides, and corn or potato starches. Non-yeast and yeast protein in a 3:1 to 9:1 ratio. Non-yeast protein sources include soy protein isolates, flours, or meals; or beef extract or protein hydrolysates. Yeast protein sources include extracts, autolysates, etc. Vitamins, inorganic elements and trace minerals: potassium, sodium calcium, boron, iron, copper zinc, etc. (undisclosed forms)
(Elsayed, Farid and Enshasy 2013)	Experimental	Glucose, beef extract, yeast extract, asparagine, and monopotassium phosphate, sodium acetate, and the sodium salt of propionic acid.
(DSM Food Specialties Inc. 2015)	Production	Undisclosed soy carbon source, inorganic salts, lye solution for pH control.

Beyond Pesticides has previously commented on the need for guidance on products of fermentation, and natamycin provides another example of the need for such guidance. While fermentation is a biological process, and no one would disagree that pickles, wine, yogurt, and apple cider vinegar are agricultural and nonsynthetic, the case is not so clear when the substrate is largely composed of inorganic or synthetic components. Furthermore, products of fermentation in or on substrates containing genetically engineered components are not compatible with policies adopted by the NOSB. Guidance is needed both for determining when the products of fermenting organic substrates are organic and for determining whether products of vat fermentation are nonsynthetic or otherwise allowable in organic production. Given that the petitioner identified as components of the production medium "undisclosed soy carbon source, inorganic salts, lye solution for pH control" in its GRAS notice to the Federal Food and Drug Administration ("DSM Food Specialties Inc. 2015" in the chart above) and did

not provide specific information in the petition, it is logical to assume that the medium is composed of genetically engineered soybeans and inorganic (possibly synthetic) nutrients.

Since a classification of nonsynthetic gives up NOSB oversight over the substance, the default classification should be synthetic –unless adequate information supports a nonsynthetic classification. In this case, natamycin should be classified as synthetic.

If the NOSB classifies natamycin as nonsynthetic, it should list natamycin as a prohibited natural on §§602 and 604.

As an antimicrobial substance that has medical applications and is known to result in antimicrobial resistance, natamycin should not be allowed in organic crop production. There is evidence of horizontal gene transfer in *Candida* and *Aspergillus* spp., leading to the spreading of antimicrobial resistance.[2]

Natamycin causes adverse effects on human health and the environment.

The petition and TR both address the issue of whether natamycin is an "antibiotic." This semantic issue is confused by differing definitions. Nevertheless, natamycin is an antimicrobial substance.[3]

Contrary to the statement in the TR, the development of antibiotic resistance is not the only concern about the use of antimicrobial substances in organic production. A second concern is the impact of antimicrobials on microbes that are important to organic production – including soil microbes and microbes that compete with spoilage organisms.

Natamycin has been shown to provoke antimicrobial resistance in human pathogens.

A unique property of the target of antimicrobials —microbes— is their short generation time, which allows them to evolve quickly in response to threats. Natamycin has a long history of use in medicine. It is effective against:

- *Candida albicans* –responsible for "thrush" infections in the mouth, "yeast" vaginal infections, and invasive candidiasis (a serious infection that can affect the blood, heart, brain, eyes, bones, and other parts of the body);[4]
- *Cryptococcus neoformans* –causal agent of cryptococcosis, which usually affects the lungs;
- *Paecilomyces* –a genus containing entomopathogens, plant pathogens, and human pathogens;
- Parasitic protozoa such as *Trypanosoma cruzi*, the causal agent of Chagas disease; and

[2] Dalhoff, A.A. and Levy, S.B., 2015. Does use of the polyene natamycin as a food preservative jeopardise the clinical efficacy of amphotericin B? A word of concern. *International journal of antimicrobial agents*, *45*(6), pp.564-567.

[3] TR lines 305-306.

[4] https://www.cdc.gov/fungal/diseases/candidiasis/index.html.

- Fungal eye infections such as blepharitis, conjunctivitis, and keratitis, caused by *Fusarium solani* and other pathogenic fungi.

As demonstrated in research included in the petition and reviewed in the TR, natamycin has resulted in resistance in *Candida albicans*.[5] Antimicrobials with medical uses should not be used in agriculture, particularly organic agriculture.

Natamycin affects soil fungi.

Natamycin may be released into the soil environment through wastewater or residues of treated produce, where it may have negative impacts on fungi. For example, natamycin is known to be active against *Trichoderma spp*. The genus is globally distributed in soils, although the presence of individual species may be either global or restricted. Although some *Trichoderma* species are pathogens that attack commercial mushrooms, others play a "benefical" role in the agroecosystem –as entomopathogens (attacking insects), decomposers, and plant symbionts.[6] Furthermore, though the petition is for use indoors on mushrooms and post-harvest application to produce, the petitioner has announced an intention to market it for use on organic strawberries pre-plant and during planting.[7]

Natamycin is not essential for organic production.

The primary means of controlling fungal contaminants of mushroom culture and post-harvest spoilage of produce is good hygiene. In the case of mushrooms, Stamets and Chilton say, "Different contaminants are associated with different stages of mushroom cultivation. …Since contamination at any phase of cultivation occurs for specific reasons, the contaminants can be the cultivator's most valuable guide for teaching one what NOT to do. …In effect, skill in mushroom culture is tantamount to skill in contamination control."[8]

For both mushrooms and produce, "good hygiene" is not equivalent to "sterile." In both cases, there are non-pathogenic organisms that may compete with pathogens.[9] We have addressed this issue at length in comments on sanitizers.[10] The TR also addresses alternative materials and practices.[11]

Natamycin is incompatible with organic practices.

Natamycin, according to information provided in the TR, is produced by fermentation in which the main carbon source is probably genetically engineered soybeans. At its Fall 2016 meeting, the NOSB adopted a proposal on excluded methods terminology that said, "This term

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[5] TR lines 916-961.
[6] Samuels, G.J., 2006. Trichoderma: systematics, the sexual state, and ecology. *Phytopathology*, *96*(2), pp.195-206.
[7] http://ir4.rutgers.edu/Biopesticides/workshoppresentations/2016WorkshopPresentations/Dsm.pdf.
[8] Paul Stamets and J.S. Chilton, 1983. *The Mushroom Cultivator*, Agarikon Press, Olympia, WA. Pp. 234-235.
[9] See, for example, lines 1174-1175
[10] See, for example, comments on Handling Subcommittee issues (hypochlorous acid) at: https://www.regulations.gov/document?D=AMS-NOP-15-0085-1528.
[11] TR lines 1118-1248.

[genetically modified organism] will also apply to products and derivatives from genetically engineered sources." Thus, natamycin, when produced by fermentation of genetically engineered soybeans, is excluded from use in organic production.

Thank you for your consideration of these comments.

Sincerely,

Teresa Ann Shistar

Terry Shistar, Ph.D.
Board of Directors