Formal Recommendation
From: National Organic Standards Board (NOSB)
To: National Organic Program (NOP)

Date: October 22, 2021

Subject: Kasugamycin for Plant Disease Control

NOSB Chair: Steve Ela

The NOSB hereby recommends to the NOP the following:
None

Statement of the Recommendation:
The NOSB voted to classify kasugamycin as synthetic and voted unanimously to not add it to the National List based on OFPA 6518(m), availability of alternatives.

Rationale Supporting Recommendation:
Kasugamycin was petitioned for use in organic crop production through addition to the National list at 205.601(j)(4) for plant disease control. The NOSB has rejected this petition by unanimous vote based on availability alternatives, and incompatibility with a system of sustainable agriculture. Historically antibiotics used in agriculture create microbial resistance, and the NOSB has voted to remove other antibiotics in the same family, such as streptomycin, from the National List for this reason.

NOSB Vote:

Classification Motion:
Motion to classify kasugamycin as synthetic
Motion by: Rick Greenwood
Seconded by: Steve Ela
Yes: 14 No: 0 Abstain: 0 Absent: 0 Recuse: 0

Motion Passed

National List Motion:
Motion to add kasugamycin to the National List at §205.601(j)(4) for plant disease control
Motion by: Rick Greenwood
Seconded by: Amy Bruch
Yes: 0 No: 14 Abstain: 0 Absent: 0 Recuse: 0

Motion Failed

See recommendation below

National Organic Standards Board
Crops Subcommittee
Petitioned Material Proposal
Kasugamycin for Plant Disease Control
July 20, 2021

Summary of Petition:

Kasugamycin is an antibiotic that inhibits bacterial protein synthesis and has been approved by the U.S. Environmental Protection Agency (EPA) for control of plant diseases, especially fire blight caused by Erwinia amylovora on apples and pears. The registered formulations are Kasumin 2L and Kasumin 4L containing the active ingredient kasugamycin hydrochloride hydrate. Kasugamycin is obtained by aerobic fermentation of the microorganism Streptomyces kasugaensis. The technical grade active ingredient, kasugamycin hydrochloride hydrate, was registered with the EPA in 2014 and a formulation Kasumin 2L containing two percent kasugamycin was registered in 2018. In 2020 Kasumin 4L containing four percent kasugamycin was registered with the EPA. Kasumin 2L and 4L were registered with a number of restrictions including those that prohibit application where animals are grazing or in areas where crops have been fertilized with animal or human waste. Users are also required to follow a resistance management plan. Applications are limited to four per year with California limiting applications to two per year.

Summary of Review:
Kasugamycin is an aminoglycoside antibiotic that is manufactured through fermentation and isolated as hydrochloride. Kasugamycin is a colorless solid at room temperature and is soluble in water. The hydrochloride has relatively low volatility and does not volatilize readily from soil into the air.

Kasugamycin is characterized by the EPA as moderately persistent to persistent. A major source of degradation is aerobic microbial metabolism in soil with a half-life of 43-73 days. About 4% remains after a year. Hydrolysis in water is very slow and metabolites are also persistent (TR 278). Persistence on fruit is low and about half the amount applied to foliage ends up on the soil and non-target surface vegetation. Residues on fruit decrease 10-fold in 27-32 days.

Kasugamycin has low acute toxicity to mammals and is classified EPA Category IV (least toxic, no warning label) for all exposures other than dermal, for which it is classified EPA Category III (next least toxic, requires "Caution" warning on label). It also has low chronic toxicity from rat feeding studies and there was no evidence of carcinogenicity in mice or was there evidence of chromosome damage.

Normal labeled use of kasugamycin has led to field resistance in several pathogens. Kasugamycin was first used to control diseases of rice in Japan starting in 1965 with rice blast caused by Magnaporthe grisea and resistance was noticed in 1971. Field resistance in Acidovorax sp. occurred in 1990 and in B. glumae in 2001. In Florida, rapid field resistance to bacterial spot of tomato caused by Xanthomonas perforans was also seen. In orchards that had been treated at least once with kasugamycin studies found resistant bacteria in 401 field isolates from apple flowers, leaves and soil samples. Additionally, Erwinia resistance to kasugamycin has been generated in the laboratory. Kasugamycin has not been evaluated to determine if its use for orchard sprays would lead to kasugamycin-resistant pathogens in animals grazing orchard grass, but spraying orchard grass with streptomycin at concentration levels used for fire blight leads to an increase in antibiotic-resistant human pathogens found in sheep grazing on sprayed grass. (TR 805).

The TR contractor was asked to answer the question, "is kasugamycin susceptible to development of resistance with normal (labeled) use?" It was reported (TR 1152) that some level of resistance has occurred, and this is why the Kasumin label requires a resistance management plan. The plan includes use of kasugamycin as part of an IPM program and less than four applications per year (2 in California).

The alternative to kasugamycin is an integrated organic program that attacks fire blight at every point in its life cycle. Cultural controls can be combined with application of fixed copper sprays in dormant and pre-bloom periods, application of lime sulfur for mildew control and thinning of apple blossoms, biological controls such as *Aureobasidium pullulans* products during bloom time, and bio-control antagonists such as *Bacillus subtilis* products later in the blooming period. Other organic procedures are also available to control fire blight, but they are more effective on the West Coast.

Summary of Review:

Category 1: Classification

1. For CROP use: Is the substance **Non-synthetic** or X **Synthetic?**
   Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources? [OFPA §6502(21)] If so, describe, using NOP 5033-1 as a guide.

   Kasugamycin is an aminoglycoside antibiotic that is manufactured through fermentation and isolated as hydrochloride. Kasugamycin is a colorless solid at room temperature and is soluble in water. The hydrochloride has relatively low volatility and does not volatilize readily from soil into the air.

2. Reference to appropriate OFPA category:

   Is the substance used in production, and does it contain an active synthetic ingredient in the following categories: [§6517(c)(1)(B)(i)]; copper and sulfur compounds; toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers; or (ii) is used in production and contains synthetic inert ingredients that are not classified by the Administrator of the Environmental Protection Agency as inerts of toxicological concern?

   The National Organic Standards Board (NOSB) was petitioned to add kasugamycin as an allowed synthetic to the synthetic substances National List at 7 CFR §205.601. Kasugamycin does contain an active synthetic ingredient: toxins derived from bacteria, as it is isolated from bacterial fermentation.

Category 2: Adverse Impacts

1. What is the potential for the substance to have detrimental chemical interactions with other materials used in organic farming systems? [§6518(m)(1)]

Kasugamycin is an antibiotic that inhibits bacterial protein synthesis and would not be expected to have chemical interactions with other materials used in organic farming.

2. What is the toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment? [§6518(m)(2)]

   Kasugamycin is characterized by the EPA as moderately persistent to persistent. A major source of degradation is aerobic microbial metabolism in soil with a half-life of 43 - 73 days. About 4% remains after a year. Hydrolysis in water is very slow and metabolites are also persistent (2021 TR 278). Persistence on fruit is low and about half the amount applied to foliage ends up on the soil and non-target surface vegetation. Residues on fruit decrease 10-fold in 27-32 days.

3. Describe the probability of environmental contamination during manufacture, use, misuse or disposal of such substance? [§6518(m)(3)]

   The probability of environmental contamination during manufacture is low because it is confined within a facility as a fermentation product. Kasugamycin is characterized as moderately persistent to persistent (U.S. EPA 2013). A major source of degradation is aerobic microbial metabolism in soil with a half-life of 43-73 days. About four percent remains after a year. Because laboratory studies used only one soil type, the EPA uses a 219-day soil half-life in persistence calculations (U.S. EPA 2013). Both aerobic and anaerobic degradation occurs. Aerobic degradation is faster than anaerobic. Typical aerobic half-life in water is seven days and half-life in sediment is 108 days. Anaerobic half-life was 32 days in water and 141 days in sediment (NYS 2015; U.S. EPA 2013). Hydrolysis in water is very slow, especially in acidic conditions (NYS 2015). Kasugamycin moves freely in sandy soil, less so in clay soils. It is likely to move both into surface water and ground water, but movement into ground water is less likely (U.S. EPA 2013). Because of soil movement, field dissipation is faster than molecular degradation seen in the laboratory. Field dissipation half-life in soil is 5.7 to 12.3 days. It does not volatilize readily from water or soil. Half-life of Kasugamycin in the gas phase is 1.6 hours (NYS 2015) (TR 264).

4. Discuss the effect of the substance on human health. [§6517(c)(1)(A)(i); §6517(c)(2)(A)(i); §6518(m)(4)]

   Kasugamycin has low acute toxicity to mammals and is classified EPA Category IV (least toxic, no warning label) for all exposures other than dermal, for which it is classified EPA Category III (next least toxic, requires "Caution" warning on label). It also has low chronic toxicity from rat feeding studies and there was no evidence of carcinogenicity in mice or was there evidence of chromosome damage.

   Normal labeled use of kasugamycin has led to field resistance in several pathogens. Kasugamycin was first used to control diseases of rice in Japan starting in 1965 with rice blast caused by <u>Magnaporthe grisea</u> and resistance was noticed in 1971. Field resistance in <u>Acidovorax</u> sp. occurred in 1990 and in <u>B. glumae</u> in 2001. In Florida, rapid field resistance to bacterial spot of tomato caused by <u>Xanthomonas perforans</u> was also seen. In orchards that had been treated at least once with kasugamycin studies found resistant bacteria in 401 field isolates from apple flowers, leaves, and soil samples. Additionally, Erwinia resistance to kasugamycin has been generated in the laboratory. Kasugamycin has not been evaluated to determine if its use for orchard sprays would lead to kasugamycin-resistant pathogens in animals grazing orchard grass, but spraying orchard grass with streptomycin at concentration levels used for fire blight leads to an increase in antibiotic-resistant human pathogens found in sheep grazing on sprayed grass. (2021 TR 805).

The TR contractor was asked to answer a question about kasugamycin's susceptibility to development of resistance with normal (labeled) use. It was reported (2021 TR 1152) that some level of resistance has occurred, and this is why the Kasumin label requires a resistance management plan. The plan includes use of kasugamycin as part of an IPM program and less than four applications per year (Two in California).

5. Discuss any effects the substance may have on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock. [§6518(m)(5)]

   Up to five percent of applied amounts of kasugamycin move into surface water. Kasugamycin had the largest harmful effect on aquatic plants, especially blue-green algae. For duckweed, *Lemna gibba*, frond count was reduced with EC50 = 86 ppm. For green algae, *Pseudokirchneriella subcapitata*, 96-hour cell density was reduced with EC50 of 3.9 ppm. For blue-green algae, Anabaena flos-aquae, 96-hour cell density was reduced with EC50 of 0.65 ppm (NYS 2015). The most sensitive plant tested was blue-green algae, *Anabaena sp.*, with EC50 0.65 ppm and a no-observed-adverse-effect concentration (NOAEC) of 0.08 ppm (U.S. EPA 2013). Kasugamycin water contamination measured in rice paddy irrigation water was <2 ppm (Sheu et al. 2010). Huang et al. (2010) noted bacterial population changes when adding kasugamycin at high rates to river water microcosms in the laboratory. The EPA states that Kasugamycin is classified as practically non-toxic to freshwater and estuarine/marine fish and invertebrates on an acute exposure basis (U.S. EPA 2013).

6. Are there any adverse impacts on biodiversity? (§205.200)

   Yes. There are subtle changes in the microbial population as some bacterial species develop kasugamycin resistance. As was stated in an earlier section, in orchards that had been treated at least once with kasugamycin studies found resistant bacteria in 401 field isolates from apple flowers, leaves and soil samples. It is also postulated that the microbial flora of animals that have grazed in orchards sprayed with kasugamycin could develop resistance as has been shown for other aminoglycoside antibiotics. Negative changes in the soil microflora are not in concordance with OPFA criteria for listing on the National List.

Category 3: Alternatives/Compatibility

1. Are there alternatives to using the substance? Evaluate alternative practices as well as non-synthetic and synthetic available materials. [§6518(m)(6)]

The alternative to kasugamycin is an integrated organic program that attacks fire blight at every point in its life cycle. Cultural controls can be combined with application of fixed copper sprays in dormant and pre-bloom periods, application of lime sulfur for mildew control and thinning of apple blossoms, biological controls such as *Aureobasidium pullulans* during bloom time, and bio-control antagonists such as *Bacillus subtilis* later in the blooming period. Other organic procedures are also available to control fire blight, but they are more effective on the West Coast.

2. In balancing the responses to the criteria above, is the substance compatible with a system of sustainable agriculture? [§6518(m)(7)]

   Kasugamycin has been in agricultural use since 1965. It has been used against a number of plant pathogens. In every instance, some level of resistance has occurred (Vallad et al. 2010; Yoshii et al. 2012). The EPA believes that resistance of the fire blight pathogen *Erwinia amylovora* to kasugamycin is possible, and the Kasumin label requires a resistance management plan. This plan includes use of kasugamycin as part of an IPM program and less than four applications per year (U.S. EPA 2018). (2021 TR 1145

   Given the history that antibiotics used in agriculture create microbial resistance, and that the NOSB has voted to remove other antibiotics in the same family, such as streptomycin, from the National List, the Crops Subcommittee finds that kasugamycin, is not compatible with a system of sustainable agriculture under OPFA criteria.

Classification Motion:
Motion to classify kasugamycin as synthetic
Motion by: Rick Greenwood
Seconded by: Steve Ela
Yes: 8 No: 0 Abstain: 0 Absent: 0 Recuse: 0

National List Motion:
Motion to add kasugamycin to the National List at §205.601(j)(4) for plant disease control
Motion by: Rick Greenwood
Seconded by: Amy Bruch
Yes: 0 No: 8 Abstain: 0 Absent: 0 Recuse: 0

Approved by Rick Greenwood, Crop Subcommittee Chair, to transmit to NOP July 22, 2021.