

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

Date: November 18, 2016

Subject: Removal of Ivermectin from National List

NOSB Chair: Tracy Favre

The NOSB hereby recommends to the NOP the following:

Rulemaking Action: X – Remove Ivermectin from the National List

Guidance Statement:

Other:

Statement of the Recommendation:

That ivermectin (CAS # 70288-86-7) be removed from the National List §205.603.

Rationale Supporting Recommendation (including consistency with OFPA and Organic Regulations):

The NOSB finds that new information indicates that ivermectin should be removed from the National List, pursuant to Section 6518(m) of the OFPA, with particular reference to Criteria 2, 5, 6, and 7 at Section 6518(m) as cited below:

(2) 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;

(5) The effects of the substance 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;

(6) The alternatives to using the substance in terms of practices or other available materials; and

(7) Its compatibility with a system of sustainable agriculture.

When evaluating ivermectin with reference to the OFPA Criteria at 6518(m), this material clearly demonstrates:

- That it is toxic in the environment – Criteria 2;

- That it has a negative impact on dung beetles which are a critical component of good pasture management. Pasture management is a requirement of organic livestock production – Criteria 5;
- That there are two alternative synthetic parasiticides which can be used as alternative medications during an emergency; that high quality pasture and range management grazing techniques can reduce the need to use any parasiticide; and that there are many alternative herbal remedies – Criteria 6;
- That use of ivermectin is incompatible with a system of sustainable agriculture – Criteria 7.

NOSB Vote:

Motion to remove ivermectin from §205.603

Motion by: Jean Richardson

Seconded by: Harriet Behar

Yes: 14 No: 0 Abstain: 0 Absent: 1 Recuse: 0

Motion Passed

National Organic Standards Board (NOSB)
Livestock Subcommittee
Proposal to remove ivermectin (CAS # 70288-86-7) from the National List
July 19, 2016

I SUMMARY:

This proposal to remove ivermectin from §205.603 of the National List of Allowed and Prohibited Substances is made pursuant to the Organic Foods Production Act (OFPA), Section 6518, in accordance with NOP 3011 effective March 11, 2016, and in response to a petition to remove ivermectin submitted to NOP on June 26, 2016.

The NOSB finds that new information indicates that ivermectin should be removed from the National List, pursuant to Section 6518(m) of the OFPA, with particular reference to Criteria 2, 5, 6, and 7 at Section 6518(m) as cited below:

(2) 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;

(5) The effects of the substance 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;

(6) The alternatives to using the substance in terms of practices or other available materials; and

(7) Its compatibility with a system of sustainable agriculture.

II BACKGROUND:

The USDA standards prohibit the use of parasiticides in slaughter stock.

The use of synthetic parasiticides in organic production is strictly confined to emergencies. Synthetic parasiticides cannot be used routinely, but sick animals must be treated. Typically farmers bring clean animals into their herds or flocks, select breeds which have high resistance to parasites, and manage their land, especially pastures, in a manner which reduces the likelihood of parasite infection. If an increased parasite load is noted in fecal egg counts, farmers have a broad array of alternative treatments available. But when all else fails and animals are not doing well, the farmer, working with the veterinarian, may need to use one of the synthetic parasiticides on the National List.

At the present time, there are three (3) substances on the National List which are approved for use as parasiticides for organic livestock: Ivermectin, moxidectin and fenbenzadole. All three of

these materials were recently reviewed as part of the regular five-year Sunset process. All three materials have annotations and other language limiting usage.

In 2015 a comprehensive technical evaluation report (TR) on parasiticides was requested by the NOSB as part of its regular five year review of materials. A research bibliography is included in the technical report dated June 3, 2015. This research information is comprehensive in nature and reviews all aspects of use of ivermectin and comparisons with alternative herbal and synthetic parasiticides as well as management techniques on farms and ranches which can be used to reduce or eliminate use of parasiticides.

During 2015 the NOSB received public comment on ivermectin as part of the five year review for materials scheduled to Sunset in 2017. New information was provided which indicated that ivermectin was not always effective, that both moxidectin and fenbenzadole were also available for use, and that dung beetles, a critical component of good pasture management, are negatively impacted by use of ivermectin.

With strong stakeholder support from all sectors the Subcommittee recommended removing ivermectin from the National List by a vote of 5 yes, 1 no and 2 absences. However, during the second posting of this material, public comment from a sector of producers, notably in western states, indicated that ivermectin was their preferred parasiticide, in part because fenbenzadole requires veterinarian prescription. Therefore the final NOSB vote at the October 2015 NOSB Meeting was to reluctantly continue to list ivermectin, but to immediately review all the parasiticides as a group. This additional review resulted in a Recommendation to make some changes to the parasiticide annotations as follows:

- * *That parasiticides continue to be prohibited in slaughter stock.*
- * *That the milk withholding period after treatment with fenbenzadole or moxidectin be changed from 90 days to 2 days for dairy cows, and 36 days for goats and sheep.*
- * *That the listing for ivermectin remains as presently listed, with a 90 day withdrawal period.*
- * *That moxidectin be allowed for both internal and external use.*
- * *That fleece and wool from fiber bearing animals be allowed to be certified organic even if use of parasiticides was necessary at some time in the animal's life.*
- * *That fenbenzadole be allowed without written order of a veterinarian.*

This parasiticide recommendation of April 27 2016 passed unanimously, 15:0.

At that meeting the NOSB was again urged by a broad sector of stakeholders to petition to Remove ivermectin from the National List, based on the expectation that the April 27, 2016 Recommendation on parasiticides is approved by the NOP and is successful in the rulemaking process.

Reference is also made to the following:

Technical Report: 1999 Technical Advisory Panel Report (TAP)(fenbendazole, ivermectin); 2015 Technical Evaluation Report on parasiticides; fenbenzadole, ivermectin, moxidectin.

Past NOSB Actions: 10/1999 NOSB minutes and vote; 11/2005 sunset recommendation; 10/2010 sunset recommendation; 10/2015 sunset recommendation.

4/27/16 Parasiticide Recommendation

Recent Regulatory Background: Sunset renewal notice published 06/06/12

Sunset Date: 06/27/17

III RELEVANT AREAS OF THE RULE:

Section 205.603(a) – with language as recommended to NOP on April 27, 2016

As disinfectants, sanitizer, and medical treatments as applicable

(18) Parasiticides—Prohibited in slaughter stock, allowed in emergency treatment for dairy and breeder stock when organic system plan-approved preventive management does not prevent infestation. Allowed in fiber bearing animals, when used a minimum of 90 days prior to harvest of fleece or wool that is to be sold, labeled or represented as organic. In breeder stock, treatment cannot occur during the last third of gestation if the progeny will be sold as organic and must not be used during the lactation period for breeding stock.

(i) Fenbendazole (CAS #43210-67-9)—milk or milk products from a treated animal cannot be labeled as approved for in subpart D of this part for: 2 days following treatment of cattle; 36 days following treatment of goats and sheep.

(ii) Ivermectin (CAS #70288-86-7)—milk or milk products from a treated animal cannot be labeled as approved for in subpart D of this part for 90 days following treatment.

(iii) Moxidectin (CAS #113507-06-5)—milk or milk products from a treated animal cannot be labeled as approved for in subpart D of this part for: 2 days following treatment of cattle; 36 days following treatment of goats and sheep.

Section 205.238 – with language as recommended to NOP on April 27, 2016

The USDA organic regulations at 7 CFR part 205 provide guidance on livestock production practices to prevent the need for the use of parasiticides and regulate the use of parasiticides in organic livestock production:

§205.238 Livestock health care practice standard.

- (a) The producer must establish and maintain preventive livestock health care practices, including:
- (1) Selection of species and types of livestock with regard to suitability for site-specific conditions and resistance to prevalent diseases and parasites;
 - (2) Provision of a feed ration sufficient to meet nutritional requirements, including vitamins, minerals, protein and/or amino acids, fatty acids, energy sources, and fiber (ruminants);
 - (3) Establishment of appropriate housing, pasture conditions, and sanitation practices to minimize the occurrence and spread of diseases and parasites;

- (b) When preventive practices and veterinary biologics are inadequate to prevent sickness, a producer may administer synthetic medications: Provided, that, such medications are allowed under §205.603. Parasiticides allowed under §205.603 may be used on:
- (1) Breeder stock, when used prior to the last third of gestation but not during lactation for progeny that are to be sold, labeled, or represented as organically produced.
 - (2) Dairy animals, as allowed under §205.603.
 - (3) Fiber bearing animals, as allowed under §205.603

IV DISCUSSION:

Parasiticides fall into five anthelmintic drug classes differentiated by their chemical structures. Moxidectin and ivermectin are both in one class of parasiticides, and fenbendazole is in a separate class, relative to their modes of action. Some commenters suggested that it may be beneficial to keep one parasiticide from each class on the National List to allow rotation of parasiticides, prevent the development of resistance, and have alternatives in cases where resistance develops. Also, different synthetic parasiticides allow different modes of use (i.e., oral administration, subcutaneous, and pour-on). Fenbendazole is restricted to use by oral administration only, whereas ivermectin and moxidectin are both approved for topical, subcutaneous and oral administration.

Ivermectin is approved for use in swine, sheep, cattle, goats, bison, deer and reindeer. Ivermectin is not approved for use in dairy animals, and no milk withdrawal time has been established for ivermectin.^{1,2}

Moxidectin is approved for use in cattle and sheep.

Fenbendazole is approved by FDA for use in cattle, swine, sheep, turkeys, goats, and deer.

In October 1999, the NOSB voted on three parasiticides for inclusion on the National List. Only ivermectin had sufficient votes be added to the List. The votes were: ivermectin 8-3-0, fenbendazole 5-6-0, and levamisole 0-11-0.

In April 2004, the NOSB voted to add moxidectin to the National List by a vote of 11-1-1-1. The annotation “for control of internal parasites only” was included for moxidectin for the given reason that, “*There is much less chance of any kind of contamination if it is used for internal parasites versus external.*” According to the meeting notes, “*It was the committee’s opinion, that (moxidectin) failed on Criteria 1, and that was the reason for the proposed annotation because of concern about the half-life of the material and impact on soil organisms.*” However, the Board noted then that moxidectin “*is also less problematic*” than ivermectin. Further, it should be noted that just before the NOSB vote on moxidectin, a board member corrected an error that had been part of the discussion leading to the annotation: it was brought up that the

¹<http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=128-409>

² <http://www.accessdata.fda.gov/scripts/animaldrugsatfda/>

2003 TAP review indicated the half-life of moxidectin in soil is two months, not six months as reported in the evaluation criteria document (which had led to support for the annotation).

Although the NOSB approved the addition of moxidectin to the National List in 2004, the US Department of Agriculture Secretary did not initially accept NOSB's recommendation because moxidectin was labeled as a macrolide antibiotic. However, subsequent clarification found that moxidectin belongs to the polyene class of macrolides, "which unlike their erythromycin counterparts do not possess antibiotic properties" (2015 TR lines 100 – 111). Moxidectin was then added to the National List.

In May 2008, fenbendazole was approved by the NOSB for addition to the National List by a vote of 14-0. The stated intention of the Livestock Committee at that time was that when fenbendazole was added to the List, ivermectin (and possibly moxidectin) should come off the List (meeting notes, page 207).

Ivermectin is considered to be the most harmful to soil life of the three parasiticides listed. The 2015 TR indicates that the half-life for degradation of ivermectin is 127 days in soil. However, other sources indicate that the half-life of can be quite variable, depending on temperature and soil conditions. For example, the half-life of ivermectin in a soil/feces mixture was found to be 91 to 217 days during winter weather conditions and 7 to 14 days during the summer period.³

The 2015 TR includes the following: *"Fenbendazole does not appear to hinder rapid disappearance and mineralization of cattle dung pats in pastures and does not appear to affect the role that earthworms play in this process. Excreted ivermectin does delay the disappearance of dung pats, but does not affect earthworm populations or health. The delay in ivermectin treated soils may be the result of its toxicity to insects"* (2015 TR lines 580 – 583).

Ivermectin is more toxic to dung-dwelling insects than moxidectin: "The macrocyclic lactones (the class of parasiticides to which ivermectin and moxidectin belong) can be ranked in decreasing order of toxicity to dung-dwelling insects as abamectin>doramectin ≥ ivermectin > eprinomectin>>moxidectin" (TR 2015 Table 7).

Although ivermectin is not labeled for use in dairy animals of breeding age, it may be used under veterinary order under provisions of AMDUCA (TR line 321).

In its initial request for public comment, the Livestock Subcommittee asked the public: *"Are the three parasiticides (ivermectin, moxidectin and fenbendazole) different enough in their modes of action that they should all remain on the National List? If not, which one(s) would you recommend be removed from the List, and why?"*

³ Fate of Pharmaceuticals in the Environment and in Water Treatment Systems. 2008. Diana S. Aga ed., p. 128. CRC Press.

In the public response the most common comment received was that ivermectin should be removed from the National List, primarily because of its toxic effects on dung beetle larvae.

Recent research indicates that ivermectin has a negative impact on the agro-ecosystem in a number of ways, but especially on its impact on dung beetles which are critical for healthy pastures.

Ivermectin is rapidly adsorbed to soil and sediment. Up to 98% of the administered dose of ivermectin may be excreted as non-metabolized drug in feces (Horvat et al., 2012). Ivermectin does not appreciably leach from soil sediment (Krogh et al., 2008). Radio-chromatographic studies have shown the ivermectin half-life for degradation to be 127 days in soil and less than 6 hours in water (Prasse et al., 2009). The environmental burden on fields manured with feces from ivermectin treated animals ranges from 0.001 to 0.09 parts per billion (ppb) depending on animal species (Halley et al., 1989) (TR 2015, 568-573)

Ivermectin has very little solubility in water. The only route for entry into the environment is through animal excretion. Ivermectin has limited mobility in soil because it is lipophilic and tightly binds to soil particles. The half-life for degradation of ivermectin in soil can be as long 240 days in natural soil depending on the soil type. Degradation in water is much faster with a half-life as short as 2.9 days. Ivermectin is hydrolytically unstable at pH 6.3. Predicted environmental concentrations based on the introduction of manure to field is relatively low and on the order of 100 parts per billion (ppb).

Ivermectin is toxic to fish at concentrations between 3 and 17 ppb.

Generally, since its introduction, no risks from appropriate use of ivermectin have been established for the environment or for human health. However, it has been consistently shown that ivermectin is unacceptably toxic for larval forms of arthropod insects (dung organisms) and daphnids (Liebig et al., 2010; Oh et al., 2006). (TR 2015, 665-574)

There are many natural alternative parasiticides being used in organic livestock production today. Natural parasiticides include homeopathic remedies, diatomaceous earth and many herbs with anthelmintic properties. Table 10 of the 2015 TR lists over 50 botanical and alternative de-wormers. The efficacy of most of these natural alternatives is not well documented, and more research is needed. However, there does seem to be a lot of potential for the development of effective natural parasite control systems in the future.

Ivermectin is no longer necessary as there are two synthetic parasiticides, fenbendazole and moxidectin which can be used in emergencies when preventive management practices have failed to control parasite load.

Further, the negative impacts of ivermectin on dung beetles in pastures and on rangelands is not compatible with a system of sustainable agriculture.

Grazing management and the use of safe pastures for calves and sheep after weaning is an important component of helminth control in organic farming. It is important to have (1) preventive grazing management such as delayed turn-out, change of pastures between seasons, (2) diluting grazing management: mixed or alternate grazing with other host species, (3) evasive grazing management like changing the pasture within the season, and (4) supplementary feeding in the spring.

Pasture management which includes grazing management using both goats and cattle has been found effective.

Organic farmers have found that there is a biological interdependence between animals and plants with the use of a “mixed farming” approach to grazing where (1) animals succeeded one another on the field to avoid species specific transfer of disease, i.e. dairy cattle, then sheep and goats, then beef cattle; (2) only composted animal wastes for fertilizer were used to avoid transfer of known disease agents to the soil and back to their livestock and (3) overcrowding and over grazing were avoided to prevent contact with potentially parasitic worms in various stages of development naturally following bacteria and fungus into specific plants and decomposing material (Sykes, 1949; Ingham, 1999). (TR 2015 932-938)

Organic farms tend to have a higher diversity of nematodes, since animals are not normally treated with anthelmintic drugs. Helminth diversity has been related to a lower intensity of infection in extensive goat breeding and in meat cattle (Caberet et al., 2002). (TR 2015, 924-931)

Identifying and treating animals that are severely affected by parasites while leaving healthy animals that are coping with the disease untreated and maintaining a reservoir of susceptible parasites has also been effective for reducing the use of parasiticides and suppressing the development of anthelmintic resistance. This is called the FAMACHA system. It provides for a method of identifying diseased sheep using the color of their conjunctiva from deep red in healthy sheep to white in sick sheep as a guide (van Wyk and Bath, 2002). (TR 2015 lines 905-913)

Many holistic products are available and effective for worming. Anthelmintic resistance is in part the result of improper use, e.g., the consequence of under dosing, mass therapy and the use of the same class of anthelmintics for prolonged periods of time (Villalba et al., 2014). Resistance to synthetic parasiticides is not a problem, if synthetic parasiticides are not used. Livestock production based on grazing and browsing systems is directly related to the use of plant resources (Alonzo-Diaz, 2014). With proper pasture management, a good diet with plenty of forage for livestock and knowledgeable coaches to provide appropriate strategies for husbandry and treatment healthy animals can be sustainably raised without synthetic parasiticides (Brunetti and Karreman, 2006). (TR 939-946).

In Summary:

When evaluating ivermectin with reference to the OFPA Criteria at 6518(m), this material clearly demonstrates:

- That it is toxic in the environment – Criteria 2;
- That it has a negative impact on dung beetles which are a critical component of good pasture management (pasture management is a requirement of organic farming) – Criteria 5;
- That there are two alternative synthetic parasiticides which can be used as alternative medications during an emergency; that high quality pasture and range management grazing techniques can reduce the need to use any parasiticide; and that there are many alternative herbal remedies – Criteria 6;
- That use of ivermectin is incompatible with a system of sustainable agriculture – Criteria 7.

V RECOMMENDATION - MOTION TO REMOVE:

That ivermectin (CAS # 70288-86-7) be removed from the National List §205.603.

Vote in Subcommittee:

Motion by: Jean Richardson

Seconded by: Harriet Behar

Yes: 8 No: 0 Abstain: 0 Absent: 0 Recuse: 0