

National Organic Standards Board
Livestock Subcommittee Petitioned Material Proposal
Fenbendazole
July 21, 2020

Summary of Petition:

In July 2019, the NOSB received a petition requesting a revision to the annotation at 7 CFR §205.603 (23)(i) to include the use of Fenbendazole for laying hens and replacement chickens intended to become laying hens.

The targeted organisms of Fenbendazole are the parasitic roundworms *Ascaridia galli* and *Heterakis gallinarum*. Chickens infected with *A. galli* and *H. gallinarum* become unthrifty, weak and emaciated and exhibit weight loss proportional to the parasite load. Young birds are more susceptible to the parasites than are mature hens, but mature hens will exhibit significant loss of egg production when infected with *A. galli* and *H. gallinarum*.

Histomoniasis, also known as Blackhead Disease, is a disease caused by infection with *Histomonas meleagridis*. The disease was named “blackhead disease” because one of the common symptoms observed in infected birds is a bluish or blackish appearance of the skin on their face, comb and wattles. The discoloration occurs because of excessive concentration of reduced hemoglobin in the blood or cyanosis. Flocks of laying hens frequently are infected during the late summer and fall, following heavy rainfall. This is due to the association of earthworms, who commonly surface from the soil after heavy rains. If the chickens eat earthworms which carry the cecal worm, *Heterakis gallinarum*, they will indirectly become infected themselves.

Fenbendazole is an antiparasitic drug that works at the sub-cellular level preventing cell division. Benzimidazoles bind to the β -tubulin, inhibiting the cell’s microtubule assembly responsible for intracellular transport and required for mitotic cellular division. (McKellar and Scott 1990). In effect, it starves the parasite by causing intestinal cell disruption. Studies conducted by Sander and Schwarz 1994; Yazwinski and Tucker 2008, Yazwinski et al, 2013, and Alvarado and Mozisek 2018 showed that the late-stage larvae and adult stages of *A. galli* and *H. gallinarum* treated with Fenbendazole showed significantly increased mortality, but hens treated with Flubendazole passed viable eggs that was not significantly decreased in numbers. According to the Merck Veterinary Manual, “The wide safety margin of benzimidazoles is due to their greater selective affinity for parasitic β -tubulin than for mammalian tissues.” (Merck, 2006)

Fenbendazole was first approved in 1983 for use in cattle, including beef animals and dairy cows, as a treatment and control of several types of gastronomic worms, including: lungworms, stomach worms (brown stomach worm, barberpole worm and small stomach worm), and intestinal worms (hookworm, threadnecked intestinal worm, small intestinal worm, bankrupt worm, and nodular worm).

A request was submitted to FDA by Ivervet, Inc. to expand the use of Fenbendazole to chickens. The FDA determined that the ADI (Acceptable Daily Intake) in humans is 40 ug/kg of body weight per day and the tolerance for Fenbendazole is 1.8 ppm expressed as the metabolite fenbendazole sulfone. In October 2015, the FDA gave formal approval for the use of Fenbendazole in treatment and control of adult *A. galli* in broiler chickens and replacement chickens intended to become breeding chickens and for the treatment and control of adult *A. galli* and *H. gallinarum* in breeding chickens. The FDA allowed a total of 2.4 ppm residual of Fenbendazole in eggs with no withdrawal time from application.

On January 15, 2018, the approval was extended for the use of Fenbendazole under the trade name of AquaSol for the treatment and control of adult *A. galli* in broiler chickens and replacement chickens and for the treatment and control of adult *A. galli* and *H. gallinarum* in breeding chickens and laying hens.

Fenbendazole was approved to be administered to conventional laying hens and replacement hens at the following rates:

- 200 mg of fenbendazole/ml for oral administration via drinking water
- Safe-Guard® AquaSol must be administered orally to chickens via the drinking water at a daily dose of 1.0 mg/kg BW (0.454 mg/lb.) for 5 consecutive days.

Conventional poultry producers typically administer Fenbendazole to pullets (age 17 weeks of age) or before outdoor access is given to birds to ensure birds have no internal parasites before starting egg production. When birds receive access to the outdoors they come into contact with soil and in turn come into contact with internal parasites. Many producers find the need to re-treat their flocks after a period when birds have access to the soil and come into contact with many internal parasites.

Organic Summary:

In May 2012, Fenbendazole was added to the National List for use in organic livestock, as specified at 7 CFR § 205.603:

In 2016 the NOSB recommended that the annotation for Fenbendazole be amended to include the following:

- *That parasiticides continue to be prohibited in slaughter stock.*
- *That the milk withholding period after treatment with fenbendazole be changed from 90 days to 2 days for dairy cows, and 36 days for goats and sheep.*
- *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 fenbendazole be allowed without written order of a veterinarian.*

On Jan 28, 2019: The NOP issued a final rule:

Paragraph (a)(23)(i) is revised to read as follows: Fenbendazole (CAS #43210-67-9)—milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for: 2 days following treatment of cattle; 36 days following treatment of goats, sheep and other dairy species.

In addition, paragraph (b)(2) of § 205.238(b) is revised and paragraph (b)(3) is added to § 205.238(b) as follows: (b)(2) Dairy animals, as allowed under § 205.603; and (b)(3) fiber bearing animals, as allowed under § 205.603. AMS has reviewed and agrees with the NOSB recommendation that § 205.238(b) be amended to clarify its use of parasiticides for dairy animals and for fiber bearing animals.

In Spring 2018, the NOSB recommended clarifying “Emergency” for use of synthetic parasiticides in organic livestock production. The following language was recommended for a rule change:

Emergency treatment to allow synthetic pesticide use in livestock: A livestock emergency is an urgent, non-routine situation in which the organic system plan's preventive measures and veterinary biologics are proven, by laboratory analysis or visual inspection, to be inadequate to prevent life-threatening illness or to alleviate pain and suffering. In such cases, a producer must administer the emergency treatment (§205.238(c)(7)). Organic certification will be retained, provided that such treatments are allowed under § 205.603 and the organic system plan is changed to prevent a similar livestock emergency in individual animals or the whole herd/flock in future years as required under §205.238(a).

Add this to § 205.238 (b)(4) Organic livestock as provided in §205.238 (b) (1), (2), and (3) and only in the event of an emergency where management strategies have been proven insufficient to prevent

or control parasites within the accepted threshold for specific parasites, age and species of the animal. These management strategies include but are not limited to, grazing systems and living conditions that prevent infestation and re-infestation, forage height diversity, use of allowed non-synthetic botanicals, biologics and minerals to maintain parasite levels below treatment thresholds, and could include monitoring and documentation of parasites through use of methods such as fecal monitoring and FAMACHA.

(23) 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. 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. Allowed for fiber bearing animals when used a minimum of 36 days prior to harvesting of fleece or wool that is to be sold, labeled, or represented as organic.

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

In Fall 2019, the NOSB Livestock Subcommittee reviewed the petition to expand the annotation to allow Fenbendazole for use on laying hens and replacement chickens intended to become laying hens and submitted a discussion paper at the Fall 2019 NOSB meeting. Based on public comments from the Fall 2019 NOSB meeting, the Subcommittee requested a technical report (TR) limited specifically to the use of Fenbendazole in laying hens and replacement chickens intended to become laying hens. The Livestock Subcommittee gave ten specific focused questions to the TR team concerning human health issues and regulatory issues, and asked the TR team to research any effective alternative methods to the use of Fenbendazole in controlling *A. galli* and *H. gallinarum* worms in laying hens and replacement chickens intended to become laying hens.

A second discussion paper was submitted by the NOSB in Spring 2020 to elicit more public comments on amending the 7 CFR 7 CFR §205.603 (23)(i) annotation to allow fenbendazole for use in laying hens and replacement chickens intended to become laying hens.

Summary of Public Comments

The NOSB Livestock Subcommittee received many public comments during the Fall 2019 and Spring 2020 NOSB meetings.

- Many of the public comments were focused on human health concerns resulting from the FDA allowance of 2.4 ppm residual of Fenbendazole in eggs when there is no withdrawal time. Some questioned the method that FDA used to determine the safety of the 2.4 ppm residual of Fenbendazole in eggs. One commenter was concerned that spent laying hens might end up being used for slaughter in soups, etc. That concern is not valid as the current annotation prohibits the livestock from being used as slaughter animals after treatment with Fenbendazole.
- Some public commenters stated their concerns that the definition of “Emergency” had not been adopted by the NOP. They stated that without “Emergency” being adopted the use of Fenbendazole in laying hens and chickens intended to become laying hens was “ripe for fraud.”
- Some commenters stated that “small producers with hens given more access to pastures” did not have problems with worms. Other producers countered by stating that the problems with worms being present in hens and their eggs has significantly increased since producers had shifted their practices to meet the increased demand for eggs from hens with humane certifications for Free Range or Pasture Raised production models which requires 2.0-108.9 square feet per bird of outdoor access. When birds are out grazing, they are scratching and digging in the dirt for worms and in return picking up intestinal parasites.

- Certifiers and OTA took surveys of their poultry producers to determine if amending the annotation to allow use for laying hens would be of benefit to them. Results of the surveys suggested that the producers were experiencing issues with worms in eggs and that having the use of Fenbendazole on an emergency basis would be one more tool for them to utilize when needed. Other certifiers stated their clients were not having problems with worms in eggs.

Technical Review Summary

The TR addressed the specific questions asked by public commenters and the NOSB Livestock Subcommittee.

- **Health issues concerning the 2.4 ppm residual of Fenbendazole in eggs with no withdrawal period.** The TR states that the ADI was established by the FDA based on extrapolation from adverse health effects found in a six-month oral toxicity study that fed Fenbendazole fed to laboratory dogs. Prior to the FDA's 2018 approval of Fenbendazole for use in laying hens, the detection of any Fenbendazole residues in eggs was considered a violation (Marmulak et al. 2015).

The TR found that infants and children are considered at a greater risk from exposure to veterinary drug residues than adults, because of their lower weight, growth and developmental stage which many risk assessment models do not include. The study also indicated increased risks to pregnant women and fetuses exposed to the drug (Boobis et al. 2017). In a study of food safety risks, Fenbendazole was rated as having a medium likelihood of occurrence (Bobkov and Zbinden 2018).

In one human health study, five adult males were fed the equivalent of 2,500 eggs and 5,000 eggs respectively. There were no relevant changes in blood pressure, pulse rate, symptom list, self-rating scale, and clinical chemistry. (Rupp and Hajdu 1974, reported in Inchem 1998).

Human trials were conducted in 1976 to determine whether Fenbendazole would be considered as treatment for human hookworms and pinworms. Fenbendazole was found to be effective with minor side effects of constipation and burning when urinating. Nevertheless, since that time Fenbendazole has not commonly been used to treat human infestations.

Benzimidazoles (Fenbendazole) have been used as cancer chemotherapy agents and has been studied as a potential anti-cancer agent (Duan et al. 2013). Development of Fenbendazole is still in relatively early stages. Nothing was found in the scientific literature to suggest Fenbendazole residues in eggs would interfere with its use as a cancer treatment.

- **Fenbendazole Amounts in Eggs and Poultry**
The question was asked whether cooking eggs at the recommended cooking temperatures of 144-158 F would eradicate the Fenbendazole residuals. The TR found that Fenbendazole fully degrades with peaks of 222.76 F, 447.24 F, 654.66 F and 862.07 F, all considerably higher than eggs are normally cooked for consumption.
- **Natural Alternatives to using Fenbendazole**
Organic livestock producers have historically and traditionally used a wide range of botanical and naturopathic remedies to control worms in poultry. One common natural remedy is the use of Diatomaceous Earth fed to the birds. The TR provided a table of several substances and methodologies historically used. Most but not all remedies are derived from plants commonly found in the U.S. The TR states that these remedies do not have efficacy or safety data on file with the FDA and are not labeled for internal use on animals. Many of these botanical remedies do not have scientific evidence of their efficacy and safety specifically to poultry internal parasites. At least one organic parasite management guide questions the scientific evidence supporting the efficacy of homeopathic remedies.

Studies show that sanitation of poultry runs is crucial. Pastures, yards and pens should be rotated frequently. It is not clear how long the rotation period in the runs is needed to break the parasitic cycle. Worm eggs may survive in pastures for over two years, and in some experiments, rotations did not significantly reduce infestation rates. Some studies indicated that DE could more effectively be applied to the litter as ovicides to prevent re-infestation of the parasites rather than fed in the poultry feed. The use of probiotics is showing some promise of helping eradicate the worm populations in poultry.

The TR concludes that there is very little research looking at the effectiveness of the natural practices used by organic farmers to control worm populations. The efficacy and safety of these treatments are based largely on anecdotal information and not supported by peer-reviewed scientific research.

Category 1: Classification

1. Substance is for: _____ **Handling** ___X___ **Livestock**
2. For HANDLING and LIVESTOCK use:
 - a. Is the substance _____ **Agricultural** or ___X___ **Non-Agricultural**?
Describe reasoning for this decision using NOP 5033-2 as a guide:
 - b. If the substance is **Non-agricultural**, is the substance _____ **Non-synthetic** or ___X___ **Synthetic**?
 - c. 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:

The manufacturing process for Fenbendazole was included in the March 2007 petition requesting the addition of Fenbendazole as an approved material under §205.603(a)(23)(i) of the National List. The Fenbendazole in AquaSol is now further processed whereby it is reduced in particle size to create a more stable suspension in drinking water. This further processing subjects the Fenbendazole to a wet-milling process whereby a 40 percent fenbendazole suspension is recirculated between a mixing vessel and wet-mill. Utilizing a rotating axis and milling beads, the wet-mill subjects the Fenbendazole particles to impaction and shear forces, reducing the particle to a submicron size. Moreover, at the end of the manufacturing process Panacur AquaSol is a 20 percent Fenbendazole suspension whereas Panacur Suspension 10% (Safe Guard in the US) is a 10 percent suspension.

3. For **LIVESTOCK**: 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?

Fenbendazole is petitioned as a parasiticide.

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)]

Fenbendazole is insoluble in water and excreted after administration in feces. Because it is not soluble, there is little mobility of fenbendazole in soils, and a low risk of groundwater contamination. Laboratory tests show that radiolabeled fenbendazole is degraded with a half-life of 54 days. Although photo-degradation plays a role, degradation of fenbendazole in soil appears to be microbially dependent rather than photodegradative (Kreuzig et al., 2007).

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)]

Fenbendazole toxicity was demonstrated in pigeons and doves leading the authors of the study to suggest a toxic etiology for fenbendazole in birds of the order Columbiformes treatment (Howard et al., 2002).

The fate of Fenbendazole in manure and manured soils has been studied under laboratory and field conditions. In pig manure, benzimidazoles disappear slowly. After a 102-day incubation period, 80% Fenbendazole remains. The latter was accompanied by 4% of the corresponding metabolite fenbendazole-sulfoxide. Fenbendazole-sulfoxide remains in clay soil samples after 54 days (Kreuzig et al., 2007).

Excreted Fenbendazole and Ivermectin residues in cattle dung pats do not significantly affect adult dung beetles or adult dipteran flies; however, excreted Ivermectin produces toxic effects on the larval development of the same dung-colonizing families of insects, while Fenbendazole lacks such toxic effects (Strong et al., 1995).

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.

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

Fenbendazole is manufactured by a process that requires petrochemicals such as benzene and various amines. These are considered toxic compounds.

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

Fenbendazole is not generally considered toxic to humans at regulated doses (FDA, 1995).

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)]

Fenbendazole is insoluble in water, is not a leachate, binds tightly to soil and is not expected to migrate in soil. The only route for fenbendazole to enter the environment is through animal excretion or spillage. Fenbendazole degrades in soil through microbial and photodegradative processes, taking up to 60 days (Hoechst-Roussel Agrivet, 1995)

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

Fenbendazole can break into albendazole. However, there is a low likelihood of physiologic effects. (pg 5 TAP)

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)]

While diatomaceous earth (DE) is utilized widely and effectively as a control for external parasites, its effectiveness as an internal control has not been reputedly documented. Diatomaceous earth has no effect on lungworm and is not very appetizing to poultry. It may also be a lung irritant. Given that the level of dust is already quite high in barns, diatomaceous earth does not seem appropriate when the animals are fed indoors. The main motivation for adding diatomaceous earth to rations should not be to control internal parasites.

2. **For Livestock substances, and Nonsynthetic substances used in Handling:** In balancing the responses to the criteria above, is the substance compatible with a system of sustainable agriculture? [§6518(m)(7)]

Parasiticide use has been tolerated in organic livestock production on a limited basis to alleviate animal suffering. This has almost been, without exception, part of an integrated system of animal health management and requires documentation of a number of approaches other than intervention.

National List Motion:

Motion to amend the listing for fenbendazole to include: Fenbendazole-for use in laying hens or replacement chickens intended to be laying hens at 7 CFR §205.603 (23)(i).

Motion by: Sue Baird

Seconded by: Kimberly Huseman

Yes: 4 No: 2 Abstain: 0 Absent: 0 Recuse: 0

Approved by Sue Baird, Livestock Subcommittee Chair, to transmit to NOP July 22, 2020