United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/national-list/petitioned

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Fenbendazole

Livestock

Identification of Petitioned Substance

Chemical Names:
Fenbendazole
Methyl N-(5-phenylsulfanyl-3H-benzimidizaol-2-yl)carbamate
5-(Phenylthio)-2-benzimidazolecarbamic Acid Methyl Ester
Carbamic acid, N-[6-(phenylthio)-1H-benzimidazol-2-yl]-, methyl ester
Methanol, 1-methoxy-1-[[6-(phenylthio)-1H-benzimidazol-2-yl]imino]-, (E)-

Other Name:
FBZ, Fenbendazol, Phenbendasol; Fenbendazolum, HOE 881

Trade Names:
Safeguard®, AquaSol, Panacur, Worm-A-Rest; Lincomix; Zoetis-BMD®

CAS Number:
43210-67-9

Other Codes:
ChemSpider: 3217
EINECS: 256-145-7
InChi Key: HDDSHPAODJUKPD-UHFFFAOYSA-N
PubChem: CID
SMILES: COC(=O)NC1=NC2=C(N1)C=C(C=C2)SC3=CC=CC=C3

Summary of Petitioned Use

The petition is to amend the annotation at 7 CFR 205.603(a)(23)(i) to include "laying hens and replacement chickens intended to become laying hens . . ." (Flinn 2019). The target organisms of the parasiticide fenbendazole are the roundworms *Ascaridia galli* and *Heterakis gallinarum.* These nematodes, along with *Capillaria* spp., are recognized as the principal helminthic parasites of chickens, with *A. galli* by far the most common (Soulsby 1965; Macklin and Hauck 2019). The life cycles of both target nematodes are simple and direct, transmitted bird-to-bird via fecal droppings (Kaufmann 1996; Yazwinski and Tucker 2008; Weir 2016; Macklin and Hauck 2019). Infected chickens are unthrifty, weak, and emaciated, and have weight loss proportional to the parasite burden (Griffiths 1978; Kaufmann 1996; Yazwinski and Tucker 2008; Macklin and Hauck 2019). Young birds are particularly susceptible (Kaufmann 1996; Macklin and Hauck 2019). Although mature hens are less susceptible, their egg productivity may drop (Griffiths 1978; Kassai 1999), and death may occur in severe cases (Macklin and Hauck 2019). Because chickens raised as broilers have a much shorter lifespan than laying hens, parasiticides are generally not required to treat them. Turkeys have a longer grow-out than broilers and are subject to additional helminthic parasite pressure, particularly the roundworm parasite *Ascardia dissimilis* (Griffiths 1978; Macklin and Hauck 2019). Any purpose other than the treatment of laying hens and replacement of chickens intended to become laying hens is beyond the scope of this Technical Report (TR).

Fenbendazole currently appears on the USDA National Organic Program's National List of Allowed and Prohibited Substances ("National List") as an allowed synthetic medical treatment for use in organic livestock production, as follows:

> (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.

Additional information on the uses of the substance and the evaluation criteria to add substances to the National List appears in a Technical Advisory Panel (TAP) report and a previous technical report (TR) (USDA 1999; USDA 2015).

The NOSB has requested that this TR answer ten additional specific focus questions. These questions and a summary of the answers appear at the end of this document. Where possible, references that address the questions are cited in the appropriate sections of the TR.

Characterization of Petitioned Substance

Fenbendazole is a benzimidazole veterinary anthelmintic – i.e., an antiparasitic drug (US NLM 2020). The mode of action works at the sub-cellular level, preventing cell division. Benzimidazoles bind to β-tubulin, inhibiting the cell's microtubule assembly responsible for intracellular transport and required for mitotic cellular division (McKellar and Scott 1990). The mode of action is described in detail by Martin (1997). The ultimate effect on nematodes is starvation caused by intestinal cell disruption and inhibition of nematode egg production (Martin 1997; USDA / AMS / AAD 2015). The late-stage (L5) larvae and adult stages of *A. galli* and *H. gallinarum* are susceptible (Alvarado and Mozisek 2018). Efficacy studies reported that fenbendazole increased mortality of *A. galli* larvae and adult, but did not report any reduction in the number of viable parasite eggs (Sander and Schwarz 1994; Yazwinski and Tucker 2008; Yazwinski et al. 2013; Alvarado and Mozisek 2018). Hens treated with flubendazole, a related benzimidazole anthelmintic, passed viable *A. galli* eggs at a rate that was not significantly different from the no-treatment control (Tarbiat et al. 2016). Fenbendazole will bind to mammalian ß-tubulin, but with significantly less affinity than to nematode ß-tubulin (McKellar and Scott 1990; Villar et al. 2007).

The molecular structure of fenbendazole is shown in Figure 1. Table 1 contains fenbendazole's physical and chemical properties.

Figure 1. Fenbendazole Molecular Structure ($C_{15}H_{13}N_3O_2S$). Source: Royal Society of Chemistry 2020.

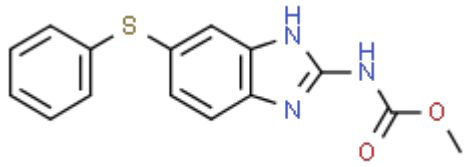

Table 1: Physical and Chemical Properties of Fenbendazole

Property	Characteristic / Value	Source
Molecular formula	$C_{15}H_{13}N_3O_2S$	(US NLM 2020)
Molecular weight	299.3g/mol	(US NLM 2020)
Percent composition	Pharmaceutical grade: 98.0–101.0% $C_{15}H_{13}N_3O_2S$ on a dry-weight basis	(USP 2007)
Physical state at 25°C / 1 Atm.	Dry powder (fenbendazole alone) Suspension (SafeGuard® Aquasol)	(Merck 2017)
Melting point	233°C (451°F)	(US NLM 2020)
Solubility	0.9 µg/mL	(US NLM 2020)

Approved Legal Uses of the Substance:

Fenbendazole is approved as a New Animal Drug Application (NADA) by the U.S. Food and Drug Administration's Center for Veterinary Medicine (U.S. FDA CVM). Intervet was the sponsor for the

evaluation of SafeGuard® AquaSol by the FDA and provided the evidence that was used as the basis for FDA granting its approval (FDA 2018). The FDA has established a tolerance of 1.8ppm fenbendazole in eggs, using the predominant metabolite fenbendazole sulfone as a marker [21 CFR 556.275]. This effectively provides a maximum residue limit (MRL) of 2.4 ppm total fenbendazole, including its metabolites fenbendazole sulfone and oxfendazole (FDA 2018). In addition to poultry, the FDA has approved fenbendazole for use in cattle, swine, sheep, horses and turkeys, as well as zoo and wildlife animals [21 CFR 520.905, 21 CFR 558.258]. Fenbendazole is also approved for use as an anthelminthic for laying hens in the European Union (EMA 2011) and Canada (Health Canada 2020).

Evaluation Questions for Substances to be used in Organic Livestock Production

A previous TAP report and TR evaluated fenbendazole using the criteria identified in the Organic Foods Production Act (OFPA) for the evaluation of substances to be included on the National List for livestock production [7 CFR 205.603] (USDA 1999; USDA 2015). This TR includes new information on fenbendazole that is relevant to the petition to amend the National List (Flinn 2019).

Evaluation Question #9: Discuss and summarize findings on whether the use of the petitioned substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

The previous TAP report and TR evaluated fenbendazole's environmental impacts (USDA 1999; USDA 2015). These reviews identified probable environmental contamination from its use, misuse, or disposal as well as the effects of fenbendazole on agroecosystems, including the physiological effects on soil organisms, crops, and livestock, as well as other non-target species. The current petition includes data on potential harm to non-target species (Flinn 2019). The NOSB has requested that this technical review answer several focus questions related to fenbendazole's potential harm to the environment.

The European Medicines Agency (EMA) published a European public assessment report on the use of Panacur AquaSol, another liquid suspension formulation of fenbendazole labeled for control of roundworm infections in pigs and poultry in the European Union (EMA 2011). The study concluded that, at the time of publication, there were no known side effects, but warned that "[r]epeated use of Panacur AquaSol or a similar anthelmintic may result in resistance."

The resistance of poultry nematodes to fenbendazole was a concern before it was registered for labeled use in the United States. Trials were conducted for fenbendazole as a treatment for *A. galli* and *H. gallinarum* in chickens and *Ascardia dissimilis* in turkeys (Yazwinski et al. 2013). The birds were treated with both medicated feed and with an oral drench. Fenbendazole-resistant *A. dissimilis* has been isolated from turkeys raised on an organic farm (Collins et al. 2019). While no known populations of fenbendazole-resistant *A. galli* or *H. gallinarum* have been mentioned in the literature, development of resistance is seen as a likely outcome (Kaplan and Vidyashankar 2012; Yazwinski et al. 2013).

The concern over the impacts of fenbendazole on aquatic environments is primarily based on studies to review it as a parasiticide in fish farming. There is also potential exposure through integrated livestock-fish farming, particularly with integrated poultry/swine/fish farms with manured ponds in various agroecosystems (Little and Edwards 2003). Such systems are relatively common in Asia and are being adopted on all arable continents, with growing interest in their use in aquaponic and hydroponic systems. Fenbendazole is toxic to the aquatic invertebrate *Daphnia magna* (Oh et al. 2006; Puckowski et al. 2014; Wagil et al. 2015), a model species that is an indicator of ecotoxicity in aquatic environments. The larvae of the freshwater aquatic insect *Chironomus riparius* exposed to fenbendazole had a 96-hour lethal concentration (LC_{50}) of 93.5 $\mu g\ L^{-1}$. The EMA summary also noted that fenbendazole has harmful effects on aquatic animals and should not be released in surface waters (EMA 2011).

Fenbendazole may be toxic to other species of birds. Pigeons and doves (Order: Columbiformes) appear to be susceptible to greater weight loss and lower survival rates when treated with fenbendazole (Howard et

al. 2002; Gozalo et al. 2006). An American white pelican (*Pelecanus erythrorhynchos*) quarantined prior to admission to an unspecified zoological park was diagnosed with ascarids and treated with fenbendazole. It died in a week, and the veterinarians suspected that the cause of death was fenbendazole toxicosis (Lindemann et al. 2016). Fenbendazole toxicosis was also suspected during incidents involving the deaths of vultures (*Gyps africanus* and *Torgos tracheliotus*) and marabou storks treated at zoos (Bonar et al. 2003). All incidents were at clinical and not residual or incidental levels. No replicated studies on bird models were found that showed similar fenbendazole toxicosis, including to chickens or other domesticated fowl.

Additional analysis of the environmental impacts of SafeGuard® AquaSol 20% are presented in the environmental assessment (EA) submitted to the FDA (Merck 2015). The FDA issued a Finding of No Significant Impact (FONSI) after reviewing Merck's EA for SafeGuard® AquaSol 20% (Vaughn 2017). The EA assumed that "chickens are typically held in enclosed buildings (not pasture)" (Merck 2015). This is not a valid assumption for organic poultry, which are required to have outdoor access and are often pastured. Thus, the EA for fenbendazole use in poultry production did not estimate the impacts of the substance on terrestrial organisms in organic poultry production systems. The Predicted Environmental Concentration in the Soil (PEC_{soil}) model in the EA was "calculated for intensively reared chickens (held in enclosed buildings) only" (Merck 2015). Supplemental information contained in the current petition does not correct the assumption that organically produced poultry are only held in enclosed buildings, nor does it provide data based on pastured poultry (Flinn 2019).

<u>Evaluation Question #10:</u> Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

Toxicity Studies

Most studies regarding fenbendazole's toxicity have been performed with animal models and veterinary applications. Benzimidazoles, which includes fenbendazole, are regarded as safe in amounts up to 20 to 30 times the recommended dose (Danaher et al. 2007). Fenbendazole's acute toxicity to mammals is low. Table 2 summarizes toxicity data based on controlled trials with animal models. All reported values for rats, mice, dogs, goats, sheep, and pigs went to the maximum dosage without reaching a lethal dose (LD_{50}) (US NLM 2020). Because a lethal dose for 50 percent of the test animals was not achieved at the highest dosage to which they were exposed, the LD_{50} for fenbendazole is undefined. No acute exposure limit is available (EMA 2011). An LD_{50} for poultry was not found.

Table 2: Toxicity of Fenbendazole

Study	Results	Source
Acute oral toxicity	LD_{50} Rat: >10 g/kg (>10,000 mg/kg); LD_{50} Mouse: >10 g/kg (>10,000 mg/kg); LD_{50} Dog: >500 mg/kg LD_{50} Goat / Sheep: >5 g/kg (>5,000 mg/kg); LD_{50} Pig: >5 g/kg (>5,000 mg/kg)	(Inchem 1998; US NLM 2020)
Teratogenicity	Rats: No evidence of embryotoxic or teratogenic effects at the highest doses (66 mg/kg bw/day)	(Inchem 1998)
Genotoxicity	Ames Test: Negative Mitotic Index: Positive Forward Mutation Index: Weakly positive DNA Repair: Negative Micronucleus test: Negative Cytogenics assay: Negative	(Inchem 1998)
Reproductive	Rats: No treatment related effects Mice: No treatment related effects Rabbits: One abortion and noted skeletal abnormalities in the highest does cohort (63 mg / kg bw / day) Dogs: No treatment related effects	(Inchem 1998)

Study	Results	Source
	Swine: No treatment related effects Sheep: No effects on lambing and no apparent abnormalities in the offspring Cattle: No effects on calving and no apparent abnormalities in the offspring Horses: No apparent effects on foals	

No studies were found to estimate human toxicity based on human exposure incidence data or extrapolation from animal models. Studies noted that the metabolites of fenbendazole, particularly febantel and the sulfoxide metabolites fenbendazole sulfone and oxfendazole, appear to be more toxic to rats than fenbendazole (Inchem 1998; Villar et al. 2007). Febantel and oxfendazole both caused increases in malformations of embryonic rats (Inchem 1998). Additional toxicity information is contained in the FDA Freedom of Information Summary (FDA 2018), the EA, and the current petition.

Acceptable Fenbendazole Intake and Presence in Eggs

According to FDA regulations, the acceptable daily intake (ADI) for total residue of fenbendazole by humans is 40 µg/kg of body weight per day [21 CFR 556.275(a)]. The tolerance for fenbendazole in eggs is 1.8 ppm expressed as the metabolite fenbendazole sulfone [21 CFR 556.275(b)(2)(ii)]. The FDA based this on a total fenbendazole MRL of 2.4 ppm (FDA 2018). 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 to laboratory dogs (FDA 2018). Because of their lower body weight, growth, development, and metabolic activity, infants and children are considered at greater risk from exposure to veterinary drug residues than adults, which many risk assessment models do not include (Boobis et al. 2017). This report also indicates that risks from exposure to veterinary drugs to pregnant women and fetuses are greater than current models estimate. In a survey of food safety risks posed by veterinary drugs administered to poultry, anthelmintics and "febendazole" [sic] were rated as having a medium likelihood of occurrence (Bobkov and Zbinden 2018).

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). Prior to its approval with a 0-day egg withdrawal, the Food Animal Residue Avoidance and Depletion Program (FARAD) recommended a 17-day withdrawal period for hens following the oral administration of fenbendazole at a dosage rate of 1 mg/kg (Marmulak et al. 2015). The extended withdrawal period was to ensure that the drug residues in eggs were below the detection limits of the USDA Food Safety and Inspection Service (FSIS). Instead of detection limits, FSIS establishes "minimum levels of applicability" (MLAs) (FSIS 2018). It is unclear whether FSIS has established an MLA for eggs.

In an early human study, five healthy male subjects were administered oral doses of 300 mg of fenbendazole with breakfast. Another group of six healthy male subjects were given 600 mg of fenbendazole 12 hours after their last meals. Fenbendazole was detected in the serum of two of the five subjects that received fenbendazole with food, and none of the six that received fenbendazole without food. No relevant changes to blood pressure, pulse rate, symptom list, self-rating scale, and clinical chemistry values were observed in the subjects (Rupp and Hajdu 1974, reported in Inchem 1998). Figuring that a USDA Graded large egg minus the shell weighs about 50 grams on average, these doses would be the equivalent of eating 2,500 eggs and 5,000 eggs, respectively, with fenbendazole at the MRL of 2.4 ppm.

Fenbendazole Use to Treat Parasites in Humans

Human trials were conducted to see if fenbendazole was a suitable anthelmintic for various internal parasites in people (Bruch and Haas 1976; Bhandari and Singhi 1980). One study involved Liberian students ages 7–18 who were infected with hookworms—mainly *Necator americanus*—and whipworms (*Trichuris*). Fenbendazole was more effective than Pyrantel, a common anthelmintic approved for human use, for treating *Trichuris* and equally effective as Pyrantel in the treatment of hookworms (Bruch and Haas 1976).

Fenbendazole and mebendazole, another benzimidazole, were also tested along with a placebo to treat 72 patients in Udaipur, India who were infected with human pinworm (*Enterobius vermicularis*) (Bhandari and Singhi 1980). The study excluded patients considered to be at risk, including pregnant women, severely debilitated patients, those with hemoglobin under 50 percent of normal, or patients with a history of heart, liver, or kidney disease. All patients treated with fenbendazole and mebendazole recovered; the patients receiving the placebo showed no improvement. Minor side effects reported by a few of the test subjects included constipation and a burning sensation during urination (Bhandari and Singhi 1980).

Since the time this study was conducted, fenbendazole has not been commonly used as an anthelmintic for treating pinworm, hookworm, or whipworms. The most common benzimidazoles used on humans are albendazole and mebendazole. Both have shown declining efficacy due to resistance (Moser et al. 2018). Hookworm resistance to mebendazole was documented in Mali in the 1990s (De Clercq et al. 1997), while hookworms resistant to Pyrantel in Western Australia were still susceptible to albendazole (Reynoldson et al. 1997). There is nothing in the literature to indicate that fenbendazole exposure played a role in that decline in efficacy. Likewise, no studies were found that specifically examined the effects of long-term, low-dose intake of fenbendazole.

Potential Fenbendazole Cancer Treatments

Benzimidazoles have been used as cancer chemotherapy agents (McKellar and Scott 1990). Oncodazole has been used as an anti-tumoral agent since the 1970s (Heobeke Van Nijen and De Brabender 1976). Fenbendazole binds to ß-tubulin and prevents the assembly of tubulin components into microtubules of cancer cells (Dogra Kumar and Mukhopadhyay, 2018). The mode of action as a cancer treatment is roughly the same as its activity as a parasiticide. The combination of fenbendazole with supplementary vitamins was observed to significantly reduce tumorigenicity in laboratory mice being treated for pinworms *Aspiculuris tetraptera* (Gao, Ping, Watson 2008). More recently, fenbendazole has been studied as a potential anti-cancer chemotherapy agent (Duan et al. 2013). Development of fenbendazole as a cancer treatment is still in relatively early stages. Fenbendazole's cytotoxicity and inhibition of cancer cell growth is described as "moderate" but it still shows promise given it relatively low mammalian toxicity (Dogra Kumar and Mukhopadhyay, 2018). Nothing was found in the scientific literature to suggest fenbendazole residues in eggs would interfere with its use as a cancer treatment.

One reported case that involved a self-administered dose of fenbendazole as a non-FDA approved treatment for chronic Lyme disease resulted in acute hepatitis (Regina et al. 2017). Incidents from the FDA's Adverse Event Reporting System (FAERS) were not accessed. The NOSB may wish to request that the FDA provide the number and types of incidents involving human exposure to fenbendazole.

Fenbendazole Amounts in Eggs and Poultry

Benzimidazoles in general—and particularly fenbendazole—can be challenging to detect using standard analytical methods (Hu et al. 2010; Domínguez-Álvarez et al. 2013; Rodríguez-Gonzalo et al. 2017). The compounds degrade rapidly into a variety of metabolites. The behavior and fate of these compounds in egg and other poultry products remains largely unknown (Bistoletti et al. 2011; Rodríguez-Gonzalo et al. 2017). As analytical techniques improve, better data on the presence of fenbendazole, its metabolites, and other benzimidazole parasiticides in eggs can be gathered, and from that it will be possible to determine acceptable withdrawal times for consumers (Rodríguez-Gonzalo et al. 2017).

Cooking is believed to reduce veterinary drug residues in eggs and poultry meat, but there are no reliable models to predict the extent of reduction (Bobkov and Zbinden 2018). Fenbendazole thermally degrades in four steps, with endothermic peaks at 105.98°C (222.76°F), 230.69°C (447.24°F), 345.92°C (654.66°F), and 461.15°C (862.07°F), with it fully degrading at 754.57°C (1,390.22°F)(Attia et al. 2017). All are considerably higher than the American Egg Board's recommendation of cooking eggs to an internal temperature of 160°F (71.1°C) (AEB 2020).

Ascarids may migrate up the oviduct via the cloaca and become enshelled within a hen's eggs (Kassai 1999; Yazwinski and Tucker 2008; Macklin and Hauck 2019; Flinn 2019). Because ascarids are host species-specific, their presence in eggs is acknowledged as an aesthetic or food quality issue, not a food safety or

public health problem (Macklin and Hauck 2019; Flinn 2019). Careful candling prior to releasing the eggs can avoid the problem (Yazwinski and Tucker 2008; Macklin and Hauck 2019). None of the helminths of poultry are regarded as a threat to public health (Yazwinski and Tucker 2008). However, there is a concern that nematodes may serve as a vector for food-borne pathogens. One study showed that the food-borne pathogen *Salmonella enterica* can infect both *A. galli* at both the egg and adult stages of the nematode. The infected *A. galli* could in turn serve as a vector for poultry and eggs to be infected with *Salmonella* (Chadfield et al. 2001). Poultry can also be co-infected with *Escherichia coli* bacteria and *A. galli* (Permin, Christensen, and Bisgaard 2006). The mechanism of co-infection is not known.

Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

Organic poultry producers have long relied on natural (non-synthetic) anthelmintics (de Baïracli Levy 1976; Lampkin 1990; Glos 2004, 2011; Bennett et al. 2011; Lans and Turner 2011). Diatomaceous earth (DE) is one commonly used non-synthetic substance, which can significantly reduce the nematode burden in a susceptible breed (Bennett et al. 2011). The same study showed the beneficial effect is less significant in a nematode-resistant breed, but the authors concluded that the evidence still showed some beneficial effect (Bennett et al. 2011). Bentonite and kaolinite clay are other mined minerals that have been anecdotally reported to be used as anthelmintics when used as feed supplements. DE, bentonite, and kaolinite are Generally Recognized As Safe (GRAS) by the FDA and appear as allowed non-organic, non-synthetic ingredients for organically handled and processed foods [7 CFR 205.605(a)].

Botanical Alternatives to Fenbendazole

Organic livestock producers have historically and traditionally used a wide range of botanical and naturopathic remedies to prevent and treat livestock parasitism (de Baïracli Levy 1976; Glos 2004, 2011; Lans and Turner 2011). Various plants, herbs, and essential oils are also used as anthelmintics. Table 3 contains a partial list of various plants used for the management of internal parasites in livestock in general, particularly organically produced poultry. A few comprehensive reviews of plant-derived parasiticides have been published (Waller et al. 2001; Mali and Mehta 2008).

Table 3: Plants and Plant Derivatives Reportedly Used for Livestock Parasite Management

English Name	Scientific Name	Comments
Absinthe	*Artemesia absinthum*	Contains santonin as an active component. May be toxic to poultry at higher doses.
Betel	*Areca catechu*	Nut derivative containing the alkaloid arecoline. Sometimes combined with tobacco or a nicotine extract. Considered carcinogenic by the International Agency for Research on Cancer (IARC).
Bishkatali	*Polygonum hydropiper*	Extracts for the leaves contain unknown active ingredients, although it is possible one is a sesquiterpene.
Blackberry	*Rubus* spp.	Sometimes referred to as "bramble leaves."
Bladder wrack	*Fucus vesiculosus*	Sea vegetable in the rockweed family. Dried meal used in starter chick formulas.
Burdock	*Arctium lappa*	Whole plant and seeds. Main biologically active ingredient is arctigenin.
Canada thistle	*Cirsium arvense*	Macerated crude extract of whole plant is high in volatile oils and tannins.
Carrots	*Daucus carota*	Both wild and domesticated are used. Roots are used for feed. Contains umbelliferone.
Comfrey	*Symphytum officinale*	Whole plant.
Dandelion	*Taraxacum officinale*	Whole plant.
Epazote	*Dysphania ambrosioides*	Also known as "Mexican tea" or wormseed. Contains ascaridole as an active component.
Fennel	*Foeniculum vulgare*	Seeds. Main constituent anethole.

English Name	Scientific Name	Comments
Garlic	*Allium sativa*	Biologically active ingredient is allicin.
Goosegrass	*Galium aparine*	Also known as bedstraw or cleavers.
Ginger	*Zingiber officinale*	Contains zingerone and other volatile oils.
Hul-hul	*Cleome viscosa*	Alcohol extract of seed contains various alkaloids.
Hyssop	*Hyssopus officinalis*	Whole plant. Contains various terpenoids.
Judean wormwood	*Artemesia Judaica*	Contains santonin as an active component. May be toxic to poultry at higher doses.
Juniper	*Juniperus* spp.	Steam-distilled byproducts from sawmills is also sold as cedarwood oil. Main biologically active components are cedrane and cedrol, also known as "cedar camphor."
Kamala	*Mallotus philippensis* formerly *Kamella philippensis*	Leaf extracts. Principal active component is rottlerin.
Kelp	*Ascophyllum nodosum*	Dried meal used in starter chick formulas.
Lambsquarters	*Chenopodium album*	Leaves contain ascaridole.
Mugwort	*Artemisia vulgaris*	Contains santonin as an active component.
Mustard	*Brassica juncea* and *Sinapsis alba*	Seeds and leaves. Various isothiocyanates have nematicidal properties.
Neem	*Azadirachta indica*	Principal active component azadirachtin. EPA registered as a pesticide.
Onion	*Allium cepa*	Main active ingredient allicin.
Oregano	*Origanum vulgare*	Main active ingredient carvacrol.
Papaya	*Carica papaya*	Alcohol-extract from seeds. Benzyl isothiocyanate is the principal active component.
Parsley	*Petroselinum crispum*	Leaves and stems.
Pepper	*Capsicum annuum*	Active component capsaicin.
Peppermint	*Mentha piperata*	Main active ingredient is menthol.
Pomegranate	*Punica granatum*	Peels contain the alkaloid pelletierine.
Poppy	*Papaver somniferum*	Seeds as a decoction.
Pumpkin	*Cucurbita maxima*	Seeds as a decoction; the amino acid cucurbitine and the alkaloids berberine and palmatine may have anthelmintic properties.
Pyrethrum	*Chrysanthemum* spp.; *Tanacetum* spp.	Active ingredients are pyrethrins. EPA registered as an external parasiticide but not labeled for internal use.
Rosemary	*Rosmarinus officinalis*	Main active components are carnosic, labiatic and rosmarinic acids; carnosol and rosmarol.
Senna	*Senna alexandrina* (formerly *Cassia acutifolia*)	Active components include various senna glycosides.
Slippery elm	*Ulmus fulva*	Inner bark contains an oily mucilage with high viscosity and tannins. Described as increasing expulsion of worms with a non-toxic mode of action.
Snakeroot	*Polygala senega*	Roots contain terpenoid saponins.
Spearmint	*Mentha virdis*	Active ingredients are menthol and carvone.
Stinging nettle	*Urtica dioica*	Leaves and stems contain the coumarins esculetin and scopoletin as well as several phenolic acids that are biologically active.
Thyme	*Thymus vulgaris*	Main biologically active ingredient is thymol.
Tobacco	*Nicotiana* spp.	Main active component is nicotine. Tobacco is a known carcinogen, and tobacco dust is prohibited in organic crop production [7 CFR 205.602]. Tobacco is allowed for organic livestock production because it is nonsynthetic and not prohibited at 7 CFR 205.604.

English Name	Scientific Name	Comments
Turmeric	*Cucurma longa*	Contains curcumin and other curcuminoids.
Western red cedar	*Thuja plicata*	Oil is a steam-distilled byproduct from sawmills. Main biologically active components are cedrane and cedrol, also known as "cedar camphor."
Wild ginger	*Asarum caudatum; Asarum canadense*	Aristolochic acid is believed to be the principal active component.
Wormseed	*Artemisia cina*	Also called "santonica." Not to be confused with epazote. The species was historically grown for pharmaceutical companies to prepare santonin.
Wormwood	*Artemisia* spp.	Various santonin-bearing plants of the genus are traditional anthelminthic herbs called "wormwood."

Sources: Lilly 1920; de Baïracli Levy 1976; Lal et al. 1976; Campbell and Rew 1986; Lampkin 1990; Moore 1990; Glos 2004, 2011; Mali and Mehta 2008; Lans and Turner 2011; Wink 2012; Symeonidou et al. 2018; Flinn 2019.

Most but not all remedies in Table 3 are derived from plants commonly found in the United States. However, most of these remedies do not have efficacy or safety data on file with the FDA and are not labeled for internal use on animals, and thus are not explicitly FDA-approved for use in animals. Many of the substances in Table 3 are common food ingredients and are allowed as feed supplements or production tools for organic flocks provided that they are organically produced and handled and do not appear in 7 CFR 205.604. Strychnine is not included in the review of botanical remedies because it appears on 7 CFR 205.604 as a prohibited non-synthetic for organic livestock production.

Many of these botanical remedies do not have scientific evidence of their efficacy and safety specifically to poultry internal parasites. Additionally, many of them function based on secondary metabolites such as terpenes, phenols, and nitrogen-containing compounds (Symeonidou et al. 2018). *A. galli* is used as a model nematode for screening plants for anthelmintic trials because of the easy availability of both the parasite and the host (Kaushik et al. 1974; Lal et al. 1976; Mali and Mehta 2008). Santonin derived from *Artemesia* spp. and ascaridole from *Chenopodium* (later *Dysphania*) spp. were both manufactured by pharmaceutical companies and used by veterinarians as botanically derived anthelmintics (Lilly 1920; APA 1955). Ascaridole has a mode of action of tubulin disruption and starvation like the benzimidazoles (Symeonidou et al. 2018). Both botanicals were almost entirely replaced by synthetic anthelmintics by the 1960s (Campbell and Rew 1986). Other secondary metabolites that have known anthelmintic properties are curcumin, aspidin, filicin (filixic acid), pelletierine, and arecoline (Wink 2012). There are also a number of tubulin-binding phytochemicals that show potential as anthelmintics, including taxol and colchine (Wink 2012). The pumpkin seed extracts demonstrated anthelmintic properties on the nematodes *Caenerhabditis elegans* and *Heligmosoides bakeri* The researchers concluded that cucurbitine, an amino acid, and the alkaloids berberine and palmatine were the primary constituents that appeared to be responsible for nematode mortality (Grzybek et al. 2016).

Pomegranate (*Punica granatum*) peels orally administered to hens in Greece reduced fecal egg counts comparable to treatment with levamisole (Symeonidou et al. 2018). An Egyptian study found that pomegranate peel alcohol extracts and pumpkin seed alcohol extracts showed anthelmintic activity against *A. galli* that was not significantly different from fenbendazole (Azziz et al. 2018).Neem leaf extracts were shown to have comparable efficacy to the chemical anthelmintic levamisole in the control of *A. galli* in clinical trials conducted in Bangladesh (Saha et al. 2015).

An ethanol extract from the stem bark of *Piliostigma thonningii* demonstrated anthelmintic properties on *A. galli*-infected cockerels, principally by stimulating the neuromuscular junction and ganglion. The active substance in the extract was isolated as D-3-*O*-methyl chiro inositol (Mali and Mehta 2008). Bitter melon (*Momordica charantia*) fruit extract, papaya (*Carica papaya*) seed extract, and marking nut (*Semecarpus anacardium*) fruit all demonstrated greater mortality and overall efficacy in the suppression of *A. galli* when compared to the synthetic parasiticide piperazine hexahydrate (Lal et al. 1976). Both aqueous and alcohol extracts from the hul-hul (*Cleome viscosa*) seed at a concentration of 100 mg/mL caused paralysis and death

of *A.galli* more rapidly than piperazine citrate at 10 mg/mL, with the alcohol extract performing better (Mali et al. 2007). Garlic oil in a water suspension increased mortality of both *A. galli* and *H. gallinarum* (Singh and Nagaich 2000). Extracts from bishkatali (*Polyganum hydropiper*), papaya, neem, mahogany, and bitter melon leaves all inhibited the development of *A. galli* eggs and growth of the larvae. Bishkatali leaves at a 10 percent concentration showed an efficacy in excess of 80 percent, with a 20 percent concentration resulting in 88 percent of eggs being undeveloped (Islam et al. 2010).

Homeopathic Alternatives to Fenbendazole

Some organic farmers use homeopathic remedies to treat parasites and have done so for many years (Lampkin 1990; Karreman 2004). Homeopathic remedies used for birds affected by worms include Aconite, Santonite 3x, and Tucrum merver (Glos 2011). Though at least one organic parasite management guide questions the scientific evidence supporting the efficacy of homeopathic remedies, some producers still use these remedies as alternatives to conventional treatments (Neeson and Love 2014).

Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Organic, free-range laying hen systems are widely reported to have higher helminth infection rates than conventional caged-layer production systems (Permin et al. 1998; Kaufmann et al. 2011b; Mullens and Murillo 2017; da Silva et al. 2018). No studies were found that empirically compared infestation rates between organic and non-organic systems in the United States. One thesis was conducted on free-range natural layer systems in Arkansas, but the flocks were not organically managed and there was no comparison with conventional caged systems (Weir 2016). Management and sanitation are the main methods for control (Macklin and Hauck 2019). Young birds are particularly susceptible to *A. galli* and should be kept separate from older birds (Griffiths 1978).

Parasite Control via Environment

To understand control of internal parasites, it is important to understand the life cycle of the individual parasites:

- *Large roundworms (Ascarids):* The life cycle of roundworms is relatively simple and can take as little as 35 days to complete. The adult worm lives in the intestines of birds. The female worm lays eggs that are passed out of the chicken via the droppings. The eggs are sporulated and need to become infective outside of the host. While in the bedding material, these eggs need to develop into the larval stage. Optimum temperature for the development of the roundworm egg is 90-93°F (32-34°C). A new host ingests the developed eggs from the infected bedding material. The larvae are released from the egg and make their way to the intestinal tract of the new host where they develop in the mucosal lining of the intestines. The larvae return to the lumen of the intestines to become adults. Worms are sexually mature 35 days after hatching, and they begin to lay eggs of their own, continuing the life cycle. Depending on the conditions, eggs can remain infective for up to 4 months. Worm eggs can also be picked up by snails, slugs, earthworms, grasshoppers, beetles, cockroaches, earwigs, and other insects. These are known as intermediate hosts; they carry the eggs and pass them on to birds that consume the insects. It is important to identify and minimize the number of intermediate hosts that poultry have contact with to help prevent birds from being re-infected with worms.

- *Cecal worms:* Cecal worms are commonly found in the ceca (two blind pouches at the junction of the small and large intestines) of chickens. Although cecal worms typically do not affect chickens, the worms can carry *Histomonas melegridis*, a species of protozoan parasite that causes histomoniasis (blackhead) in turkeys. The cecal worm eggs provide a welcoming environment and a vehicle for the fragile histomonad protozoan. Like the roundworm, the cecal worm is spread by ingesting mature eggs from contaminated litter, and earthworms are frequently carriers of the cecal worms in contaminated environments. This increases the likelihood of ingestion since poultry readily consume earthworms.

- *Tapeworms:* Tapeworms anchor themselves to the walls of the small intestines of the host. As the worms grow, they add segments to the body rather than simply increasing in size. The segments and the eggs they contain are sloughed off the end of the tapeworm and passed out of the intestine. Unlike roundworms and cecal worms, for which an intermediate host infection is optional, all tapeworms that infect poultry have an indirect life cycle, meaning that they must use an intermediate host such as snails, slugs, beetles, earthworms, grasshoppers, flies, and other insects. Once the eggs are ingested by the intermediate host, the larvae in the segment matures into the infective stage. The intermediate host must be consumed by the primary host (poultry) to complete a worm's lifecycle. Tapeworms then attach themselves to the intestinal wall of the primary host and the lifecycle continues.

Non-tapeworm helminth eggs hatch into larvae in a moist environment. Maintaining dry litter and removing it regularly is a preventive measure (Griffiths 1978; Kaufmann 1996; Glos 2004). Placing feeders in a position where the birds are not standing, scratching, or defecating into the feed is another measure to prevent parasitism (Baier 2015). Pasture, yards, and pens should be rotated frequently (Griffiths 1978; Glos 2004). Infested pastures or runs should be plowed, limed, and reseeded (Glos 2011). Guides published for organic poultry producers say that runs should be left empty for several weeks or at least two months between flocks (Spaulding 1976; Glos 2011). It is not clear how long a rotation out of poultry runs is needed to break the parasite cycle. Poultry manure should be stacked and heated (composted) and not returned to fields that will be used as poultry pasture (Glos 2011). Worm eggs may survive in pasture for two years, and in some experiments, rotations alone will not significantly reduce infestation rates. Other measures, such as treatment of pastures and runs with DE, botanicals, or beneficial organisms that reduce the viability of roundworm eggs, increase the efficacy of rotational grazing.

While sanitation is important, one Swiss study found that organic laying hens raised in litter systems did not have significantly higher helminth loads than those on outdoor runs (Maurer et al. 2009). In a study where laying hens were exposed to a mass challenge infection of *A. galli*, researchers observed that hens that were first given a low-level controlled ("trickle") exposure to *A. galli* developed acquired resistance and experienced lower infection rates after the mass challenge infection than hens that had not had controlled exposure. This creates the possibility that an immunological approach could reduce, but not eliminate, parasitism (Ferdushy et al. 2014). Notably, a Danish experiment also showed that birds subjected to a combination of low-level exposure to *A. galli* and a treatment of flubendazole had lower reinfection rates than birds only receiving the flubendazole treatment (Ferdushy et al. 2014). A potential vaccine to give poultry immunity from *A. galli* infections is being explored, but it faces significant development challenges that must be addressed before it can be tested and deemed viable for introduction to the market (Sharma et al. 2019).

Poultry Immunity and Treatments

Susceptibility appears to be breed specific (Maurer et al. 2007; Yazwinski and Tucker 2008; Kaufmann et al. 2011). In general, heavier chicken breeds such as Rhode Island Reds and Barred Plymouth Rocks are more resistant to ascarid infections than lighter White Leghorns and White Minorcas (Yazwinski and Tucker 2008). Brown Lohmann hens experience little or no parasitism, while white Lohmann hens experience significantly higher parasite loads; breeding for parasite resistance has not been a priority among poultry breeders (Kaufmann, Daş, Preisinger, et al. 2011). Brown Lohmann hens also showed significantly greater resistance to *A. galli* than Danish landrace birds (Permin and Ranvig 2001).

There is evidence that poultry infected with *A. galli* and *H. gallinarum* demonstrate gut-associated immune and electro-physiological responses to parasitism (Schwarz et al. 2011). Dietary and nutritional modifications are used by poultry producers to boost immunity and reduce internal parasites. A Danish study showed that hens infected with *A. galli* and fed rations with a high percent of protein had a lower overall worm burden than hens fed rations with low protein content (Permin et al. 1998). Survival of *A. galli* in one-week old chicks was decreased by feeding higher levels of calcium and lysine (Cuca et al. 1968). Poultry fed diets high in vitamin A and B complex show increased resistance to *A. galli* (Yazwinski and Tucker 2008). A reduction in soluble starch in poultry diets reduced *A. galli* fecundity and survival (Daş et al. 2012). However, the same diet increased fecundity and survival of *H. gallinarum* (Daş et al. 2014). An

understanding of how poultry diet and nutrition influences immune response and electro-physiological intestine function, combined with the selection of nematode-resistant breeds, may be a viable strategy to reduce parasitism and prevent re-infection of birds that are treated with parasiticides (Schwarz 2011).

Nutritional treatments that organic farmers use to help boost immunity include a laxative diet consisting of a mash of pumpkin seeds and milk after a 12 hour fast, followed by a warm mash of bran, middlings, and milk (Glos 2004, 2011). Forages and rations that are diverse and rich in aromatic herbs are also used as feed supplements by organic poultry producers to maintain flock health, boost immunity, and reduce internal parasite burden (Glos 2004).

Other ways of boosting poultry immune systems show promise to reduce the susceptibility of poultry to nematode infection (Suresh et al. 2018; Sharma et al. 2019). Probiotics have been studied for their beneficial effects on flock health, mainly as an alternative to antibiotics (Shini et al. 2013; Suresh et al. 2018). Probiotics may boost the immunological response to parasite infection and reduce the load of food-borne pathogens associated with an infestation (Shini et al. 2013). Herbal supplementation of poultry diets has been shown in at least some cases to improve overall bird health; reduce food-borne pathogen levels; and increase egg productivity, size, and quality (Diaz-Sanchez et al. 2015; Nix 2016). However, the results are somewhat inconsistent, and those studies did not specifically consider helminthic infection rates.

One source that reviewed the ovicidal properties of DE and its various botanical derivatives with anthelmintic properties stated that these substances could be more effectively applied to litter and runs as ovicides to prevent reinfection, rather than administered as feed supplements (Islam et al. 2010). Seeding pastures to crops that are unfavorable to the viability of ascarids is one approach to parasite control (Thamsborg et al. 1999). Pasture plants with demonstrated nematocidal properties can be sown and actively managed. Such an integrated approach could make pasture rotation and run management more effective strategies.

Biological and integrated control of ascarids have also been proposed as both alternatives and complements to chemotherapeutic control (Thamsborg et al. 1999). One promising biological control agent is the nematophagous fungus *Pochonia chlamydosporia.* Soil treated with the fungus was shown to have reduced *A. galli* egg counts. However, the worm burden was reduced only when the soil was first sterilized before introducing the *Pochonia chlamydosporia* (Thapa et al. 2018). Stocking density is thought in some cases to be a factor, but the evidence so far does not support that parasite loads can be lowered simply by reducing stocking density (Heckendorn et al. 2009). Hens in organic and conventional non-caged systems that were treated for *A. galli* and *H. gallinarum* with flubendazole—a benzimidazole anthelmintic with a similar mode of action to fenbendazole— and had the houses treated with the synthetic disinfectant chlorocresol were re-infected between 2 and 9 weeks after treatment

Internal parasiticides are of limited use in poultry without integrated methods that support and maintain their efficacy (Thamsborg et al. 1999; Tarbiat et al. 2016; Lozano et al. 2019). Recent sources describe how anthelmintics are best used in conjunction with other measures (Mullens and Murillo 2017; Macklin and Hauck 2019). The morphology of the adult worms is needed for a reliable diagnosis of the infecting species. As there are few compounds available for treatment, they should be used only against severe infections (Macklin and Hauck 2019).

Focus Areas Requested by NOSB

Alternatives

1. *What agricultural practices can be used to reduce parasites (and/or prevent the reintroduction of these parasites) in outdoor areas for poultry?*
   Prevention or minimizing parasite loads in organic laying hens requires several steps. Sanitation, hygiene, and regular provision of clean, dry litter is essential. It is also important to have routine pasture rotation since flocks can be infected or re-infected by eggs in the environment. This is

particularly important if flock use of the outdoor access is restricted to within 100 feet of a fixed poultry house. Pasture rotation is easier with moveable pens or poultry houses.

There is some research to show that it may be possible to select for parasite-resistant breeds, but further research is required. Although they may show more resistance, that does not mean they are immune to infection. Breed selection must be part of an integrated management plan.

Several sources indicate that, to be effective, fenbendazole and other parasiticides need to be part of an integrated management system that reduces or eliminates the sources of parasites. If management practices are not altered after treating the flock with fenbendazole, the flock will be re-infected within a week. See Evaluation Question #12 above for more information.

2. *Are there currently allowed substances and/or practices (or combinations of allowed substances and practices) to eliminate or reduce parasite infestations in poultry and/or outdoor areas?*
Several organic producers have used diatomaceous earth other mined minerals used as feed supplements to control worms. The effectiveness is, however, questionable, especially in the case of a heavy infestation. The diatomaceous earth (DE) primarily reduces the worm load but does not eliminate it. There are no standards as to how much of a worm load is needed to adversely affect the birds.

Various nutritional programs, herbs, and essential oils have been used by organic farmers with varying results. There is very little research looking at the effectiveness of these practices. The efficacy and safety of these treatments are based largely on anecdotal information and not supported by peer-reviewed scientific research. See Evaluation Question #11 above for more information.

Human Health

1. *What are the specific human health risks associated with consuming eggs from poultry that are infested with parasites?*
The parasites *A. galli* or *H. gallinarum* are host-specific to birds and are not directly transmitted to humans. It is only in severe infestations that the actual worm may appear in eggs. If such an infestation is occurring, the birds will be showing severe health depression as well, which is an animal welfare issue. Even if a worm were in the egg, the poultry parasites are not passed on to humans. Parasites, however, may be vectors of the foodborne pathogens *E. coli* and *Salmonella.* No food-borne illnesses directly attributed to elevated ascarids were found in a search of the public health literature. See Evaluation Question #10 above for more information.

2. *Is there any research on the human health effects of consuming fenbendazole or its metabolites that might be present in eggs following treatment of birds? Is there any research on the effects in young children, older adults, pregnant women and others with compromised immune systems?*
A search of the literature did not find any specific health effects to humans of low doses of fenbendazole consumed over a long period of time. Such a study would require original research involving human test subjects from populations that are generally regarded as vulnerable and thus subject to protections from such experimentation. As such, it would be difficult to obtain Institutional Review Board approval for ethically conducted experiments. While there are some fenbendazole poisoning incidents reported in toxic substance exposure incident databases, none were directly linked to egg consumption. See Evaluation Question #10 above for a summary of results on human health effects of consuming fenbendazole in a short-term trial.

3. *Have any long-term human trials been conducted to determine the effects (to humans) of low doses of fenbendazole consumed over a long period of time?*
A search of the literature did not find any human trials to determine the effects to humans of low doses of fenbendazole consumed over a long period of time. Such a trial would require original research involving human test subjects. See Evaluation Question #10 above for a summary of results on human health effects of consuming fenbendazole in a short-term trial.

4. *Is any information available on whether human exposure to fenbendazole interferes with the efficacy of mebendazole, which is used for human treatment?*
   Cross-resistance to benzimidazole anthelmintics has been observed in different animal parasites and is a concern with humans. Mebendazole and albendazole are used to treat humans in areas where internal parasites are endemic and increasing resistance is a concern. However, there is nothing to indicate that the treatment of poultry with fenbendazole has been a factor in the resistance of hookworms and whipworms to mebendazole and albendazole regimens in Mali, Vietnam, Laos, Ethiopia and Australia. See *Evaluation Question #10* above for more information.

5. *Do parasites develop resistance to fenbendazole? If so, does parasite resistance to fenbendazole diminish its usefulness as a human treatment for parasites (particularly outside the U.S. where its use for human treatment may be approved)?*
   Yes, there are documented cases of parasite resistance to fenbendazole. Fenbendazole is rarely used for treating humans, even outside the US. See Evaluation Question #10 above for more information.

6. *Fenbendazole has shown some promise as a cancer treatment. Is any information available on whether the presence of fenbendazole in eggs consumed by humans could have any effect on this cancer treatment?*
   Research on fenbendazole as a cancer treatment is in its early stages and may not be pursued. Fenbendazole has only recently been labelled for laying hen production and was not a factor at the time of the first studies conducted. Exposure to other sources of fenbendazole, such as in eggs, was not mentioned in the studies reviewed. See *Evaluation Question #10* above for more information.

7. *Does cooking eggs lessen the amount of fenbendazole or its metabolites in eggs?*
   Temperature is believed to increase the rate of degradation of fenbendazole and other residual contaminants. However, no model was found in the literature to predict the rate of degradation or the availability of fenbendazole metabolites. Temperatures required to thermally degrade fenbendazole are above the levels used for cooking. See *Evaluation Question #10* above for more information.

Regulatory Questions

1. *Are there other regulatory bodies or independent organizations (including international bodies) that have published findings regarding the toxicity (or lack thereof) of fenbendazole?*
   Yes, The European Medicines Agency has published findings (EMA 2011). Their conclusion is that fenbendazole presents a low risk of toxicity to humans consuming food products—including eggs—from animals treated with fenbendazole. However, EMA notes that fenbendazole is toxic to aquatic organisms (EMA 2011). See *Evaluation Question #9* above.

2. *What evidence was used to make the determination by FDA to allow use of fenbendazole for laying hens without an intervening period between treatment and sale of eggs? What studies, specifically, were used by the FDA to make their determination? Who provided funding for the studies?*
   The evidence used by FDA is summarized in their NADA 141-449 and the studies are cited in the Freedom of Information Summary (FDA 2018). Intervet was the sponsor of the studies. Additional information and the original studies can be obtained by filing a Freedom of Information Act request to FDA. See *Approved Legal Uses of the Substance* above.

Report Authorship

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All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11—Preventing Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.

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