USDA/AMS/NOP, Standards Division
Attention: National List Manager
1400 Independence Ave.
SWRoom 2642-So., Ag Stop 0268
Washington, DC 20250-0268

Petition to Remove Ivermectin (CAS # 70288-86-7) from Section 205.603 of the National List of Allowed and Prohibited Substances.

This Petition to Remove Ivermectin from Section 205.603 of the NOP's National List of Allowed and Prohibited Substances is made pursuant to The Organic Foods Production Act (OFPA) Section 6518 and 7 CFR 205.600 - 205.606 and in accordance with NOP 3011 effective 3/11/2016.

Petitioner contends that new information indicates that Ivermection 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.*

The following documents are attached herewith in support of this petition:

* A Technical Evaluation Report (TR, 2015), *Parasiticides:Fenbenzadole, Ivermectin , Moxidectin* , June 3,2015, complied by USDA, AMS, Agricultural Analytics Division for the USDA NOP, including an extensive research bibliography, incorporated by reference herewith.

* A Material Data Safety Sheet (MSDS) for Privermectin TM Drench for Sheep

* NOSB Sunset 17, Meeting 2 Recommendation to Remove, October 2015

* NOSB Recommendation 1/9/2016 *To Amend Use of Parasiticides in Organic Livestock Production*. – discussed and voted at Public Meeting on April 27 2016

* Extensive Public Comments on Ivermectin and other parasiticides can be found on the NOP Website and are incorporated by reference herewith.

Petition format follows NOP 3011:'

Item A.1 — Indicate which section or sections the petitioned substance will be included on and/or removed from the National List.

• Synthetic substances allowed for use in organic livestock production (§ 205.603).

Item A.2 — OFPA Category - Crop and Livestock Materials.
For substances petitioned for use in crop or livestock production, eligible substances must contain an active synthetic ingredient in one of the OFPA categories (7 U.S.C. § 6517(c)(1)(B)(i)): Petitioners should indicate which OFPA category applies to their petitioned material.

• Livestock parasiticides and medicines.

Item A.3 — Inert Ingredients If the substance is a synthetic inert ingredient intended for use in a pesticide product, please see NOP Notice 11-6 for more information.

* Not applicable

Item B

1. Substance Name.
Provide the substance's chemical and/or material common name. The name of the petitioned substance should be consistent with any name(s) used by other Federal agencies (e.g., FDA, EPA, etc.) .

* Ivermectin CAS # 70288-86-7

2. Petitioner and Manufacturer Information
Provide the name, address, and telephone number for the petitioner and manufacturer (if different).

* Petitioner is Jean Richardson Ph.D., Professor Emerita, University of Vermont, 710 Old Hollow Road, North Ferrisburgh, VT 05473, 802-425-3733

Manufacturer – There are several manufacturers of Ivermectin which is sold under various trade names. For example:

First Priority, Inc.- Privermectin TM Drench for Sheep

Merial Ltd.-Ivomec .27% Injection Grower And Feeder Pigs;

Bayer HealthCare LLC, Animal Health Division-PhoenectinTM;

Norbrook Laboratories Ltd-Noromectin Pour-On for Cattle;

Cross Vetpharm Group Ltd.-Bimectin Pour-On;

SmartVet USA, Inc., Ecomectin; Norbrook Laboratories Ltd.-Noromectin;

Sparhawk Laboratories, Inc.-SparMectin Plus Clorsulon

3. Intended or Current Use

Describe the intended or current use of the substance, e.g., use as a pesticide, animal feed additive, processing aid, nonagricultural ingredient, sanitizer, or disinfectant.

* Parasiticide

4. Intended Activities and Application Rate.

Provide a list of the crop, livestock, or handling activities for which the substance will be used. If used for crops or livestock, the substance's rate and method of application must be described.

* Parasiticide used in emergency treatment of livestock, per label. Prohibited in slaughter stock. Requires a 90 day withholding period. 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.

5. Manufacturing Process

Provide the source of the substance and a detailed description of its manufacturing or processing procedures from the basic component(s) to the final product.

The precursor for ivermectin, avermectin B1 is naturally produced by a Streptomyces avermilitis strain that was mutagenized with high energy ultraviolet light. Hydrogenation of avermectin B1 for 20 hours with Wilkinson's catalyst in benzene or toluene at 25°C under 1 atmosphere of hydrogen produces 85 percent 22,23-dihydroavermectin B1 together and 3 percent of 3,4,22,23-tetrahydroavermectin B1. 22, 23- dihydroavermectin B1, containing at least 80 percent of 22,23-dihydroavermectin B1a and not more than 20 percent of 22,23-dihydroavermectin B1b, is assigned the name ivermectin (Campbell et al., 1983). The UV mutagenized Streptomyces sp., renamed Streptomyces cyanogriseus is described in a patent for the production of ivermectin that was filed in 1990 (lines 530-537 TR June 3, 2015).

See also extensive Bibliography of peer reviewed articles attached to this petition as part of the Technical Report – TR 2015

6. Ancillary Substances

For substances petitioned for use in organic handling or processing

* Not applicable

7. Previous Reviews

Provide a summary of any available previous reviews of the petitioned substance by State or private certification programs or other organizations. If the substance has been previously reviewed and rejected by the NOSB, the petition must provide new information that was not submitted in an earlier petition or provided for in the previous technical reports for the substance.

During 2015 the NOSB received public comment on Ivermectin as part of the regular Five Year Sunset Review for materials scheduled for Sunset in 2017. New information was provided which indicated that Ivermectin was not always effective, that two other parasiticides, moxidectin and fenbenzadole, are 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 absenses. However, during the second posting of this material, public comment from a sector of producers, especially in western states, indicated that Ivermectin was their preferred parasiticide, in part because fenbenzadole requires veterinarian prescription. Therefore the final NOSB vote was to reluctantly continue to list Ivermectin, but to immediately review all the parasiticides as a group. This additional review resulted in a Recommendation (attached to Petition) to make some changes to the parasiticide listings 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.

Reference: 205.603(a) – <u>with language as recommended to NOP on April 27, 2016</u>
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: 2days 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: 2days following treatment of cattle; 36 days following treatment of goats and sheep.

See also:
Technical Report: 1999 TAP (Fenbendazole, Ivermectin);
Past NOSB Actions: 10/1999 NOSB minutes and vote; 11/2005 sunset recommendation; 10/2010 sunset recommendation 10/2015 sunset recommendation.

Sunset Date: 06/27/17

The Parasiticide Recommendation of April 27 2016 passed unanimously, 15:0.

As part of written comment and in oral comment at the public meeting, the NOSB was again urged by a broad sector of stakeholders to Petition to Remove Ivermectin, based on the expectation that the April 27, 2016 Recommendation on parasiticides is approved by the NOP and is successful in the Rulemaking process. This petition is presented in response to public request.

8. Regulatory Authority

Provide information regarding EPA, FDA, and State regulatory authority registrations, including registration numbers. The information provided must confirm that the intended use of the substance is permitted under EPA or FDA regulations, as applicable.

Table 4 in the Parasiticides Technical Report of June 3 2015, provides an overview of the synthetic processes involved in producing all eleven parasiticides approved by US Food and Drug Administration (FDA) for use in livestock for food production.

Because all veterinary drugs must be approved by the FDA, their manufacture is an aspect of production overseen by the US federal government. The FDA provides guidance for inspection of sterile drug manufacturers (FDA, 2014a; 2014b).

The FDA Center for Veterinary Medicine has published a number of guidelines focused on the new drug approval process. Some of these publications focus on anthelmintic drugs, and the manufacturing, processing or holding active of pharmaceutical ingredients.

9. Chemical Abstracts Service (CAS) Number and Product Labels

This item should also include labels of products that contain the petitioned substance. If a product label does not apply to this substance, please provide a brief explanation. Product specification sheets, product data sheets, non-retail labels, or other product information may be substituted for the product label, if appropriate.

The CAS # for Ivermectin is: 70288-86-7

Ivermectin is sold under several labels, for example:

Privermectin TM Drench for Sheep; The MSDS for Privermectin TM, manufactured by First Priority Inc, is attached to this petition

Heart Guard.

10. Physical and Chemical Properties

Provide the substance's physical properties and chemical mode of action including the following: (a) Chemical interactions with other substances, especially substances used in organic production; (b) Toxicity and environmental persistence; (c) Environmental impacts from its use and/or manufacture; (d) Effects on human health; and (e) Effects on soil organisms, crops, or livestock

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 soil particles. The half-life for degradation of ivermectin in soil can be as long 240 d 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)

11. Safety Information

Provide safety information about the substance including a Material Safety Data Sheet (MSDS) and a substance report from the National Institute of Environmental Health Studies. If this information does not exist or is not applicable, the petitioner should state so in the petition.

MSDS for Privermectin TM is attached to this Petition.

12. Research Information

This item should include research information about the substance. The research should include comprehensive substance research reviews and research bibliographies, including reviews and bibliographies that present contrasting positions to those presented by the petitioner in supporting the substance's inclusion on or removal from the National List.

A comprehensive research bibliography is included in the Technical Report dated June 3, 2015 and attached to this petition. 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.

13. Petition Justification Statement

Provide a "Petition Justification Statement," which provides justification for any of the following actions requested in the petition:

B. Removal of a Synthetic from the National List (7 C.F.R. §§ 205.601, 205.603, 205.605(b))

• Explain why the synthetic substance is no longer necessary or appropriate for the production or handling of an organic product, making sure to cover all uses of the listed substance.

Ivermectin is no longer necessary as there are two synthetic parasiticides, fenbenzadole 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.

• Describe any nonsynthetic substances, synthetic substances on the National List or alternative cultural methods that could be used in place of the petitioned synthetic substance, and their availability and applicability to all situations where the substance is used.

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 , 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

****

Parasiticides: Fenbendazole, Ivermectin, Moxidectin

Livestock

Identification of Petitioned Substance*

Chemical Names:

Moxidectin:(1'R,2R,4Z,4'S,5S,6S,8'R,10'E,13'R,14'E,16'E,20'R,21'R,24'S)-21',24'-Dihydroxy-4(methoxyimino)-5,11',13',22'-tetramethyl-6-[(2E)-4-methyl-2-penten-2-yl]-3,4,5,6-tetrahydro-2'H-spiro[pyran-2,6'-[3,7,1 9]trioxatetracyclo[15.6.1.1^{4,8}.0^{20,24}] pentacosa[10,14,16,22] tetraen]-2'-one; (2a*E*, 4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,-15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6′-[(*E*)-1,2-Dimethyl-1-butenyl]-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5′6,8,19-tetra-methylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-pq][2,6]benzodioxacylooctadecin-13,2′-[2*H*]pyrano]-4′,17(3′*H*)-dione,4′-(*E*)-(*O*-methyloxime)

Fenbendazole: methyl N-(6-phenylsulfanyl-1H-benzimidazol-2-yl) carbamate

Ivermectin: 22,23-dihydroavermectin B1a +22,23-dihydroavermectin B1b

Thiabendazole: 4-(1H-1,3-benzodiazol-2-yl)-1,3-thiazole

Albendazole: Methyl [5-(propylthio)-1H-benzoimidazol-2-yl]carbamate

Levamisole: (S)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-b][1,3]thiazole

Morantel tartrate: 2,3-dihydroxybutanedioic acid;1-methyl-2-[(E)-2-(3-methylthiophen-2-yl)ethenyl]-5,6-dihydro-4H-pyrimidine

Pyrantel: 4-[(3-carboxy-2-hydroxynaphthalen-1-methyl]-3-hydroxynaphthalene-2-carboxylic acid;1-methyl-2-[(E)-2-thiophen-2-ylethenyl]-5,6-dihydro-4H-pyrimidine

Doramectin: 1.25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)avermectin A1a

Eprinomectin: (4″R)-4″-(Acetylamino)-4″-deoxy-avermectin B1

Piperazine: Hexahydropyrazine; Piperazidine; Diethylenediamine

Other Name:

Moxidectin: Milbemycin B

Fenbendazole

Ivermectin: Dihydroavermectin

Trade Names:

Moxidectin: Equest, Cydectin, ProHeart 6

Fenbendazole: Panacur, Safe Guard

Ivermectin: Heart Guard, Sklice, Stomectol, Ivomec, Mectizan, Ivexterm, Scabo 6

Thiabendazole: Mintezol, Tresaderm, Arbotect

Albendazole: Albenza

Levamisole: Ergamisol

Morantel tartrate: Rumatel

Pyrantel: Banminth, Antiminth, Cobantril

Doramectin: Dectomax

Eprinomectin: Ivomec, Longrange

Piperazine: Wazine, Pig Wormer

CAS Numbers:

Moxidectin: 113507-06-5;

Fenbendazole: 43210-67-9;

Ivermectin: 70288-86-7

Thiabendazole: 148-79-8

Albendazole: 54965-21-8

Levamisole: 14769-72-4

Morantel tartrate: 26155-31-7

Pyrantel: 22204-24-6

Doramectin: 117704-25-3

Eprinomectin: 123997-26-2

Piperazine: 110-85-0

Other Codes:

Moxidectin: Pubchem: CID 16760141; InChI Key: YZBLFMPOMVTDJY-CBYMMZEQSA-N; ChemSpider 167363424

Fenbendazole: PubChem: CID 3334; InChI Key HDDSHPAODJUKPD-UHFFFAOYSA-N; ChemSpider: 3217

Ivermectin: PubChem CID 4330618; InChI Key: AZSNMRSAGSSBNP-UHFFFAOYSA-N; ChemSpider 7988461

Thiabendazole: PubChem: CID 5430

Albendazole: PubChem: CID 2082

Levamisole: PubChem: CID 26879

Morantel tartrate: PubChem: CID 6419965

Pyrantel: PubChem: CID 5281033

Doramectin: PubChem: CID 9832750

Eprinomectin: PubChem: CID 6426924

Piperazine: PubChem: CID 4837

*substances within the scope of this review are in bold

Summary of Petitioned Use

The Organic Foods Production Act (OFPA), 7 U.S.C. 6501 et seq., authorizes the establishment of the National List of allowed and prohibited substances. Exemptions and prohibitions granted under the OFPA are required to be reviewed every 5 years by the National Organic Standards Board (NOSB). The NOSB requested a Technical Advisory Panel (TAP) review of parasiticides in 1995 (NOP, 1995). At the time, ivermectin, fenbendazole and levamisole were under consideration by the NOSB for addition to the National List, § 205.603 Synthetic substances allowed for use in organic livestock production.

The National Organic Standards Board (NOSB) considered the use of parasiticides during its February, 1999 meeting (NOP, 1999a). A TAP review was accepted by the NOSB for parasiticides, November 25, 1999 (NOP, 1999b). Levamisole was reviewed by the NOSB in 1999, but failed to obtain the NOSB's recommendation and was subsequently prohibited. Ivermectin was the first parasiticide included in the National List of Allowed and Prohibited Substances by the same final rule establishing the National Organic Program (NOP, 2000). It was listed as follows:

> § 205.603 Synthetic substances allowed for use in organic livestock production as
>
> (a) medical treatment
>
> (12) parasiticides—ivermectin—prohibited in slaughter stock, allowed in emergency treatment for dairy and breeder stock when organic system plan-approved preventive management does not prevent infestation. Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment. 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 of breeding stock.

In a subsequent proposed rule, a petition for a second parasiticide, moxidectin, as a medical treatment for use in organic livestock production to control internal and external parasites was considered by the NOSB. The NOSB recommendation for adding moxidectin to the National List and a ruling by the US Agricultural Secretary preventing adoption of this recommendation were also published (NOP, 2006; NOP, 2003). Although the NOSB approved addition of moxidectin to the National List, the US Agriculture Secretary could not accept NOSB's recommendation because moxidectin was labeled as a macrolide antibiotic (§205.238(c)(1), §205.238(c)(7), 7 USC Sec. 6517).

In a final rule, the exemption for ivermectin was renewed on October 21, 2007 (NOP, 2007a).

The exclusion of moxidectin was addressed in a final rule amending the National List (NOP, 2007b). Moxidectin and its precursor nemadectin are members of a group of compounds called macrolides. Macrolides contain a signature molecular structure called a macrolide lactone ring. Based on their molecular characteristics, macrolides are divided into two chemical groups, the erythromycins and the polyenes. Moxidectin and nemadectin are members of the polyene group of chemical products. The polyenes unlike their erythromycin counterparts do not possess antibiotic properties. They are inactive against bacteria and not considered antibiotics *sensu stricto* an antibiotic is a type of antimicrobial substance used specifically against bacteria (Hamilton-Miller, 1973). As a result of comments received by the NOP, proposed rulemaking was initiated to authorize moxidectin as a livestock medication to control internal parasites (NOP, 2007b).

A petition for inclusion of fenbendazole on the National List was received by the NOP, March 23, 2007 (NOP, 2007c). Subsequently, a proposed rule addressed NOSB recommendations to establish exemptions (uses) for two substances, fenbendazole and moxidectin, on the National List as parasiticides in organic livestock production (NOP, 2011). A final rule established practice for the use of parasiticides and exemptions (uses) for fenbendazole and moxidectin (NOP, 2012):

> Under the authority of 7 U.S.C. 6501–6522.
>
> § 205.238 Livestock health care practice standard.
>
> (b) 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; and

(2) Dairy stock, when used a minimum of 90 days prior to the production of milk or milk products that are to be sold, labeled, or represented as organic.

(c) The producer of an organic livestock operation must not:

(4) Administer synthetic parasiticides on a routine basis;

(5) Administer synthetic parasiticides to slaughter stock;

(7) Withhold medical treatment from a sick animal in an effort to preserve its organic status. All appropriate medications must be used to restore an animal to health when methods acceptable to organic production fail. Livestock treated with a prohibited substance must be clearly identified and shall not be sold, labeled, or represented as organically produced.

§ 205.603 Synthetic substances allowed for use in organic livestock production.

(a) As 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. Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment. 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)—only for use by or on the lawful written order of a licensed veterinarian.

(ii) Ivermectin (CAS # 70288–86–7).

(iii) Moxidectin (CAS # 113507–06–5)—for control of internal parasites only.

Characterization of Petitioned Substance

Composition of the Substance:

In veterinary medicine the term parasiticide refers to anthelmintic drugs, although ivermectin and moxidectin are also effective against arthropod parasites. Anthelmintics are medications capable of causing the evacuation of parasitic intestinal worms. Fenbendazole, ivermectin and moxidectin are the only anthelmintics approved for use in organic livestock production. They represent two of five anthelmintic drug classes differentiated by their chemical structures. The five known classes of livestock anthelmintics are benzimidazoles, imidazothiazoles, tetrahydropyrimidines, macrocyclic lactones and piperazines (Table 1). Each drug targets a vital system of the parasitic worm to cause incapacitation, death and excretion.

Including fenbendazole, ivermectin and moxidectin, there are eleven parasiticides currently approved by the US Food and Drug Administration Center for Veterinary Medicine for use in livestock production. All available parasiticides including fenbendazole, moxidectin and ivermectin are subject to parasiticide resistance. Populations of naturally drug resistant worms and their eggs present in dairies, stockyards, barns, forages, fields and in infested livestock can cause the failure of anthelmintics to effectively remove parasites from infested animals. If one drug is shown to be ineffective because of resistance, producers and veterinarians can chose a different drug that is likely to be effective (Martin, 1997). Organic livestock production does not require the use of parasiticides; however, information on eight additional parasiticides is included to provide context for the "emergency toolkit" of parasiticides available to livestock producers for chemically controlling parasitic nematodes (Table 1).

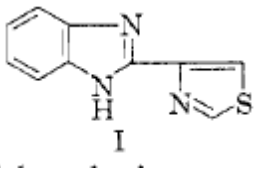
Fenbendazole is the only benzimidazole approved for use in organic livestock production. Two other benzimidazoles approved by the US Food and Drug Administration are thiabendazole and albendazole. Thiabendazole was the first to be described in 1961. It was selected from several hundred analogous compounds with broad spectrum anthelmintic and larvacidal activity (Fig 1). Its potency coupled with the absence of activity toward other microorganisms and negligible mammalian toxicity provided a basis for using this compound

commercially. The mode of action of thiabendazole was not understood at the time of its discovery (Brown et al., 1961).

Table 1 Anthelmintics approved in the United States for Livestock*

Group	Active Ingredient	Manufacturer(s)-Trade Name***
Benzimidazoles	Thiabendazole	Merial Ltd.-Thiabendazole Sheep &Goat Wormer, Thiabenzole, Omnizole, TBZ Cattle Wormer Thibenzole; ADM Alliance Nutrition, Inc.-E-Z-X-Wormer
	Albendazole,	Zoetis-Valbazen
	Fenbendazole	Intervet (Merck)-Panacur®, Safe-Guard®, Lincomix; Virbac-Purina Worm-A-Rest Litter Pack; Zoetis-BMD®/Safe-Guard®
Imidazothiazoles	Levamisole	Zoetis-Riperacol, Tramisol; Intervet (Merck)-Levasole, Tramisol; Agri Laboratories-Prohibit, levamisole phosphate; Cross Vetpharm Group, Ltd.-Levamisole hydrochloride
Tetrahydropyrimidines	Morantel tartrate	Phibro Animal Health Corp.-Rumatel; Zoetis, Inc.-Rumatel, Paratect Flex
	Pyrantel	Phibro, Inc.-Banminth; Virbac AH, Inc.- Purina Ban Worm for Pigs; ADM Alliance Nutrition, Inc.-Ban-A-Worm Pyrantel Tartrate; Virbac AH, Inc. Check-E-Ton BM
Macrocyclic lactones	**Ivermectin**	Merial Ltd.-Ivomec .27% Injection Grower And Feeder Pigs; Bayer HealthCare LLC, Animal Health Division-Phoenectin™; Norbrook Laboratories Ltd-Noromectin Pour-On for Cattle; Cross Vetpharm Group Ltd.-Bimectin Pour-On; First Priority, Inc.-Primectin™ Drench for Sheep, Privermectin; SmartVet USA, Inc., Ecomectin; Norbrook Laboratories Ltd.-Noromectin; Sparhawk Laboratories, Inc.-SparMectin Plus Clorsulon
	Doramectin	Zoetis-Dectomax
	Eprinomectin	Merial Ltd.-Eprinex, Longrange
	Moxidectin	Boehringer Ingelheim Vetmedica, Inc.-Cydectin,
Piperazines	Piperazine	Fleming Laboratories-Pig Wormer, Wazine

Broader spectrum carbamate sulphides and sulphoxide benzimidazoles, respectively fenbendazole and albendazole with high efficacy against lungworms and larvacidal inhibition of *Ostertagia ostertagi* were introduced in the mid-1970s (Table 1; Fig 2.). More effective and marketable benzimidazoles have not been found (McKellar and Scott, 1990).



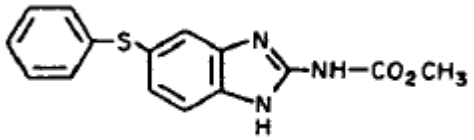
I

Fig 1 Thiabendazole

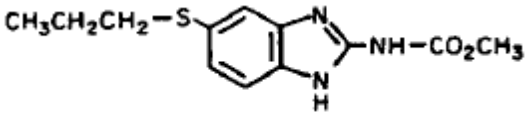
(Brown et al., 1961)

Levamisole is not currently approved for use in organic livestock production. It is also known as tetramisole, a derivative of 6-arylimidazo[2,1-b]thiazole, and the only member of the imidazothiazole class of anthelmintics

approved by the FDA and marketed in the United States. The result of screening a large series of compounds, levamisole is active against parasites of sheep and chickens (Raeymakers et al., 1966; Merck, 1983; Table 1; Fig. 3).



Fenbendazole



Albendazole

Fig 2. Carbamate sulphide and sulphoxide benzimidazoles
(McKellar and Scott, 1990)

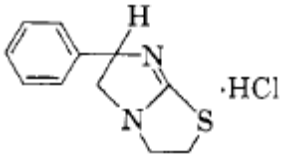
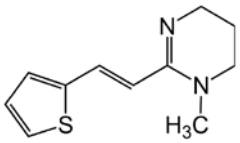


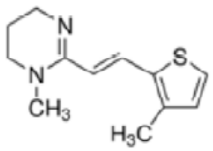
Figure 3. Levamisole

(Raeymaker et al., 1966)

Neither pyrantel tartrate nor morantel are approved for use in organic livestock production. Both are members of the tetrahydropyrimidine class of parasiticides. Morantel is the methyl derivative of pyrantel (Bogan and Armour, 1980). The efficacy of pyrantel as a veterinary anthelmintic was first described in 1966, shortly after the introduction of levamisole. Pyrantel is an imidazothiazole-derived tetrahydropyrimidine with a broad spectrum of activity against immature and adult nematodes (Fig 4; Kopp et al., 2008). Morantel is more potent than pyrantel and requires a lower dose rate for its anthelmintic effect. It is generally formulated as a tartrate salt (Table 1; Fig 4; Lanusse and Pritchard, 1993).



Pyrantel



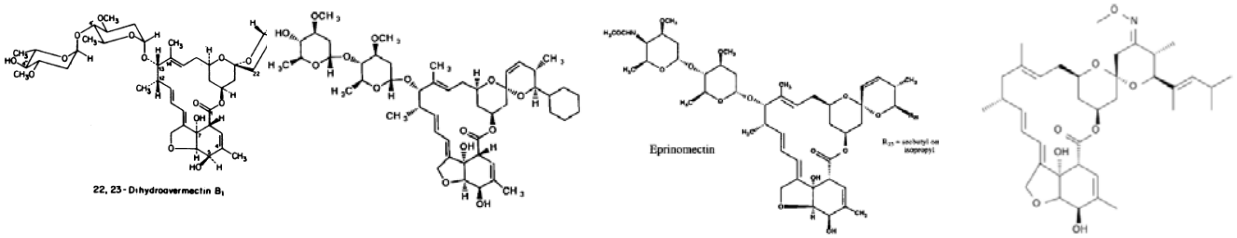
Morantel

Fig 4. Tetrahydropyrimidines: Pyrantel and Morantel

The avermectins and milblemycins are anthelmintic macrocyclic lactones derived from the *Streptomycetaceae* family of Actinobacteria (Prichard et al., 2012; Hamilton-Miller, 1973). They are members of the polyene family of antimicrobial substances (Hamilton-Miller, 1973). Four veterinary drugs in this class are approved for use by the FDA: ivermectin, doramectin, eprinomectin and moxidectin (Table 1; Fig 5).

Ivermectin is approved for use in organic livestock production. Ivermectin was the first of the macrocyclic lactone anthelmintics to be discovered. It is a semi-synthetic chemically reduced 22,23-dihydro derivative of abamectin (Campbell et al., 1983). Abamectin is produced by fermentation of the actinomycete, *Streptomyces avermilitis* which was first isolated from soil in Japan. Abamectin is a mixture of avermectin B_{1a} and avermectin B_{1b} (Stapley, E.O. and Woodruff, H.B., 1982, Prichard et al., 2012). Doramectin was initially isolated through a process called "mutational biosynthesis." Briefly, mutant strains of *Streptomyces avermilitis* lacking branched chain 2-oxo-acid dehydrogenase activity were isolated, cultured and provided with an alternative carboxylic acid as a nutrient source. Fractions of broth from cultures of these strains were then tested for anthelmintic activity.

One fraction contained Doramectin—25-cyclohexyl-5-*O*-demethyl-25-de(1-methylpropyl) avermectin A_{1a} (Goudie et al., 1993; Dutton et al., 1990). An increased frequency in homologous DNA recombination and relaxation of double stranded DNA repair in stationary phase bacteria under nutritional stress is thought to be the mechanism for mutational biosynthesis (Aravind and Koonin, 2000, Lopez-Olmos et al., 2012). Doramectin is not approved for use in organic livestock production.



Ivermectin (Campbell et al., 1983) | Doramectin (Goudie et al., 1993) | Eprinomectin (Shoop et al., 1996) | Moxidectin

Fig 5. Avermectins and Miblemycin

Table 2 Physical and Chemical Properties of the Veterinary Parasiticides

Drug	Formula	Mol. Wt. (grams/mole)	Melting/Boiling Point, °C	Appearance	Solubility
Thiabendazole[1]	$C_{10}H_7N_3S$	201.25	304-305	White to tan crystals	50 mg/L @25°C in water
Albendazole[2]	$C_{12}H_{15}N_3O_2S$	265.33	208-210	Colorless crystals	41 mg/L @25°C in water
Fenbendazole[3]	$C_{15}H_{13}N_3O_2S$	299.35	233	White to tan powder	Insoluble in water
Levamisole[4]	$C_{11}H_{12}N_2S$	204.29	227-227.5	White to tan powder	210 mg/mL in water
Morantel tartrate[5]	$C_{16}H_{22}N_2O_6S$	370.42	167-172	White or pale yellow crystalline powder	Very soluble in water
Pyrantel[6]	$C_{11}H_{14}N_2S$	206.31	178-179	Yellow crystals	Insoluble in water
Ivermectin[7]	$C_{48}H_{74}O_{14}$	875.10	155	Off white powder	Insoluble in water, soluble in methanol or ethanol
Doramectin[8]	$C_{48}H_{74}O_{14}$	899.14	160.5-162.2	White to tan powder	0.003 g/L @25°C in water, very low solubility in water
Eprinomectin[9]	$C_{48}H_{74}O_{14}$	914.14	173	White crystalline solid	0.0035 g/L @25oC in water, very low solubility in water
Moxidectin[10]	$C_{37}H_{53}NO_8$	639.84	145-154	White to pale yellow crystalline powder	0.51 mg/L in water
Piperazine[11]	$C_4H_{10}N_2$	86.14	106/146	Leaflets from alcohol	Soluble in water

[1](FAO, 1993), [2](FAO, 1990), [3](FAO, 1991), [4](FAO, 1993, 1994), [5](Merck, 1983), [6](Merck, 1983), [7](FAO, 2000a, 1991, 1993, 2000b), [8](FAO, 2004), [9](FAO, 1999), [10](FAO, 1999), [11](Merck, 1983),

Eprinomectin is not approved for use in organic livestock production, but was developed in an effort to find a safe and efficacious anthelmintic macrolide for use in dairy production. A large number of synthetic ivermectin

analogs were screened to identify eprinomectin, 4"-epi-acetylamino-4"-deoxy-avermectin B_1. It was chosen for its wide therapeutic index and lowest residue level in milk (Shoop et al., 1996).

Moxidectin is the only milblemycin approved for use in organic livestock production (Takiguchi et al., 1980). Moxidectin, a derivative of nemadectin is a chemically modified *Streptomyces cyanogriseus* fermentation product (Asato and France, 1990). Moxidectin is related to ivermectin, but lacks a disaccharide moiety and has an *O*-methyl substituent at the 23-position (Deng et al., 1991).

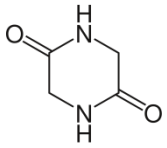


Fig. 6 Piperazine

Piperazine is not currently approved for use in organic livestock production. It is prepared by the action of alcoholic ammonia on ethylene chloride, the reduction of parazine with sodium alcohol and the catalytic deamination of diethylenetriamine and ethylene diamine (Fig 6; Merck, 1983). Piperazine dihydrochloride, piperazine sulfate and piperazine phosphate are effective anthelmintics when used as feed additives in hogs (Guthrie and Briggs, 1956; Praslicka et al., 1997; Steffan et al., 1988).

Source or Origin of the Substance:

As veterinary drugs, parasiticides are articles intended for use in treatment or prevention of disease in animals (Section 201(g)(1)(B) & (C) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(g)(1)(B) & (C)]). The Federal Food, Drug and Cosmetic Act gives the US Food and Drug Administration (FDA) legal authority to approve and regulate veterinary drugs for animals. FDA's Center for Veterinary Medicine (CVM) approves and regulates all new animal drugs. An approved animal drug is one that has gone through the FDA's new animal drug application (NADA) process and has been stamped approved by the CVM. CVM's approval means that the drug is safe and effective. Safety includes safety to the animal and of food products made from the treated animal. CVM also ensures that the drug's strength, quality and purity are consistent from batch to batch and labeling is complete and truthful. The NADA process also considers impact to the environment and the safety of those who administer the drug to animals (FDA, 2015a).

The use of fenbendazole for food animals is approved under six FDA new animal drug applications (Table 3). It is dispensed over the counter. The use of ivermectin for food animals is approved under nineteen FDA new animal drug applications. It is dispensed both by veterinary prescription and over the counter (Table 3). The use of moxidectin is approved under three new drug approval applications. It is available over the counter (Table 3). The approved FDA NADA numbers for the eight additional anthelmintics approved by the FDA are provided in Table 3.

Once a NADA is approved, the FDA, under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), can permit the use of the approved drug under specific conditions outside the designated or intended label use, e.g. use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses (FDA, 1994). This "off-label use" is only permitted in the context of a valid veterinarian-client-patient relationship and is limited to treatments when the health of an animal is threatened or suffering or death may result from failure to treat. A valid veterinarian-client-patient relationship is one in which: (1) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian; (2) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and (3) The practicing veterinarian is readily available for follow up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept (FDA, 2015b).

For example, there is not a FDA approved use for fenbendazole in domestic sheep; however, it is used under veterinary supervision for this purpose (de la Concha-Bermejillo et al., 1998). Furthermore, the National List permits the use of fenbendazole only under veterinary supervision (§ 205.603(18)(a)(i)).

There are some limitations for the AMDUCA including extralabel use of an approved new animal or human drug by a lay person (except when supervised by a veterinarian), extralabel use of an approved new animal or human drug in animal feed, extralabel use resulting in any residue that may present a risk to public health and extralabel use resulting in any residue above an established safe level, safe concentration or safe tolerance. Extralabel use of an approved new animal or human drug in food producing animals is further restricted to times when no approved animal drug with the same active ingredient is available for use or a veterinarian has found the approved animal drug ineffective, only after a diagnosis and evaluation of the conditions of the animal, after establishment of an extended withdrawal time, after assuring the maintenance of the animal's identity and after taking appropriate measures to assure assigned time frames for withdrawal are met and no illegal drug residues occur in any food producing extralabel treated animal (FDA, 2015b).

Properties of the Substance:

Descriptions of the physical and chemical properties of all US Food and Drug Administration Center for Veterinary Medicine approved veterinary parasiticides are provided in Table 2.

Specific Uses of the Substance:

The US Food and Drug Administration Center for Veterinary Medicine and the US Department of Agriculture National Organic Program permit oral administration of fenbendazole in dairy cattle for the removal and control of lungworm (*Dictyocaulus viviparus*); brown stomach worm (*Ostertagia ostertagi*), barberpole worm (*Haemonchus contortus* and *H. placei*), small stomach worm (*Trichostrongylus axei*), hookworm (Bunostom*um phlebotomum*), threadnecked intestinal worm (*Nematodirus helvetianus*), small intestinal worm (*Cooperia punctata* and *C. oncophora*), bankrupt worm (*Trichostrongylus colubriformis*) and nodular worm (*Oesophagostomum radiatum*); in beef cattle (beef) for the removal and control of stomach worm (*Ostertagia ostertagi)* and tapeworm (*Moniezia benedeni*); in goats for the removal and control of stomach worms (*Haemonchus contortus* and *Teladorsagia circumcincta*); in swine for the removal and control of lungworms (*Metastrongylus apri* and *M. pudendotectus*), roundworms (*Ascaris suum*), nodular worms (*Oesophagostomum dentatum*, *O. quadrispinulatum*), small stomach worms (*Hyostrongylus rubidus*), whipworms (*Trichuris suis*) and kidney worms (*Stephanurus dentatus)* and in turkeys for the removal and control of round worms (*Ascaridia dissimilis*) and cecal worms (*Heterakis gallinarum)*. Fenbendazole is sold by Merck Animal Health as Panacur® and Safe-Guard®. It is available in liquid suspension, as granules, as a paste and in blocks. Products are dispensed both by veterinarian's prescription and over the counter, but must be used in organic production only under veterinary supervision. For swine, turkeys, and wild sheep the NADA (141-144, 140-954, 136-116, 131-675) for fenbendazole is for use in medicated feed only. Other uses for these animals are extralabel. Furthermore, the use of fenbendazole in medicated feed for domestic sheep in food production is not permitted by the FDA (2015b).

The US Food and Drug Administration Center for Veterinary Medicine and the US Department of Agriculture National Organic Program permit topical, subcutaneous and oral administration of ivermectin in cattle for the treatment and control of gastrointestinal nematodes: *Haemonchus placei*, *Ostertagia ostertagi*, *O. lyrata*, *Trichostrongylus axei*, *T. colubriformis*, *Cooperia oncophora*, *C. punctata*, *C. pectinata*, *Oesophagostomum radiatum*, *Nematodirus helvetianus*, *N. spathiger*, *Bunostomum phlebotomum*, lungworms: *Dictyocaulus viviparous*, grubs *Hypoderma bovis, H. lineatum*, sucking lice: *Linognathus vituli*, *Haematopinus eurysternus*, *Solenopotes capillatus*, mites: *Psoroptes ovis* (syn. *P. communis* var. *bovis*), *Sarcoptes scabiei* var. *bovis*, in reindeer for treatment and control of warbles (*Oedemagena tarandi*), in swine for treatment and control of gastrointestinal roundworms: *Ascaris suum*; red stomach worm, *Hyostrongylus rubidus*; nodular worm, *Oesophagostomum* species; threadworm, Strong*yloides ransomi,* somatic roundworm larvae-threadworm, Strongyloides ransomi, lungworms: *Metastrongylus* species, lice: *Haematopinus suis*, mites: *Sarcoptes scabiei* var. *suis* and ear mites*: Otodectes cynotis*, in american bison for the treatment and control of grubs: *Hypoderma bovis* and in sheep for treatment and control gastrointestinal roundworms: *Haemonchus contortus*, *H. placei*, *Ostertagia circumcincta*, *Trichostrongylus axei*, *T. colubriformis*, *Cooperia oncophora*, *C. curticei*, *Oesophagostomum columbianum*, *O. venulosum*, *Nematodirus battus*, *N. spathiger*, *S. papillosus,*

Chabertia, Trichuris ovis, lungworms: *Dictyocaulus filaria* and all larval stages of the nasal bot *Oestrus ovis*. Ivermectin is marketed by Merial, Inc. and other companies under a number of pharmaceutical labels. It is available as a drench, in liquid solution, for medicated feed, as a sustained release bolus and as a paste. Products are dispensed both by veterinarian's prescription and over the counter.

The US Food and Drug Administration Center for Veterinary Medicine and the US Department of Agriculture National Organic Program permit topical, subcutaneous and oral administration of moxidectin in cattle for treatment and control of internal and external parasites, gastrointestinal roundworms: *Ostertagia ostertagi*, *Haemonchus placei*, *Trichostrongylus axei*, *T. colubriformis*, *Cooperia oncophora*, *C. pectinata*, *C. punctata*, *C. spatulata*, *C. surnabada*, *Bunostomum phlebotomum*, *Oesophagostomum radiatum*, *Nematodirus helvetianus*, lungworms: *Dictyocaulus viviparus*, cattle grubs: *Hypoderma bovis, H. lineatum*, mites: *Chorioptes bovis*, *Psoroptes ovis*, *P. communis* var. *bovis*, lice: *Linognathus vituli*, *Haematopinus eurysternus*, *Solenopotes capillatus*, *Bovicola(Damalinia) bovis* and horn flies: *Haematobia irritans* and in sheep for the treatment and control of *Haemonchus contortus*, *Teladorsagia circumcincta*, *T. trifurcata*, *Trichostrongylus axei*, *T. colubriformis*, *T. vitrinus*, *Cooperia curticei*, *C. oncophora*, *Oesophagostomum columbianum*, *O. venulosum*, *Nematodirus battus*, *N. filicollis*, and *N. spathiger*. Moxidectin is sold by Boehringer Ingelheim Vetmedica, Inc. as Cydectin. It is available in liquid solution. Products are dispensed over the counter.

Approved Legal Uses of the Substance:

The US Food and Drug administration (FDA) regulates veterinary drugs. A new animal drug is defined, in part, as any drug intended for use in animals other than man, including any drug intended for use in animal feed but not including the animal feed, the composition of which is such that the drug is not generally recognized as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling of the drug (21 U.S.C. § 321(v)). As mandated by the Federal Food, Drug, and Cosmetic Act, a new animal drug may not be sold into interstate commerce unless it is the subject of an approved new animal drug application (NADA), abbreviated NADA (ANADA), or there is a conditional approval (CNADA) in effect pursuant to 21 U.S.C. § 360ccc or there is an index listing in effect pursuant to 21 USC § 360ccc-1 (21 U.S.C. §§ 331(a) and 360b(a)). FDA approved new drug application numbers (NADA) for parasiticides and an overview of information available at Animal Drugs@FDA for livestock parasiticides is provided in Table 3.

Action of the Substance:

Effective veterinary parasiticides have selective toxic effects against nematode worms, i.e., kill the worm, allow the host to evacuate the worms and leave the host safe and healthy. This is true for fenbendazole, ivermectin and moxidectin which act selectively by binding to nematode β-tubulin in the case of fenbendazole and potentiating the glutamate-gated chloride (GLUCL) channel in the cases of ivermectin and moxidectin (Table 3). Binding β-tubulin disrupts the nematode digestive system and prevents egg formation, while potentiating the GLUCL channel causes spastic paralysis.

Fenbendazole, ivermectin and moxidectin work very well for susceptible parasites. However, some worms have a natural mechanism that causes subtle mutations in the genes for the β-tubulin and ion channel proteins targeted by these anthelmintics. This allows the worms in subsequent generations to avoid drug binding and enables drug resistance. Parasiticide resistance management has become an important issue in animal health. Increased use of anthelmintics in livestock production may lead to subsequent selection and increased parasiticide resistance (Xu et al., 1998; James et al., 2009). As a result, if resistance to one drug occurs, then other drugs with the same mode of action or binding site will also be ineffective. It is important to consider parasiticide mode of action in anthelmintic selection, to choose the most effective therapeutic drug (Martin, 1997).

The eleven drugs approved by the FDA for anthelmintic use in food producing animals and their modes of action, (1) nicotinic agonists, (2) γ-amino-butyric acid (GABA) agonists, (3) glutamate-gated chloride receptor potentiators and (4) microtubule blockers, are listed in Table 3.

Combinations of the Substance:

Moxidectin is sold as Cydectin. Cydectin 1% for subcutaneous injection contains the excipients benzyl alcohol, polysorbate 80, propylene glycol, butylated hydroxytoluene, disodium edentate dehydrate, anhydrous sodium phosphate sodium acid phosphate monohydrate and water for injections. Cydectin

Table 3. FDA approval for Anthelmintics in use in the United States for Livestock*

Active Ingredient: Species	Manufacturer(s)-Trade Name***	NADA-Numbers**	Mode of Action***
Thiabendazole: Goats, Sheep, Swine, Cattle, Pheasants	Merial Ltd.-Thiabendazole Sheep & Goat Wormer, Thiabenzole, Omnizole, TBZ Cattle Wormer Thibenzole; ADM Alliance Nutrition, Inc.-E-Z-X-Wormer	013-022, 013-954, 014-350, 015-123, 015-875, 030-103, 030-578, 034-631, 035-631, 042-910, 043-141, 048-487, 049-461	β-tubulin binding: Selective binding to nematode β-tubulin and consequent inhibition of microtubule formation disrupting nematode intestine cells (causing starvation) and inhibiting egg production.
Albendazole: Cattle, Sheep, Goats	Zoetis-Valbazen	110-048, 128-070, 140-934	
Fenbendazole: Cattle, Swine, Wild Sheep (Ovis), Turkeys, Goats, Deer	Intervet (Merck)-Panacur®, Safe-Guard®, Lincomix; Virbac-Purina Worm-A-Rest Litter Pack; Zoetis-BMD®/Safe-Guard®	128-620, 131-675, 132-872, 136-116, 137-600, 139-189, 140-954, 141-144	
Levamisole: Cattle, Sheep, Swine	Zoetis-Riperacol, Tramisol; Intervet (Merck)-Levasole, Tramisol; Agri Laboratories-Prohibit, levamisole phosphate; Cross Vetpharm Group, Ltd.-Levamisole hydrochloride	039-356, 039-357, 042-740, 042-837, 044-015, 045-455, 045-513, 049-553, 091-826, 092-237, 093-688, 101-079, 102-437, 107-085, 112-049, 112-051, 112-052, 126-237, 126-742, 139-858, 139-877, 140-844, 200-225, 200-271, 200-313, 200-386	Nicotinic Agonists: Selectively bind to the synaptic and extra-synaptic nicotinic acetylcholine receptors on nematode muscle cells producing contraction and spastic paralysis.
Morantel tartrate: Cattle, Goats,	Phibro Animal Health Corp.-Rumatel; Zoetis, Inc.-Rumatel, Paratect Flex	092-444, 093-903, 134-779	
Pyrantel: Swine	Phibro, Inc.-Banminth; Virbac AH, Inc.- Purina Ban Worm for Pigs; ADM Alliance Nutrition, Inc.-Ban-A-Worm Pyrantel Tartrate; Virbac AH, Inc. Check-E-Ton BM	043-290, 092-955, 097-258, 100-237, 110-047, 116-044, 1190-877, 135-941, 141-257, 141-261, 200-302	
Ivermectin: Swine, Sheep, Cattle, Goats, Bison, Deer, Reindeer	Merial Ltd.-Ivomec .27% Injection Grower And Feeder Pigs; Bayer HealthCare LLC, Animal Health Division-Phoenectin™; Norbrook Laboratories Ltd-Noromectin Pour-On for Cattle; Cross Vetpharm Group Ltd.-Bimectin Pour-On; First Priority, Inc.-Primectin™ Drench for Sheep, Privermectin; SmartVet USA, Inc., Ecomectin; Norbrook Laboratories Ltd.-Noromectin; Sparhawk Laboratories, Inc.-SparMectin Plus Clorsulon	128-409, 131-392, 137-006, 140-833, 140-841, 140-974, 140-988, 141-054, 141-097, 200-219, 200-228, 200-272, 200-327, 200-340, 200-348, 200-436, 200-437, 200-447, 200-466	Glutamate-gated Chloride (GLUCL) Channel Receptor Potentiator: Selectively binds to the Glutamate chloride channel receptor increasing pharyngeal muscle chloride permeability and paralyzing the parasite. The avermectins also open somatic muscle non- γ-amino butyric acid activated channels and inhibits γ-amino butyric acid activated channels.
Doramectin: Cattle, Swine	Zoetis-Dectomax	141-061, 141-061	
Eprinomectin: Cattle	Merial Ltd.-Eprinex, Longrange	141-079, 141-327	
Moxidectin: Cattle, Sheep	Boehringer Ingelheim Vetmedica, Inc.-Cydectin,	141-099, 141-220, 141-247,	
Piperazine: Chickens, Swine, Turkeys	Fleming Laboratories-Pig Wormer, Wazine	010-005	γ-Amino Butyric Acid Agonist: Selectively binds to the nematode γ-amino butyric acid receptors increasing the opening of muscle membrane chloride channels. Hyperpolarizes the membrane potential and produces spastic paralysis.

*anthelmintic drugs approved by the FDA for use in livestock, links are provided for fenbendazole, ivermectin and moxidectin products. Others can be found at Animal Drugs@FDA.
**Animal Drugs@FDA (2015)
***Martin, 1997.

-Pour On is formulated with Aromatic 100 solvent. Aromatic 100 solvent is composed of solvent naptha (petroleum), CAS #64742-95-2. This product potentially contains the toxic compounds, cumene (<1.1%), pseudocumene (<32%) and xylenes (< 2.2%).

Ivermectin is sold as Ivomec for injection. This product contains the excipients glycerol formal and propylene glycol. The pour on ivermectin product contains the excipients trolamine, crodamol CAP and isopropyl alcohol.

Fenbendazole is sold a Panacur and Safe Guard. The orally administered product contains polysorbate 80, simethicone emulsion 30%, benzyl alcohol and purified water. Febendazole paste contains the excipients carbome homopolymer type B (Allyl pentaerythritol crosslinked), propylene glycol, glycerin, sorbitol, sodium hydroxide, water, methylparaben and propylparaben.

All of the FDA livestock approved parasiticides are synthetically produced substances shown by experimental and clinical studies to be safe for application to food animals. The excipients are usually United States Pharmacopoeia (USP) grade chemicals and also subject to FDA approval.

The use of parasiticides in organic production is strictly confined to emergencies and the practice of returning livestock production to a healthy steady state that does not include the routine use of parasiticides. The current allowance of three parasiticides covering only two modes of action does not address issues of uncontrolled infection when a parasiticide fails to be effective. Combinations of parasiticides and the availability of anthelmintics with all four modes of action are considered in conventional livestock production when addressing infection and the development of anthelmintic resistance (Sargison, 2014; Bath, 2014; Taylor, 2013; Dolinska et al., 2013; McArthur and Reinemeyer, 2014; Leathwick, 2013; Busin et al., 2013; Leathwick, 2014; Le Jambre et al., 2010; Epe and Kaminsky, 2013; Leathwick and Besier, 2014; Bartram et al., 2012; Bartram, 2013).

Status

Historic Use:

Parasitism may be the weakest link in organic livestock production (Karreman, 2004). Outbreaks of disease due to nematode parasites can happen even in well managed flocks. When changes in a production system occur as a result of land use, weather, or transient exposure of susceptible animals to parasites the natural imbalance favors parasite infestation. When unnoticed, undetected and without treatment parasite infestation can lead to disease and potentially death (Stockdale, 2008). The objective of a pest control program in organic farming is to use deworming treatments only in emergencies regardless of whether the treatment is administered with natural products or not (Duval, 1997). This has not been the case with conventional farming where continuous use of parasiticides has resulted in manifold anthelmintic resistance. Anthelmintics were originally described as medicines that "kill or expel parasites from their various locations in the body." They were divided into the vermifuges (did not kill the worms) and the vermicides (killed the worms). The areca-nut from the palm and male fern root, both natural treatments were among the first effective anthelmintics (Hoare, 1896).

During the 1920s, interest in veterinary pharmaceutical drugs, particularly anthelmintics increased prompting the discovery and development for marketing of Antimosan, Ascaridole and Avomin by Bayer.

Antimosan was to be used for lungworms in cattle, Ascaridole for ascarids of pigs and Avomin for chickens. Bayer introduced levamisole in 1966, pyrantel in 1983 and ivermectin in 1997 (Harder, 2002).

Food security is the sustainable production of sufficient amounts of high quality, affordable and safe food required to underpin health and well-being of human populations worldwide (Fitzpatrick, 2013). Many aspects of livestock production including organic production have already moved from rural to peri-urban and urban settings. This change and the growing expectation for "sustainable intensification,"i.e. producing more food from less land, accompanied by more diligent land use are confounding principles for organic livestock production when parasites are considered. Much information is now known about the nematodes, their anatomy, morphology, life cycles, pathogenesis and epidemiology. Not as much is known about their ecology, but this body of research is also growing. Increasing parasiticide resistance spurred a strong movement toward understanding its underpinning molecules and mechanisms improving

diagnostics, epidemiology and management of flocks and herds, while research into alternative approaches to disease control, including genetic selection for resistant or resilient hosts, and vaccination, continues (Fitzpatrick, 2013).

Organic Foods Production Act, USDA Final Rule:

The three parasiticides currently allowed for use by the National Organic Program in organic livestock production as medical treatments are (i) fenbendazole (CAS # 43210–67–9)—only for use by or on the lawful written order of a licensed veterinarian, (ii) ivermectin (CAS # 70288–86–7) and (iii) moxidectin (CAS # 113507–06–5)—for control of internal parasites only (§ 205.603). Their use is prohibited in slaughter stock, but allowed for emergency treatment of dairy and breeder stock when the producer's approved preventive management system does not prevent infestation. Milk or milk products from a treated animal cannot be labeled as organically produced for 90 days following treatment. In breeder stock, treatment cannot occur during the last third of gestation if the progeny will be sold as organic and cannot be used during the lactation period for breeding stock.

International

Canada -

The Canadian Organic Production Systems General Principles and Management Standards (CAN/CGSB-32.310-2006) generally prohibit the use of parasiticides with exceptions. If no alternative treatment exists a parasiticide may be administered under veterinary supervision as directed by the standard and mandated by law. Treated livestock with a withdrawal period equivalent to double the label requirement or 14 days, whichever is longer is still considered organic. Organic status for chronically infected animals is discontinued. The Canadian Organic Standard requires organic livestock operations to have a comprehensive plan to minimize parasite problems in livestock, including monitoring and emergency measures. Normally, parasiticides cannot be administered to meat, dairy or laying animals, but in emergencies, production operations can use them: (1) if parasites are detected, (2) under veterinary instructions, (3) with double the label withdrawal time or 14 days whichever is longer, (4) with one treatment for slaughter animals under one year and two treatments for older animals (requiring more treatments will lose organic status), (5) but dairy animals requiring more than two treatments lose organic status and require a 12 month transition, (6) but dairy animals cannot be organic for slaughter, (7) and a dam may be treated during gestation, (8) and poultry flocks can be treated, but laying hens with more than one treatment per 12 months lose organic status and (9) the operator must provide a written action plan with amendments to the parasite control plan.

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999) - ftp://ftp.fao.org/docrep/fao/005/Y2772e/Y2772e.pdf

Codex Alimentarius guidelines GL 32-1999, Guidelines for the production, processing, labelling and marketing of organically produced foods permits the use of parasiticides where specific disease or health problems occur, or may occur, and no alternative permitted treatment or management practice exists. Phytotherapeutic, homeopathic or ayurvedic products and trace elements are preferred to chemical allopathic veterinary drugs or antibiotics, provided that their therapeutic effect is effective for the species of animal and the condition for which the treatment is intended. If these are not effective in combating illness or injury, parasiticides may be used under the responsibility of a veterinarian. Withdrawal periods should be the double of that required by legislation with, in any case, a minimum of 48 hours. The use of parasiticides for preventative treatments is prohibited.

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008

Preventive use of chemically-synthesized allopathic medicinal products is not permitted in organic farming. However, in the case of a sick animal requiring an immediate treatment, the use of chemically synthesized allopathic medicinal products is limited to a strict minimum. Doubling withdrawal periods after use of chemically synthesized allopathic medicinal products is suggested to guarantee the integrity of organic production for consumers. Because widespread animal diseases would seriously affect organic production, measures may be taken to ensure maintenance of farming or reestablishment of farming with nonorganic animals or non-organic for a limited period in the affected areas.

Japan Agricultural Standard (JAS) for Organic Production—
http://www.ams.usda.gov/nop/NOP/TradeIssues/JAS.html

The Japan Agricultural Standard (JAS) for Organic Production emphasizes that disease shall be prevented by strengthening resistance to disease and prevention of infestation through livestock dependent husbandry practices without unnecessary suffering. In cases where disease occurs or may occur and there is no alternative permitted treatment or management practice or laws and ordinances provide, veterinary drugs can be used. Parasiticides may only be used on livestock for the therapy purpose. In cases where parasiticides are licensed according to the Ministry Ordinance of Regulation on Use of Veterinary Drugs (Ministry Ordinance No. 42, Ministry of Agriculture, Forestry, and Fisheries (MAFF), 1980), the withdrawal period is twice the specified time. In cases where parasiticides are not licensed by MAFF, the withdrawal period is 48 hours prior to slaughter for foods, milking, and egg collection or twice the period of drug withdrawal (the period from the last administration of drugs to slaughter for foods, milking, or egg collection) defined for approval of drugs, change of approvals, reexamination of drugs, and drug efficacy review by Article 14-1, 9, 4, and 6 of the Pharmaceutical Law of Japan, whichever the longer. No specific anthelmintics are specified.

International Federation of Organic Agriculture Movements (IFOAM) –
http://www.ifoam.org/standard/norms/cover.html

Use of synthetic allopathic anthelmintics will cause an animal to lose its organic status, although producers cannot withhold such medication where doing so will result in unnecessary suffering of the livestock. An exception is included, and an animal can retain its organic status if the operator can demonstrate treatment is in compliance with IFOAM preventive animal husbandry practices, and natural and alternative medicines and treatments are unlikely to be effective to cure sickness or are not available to the operator, and the chemically synthetized allopathic veterinary medical products or antimicrobials are used under the supervision of a veterinarian, withdrawal periods are not less than double the withdrawal period required by legislation, or a minimum of 14 days, whichever is longer. The exception is granted for a maximum of three courses of remedial treatments within 12 months, or one course of treatment if the productive lifecycle of the animal is less than one year. Prophylactic use of any synthetic allopathic veterinary drug is prohibited. Vaccinations are allowed only when an endemic disease is known or expected to be a problem in the region of the farm and where this disease cannot be controlled by other management techniques, or when a vaccination is legally required.

IFOAM requires documentation of the impact of the parasiticide on the communities where they are made and used, whether the use of the substance favors any economic structure and scale, and the historical use of the substance in traditional foods. IFOAM also requires that consumer perceptions of the compatibility of inputs be taken into account, that inputs should not meet resistance or opposition of consumers of organic products, that there is scientific certainty about the impact of the substance on the environment or human health, that inputs respect the general opinion of consumers about what is natural and organic, that inputs used for animal feed and livestock production are evaluated for their impact on animal health, welfare, and behavior, that medications alleviate or prevent animal suffering and that inputs causing suffering or having a negative influence on the natural behavior or physical functioning of farm kept animals are prohibited or restricted.

Evaluation Questions for Substances to be used in Organic Livestock Production

Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: 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? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?

The livestock anthelmintics, fenbendazole, ivermectin and moxidectin fall under the Organic Foods Production Act category "livestock parasiticides" (7 U.S.C. § 6517(c)(1)(B)(i)). The National List provides

for the use of livestock parasiticides in an organic farming operation. Three parasiticides are included in the National List: ivermectin, moxidectin and fendbendazole (7 CFR § 205.603(a)(18)).

Table 4. Methods of Synthesis for Anthelmintics approved for use in the United States for Livestock*

Chemical Group	Active Ingredient	Manufacturer(s) **	Methods of Synthesis*
Benzimidazoles	Thiabendazole	Merial Ltd., ADM Alliance Nutrition, Inc.	Benzimidazoles are prepared chemically using a condensation of *o*-phenylenediamine or *o*-nitroaniline with a carboxylic acid derivative. N-arylamide hydrochlorides can also be transformed to benzimidazoles with sodium hypochlorite and base. (Brown et al., 1961; Grenda et al., 1965; Loewe et al, 1976).
	Albendazole	Zoetis	
	Fenbendazole	Intervet (Merck), Virbac, Zoetis	
Imidazothiazoles	Levamisole	Zoetis, Intervet (Merck), Agri Laboratories, Cross Vetpharm Group, Ltd.	Levamisole is chemically synthesized through a number steps. The racemic form was prepared using phenacyl bromide (Raeymakers et al., 1966). More recently, a highly enantioselective synthesis of levamisole has been accomplished by employing (R)-3-acetoxy-3-phenylpropanenitrile and (R)-3-hydroxy-3-phenylpropanenitrile obtained by both enzymatic transesterification and hydrolysis processes (Kamal et al., 2005).
Tetrahydropyrimidines	Morantel tartrate	Phibro Animal Health Corp., Zoetis, Inc.	The chemical name of morantel tartrate is 1,4,5,6-tetrahydro-l-methyl-2-[trans-2-(3-methyl-2-thieny1)vinyllpyrimidine hydrogen tartrate. Synthesis of morantel involves the condensation of 3-methylthiophene-2-carbaldehyde with 1,4,5,6-tetrahydro-1,2-dimethylpyrimidinien the presence of methyl formate (Addison et al., 1974).
	Pyrantel	Phibro, Inc., Virbac AH, Inc., ADM Alliance Nutrition, Inc., Virbac AH, Inc.	1,4,5,6-tetrahydro-1-methyl-[trans-2(2-thienyl)vinyl]-pyrimidine, a derivative of tetrahydropyrimidine is made from 3-(2-thienyl)-acrylonitrile. 3-(2-thienyl)-acrylonitrile in a Knoevangel condensation of furfural with cyanoacetic acid. Acid hydrolysis of this compound makes 3-2(-thienyl)acrylamide. Reacting this product with propansulfone gives an iminoester which when reacted with N-methyltrimethylenidiamine gives pyrantel (Vardanyan and Hruby, 2006)
Macrocyclic lactones	**Ivermectin**	Merial Ltd., Bayer HealthCare LLC, Animal Health Division, Norbrook Laboratories Ltd, Cross Vetpharm Group Ltd., First Priority, Inc., SmartVet USA, Inc., Norbrook Laboratories Ltd., Sparhawk Laboratories, Inc.	The first macrocyclic lactone to be discovered and isolated was Streptomycin. It was extracted directly from *Streptomyces spp.* culture medium (Addinal, 1945). Ivermectin is a semi-synthetic chemically reduced 22,23-dihydro derivative of abamectin (Campbell et al., 1983). Doramectin was initially isolated through a process called "mutational biosynthesis"(Goudie et al., 1993; Dutton et al., 1990). Eprinomectin was developed by screening a large number of synthetic ivermectin analogs (Shoop et al., 1996). Milbemycins were first identified as macrocyclic lactones and isolated from cultures of *Streptomyces hygroscopicus*. Thirteen were initially purified and characterized (Takiguchi et al., 1980). Moxidectin is a derivative of nemadectin. Nemadectin, a milblemycin is a *Streptomyces cyanogriseus* fermentation product (Asato and France, 1990). Moxidectin is related to ivermectin, but lacks a disaccharide moiety and has an *O*-methyl substituent at the 23-position (Deng et al., 1991).
	Doramectin	Zoetis	
	Eprinomectin	Merial Ltd.	
	Moxidectin	Boehringer Ingelheim Vetmedica, Inc.	
Piperazines	Piperazine	Fleming Laboratories	Piperazine is synthesized from ethanolamine by heating it in ammonia at 150-220°C and 150-250 atmospheres of pressure (Vardanyan and Hruby, 2006).

*anthelmintic drugs approved by the FDA for use in livestock ***Animal Drugs@FDA (2015)
**FDA, 2012

<u>Evaluation Question #2:</u> Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

Fenbendazole is an anthelmintically active 2-carboxyl-amino-benzimidazole-5(6)-phenyl ether (benzimidazole carbamate). Production of fenbendazole is described in US Patent 3954791 (Loewe et al., 1976; Table 4).

The precursor for ivermectin, avermectin B_1 is naturally produced by a *Streptomyces avermilitis* strain that was mutagenized with high energy ultraviolet light. Hydrogenation of avermectin B_1 for 20 hours with Wilkinson's catalyst in benzene or toluene at 25°C under 1 atmosphere of hydrogen produces 85 percent 22,23-dihydroavermectin B_1 together and 3 percent of 3,4,22,23-tetrahydroavermectin B_1. 22, 23-dihydroavermectin B_1, containing at least 80 percent of 22,23-dihydroavermectin B_1a and not more than 20 percent of 22,23-dihydroavermectin B_1b, is assigned the name ivermectin (Campbell et al., 1983). The UV mutagenized Streptomyces sp., renamed *Streptomyces cyanogriseus* is described in a patent for the production of ivermectin that was filed in 1990 (Asato and France, 1990; Table 4).

Moxidectin otherwise known as 23-(C1-C6 alkyloxime)-LL-F28249 is manufactured by a process described in US Patent 4988824 (Maulding and Kumar, 1991). Moxidectin is prepared by oxidation of crystalline nemadectin, a naturally produced fermentation product. Purification of moxidectin through crystallization is covered by US Patent, US 2008/0119543 A1 (Sorokin et al., 2008).

Table 4 provides an overview of the synthetic processes involved in producing all eleven parasiticides approved by US Food and Drug Administration (FDA) for use in livestock for food production. Because all veterinary drugs must be approved by the FDA, their manufacture is an aspect of production overseen by the US federal government. The FDA provides guidance for inspection of sterile drug manufacturers (FDA, 2014a; 2014b). The FDA Center for Veterinary Medicine has published a number of guidelines focused on the new drug approval process. Some of these publications focus on anthelmintic drugs, and the manufacturing, processing or holding active of pharmaceutical ingredients.

Veterinary diagnostic tests are in development to determine whether parasites are anthelmintic resistant (Pena-Espinoza, 2014). These tests for infested livestock when available to producers will be regulated by the US Department of Agriculture, Animal Plant Health Inspection Service, National Veterinary Services Laboratory. The National Animal Health Monitoring System (NAHMS) is currently collecting data to estimate the prevalence of gastrointestinal parasites and anthelmintic resistance in sheep and cattle. Showing that one drug should be used in treatment over another in an emergency situation will provide an important tool in parasite management (Gilleard and Beech, 2007; Beech et al., 2011; Tyden et al., 2014).

Evaluation Question #3: Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Parasiticides approved for use by the US Food and Drug administration (FDA) are manufactured synthetically with starting materials originating from the petroleum, mining or agriculture sector or as chemically modified products of bacterial (mostly *Streptomyces spp.)* fermentation.

Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

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).

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).

Excretion of moxidectin is primarily through the manure of treated cattle. It is very lipophilic and not very soluble in water. Moxidectin in feces peaks at 349 ppb, 2 days after treatment and decreases to less than 10 ppb by 37 days after treatment. Feces from cattle contain no detectable levels of moxidectin thirty seven days after treatment. The half-life for degradation of moxidectin in the environment may be up to 130 days.

Table 5 Environmental Persistence and Concentration of Parasiticides

Drug	Environmental Impact*
Thiabendazole, Albendazole, Fenbendazole[1,2]	Thiabendazole's affinity for binding to soil particles increases with increasing soil acidity. It is highly persistent. The field half-life for thiabendazole has been reported as 403 days. Due to its binding and slight solubility in water, it is not expected to leach readily from soil. The benzimidazoles are generally insoluble in water and sticks to humic material in terrestrial and aquatic environments. They are readily photodegradable. Benzimidazoles are introduced into the environment when they are excreted by treated animals. It is expected that 100% of the administered dose is excreted within 7days. On a conventional 10 animal per acre cattle farm, with an expected dosage of approximately 3.5 grams per animal per treatment, and three treatments per year, the amount of benzimidazole excreted onto one acre is about 110 per year. Because the benzimidazoles stick to humic material they are not expect to run off into aquatic environments, and because they are photodegradable benzimidazoles are not expected to persist in the environment.
Levamisole[3,4]	Levamisole is highly soluble in water. Thus it can leak into the aquatic environment via runoff. Levamisole may non-enzymatically decompose to form three degradation products. The decomposition is temperature and pH dependent. Storage for a period of time under relatively mild, neutral and alkaline conditions causes degradation into three products one of which is responsible could be responsible for the immunomodulatory activity.
Morantel tartrate[4,5,6] Pyrantel	Morantel could not be detected (< 0.05 microgram/ml) in the plasma of cattle or goats following the oral administration of morantel tartrate at a dose rate of 10 mg/kg bodyweight. Morantel is difficult to detect in the milk of lactating goats, but has been detected at a concentration of 0.092 microgram/ml at 8 h after drug administration. Morantel could be detected at a concentration of 96 +/- 4.5 micrograms/g (dry weight) in the feces of a calf 24 h after treatment with 10 mg/kg bodyweight of morantel tartrate. The concentration of morantel in replicate samples of feces exposed to natural atmosphere, but not to soil or soil organisms, declined slowly over the following 322 days. At day 322 after the start of the experiment 8.8 micrograms/g of morantel could be measured in the remaining fecal material. Throughout a fecal degradation study the concentration of morantel in the crusts of replicate sample pats was lower than the concentration in the core samples. This is the result of photodegradation. Morantel is not active against bacteria or fungi. It is degraded in the soil. Pyrantel and morantel are chemically related. Persistence of either is not expected in the environment.
Ivermectin[8] Doramectin[7] Eprinomectin[9] Moxidectin[8]	Avermectins are excreted mainly through feces as non-metabolized drug, and their excretion profile depends strongly on the drug formulation, dosage, animal species, and sex of the animal. The fecal excretion of doramectin was studied for 56 days in treated female and castrated cattle and found that the excretion was approximately 38%, with the maximum excretion levels appearing 21 days after treatment. A similar time profile was observed for abamectin and doramectin excretion in sheep feces, observing maximum levels in the first days after treatment. Pigs excrete the highest levels of doramectin in the feces in the early days after treatment, although doramectin could still be detected in the feces after 60 days. In the field experiment, the application of manure containing doramectin under the specified conditions led to the presence of low levels (<5 ng/g) of the drug in the soil. Seven months after the manure application, traces of doramectin were still detected from the surface of the soil to a 90 cm depth. Successive applications of manure from pigs treated with doramectin in a specific area would produce an accumulation of this drug in the soil that reached toxic levels for soil fauna. Ivermectin and moxidectin have been evaluated for their toxicity to insects, particularly those involved in compost production. Both were found to be toxic to these animals. Eprinomectin is used for treatment of parasites in cattle, including lactating cows. The recommended dosage is a single dose of 0.5 mg kg−1 b.w. applied topically along the midline of the animal's back. Eprinomectin, a drug with high efficacy and a large safety margin for mammals, is mainly excreted in the bile and feces; only a small proportion is excreted in the urine or is present in milk. During the 28 days after topical application of 0.5 mg kg−1 b.w. radiolabelled eprinomectin to 8–10 month old calves only 0.35% of the applied dose was found in the urine whereas 17 to 19.8% was found in the feces. Eprinomectin B1a was the most abundant residue in the feces, representing 78.3% of total residues. During the 14 days after drug administration the amount of radioactivity present in the milk represented 0.32 to 0.54% of the drug. **Moxidectin** is excreted in feces. It is the least toxic to dung beetles of the macrocyclic lactone anthelmintics. Moxidectin is both microbially and photo-degraded in dung pats in the soil.
Piperazine[10]	In pigs, piperazine is readily absorbed from the gastrointestinal tract, and the major part of the resorbed compound is excreted as unchanged piperazine during the first 48 hours. The principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from feces (16 %). Piperazine can be assumed to be rapidly photolysed in the atmosphere, the half-life was calculated to be 0.8 hours. In natural water it is considered to be stable towards photolysis. From non-standard studies it can be expected that piperazine is hydrolytically stable under environmentally relevant conditions. Piperazine is not readily biodegradable but can be considered to be inherently degradable.

*mg-milligrams, kg-kilograms, b.w.- body weight, g-grams, ng-nanogram, ml-milliliter, cm-centimeter

[1]EPA, 2002	[4]Horvat et al., 2012	[7]Gil-Diaz et al., 2011	[9]Nenka et al., 2007
[2]US Food and Drug Administration, 1995	[5]McKellar et al., 1993	[8]Blanckenhorn et al., 2012	[10]OECD, 2004
[3]Phoenix Scientific, 2002	[6]Pfizer, 1979		

The environmental burden on fields manured with feces from moxidectin treated animals ranges is estimated at 0.526 parts per billion (ppb) for cattle (Fort Dodge Animal Health, 2001).

Table 5 provides an overview of the environmental fate of the parasiticides. Most reports on the environmental persistence of the parasiticides reflect continuous use for prevention and treatment.

Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

Table 6. Typical Numbers of Soil Organisms in Health Ecosystems*

		Agricultural Soils	Prairie Soils	Forest Soils
Bacteria	Per teaspoon of soil (one gram dry)	100 million to 1 billion	100 million to 1 billion	100 million to 1 billion
Fungi		Several diverse isolates. (Dominated by vesicular arbuscular mycorhizal fungi).	Tens to hundreds of diverse isolate. (Dominated by vesicular arbuscular mycorhizal fungi).	Several hundred diverse isolates in deciduous forests. One to forty miles in coniferous forests (dominated by ectomycorhizzl fungi),.
Protozoa		Several thousand flagellates and amoebae, one hundred to several hundred ciliates.	Several thousand flagellates and amoebae, one hundred to several hundred ciliates.	Several hundred thousand flagellates and amoebae, fewer flagellates.
Nematodes		Ten to twenty bacterial feeders. A few fungal-feeders. Few predatory nematodes	Tens to several hundreds	Several hundred bacterial and fungal feeders. Many predatory nematodes.
Arthropods	Per square foot	Up to one hundred	Five hundred to two thousand	Ten to twenty five thousand. Many more species than in agricultural soils
Earthworms		Five to thirty. More in soils with high organic matter	Ten to fifty. Arid or semi-arid areas have none	Ten to fifty in deciduous woodlands, very fe in coniferous forests.
*(Ingham, M.R., 1999)				

Maintaining healthy forage fields and healthy soils is important for livestock health (Brunetti and Karreman, 2006). Fields and pastures have unique soil ecologies with specific ratios of bacteria, fungi, and other microorganisms, and a particular level of complexity within each group of organisms (Table 6). These differences result from soil, vegetation, and climate factors, as well as land management practices. Grasslands and agricultural soils usually have bacterially-dominated food webs. Highly productive agricultural soils tend to have ratios of fungal to bacterial biomass near 1:1 or somewhat less. Organisms reflect their food source. For example, protozoa are abundant where bacteria are plentiful. Where bacteria dominate over fungi, nematodes that eat bacteria are more numerous than nematodes that eat fungi (Lavelle et al., 2006).

This balance influences the survival and persistence of pathogenic nematodes and their predators. Management practices change food webs. For example, in reduced tillage agricultural systems, the ratio of

fungi to bacteria increases over time, and earthworms and arthropods become more plentiful (Ingham, 1999).

These organisms are all essential in breaking down manure, particularly manure containing parasites. Fenbendazole, ivermectin and moxidectin are very effective anthelmintics. Their residues are excreted in urine and feces, and may hinder the soil food webs from effectively breaking down manure and maintaining pasture health (Karreman, 2004). When undegraded, dung pats harbor nematodes parasitic in livestock, reduce available grazing area, and represent a loss of soil nitrogen in pastures. (Floate et al., 2005).

Fenbendzaole toxicity was demonstrated in pigeons and doves leading the authors of the study to suggestion 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. 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 (Svendsen et al., 2003). Ivermectin has low level toxicity to fish and aquatic life (Halley et al., 1993).

Much work has been done to study the macrocyclic lactones particularly ivermevtin, and others, highlighting the effects of these parasiticides (Forster et al., 2011). Among the macrocylic lactones, ivermectin is generally more toxic to insects than moxidectin. Little information is available regarding the effects of parasiticide residues on other soil food web microorganisms that facilitate the process of dung degradation (e.g., fungi, free-living nematodes, collembolans, mites). Residues of ivermectin and fenbendazole are toxic to the soil nematode *Pristionchus maupasi* at concentrations greater than 3 ppm and 10 to 20 ppm wet weight of dung, respectively, but sub-lethal concentrations may enhance the growth of the nematode in dung of treated cattle (Floate et al., 2005). Moxidectin has been shown to adversely affect the larvae of *Musca autumnalis*, *Onthophagus gazella*, *Onitis alexis* and *Haematobia irritans*, adult and larvae of *Onthophagus binodis* and to reduce the brood mass production of *O. binodis* and *O. alexis* (McKellar, 1997).

Harmonization of veterinary medicine testing requirements is coordinated by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). Members are the European Union (EU), Japan, and the USA, with Australia/New Zealand and Canada as observers. The VICH Ecotoxicity/Environmental Impact Assessment Working Group is developing ring-tested toxicity test methods for dung beetles and dung flies. The Dung Organism Toxicity Testing Standardization (DOTTS) Group in cooperation with VICH has developed several tests for dung fly and beetle ecotoxicity. In conjunction with VICH and the DOTTS Group, the FDA has also provided guidance for industry on assessing ecotoxicity (FDA, 2006).

The parasiticides belong to widely different chemical groups making it difficult to generalize their environmental risk. Exposures, biocidal properties and the effects of combinations of products have been or still need to be assessed for each group or individual drug. Data including persistence and adsorption in soil and manure, the influence of temperature and soil properties and specific toxicity which can range over several orders of magnitude is still being gathered for the parasiticides (Schmitt and Rombke, 2008). Residues persisting in the dung of treated animals for days, weeks or months after treatment can adversely affect guilds of coprophilous insects, mites, nematodes, earthworms, and fungi that accelerate degradation of the dung pat. Table 7 provides an overview of toxicity resulting from the eleven anthelmintics approved by the US Food and Drug Administration.

Evaluation Question #6: Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

Fenbendazole is manufactured by process that requires petrochemicals such as benzene and various amines. These are considered toxic compounds. Fenbendazole is not generally considered toxic to humans at regulated doses (FDA, 1995).

Both ivermectin and moxidectin are produced by processes involving bacterial fermentation and subsequent chemical modification after the fermentation product is isolated. Environmental contamination as a result of the manufacture of either product is unlikely. Table 7 provides an overview of environmental persistence and toxicity for the FDA approved livestock parasiticides.

Table 7 Environmental Toxicity of Parasiticides

Drug	Toxicity
Thiabendazole[1] Albendazole[2] Fenbendazole[3,4]	Thiabendzole is toxic to species of freshwater estuarine fish and freshwater/estuarine invertebrates and practically non-toxic to birds and mammals. Birds and mammals can be exposed to pesticides applied as foliar sprays or powders by a variety of routes, including ingestion, dermal contact, and inhalation. It is not expected to appreciably accumulate in aquatic organisms, although the bio-concentration factor for thiabendazole in whole fish is 87 times the ambient water concentrations. Fish eliminated the compound within 3 days after being placed in thiabendazole-free water. Earthworms are sensitive to thiabendazole (LD50 = approx. 20 ug/worm), while bees are not. Administration of Albendazole during gestation has been shown to cause embryotoxic effects in cattle, rat, rabbit and sheep. Observed effects include increase of resorptions, decreased fetal weight and increase of teratogenic effects, such as vascular, craniofacial, skeletal and external malformations. The dung from fenbendazole-treated animals has no obvious impact on the coleopteran or dipteran species encountered in this study, and the dung pats from the fenbendazole-treated animals were not consistently different from the pats of untreated animals. Earthworms are not significantly affected by fenbendazole.
Levamisole[5, 6]	Levamisole does not affect the fauna or the degradation of dung from inoculated animals. Breakdown products levamisole may be associated with immunomodulation effects.
Morantel tartrate[7,9] Pyrantel[8]	Morantel is non-toxic for aquatic species. It is considered a substrate for microbial degradation in the soil. No adverse interactions with soil or aquatic environment have been observed. Both pyrantel and morantel are counter indicated for gestating animals. Pyrantel is permitted at 10 parts per million (PPM) in the kidney and 1 ppm in muscle. Morantel does not alter the rate of dung digestion.
Ivermectin[9] Doramectin[3,9] Eprinomectin[10] Moxidectin[11]	The macrocyclic lactones can be ranked in decreasing order of toxicity to dung-dwelling insects as abamectin>doramectin ≥ ivermectin > eprinomectin>>moxidectin. Ivermectin has been shown to exhibit toxicity for certain dung-colonizing insects. Patterns of interaction are complex since some of these drugs are insect attractants as well as insecticide and some studies have not considered all of the aspects involve in short and longer term effects since insect activity is a composite measure of residue toxicity, the number and species of composition of insect colonists and mortality factors associated with the co-occurrence of species in dung. Flies that are sensitive to ivermectin are also sensitive to moxidectin.
Piperazine	Piperazine is rapidly photolysed in the atmosphere with a half-life of 0.8 hours. In natural water it is considered to be stable towards photolysis. Piperazine is hydrolytically stable under environmentally relevant conditions and not readily biodegradable but can be considered to be inherently degradable. There is no considerable potential for bioaccumulation; a bioconcentration factor of < 3.9 for *Cyprinus carpio* is reported. Short-term effect studies on aquatic organisms are available for algae, aquatic invertebrates and fish. For algae (*Selenastrum capricornutum)* the no observed effedt concentration (72 h growth inhibition test) is > 1000 mg/l. For *Daphnia magna* the 48 hour 50% effective concentration for is 21 mg/l and for fish (*Poecilia reticulata*) the 96 hour 50% lethal concentration is > 1800 mg/l. A long-term study for *Daphnia magna*, which is the most sensitive of the species tested in short term studies, results in a no observable effect concentration (21 d semi-static reproduction study) of 12.5 mg/l.

[1]EPA, 2002 [4]Svendson et al., 2003 [7]Pfizer, 1979 [10]Floate, K.,D., 2007
[2]Mattsson, 2012 [5]Barth et al., 1994 [8]§9CFR556.540 [11]Blanckenhorn et al., 2013
[3]Strong et al., 1996 [6]Horvat, 2012 [9]Floate et al., 2005 [12]OECD, 2004

Evaluation Question #7: Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

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)

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 soil particles. The half-life for degradation of ivermectin in soil can be as long 240 d 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). It 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).

Evaluation Question #8: Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).

Soil invertebrates are enormously diverse representing as much as 23% of the total diversity of living organisms. Their sizes range across three orders of magnitude: the smallest nematodes and protozoa (protists) of the microfauna less than 200 µm on average live in the water-filled porosity (Lavelle et al., 2006). The biological effect of fenbendazole, ivermectin and moxidectin on the agro-ecosystem is twofold: 1) sub-lethal or lethal toxicity for soil food guild organisms, such as dung beetles and beneficial nematodes, involved in degrading manure, processing humus and maintaining soil and forage field health and 2) selection and transmission of populations of anthelmintic resistant organisms such as nematodes to the soil that will subsequently be untreatable with fenbendazole, ivermectin or moxidectin upon reinfection. More than ninety percent of nematodes can be found in a non-parasitic or free living stage (Fiel et al., 2012).

The algorithm for treatment on organic farms includes fecal soiling/diarrhea, anemia, low weight gains and high fecal egg counts (Cabaet et al., 2009). Ivermectin and moxidectin are excreted into the environment in feces, while fenbendazole is excreted in urine and feces. In addition, the wash off of topically applied anthelmintics, spillage and inappropriate disposal provide additional routes of entry into the environment (Beynon, 2012). Healthy adult animals develop immunological tolerance to helminth parasites (Tizard, 2013). Treatment with parasiticides is necessary only for sick and very young animals (Karreman, 2004). Under treatment, resistant parasites, their eggs and residual anthelmintic drugs are shed in feces and urine returning to the soil. Coprophilous arthropods and microorganisms normally involved in dung pat disappearance avoid the treated dung pat or are killed as a result of anthelmintic treatment prolonging the survival of residual pathogens and promoting their return to soil and forage, where they are untreatable (Strong et al., 1996; Svendsen et al., 2003; McKellar, 1997). Some species of nematodes are both plant and animal pathogens (Jasmer et al., 2003). Further loss as a result of introduction of fenbendazole, ivermectin and moxidectin to dung pats and the soil, of otherwise predatory or competitive nematodes removes selective pressure against the parasites decreasing sustainability (Lavelle et al., 2004).

There are several nematode food guilds, including bacteria eaters, fungus eaters, and predatory nematodes. Any of these have the potential for parasitism. Parasiticides are not specific and beneficial nematodes may be killed by secondary excretion. Disturbing the ecosystem and eliminating respective food sources leaves the most aggressive parasite species without competitors. This is currently the most important interaction of anthelmintic drugs with the agro-ecosystem and there is still much to discover regarding interactions in soils and the multiple roles that invertebrates may play in controlling pests and diseases (Lavelle et al., 2006).

Anthelmintic drug resistance stems from the inability of the anthelmintic drug to affect specific nematode functions or anatomical changes, i.e., mode of action. Only four modes of action have been identified for anthelmintic drugs: 1) neuromuscular inhibition, 2a) ion channel inhibition: GABA-gated, 2b) GLUCL-gated and 3) β-tubulin binding/inhibition of microtubule formation. If resistance to a particular

anthelmintic has occurred, it is likely that another anthelmintic with the same mode of action will also be ineffective although other anthelmintics with another mode of action may still be effective. Table 8 provides the dates of introduction of some anthelmintic drugs and the subsequent report dates of anthelmintic resistance.

Piperazine and morantel are GABA (γ-amino-butyric acid) agonists of receptors on nematode muscles and causes flaccid paralysis. The macrocyclic lactones increase the opening of glutamate-gated chloride channels and produce paralysis of pharyngeal pumping. Moxidectin was initially identified as a GABA antagonist, but its primary anthelmintic activity was subsequently shown to be a GLUCL potentiator. The benzimidazole drugs bind selectively to β-tubulin of nematodes and inhibit microtubule formation (Martin, 1997).

The imidazothiazole, levamisole and the tetrahydropyrimidines, pyrantel and morantel are anthelmintics that target the nicotinic acetylcholine gated cation-channels. These mediate fast synaptic signaling in the neuro-musculature of nematodes acting as agonists to increase the flow of cations leading to a rigid paralysis. These gated channels share a pentameric quaternary subunit structure in which a single subunit can produce a homomeric channel, but more commonly different subunits combine to form a heteromeric channel. Thus, resistance can occur as a result of subunit polymorphism, at the protein level or allele variation at the DNA level. Deoxyribonucleic acid (DNA) sequence changes at three sites in the beta-tubulin gene are thought to be the major cause of fenbendazole resistance. However, changes in the gene for the drug transporter P-glycoprotein have also been linked with fenbendazole resistance. Ivermectin, doramectin, eprinomectin and moxidectin are allosteric modulators of nematode glutamate channels and cause an inhibition of pharyngeal pumping, motility and egg-laying. These channels are also composed of protein subunits and may be homo- or heteromeric. Resistance to fenbendazole affects resistance to ivermectin and moxidectin. However, the specific allele associated with fenbendazole resistance is different from that associated with ivermectin and moxidectin resistance, the possibility of a mechanistic link between resistance to fenbendazole, ivermectin and moxidectin suggests that selection for resistance with one drug could alter the development of resistance to the second drug (Beech et al., 2011).

Table 8 The development of anthelmintic resistance

Drug Class	Drug Name	Host	Year of Introduction	Year Resistance Reported
Benzimidazoles	Thiabendazole	Sheep	1961	1964
		Horse	1962	1965
	Fenbendazole	Sheep	1990	2011
Imodothaizoles-Tetrahydropyrimidines	Levamisole	Sheep	1970	1979
	Pyrantel	Horse	1974	1996
Macrocyclic Lactones	**Ivermectin**	Sheep	1981	1988
		Horse	1983	2002
	Moxidectin	Sheep	1991	1995
		Horse	1995	2003

Adapted from James et al., 2009; Kaplan, 2004; George et al., 2011

P-glycoprotein is a large (170 kDa) integral membrane protein. It is able to transport a wide variety of lipophilic substances, including many drugs. P-glycoprotein confers multidrug resistance (MDR) by active transport of drugs, coupled to the binding and/or hydrolysis of ATP. This transport reduces the amount of drug reaching its target and consequently reduces the effect of the drug. MDR drugs enter the cell by passive diffusion and are actively extruded by the transport protein P-glycoprotein. P-glycoprotein can be

induced by drug treatment. P-glycoprotein is able to transport many different drugs and consequently confers cross-resistance to many other drugs. The level of this cross-resistance varies and might be different for different cells. P-glycoprotein-expressing cells might be more resistant to other drugs than to the drug used to induce its expression (James et al., 2009).

An experimental model for the development of ivermectin-resistant strains of the model nematode *Caenorhabditis elegans* through step-wise exposure to increasing doses of ivermectin commencing with a non-toxic dose of 1 ng/ml also showed a multidrug resistance phenotype with cross-resistance to the related drug moxidectin and to other anthelmintics, levamisole and pyrantel, but not albendazole. The resistance phenotype was associated with increased expression of the multidrug resistance proteins (MRPs) and P glycoproteins (James and Davey, 2009).

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)).

Land use and chemical application respectively for livestock production and/or control of specific pathogenic species potentially perturbs or destroys the habitat for many other beneficial organisms (Rasmann, 2012; Zhou et al., 2012). A chemical prescription to kill an enemy (whipworm) of the farmer can also lead to the destruction of a friend (Sykes, 1949). The impact and effects of prolonged use of anthelmintic parasiticides on terrestrial ecology are not well understood. Table 7 provides an overview of environmental toxicity for FDA approved anthelmintics.

Parasiticides used preventively are detectable in soils, surface water and groundwater. Estimates based on animals dosage, land usage and degradation rate range from 0.01 parts per billion (ppb) to 500 or more ppb (Oh et al., 2006; Liebig et al., 2010). Although fenbendazole, ivermectin and moxidectin have not been found in agricultural products grown on fields manured with dung from treated animals, low concentrations of levamisole have been detected experimentally in carrot and corn (Boxall et al., 2006).

Diversity and abundance of the soil invertebrate community, particularly the nematode population is not affected by a shift from conventional to organic farming. However, there is a significant different between either conventional or organic grazed pastures and unfertilized, ungrazed pasture. Physically, the pore size of soil from the un-grazed, unfertilized pasture is large. This is likely to be due to the absence of livestock treading on the soil. There is a considerable effect in both organic and conventional farming from the presence of animals on the pasture, suggesting that land management practices such as stocking rate are important in influencing nematode populations and that fallowing a pasture is important (Schon et al., 2011a).

Organic livestock production avoids the development of anthelmintic drug resistances, through good forage maintenance, exercise for livestock and practices limiting the use of holistic anthelmintic treatments. Parasiticides may only be needed in emergencies where the organic production plan has failed (Lund and Algers, 2003). High forage consumption and increased livestock grazing creates pasture heterogeneity and potential imbalance between nutrition and parasitism for foraging livestock, particularly in the transition from conventional farming (regular and prophylactic parasiticide use) to organic farming (no parasiticide use). Overcoming these disturbances while converting forage fields from conventional to organic farming requires careful attention to pasture conditions, water quality and the relationships between the organisms, e.g. between plants and fungi and between invertebrates and gut organisms (Callaham et al., 2006; Smith et al., 2009; Brunetti and Karreman, 2006; Perry, 1995).

Among the nematodes, larger, predatory and omnivorous nematodes are sensitive to the influence of livestock on the soil environment. These nematodes are less abundant in grazed paddocks. While larger nematodes are sensitive to livestock disturbance, they are abundant in mown and irrigated plots (Schon et al., 2011b).

Especially in grasslands, nematodes have been found to play an important role in the transfer of energy and matter through the soil food web because of their central and diverse trophic positions. Different functional groups can be distinguished within the nematode community: nematodes may belong to the primary consumer group (plant feeders), the secondary consumer group (bacterivores and fungivores), or the tertiary consumer group (predators and omnivores). Management practices such as high stocking

Table 9 Maximum Residue Limits for Veterinary Parasiticides

Drug	Maximum Residue Limit*					
Animal Species	Cattle	Goat	Pig	Sheep	Poultry	Deer
Thiabendazole [1]	Milk/100 µg/liter ; Kidney, Muscle, Fat, Liver/100 µg/kilogram	Kidney, Muscle, Fat, Liver/100 µg/kilogram	Kidney, Muscle, Fat, Liver/100 µg/kilogram	Kidney, Muscle, Fat, Liver/100 µg/kilogram		
Albendazole[1]	Milk/100 µg/liter ; Muscle, Fat, 100 µg/kilogram; Kidney, Liver/5000 µg/kilogram					
Fenbendazole[1]	Milk/100 µg/liter ; Kidney, Muscle, Fat/100 µg/kilogram ; Liver/500 µg/kilogram	Kidney, Muscle, Fat /100 µg/kilogram; Liver/500 µg/kilogram	Kidney, Muscle, Fat/100 µg/kilogram; Liver/500 µg/kilogram	Milk/100 µg/liter ; Kidney, Muscle, Fat Milk/100 µg/kilogram; Liver/500 µg/kilogram		
Levamisole[1]	Kidney, Muscle, Fat /10 µg/kilogram; Liver/100 µg/kilogram	Kidney, Muscle, Fat /10 µg/kilogram; Liver/100 µg/kilogram	Kidney, Muscle, Fat /10 µg/kilogram; Liver/100 µg/kilogram	Kidney, Muscle, Fat /10 µg/kilogram; Liver/100 µg/kilogram	Kidney, Muscle, Fat /10 µg/kilogram; Liver/100 µg/kilogram	
Morantel tartrate[2]	Milk/100 µg/liter; Muscle/100 µg/kilogram ; Fat/100 µg/kilogram; Liver/800 µg/kilogram; Kidney/200 µg/kilogram		Muscle/100 µg/kilogram ; Fat/100 µg/kilogram; Liver/800 µg/kilogram; Kidney/200 µg/kilogram	Milk/100 µg/liter; Muscle/100 µg/kilogram ; Fat/100 µg/kilogram; Liver/800 µg/kilogram; Kidney/200 µg/kilogram		
Pyrantel[3]			Muscle/1µg/kilogram ; Liver/10 µg/kilogram; Kidney/10 µg/kilogram			
Ivermectin[1]	Milk/10 µg/liter ; Fat/40 µg/kilogram; Liver/100 µg/kilogram		Fat/20 µg/kilogram; Liver/15 µg/kilogram	Fat/20 µg/kilogram; Liver/15 µg/kilogram		
Doramectin[1]	Milk/15 µg/liter ; Muscle/10 µg/kilogram ; Fat/150 µg/kilogram; Liver/100 µg/kilogram; Kidney/30 µg/kilogram		Muscle/5 µg/kilogram ; Fat/150 µg/kilogram; Liver/100 µg/kilogram; Kidney/30 µg/kilogram			
Eprinomectin[1]	Milk/20 µg/liter; Muscle/100 µg/kilogram ; Fat/250 µg/kilogram; Liver/2000 µg/kilogram; Kidney/300 µg/kilogram					
Moxidectin[1]	Muscle/20 µg/kilogram ; Fat/500 µg/kilogram; Liver/100 µg/kilogram; Kidney/50 µg/kilogram			Muscle/20 µg/kilogram ; Fat/500 µg/kilogram; Liver/100 µg/kilogram; Kidney/50 µg/kilogram		Muscle/20 µg/kilogram ; Fat/500 µg/kilogram; Liver/100 µg/kilogram; Kidney/50 µg/kilogram
Piperazine[3]			Muscle/0.1µg/kilogram ; 0.1µg/kilogram; Kidney/0.1µg/kilogram		Muscle/0.1µg/kilogram ; 0.1µg/kilogram; Kidney/0.1µg/kilogram	

[1] Codex Alimentarius, 2014 [2] Committee for Veterinary Medicinal Products: Morantel [3] Animal Drugs@FDA

796

density cause shifts in the functional groups and ultimately affect soil nutrient dynamics. Ecological modelling suggests that a strong, selective, human-induced pressure is acting on most taxa, indicating decreased ecosystem resilience (lower biodiversity within functional groups) as a result of increased management intensity. Many taxa are endangered as even cosmopolitan, unspecialized nematodes such as the *Teratocephalidae* (*Secernentea*) appear suppressed under intensive management. In organic farming systems, manuring provides a positive influence on microflora and bacterivorous nematodes such as *Metateratocephalus* and *Teratocephalus* (Mulder et al., 2003).

Evaluation Question #10: 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)).

The no observable effect level (NOEL) for parasiticides is determined by drug manufacturer and approved by the US Food and Drug Administration, Codex Alimentarius or other national or international standard setting organization. Protocols are provided by these federal agencies that detail testing and evaluation of the drugs. The NOEL is usually determined in an animal model. The NOEL values for fenbendazole, ivermectin and moxidectin are respectively, 0.7 milligram/kilogram body weight per day (mg/kg bd/day), 1.5 mg/kg bd/day and 10 mg/kg bd/day. The NOEL is used to determine the Adult Daily Intake (ADI) or the maximum residue limit (MRL). Withdrawal time is the time that it takes for the concentration in milk, eggs and meat that will be consumed by people to drop from the residue level at administration to the ADI, MRL, or safe level. Drug side effects are provided on the respective drug label. Some maximum residue limits according for the US Food and Drug administration approved parasiticides are provided in Table 10.

Fenbendazole has been determined to be safe to human health when food derived from treated animals is ingested (FDA, 1995). In 2014, the US Food Safety Inspection Service found no violative positive meat samples containing moxidectin or ivermectin in the 2014 National Residue Program for Meat Poultry and Egg Products out of 237 samples tested. In 2011, the FSIS found 3 violations for moxidectin and 2 violations for ivermectin from 2019 samples including beef cows, boars, dairy cow, veal, goats, heavy calves, market hogs, mature sheep, roaster hogs and steer. Fenbendazole has not appeared recently in this survey, but will be surveyed in 2015.

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)).

Naturally, livestock develops an immune response to nematodes and becomes resistant or tolerates them without signs of disease. Because calves do not have a mature immune system, they may not be able to mount an immune response upon infection. The same is also true for older and immunocompromised animals (Tizard, 2013). Worming with homeopathic and botanical remedies should begin strategically during the first autumn of life to accommodate the low body reserves expected with calves (Karreman, 2004).

Homeopathic wormers are available commercially that satisfy the organic rule. These are available as veterinary preparations with valid labeling systems so that their use may easily be audited (Brunetti and Karreman, 2006). Users of these remedies should be sure that the material has an appropriate potency and the source from which it was extracted is verified and correct. A list of natural wormers is provided in Table 11. Herbal remedies with anthelminthic properties were commonly adopted and used as a part of traditional animal husbandry. Some have not been evaluated with modern techniques, but may cause toxic side effects, however in most cases they represent a good alternative to the use of synthetic drugs (Duval, 1997). Crude drugs are not as efficient in their anthelmintic effects as synthetics, but are nonetheless effective and used among many cultures throughout the world (Mali, R. G. and Mehta, A.A., 2008).

The seeds from *Chenopodium ambrosioides* L. var. *anthermintic*um A. Gray (Chenopodiaceae) also known as American wormseed are used to produce chenopodium oil (USP) (Kiuchi et al., 2002). Chenopodium oil is used as an anthelmintic treatment for hookworm and round worms. It is very effective against ascarids (Karreman, 2004). Chenopodium does not kill the worms but paralyzes them. They are expelled with a cathartic such as castor oil (Hatcher and Wilbert, 1915).

Sabina, USP is the tops of *Juniperous Sabina*, an evergreen shrub of Northern Europe, Asia and America. It contains oleum sabinae (volatile oil), fixed oil, gum, resin, gallic acid, chlorophyll, lignin and calcareous salts and salts of potassium (Karreman, 2004; Hare, 1904). Oleum Sabina is used as an anthelmintic. It is effective, but also inflammatory and poisonous (Hare, 1904).

Table 10 Botanical and Alternative De-wormers

from Duval, 1997			*from Karreman, 2004*		
Garlic	Yarrow	Periwinkle	Levant wormseed	Scammony	Garlic
Wormwood	Sweet Flag or Calamus	Diatomaceous earth	Spigella marilandca	Kamala	Goldenseal marshmallow
Tarragon	Agrimony	Shaklee's Basic H	Maryland pink	Kousso	Quassia
Wild Ginger	Roots or root infusions of Indian hemp	Copper sulfate	American wormseed	Pomegranite	Neem leaves
Goosefoot	Calendula	Peroxide	Male fern	Butternut bark	Black walnut hulls,
Conifers	Hemp	Charcoal	Wormwood leaf	Chaparro,	Echinacea root,
Crucifers	Blue cohosh	Rue	Biva bulb	Embella ribes	Eclipta alba
Cucurbits	Lady slipper root extract	Bloodroot	Phylanthus amarus	Gentian root	Ginger
Fern	Sweet gale or bog myrtle	Sacory	Cayenne	Eucalyptus	Rosemary
Lupine	Pokeweed	Skullcap	Rue	Pumpkin Seeds	Oats
Nuts	Common knotgrass	SkunkCabbage or skunk weed	Slippery Elm powder	Butternut	Milk
Umbilliferae	Tansy Seeds	Nettle	Copper Sulfate	Fenugreek	Chenopodium
Pyrethrum	Blackberries	Valerian	Camphor	Aloe	Thymol
Tobacco	Rasberries	Verbena			
Beech creosote	Young ash and elder shoots				

Areca nut (betel nut), Granatum (pomegranate), Male fern (Aspidium), pepo (pumpkin seed), santonin (levant wormseed) are used as anthelmintics for all animals to expel tapeworm (Karreman, 2004; Hatcher and Wilbert, 1915).

Diatomaceous earth (DE) is the skeletal remains of single-celled algae, or diatoms that formed sedimentary deposits when they died. Diatomaceous earth is comprised predominantly of silicon dioxide. It is a non-synthetic substance and not prohibited for use in organic livestock production (§ 205.105; § 205.237(a); § 205.237(b)). Diatomaceous earth can be added to grain mixes to prevent internal parasite burden in intensively grazed cattle (Karreman, 2004). DE is also used in chicken feed to reduce parasite load from nematodes such as *Capillaria aerophila* (Bennett et al., 2011). Attempts to use diatomaceous earth to reduce parasite level in goats have not been successful (Bernard et al., 2009). In another study involving sheep, diatomaceous earth mixed with feed, *bacillus thuringensis* and *Clonostachys rosea f. rosea* showed efficacy in reducing egg counts for gastrointestinal nematodes (Amhed et al, 2013).

Santonica (*Artemsia pauciflora*), swamp milkweed (*Asclepsia incarnate*), brayera or kousso (*Brayera anthelmintica*), bonduc (*Caesalpinia bonducella*), Calumba (*Jateorrhiza palmate*), Pigella or Maryland pink (*Spigella marilandica*), and turpentine long-leaved Georgia, swamp or pitch pine (*Oleum terebinthinae*) have also shown anthelmintic properties. They are listed in American Materia Medica, Therapeutics and Pharmacognosy with directions for use (Ellingwood, 1919; Karreman, 2004).

Karreman provides a number of references to homeopathic anthelmintic remedies in his book Treating Dairy Cows Naturally: Thoughts and Strategies including Nuzzi, Grainger and Moore, Lust, Levy, Mowry, Dadd, Waterman, Alexander, Burkett, An M.R.C.V.S., Dun, Udall, Winslow and Grosjean (Nuzzi, 1992;

Grainger and Moore, 1991; Lust, 2001; Levy, 1984; Mowry, 1986; 1990; Dadd, 1897; Waterman, 1925; Alexander, 1929; Burkett, 1913; An M.R.C.V.S., 1914; Dun, 1910; Udall, 1943; Winslow, 1919; Grosjean, 1994; Karreman, 2004).

Wormwood (*Artemisia absinthium*) is known for its ancient use as anthelmintic. The lactones absinthin and anabsinthin are responsible for the anthelmintic activity of wormwood. *A. absintium* acts on nicotinic and muscarinic cholinergic receptors (Pepping, 2004).

An in vitro study of susceptibility of *Lumbricoides ascaris* to a number of plant alcohol extracts disclosed the activities of *Acorus calamus* (rhizome), *Agati gratifola* (seeds), *Carum copticum* (seeds), *Cassia tora* (seeds), *Citrus limonum* (seeds), *Caesalpinia bondue* (seeds), *Curcuma longa* (rhizome), *Helleborus niger* (stem), *Mangifera indica* (seed kernel) and *Ziniber officinale* (rhizome) to either paralyze or kill the parasites. From this study, *Mangifera indica* extracts were used clinically to cure patients (Kaleysa, 1974).

In a study comparing efficacy to control nodular worm (*Oesophagostomum* spp.) of four medicinal plants fed to pigs with ivermectin treatment sweet flag rhizome (*Acorus calamus*, 5 grams/kilogram (g/kg)), tansy flowers and leaves (*Tancetum vulgare*, 5 g/kg) and pumpkin seeds (*Cucurbita pepo*, 5 g/kg) reduced worm burden respectively, 98%, 95.8% and 97%, with respect to ivermectin, 96.1% (Magi et al., 2005).

Cassava leaves (*Leucaena pallida*) added to the diet of goats as a feed additive significantly reduced nematode parasite egg counts and improved weight gain (Merera et al., 2013).

Duddingtonia flagrans is a nematophagous fungus with potential to control trichostrongyles in cattle. Twenty calves, six-month-old, divided in two groups (fungus-treated and control without fungus) were fed on a pasture of Surinam grass known to contain bovine trichostrongyles. Treated animals received sodium alginate mycelial pellets. There was a significant reduction in fecal egg count (56.7%) and infective larvae (L3) in co-procultures (60.5%) in treated animals suggesting that nematophagous fungus might be useful for parasite control (Assis et al., 2012).

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

Good husbandry and nutrition are vitally important for good parasite control. The level and quality of feed influences how the animal will cope with parasites, and the level of immunity it will develop against them. Forage crops that support mycorrhizial fungi, and contain high levels of tannins are also good for suppressing parasites (Stockdale, 2008). The use of parasiticides in organic livestock production is meant only as an emergency action to alleviate economic loss and animal suffering (Spoolder, 2007; Charlier et al., 2014).

A number of management practices such as whole-flock treatment of adult ewes around lambing, and treatment of lambs with low parasite contamination as they are moved onto pastures reduces but does not eliminate the use of parasiticides. In addition these practices have been identified as high risk for selecting resistant parasites (Leathwick et al., 2015). 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). Healthy un-infested animals left untreated in these management systems are still considered organically produced livestock (§205.603(a) (18). The rule is explicit concerning the treated animal.

In an indoor experiment the development of thiabendazole resistance slowed after exposing smaller proportions of each generation of *Haemonchus contortus* to treatment with the anthelmintic. Subsequent studies demonstrated that creating a reservoir of unselected parasites, refugia, slows the development of anthelmintic resistance, and emphasizes the risk of treating all animals prior to a shift on to low-contamination pasture. However, higher levels of pasture contamination, resulting from untreated animals, highlight the difficulty in managing both worm control and resistance (Waghorn et al., 2015). Healthy un-infested animals left untreated in these management systems are still considered organically produced livestock (§205.603(a) (18)). The rule is explicit concerning the treated animal.

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, and the use of more aftermath, (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. 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).

Early organic farmers recognized the 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).

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).

References

Addinal, C.R. (1945) Streptomycin, method of preparation, The Chemical Age, p. 404.

Addison, E., Davison, E., and Wadsworth, P.F. (1974) Determination of an isomeric impurity in samples of morantel tartrate by gas-liquid chromatographic analysis of the products of a controlled procedure, Analyst, 99, pp. 114-119.

Alexander, A. S. (1929) The Veterinary Advisor, Orange Judd Co., New York.

Alonso-Diaz, M.A., Toreres-Acosta, J.F.D.J., Sandoval-Castro, C.A., and Campbell, W.B. (2014) Controlling the introduction and augmentation of parasites in and on domesticated livestock *in* Sustainable Food-Production includes Human and and Environmental Health, Issues in Agroecology, Springer, pp. 191-228.

Amhed, M.A, Laing, M.D., and Nsahlai (2013) Studies on the ability of two isolates of *Bacillus thuringiensis*, an isolate of *Clonostachys rosea f. rosea* and a diatomaceous earth product to control gastrointestinal nematodes of sheep, Biocontrol Science and Technology, 23:9, pp. 1067-1082.

An. M.R.C.V.S. (1914) The Farm Vet, MacDonald & Martin, 1914

Aravind, L. and Koonin, E.V. (2000) The α/β fold uracil DNA glycosylases: a common origin with diverse fates, Genome Biology, pp. 1-8.

Asato, G. and France, D.J. (1990) 23-Imino derivatives of LL-F28249 Compounds, United States Patent, 4,916,154.

Assis, R.C.L., Luns, F.D., Araujo, J.V. and Braga, F.R. (2012) Biological control of trichostrongyles in beef cattle by the nematophagous fungus *Duddingtonia flagrans* in tropical southeastern Brazil, Experimental Parasitology, 132pp. 373–377.

Barth, D., Heinze-Mutz, E.M., Langholff, W., Roncalli, R.A. and Schlüter, D. (1994) Colonisation and degradation of dung pats after subcutaneous treatment of cattle with ivermectin or levamisole., Appl Parasitol., 35:4, pp. 277-293.

Bartram, D.J. (2013) Multiple-active anthelmintic formulations: Friend or foe in sustainable parasite control?, Small Ruminant Research, 110, pp. 96– 99

Bartram, D.J., Leathwick, D.M., Taylor, M.A., Geurden, T., Maeder, S.J. (2012) The role of combination anthelmintic formulations in the sustainable control of sheep nematodes, Veterinary Parasitology, 186, pp. 151–158.

Bath, G.F. (2014) The "BIG FIVE" – A South African perspective on sustainable holistic internal parasite management in sheep and goats, Small Ruminant Research, 118, pp. 48–55.

Beech, R.N., Skuce, P., Bartley, D.J., Martin, R.J., Prichard, R.K. and Gilleard, J.S. (2011) Anthelmintic resistance: markers for resistance, or susceptibility, Parasitology, 138, pp. 160-174.

Bennet, D.C., Yee, A., Rhee, Y-J. and Cheng, K.M. (2011) Effect of diatomaceous earth on parasite load, egg production, and egg quality of free-range organic laying hens, Poultry Science, 90, pp. 1416-1426.

Bernard, G., Worku, M., and Ahmedna, M. (2009) The Effects of Diatomaceous Earth on Parasite Infected Goats, Bulletin of the Georgian National Academy of Sciences, 3:1, pp. 129-135.

Blanckenhorn, W.U., Puniamoorthy, N., Scheffczyk, A. and Rombke, J. (2013) Evaluation of ecotoxicological effects of the parasiticide moxidectin in comparison to ivermectin in 11 species of dungflies, Ecotoxicology and Environmental Safety, 89, pp. 15–20.

Bogan, J. and Armour, J. (1980) Anthelmintics for ruminants, International Journal for Parasitology, 17:2, pp. 483-491.

Boxall, A.B.A., Johnson, P., Smith, E.J., Sinclair, C.J. Stutt, E. and Levy, L.S. (2006) Uptake of veterinary medicines from soils into plants, J. Agric. Food Chem., 54, pp. 2288-2297

Brown, H.D., Matzuk, A.R., Ilves, I.R., Peterson, L.H., Harris, S.A., Sarett, L.H., Egerton, J.R., Yakstis, J.J., Campbell, W.C, and Cuckler, A.C. (1961) Antiparasitic drugs. IV. 2-(4'-thiazolyl)-benzimidazole, a new anthelmintic, Journal of the American Chemical Society, 83, pp. 1764-1765.

Brunetti, J. and Karreman, H.J. (2006) Holistic veterinary care, DVD, Acres, USA.

Bultman, M.W., Fisher, F.S. and Pappagianis, D. (2013) The ecology of soil-borne human pathogens, in The Essentials of Medical Geology, Selinus, Olie, (ed.), Springer, NY., pp. 477-504.

Burkett, W. (1913) The Farmer Veterinarian, Orange Judd Co., New York.

Busina, V., Kenyon, N., Laing, M.J., Denwood, D., McBean, D., Sargison, N.D. and Ellis, K. (2013) Addressing sustainable sheep farming: Application of a targeted selective treatment approach for anthelmintic use on a commercial farm, Small Ruminant Research, 110, pp. 100– 103.

Cabaret, J., Benoit, M., Laignel, G. and Nicourt, C. (2009) Current management of farms and internal parasites by conventional and organic meat sheep French farmers and acceptance of targeted selective treatments, Veterinary Parasitology, 164, pp. 21–29.

Cabaret, J., Bouilhol, MJ., and Mage, C. (2002) Managing helminths of ruminants in organic farming, Vet. Res., 33, pp. 625–640.

Callaham, M.A., Richter, D.D., Coleman, D.C. and Hofmockel, M. (2006) Long term land-use effects on soil invertebrate communities in Southern Piedmont soils, USA, European Journal of Soil Biology, 42, S150–S156.

Campbell, W.C., Fisher, M.H., Stapley, E.O., Albers-Schonberg, G. (1983) Ivermectin: a potent new antiparasitic agent, Science, 221, pp. 823-828.

Charlier, J., van der Voort, M., Kenyon, F., Skuce, P. and Vecruysse, J. (2014) Chasing helminths and their economic impact on farmed ruminants, Trends in Parasitology, 30:7, pp. 361-367.

Dadd, G.H. (1897) American Cattle Doctor, Orange Judd Co., New York.

de Bairicli-Levy, J. (1984) The Complete Herbal Handbook for Farm and Stable, Faber & Faber, Boston.

De la Concho-Bermejillo, A., Anderson, N.V., Bretzlaff, K., Kimberling, C.V., Moore, G., Rowe, J.D. and Wolfe, C. (1998) Overview of diseases and drug needs for sheep and goats. Veterinarians and producers' perspectives, Veterinary and Human Toxicology, 40 Suppl 1, pp. 7-12.

Del Mar Gil-Díaz, M., Perez-Sanz, A., Martín, M. and Carmen Lobo, M. (2011) Potential Diffusion of Doramectin into a Soil Amended with Female Pig Manure. A Field Experiment, J. Agric. Food Chem., 59, pp. 10635–10640.

Deng, Y., Palmer, C.J. and Casada, J.E. (1991) House fly brain γ-aminobutyric acid-gated chloride channel for multiple classes of insecticides, Pesticide Biochemistry and Physiology, 41, pp. 50-65.

Dolinská, M. Königová, A. Letková, V. Molnár, L. and Várady, M (2013) Detection of ivermectin resistance by a larval developmenttest—Back to the past or a step forward?, Veterinary Parasitology, 198, pp. 154–158.

Dun, F. (1910) Veterinary Medicines, 12th ed., David Douglas, Edinburgh.

Dutton, C.J., Gibson, S.P., Goudie, A.C., Holdum, K.S., Pacey,M.S., Ruddock, J.C., Bu'Lock, J.D. and Richards, M.K. (1990) Novel avermectins produced by mutational biosynthesis, Journal of Antibiotics, 44:3, pp. 357-365.

Duval, J. (1997) The control of internal parasites in cattle and sheep, Ecological Agriculture Projects, EAP Publication 70.

Ellingwood, F. (1919) American Materia Medica, Therapeutics and Pharmacognosy, Southwest School of Botanical Medicine

Epe, C. and Kaminsky, R. (2013) New advancement in anthelmintic drugs in veterinary medicine, Trends in Parasitology March 2013, 29: 3, pp. 129-134.

Faedo, M., Larsen, M., Dimander, S.O., Yeates, G.W., Hoglund, J. and Waller, P.J. (2002) Growth of the fungus duddingtonia flagrans in soil surrounding feces deposited by cattle or sheep fed the fungus to control nematode parasites, Biological Control, 23, pp. 64–70.

Fiel, C.A., Fernandex, A.S., Rodriguez, E.M., Fuse, L.A. and Steffan, P.E. (2012) Observations on the free-living stages of the cattle gastrointestinal nematodes, Veterinary Parasitology, 187, pp. 217– 226.

Fitzpatrick, J.L. (2013) Global food security: The impact of veterinary parasites and parasitologists, Veterinary Parasitology, 195, 233– 248.

Floate, K.D. (2007) Endectocide residues affect insect attraction to dung from treated cattle: implications for toxicity tests, Medical and Veterinary Entomology, 21, pp. 312–322.

Floate, K.D., Wardhaugh, K.G., Boxall, A.B.A. and Sherratt, T.N. (2005) Fecal residues of veterinary parasiticides: nontarget effects in the pasture environment, Annu. Rev. Entomol., 50:153–79

Food and Agriculture Organization of the United Nations—FAO (1990) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/2, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1991) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/4, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1991) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/3, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1993) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/5, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1993) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/6, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1993) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/5, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1995) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/8, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (1999) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/11, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (2000b) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/12, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (2000a) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/13, Geneva, Switzerland.

Food and Agriculture Organization of the United Nations—FAO (2004) Residues of some veterinary drugs in animals and foods, FAO food and nutrition paper, 41/16, Geneva, Switzerland.

Forster, B., Boxall, A., Coors, A., Jensen, J., Liebig, M., Pope, L., Moser., T. and Rombke, J. (2011) Fate and effects of ivermectin on soil invertebrates in terrestrial model systems, Ecotoxicology, 20, pp. 234-245.

Fort Dodge Animal Health (2001) Environmental Assessment: Cydectin (moxidectin) injectable solution for cattle.

George, N., Persad, K., Sagam, R., Offiah, V.N., Adesiyun, A.A., Harewood, W., Lambie, N. and Basu, A.K. (2011) Efficacy of commonly used anthelmintics: First report of multiple drug resistance in gastrointestinal nematodes of sheep in Trinidad, Veterinary Parasitology, 183, pp.194– 197

Goudie, A.C., Evans, N.A., Gration, K.A.F., Bishop, S.P., Holdom, K.S., Kaye, B., Wicks, S.R., Lewis, D., Weatherley, A.J., Bruce, C.I., Herbert, A. and Seymour, D.J. (1993) Doramectin—a potent novel endectocide, Veterinary Parasitology, 49, pp. 5-15.

Grainger, J. and Moore, C. (1994) Natural Insect Repellents, The Herb Bar, Austin, Texas

Grenda, V.J., Jones, R.E., Gal, G.> and Sletzinger, M. (19656) Novel preparation of benzimidazoles from N-Arylamidines. New synthesis of Thiabendazole, Journal of Organic Chemistry, 30:1, pp. 259-261.

Grosjean, N. (1994) Veterinary Aromatherapy, C. Daniel Co., Ltd., Essex, England.

Guthrie, J.E. and Briggs, J.E. (1957) Ascaricidal activity of piperazine administered in the feed of swine, Journal of Animal Science, 15:4, pp. 943-945.

Halley, B., Nessel, R.J., Lu, A.Y.H., and Ronacalli, R.A. (1989) The environmental safety of ivermectin: an overview, Chemoshpere, 18:7-8, pp. 1565-1572.

Hamilton-Miller, J.M.T. (1973) Chemistry and biology of the polyene macrolide antibiotics, Bacteriological Reviews, 37:2, pp.166-196.

Hare, H.A. (1904) A text-book of practical therapeutics: with especial reference to the application of remedial measures to disease and their employment upon a rational basis, 10th ed., Lea Brothers, Harvard University Press, Boston. Mass.

Hatcher, R.A. and Wilbert, M.I. (1915) Anthelmintics, Practical Pharmacology, XXXI, Journal of the American Medical Association, 65, pp. 622-623.

Hoare, E.W. (1896) A manual of veterinary therapeutics and pharmacology, J.A. Carveth & Co., Toronto.

Hoechst-Roussel Agrivet (1995) Environmental Assessment NADA 128-620, Fenbendazole suspension 10% in Dairy Cattle of Breeding Age.

Hopwood, D.A. (2007) How do antibiotic-producing bacteria ensure their self-resistance before antibiotic biosynthesis incapacitates them? Molecular Microbiology, 63:4, pp.937-940.

Horvat, A.J.M., Petrovic, M., Babic, S., Pavlovic, D.M., Asperger, D., Pelko, S., Mance, A.D., and Kastelan-Macan, M. (2012) Analysis of the occurrence and fate of anthelmintics and their transformation products in the environment, Trends in Analytical Chemistry, 31, pp. 61-84.

Howard, L., Papendicki, R., Stalis, I.H., Allen, J.L. Sutherland-Smith, M. and Zuba, J.R. (2002) Fenbendazole and albendazole toxicity in pigeons and doves, Journal of Avian Medicine and Surgery, 16:3, pp. 203-210.

Ingham, M.R. (1999) Food and Soil Health, USDA Natural Resources Conservation Service

James, C.E. and Davey, M.W. (2009) Increased expression of ABC transport proteins is associated with ivermectin resistance in the model nematode *Caenorhabditis elegans*, International Journal for Parasitology, 39, 213–220.

James, C.E., Hudson, A.L. and Davey, M.W. (2009) Drug resistance mechanisms in helminths: is it survival of the fittest? Trends in Parasitology, 25:7, p. 328-335.

Jasmer, J., Goverse, A., and Smant, G. (2003) Parasitic nematode interactions with mammals and plants, Annu. Rev. Phytopathol., 41, pp. 2245-270.

Kaleysa, R.R. (1974) Screening of some indigenous plants for anthelmintic action against human *Ascaris lumbricoides*, Ind. J. Physiol. Pharmac., 18:2, pp. 129-132.

Kamal, A., Khanna, G.B.R., Krishnaji, T. and Ramu, R. (2005) A new facile chemoenzymatic synthesis of levamisole, Bioorganic & Medicinal Chemistry Letters, 15, pp. 613–615.

Kaplan, R.M. (2004) Drug resistance in nematodes of veterinary importance: a status report, TRENDS in Parasitology, 20:10, p. 477-481.

Karreman, H.J. (2004) Treating dairy cows naturally: thoughts and strategies, Paradise Publications, Paradise, PA., p. 165.

Kiuchi, F., Itano, Y., Uchiyama, N., Honda, G., Tsubouchi, A., Nakajima-Shimada, J. and Aoki, T. (2002) Monoterpene hydroperoxises with trypanocidal activity from cheopodium ambrosioides, J. Nat. Prod., 65, pp. 509-512.

Kopp, S.R., Kotze, A.C., McCarthy, J.S., Traub, R.J. and Coleman, G.T. (2008) Pyrantel in small animal medicine: 30 years on, The Veterinary Journal, 178, pp. 177-184.

Kreuzig, R., Blumlein, K. and Holtge, S. (2007) Fate of the Benzimidazole antiparasitics flubendazole and fenbendazole in manure and manured Soilssoils, Clean, 35:5, pp. 488-494.

Krogh, K.A, Soeborg, T., Brodin, B., and Hallin-Sorenen, B. (2008) Sorption and Mobility of Ivermectin in different soils, Journal of Environmental Quality, 37, pp. 2202-2211.

Lanusse, C. E. and Prichard, R.K. (1993) Relationship between pharmacological properties and clinical efficacy of ruminant anthelmintics, Veterinary Parasitology, 49, pp. 123-158.

Lavelle, P., Blouin, M., Boyer, J. Cadet, P., Laffray, D. Pham-Thi, A., Reversat, G., Settle, W. and Zuily, Y. (2004) Plant parasitic control and soil fauna diversity, C. R. Biologies, 327, pp. 629–638.

Lavelle, P., Decaëns, T., Aubert, M., Barot, S., Blouin, M., Bureau, F., Margerie, P., Mora, P. and P Rossi, J-P. (2006) Soil invertebrates and ecosystem services, European Journal of Soil Biology, 42, pp. S3–S15.

Le Jambre, Martin, P.J. and Johnston, A. (2010) Efficacy of combination anthelmintics against multiple resistant strains of sheep nematodes, Animal Production Science, 50, pp. 946–952

Leathwick, D. M., Hosking, B.C., Bisset, S.C. and McKay, C.H. (2009) Managing anthelmintic resistance: Is it feasible in New Zealand to delay the emergence of resistance to a new anthelmintic class?, New Zealand Veterinary Journal, 57:4, pp. 181-192.

Leathwick, D.M. (2013) Managing anthelmintic resistance – Parasite fitness, drug use strategy and the potential for reversion towards susceptibility, Veterinary Parasitology, 198, pp. 145– 153.

Leathwick, D.M. (2014) Sustainable control of nematode parasites – A New Zealand perspective, Small Ruminant Research, 118, pp. 31–34.

Leathwick, D.M. and Besier, R.B. (2014) The management of anthelmintic resistance in grazing ruminants in Australasia—Strategies and experiences, Veterinary Parasitology, 204, pp. 44–54.

Leathwick, D.M., Waghorn, T.S., Miller, C.M., Candy, P.M. and Oliver, A.-M.B. (2012) Managing anthelmintic resistance – Use of a combination anthelmintic and leaving some lambs untreated to slow the development of resistance to ivermectin, Veterinary Parasitology, 187, pp. 285– 294.

Liebig, M., Fernandez, Alvaro, A., Blubaum-Gronau, A,E., Boxall, A., Brinke, M., Carbonell, G., Egeler, P., Fenner, K., Fernandez, C., Fink,G., Garric, J., Halling-Sørensen, B., Knacker, T., Krogh, K.A., Kuster, A., Loffler, D., Angel, M., Cots, P., Pope, L., Prasse, C., Rombke, J., Ronnefahrt,I., Schneider, M.K., Natascha Schweitzer, N., Tarazona, J.V., Ternes, T.A., Traunspurger,W., Wehrhan, A. and Duisy, K. (2010) Environmental Risk Assessment of Ivermectin: A Case Study, Integrated Environmental Assessment and Management, 6, Supplement 1, pp. 567–587.

Loewe, H., Urbanietz, J., Kirsch, R., Duwel, D. (1976) Anthelmintically active 2-carboalkoxy-amino-benzimidazole-5(6)-phenyl ethers, US Patent 3,954,791.

Lopez-Olmos, K., Hernandez, M.P., Contreras-Garduno, J.A., Robleto, E.A., Setlow, P,.Yasbin, R.E. and Pedraza-Reyes, Marlo (2012) Roles of Endonuclease V, Uracil-DNA Glycosylase, and Mismatch Repair in Bacillus subtilis DNA Base-Deamination-Induced Mutagenesis, Journal of Bacteriology, 194:2, pp. 243-252.

Lund, V. and Algers, B. (2003) Research on animal health and welfare in organic farming—a literature review, Livestock Production Science, 80, pp. 55–68.

Lust, J.U. (2001) The Herb Book, Beneficial Books, New York.

Magi, E., Talvik, H. and Jarvis, T. (2005) In vivo studies of the effect of medicinal herbs on the pig nodular worm (Oesophagostomum spp.), Helminthologia, 42, pp. 67-69.

Mali, R. G. and Mehta, A.A. (2008) A review on Anthelmintic Plants, Natural Product Radiance, 75:5, pp. 466-475

Martin, R.J. (1997) Modes of Action of antihelmintic drugs, The Veterinary Journal, 154, pp. 11-34.

Mattsson, A. Ulleras, E., Patring, J. and Oskarsson, A. (2012) Albendazole causes stage-dependent developmental toxicity and is deactivated by a mammalian metabolization system in a modified zebrafish embryotoxicity test, Reproductive Toxicology, 34, pp. 31– 42.

Maulding, D.R. and Kuma, A. (1991) Process for the preparation of 23-(C1-C6 Alkyloxime)-LL-F28249 Compounds, US Patent 4988824.

McArthur, M.J. and Reinemeyer, C.R. (2014) Herding the U.S. cattle industry toward a paradigm shift in parasite control, Veterinary Parasitology, 204, pp. 34–43.

McKellar, Q.A and Scott, E.W. (1990) The benzimidazole anthelmintic agents—a review, J. Vet. Pharmacol. Therap., 13, pp. 223-247

McKellar, Q.A. (1997) Ecotoxicology and residues of anthelmintic compounds, Veterinary Parasitology, 72, pp. 413-435.

McKellar, Q.A., Scott, E.W., Baxter, P., L.A. and Bairden, K. (1993) Pharmacodynamics, pharmacokinetics and faecal persistence of morantel in cattle and goats, Journal of Veterinary Pharmacological Therapeutics, 16:1, pp. 87-92.

Merera, C., Ayana, T. and Gudeta, T. (2013) Effect of feeding *Leucaena pallida* with concentrate and antihelmintic treatment on growth performance and nematode parasite infestation of Horro ewe lambs in Ethiopia, International Journal of Livestock Production, 4:10, pp. 155-160.

Mowry, D. (1986) The Complete Validation of Herbal Medicine, Keats Publishing, Inc. New Canaan, CT.

Mulder, CH., de Zwart, D., van Wijnen, Schouten, A.J. and Breure, A.M. (2003) Observational and simulated evidence of ecological shifts within the soil nematode community in agroecosystems under conventional and organic farming, Functional Ecology, 17, pp. 516-525.

National Organic Program—NOP (1995) Final minutes of the National Organic Standards Board, Full Board meeting, Austin, Texas, October 31-November 4, 1995.

National Organic Program—NOP (1999a) National organic standards board draft minutes of meeting, February 9-11, 1999.

National Organic Program—NOP (1999b) Parasiticides, Technical Advisory Panel Review, Livestock Subcommittee, November 25, 1999.

National Organic Program—NOP (2000) Final Rule with request for comments, Agricultural Marketing Service, US Department of Agriculture, Federal Register, 65:246, pp. 80548-80684.

National Organic Program—NOP (2003) Moxidectin, Date Petition Received: 03/26/03, Petition Area and Use: Livestock: Add to 205.603, treatment, Status: Added to National List with annotation, effective May 16, 2012 {77 FR 28472}.

National Organic Program—NOP (2006) Proposed Amendments to the National List of Allowed and Prohibited Substances (Livestock); Proposed Rule, Agricultural Marketing Service, US Department of Agriculture, Federal Register, 71:136, pp. 40624-40632.

National Organic Program—NOP (2007a) Sunset Review, Final Rule, Agricultural Marketing Service, US Department of Agriculture, Federal Register, 72:199, pp. 58469-58473.

National Organic Program—NOP (2007b) Amendments to the National List of Allowed and Prohibited Substances (Livestock) Proposed Rule, Agricultural Marketing Service, US Department of Agriculture, Federal Register, 72:238, pp. 70479-70486.

National Organic Program—NOP (2007c) Fenbendazole, Date Petition Received: 03/23/07, Petition Area and Use: Livestock: Add to 205.603, treatment, Status: Added to National List with annotation, effective May 16, 2012 {77 FR 28472}.

National Organic Program—NOP (2011) Proposed Amendments to the National List of Allowed and Prohibited Substances (Livestock), Agricultural Marketing Service, US Department of Agriculture, Federal Register, 76:87, pp. 25612-25617.

Nevenka, K.E., Hodošček, L. and Cerkvenik-Flajs, V. (2007) Analytical procedure for determination of the time profile of eprinomectin excretion in sheep feces, Anal Bioanal Chem, 387, pp. 1329–1335.

Nuzzi, D. (1992) Pocket Herbal Reference Guide, The Crossing Press, Freedom, CA.

Oh, S.J., Park, J., Jung Lee, M., Park, S.Y., Lee, J-H., and Choi, K. (2006) Ecological hazard assessment of major veterinary benzimidazoles: acute and chronic toxicities to aquatic microbes and invertebrates, Environmental Toxicology and Chemistry, 25:8, pp. 2221–2226.

Organization for Economic Cooperation and Development—OECD (2004) SIAM 18, 20-23 April 2004 Piperazine

Pena-Espinoza, M., Thamsborg, S.M., Demeler, J. and Enemark, H.L. (2014) Field efficacy of four anthelmintics and confirmation of drug-resistant nematodes by controlled efficacy test and pyrosequencing on a sheep and goat farm in Denmark, Veterinary Parasitology, 206, pp. 208–215.

Pepping, J. (2004) Alternative Therapies: Wormwood, Am. J Healt-Sys Pharm, 61, pp. 239-242.

Perry, D.A. (1995) Self-organizing systems across scales, TREE, 10: 6, pp. 241-244.

Pfizer (1979) Environmental Impact Statement

Praslicka, J., Bjorn, H., Nansen, P. and Hennessy, D.R. (1997) The influence of high and low fibre diets on the activity of piperazine against *Oesophagostomum spp.* in pigs, International Journal for Parasitology, 27: 12, pp. 1523-1529.

Prasse, C., Loffler, D., and Ternes, T.A. (2009) Environmental fate of the anthelmintic ivermectin in aerobic sediment/water system, Chemoshpere, 77, pp. 1321-1325.

Prichard, R., Menez, C., and Lespine, A. (2012) Moxidectin and the avermectins: consanguinity but not identity, International Journal for Parasitology: Drugs and Drug Resistance, 2, pp. 134–153.

Raeymaekers, A.H.M., Allewijn, F.T.N., Vandenberk, J., Demoen, P.J.A., Van Offenwert, T.T.T. and Janssen, P.A.J. (1966) Novel broad-spectrum anthelmintics. Tetramisole and related derivatives of 6-Arylimidazo(2,1-b)thiazole, Journal of Medicinal Chemistry, 9, pp. 545–551.

Rasmann, S., Ali, J.G., Helder, J, van der Putten, W.H. (2012) Ecology and evolution of soil nematode chemotaxis, J. Chem. Evol., 38, pp. 615-628.

Sargison, N.D. (2104) Sustainable helminth control practices in the United Kingdom, Small Ruminant Research, 118, pp. 35–40.

Schmitt, H. and Rombek, J. (2008) The ecotoxicological effects of pharmaceuticals (antibiotcs and anti-parasiticides in the terrestrial environment—a review, *in* Pharmaceuticals in the environment Kummerer, K. ed., Springer Science and Business Media, pp. 285-303.

Schon, N.L., Mackay, A.D. and Minor, M.A. (2011a) Soil fauna in sheep-grazed hill pastures under organic and conventional livestock management and in an adjacent ungrazed pasture, Pedobiologia, 54, pp. 161–168.

Schon, N.L., Mackay, A.D. and Minor, M.A. (2011b) Vulnerability of soil invertebrate communities to the influences of livestock in three grasslands, Applied Soil Ecology, 53, pp. 98– 107

Smith, L.A., Marion, G., Swain, D,L., White, P.C.L., and Hutchings, M.R. (2009) The effect of grazing management on livestock exposure to parasites via the faecal–oral route, Preventive Veterinary Medicine, 91, pp. 95–106.

Sorokin, I.H., DiRaimondo and Chou, Chin-Liang (2008) Method of purifying moxidectin through crystallization, US Patent 2008/0119543 A1.

Spoolder, H. A. M. (2007) Animal welfare in organic farming systems, Journal of the Science of Food and Agriculture, 87, pp. 2741-2746.

Stapley, E.O. and Woodruff, H.B. (1982) Avermectin, antiparasitic lactones produced by *Streptomyces avermitilis* isolated from a soil in Japan. In: Umezawa, H., Deamin, A.L., Hata, T., Hutchinson, C.R. (Eds.), Trends in Antibiotic Research. Japan Antibiotics Research Association, Tokyo, pp. 154–170.

Steffan, P., Olaechea, F., Roepstorff, Bjorn, H. and Nansen, P. (1988) Efficacy of piperazine dihydrochloride against *Ascaris suum* and *Oesophogostomum* species in naturally infected pigs, Veterinary Record, 123, pp.128-130.

Stockdale, P. (2008) Living with worms in organic sheep production, Canadian Organic Growers, Inc., Ontario, Canada.

Strong, L., Wall, R., Woolford, A. and Djeddour, D. (1996) The effect of faecally excreted ivermectin and fenbendazole on the insect colonization of cattle dung following the oral administration of sustained-release boluses, Veterinary Parasitology, 62, pp. 253-266.

Svendsen, T.S., Grønvold, J., Holter, P. and Sommer, C. (2003) Field effects of ivermectin and fenbendazole on earthworm populations and the disappearance of dung pats from bolus-treated cattle, Applied Soil Ecology, 24, pp. 207–218

Sykes, F. (1949) Humus and the Farmer, Rodale Press, Emmaus, PA.

Takiguchi, Y., Mishima, H., Okuda, M., and Terao, M. (1980) Milbemycins, a new family of macrolide antibiotics: fermentation, isolation and physico-chemical properties, The Journal of antibiotics, 33:10, pp. 1120-1127.

Taylor, M.A. (2013) Parasite control in sheep: A risky business, Small Ruminant Research, 110, pp. 88– 92.

The Merck Index, (1983) 10th Ed., Rahway: Merck & Co.

Tizard, I. (2013) Veterinary Immunology, Elsevier, St Louis, MO.

Tyden, E., Dahlberg, J., Karlberg, O. and Hoglund (2014) Deep amplicon sequencing of preselected isolates of Parascaris equorum in β-tubulin codons associated with benzimidazole resistance in other nematodes, Parasites & Vectors, 7:410, pp. 1-8.

Udall, D.H. (1943) The Practice of Veterinary Medicine, 4th ed., Udall, Ithaca, New York.

US Environmental Protection Administration—EPA (2002) Reregistration Eligibility Document (RED) Thiabendazole, EPA738-R-02-xxx.

US Food and Administration—FDA (2012) FDA's public meeting on antiparasitic drug use and resistance in ruminants and equines – an overview, March 5 and 6, 2012.

US Food and Drug Administration—FDA (1994) Animal Medicinal Drug Use Clarification Act of 1994, Public Law 103-396

US Food and Drug administration—FDA (1995) Finding of no significant impact for fenbendazole.

US Food and Drug Administration—FDA (2006) Guidance for Industry, Environmental impact assessments (EIA's) for veterinary medicinal products (VMP's)-phase II, VICH GL38, Final Guidance US Department of Health and Human Services.

US Food and Drug Administration—FDA (2012) FDA's public meeting on antiparasitic drug use and resistance in ruminants and equines – an overview, March 5 and 6, 2012.

US Food and Drug Administration—FDA (2014a) Sterile Drug Substance Manufacturers (7/94).

US Food and Drug Administration—FDA (2014b) Foreign Pharmaceutical Manufacturers (5/96) Guide to inspections of foreign pharmaceutical manufacturers

US Food and Drug Administration—FDA (2015a) From an idea to the marketplace: the journey of an animal drug through the approval process, US Department of Health and Human Services.

US Food and Drug Administration—FDA (2015b) Extralabel drug use in animals, US code of federal regulationsm, Title 21, Chapter 1, subchapter E, Part 530

Van Wyk, J.A. and Bath, G.F. (2002) The FAMACHA system for managing haemonchus in sheep and goats by clinically identifying individual animals for treatment, Vet. Res., 33, pp. 509-529.

Vardanyan, R. and Hruby, V. (2006) Synthesis of essential drugs, Anthelmintic drugs, Elsevier.

Villalba, J.J., Provenza, F.D., Gibson, N., and Lopez-Ortiz, S. (2014) Veterinary Medicine: the value of plant secondary compounds and the diversity in balancing consumer and ecological health *in* Sustainable Food-Production includes Human and and Environmental Health, Issues in Agroecology, Springer, pp. 165-190.

Waghorn, T.S., Leathwick, D.M., Miller, C.M. and Atkinson, D.S., (2015) Brave or gullible: Testing the concept that leaving susceptible parasites in refugia will slow the development of anthelmintic resistance, New Zealand Veterinary Journal, 56:4, pp. 158-163.

Waterman, G.A. (1925) The Practical Stock Doctor, F.B. Dickerson Company, Lincoln, NE.

Winslow, K. (1919) Veterinary Medicine Medica and Therapeutics, 8th, ed., American Veterinary Publishing Co., Chicago.

Xu, Ming, Molento, M., Blackhall, W., Ribiero, P. Beech, R. and Prichard, R. (1998) Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog, 91, pp. 327-335.

Zhou, J., Sun, X., Jiao, J., Liu, M., Hu, F. and Li, H. (2013) Dynamic changes of bacterial community under the influence of bacterial-feeding nematodes grazing in prometryne contaminated soil, Applied Soil Ecology, 64, pp. 70– 76.

FIRST PRIORITY, INC.

PRODUCT NAME: **Privermectin™ Drench for Sheep**

This Material Safety Data Sheet is being provided to your company, for the purpose of providing current health and safety information to your management and employees who work with this product. Please read the data provided and then provide it to those people at your company who have the responsibility to insure compliance with both FEDERAL and STATE Right to Know regulations, and to those employees that request information on this product.

Federal Regulations: Parts 29 and 42 Code of Federal Regulations.

State of Illinois: Public Act 83-240

SECTION 1 - PRODUCT IDENTIFICATION

Manufacturer: First Priority, Inc.
1585 Todd Farm Drive
Elgin, Il 60123

Telephone Number: 800-650-4899
Emergency Number: Chemtrec
800-424-9300

Chemical Family: Mixture

Formula: N/A

Hazard Classification: Toxic (R 25 Toxic if swallowed)

HMIS Rating System: Health-0/Flammability-0/Reactivity-0

SECTION 2 - HAZARDOUS COMPONENTS

Ingredient	CAS#	PEL/TLV	Percent
Propylene Glycol	57-55-6	--	20.7% (w/v)
Benzyl Alcohol	100-51-6	--	3.14% (w/v)
Ivermectin	28-36-50	--	0.08% (w/v)

The hazard communication standard requires that such mixtures be assumed to present the same health hazard as do components that constitute as least 1% of the mixture (0.1% for carcinogens) although OSHA has noted that the hazards of individual components may be altered by including them in a mixture. Some of the ingredients of this mixture are a trade secret. NE = not established.

SECTION 3 - PHYSICAL DATA

Boiling Point: N/A
Vapor Pressure: N/A
Vapor Density: N/A
Solubility in Water: Miscible

Specific Gravity: Approx. 1.0
Percent Volatile: 66.0%
Evaporation Rate: N/A
Appearance & Odor: Pale Yellow Liquid

SECTION 4 - FIRE & EXPLOSION DATA

Flash Point (Method):	101°C
Estimated Flammable Limits in Air:	NE
Extinguishing Media:	Water, or all purpose dry chemical.
Special Fire Fighting Procedures:	Must wear MSHA/NIOSH approved self-contained breathing apparatus and protective clothing. Cool fire-exposed containers with water spray.
Unusual Fire & Explosion Hazards:	NE

SECTION 5 - HEALTH HAZARD DATA

Effects Of Overexposure

Eyes:	Irritating effect.
Skin:	No irritating effect
Inhalation:	Not an expected route of entry
Ingestion:	Toxic

Emergency First Aid Procedures:

Eye Contact:	Flush eyes with large amounts of water for at least 15 minutes. Consult a doctor.
Skin Contact:	Flush with large amounts of water.
Inhalation:	Not an expected route of entry.
Ingestion:	If swallowed, get immediate medical atttention.

SECTION 6 - REACTIVITY DATA

Stability:	No decomposition.
Conditions to avoid instability:	None known.
Incompatibility:	None known.
Hazardous Decomposition Byproducts:	None.
Hazardous Polymerization:	Will not occur.

SECTION 7 - SPILL OR LEAK PROCEDURES

Steps To Be Taken In Case Of Large Amount Of Material Is Released Or Spilled:
Absorb with liquid-binding material. Sweep or scoop up and place in chemical waste containers. Do not allow product to reach sewage system or any water source.

Waste Disposal Methods:
Dispose of in accordance with all local, state and federal regulations. Incinerate at an EPA approved incinerator facility.

SECTION 8 - SPECIAL PROTECTION

Respiratory Protection:	Not an expected route of entry.
Ventilation:	Provide sufficient ventilation.
Protective Gloves:	Disposable gloves recommended.
Eye Protection:	Use proper protection - safety glasses, as a minimum.
Other Protective Equipment:	Not normally needed.

SECTION 9 - SPECIAL PRECAUTIONS OR COMMENTS

Special precautions to be taken in handling & storing:	Keep closures tight. Avoid exposure to excessive heat.
Other precautions:	**Wash hands thoroughly after handling.** Highly toxic to aquatic organisms.

Initial Date: **June 17, 2002**

Although the information and recommendations set forth herein (hereinafter "information") are presented in good faith and believed to be correct as of the date hereof. First Priority, Inc. makes no representations as to the completeness or accuracy thereof. Information is provided upon the condition that the persons receiving same will make their own determination as to its suitability for their purposes prior to use. In no event will First Priority be responsible for damages of any nature whatsoever resulting from use of or reliance upon said information presented herein. NO REPRESENTATIONS OR WARRANTIES, EITHER EXPRESSED OR IMPLIED, OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR OF ANY OTHER NATURE ARE MADE HEREUNDER WITH RESPECT TO INFORMATION OR THE PRODUCT TO WHICH INFORMATION REFERS.

Parasiticides, Ivermectin

Reference: 205.603(a) 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. Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment. 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)—only for use by or on the lawful written order of a licensed veterinarian.

(ii) Ivermectin (CAS #70288-86-7).

(iii) Moxidectin (CAS #113507-06-5)—for control of internal parasites only.

Technical Report: 1999 TAP (Fenbendazole, Ivermectin);
Petition(s): N/A

Past NOSB Actions: 10/1999 NOSB minutes and vote; 11/2005 sunset recommendation; 10/2010 sunset recommendation
Recent Regulatory Background: Sunset renewal notice published 06/06/12 (77 FR 33290)
Sunset Date: 06/27/17

Subcommittee Review

The USDA organic regulations at 7 CFR part 205 provides guidance on livestock production practices to prevent the need for the use of parasiticides, and on regulation of 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; and
(2) Dairy stock, when used a minimum of 90 days prior to the production of milk or milk products that are to be sold, labeled, or represented as organic.

§205.603 Synthetic substances allowed for use in organic livestock production.

(a) 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. Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment. 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)—only for use by or on the lawful written order of a licensed veterinarian.
(ii) Ivermectin (CAS #70288-86-7).
(iii) Moxidectin (CAS #113507-06-5)—for control of internal parasites only.

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

The 2015 TR indicates that "The half-life for degradation of moxidectin in the environment may be up to 130 days," and the half-life of Ivermectin to be "127 days in soil." However, other sources indicate that the half-life of these materials can be quit 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.[1]

---

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

Although the NOSB approved the addition of Moxidectin to the National List in 2004, the US 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).

The organic standards of Canada prohibit the use of parasiticides with exceptions (2015 TR): "If no alternative treatment exists a parasiticide may be administered under veterinary supervision as directed by the standard and mandated by law. Treated livestock with a withdrawal period equivalent to double the label requirement or 14 days, whichever is longer is still considered organic. Organic status for chronically infected animals is discontinued. The Canadian Organic Standard requires organic livestock operations to have a comprehensive plan to minimize parasite problems in livestock, including monitoring and emergency measures. Normally, parasiticides cannot be administered to meat, dairy or laying animals, but in emergencies, production operations can use them: (1) if parasites are detected, (2) under veterinary instructions, (3) with double the label withdrawal time or 14 days whichever is longer, (4) with one treatment for slaughter animals under one year and two treatments for older animals (requiring more treatments will lose organic status), (5) but dairy animals requiring more than two treatments lose organic status and require a 12 month transition, (6) but dairy animals cannot be organic for slaughter, (7) and a dam may be treated during gestation, (8) and poultry flocks can be treated, but laying hens with more than one treatment per 12 months lose organic status and (9) the operator must provide a written action plan with amendments to the parasite control plan."

The organic standards of CODEX Alimentarius, the European Economic Community, Japan, and IFOAM also do not allow routine use of parasiticides, but they allow some provisions for emergency uses of parasiticides if preventative animal husbandry practices and natural remedies have been used and not found to be effective.

Like the Canadian standards, IFOAM organic standards require that when livestock are treated with synthetic parasiticides the required withdrawal time is not less than double the withdrawal period required by legislation, or a minimum of 14 days, whichever is longer. The organic standards of Japan and CODEX Alimentarius both require a withdrawal period of double the period required by legislation or a minimum of 48 hours.

For conventional livestock production no milk withdrawal time is required for either Fenbendazole[2,3] or Moxidectin.[4,5] Ivermectin is not approved for use in dairy animals, and no milk withdrawal time has been established for Ivermectin.[6,7]

---

[2]http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm069880.pdf

Ivermectin is considered to be the most harmful to soil life. From the 2015 TR: "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 Table 7).

Considering that the NOP standards prohibit the use of parasiticides in slaughter stock and that Ivermectin is not approved by FDA for use in dairy animals of breeding age, there seems to be little opportunity for the use of Ivermectin in organic production. The only opportunity for use of Ivermectin would be in breeder stock, before the last third of gestation for progeny to be sold as organic.

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?"

In the public comments received from those questions, and from additional comments from veterinarians and producers queried by members of the Livestock Subcommittee, 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.
Parasiticides fall into five anthelmintic drug classes differentiated by their chemical structures (TR line 151–152). Moxidectin and Ivermectin are both in one class of parasiticides and Fenbendazole is in a separate class, relative to modes of action, so some commenters suggested that it may be beneficial to keep one parasiticide from each class on the List to allow rotation of parasiticides to prevent the development of resistance and to have an alternative 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.

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

---

[3] http://www.asp-inc.com/products/documents/prodinfo/s/safeguard20spec.pdf
[4]http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm117119.pdf
[5]http://www.bi-vetmedica.com/content/dam/internet/ah/vetmedica/com_EN/product_files/cydectin-pour/Cydectin_Pour_On_label.pdf
[6]http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=128-409
[7] http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11162

Moxidectin is approved for use in cattle and sheep.
There are many natural alternative parasiticides being used in organic livestock production today. Natural parasiticides include homeopathic remedies, diatomaceous earth and many herbs with anthelminthic 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. There are some inherent contradictions and problems in the way the three parasiticides are listed and annotated on the National List:

1. Fenbendazole, which is considered the most environmentally benign, is annotated to require the "written order of a licensed veterinarian. Ivermectin and Moxidectin have no such requirement. That may lead producers to choose a more environmentally detrimental parasiticide for convenience.
2. Moxidectin is annotated "for control of internal parasites only." However, Moxidectin is widely used as a pour-on, and when used in that form for control of internal parasites it is also a *de facto* control for external parasites. Moreover, as mentioned above, the annotation "for control of internal parasites only: was apparently written based on incorrect information on the half-life of Moxidectin in the soil.
3. §205.603(a)(18) requires a 90-day withholding period for milk or milk products from a treated animal. There seems to be wide consensus that 90 days is much too long of a withholding period, because 1) it may motivate a producer to withhold needed treatment of an animal because of the severe consequences of a 90-day withdrawal, and 2) that is considered an excessive withdrawal time for food safety. Fenbendazole and Moxidectin have no milk withdrawal time for use in conventional production.
4. Ivermectin is not allowed for use in slaughter stock under the NOP, and it is not allowed for use in dairy animals of breeding age by the FDA, leaving the only legal use of Ivermectin to be on breeder stock before the last third of gestation for progeny to be sold as organic.

Motion to Remove
This proposal to remove Ivermectin will be considered by the NOSB at its public meeting.

The Subcommittee proposes removal of Ivermectin from the National List based on the following criteria in the Organic Foods Production Act (OFPA) and/or 7 CFR 205.600(b): Harmful to human health and the environment.

Vote in Subcommittee
Motion by:

Seconded by:

Yes: No: Abstain: Recuse: Absent :

National Organic Standards Board
Livestock Subcommittee
Proposal to Amend Use of Parasiticides in Organic Livestock Production
January 19, 2016

I. INTRODUCTION:

The use of parasiticides in organic production is strictly confined to emergencies. 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 reviewed in 2015 as part of the regular five-year Sunset process. At the October 2015 meeting in Stowe, Vermont, after considerable discussion and extensive public comment, it was recommended that all three parasiticides continue to be listed. Ivermectin was renewed with great reluctance owing to the recent research indicating serious negative impact of ivermectin on dung beetles in pastures. A Discussion Document was also presented at the October 2015 meeting seeking public comment on possible changes in use of the parasiticides. Extensive public comment indicates broad support to propose amendments on parasiticide use.

All three materials have annotations and other language limiting usage. Such language was developed when ivermectin was first added to the National List. Recent data and information indicates that milk withholding and other restrictions could be modified in a manner which would be beneficial to the sick animal in emergency situations without jeopardizing the quality of the organic product. In conventional milk production, there is no withholding period for fenbenzadole or moxidectin. For organic production, there is a 90 day withholding period for organic milk. Synthetic parasiticides are prohibited in organic slaughter stock. Wool and fleece from organic fiber bearing animals, such as sheep, cannot be sold as organic even with a single use of a synthetic parasiticide. Organic regulations allowed moxidectin for internal use only. Fenbenzadole use requires a veterinarian order prior to use in organic production, but ivermectin and moxidectin do not have such a requirement.

As discussed below, in 2007 it was agreed that the NOSB could use double FDA or Food Animal Residue Avoidance Databank (FARAD) withholding periods.

This proposal recommends:

* 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**.**

Acronyms used herewith:
FDA – Food and Drug Administration
FARAD – Food Animal Residue Avoidance Databank
CVM – Center for Veterinary Medicine
NADA – New Animal Drugs Application – under the FDA
AMDUCA – Animal Medical Drug Use Clarification Act
NOEL – No Observable Effect Level is used by the FDA, CODEX etc.
NRP – National Residue Program
ADI – Adult Daily Intake
MRL – Maximum Residue Limit
TR – Technical Report

Trade names—examples:
Fenbenzadole: Panacur, Safeguard
Ivermectin: Ivomec, Primectin
Moxidectin: Cydectin

II BACKGROUND:
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". Moxidectin was added to the National List in 2012 (77 FR 28472).

In December 2007, after much public comment and consultation, the NOP agreed that the NOSB could require double FDA withdrawal times, or double Food Animal Residue Avoidance Databank (FARAD) times (when appropriate), on a number of livestock materials:

> As a proposed compromise to satisfy the intent of the NOSB, many commenters suggested that USDA should consider amending the annotations of Atropine, Butorphanol, Flunixin, Furosemide, Tolazoline, and Xylazine by establishing extended withdrawal periods, calculated using withdrawal times from the Food Animal Residue Avoidance Databank (FARAD).The FARAD is a National Food Safety Project administered through the USDA Cooperative State Research, Education, and Extension Service. It is a system designed to provide livestock producers, extension specialists, and veterinarians with practical information on how to avoid drug, pesticide and environmental contaminant residue problems. FARAD is a repository of comprehensive residue avoidance information. It is also sanctioned to provide ''withholding period'' (also known as withdrawal period) estimates to the U.S. Pharmacopeia-Drug Information (USP–DI) Veterinary Medicine Advisory Committee. Commenters suggested that USDA account for an extra margin of at least double the withdrawal times of FARAD to safely capture the intent of the NOSB. USDA agrees with the position stated in the comments…
>
> Based on public comment, USDA consulted further with the FDA, concerning the ability to extend the withdrawal period on these approved drugs. Based on our consultations, USDA agreed to clarify the rationale for extending the FDA established withdrawal period. Secondly,

USDA agreed to clarify the language used to authorize the use of the substances by indicating the extended withdrawal periods (at least two-times that required by the FDA) were only relevant for use of the substances under the NOP regulations. Therefore, to clarify our rationale for extending the withdrawal periods established by the FDA, we acknowledge that this determination was not based on scientific research or risk assessments. The decision to extend the FDA withdrawal periods (or any other withdrawal period) for the use of Flunixin and Furosemide (and other substances) was based on consumer preference and the recommendations of the NOSB. FDA exercises full responsibility for determining and enforcing the withdrawal intervals for animal drugs. No food safety arguments are used or implied to support the use of extended withdrawal periods authorized under the NOP regulations. Rather, we determined that extended withdrawal periods are more compatible with consumer expectations of organically raised animals. (72 FR 70479)

In May 2008, Fenbendazole was approved by the NOSB for addition to the National List by a vote of 14-0 and added to the National List in 2012 (77 FR 28472). The Withholding period was the same as for Ivermectin.

Three Technical Reports are relevant for this proposal: A 1999 TAP (fenbendazole, ivermectin); a 2003 TAP for moxidectin; and a June 2015 Technical Report on all three parasiticides (fenbenzadole, ivermectin and moxidectin) requested by the Livestock subcommittee as part of its Sunset Review of these parasiticides.

In 2015, all three parasiticides were reviewed as part of the regular Five Year Sunset Review. At the October 2015 NOSB meeting in Stowe, Vermont:

- Moxidectin was recommended for continued listing on a Motion to Remove: 0 Yes; 12 No ; 2 abstentions.
- Fenbenzadole was recommended for continued listing on a Motion to Remove: 0 Yes ; 12 No ; 2 abstentions.
- Ivermectin was recommended for continued listing on a Motion to Remove: 6 Yes ; 4 No; 4 abstentions.

In addition a Discussion Document on parasiticides was presented at the October 2015 NOSB meeting. This is discussed below in the Discussion section.

III RELEVANT AREAS OF THE RULE:

The USDA organic regulations at 7 CFR part 205 describe required preventive health care practices and regulations for the use of synthetic 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; and
(2) Dairy stock, when used a minimum of 90 days prior to the production of milk or milk products that are to be sold, labeled, or represented as organic.

§205.603 Synthetic substances allowed for use in organic livestock production.

(a) 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. Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment. 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)—only for use by or on the lawful written order of a licensed veterinarian.
(ii) Ivermectin (CAS #70288-86-7).
(iii) Moxidectin (CAS #113507-06-5)—for control of internal parasites only.

IV DISCUSSION:

Fenbenzadole, ivermectin and moxidectin are the only antihelmintics approved for use in organic livestock production. They represent two of five antihelmintic drug classes. Fenbenzadole is in the benzimidazole group and Ivermectin and Moxidectin are in the polyene group within the macroyclic lactone group. In organic livestock production they are never used on a routine basis, only in emergency situations. They are used in doses as indicated on the label, by body weight and species of animal, and, under veterinarian supervision can be used "extra label/off-label" (see detailed discussion below).

Parasiticide Uses:

Fenbenzadole:

The US Food and Drug Administration Center for Veterinary Medicine and the US Department of Agriculture National Organic Program permit oral administration of fenbendazole in dairy cattle for the removal and control of lungworm (Dictyocaulus viviparus); brown stomach worm (Ostertagia ostertagi), barberpole worm (Haemonchus contortus and H. placei), small stomach worm (Trichostrongylus axei), hookworm (Bunostomum phlebotomum), threadnecked intestinal worm (Nematodirus helvetianus), small intestinal worm (Cooperia punctata and C. oncophora), bankrupt worm (Trichostrongylus colubriformis) and nodular worm (Oesophagostomum radiatum); in beef cattle (beef) for the removal and control of stomach worm (Ostertagia ostertagi) and tapeworm (Moniezia benedeni); in goats for the removal and control of stomach worms (Haemonchus contortus and Teladorsagia circumcincta); in swine for the removal and control of lungworms (Metastrongylus apri and M. pudendotectus), roundworms (Ascaris suum), nodular worms (Oesophagostomum dentatum, O. quadrispinulatum), small stomach worms (Hyostrongylus rubidus), whipworms (Trichuris suis) and kidney worms (Stephanurus dentatus) and in turkeys for the removal and control of round worms (Ascaridia dissimilis) and cecal worms (Heterakis gallinarum). Fenbendazole is sold by Merck Animal Health as Panacur® and Safe-Guard®. It is available in liquid suspension, as granules, as a paste and in blocks. Products are dispensed both by veterinarian's prescription and over the counter, but must be used in organic production only

under veterinary supervision. For swine, turkeys, and wild sheep the NADA (141-144, 140-954, 136-116, 131-675) for fenbendazole is for use in medicated feed only. Other uses for these animals are extralabel. Furthermore, the use of fenbendazole in medicated feed for domestic sheep in food production is not permitted by the FDA. (TR 2015, 284-302).

Ivermectin:
The US Food and Drug Administration Center for Veterinary Medicine and the US Department of Agriculture National Organic Program permit topical, subcutaneous and oral administration of ivermectin in cattle for the treatment and control of gastrointestinal nematodes: Haemonchus placei, Ostertagia ostertagi, O. lyrata, Trichostrongylus axei, T. colubriformis, Cooperia oncophora, C. punctata, C. pectinata, Oesophagostomum radiatum, Nematodirus helvetianus, N. spathiger, Bunostomum phlebotomum, lungworms: Dictyocaulus viviparous, grubs Hypoderma bovis, H. lineatum, sucking lice: Linognathus vituli, Haematopinus eurysternus, Solenopotes capillatus, mites: Psoroptes ovis (syn. P. communis var. bovis), Sarcoptes scabiei var. bovis, in reindeer for treatment and control of warbles (Oedemagena tarandi), in swine for treatment and control of gastrointestinal roundworms: Ascaris suum; red stomach worm, Hyostrongylus rubidus; nodular worm, Oesophagostomum species; threadworm, Strongyloides ransomi, somatic roundworm larvae-threadworm, Strongyloides ransomi, lungworms: Metastrongylus species, lice: Haematopinus suis, mites: Sarcoptes scabiei var. suis and ear mites: Otodectes cynotis, in american bison for the treatment and control of grubs: Hypoderma bovis and in sheep for treatment and control gastrointestinal roundworms: Haemonchus contortus, H. placei, Ostertagia circumcincta, Trichostrongylus axei, T. colubriformis, Cooperia oncophora, C. curticei, Oesophagostomum columbianum, O. venulosum, Nematodirus battus, N. spathiger, S. papillosus Chabertia, Trichuris ovis, lungworms: Dictyocaulus filaria and all larval stages of the nasal bot Oestrus ovis. Ivermectin is marketed by Merial, Inc. and other companies under a number of pharmaceutical labels. It is available as a drench, in liquid solution, for medicated feed, as a sustained release bolus and as a paste. Products are dispensed both by veterinarian's prescription and over the counter. (TR 2015, 303-321).

Moxidectin:
The US Food and Drug Administration Center for Veterinary Medicine and the US Department of Agriculture National Organic Program permit topical, subcutaneous and oral administration of moxidectin in cattle for treatment and control of internal and external parasites, gastrointestinal roundworms: Ostertagia ostertagi, Haemonchus placei, Trichostrongylus axei, T. colubriformis, Cooperia oncophora, C. pectinata, C. punctata, C. spatulata, C. surnabada, Bunostomum phlebotomum, Oesophagostomum radiatum, Nematodirus helvetianus, lungworms: Dictyocaulus viviparus, cattle grubs: Hypoderma bovis, H. lineatum, mites: Chorioptes bovis, Psoroptes ovis, P. communis var. bovis, lice: Linognathus vituli, Haematopinus eurysternus, Solenopotes capillatus, Bovicola(Damalinia) bovis and horn flies: Haematobia irritans and in sheep for the treatment and control of Haemonchus contortus, Teladorsagia circumcincta, T. trifurcata, Trichostrongylus axei, T. colubriformis, T. vitrinus, Cooperia curticei, C. oncophora, Oesophagostomum columbianum, O. venulosum, Nematodirus battus, N. filicollis, and N. spathiger. Moxidectin is sold by Boehringer Ingelheim Vetmedica, Inc. as Cydectin. It is available in liquid solution. Products are dispensed over the counter (TR 2015, 322-332).

<u>Regulated approvals:</u>
The use of fenbendazole for food animals is approved under six FDA New Animal Drug Applications (NADA) (TR 2015, Table 3). It is dispensed over the counter. The use of ivermectin for food animals is approved under nineteen FDA new animal drug applications. It is dispensed both by veterinary prescription and over the counter (Table 3). The use of moxidectin is approved under three NADAs. It is available over the counter. Moxidectin is in the polyene group and of macrolides and is not antibiotitic in its function. (TR 105-113). The approved FDA NADA numbers for the eight additional anthelmintics

approved by the FDA are provided in Table 3 of the TR. (TR 2015, 243-248).

"Off label/ Extra label use". Once a NADA is approved, the FDA, under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), can permit the use of the approved drug under specific conditions outside the designated or intended label use, e.g. use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses (FDA, 1994).

This "off-label use" is only permitted in the context of a valid veterinarian-client-patient relationship and is limited to treatments when the health of an animal is threatened or suffering or death may result from failure to treat.

A valid veterinarian-client-patient relationship is one in which: (1) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian; (2) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and (3) The practicing veterinarian is readily available for follow up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept (FDA, 2015b). (TR 2015, 249-266)

For example, there is not an FDA approved use for fenbendazole in domestic sheep; however, it is used under veterinary supervision for this purpose. (TR 2015, 266-267)

There are some limitations for the AMDUCA including extra label use of an approved new animal or human drug by a lay person (except when supervised by a veterinarian). (TR 2015, 269-270).

The no observable effect level (NOEL) for parasiticides is determined by drug manufacturer and approved by the US Food and Drug Administration, Codex Alimentarius or other national or international standard setting organization. Protocols are provided by these federal agencies that detail testing and evaluation of the drugs. The NOEL is usually determined in an animal model. The NOEL values for fenbendazole, ivermectin and moxidectin are respectively, 0.7 milligram/kilogram body weight per day (mg/kg bd/day), 1.5 mg/kg bd/day and 10 mg/kg bd/day. The NOEL is used to determine the Adult Daily Intake (ADI) or the maximum residue limit (MRL). Withdrawal time is the time that it takes for the concentration in milk, eggs and meat that will be consumed by people to drop from the residue level at administration to the ADI, MRL, or safe level. (TR 2015 807-814)

<u>Withdrawal periods for Milk</u>:

Fenbenzadole: FDA—zero withdrawal; FARAD does not include recommendations.

Moxidectin: FDA—zero withdrawal, although some products state not established; FARAD—Cows: zero withdrawal when administered topically, and not established when administered subcutaneously; FARAD—Goats one day for topical administration and up to 18 days if administered orally (drench) (based on weight of animal and dosage)

<u>International Use and Restrictions (TR 2015, 432-507)</u>:

CANADA:

The organic standards of Canada prohibit the use of parasiticides with exceptions: If no alternative treatment exists a parasiticide may be administered under veterinary supervision as directed by the standard and mandated by law. Treated livestock with a withdrawal period equivalent to double the label requirement or 14 days, whichever is longer is still considered organic. Organic status for chronically infected animals is discontinued, but **use in slaughter stock is allowed within limitations**.

The Canadian Organic Standard requires organic livestock operations to have a comprehensive plan to minimize parasite problems in livestock, including monitoring and emergency measures. Normally, parasiticides cannot be administered to meat, dairy or laying animals, but in emergencies, production operations can use them: (1) if parasites are detected, (2) under veterinary instructions, (3) with double the label withdrawal time or 14 days whichever is longer, (4) with one treatment for slaughter animals under one year and two treatments for older animals (requiring more treatments will lose organic status), (5) but dairy animals requiring more than two treatments lose organic status and require a 12 month transition, (6) but dairy animals cannot be organic for slaughter, (7) and a dam may be treated during gestation, (8) and poultry flocks can be treated, but laying hens with more than one treatment per 12 months lose organic status and (9) the operator must provide a written action plan with amendments to the parasite control plan.

CODEX:

The organic standards of CODEX Alimentarius, do not allow routine use of parasiticides, but they allow some provisions for emergency uses of parasiticides if preventive animal husbandry practices and natural remedies have been used and not found to be effective. Withdrawal periods should be double that required by legislation, with a minimum of 2 days.

IFOAM:

Like the Canadian standards, IFOAM organic standards require that use of antihelmintics will cause animal to lose its organic status – But an exception is allowed when livestock are treated with synthetic parasiticides the required withdrawal time is not less than double the withdrawal period required by legislation, or a minimum of 14 days, whichever is longer. And **use in slaughter stock is allowed within limitations.**

The International Federation of Organic Agricultural Movements (IFOAM) Exception states that an animal can retain its organic status if the operator can demonstrate treatment is in compliance with IFOAM preventive animal husbandry practices, and natural and alternative medicines and treatments are unlikely to be effective to cure sickness or are not available to the operator, and the chemically synthesized allopathic veterinary medical products or antimicrobials are used under the supervision of a veterinarian, withdrawal periods are not less than double the withdrawal period required by legislation, or a minimum of 14 days, whichever is longer. The exception is granted for a maximum of three courses of remedial treatments within 12 months, or one course of treatment if the productive lifecycle of the animal is less than one year. (TR 2015 486-494)

EEC:

The European Economic Community states that preventive, routine use of parasiticides is not allowed but in the case of a sick animal needing immediate treatment the withholding period is double the withdrawal. And **use is allowed in slaughter stock.**

JAS:

The organic standards of Japan do not specify which parasiticides may be used. The withdrawal period is 2 days prior to slaughter for foods, milk or egg collection or twice the period of drug withdrawal. **Use in slaughter stock is allowed.**

NOP: Does not allow for use in slaughter stock, and this proposal does not recommend any changes to this prohibition.

Alternatives:

There are many natural alternative parasiticides being used in organic livestock production today. Natural parasiticides include homeopathic remedies, diatomaceous earth and many herbs with antihelminthic 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.

Livestock develop an immune response to nematodes and becomes resistant or tolerates them without signs of disease. Because young livestock do not have a mature immune system, they may not be able to mount an immune response upon infection. The same is also true for older and immuno-compromised animals. Worming with homeopathic and botanical remedies should begin strategically during the first autumn of life to accommodate the low body reserves expected with calves (Karreman, 2004).

Homeopathic wormers are available commercially that satisfy the organic rule. These are available as veterinary preparations with valid labeling systems so that their use may easily be audited (Brunetti and Karreman, 2006). Users of these remedies should be sure that the material has an appropriate potency and the source from which it was extracted is verified and correct. A list of natural wormers is provided in Table 11 of the TR. Herbal remedies with anthelminthic properties were commonly adopted and used as a part of traditional animal husbandry. Some have not been evaluated with modern techniques, but may cause toxic side effects, however in most cases they represent a good alternative to the use of synthetic drugs (Duval, 1997) (TR 2015, 828-840).

Brunetti and Karreman found that 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 (TR 2015 943-946).

Public comment included many producers, all species of livestock, who consistently use alternative natural materials and plants, pasture and browse, who never use any synthetic parasiticides. Emergency use of synthetic antihelmintics is not common in organic livestock production. This proposal only relates to milk production, not to slaughter stock, and only in emergency situations.

Confusion in present annotation language:

There are some inherent contradictions and problems in the way the three parasiticides are listed and annotated on the National List:

1. Fenbendazole, which is considered the most environmentally benign, is annotated to require the "written order of a licensed veterinarian". Ivermectin and moxidectin have no such requirement. That may lead producers to choose a potentially more environmentally detrimental parasiticide for convenience.
2. Moxidectin is annotated "for control of internal parasites only." However, moxidectin is widely used as a pour-on in conventional livestock production, and when used in that form for control of external parasites it is also a de facto control for internal parasites. Moreover, as mentioned above, the annotation "for control of internal parasites only": was apparently written based on incorrect information on the half-life of moxidectin in the soil.
3. §205.603(a)(18) requires a 90-day withholding period for organic milk or milk products from a treated animal. There seems to be wide consensus that 90 days is much too long of a withholding period, because 1) it may motivate a producer to withhold needed treatment of an animal because of the severe consequences of a 90-day withdrawal, and 2) fenbendazole and moxidectin have no milk withdrawal time for use in conventional production. There is no scientific rationale for the 90 day withholding for milk. The 90 days reflects a desire to assure consumers that organic standards exceed conventional use of restricted materials.

Based on public comment during the first posting of these materials, in fall 2015 the NOSB posted a Discussion Document for public comment. The Discussion Document included the following questions:

1. Should the milk withholding period be modified for any or all of the parasiticides? If so, how many days for moxidectin, fenbenzadole and ivermectin?
2. Should minimal use of parasiticides be allowed in organic slaughter stock such as is permitted under Canadian Organic standards with one treatment for slaughter animals under one year and two treatments for older animals (requiring more treatments will lose organic status)?
3. Should Sheep fleece and wool be allowed to be certified organic even if use of parasiticides was necessary at some time in the animal's life?
4. Should use of Moxidectin be changed to allow both internal and external use?
5. Should use of parasiticides be allowed only under Veterinarian advice?

Public Comment:

Considerable public comment was received from a broad range of stakeholder groups and producers.

To summarize public comment*:*

* There was strong support to reduce the withholding period for milk following use of either fenbenzadole or moxidectin. Recommendations, based on science and research, suggested adoption of a withdrawal period of between zero days and 14 days as opposed to the present 90 days.

One large dairy stated the following: "We support the NOP's consistent position of an organic milk withdrawal period of twice what is required by the…FDA and/or…FARAD for substances on the National List. However… Fenbenzadole and Moxidectin have no FDA required milk withdrawal interval and therefore organic dairy livestock treated with either of these substances should have milk requirement

withdrawal of zero days. Three other commenters also suggested zero withholding and one researcher commented that science indicates that small ruminants metabolize fenbenzadole even more rapidly than large ruminants. Research presented as part of public comment indicates Fenbenzadole in blood samples peaks at 7 hours and is gone from the blood in 72 hours.

Veterinarians, consumer organizations, a trade organization, individual producers , certifiers, an inspector association, and dairy groups all supported reduction of the withholding period based on science and the FDA and FARAD.

* There was no support for reducing withholding from 90 days after treatment with ivermectin based on science and FARAD. Some commenters suggested the need to prohibit ivermectin treatment for lactating cows.

* One certifier (Western US) noted that synthetic parasiticides are rarely used in dairy production. Several producers stated that they never use parasiticides.

* There was widespread public comment to remove ivermectin completely from the National list especially in light of recent science indicating the negative impact of ivermectin on dung beetles in pastures. However, some producers, notably small ruminant producers, urged that ivermectin be kept on the list at present for the following reasons: the fact that ivermectin is well known; has been allowed for the longest time; is commonly available without prior veterinarian advice or prescription; lack of experience of use of fenbenzadole. Veterinarians and a large dairy producer group recommended that ivermectin be prohibited for use on lactating cows. Since parasiticides, if used, are typically given to young stock, several public commenters requested that NOSB consider an annotation to state – Ivermectin- not for use in dairy animals of breeding age or older. Other commenters noted that because ivermectin is ONLY used in an emergency and not on a regular basis, dung beetle impact on organic pastures will be minimal.

* There was strong support to allow both external and internal use of moxidectin from individual dairy producers, larger dairy organizations, certifiers, an inspector organization, a trade group, and veterinarians. One certifier commented that the present annotation for internal and not external use makes verification difficult. A large dairy commented that moxidectin for both internal and external use is particularly critical in the Southern US states.

* There was little support for possible adoption of allowing parasiticide use in slaughter stock as per the Canadian Organic Standards. Consumer groups and dairy producer organizations expressed concern that this would reduce consumer confidence in organic food. Certifiers and veterinarians also did not support this suggestion. There were two individuals who felt that use of limited parasiticides could be allowed for slaughter stock.

* There was strong support for certification of sheep fleece and wool even after use of parasiticides. This support came from farmer producers, certifiers, veterinarians, farm producers in the West, consumer groups, an inspector organization, and trade groups. We were reminded that this is not a new idea, but one that was proposed to the NOSB in 1990 and never taken up by the NOSB.

* There was mixed response to requiring veterinarian advice before use of parasiticides. Certifiers like the idea that veterinarians would be involved as this would make the audit trail far easier to verify. One certifier stated:

> Overall we support an annotation update that requires veterinarian advice because it would clarify how producers should document the emergency necessity for treatment and provide for a clear audit. Currently parasiticides are "allowed for emergency treatment," which requires that organic producers describe and provide documentation about how they determined that it was an emergency (fecal tests, animal condition, etc.)…A vet recommendation requirement would be more straightforward to document and audit than the existing annotation…but…situations also exist when a veterinarian may not be available to assess the situation quickly, such as when animals are in a remote location.

Most, but not all, veterinarians support requiring veterinarian advice prior to use of parasiticides. This would ensure that the right dosage of the most effective parasiticide is given to the various animal species. One large cow dairy organization stated that there was plenty of most of the parasiticides available without veterinarian advice.

To quote one of the public comments:

> In preparing this proposal to recommend amendments to use of parasiticides, the NOSB must be very mindful that we need to remember that livestock producers are raising multiple species in diverse geographic regions facing diverse climatic conditions.

V RECOMMENDATION:

§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; and
(2) Dairy animals ~~stock, when used a minimum of 90 days prior to the production of milk or milk products that are to be sold, labeled, or represented as organic~~, as allowed under §205.603.
(3) Fiber bearing animals, as allowed under §205.603.

§205.603 Synthetic substances allowed for use in organic livestock production.

(a) 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 production of fleece or wool that is to be sold, labeled, or represented as organic. ~~Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment.~~ 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)—~~only for use by or on the lawful written order of a licensed veterinarian.~~ 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.

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

(iii) Moxidectin (CAS #113507-06-5)—~~for control of internal parasites only~~ 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.

Sub Committee Vote:

1. That the strikethrough language be removed, and the underlined language be added at:

Section 205.238(b)(2) Dairy animals, ~~stock when used a minimum of 90 days prior to the production of milk or milk products that are to be sold, labeled, or represented as organic.~~ as allowed under 205.603.

AND

205.603(a)(18) ….~~Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment~~ .

Motion by: Jean Richardson
Seconded by: Francis Thicke
Yes: 6 No: 0 Abstain: 0 Recuse: 0 Absent: 0

2. That the underlined language be added at:

§205.238(b)(3) Fiber bearing animals, as allowed under §205.603.

AND

§205.603(a)(18) … Allowed for fiber bearing animals when used a minimum of 90 days prior to production of fleece or wool that is to be sold, labeled or represented as organic.

Motion by: Jean Richardson
Seconded by: Francis Thicke
Yes: 6 No: 0 Abstain: 0 Recuse: 0 Absent: 0

3. That the strike through language be removed and the underlined language added at:

205.603(a)(18)(i) Fenbendazole (CAS #43210-67-9)~~—only for use by or on the lawful written order of a licensed veterinarian.~~ 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.

Motion by: Jean Richardson
Seconded by: Francis Thicke
Yes: 6 No: 0 Abstain: 0 Recuse: 0 Absent: 0

4. That the underlined language added at:

205.603(a)(18) (ii) Ivermectin (CAS #70288-86-7)—Milk or milk products from a treated animal cannot be labeled as provided for in subpart D of this part for 90 days following treatment.

Motion by: Jean Richardson
Seconded by: Francis Thicke
Yes: 6 No: 0 Abstain: 0 Recuse: 0 Absent: 0

5. That the strike through language be removed and the underlined language added at:

205.603(a)(18) (iii) Moxidectin (CAS #113507-06-5)~~—for control of internal parasites only~~ 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 animals.

Motion by: Jean Richardson
Seconded by: Francis Thicke
Yes: 6 No: 0 Abstain: 0 Recuse: 0 Absent: 0