

Executive Summary

Moxidectin was petitioned for use as a broad spectrum topically applied antiparasitic drug with activity against both internal and external parasites. It is a derivative of nemadectin, an antibiotic produced during the fermentation of *Streptomyces cyaneogriseus* sp. *noncyanogenus*¹. All three reviewers find moxidectin to be a synthetic material. One reviewer supports prohibition of moxidectin, finding that the Final Rule is very specific in prohibiting the use of synthetic parasiticides and that there are adequate alternatives available in organic farming systems. Two reviewers support the addition of moxidectin to the National List with restrictions on its use. These restrictions included the administration of moxidectin by a topical route and for emergency treatment only. Additionally, one of the reviewers supporting approval of moxidectin recommended that it be approved for use only in documented cases of horn flies and cattle grubs. One of the reviewers supporting approval found that approved treatment options for parasites need to be available for use when organically allowed treatment and prevention fail.

Summary of TAP Reviewer's Analyses

<i>Synthetic/ Nonsynthetic</i>	<i>Allow without restrictions?</i>	<i>Allow only with restrictions? (See Reviewers' comments for restrictions)</i>
Synthetic (3) Nonsynthetic ()	Yes (0) No (3)	Yes (2) No (0)

Identification

Chemical names¹:

moxidectin
 (2aE,4E,5'R,6R,6'S,8E,11R,13S,15S,17aR,20R,20aR,20bS)-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-2H,13H,17H-furo[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2'-[2H]pyrano]-4',17(3')-dione,4'-(E)-(O-methyloxime)

¹ This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(M) of the OFPA [7 USC 6517(m)]. The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other factors that the NOSB and the USDA may want to consider in making decisions.

Other Names:

23-(O-Methyloxime)-F28249- α
Moxidectin technical
CL301,423²
Cydectin ®¹

Trade Names:

Cydectin® Cattle Pour-On consists of a 0.5% moxidectin solution.

CAS Registration Number

113507-06-5

Characterization

Composition:

Moxidectin is a semisynthetic macrolide antibiotic, the methyloxime derivative of nemadectin¹.

Properties^{2,3}:

APPEARANCE AND ODOR:	White/Yellow Powder
MELTING POINT:	Liquefies at 145-154C
VAPOR PRESSURE:	< 3.2 x 10 ⁻⁸ < TORR-Limit of Detection
% VOLATILITY (BY Negligible VOL.):	OCTANOL / HO 58,300
EVAPORATION RATE:	Negligible
SOLUBILITY IN WATER	0.51 mg/L at 25C

Cydectin® Cattle Pour-On consists of a 0.5% moxidectin solution. Moxidectin is lipophilic, poorly soluble in water and binds tightly to soil³.

How Made:

Moxidectin is a semisynthetic macrolide antibiotic, specifically the methyloxime derivative of nemadectin. It is chemically synthesized from nemadectin, an antibiotic produced in the fermentation of *Streptomyces cyaneogriseus* sp. *noncyanogenus*¹.

The synthesis of moxidectin involves protecting the 5-hydroxy group of nemadectin with p-nitrobenzoyl chloride to give the corresponding 5-O(p-nitrobenzoyl)- nemadectin, which is then oxidized to give a 5-O(p-nitrobenzoyl)-23-oxo- nemadectin derivative in a crystalline state. The 5-O(p-nitrobenzoyl)-23-oxo- nemadectin derivative is then reacted with methoxylamine to give the 23-(methyloxime)5-O(p-nitrobenzoyl)- nemadectin intermediate in a crystalline state. This intermediate is then deprotected in the presence of base to give the desired 23-(methyloxime)- nemadectin. These reactions take place in the presence of various organic solvents (U.S. Patent Number 4,988,824). Research has not shown that the manufacture of moxidectin is detrimental to the environment or to people who work in the manufacturing facility.

Specific Uses:

Cydectin® pour-on has been approved by the Food and Drug Administration (FDA) for use in cattle at a topical dose of 0.5mg moxidectin per 10kg body weight. It is effective against gastrointestinal roundworms, lungworms, cattle grubs, mites, lice and horn flies⁴. Although moxidectin is a macrolide antibiotic, it has not been approved for use as such.

Action:

Moxidectin activates glutamate-gated chloride channels and GABA-gated chloride channels, causing paralysis of certain arthropods and nematodes⁵. Moxidectin is effective against a wide range of adult and larval internal and external parasites including gastrointestinal roundworms, lungworms, cattle grubs, mites, lice and horn flies⁴.

Combinations:

Cydectin® Pour On for Cattle contains 5mg moxidectin per ml⁴. Cydectin® is a deep violet color, with an oily texture and a characteristic odor³.

Status

Historic Use by Organic Farmers:

There is no history of the use of moxidectin by organic farmers because the National Standards does not allow the use of synthetic parasiticides on a routine basis⁶, and only ivermectin is currently approved for emergency treatment of parasite infections⁷. Moxidectin can be used either as single dose treatment for an existing infection or, on a routine basis, to maintain an animal's parasite burden below that which would cause disease or decreased production.

OFPA, USDA Final Rule:

The Organic Foods Production Act of 1990 states that organically produced livestock may not be treated with synthetic internal parasiticides on a routine basis (6509.d.1.B). Cydectin® is the only moxidectin product approved for use in livestock, but it is approved for topical administration only.

Regulatory: EPA/NIEHS/Other Sources

Moxidectin has been approved for use by the FDA at a dose of 0.5mg per kg body weight. It is approved for the treatment and control of internal and external parasites⁸

Status Among U.S. Certifiers

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Beginning in 2002, state certifying agencies were required to follow NOP guidelines. Prior to that time, state regulations for moxidectin were as follows:

California Certified Organic Farmers standards did not specifically mention moxidectin. However, synthetic dewormers were allowed only for emergency medical treatment and extended withdrawal times were required.

Connecticut Chapter of the New England Organic Farmers Association did not allow the routine use of parasiticides for preventative purposes. However, treatment with parasiticides was permitted for existing infections that threatened the health of an animal. No specific parasiticides were allowed or disallowed, instead, they were taken on a case-by-case basis. Ivermectin had been allowed in the past for treatment of existing infections..

Texas Department of Agriculture's Organic Program did not have standards for organic livestock production prior to the NOP regulations.

International

Australia

The Australian organic standards do not specifically mention moxidectin; however, only the following parasite control methods are allowed: selective breeding, grazing management, adequate feed and adequate mineral nutrients⁹.

Canada

The National Standard for Organic Agriculture does not mention moxidectin. Synthetic parasiticides are allowed for animal treatment when no alternatives are available, however, treated animals cannot be marketed as organic until a period of time that is twice the federally established withdrawal time of the product has passed (CAN/CGSB-32.310-99, 7.4.4)¹⁰.

Japan

The Japanese Standards of Organic Agricultural Products do not currently regulate organic livestock production¹¹.

Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

- 1. The potential of the substance for detrimental interactions with other materials used in organic farming systems.*

Currently, Cydectin® is approved for only topical administration, with the appropriate dose applied along the dorsum of the animal. This route of administration limits the possible interaction that moxidectin could have with other materials used in organic farming systems⁴.

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2. *The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment.*

Moxidectin causes paralysis of nematodes and arthropods by activating glutamate-gated and GABA-gated chloride channels. In the body, moxidectin is metabolized primarily through hydroxylation¹², with the primary products being C₂₉₋₃₀ hydroxymethyl and C₁₄ hydroxymethyl metabolites¹³. When administered according to label directions, moxidectin has been shown to have persistent activity against *Haemonchus placei* for 14 days, *Oesophagotomum radiatum* and *Ostertagia ostertagi* for 28 days and *Dictyolcaulus viviparus* for 42 days⁴. Moxidectin is very lipophilic, so high concentrations of residues within the animal are seen in fat compared to other tissues¹². Moxidectin is labeled as having a meat and milk withdrawal period of zero days when administered according to label directions⁴. The main mode of excretion is through the feces, with 26% of the residues excreted as the active parent compound⁵ and the remainder excreted as less active hydroxylated metabolites (see above)¹⁴. Because of the lipophilic nature of the product, it binds very tightly to soil so is unlikely to contaminate water sources^{3,15}. In horses, moxidectin residues were detectable in the feces for 75 days and approximately 90% of the total residue was excreted by 8 days after treatment¹⁶. Under aerobic conditions, the half-life of moxidectin in soil was found to be approximately two months. In water, moxidectin breaks down fairly rapidly through photodegradation, and has a half-life of 6.8 hours³.

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*

In data submitted to the FDA, Fort Dodge Animal Health references studies that indicate that less than 1% of the applied dose of moxidectin was found to wash off treated cattle when rainfall occurred within 30 minutes of product application³. Any product that reaches the environment during manufacture, application or disposal is expected to bind tightly to the soil due to the lipophilic nature of moxidectin^{3,15}. Once in the environment, moxidectin is broken down by exposure to sunlight, with a half-life of approximately two months³. No research has been found to indicate that the manufacture of moxidectin is detrimental to the environment.

4. *The effects of the substance on human health.*

Moxidectin may be irritating to the eyes and skin. It has not been found to cause skin sensitization after repeated exposure¹². Inhalation or ingestion of Cydectin® may cause gastrointestinal distress and central nervous system effects². During testing for product approval, no structural similarities to any known carcinogen were reported. Additional tests demonstrate that moxidectin causes no increase in unscheduled DNA synthesis and does not have reproductive or oncotic effects. Research also indicates that the drug is neither a selective developmental toxicant nor a teratogen in rabbits. Conflicting test results were reported for mutagenicity studies: bacterial and microsomal assays indicated

that moxidectin was not a mutagen while mammalian cell CHO/HGPRT tests were inconclusive¹².

During the drug approval process, an acceptable daily intake (ADI) of 4.0 micrograms moxidectin per kilogram body weight was determined. Tolerances of 200ppb in cattle liver, 50ppb in cattle muscle and 40 ppb in cattle milk were set to maintain exposure levels below the ADI¹⁷.

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.*

Moxidectin, like avermectins and other milbemycins, is a macrocyclic lactone. These types of drugs are excreted in the feces, partly as the active parent compound and partly as less active metabolites, which could potentially be harmful to insects in the environment¹⁴. Product labels for Cydectin® and Quest® indicate that moxidectin may be harmful to aquatic life^{18,19}. However, the high soil binding capacity of moxidectin and its lipophilic nature are likely to limit the adverse effects on aquatic organisms¹⁵. One concern regarding the use of milbemycins is that they may adversely affect non-target organisms⁵. Non-target organisms play a role in the natural dispersion of dung, so help maintain pasture cleanliness, nutrient cycling and pasture productivity, among other things¹⁶. Ecological studies of moxidectin have shown conflicting results. Some studies have reported adverse effects on several non-target organisms, including *Musca autumnalis*, *Onthophagus gazella*, *Onthophagus binodis* and *Onthophagus alexis*, while others have shown that the drug does not increase the mortality rates in these insects^{5,14,20}. Different studies have concluded that moxidectin appears to be less harmful to arthropods than other endectocides and has been shown to be less toxic to *Onthophagus gazella* and *Hameatobia irritans*. Additional research indicates that moxidectin, when administered at the recommended dosage, is unlikely to have an adverse effect on earthworms^{15,21,22}. Additionally, one study that examined the fauna in dung pats found no difference in dung from moxidectin treated animals and dung from untreated control animals²². In data submitted to the FDA during the drug approval process, it was found that moxidectin had no adverse effect on the ability of plants to germinate, and did not cause damage to the leaves of growing plants³.

During the application for drug approval, the FDA issued a “Finding of No Significant Impact,” which was based on research results submitted by Fort Dodge Animal Health, the manufacturers of Cydectin®. In this, the FDA found that moxidectin is very toxic to aquatic vertebrates and invertebrates and relatively non-toxic to birds, plants and earthworms. Additionally, it found that moxidectin does not have an adverse effect on dung dependent insects and is less toxic than other, similar drugs. The “No Significant Impact” statement closes by saying that 0.5% moxidectin, when administered at the recommended dosage, is unlikely to have any adverse impact on the environment¹⁵.

6. *The alternatives to using the substance in terms of practices or other available materials.*

Organic livestock production practices do not allow the use of synthetic parasiticides on a regular basis or the administration of synthetic parasiticides to slaughter stock⁶. The use of ivermectin is prohibited in slaughter stock, but is allowed, with restrictions, as an emergency treatment when appropriate management has failed to prevent parasite infection or infestation⁷. Alternate parasite control mechanisms primarily focus on grazing management techniques including evasive, preventative and diluting practices²³. Evasive techniques include moving animals to a clean pasture one time or multiple times in a grazing season¹³.

Preventative practices include turning uninfected animals onto “clean” pastures that are free of parasites^{13,23}. One study has shown that lambs turned onto clean pastures that hadn’t been grazed by sheep in the previous year had lower fecal egg counts than lambs turned on pastures that permanently graze sheep²⁴.

Diluting practices include mixing younger, more susceptible animals with older animals or animals of another species (mixed or alternate grazing), as well as reducing the stocking rate of a pasture. Studies comparing the efficacy of these techniques have yielded conflicting results. For example, alternating sheep and cattle grazing has resulted in good nematode control for the sheep but unsatisfactory control in the cattle. Mixed and alternate grazing of heifers and sows resulted in acceptable control of *Ostertagia spp.* in the cattle, but unacceptable parasite control in the sow. Additionally, this type of grazing has occasionally been reported to cause negative effects in sheep and calves²³. One problem associated with mixed or alternate grazing systems is the potential for a host-specific parasite to adapt so that it can survive in other host species¹³. Grazing management has not been shown to be sufficient as the only means of helminth control in areas where grazing occurs year-round²³. Several studies have shown that as stocking rate of a pasture increases nematode egg count or worm burden also increases in dairy cattle and sheep. Other studies have demonstrated contradictory results¹³.

Biological control is a possible method of controlling parasites that utilizes one organism to control the population of another organism. Nematophagus fungi generally work to decrease the number of larvae that develop in the feces, but do not effect the worm burden of any individual animal, so can’t be used to treat clinical symptoms of parasites¹³. The nematode control properties of predacious fungus such as *Duddintonia flarans* is the most extensively tested biological control mechanism. It has been shown to reduce the population of nematodes on a pasture and is also easy to culture and easy to use. Biological control of nematodes is a potential alternative to more conventional methods; however, more extensive testing needs to be conducted to determine the efficacy and side effects of these procedures. Problems associated with the use of nematophagus fungi include lack of acceptance by producers, lack of application systems and lack of knowledge concerning the long term side effects of usage¹³.

Additional means of control that are compatible with organic livestock production include the selection of stock for resistance to parasite infections²³ and proper herd management, including good living conditions and adequate nutrition²⁵.

Natural parasiticides may be considered an alternative to the use of synthetic products in organic production. Examples include garlic, wormwood, wild ginger, conifers, diatomaceous earth and charcoal, among others²⁵. Because these products do not go through the FDA's drug approval process, their safety and efficacy may be unknown. Av Singh reports that natural dewormers may be poisonous so it is crucial that recommended dosages be followed. Additionally, some research has indicated that while diatomaceous earth administered to sheep seemed to promote lower fecal egg counts, this claim was not supported by statistical analysis and there was no improvement in the performance of treated sheep²⁶. Nemadectin is a parasiticide that is the product of a natural fermentation product. Studies have indicated that it is as effective as moxidectin in the treatment of *Haemonchus contortus* infections in sheep²⁷ and that it is effective against common gastrointestinal parasites of canines²⁸. However, no approved formulations of nemadectin are available for use in the United States.

7. *Its compatibility with a system of sustainable agriculture.*

Internal parasites are considered a cause of concern in livestock production because they can lead to decreased growth and decreased milk production, resulting in economic losses for the producer²³. One estimate indicates that parasites cost the United States cattle industry 2500 million dollars each year⁵. Organic animal production places an emphasis on grazing and allowing animals access to outdoor pasture. These practices may increase the importance of soil and pasture parasites to organic producers¹³. Recent studies have indicated that parasite control is one of the top areas of concern of organic producers in the UK and France²³ and it is expected that it is also a concern of organic producers in the United States. Organic livestock producers in the United States rely on non-chemical methods such as herd management, grazing management and proper nutrition to control parasite infections within their herds, but these methods are not always effective. Currently, NOP regulations limit the use of synthetic parasiticides to treatment in disease states only, and then only ivermectin is allowed. Under NOP regulations, ivermectin cannot be administered to slaughter stock and a 90 day withdrawal period must be observed when ivermectin is given to lactating animals. While widespread parasite resistance to ivermectin has not yet been reported, research has shown that some ivermectin resistant strains of parasites have been isolated and that these resistant strains were effectively reduced by treatment with moxidectin²⁷. Additionally, research indicates that ivermectin may have more of an adverse environmental impact than moxidectin^{14,16,22}, but the importance of this impact is still under debate.

TAP Reviewer Discussion

Reviewer 1: *[Ph.D. biochemistry, research and consulting in the food industry; southeast]*

Comments on Database

I find the database (Characterization and Status) to be reasonably complete and accurate.

The significance of the statement that moxidectin is a macrolide antibiotic is not clear [the statement is bolded; why?; is the antibiotic reference to its parasiticide effects or does it have further antibiotic activities?].

A product "Quest" is mentioned in the document but this is a 2% moxidectin gel product intended for horses.

1. Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

1. The potential of the substance for detrimental chemical interactions with other materials used in organic farming systems.

The composition of the allowed form of moxidectin, "Cydectin Cattle Pour-On," is described merely as "a 0.5% solution." No inerts, diluents or other ingredients are described in the review. The label is referred to but was not provided for review.

The package insert similarly does not specify other ingredients which may enable moxidectin to be absorbed transdermally and distributed internally to the areas of the body affected by endoparasites and ectoparasites.

The document appears to be correct in concluding that there is limited possible interaction with other materials used in organic farming systems.

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.

The document is adequate on this point. The zero withdrawal period for meat and milk from treated cattle speaks to the relatively low mammalian toxicity of moxidectin.

3. The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.

Rain will not rinse moxidectin off an animal's back if the moxidectin solution is applied to the clean, healthy skin of the back as directed.

Moxidectin binds tightly to the soil and becomes inactive as the document describes, so the probability of contamination when used as directed is low.

Free moxidectin may adversely affect fish and certain aquatic organisms, according to the package insert. Water can be contaminated by direct application of moxidectin to water or via improper disposal of drug containers.

4. The effects of the substance on human health.

The document is adequate on this point.

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.

The document is adequate on this point. Moxidectin has some adverse effects on dung beetles but less than those of ivermectin and insufficient to change the population of dung insects.

6. *The alternatives to using the substance in terms of practices or other available materials.*

Grazing management practices can alter the exposure to intestinal parasites that cycle from feces to grass. An example of such a parasite is *Haemonchus contortus* in sheep. On the other hand, parasites such as cattle grubs and horn flies that are transmitted by flying insects cannot be controlled by grazing management practices for pastured cattle.

Heel flies and bomb flies, whose larvae constitute cattle grubs, lay eggs only in the daytime and do not enter stables. One nonchemical pest management practice, therefore, is that of stabling cattle during the day and running them on the pasture at night during those weeks when the flies are active. A less effective but perhaps more practical alternative is to provide darkened sheds or shelters into which cows can retreat as the flies approach. This may not be practical in all situations. < <http://www.caf.wvu.edu/~forage/10621.htm>>

Dung beetles can limit horn fly populations by removing and burying the manure before the fly completes its development. In the United States, however, dung beetle populations have not increased in proportion to the increase in livestock production and the corresponding increase in dung pats. It is possible that the widespread use of certain dewormers (parasiticides) and systemic insecticides in manure may be responsible. In recent years, several species of exotic dung-burying beetles have been introduced by USDA in efforts to implement biological control of dung-breeding flies. Unfortunately, the program has not yet reached the stage where individual producers are able to obtain and use dung beetles for horn fly control. < <http://www.caf.wvu.edu/~forage/10623.htm>>

A walk-through fly trap, first proposed in the 1930s, is the most promising tool for non-chemical horn fly control. The trap is placed where cattle must pass through it to obtain water or to access salt. The trap works on the inverted-cone principle, whereby insects are funneled in through a large opening and subsequently are unable to find an escape route through a small opening. As cattle enter the trap, strips of canvas brush along their backs and dislodge the flies. The flies are attracted to light, move toward the screened sides of the trap, and are unable to escape. Research indicates that use of such a trap can provide a 50 percent reduction in the number of horn flies in a herd.

< <http://www.caf.wvu.edu/~forage/10623.htm>>

7. *Its compatibility with a system of sustainable agriculture.*

The document is correct in its description of the importance of the impact of parasitism of livestock. Endoparasites and ectoparasites cause great economic loss to farmers, thus making the farm less financially secure and thus less sustainable. Conversely, moxidectin adversely impacts arthropods and nematodes other than those parasitizing the livestock. Fewer dung beetles mean more horn flies.

A parasiticide such as moxidectin can be used as part of an integrated pest management strategy.

Moxidectin appears to be less environmentally unfriendly than ivermectin.

Reviewer 1: Conclusion – Summarize why this material should be allowed or prohibited for use in organic systems.

Reviewer 1: Recommendation Advised to the NOSB:

- a. The substance moxidectin is synthetic.
- b. The substance moxidectin should be allowed as an externally applied parasiticide for emergency treatment of documented parasitism with horn flies and/or cattle grubs.

Rationale: Moxidectin is less toxic than ivermectin which is currently allowed on the National List [7 CFR 205.603(a)(12)].

Reviewer 2: [M.S. dairy science (nutrition), PAS, ruminant nutritionist, dairy management consultant, organic dairy, livestock and feed industry consultant, Western US]

Comments on Database

This database focuses almost exclusively on the Cydectin® commercial version of moxidectin even though other commercial products are mentioned in the database. Since the database focuses on a commercial product and not simply on the chemical compound itself, it must be noted that the database does not mention carriers, or any other active or inert ingredients that are included in this commercial product as part of the 0.5% moxidectin solution. While this database is presented as a review of the chemical compound, the decision to include moxidectin on the National List based on the TAP review document could become, in effect, a confidence vote on the Cydectin® product. Other ingredients in Cydectin® or any other commercial product may affect the product's status in regard to being allowed for certified organic use, outside of the recommendation and final decision to include moxidectin in the National List.

Moxidectin is synthetic

Moxidectin is a semi-synthetic parasiticide. The first step in the process is creating a fermentation product of *Streptomyces cyaneogriseus sp. noncyanogenus*. This intermediate product would be considered natural and allowed, assuming the *Strep. sp.* is not created using prohibited techniques.

The second step in the manufacturing of this compound is a synthetic process.

OFPA, Final Rule status

The use of synthetic internal parasiticides on a routine basis is prohibited according to the OFPA 6509(d)(1)(B).

In the Final Rule, the Secretary seems to take further steps by prohibiting all synthetic parasiticides in regard to slaughter stock. The only synthetic parasiticide allowed is ivermectin. The use of ivermectin (205.206(a)(12)) is restricted to emergency

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treatment for dairy and breeder stock. In dairy, ivermectin treatment carries a 90-day organic milk-withholding period. In breeder stock, treatment cannot occur during the last third of gestation, prior to weaning, or during lactation if the offspring drinking the milk will be sold as organic slaughter stock.

The Final Rule seems to stretch the directive provided in the OFPA from prohibiting synthetic internal parasiticides on a routine basis in all livestock to a total prohibition of their use in all slaughter stock. The designation between slaughter stock, breeder stock and dairy animals in the OFPA is not stated.

To follow the Secretary's lead on this issue, moxidectin seems to fall into a similar category as ivermectin.

Flow of the substance through the animal and into the environment

The only allowed method of application of the Cydectin® product is topically. The database notes that in FDA submitted data, most of the product seems to stay on the animal, when administered properly. Less than 1% of the applied dose washed off the treated animals when rainfall occurred within 30 minutes of application.

The primary mode of excretion of the residue from this product is via the feces. In one study, using horses, while 90% of the total residue was excreted within 8 days of treatment, moxidectin residue levels were detectable in the feces for 75 days after treatment. In another study, of the various products and metabolites excreted, the active moxidectin compound represented 26% of all residues measured.

Once excreted by the animal, the lipophilic nature of the product causes it to bind very tightly to the soil. The half-life of moxidectin in soil was approximately six months. In water, the half-life of moxidectin is 6.8 hours. In sunlight, moxidectin has a half-life of approximately two months.

The database states that the Cydectin® product is oily in nature, and that moxidectin is poorly soluble in water. These factors should indicate that very little of the compound would contaminate water sources. The database indicates the FDA found that moxidectin, when administered in the proper dilution and at the recommended dosage, was unlikely to have a significant or adverse impact on the environment. However, accidents or abuses near water sources could be harmful to aquatic life.

While Cydectin® is approved for only topical administration, notes in the database indicate that there is research where moxidectin was administered orally. Any unique aspects of this form of treatment were not discussed in the database.

Alternatives

Sound pasture/grazing management, proper herd management, safe and comfortable living conditions and adequate nutrition should be assumed and not considered as alternatives to parasiticide treatment but a requirement in any and all livestock situations. Even in emergency cases that allow for the use of ivermectin as described in the Final Rule, actions should be taken to assure that the environment, the handling and the feeding of organic livestock are adequate to minimize the need for parasiticides in the future. Even still, the requirement of the various species of livestock to have access to the outdoors, and in some cases, exposure to pasture, means that parasitic infestation may occur. It took great foresight of the Secretary to recognize the fact that the best preventative measures may breakdown.

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In cases of biological and natural control mechanisms, a very cautious disposition and a critical eye must be encouraged. Biological controls such as the fungal treatment of pastures must be accepted with no less caution than used to evaluate the synthetic compounds that they are trying to replace. Long-term side effects must be studied and evaluated by the scientific/organic community. Natural parasiticides should undergo the same critical review. As stated in the database, without needing FDA approval, these products can be anywhere from worthless to poisonous. Sometimes, soundly researched and controlled synthetic compounds may be safer and more useful than their natural counterparts.

In the case of selection of stock for resistance to parasite infections, economics and various husbandry factors may prevent this from being a truly viable alternative.

Parasite resistance

In situations where the use of synthetic parasiticides are needed and allowed, the possibility of the development of parasite resistance to available products would be devastating. As stated in the database, some ivermectin resistance strains of parasites already exist. These resistant strains were reduced by treatment with moxidectin. Less resistance could develop if options in the treatment of parasites were available.

Reviewer 2: Conclusion

Moxidectin is a synthetic parasiticide. However, in the Final Rule, the Secretary foresaw the situation where the need for a synthetic parasiticide could occur and allowed for such compounds in specific situations that should not compromise the integrity of the organic program.

Proper management, a healthy environment and sound nutrition are paramount and the frontline of defense against infestation. When these practices are in place but fail, there need to be treatment options that do not compromise the integrity of the organic industry. At the same time, these options need to have a high probability of achieving the desired results and do so without the risk of poisoning or otherwise harming the animal. These types of unfortunate circumstances are possible with unstudied and unregulated alternatives.

The proper administration of moxidectin seems to minimize the exposure of the compound to contamination in the environment. The binding nature of the compound to soil minimizes possible run-off into the water supplies.

The potential for parasite resistance to various parasiticides, and ivermectin in particular, support the need for alternative treatment options.

Should moxidectin be allowed on the National List, with or without restrictions, this reviewer does not believe that Cydectin® is automatically allowed for use without review of carriers and other ingredients in the 0.5% commercially marketed product. If the *Strep. sp.* used in the manufacture of moxidectin is found to be genetically modified or created using other prohibited techniques then this product should be prohibited.

Reviewer 2: Recommendations advised to the NOSB

The substance is Synthetic.

For Livestock, the substance should be Not Allowed to the National List without restrictions.

For Livestock, the substance should be Allowed to the National List with restrictions, similar to restrictions stated for the use of ivermectin in 205.603(a)(12). In all cases, use should be limited to topical application only.

Reviewer 3: *[MS, Biochemistry, Forensic Drug Testing, Adjunct Instructor, Eastern US]*

Comments on Database

Moxidectin is a milbemycin, a macrocyclic lactone derived from the synthetic chemical modification of nemadectin, a fermentation product of *Streptomyces cyanogriseus noncyanogenus*. The product is marketed by the Fort Dodge Animal Health Division of Wyeth Pharmaceuticals as Cydectin® .

The Identification and Characterization sections are reasonably well summarized and accurate except that the CAS registration number is 113507-06-5 vice 113507-06-05.

There is no precedent based on the information provided under Status Among U.S. Certifiers and International for the routine use moxidectin or any other synthetic parasiticide and Canadian regulations permit synthetic parasiticide use only in the “case of disease and health problems” (application reference 10) followed by other restrictions.

1. Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

1. The potential of the substance for detrimental interactions with other materials used in organic farming systems

I agree with the criterion evaluation.

2. The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment

I agree with the criterion evaluation. The studies submitted in support of the FDA application for the use of moxidectin support the application evaluation.

3. The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance

I agree with the criterion evaluation. The hydrophobic nature of moxidectin makes it unlikely to contaminate water based components of the environment.

4. The effects of the substance on human health

I agree with the criterion evaluation. Again the studies submitted in support of the FDA application for the use of moxidectin support the application evaluation.

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.*

I agree with the criterion evaluation.

6. *The alternatives to using the substance in terms of practices or other available materials.*

I agree with the criterion evaluation. The application provides an extensive summary of alternate methods and practices to the use of the synthetic moxidectin for the control of parasites.

7. *Its compatibility with a system of sustainable agriculture*

I agree with the criterion evaluation in part. Of course the control of internal parasites is a cause for concern for all livestock producers including organic livestock producers. The conclusion that reliance by organic livestock producers on non-chemical methods of herd and grazing management and proper nutrition to control parasite infections is not always effective seems vague and is not documented.

Reviewer 3 Conclusion – Summarize why this material should be allowed or prohibited for use in organic systems.

- a. In my opinion moxidectin is a synthetic compound as defined by the OFPA, 6502 Definitions, (21).
- b. It should not be permitted for use in organic livestock production. The application provides a very detailed analysis of the chemistry and use of the drug. The various environmental and toxicological studies submitted as part of the FDA approval process are discussed and the drug appears to be safe and effective for the purposes for which it has been licensed. The requirements of the National List in the Final Rule however are very specific. The use of synthetic parasiticides on a regular basis is prohibited in slaughter stock and permitted in emergency treatment of dairy and breeder stock followed by a required holding period. (§ 205.603 (12)). The application presents alternative methods (grazing techniques, use of more parasite resistant stock and natural parasiticides) to using the petitioned drug that are consistent with organic production practices used in at least some other countries. These alternative methods may be adequate to achieve the same objectives that the use of moxidectin would provide. If they are not satisfactory then more extensive documentation of the inadequacies of these alternate methods needs to be submitted. In my opinion the use of moxidectin would violate the letter and spirit of the OFPA.

Reviewer 3: Recommendation Advised to the NOSB:

- a. Moxidectin is a synthetic parasiticide

b. Moxidectin should not be added to the National List of synthetic substances allowed for use in organic livestock production.

[End of TAP reviewer comments]

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