## Identification

**Chemical Names**
Fenbendazole: 5-(phenylthio)-1H-benzimidizol-2y]carbamic acid methyl ester
Ivermectin: 22,23 dihydroabamectin
Levamisole: (-)-2,3,5,6,-tetrahydro-6-phenylimidazo[2,1-b] thiazole

**CAS Numbers:**
Fenbendazole: 43210-67-9
Ivermectin: 70288-86-7
Levamisole: 14769-79-4

**Other Names:**
Fenbendazole (Panacur, Safe-Gard)
Ivermectin: Ivomec
Levamisole: Levasole, Tramisol, Ketrax, R12,564, Ripercol L

**Other Codes:** none

## Characterization

**Composition:** Fenbendazole: $C_{15}H_{13}N_3O_2S$
Ivermectin: $C_{48}H_{74}O_{14}$
Levamisole (the L- isomer of Tramisol): $C_{11}H_{12}N_2S$

**Properties:**
Fenbendazole: Light brownish-gray odorless, tasteless crystalline powder. MP 233°, insoluble in water, soluble in dimethyl sulfoxide.
Ivermectin: Off-white powder. Solubility in water ~4 mg/ml; insoluble in saturated hydrocarbons, highly soluble in methyl ethyl ketone, propylene glycol, polyethylene glycol.
Levamisole: Crystals, MP 264-265°, solubility in water: 21 g/ 100 ml at 20°. Also soluble in ethanol. Slightly soluble in chloroform, hexane, acetone.

**How Made:**
Fenbendazole: Process described in German patent #2,164,690 (1973) and US patent 3,954,791 (1976 Hoechst). Member of the benzimidazole family of fungicides and anthelmintics (Merck).

Ivermectin: Process described in Japanese patent 79-61198 and US Patent 4,199,569 (1979 Chabala et al). Abamectin is isolated from Streptomyces avermitilis and is selectively reduced by hydrogenation in the presence of Wilkinson's catalyst (chorotris(triphenylphosphine)rhodium) (Kirk-Othmer).

Levamisol: Process described in US Patent 3,274,209 (1966 Janssen). Ethylene dibromide + thiourea + styrene oxide (dehydrobromination/epoxidation/alcohol chlorination / amine formation) (Ashford's Dictionary of Industrial Chemicals: 879).

**Specific Uses:**

### Specific Uses for Beef and non-lactating dairy cattle

*Fenbendazole (as Panacur)*
Beef cattle: Use for the removal and control of lungworms (Dictyocaulus viviparus), barberpole worms (Haemonchus contortus), brown stomach worms (Ostertagia ostertagi), small stomach worms (Trichostrongylus axei), hookworms (Bunostomum phlebotomum), thread-necked intestinal worms (Nematodirus helvetianus), small intestinal worms (Cooperia punctata and C. oncophora), bankrupt worms (Trichostrongylus colubriformis), and nodular worms (Oesophagostomum spp radiatum).
Dosing Information: Administer orally at 5 mg/kg bwt (2.3 mg/lb). Re-treatment may be needed after 4 weeks to 6 weeks under conditions of continuous exposure to parasites.
Slaughter withdrawal: 8 days.

*Ivermectin (as Ivomec)*
Use for the treatment and control of gastrointestinal nematodes (adults and fourth-stage larvae) [Haemonchus placei, Ostertagia ostertagi (including inhibited larvae), O. lyrata, Trichostrongylus axei, T. colubriformis, Cooperia oncophora, C. punctata, C. pectinata, Oesophagostomum spp radiatum, Nematodirus helvetianus (adults only), N. spathiger (adults only)], lungworms (adults and fourth-stage larvae) (Dictyocaulus viviparus), grubs (first, second, and third instars) (Hypoderma bovis, H. lineatum), lice (Linognathus vituli, Haematopinus eurysternus), and mites [Psoroptes ovis (P. communis var. bovis), Sarcoptes scabiei var. bovis].
Dosing information: 10 mg/ml (1%) or 2.7 mg/ml (0.27%).
Slaughter withdrawal: 35 days.

*Levamisole (as Levasole Cattle Wormer Boluses)*
Use as a broad spectrum anthelmintic effective against the following nematode infections--stomach worms (Haemonchus spp, Trichostrongylus spp, and Ostertagia spp), intestinal worms (Trichostrongylus spp, Cooperia spp, Nematodirus spp, Bunostomum spp, and Oesophagostomum spp), and lungworms (Dictyocaulus spp).
Dosing information: Weighing 250 lb to 450 lb: Administer 0.5 bolus. Weighing 450 lb to 750 lb: Administer 1 bolus. Weighing 750 lb to 1,050 lb: Administer 1.5 boluses.
Slaughter withdrawal: 2 days.

## Specific Uses for Sheep

*Ivermectin (as Ivomec for Sheep)*
Sheep and lambs: Use for the treatment and control of the adult and fourth-stage larvae of the following parasites of sheep: gastrointestinal roundworms (Haemonchus contortus, H. placei [adults only], Ostertagia circumcincta, Trichostrongylus axei, T. colubriformis, Cooperia oncophora [adults only], C. curticei, Oesophagostomum spp columbianum, O. venulosum [adults only], Nematodirus battus, N. spathiger, Strongyloides papillosus [adults only], Chabertia ovina [adults only], Trichuris ovis [adults only]), lungworms (Dictyocaulus filaria), and all larval stages of the nasal bot Oestrus ovis.
Dosing information: Administer 3.0 ml (2.4 mg of ivermectin)/26 lb bwt (or 200 mcg/kg bwt).
Slaughter withdrawal: 11 days.

*Levamisole (as Levasole Sheep Wormer Bolus)*
Use as an anthelmintic effective against the following nematode infections--stomach worms (Haemonchus spp, Trichostrongylus spp, and Ostertagia spp), intestinal worms (Trichostrongylus spp, Cooperia spp, Nematodirus spp, Bunostomum spp, Oesophagostomum spp, and Chabertia spp), and lungworms (Dictyocaulus spp).
Dosing information: Administer 1 tablet/50 lb bwt.
Slaughter withdrawal: 3 days.

## Specific Uses for Swine

*Fenbendazole (as Safe-Guard Premix)*
Use for the removal and control of adult stage lungworms (Metastrongylus apri and M. pudendotectus), adult larvae (L3, 4 stages--liver, lung, intestinal forms) large roundworms (Ascaris suum), adult stage nodular worms (Oesophagostomum spp dentatum and O. quadrispinulatum), small stomach worms (Hyostrongylus rubidus), adult and larvae (L2, 3, 4 stages--intestinal mucosal forms) whipworms (Trichuris suis), adult and larvae kidney worms (Stephanurus dentatus).

Dosing information: Type A medicated articles containing 4% (18.1 g/lb), 8% (36.2 g/lb) and 20% (90.7 g/lb) fenbendazole.
Slaughter withdrawal: 0 days.

*Ivermectin (as Ivomec)*
Use for the treatment and control of gastrointestinal roundworms (adult and fourth-stage larvae) [Ascaris suum, Hyostrongylus rubidus, Oesophagostomum spp, Strongyloides ransomi (adults only)], somatic roundworm larvae [threadworm, Strongyloides ransomi (somatic larvae)], lungworms [Metastrongylus spp (adults only)], lice (Haematopinus suis), and mites (Sarcoptes scabiei var. suis).
Dosing information: Administer 10 mg (1 ml)/75 lb bwt in the neck. In swine weighing more than 70 lb, use the formulation containing 10 mg/ml (1%). In swine weighing 70 lb or less, use the formulation containing 2.7 mg/ml (0.27%).
Slaughter withdrawal: 18 days.

*Levamisole (as Tramisol Soluble Pig Wormer)*
Use as an anthelmintic effective against the following nematode infections--large roundworms (Ascaris suum), nodular worms (Oesophagostomum spp), intestinal threadworms (Strongyloides ransomi), and lungworms (Metastrongylus spp).
Dosing Information: Mix in drinking water to attain a final concentration of 9.075 g/250 ml or 18.15 g/500 ml. Add 10 ml (2 tsp) of this concentrate solution to each gallon of drinking water. Allow 1 gal of medicated drinking water/100 lb bwt of pigs to be treated. No other source of water should be offered. After pigs have consumed medicated water, resume use of regular water.
Slaughter withdrawal: 3 days.

None of the internal parasiticides referred to the TAP are labeled for lactating dairy animals or poultry. There is a pour-on formulation of ivermectin labeled for lactating dairy.

Source: Farm Animal Residue Avoidance Database: http://www.farad.org

**Action:**
Benzimidizoles bind the structural protein ß-tubulin. This blocks polymerization of tubulin into microtubles, causing damage to the integrity & transport functions of the parasites' cells.

Ivermectin stimulates the release of gamma amino butyric acid (GABA) from nerve endings and enhances binding of GABA to special receptors at nerve junctions. This interrupts nerve impulses that paralyze and kill the parasite. The mode of action is similar for both nematodes and arthropods. Ivermectin is very broad spectrum and also has some antimicrobial activity that has led to sources considering it an "antibiotic."

Levamisole is a cholinergic antagonist that causes sustained muscle contraction leading to paralysis in nematodes and other parasites.

**Combinations:**
Most references recommend the rotation of anthelmintics to prevent the development of resistant strains. All are packaged in formulations where the greatest proportion is excipients that are USP grade and FDA approved. Drench and paste preparations are generally in a paraffin base. Fenbendazole is FDA approved for use in feed. As such, it is used in combinations with subtherapeutic antibiotics administered to increase weight gain in swine (FOI Summary; NADA 140-954). It is also combined in feedblocks with molasses and an unspecified protein source (FOI Summary; NADA 139-189). Some of the controlled release formulations use plastic pellets (Merck Veterinary Manual, 1803). Injectable ivermectin (Ivomec Injection) is presented in a glycerol formal / propylene glycol solution (Talbot, 1990). The micelle formulation uses polysorbate 80 (Courtney and Roberson, 1995).

## Status

**OFPA**
Parasiticides are included in the list of potentially exempt synthetic allowed materials in section 2118(c)(1)(b)(i) (7 USC 6517(c)(1)(b)(i)).

**Regulatory**
Internal parasiticides are regulated as farm animal drugs under the Food, Drug, and Cosmetic Act.

**Status among Certifiers**
Varies widely among certifiers. Some appear to prohibit their use. Others allow their use with extended withdrawals. Others are silent and apparently allow their use without restriction. The TAP reviews and recommendations are reflective of the full range of approaches taken by the different certifiers.

**Historic Use**
Non-routine use has been tolerated on a restricted basis with documentation of alternative practices and extended withdrawal periods.

**International**
Livestock materials have not been proposed in Codex; IFOAM Basic Standards do not distinguish parasiticides from other conventional veterinary medicines. In general, IFOAM discourages their use, and requires a minimum of twice the legal withdrawal period.

## OFPA 2119(m) Criteria

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems.

All three substances have the potential to chemically interact with other chemicals used in organic farming when excreted by the treated animals. The detrimental effects are considered in the discussion section. The benzimidizoles exhibit a high degree of chemical stability (Budavari, 1996).

(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.

*Ivermectin*
A report on the use of ivermectin for the treatment of sea lice on farmed salmon found that ivermectin was highly toxic to marine life (at levels equivalent to one ounce of ivermectin per 10 thousand Olympic size swimming pools) and persisted in sediments for months (Grant, 1998).

*Fenbendazole*
Between 44 and 50% of fenbendazole is excreted unchanged in the feces in sheep, cattle and pigs with the greatest number of metabolites occurring in pigs (Adams, 1995). In the milk of dairy cattle, fenbendazole sulphoxide and fenbendazole sulphone were the primary metabolites and essentially the only radiolabeled metabolites detectable other than traces of the parent compound (Kappel and Barker, 1996). The major metabolites of fenbendazole found in the plasma of beef cattle were fenbendazole sulphoxide and sulphone (Knox and Steele, 1997). While fenbendazole itself has no known teratogenic effect, administration of albendazole to both cattle and sheep is contraindicated in early pregnancy, the evidence for teratogenicity (and embrotoxiciy) seems to be greater for sheep and can occur at a single dose close to concentrations used for therapeutic purposes (Adams, 1995). None of the compounds appear in the National Toxicology Program Report on Carcinogens 8th Ed. (National Institute for Environmental Health and Safety).

*Levamisole*
Acute toxicities: LD50 (mice / rats): 22 / 24 iv, 84 / 130 s.c., 210 / 480 oral (Thienpoint, reported in Merck).

(3) The probability of environmental contamination during manufacture, use, misuse or disposal of such substance.

*Fenbendazole*
Fenbendazole is produced by petrochemicals involving the use of benzene and amines considered to be carcinogenic compounds. The product decomposes into fenbendazole sulfone, that is considered

to be biologically inactive. Other decomposition metabolites are not as well understood. There is concern that albendazole may be a metabolite that is still biologically active & teratogenic. Co-administration of fenbendazole with albendazole may result in greater bioavailability of the metabolite, albendazole sulphoxide (Merino, 1999). Perhaps, this association is, in part, responsible for early reports of teratogenicity related to the use of fenbendazole. If albendazole is a metabolite of fenbendazole, it is a minor one unlikely to be present at levels sufficient to cause teratogenicity.

*Ivermectin*
Ivermectin is produced by fermentation of Streptomyces avermitilis and hydrogenation in the presence of a catalyst. The likelihood of environmental contamination from the fermentation process is relatively minor.

*Levamisole*
Levamisole is produced from ethylene dibromide, thiourea, and styrene oxide. EDB is a volatile liquid used in leaded gasoline and fumigants. EDB has an acute toxicity rating of 4 on a scale of 1 to 6, with 6 being very toxic. Fatal reactions are rare because fume concentrations high enough to cause serious illness have a definite and sickening odor. It is also mutagenic and associated with decreased fertility in animals and man. The acute toxicity rating of styrene is 3, but that of styrene oxide itself being one-quarter of the parent family of compounds. They are widely used in the manufacture of plastics, synthetic rubber, and resins. Styrene sickness is not uncommon in industry after ambient air exposure and it may accumulate in adipose tissue after repeated industrial exposure. Thiourea is found in silver polishes. It has an acute toxicity rating of 3-4 and may induce agranulocytosis and thrombopenia with repeated exposures (Gosselin, 1984).

(4) The effect of the substance on human health.

*Fenbendazole*
Fenbendazole has no known teratogenic effects and consecutive daily dosing for 30 and 90 days in dogs and 30 days in sheep were well-tolerated (Adams, 1995). Although further toxicological studies were required by FAO/WHO in 1991 to evaluate a reported incidence of tumors in female rats given fenbendazole in high doses, in February 1998, the Joint FAO/WHO Expert Committee on Food Additives recomended an ADI of 0-7 micrograms total of fenbendazole, febantel and oxfendazole per kg of bw resulting from veterinary use individually or in combination. In adverse drug experiences reported on the FDA's Center for Veterinary Medicine (CVM) website from 1987 to 1997 and considered at least possibly related to the drug by FDA, there were only 6 humans treated for exposure to veterinary fenbendazole with no deaths as opposed to over 5,000 reports of animals treated for fenbendazole exposure in that same time period.

However, fenbendazole is considered to be structurally related to mebendazole, that is teratogenic in rats (Reynolds, 1996). Due to the scant evidence in the human literature for fenbendazole and its close structural relatedness to mebendazole, a brief summary for the human health effects of mebendazole follows. Interaction with the commonly taken human drug cimetidine (Tagamet) may result in increased metabolic availability of mebendazole. In mice and rat studies, there was no evidence of carcinogenicity, impaired fertility, or mutagenicity (also Ames test negative). Mebendazole is classified as a Pregnancy Category C drug based on embyrotoxic and teratogenic activity in rats, although a post-marketing study of women who accidentally took the human formulation during the first trimester of pregnancy did not show an excess incidence of spontaneous abortions and malformations above that in the general population (Physicians Desk Reference, 1998). Overall, the evidence of teratogenicity, in particular, and serious chronic or acute effects, in general, are not overwhelming for fenbendazole.

*Ivermectin*
There are a number of adverse reactions discussed for ivermectin that are related to treatment for a particular parasite. However, the following adverse reactions were attributable to accidental intoxications with or significant exposure to unknown quantities of ivermectin in veterinary formulations: asthenia, diarrhea, dizziness, edema, headache, nausea, rash, and vomiting - most frequently; and abdominal pain, ataxia, dyspnea, paresthesia, seizure, and urticaria - other adverse

effects reported (Drug Facts and Comparisons, 1999). There were almost 13,000 animals treated for exposure to ivermectin in reports to FDA's CVM from 1987-1997 (the compilation contained no mention of human exposures, possibly because it does not track topically applied, externally acting parasiticides - the formulation most likely to result in accidental human exposure). Results of accidental overdosing with ivermectin containing veterinary products indicate that the acute signs and symptoms are similar in man as those observed in laboratory animals but require much higher doses. The primary food safety concern for ivermectin is related to its neurotoxic effects; the new ADI for ivermectin based on this effect is 1 microgram/kilogram/day (NADA, 1995). Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin. Ivermectin was not genotoxic by the Ames test and had no adverse effects on fertility in rats. Although there are no adequate studies in pregnant women, ivermectin has been classified as Pregnancy Category C teratogen based on studies in mice, rats, and rabbits (Physicians Desk Reference, 1998).

In general, the relative safety from acute effects of parasiticides, in general, for humans from incidental exposure seems to be borne out by statistics from the 1997 annual report of the American Association of Poison Control Centers that contained reports of over 2 million human poisonings reported in 1997. Of 3,500 poisonings attributed to anthelmintics and antiparasitics (classified as related to exposure to DEC, piperazine, metronidazole, antimalarials, other, or unknown), there were about 1,000 reports that could potentially have been related to the chemicals being discussed. Of those, there was only 1 death, 0 major health outcomes, 37 moderate health outcomes, and the rest were minor or no health outcome (96%).

*Levamisole*
Levamisole has the narrowest margin of safety of the three, with intoxication that mimics organophosphate toxicity. However, because Levamisole is used in chemotherapy for cancer patients, it is considered safe for humans. Levamisole can cause prolonged prothrombin time in patients taking coumarin-like drugs and has been associated with sporadic cases of encephalopathy-like syndrome (Mosby, 1997). Levamisole may produce an "Antabuse" reaction (nausea, vomiting, headache, dizziness, faintness, mental confusion, dyspnea, chest and abdominal pain, profuse sweating, and skin rash) with concomitant alcohol ingestion. It is excreted in cow's milk and considered to represent the potential for serious adverse reactions for infants. Adverse reactions noted most frequently in a study of 440 adverse events were: dermatitis, fatigue, nausea, diarrhea, vomiting, taste perversion, arthalgia, and infection. Label warnings for the human drug include: agranulocytosis s with flu-like syndrome, fertility impairment, and pregnancy Class C toxicity (embryotoxicity in rats and rabbits) (Drug Facts and Comparisons, 1999). There were only 14 humans treated for exposure to veterinary formulations of levamisole with no deaths as opposed to 26,000 animals treated for exposure in reports to the FDA's CVM from 1987 to 1997. Overall, there is some limited evidence of embryotoxicity but little showing of acute toxic effects.

*Summary*
Of the three substances considered, Ivermectin has the longest withdrawal times for dairy cattle. The public health implications of helminth infections must also be taken into consideration. Ascaris nematodes (treatable with ivermectin and fenbendazole) infect humans through soil, vegetation, dust, water, or even objects to that the parasite's eggs have attached that are then ingested by humans (or possibly inhaled), especially preschool children. Trichostrongylus infection (treatable with benzimidizoles, ivermectin, or levamisole) can similarly be acquired through oral infection from soil or vegetation. Anthelmintic treatment along with sanitation and pasture management have been recommended as suggested control measures (Acha and Szyfres, 1987). Human outbreaks of giardiosis--caused by a parasite effectively treated with fenbendazole in calves--have been attributed to contamination of drinking water by pasture run-off (O'Handley, et al., 1999).

(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 risks associated with chemical treatment of parasites include (1) immediate non-target effects, (2) obligation for repeat treatments, (3) potential risk to domestic animals and human health, (4) target

organism resistance to the treatment, (5) potential residue buildup and (6) potential food chain contamination (Rudd, 1985). Dung fauna play an important role in decomposing animal manure, and the impact of the use of parasiticides is only now being considered (Spratt, 1997). As nematicides, these compounds can be expected to have a deleterious effect on soil nematodes.

The avermectins are extremely broad-spectrum biocidal agents and are variably categorized as antiparasiticides, anthelmintics, acaricides, insecticides, or macrolide antibiotics. Free ivermectin will bind to the soil. Once in the soil, as well as in the feces, ivermectin has been linked to the killing of dung beetles (Wall and Strong, 1987). A recent study from Ohio State University confirmed that fecal concentrations of cattle given ivermectin were lethal or sublethal to many dung breeding invertebrates beneficial to the ecosystem. This has been replicated in subsequent studies (Madsen, et al., 1990). It also demonstrated, however, that ecotoxicity is dependent on the type of formulation with the SR Bolus being the most ecotoxic and the Ivomec injection being the least. The authors note that fenbendazole SR bolus had no such effects (Herd, et al., 1996). Another study reported that grain-fed cattle had five times the level of ivermectin in their feces compared to cattle grazed on pasture (Cook, et al., 1996). The ecotoxic effect of ivermectin may be mitigated by plowing treated feces into the soil since this appears to facilitate the binding of ivermectin to soil particles enabling its more rapid breakdown (Spratt, 1997). Evidence for ecotoxic effects of ivermectin on dung-feeding insects such as the Order Diptera (flies) has also been noted (Waller and Faedo, 1996).

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

The most promising alternatives to internal parasiticides require methods that disrupt the life cycle of the target organism outside the host (Waller and Faedo, 1996). Rotational grazing, fecal examination, culling heavily infected animals, selection of resistant breeds, biological control at susceptible (usually free-living) stages in the life-cycle. While some non-synthetic herbal remedies, botanicals, and mined minerals are claimed to have anthelmintic properties, most of these materials have not had their efficacy substantiated in controlled experimental trials. Pharmaceutical companies are in the process of screening a number of natural compounds derived both from plants and from micro-organisms (Londerhausen, 1996).

The evolution of host-parasite relationships are believed to be the result of immunological phenomena (Soulsby, 1968). Biological control and immune systems response research is experiencing a resurgence in parasitology as pharmaceutical products fail because of resistance. Given the nature of anthelmintic resistance, these particular substances cannot necessarily be relied upon to control parasites over the long run. Understanding the ecology, phenology, morphology, and genetics of parasitism in a broader context is crucial to develop a classical biological control program for nematodes. Livestock host a broad array of organisms: many if not most are beneficial, a great number innocuous or obscure in their biological function, and only a few clearly pathogenic or parasitic to domesticated animals. A wide variety of micro-arthropods, protozoa, viruses, bacteria, and fungi are potential biocontrol agents for nematode parasites of farm animals (Waller and Faedo, 1996).

Another method would be to extend the principles of Integrated Pest Management (IPM) to parasite control through the practice of Sustainable Parasite Control (SPC) (Herd et al., 1996). This would involve pasture management to reduce reliance on chemical anthelmintics or substitution with non-chemotherapeutic control agents (Courtenay, 1995). Others have suggested that SPC may best be implemented through strategic worming of weaned cattle as they are first placed on pasture. Alternatively, it has been reported that nursing calves have less worms and acquire far fewer worms if pastured only with nursing cows and calves (Courtney, 1995). In general, as discussed in criteria 5, ecotoxic effects of parasiticides may be mitigated by the choice of parasiticide and formulation used, as well as feeding, pasture, and soil management practices.

Non-synthetic and NOSB recommended synthetic therapeutic agents exist, such as lime-sulfur to treat mites in cattle, swine, sheep; rotenone for grubs in lactating cattle, and lice in swine and cattle; and diatomaceous earth for intestinal parasite and ectoparasite control (Haynes, 1981; Olkowski, Daar, and Olkowski, 1991; National Research Council, 1989). Fungal hyperparasites of the infective

stage of nematodes can also show significant (99.5%) reduction in fecal counts (Charles, et al., 1996). Additionally, other methods being developed include new antiparasitic agents such as certain B.t. isolates, Penicillium species, new Streptomyces species, among others (Waller and Faedo, 1996; Londerhausen, 1996). These may not necessarily be considered non-synthetic depending on how they are derived or if a synthetic analog of a natural compound is commercialized from the natural compounds that are the original subject of research. In any case, the prospects for commercial availability of any truly sustainable approaches to parasite control such as vaccines, resistant hosts, biological controls--especially the nematophagous fungi--appear to be at least 5 years away (Barger, 1996).

One method of intestinal parasite control that is available now is control through grazing systems involving spelled pastures, alternating sheep and cattle on pasture, or alternation between irrigated and non-irrigated pastures. In conjunction with pasture management, there is evidence that organic farming practices such as green manuring and decreased emphasis on anthelmintic use increase the abundance and variety of coprophilic micro-organisms and arthropods in the dung of pasturing animals that, in turn, act to control fecal forms of intestinal parasites (Waller and Faedo, 1996). There are three systems of grazing that have been utilized: deferred grazing; alternate grazing of two or more ruminant species; and, alternate use. Deferred grazing is a form of pasture rotation in that the pasture is rested for 6 months during the cool season and 3 months in the warm part of the year, pastures are tilled and replanted with infective larvae succumbing to the effects of UV light and desiccation. Alternate grazing depends on the two species ingesting different parts of the forage and coincidentally ingesting each other's parasite larvae. Alternate use relies on intensive grazing of the pasture for a short period of time, leaving that pasture to the production of harvestable hay that when baled and removed takes away most of the parasite burden, and returning animals to the original pasture when new growth emerges after haying (Scarfe).

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

The anthelmintics being reviewed are chemotherapeutics that are manufactured, formulated, and have modes of action similar or identical to synthetic chemical pesticides and / or antibiotics. For example, fenbendazole is closely related to the plant pesticides benomyl and thiabendazole. Ivermectin is considered an antibiotic, and is difficult to reconcile its use given the categorical prohibition on antibiotics for use in organic systems and questions raised about their sustainability. These compounds have historically been considered not compatible with a system of sustainable agriculture in plant crop production by those in the organic community. Parasiticide use has been tolerated in organic livestock production on a limited basis to alleviate animal suffering. This has almost without exception been part of an integrated system of animal health management and requires documentation of a number of approaches other than intervention, as well as an extended withdrawal period well beyond the minimum allowed by the FDA label. In light of the NOSB's other policies on animal health, use of such materials would not be considered compatible and administration of any of the above anthelmintics would result in the loss of organic status of the animal, particularly if extended withdrawal is not an option. Producers could not withhold treatment from infested animals and have them considered organic. Such animals would have to be treated and diverted to the conventional market. Other considerations of the sustainability of these substances appear below.

## Discussion

### *Condensed Reviewer Comments*

None of the reviewers have a direct commercial or financial interest in any of the specific materials being used. Reviewer 1 and Reviewer 3 both raise livestock and have on occasion used some of the materials under consideration. Reviewer 2 is involved in research related to the development of pharmaceuticals for human use.

**Reviewer 1**

For the purposes of organic standards I do not believe these products should be used at all. On large scale operations for purposes of sustainability these products would probably need to be used, therefore limiting

organic producers to size and probably location. My definition of sustainable livestock operations is utilizing management and in this case parasiticides to produce a product optimally and economically. Often herd health equates to efficiency and therefore sustainability. We continue to try to find ways to minimize and even eliminate these products through management of rotational grazing and disrupting the life cycle of the target organism outside the host.

I do believe that if a producer administers a parasiticide every year it constitutes routine use. NOSB guidelines for routine use is difficult to recommend. My thought is that breeding stock could have some potential exemption as to producing offspring as labeled organic because of their longevity. However, once they reach their terminal point in the production system the breeding stock should not be sold as organic.

Routine use should only cover synthetic material and any prohibited non-synthetic.

**Reviewer 2**
The use of levamisole may pose some conflict with organic principles given the the human health problems attendant to its manufacture and disposal. However, the volume of levamisole products used in organic livestock production is dwarfed by its use in veterinary medicine and as an immunologic adjuvant in human medicine. Similarly, the by-products of its manufacture are ubiquitous in industry. Nonetheless, a criteria argument against its use in organic farming based on its detrimental environmental character would be similar to an argument against farming practices that encourage the excessive use of fossil fuels, i.e. that its use should be discouraged for lack of sustainability.

These are synthetic compounds. Ivermectin may be a closer call on that issue than the other two but the NOSB Materials Database describes the process of its derivation as involving hydrogenation that according to the OMRI "parameters about synthetics" document renders it synthetic. Similarly, ivermectin has been described in the literature as a a semi-synthetic derivative of abamectin (Budavari, 1996).

Compatibility with a system of sustainable agriculture must be evaluated on several levels. One is the welfare of the animals being raised. In addition to alleviating animal suffering related to lack of thrift and itching, parasites controlled by the anthelmintics under discussion can have more serious consequences for the animals themselves. Internal parasitism is a common cause of anemia in small ruminants (Waldridge, 1998). In fact, in small ruminants, a frequent reason for using anthelmintics is salvage--i.e., treatment to save the life of the animal, not just for parasite control (Luginbuhl, 1997). Additionally, there are human public health implications of uncontrolled infections, that would typically impact livestock handlers and their families, especially small children who may be exposed to infection accidentally if infestation leads to contamination of soil, pasture, or water sources.

Another aspect of the sustainability issue for parasite control is whether limited infection is necessary for immunity or whether eradication or chemical control abrogates the need for naturally acquired resistance. There is continued accumulation of scientific evidence for the existence of widespread resistance to many parasiticides together with increasing evidence of decreased natural resistance resulting from early chemoprophylaxis (Claerebout, et al., 1998; Sutherland, 1999). However, the problem is that much of the current research is still focused on preserving the utility of chemical parasiticides through the use of: immunization of calves with chemically attenuated parasite infections; methods to better detect resistance to particular parasite control agents so that other agents may be used; and, the use of resistance reversing agents or multidrug regimens to extend the lifespan of synthetic agents (Almeria, 1998; Maingi, 1998; Molento, 1998). Yet, sustainability of chemotherapeutic agents will always be compromised by interdependent factors such as underdosing of animals by owners treating their own livestock, leading to increasing anthelmintic resistance, leading to continued high environmental contamination, and resulting in greater use of anthelmintics with less control achieved.

Currently, there is a paucity of sustainable therapeutic or biological control agents to address the diversity of livestock, parasites, geographic and husbandry conditions involved. Failure to control helminths can be complicated by state laws involving breach of warranty under the Uniform Commercial Code for the sale of livestock lacking "merchantability or fitness of purpose" and possible violations of state sanitation and food hygiene codes, such as transmitting sheep scabies, a reportable disease, through the sale of an infected animal to a herd off-site (Hannah, 1999). Also, there is the need for continued research on the magnitude and

mitigation of the ecotoxic effects of ivermectin and perhaps other parasiticides.

Although the use of parasiticides represents a conflict with organic criteria, the science and the art of organic livestock production are not sufficently advanced to currently permit their total prohibition. For these reasons, there needs to be a phase-in period of 5 years to allow producers: to adapt to non-parasiticide control and prevention practices; to allow time for the commercial development of alternatives to synthetic parasiticides, and to identify state and local laws in conflict with the OFPA and pursue harmonization or exemption options. Therefore, during this period, IPM use should be permitted for locally recalcitrant infestations as detailed in the Farm Plan reviewed and aproved each year by certifiers. The plan should provide the basis for the continued need for parasiticide use and detail how management practices are being implemented to keep reliance on parasiticides to a minimum and mitigating their ecotoxic effects. Emergency use should be allowed at the direction of a veterinarian as specified in writing that will be kept on record and made available for inspection to the certifying authority. Routine use of parasiticides should be prohibited. Routine use should be defined as use not specified in an annual Farm Plan, or use not at the direction of a veterinarian, or any use in the same livestock species/production type for the same parasite as detailed in the Farm Plan that exceeds two consecutive years.

**Reviewer 3**
I suggest more leniency in terms of reentry issues, especially for production / breeding herds / flocks.

Case by Case

Fenbendazole (and the TBZ family): Allowed. Considered useable in animal moms. Considered "more benign" than many of the older approved wormers. Effective on certain families of parasites, and not others, so use would need to be paired with infestations for appropriate uses. Should be lots of documentation on this family due to possible human consumption of TBZ in fruit waxes, etc. Most documented resistant parasite populations.

Ivermectin (and avermectin, etc.) Allowed. Most effective of current parasiticides, has a low toxicity to animals with a large +/- in dosage (so lack of precision will not adversely affect the animal). Possible immune worm documentation in sheep that were routinely wormed every 4-6 weeks for several years. Feed through documented with long-term bolus use in cows. Couldn't find documentation about feed through for one-time usage. A very good on-shot all around wormer. Good across many species. Maybe the best for the isolated usage that we expect to see, if any wormers are allowed. More documented

Levamisole: Not allowed. Simply because I don't know enough about it to make any kind of decision.

1) synthetic wormers as a class should be considered "not allowed."
2) synthetic parasiticides should be used only with empirical documentation of need, and veterinary supervision.
3) [Treated a]nimals should either be
a) diverted to conventional sales, or
b) should have a prolonged reentry time if synthetics are used (60 days, or twice teh FDA reentry time, thatever is longer).
4) Fenbendazole and ivermectin should be allowed under very specific conditions.

Conflict of interest statement: I am not a dealer for any of the parasiticide products reviewed. I have animals, and dose the breeding stock occasionally on a need only basis.

## *Conclusion*

The TAP had three reviewers with three very different opinions about the appropriate use of parasiticides in organic livestock production. Despite the deep-seated differences, the TAP asks the NOSB to consider those items where there is consensus.

**1) All of the substances considered are synthetic**.

This includes ivermectin. It follows that these substances are prohibited unless they are explicitly added to the National List.

**2) Parasite-infested animals must be treated to abate serious infestations.**
Any producer who withholds treatment from an infested animal must be decertified. The Reviewers have a consensus that infested animals must be treated to abate any infestation that represents a threat to public health and the welfare of the animal. Therefore, the NOSB should not concern itself with whether or not infested animals should be treated--the consensus is that they should. The real question is what to do with treated animals and what to do with operations that regularly use synthetic parasticides on a large portion of their herds. A reasonable case can be made to support either side.

**3) Routine use needs to be better defined and independently monitored.**
While the three reviewers disagreed as to the specific definition, this points to a need for the NOSB to define what constitutes a violation of the spirit and letter of OFPA. OFPA prohibits the routine use of parasiticides. The NOSB and NOP should provide clear guidelines to certifiers and producers as to

(a) what constitutes routine use,
(b) what--if any--uses are permitted under OFPA given the preclusion of routine use, and
(c) the appropriate withdrawal periods and/or intervening events that need to take place after administration of parasticides if their use is permitted.

All of the reviewers agreed that the producer could not render an unbiased judgement as to whether or not use was necessary or routine. The TAP reached a consensus that any use of parasiticides requires documentation of alternatives in the Farm Plan. Certification agents need to give prior approval to a Farm Plan that includes the use of synthetic parasiticides, and inspectors would verify compliance with any non-routine use that is contingent upon clearly specified documented needs. Veterinarians play a role of providing independent professional judgement.

**Background**
Having identified where there is agreement, some background on parasitism in domestic animals merits review. A number of factors contribute to parasitism. As with everything else in organic agriculture, parasitism needs to be understood as part of the whole farming system. Animals have evolved a complex set of defenses to parasites (Wakelin, 1984). Disruption of those defenses can take place at both the micro (single animal) and macro (ecosystem) levels. Selection for maximum production and uniformity often will reduce immunity and resistance of a given breed. Genetic diversity provides variable host responses. If a uniform breed produces a consistent set of antigens, then a parasite that is resistant to that set of antigens will be selected for that uniform population. Given the opportunity, that parasite will result in infection levels that approach 100%. On the other hand, if a diverse population is producing a wide variety of combinations of antigens, then the probability of a parasite to infect the population is diminished.

A number of factors increase the susceptibility of livestock to internal parasites. Control without synthetic anthelmintics requires a complete understanding of the life cycle of the parasite. Most internal parasites have a free-living stage. The period outside the host is often the most susceptible period for parasites (Waller and Faedo, 1996). It is during this phase when biological and cultural controls are most likely to succeed. Water management, rotational grazing, host-free periods, and the release of biological control agents will succeed during this phase, but not when the host is infested. Parasite infection rates generally increase with host animal population density (Wakelin, 1984). Overstocked pastures and continuous grazing will not break the host cycle for most parasites (Porter, 1942). While there are other factors, and density may be correlated with those factors--such as quality of forage and animal stress--it stands to reason that reduced densities will help reduce parasite loads. Rigorous sanitation programs are capable of reducing and in some cases eliminating internal parasites in well-managed operations (Spindler, 1942). However, high density by itself need not entail high rates of parasitism if the range and / or pasture are rotated in such as way as to break the host-parasite cycle (Savory, 1988).

## Choices

The TAP has presented the NOSB and the NOP with three clear alternatives in this review.

*Allow All FDA Approved Synthetic Parasiticides*

**Pros:**

- Greatest flexibility and choice of materials.
- No conflicts with FDA, APHIS, or FSIS.
- Works in the context of existing veterinarian-client-patient relationships.
- Enables production in all regions, including heavily infested areas.
- Most favorable to rapid growth of organic meat.

**Cons:**

- May undermine consumer confidence, particularly if the gray area between parasiticides, pesticides, and antibiotics becomes focused on the similarities rather than the differences.
- Does not provide incentives to develop alternatives.
- Most difficult to enforce against routine use.
- Enables farmers and ranchers to overstock, overgraze, and not rotate grazing land.

*Prohibit All Synthetic Parasiticides*

**Pros:**

- Offers a clear alternative to conventional production.
- Easiest to administer and determine compliance.
- Provides the greatest incentive to develop non-chemical parasite management.
- Least disruptive to the agroecosystem.

**Cons:**

- Most restrictive and constraining on expansion of organic meat production.
- Not all species in all regions will be able to meet the standard.

*Review and Approve Parasiticides on a Case-By-Case Basis with Extended Withdrawal*

**Pros:**

- Gives producers an opportunity to cut their losses in an extreme emergency.
- Provides a measure of security for risk-averse producers reluctant to otherwise convert.
- Involves the certifier more directly in the decisionmaking process than the other two options.
- Provides an incentive to develop alternatives, but doesn't force farmers and ranchers to go 'cold turkey.'

**Cons:**

- The most difficult of the three options to administer.
- Difficult to enforce against routine use.
- Extended withdrawal may not be acceptable to FDA and USDA.
- May interfere with established veterinarian-client-patient relationships.
- Reliance on a limited number of anthelmintics more likely to lead to resistance problems than the other two approaches.

Note: The TAP asks the NOSB to make it clear that if the USDA does not accept extended withdrawals and additional oversight of the veterinarian-client-patient relationship that goes with Case-by-Case review, the second choice is a categorical prohibition. Also, most of the review has focused on slaughter stock. The reviewers agree that no parasticide should be administered to lactating cattle producing for organic human consumption out of concern for human exposure to residues. However, the reviewers don't agree on the appropriate use or intervening event following treatment.

## Conclusion

The TAP reviews are divided between three very different alternatives. The NOSB will need to choose between all, some or none of the synthetic parasiticides as being allowed to produce organic livestock. Each choice has strengths and weaknesses. In any case, the TAP urges the NOSB to recommend that infested animals be properly treated, that routine use be more clearly defined and independently monitored.

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