

ENVIRONMENTAL ASSESSMENT

FENBENDAZOLE TYPE A MEDICATED ARTICLE IN GROWING TURKEYS

1. DATE:

March 2000

2. NAME OF APPLICANT/PETITIONER:

Hoechst Roussel Vet

In the United States, Hoechst Roussel Vet will be the distributor of the product and will control the manufacture of the Type A Medicated Article.

3. ADDRESS:

Perryville Corporate Park
P.O. Box 4010
Clinton, NJ 08809-4010

4. DESCRIPTION OF THE PROPOSED ACTION:

Hoechst Roussel Vet is requesting approval to expand the use of the Fenbendazole Type A Medicated Article as an oral dewormer for growing turkeys. Fenbendazole (fbz) is added to the ration at a concentration of 16 ppm (14.5 g fbz per ton of feed) and fed for six (6) consecutive days as the sole ration. The recommended dose is given once. There is no withdrawal period following treatment, as fbz can be fed to the day of slaughter for human consumption.

NADA - 131-675

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Type A Medicated Article for Turkeys

Fenbendazole (Safe-Guard®) Type A Medicated Article will be used in growing turkeys only. Fenbendazole will serve as a partial replacement for the existing agent, piperazine, which is used for the control of adult roundworms of the genus *Ascaridia*.

Populations

The annual U.S. production of turkeys is approximately 300 million. Of that number, approximately 25% or about 75 million are projected to receive fenbendazole as Safe-Guard® Type A Medicated Article admixed in feed.

**5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE
SUBJECTS OF THE PROPOSED ACTION:**

Fenbendazole is a member of a well-known and widely used chemical class of compounds, the benzimidazoles, and is related in chemical structure and pharmacological properties to other drugs commercially available in the United States, such as thiabendazole, oxfendazole, oxibendazole, mebendazole and albendazole. Other related compounds available on the international market include febantel and triclabendazole. Albendazole, mebendazole and thiabendazole are currently approved for use in humans in the United States.

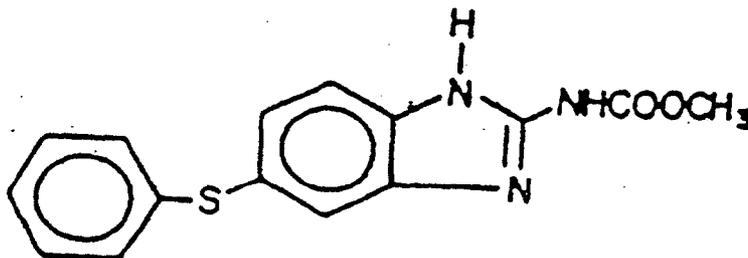
Substance: Fenbendazole (United States Adopted Name)

CAS Registry No: 43210-67-9

CAS Nomenclature: [5-(phenylthio)-1 H-benzimidazol-2-y1]-
carbamic acid methyl ester.

Also: methyl 5-(phenylthio)-2-benzimidazol-
carbamate.

Structural Formula:



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<u>Molecular Formula:</u>	C ₁₅ H ₁₃ N ₃ O ₂ S
<u>Molecular Weight</u>	299.4
<u>Description:</u>	White to light brownish or grayish powder essentially odorless.
<u>Melting Point:</u>	Approximately 233° (with decomposition)
<u>Solubility:</u>	Insoluble in water (approx. 10-40 ppb.) Insoluble or only slightly soluble in the usual solvents. Freely soluble in DMSO.
<u>Octanol/Water Partition Coefficient:</u>	Log K _{ow} 3.9
<u>U.V. Absorption Spectrum:</u>	Representative spectrum with maximum absorptivity at 296 nm.
<u>Mode of Administration:</u>	Oral

PRODUCT DESCRIPTION

Fenbendazole currently is sold as Safe-Guard® Type A Medicated Article which has an active ingredient concentration of 200 grams fenbendazole per kilogram.

MODE OF ACTION

Fenbendazole exerts it's primary anthelmintic effect by binding to tubulin and inhibiting microtubulin formation in the gut of the parasite. The secondary mechanism of action is via inhibition of fumarate reductase in the metabolic pathway of the parasite. The combined effect is thus interference with energy metabolism in the parasite.

Anthelmintic spectrum: Fenbendazole is active against gastrointestinal nematode parasites. Fenbendazole has been demonstrated effective for removal and control of the following nematodes of turkeys:

Gastrointestinal Worms; Roundworms, adults and larvae (*Ascaridia dissimilis*);

Cecal Worms; adults and larvae (*Heterakis gallinarum*), an important vector of *Histomonas meleagridis* (Blackhead).

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

Approval of the proposed action would allow for the increased production of fenbendazole bulk drug substance at the plant of Hoechst AG in Frankfurt, Germany. The environmental and occupational safety regulations of Germany were presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996). Fenbendazole bulk drug substance will be shipped to the United States to ADM – Animal Health and Nutrition Division (formerly Feed Specialties Company, Inc.), 1877 NE 58th Avenue, Des Moines, Iowa 50313 for manufacturing and packaging of fenbendazole (Safe-Guard®) Type A Medicated Article. The drug will be distributed in the United States for use in growing turkeys.

Introduction of Substances Through the Manufacturing Process

1. The environment adjacent to the plant in Frankfurt, Germany.
2. The environment adjacent to the plant in Des Moines, Iowa.
3. Turkey facilities receiving residues of the drug contained in animal wastes.
4. Agricultural lands potentially receiving residue containing wastes.
5. Aquatic systems potentially receiving runoff from agricultural lands containing drug residues.

The manufacturing facilities in Frankfurt, Germany comply with local regulations. A statement by Hoechst AG, Frankfurt, Germany is included in the original NADA 128-620 (Fenbendazole for Cattle, 48 FR 42809, September 20, 1983). A current manufacturing Environmental Assessment for bulk drug substance manufactured at the Hoechst AG facility, as well as for the finished dosage form manufactured by ADM – Animal Health and Nutrition Division, at the facility in Des Moines, Iowa (USA), was presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

The manufacturing process of Fenbendazole Type A Medicated Article consists of carefully controlled weighing and mixing operations conducted in a manufacturing plant. These processes are controlled to arrive at a full material balance, and no effluents or pollutants are formed.

Introduction of Substances from the Use Site

For practical purposes, the product will only be introduced into the environment when it is excreted by treated animals. Handling, distribution and storage of the finished product should not cause environmental exposure since the drug is marketed in closed, double-

walled bags. Calculation of environmental drug substance exposure from the use site into the soil, [Predicted Environmental Concentration in the soil (PEC_{soil})] consists of determining:

- A. the concentration of drug in the excreta
- B. the concentration of the drug in the soil once the excreta is spread on fields
- C. the concentration of the drug in the run-off water once excreta is spread on fields.

A. Estimation of Drug Concentration in the Excreta

Target animals excrete quantities of the drug as parent compound and metabolites. The excretion of fenbendazole plus metabolites was measured in a study with turkeys treated with radiolabeled fenbendazole. The study showed that practically the entire dose, as measured by radioactivity, is excreted within a few days. For the purpose of this evaluation, we assume that 100% of the administered dose is excreted within 7 days. In calculating the Predicted Environmental Concentration (PEC) we assume that the concentration of the drug should include the addition of 15% diluent (*e.g.*, wood shavings) to the litter. According to the tenth draft of the document entitled "Guidance for Industry for Environmental Risk Assessment Covering New Animal Drug Applications for Veterinary Use", dated 21 August 1996, the equation for calculating the maximum concentration of drug in the litter which is applied to the fields is as follows:

$$(a) = \frac{(b) \times (c) \times (d)}{(e)}$$

where (a) = wet-weight concentration of drug substance in manure (ppm)
 (b) = Total dose administered to each animal per day in mg/day
 (c) = Fraction of animals treated: using 1.0 (100%) for whole flock
 (d) = Number of days that animals were treated
 (e) = Total amount of manure (in kg) produced per animal within confinement facility during the manure production period (*i.e.*, manure produced daily x manure production period).

Average turkey values prescribed for such calculations in the tenth draft document stated above are as follows: mean weight = 10 kg; feed intake (on a 90% dry matter basis) = 0.3 kg/bird/day; and manure production = 0.34 kg/bird/day.

Fenbendazole treatment will consist of six (6) consecutive days of feed containing 16 ppm fenbendazole. Since the birds will be continually exposed to worm ova from the litter, treated flocks are expected to receive fenbendazole medication twice/flock. The U.S.

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poultry industry routinely reuses litter and only removes used litter from the poultry houses approximately once per year. Also, hen turkeys are generally about 14 weeks of age when they are marketed, and tom turkeys are usually grown to about 20 weeks of age. Therefore, using 17 weeks as the average age, one can assume that, on average, three flocks of turkeys will be grown on the same litter in one year (51 weeks or 357 days). Thus the total number of treatment days for flocks raised on the same lot of litter is assumed to be 36 (6 treatments x 6 days/treatment).

According to the above equation, the wet-weight concentration of total fenbendazole drug substance in the litter of a turkey house after three flocks would be:

$$a = \frac{(16 \text{ mg fbz/kg feed} \times 0.3 \text{ kg feed/day}) \times 1 \times 36 \text{ days}}{357 \text{ days} \times 0.34 \text{ kg feces/day} \times 1.15^*}$$

$$= 1.24 \text{ mg fbz/kg litter}$$

* 1.15 corrects for additional 15% diluent added to manure.

B. Estimation of Drug Concentration in the Soil once Excreta is Spread on Fields

The concentration of the drug in the soil is the amount of the drug in the litter which is applied to an acre of soil divided by the weight of the soil into which the litter is mixed. The top 15 cm (6 in.) of soil (average plow depth) weighs an estimated 910,500 kg. The amount of poultry litter which is applied to the soil is 9,200 kg/acre. Soil concentration is calculated according to the formula:

$$\text{Soil Concentration} = \frac{\text{Drug Concentration in litter (ppm)} \times \text{kg of Litter per Acre}}{910,500 \text{ kg of soil}}$$

Using the concentration of 1.24 mg fbz/kg litter, as calculated in part A above, the calculation of soil concentration is:

$$\text{Soil Concentration} = \frac{1.24 \text{ mg fbz/kg litter} \times 9,200 \text{ kg/acre}}{910,500 \text{ kg of soil}}$$

$$= 0.013 \text{ mg fbz/kg soil}$$

$$= 0.013 \text{ ppm} = 13 \text{ ppb.}$$

As indicated by the above calculations, the amount of fenbendazole that would be released into the soil, even assuming no degradation, would be extremely low.

C. Estimation of Drug Concentration in Run-Off Water once Excreta is Spread on Fields

During the year it is assumed there will be 2 inches of rainfall over an acre of land; this volume of water weighing 205,500 kilograms. As noted in section B above, a maximum of 9,200 kg of litter containing 1.24 mg fbz/kg will be distributed on an acre, thus the total amount of fenbendazole per acre is 11.408 g per year (9,200 kg x 1.24 mg fbz/kg = 11,408 mg = 11.408 g fbz).

Fenbendazole is not soluble in water (solubility \leq 40 ppb). However, if we assume that it is possible to have all of the residue in the run-off, the maximum fenbendazole concentration, assuming no degradation, is calculated as follows:

$$\begin{aligned} \frac{11.408 \text{ mg fbz}}{205,500 \text{ kg water}} &= 0.0555 \text{ mg fbz/kg water} \\ &= 56 \text{ ppb fbz in run-off water} \end{aligned}$$

It would be expected that the amount of fenbendazole released into the run-off water would be very much lower than 56 ppb because fenbendazole is very insoluble in water, and absorbs tightly to soil particles. Based strictly upon solubility, for example, it is expected that the maximum concentration of fenbendazole in the run-off water would be 0.02 ppt (56 ppb x 0.04 ppt solubility), fenbendazole is not expected to migrate from application sites into run-off or leachate water, and hence is not expected to be available to aquatic species. Exposure would be limited by adsorption and available pathways for rapid degradation (e.g., photolysis).

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT:

Since the primary route of introduction of fenbendazole into the environment is through excretion by the target animal, the firm conducted several studies of the fate of this drug in the environment. All studies are part of original application NADA 128-620 (48 FR 42809, September 20, 1983).

Water Solubility of Fenbendazole

Fenbendazole was determined to be very insoluble in water. The solubility was determined by passing saturated dilutions through filters with .45 micron pore size. The water solubility

was determined to be between 10 and 40 ppb. It is clear from these data that fenbendazole is water-insoluble.

Hydrolytic Behavior of Fenbendazole.

A study was done to determine if fenbendazole is decomposed depending on various pH values.

Three aqueous reaction mixtures of fenbendazole, one mildly acidic, one neutral, and one mildly basic (pH levels of 5, 7 and 9, respectively) were stored at 25°C in the dark. At specified time intervals, through 28 days, aliquots of the reaction mixtures were extracted with dichloromethane and analyzed by high performance liquid chromatography (HPLC). The levels of fenbendazole found by HPLC were unchanged throughout the time period. At selected intervals, the dichloromethane extract from the sample aliquots were also assayed by thin layer chromatography (TLC) which show one spot attributable to parent fenbendazole upon visualization by ultraviolet light (UV). After 28 days, no significant hydrolysis of fenbendazole was detected by HPLC or TLC.

We conclude from these studies that fenbendazole is not hydrolyzed in the tested range of conditions.

Photolytic Decomposition of Fenbendazole in Aqueous Solution

A study designed to conform to Method 3.10 of the FDA Environmental Assessment Technical Assistance Document was conducted by Springborn Laboratories, Inc. to measure the photodegradation of fenbendazole in aqueous solution.

Photolytic decomposition is a known degradative pathway for benzimidazoles. The effect of simulated sunlight on the photolytic degradation of aqueous solutions of fenbendazole was tested at pH 5, 7 and 9. Actinometer (reference material) solutions of para-nitroacetophenone (PNAP) were analyzed concurrently with the pH 5, 7 and 9 test solutions.

Sampling and analysis for ¹⁴C fenbendazole consisted of an extraction method where 4 to 5 separate tubes for the light-exposed and dark control solutions were separately combined, each containing approximately 12 mL, to provide triplicate replicates for solid phase extraction (SPE). Eluent from the solid phase columns were analyzed utilizing high performance liquid chromatography (HPLC) with fraction collection and subsequent radioassay. Radiochromatograms (histograms) were conducted to quantify the

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concentration of fenbendazole present and to determine its degradation rate. Samples for PNAP were analyzed by high performance liquid chromatographic analysis with UV detection.

Since degradation was so rapid, and insufficient quantities of photolyzed samples existed for identification of degradates, additional exposures at pH 5, 7 and 9 were conducted upon completion of the definitive portion of the study, with a large number of replicates, to provide enough volume for photodegradate identification. The combined volume of these replicates was extracted using a solid phase system and a photodegradate profile determined based on chromatographic comparison of retention times with supplied standards. None of the degradation products comprised more than 10% of the original concentration of fenbendazole, indicating that photolysis was severely destructive to the molecule.

The half-life ($T_{1/2}$, days) of fenbendazole at pH 5, 7 and 9 are presented below.

<u>pH</u>	<u>$T_{1/2}$ (days)</u>
5	0.713
7	0.527
9	0.471

This study conclusively demonstrates a rapid degradation process for fenbendazole exists (less than one day) with photolysis proceeding to many insignificant degradate compounds in which none comprise more than 10% of the original concentration.

A summary is presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

Migration of Fenbendazole in Soil

A migration study using soil thin layer chromatography was done to determine if fenbendazole migrates from the site of introduction into the environment. Radiolabeled fenbendazole was studied in a silt loam soil sample. Fenbendazole adsorbed tightly to particles of this soil type and is not expected to migrate from application sites into runoff or leachate water.

Adsorption of Fenbendazole to Particulate Matter

An adsorption study was done to determine how tightly fenbendazole is bound to particulate matter in the soil. Radiolabeled fenbendazole was used and 3 soils and 1 sediment were fortified with the radiolabeled drug at 5 different concentration levels. After continuously shaking the soil/water mixture for 48 hours, the level of radioactivity was determined in water, dichloromethane, soil extracts and extracted soil. The adsorption isotherms of fenbendazole were determined to be log 3 for a sample of New Jersey soil, New Jersey sediment and Texas soil. The adsorption isotherms for a Louisiana soil was determined to be log 2.8. A clear correlation was found between the adsorption isotherm values and the soil variables or organic matter, sand and silt content. Overall, fenbendazole was adsorbed very tightly to the soil samples. The study demonstrated again that fenbendazole was bound tightly to all soils examined.

Laboratory Run-Off Studies with Feces from Animals Treated with Fenbendazole

Studies have shown that the same metabolites are found in the feces of swine, cattle and turkeys treated with fenbendazole. Feces from pigs treated with ^{14}C fenbendazole were mixed with soil to a final concentration equivalent to 11.07 micrograms of ^{14}C fenbendazole/g of soil. The soil feces mixture was incubated with a 10 fold excess of distilled water for 72 hours with constant shaking to achieve an equilibrium distribution of fenbendazole + metabolites between the soil and the aqueous phase. The final concentration of ^{14}C fenbendazole in the aqueous phase was .045 micrograms/mL which represented 3.19% of the initial ^{14}C activity. The result of this study shows that fenbendazole metabolites, just as fenbendazole parent substance, are bound tightly to particulate matter and do not migrate into surface waters. (Bio/dynamics, Bound Brook, NJ.)

Biodegradation of Fenbendazole

The biodegradation of fenbendazole was determined in an experimental setting. Fenbendazole was incubated with a secondary effluent for 30 days. During the experiment, aliquots were removed for dissolved organic carbon (DOC) analyses at intervals of 1, 2, 3, 4, 7, 10, 15, 21 and 30 days. In addition, aliquots were removed at 1, 2 and 30 days of incubation for high performance liquid chromatography (HPLC) analyses of fenbendazole. The biodegradation of fenbendazole was extremely difficult to follow using DOC determinations because of the insolubility of fenbendazole in aqueous media. During the incubation period, fenbendazole apparently precipitated in the incubation flasks resulting in

non-homogeneous mixtures. The DOC determinations from the aliquots fluctuated considerably but suggested a general trend toward biodegradation. Extraction of the total remaining mixtures in the incubation flask after 30 days followed by HPLC analyses indicated that there was no degradation of fenbendazole.

It can be concluded from this study that fenbendazole may biodegrade very slowly under the test conditions.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

Human Food Safety Studies

The acute oral toxicity of fenbendazole was evaluated in laboratory and target animals. Standard protocols were used for studies in mice and rats. Large animals (horses, cattle, sheep) were also treated with relatively high doses of fenbendazole. Fewer large animals were exposed to the various dose levels since the individual animals were studied more thoroughly. In those studies no toxicity was found after the highest administered dose, with the exception of the study in rabbits, which was conducted as a pilot study. One out of 3 animals died after 3,200 mg/kg and 2 out of 3 after 5,000 mg/kg.

The results of single dose, oral acute toxicity studies are summarized in the following table:

ACUTE ORAL TOXICITY OF FENBENDAZOLE SINGLE DOSE MG/KG B.W.

	<u>Toxic Dose</u> <u>Greater Than</u>
Mice	10,000 mg/kg*
Rats	10,000 mg/kg*
Dogs	500 mg/kg
Sheep	5,000 mg/kg
Horses	1,000 mg/kg
Cattle	2,000 mg/kg
Rabbits	LD ₅₀ 3,200 mg/kg

*These doses were the highest that could be administered technically because of the large volume.

Fenbendazole was also studied for its effect on reproducing animals. Studies were done in rats, rabbits, horses, cattle and swine. No adverse effects were found. Details are

described in the Freedom of Information summary which is part of the NADA (48 FR 42809, September 20, 1983). Chronic toxicity studies (up to 90 days) have been performed with dogs and rats. The levels fed in the studies were much higher than levels expected to occur in the environment. The data are summarized below:

Chronic (90 day) studies with Laboratory Animals.

The 90-day studies in rats (up to 2,500 mg/kg) and dogs (up to 125 mg/kg) did not reveal any clinical signs of toxicity in any of the animals. No drug related postmortem lesions were found.

In addition, 6 month oral toxicity studies in dogs, a 3 generation reproduction study in rats, a lifetime oral toxicity study in rats in which offspring from the 3 generation study were used, and a lifetime mouse study were conducted to determine if fenbendazole is a carcinogen. No oncogenic properties of the drug were found. Based on these studies, a finite tolerance of 12 ppm fenbendazole residues in cattle liver was established.

Metabolism by Target Animals

A metabolism study in turkeys conducted using ^{14}C Fenbendazole (see FOI summary for this NADA) demonstrated approximately 84% of the oral dose of fenbendazole was excreted during the dose period, and excretion exceeded 99% of the oral dose by 48 hours after cessation of treatment. None of the tissues examined at 96 hours after cessation of treatment had more than 0.05% of the total administered radioactivity. High recoveries of radioactivity in the excreta (average = 90.5%, range = 76.5% to 99.2%) and the very small fraction remaining in tissues indicates that neither fenbendazole nor its major metabolites accumulate in the major organ systems. Over the 6 day treatment and 4 day post-treatment experimental period, fenbendazole made up approximately 45.2% of extractable residue in excreta, with oxfendazole ($\approx 29.2\%$), fenbendazole-sulfone ($\approx 7.8\%$), *p*-Hydroxy-fenbendazole ($\approx 4.9\%$) and other much more minor components ($\approx 12.9\%$) comprising the remainder. Of the metabolites previously identified in other species, only the 5-Phenylthio-2-aminobenzimidazole metabolite was not present in the excreta from the turkeys. There were no new or previously unidentified metabolites observed in the excreta from the turkeys in this study.

The turkey metabolism study evaluated six consecutive daily dosages of 4 mg fbz/kg body weight (total dose = 24 mg fbz/kg). Although the label dose of 16 ppm in the feed for six consecutive days provides a lower daily dosage (approximately 1 - 2 mg fbz/kg/day), the values documented with 24 mg fbz/kg are used for computations. Realistic estimates are

thus expected to be lower than the numbers provided here. In the metabolism study, the radioactivity concentration in the tissues peaked at 6 hours post-dose. The highest levels of all tissues examined were found in the livers; maximum levels in the livers averaged less than 7 ppm. A finite tolerance of 10 ppm in turkey liver has been established based on extensive safety studies. Therefore, during six day treatment at total dosages up to 24 mg fbz/kg body weight, the total residue in the livers of turkeys is expected never to exceed the safe level of 10 ppm.

Environmental Effect Studies

Tests Evaluating the Antimicrobial Activity of Fenbendazole

A number of microorganisms were exposed to fenbendazole and no activity of fenbendazole was found. The microorganisms included:

Gram positive aerobic bacteria:

Staphylococcus aureus S.G. 511

Streptococcus pyogenes A (308)

Streptococcus faecium D.

Gram negative bacteria:

Escherichia coli 055

Proteus mirabilis

Pseudomonas aeruginosa

Mycoplasma:

Mycoplasma gallisepticum 15302

The test method was a bacteriostatic (growth inhibition) test. Serial dilutions in Mueller-Hinton-Broth were used. The inoculum per mL medium was .05 mL of a 24 hour stationary fluid culture of the respective organism diluted 1:100. The minimum inhibitory concentration (MIC) was determined after an incubation of 18 hours at 37°C. MIC was the concentration of the last test tube in which no macroscopically visual bacterial growth was observed. The highest tested concentration of fenbendazole was 100 micrograms/mL. No antibacterial effect could be found against any of the tested aerobic bacteria.

In addition to these aerobic bacteria, anaerobic bacteria were also tested as follows:

Several strains of *Bacteroides fragilis*

Bacteroides ovatus

Bacteroides thetaiotaomicron

Sphaerophorus varius

Sphaerophorus freundii

Peptococcus anaerobius and *variabilis*

Peptostreptococcus anaerobius and *variabilis*

Propionibacterium acnes as well as several clostridia strains including *Clostridium perfringens* and *Clostridium septicum*.

The highest tested concentration of fenbendazole was 100 micrograms/mL agar. No antibacterial effect could be found against any of the tested anaerobic bacteria.

Fenbendazole was further evaluated for *in vitro* activity against *Trichomonas vaginalis* and *Entamoeba histolytica*. The study was done as an *in vitro* model for activity against *Histomonas meleagridis*. No *in vitro* effect was seen at concentrations of up to 200 micrograms/mL *in vitro*.

Fenbendazole was tested against these protozoa in *in vivo* experiments:

Eimeria tenella

Entamoeba histolytica

Trichomonas foetus

Aegyptianella pullorum

Trypanosoma brucei

Plasmodium vinckei

Babesia rodhaini

No activity was found in any of the experiments.

An antifungal test was also performed against:

Trichophyton mentagrophytes

Trichophyton rubrum

Microsporum canis

Candida albicans

Aspergillus niger

Two test media were used: malt extract peptone glucose agar and serum glucose agar. The concentration of fenbendazole was up to 100 micrograms/mL. No inhibition of fungi was observed in this study.

We conclude from the available information that fenbendazole would not have any effect on soil microbes because no growth inhibition could be demonstrated at the 100 and 200 ppm

concentrations which are greater than the maximum solubility of the compound (10-40 ppb).

Earthworm Toxicity (*Eisenia foetida*)

An earthworm study was conducted with *Eisenia foetida*.

A preliminary range-finding test using earthworms (*Eisenia foetida*) tested the toxicity of fenbendazole doses of 1,000, 500 and 100 mg fbz/kg soil. Worm mortality was not observed until 14 days and then only in the 1,000 and 500 mg/kg groups. The 14 day LC₅₀ was calculated to be 1,068 mg/kg with the 95% confidence interval being from about 900-1600 mg/kg. The worms at 100 mg/kg suffered no mortalities, however, by 14 days they had lost almost as much weight (35%) as had the worms at the two higher doses. In comparison to control worms, all treatment with fenbendazole resulted in significant weight losses.

The control worms were able to reproduce (produce cocoons). The only other test group able to reproduce was the 100 mg/kg worms, however, they did so to a lower degree than did the control worms. By 7 days at both the 1,000 and 500 mg/kg dose levels there was a considerable reduction in the ability of the worms to burrow.

The study demonstrated the absence of an acute lethal effect of fenbendazole on earthworms at concentrations below 100 ppm. It did not determine the minimum effect level for sublethal effects since doses lower than 100 mg/kg were not tested.

Earthworm Toxicity (*Lumbricus terrestris*)

The subacute toxicity of fenbendazole on earthworms (*Lumbricus terrestris*) was evaluated in a study conducted by Springborn Laboratories, Inc. in accordance with FDA Environmental Assessment Technical Document 4.12.

A preliminary range-finding test, consisting of two replicate test vessels per concentration and control, using earthworms (*Lumbricus terrestris*) tested the toxicity of fenbendazole doses of 1,000, 100, 10, 1.0, 0.10 and 0 (control) mg drug/kg artificial soil (dry weight basis). Percent survival was 95% or greater at all levels tested except 1000 mg/kg where 5% survival rate was observed. Definitive test concentrations were then established to be 960, 500, 240, 120, 56 and 0 (control) mg fbz/kg artificial soil (dry weight basis). For each exposure concentration and control, four replicate test vessels were utilized during the definitive test. When compared with burrowing time and percent weight change, statistical

analysis of the data determined that earthworm survival was the most sensitive parameter to the toxicity of fenbendazole. At test termination survival in 960, 500, 240, 120, 56 and 0 (control) mg fbz/kg artificial soil was 0, 25, 35, 53, 93, and 100%, respectively. Therefore, earthworm survival was used to establish the LC₅₀, Lowest-Observed-Effect and No-Observed-Effect Concentrations.

The LC₅₀ for earthworms exposed to fenbendazole for 28 days was calculated by moving average angle analysis to be 180 ppm fenbendazole. The Lowest-Observed-Effect Concentration (LOEC) was determined to be 120 ppm fenbendazole, and the No-Observed-Effect Concentration (NOEC) was determined to be 56 ppm fenbendazole in artificial soil containing 50 g cattle manure per kg dry artificial soil. The concentration of fenbendazole in soil with waste from treated turkeys would be significantly lower (13 ppb) than the NOEC of 56,000 ppb.

A summary is presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

The following studies were done to determine the toxicity of fenbendazole to aquatic organisms.

Acute Toxicity of Fenbendazole to the Water Flea (*Daphnia magna*)

Nominal concentrations of fenbendazole in water were prepared at 16, 10, 6.4, 3.8, 2.6, 1.6 micrograms/L and the appropriate controls added. Three replicates of each concentration were prepared and 5 water fleas were added to each container. The 48 hour LC₅₀ (and 95% confidence interval) for the water flea exposed to fenbendazole was estimated to be 12 micrograms/L (11-14 micrograms/L).

Acute Toxicity of Fenbendazole to Rainbow Trout (*Salmo gairdneri*)

The acute toxicity as expressed by a 96 hr. LC₅₀ could not be determined in rainbow trout. Based on results of the studies, it was estimated to be greater than 7.5 mg/L. The reason for the difficulties may be the low solubility of fenbendazole in water; undissolved fenbendazole was visibly present in all concentrations higher than 1.6 mg/L. The water solubility of fenbendazole was determined to be 0.01-0.04 mg/L. Concentrations tested ranged from 0.58-7.5 mg/L in one and 7.8-100 mg/L in another study. Only the results of the study with concentrations of 0.58-7.5 mg/L could be used because those at higher concentrations were inconsistent. Signs such as darkened pigmentation, lethargy, rapid respiration were observed at the estimated limits of water solubility of fenbendazole.

Acute Toxicity of ¹⁴C Fenbendazole to Bluegill (*Lepomis macrochirus*)
During 21 Days Continuous Exposure

The study was undertaken to estimate the toxicity, uptake, and elimination of ¹⁴C fenbendazole with bluegill during 21 days exposure and 7 days depuration under flowthrough conditions. Measured concentrations of ¹⁴C fenbendazole in water were prepared at 0.061, 0.029, 0.014, 0.0074 and 0.0041 micrograms/mL and the appropriate controls added. Ten bluegill were randomly distributed into duplicate test aquaria for a total of 20 fish per concentration. Survival and general appearance were assessed daily. The exposure of bluegill to ¹⁴C fenbendazole was continuous for 20 days. After 21 days exposure, all the remaining fish from the lowest test concentration which partially affected the survival of the test population (0.0074 micrograms/mL) were transferred to a clean aquarium and held for a depuration period of 7 days. During the initial 10 days of the exposure, ¹⁴C fenbendazole did not elicit any effects on the survival of bluegill at any concentration tested. A sharp increase in toxicity occurred between day 10 and 11. From days 11 through 21, a steady increase in the cumulative toxicity of ¹⁴C fenbendazole was observed:

LC₅₀ in micrograms fbz/mL (95% confidence interval)

Day	4	7	14	21
	>0.061 ^a	>0.061 ^a	0.035 ^b (0.030-0.041)	0.019 ^b (0.015-0.024)

^a empirically estimated.

^b estimated by moving average method.

Residue concentrations in muscle, viscera and remaining carcass of bluegill after 21 days of continuous aqueous exposure to 0.0074 micrograms/mL ¹⁴C fenbendazole indicate that the concentration of ¹⁴C residues in muscle and carcass were similar with bioconcentration factors of 43X and 92X, respectively. The greatest uptake of ¹⁴C residues occurred in the viscera which had a bioconcentration factor of 6600X. The whole body bioconcentration factor for bluegill exposed to 0.0074 micrograms fbz/mL for 21 days was 580X. After 7 days of depuration, 99% of the ¹⁴C residues concentrated in the viscera had been eliminated. The average concentration of ¹⁴C residue present in the muscle throughout depuration appears to have been approximately 0.28 mg/kg (average residue measured on days 0, 1 and 7). Based on whole body residues, the half-life for ¹⁴C fenbendazole in bluegill tissues was between 1 and 3 days (>1 <3 days).

The Acute Toxicity of Fenbendazole to Bluegill (*Lepomis macrochirus*) During 21 Days Continuous Exposure

The study was undertaken to determine if radioactivity was responsible for deaths of bluegills observed in a study with ^{14}C fenbendazole.

The same procedures were used as in the above study, and the results in this study were very similar to those observed with ^{14}C fenbendazole. During the initial 7 days of the exposure, fenbendazole did not elicit any effects on the survival of bluegill at any concentration tested.

By day 8 of the exposure, 30% and 20% mortality had occurred from exposure to 0.040 and 0.080 micrograms fbz/mL respectively. The highest mortality of bluegill exposed to 0.040 and 0.080 micrograms fbz/mL occurred between days 8 and 12. From days 12 through 21 of the exposure, relatively few fish died. Estimated LC_{50} in micrograms/mL (95% confidence interval) was:

 LC_{50} in micrograms fbz/mL (95% confidence interval)

Day	4	7	14	21
	0.080 ^a	0.0801 ^a	0.033 ^b	0.028 ^b
			(0.028-0.040)	(0.022-0.037)

^a empirically estimated.

^b estimated by moving average method.

Water samples from the study were analyzed by a validated analytical method (98% recovery, standard deviation about 5%) at Hoechst-Roussel Pharmaceuticals Inc. The total concentrations (*i.e.* fenbendazole in solution plus fenbendazole in suspension) of fenbendazole claimed to have been in the fish tanks were, essentially, correct. They agreed with the fenbendazole concentrations found by ^{14}C measurements in the previous radioactive ^{14}C study.

Many of the concentrations in the tanks were above the saturation point of fenbendazole in water (0.01 mg/L); in these there is strong evidence that it was present as a mixture of:

- Soluble fenbendazole.
- Fine particulate - *i.e.* less than 0.45 micron
- Course particulate - *i.e.* greater than 0.45 micron.

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However, even the coarse particulates could not be observed with the naked eye. The tanks at 0.01 mg/L and 0.005 mg/L (*i.e.* the saturation concentration, and 1/2 saturation) where the fish did not die, were confirmed as having fenbendazole present. The actual results were about 0.007 mg/L (70% of 0.01 mg/L) and 0.0033 mg/L (66% of 0.005 mg/L), respectively. In the ¹⁴C fenbendazole study, this level could not be measured by the radio carbon ¹⁴C assay.

In summary, fenbendazole was tested for toxicity to water flea, bluegill, and rainbow trout. The 48 hour LC₅₀ for the water flea exposed to fenbendazole was estimated to be 12 micrograms/L (11-14 micrograms/L). Toxicity was found when bluegill were exposed for more than 10 days to concentrations of more than 12-19 micrograms fenbendazole/L.

Some signs of toxicity (darkened pigmentation, lethargy, rapid respiration, etc.) were found in rainbow trout but no fish died at concentrations representing the limits of fenbendazole solubility in water. Rainbow trout were not as sensitive as bluegill sunfish and daphnia.

It would be expected that the amount of fenbendazole released into water run-off would be very much lower than 496 ppb because fenbendazole is very insoluble in water, absorbs tightly to soil particles and is rapidly photodegraded. Therefore, fenbendazole is not expected to migrate from application sites into runoff or leachate water; and hence, is not expected to be toxic to aquatic species. Also, fenbendazole will be present at very low levels in the soil, and it is soluble in water only at a maximum level of 10-40 micrograms/L.

Seed Germination and Root Elongation

A study was undertaken to define the effect of fenbendazole on corn (*Zea mays*), cucumber (*Cucumis sativus*), perennial ryegrass (*Lolium perenne*), soybean (*Glycine max*), tomato (*Lycopersicon esculentum*), and wheat (*Triticum aestivum*) germination and root elongation. This study was conducted by Springborn Laboratories, Inc. in accordance with FDA Environmental Assessment Technical Assistance Document 4.06.

Seeds of corn, cucumber and perennial ryegrass were exposed to fenbendazole suspensions of 970, 480, 240, 110, 61 and 0 ppm while wheat seeds were exposed to fenbendazole suspensions of 1000, 530, 310, 150, 61 and 0 ppm. Soybean and tomato seeds were exposed to fenbendazole suspensions of 1000, 530, 310, 150, 61, 36, 3.6, 0.36 and 0 ppm. Each treatment group consisted of six replicates of 50 seeds each. All tests were conducted in the absence of light. The test was initiated by adding 50 seeds each to appropriately labeled petri dishes containing treated or control filter paper and 15 mL ASTM Type 2 water.

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At test termination, percent germination and root length data for the treatments were statistically compared on a per replicate basis to the solvent control data. No morphological abnormalities were observed in any seeds at test termination. A No-Observed-Effect Concentration (NOEC) was defined as the highest treatment level where there was no statistically toxicant-related reduction in percent germination and root length when compared to the solvent control. The Lowest-Observed-Effect Concentration (LOEC), defined as the lowest concentrations demonstrating a statistically significant effect, was determined for each species. Results are as follows:

Species	Germination		Root Elongation	
	NOEC (mg/L)	LOEC (mg/L)	NOEC (mg/L)	LOEC (mg/L)
Corn	970	> 970	970	> 970
Cucumber	970	> 970	970	> 970
Ryegrass	970	> 970	970	> 970
Soybean	1000	> 1000	1000	> 1000
Tomato	1000	> 1000	1000	> 1000
Wheat	1000	> 1000	1000	> 1000

A summary of this study is presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

Seedling Growth

The effect of fenbendazole on seedling growth was determined in a study in which six species of angiosperms were selected. They included three monocotyledons, corn (*Zea mays*), wheat (*Triticum aestivum*) and perennial ryegrass (*Lolium perenne*), and three dicotyledons, soybean (*Glycine max*), tomato (*Lycopersicon esculentum*) and cucumber (*Cucumis sativus*). This study was conducted by Springborn Laboratories, Inc. in accordance with FDA Environmental Assessment Technical Assistance Document 4.07.

A range of six concentrations were chosen for the definitive tests which were expected to yield NOEC and LOEC values for each species. The measured treatment levels were 1600, 810, 360, 150, 64, 36 and 0 (control) mg fenbendazole/kg support medium. At test initiation, appropriately labeled replicate pots, each containing 1.5 kg of treated or control silica sand, were surface watered with 250 mL of nutrient solution. Germinated seedlings

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of uniform root and shoot development were selected by random assignment for planting in the treated or control support medium (silica sand). For each species, five seedlings were planted in each of five replicate pots per concentration and controls. Artificial lighting of 1000 to 1200 foot-candles was provided on a day/night schedules (16 hours light/8 hours dark) to allow for proper shoot orientation and the initiation of photosynthesis. During the test, all pots were subirrigated daily, and in addition the 360, 810 and 1600 mg/kg pots were watered on the surface on days 0, 1, 2 and 4 for corn, cucumber and perennial ryegrass and on days 0, 1 and 3 for soybean, tomato and wheat due to the hydrophobic nature of the test article on the sand.

Seedling shoot lengths were measured on days 1, 3, 5, 7, 14 and 21 to establish growth rate curves. Plant survival, dry shoot weight and dry root weight were measured at the conclusion of the 21-day test period. The results are as follows:

Species	NOEC ^a (mg/kg)	LOEC ^a (mg/kg)
Corn ^b	1600	>1600
Cucumber ^b	1600	>1600
Ryegrass ^b	1600	>1600
Soybean ^b	1600	>1600
Tomato ^c	36	64
Wheat ^b	1600	>1600

^a NOEC and LOEC based on the most sensitive parameter measured (percent survival, shoot length, shoot and root weight).

^b No effect was observed for percent survival, shoot length, shoot dry weight and root dry weight at the highest measured concentration tested.

^c NOEC and LOEC based on root weight, the most sensitive parameter for tomato.

A summary of this study is presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

Studies in Plants

Another study was conducted to determine if fenbendazole is accumulated in plants.

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Feces from a cow which had been treated with ^{14}C fenbendazole at a dose level of 5 mg fenbendazole/kg body weight were used to determine if fenbendazole or its metabolites are taken up by plants.

Barley and bean plants were raised under laboratory conditions on sandy loam soil to which 3.5% of a mixture of urine and feces had been added. The plants and new crop, tested for their radioactive content at various times after sowing 6 days, 14 days, 11 weeks - showed concentrations varying between the level of detection and twice the level of detection of 3 nanograms/gram (3 ppb). The comparative value for the soil was 490 nanograms/gram.

Bioaccumulation

Octanol/water partitioning coefficient is a chemical measure often indicative of the potential for a chemical to accumulate in lipid-containing tissues of animals and plants. The octanol/water partitioning coefficient (EPA Method, FEDERAL REGISTER, March 16, 1979) for fenbendazole was found to be approximately $\log K_{ow}$ 3.9, an intermediate partition coefficient compatible with other test results concerning bioaccumulation of fenbendazole.

Bioaccumulation was determined in additional studies as follows:

Residue studies with radiolabeled fenbendazole in various mammals (cattle, sheep, pigs, rats) showed that the majority of the administered dose of fenbendazole is excreted rapidly with only traces left after 7 days.

Specific studies in fish.

Accumulation and Elimination of ^{14}C Residues by Bluegill Sunfish exposed to ^{14}C Fenbendazole.

Bluegill sunfish were continuously exposed to a nominal concentration of 0.92 nanograms/mL (ng/mL) of ^{14}C labeled fenbendazole in well water for 31 days after which all remaining fish were transferred to flowing, uncontaminated water for a 14 day depuration period.

The concentration of ^{14}C residues measured in the muscle tissue increased during the initial three days of exposure after which a period of equilibrium existed during the remaining 28 days of exposure. The mean equilibrium bioconcentration factor for ^{14}C fenbendazole in muscle tissues (days 3 through 30) was 31X.

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Similarly, an equilibrium was reached in the visceral tissues after 3 days of exposure. The mean equilibrium bioconcentration factor in viscera was calculated to be 3,500X.

The ^{14}C residue content measured in the carcass tissue increased during the initial 7 days of exposure after which there was a period of apparent equilibrium for the duration of the exposure period. The mean bioconcentration factor for ^{14}C fenbendazole in bluegill carcass during the equilibrium period (days 7 through 30) was 85X.

The pattern of accumulation and persistence of ^{14}C residues in the whole body of bluegill exposed to ^{14}C fenbendazole was similar to that observed in the viscera tissue. The mean equilibrium bioconcentration factor for ^{14}C fenbendazole in the whole body of bluegill during the period 3 through 30 days of exposure was 240X.

Of the ^{14}C residues accumulated in the muscle tissue of bluegill after 31 days of continuous aqueous exposure to ^{14}C fenbendazole, 27% were extractable with hexane, 20% were extractable with methanol, and 53% were nonextractable with either solvent.

The elimination of ^{14}C residues from the selected tissue portions of bluegill exposed for 31 days to ^{14}C fenbendazole was continuous during the 14 day depuration period. Depletion half-life of ^{14}C residues present in the bluegill tissue on day 30 of exposure occurred within the first 24 hours after the transfer to flowing uncontaminated water. By day 14 of depuration, bluegill had eliminated 81%, 99% and 70% of the ^{14}C residues measured in the muscle, viscera and carcass tissue respectively and 93% of the ^{14}C residues calculated for the whole fish on day 30 of exposure.

It should be noted that the results of this study suggest a factor of temporary bioaccumulation that may be higher than under natural circumstances. The water solubility of fenbendazole was determined to be 10-40 ppb. Migration studies showed that fenbendazole and its metabolites are tightly bound to soil particles. Therefore, low concentrations will occur in surface water.

In summary, an intermediate level of accumulation was observed in bluegill continuously exposed to ^{14}C fenbendazole. The calculated mean equilibrium (plateau) bioconcentration factor in the whole body of bluegill was 240X. The factors mitigating concern for the accumulation of fenbendazole in fish consist of 1) the fact that plateau was attained within the first three days of the exposure and continued accumulation did not occur during the remainder of the thirty-day exposure and 2) upon transfer to clean water, the fenbendazole residue accumulated in bluegill (whole body) was rapidly eliminated (half-life less than 24 hours) and within 14 days had decreased to 7% of the body burden attained at plateau.

These data indicate that fenbendazole would not be expected to concentrate or be retained to any great degree by aquatic organisms. From all of the available information we conclude that fenbendazole should not pose a significant problem concerning bioaccumulation.

From all available information, we conclude that fenbendazole should not cause an environmental problem after the treatment of turkeys as far as bioaccumulation in warm blooded animals or fish is concerned.

Acute Toxicity of Fenbendazole to *Onthophagus gazella*

An investigation was conducted by Springborn Laboratories, Inc. to determine the NOEC and LD₅₀ of fenbendazole to dung beetles. The 7-day toxicity test with dung beetles (*Onthophagus gazella*) included a single measured fenbendazole concentration of 770 mg/kg and a control. Five replicate vessels were maintained for the treatment and control. Treated cattle manure (1000 mg/kg, nominal) was divided into five 300 g aliquots formed into oval shaped patties and placed in the plastic pail vessels, each containing 2.4 kg of moistened artificial soil. Five replicates of 300 g aliquots of untreated cattle manure (control) were also maintained. Test vessels were randomly positioned in a temperature controlled water bath designed to maintain temperature at $28 \pm 2^\circ$ C. Relative humidity was maintained at 58 to 66%. Light intensity was 60 foot-candles with a photoperiod of 16 hours light and 8 hours darkness. Each vessel was misted with deionized water once daily. Two male-female pair of dung beetles were placed in each replicate vessel. Survival rate, physical or behavioral abnormalities (e.g. lethargy) and presence of dung balls were recorded at test termination (day 7).

At test initiation (day 0) and test termination manure samples for the treatment level and the control were analyzed for fenbendazole concentration. The mean of the day 0 and the normalized day 7 concentrations defined the measured treatment level to be 770 mg/kg. Mean survival among dung beetles exposed to the treatment level of fenbendazole tested (770 mg/kg, measured) was 100%. Based on the absence of mortality and sublethal effects during the study, the 7-day LD₅₀ was empirically estimated to be greater than 770 mg/kg. The No-Observed-Effect Concentration was determined to be 770 mg/kg. The concentration of fenbendazole in waste litter from treated turkeys would be significantly lower (1.24 mg fbz/kg litter or 1.24 ppm) than the NOEC of 770 ppm.

A summary is presented in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

Environmental Hazard Assessment

Aquatic Environment

Under "worst case" conditions (assuming that all fenbendazole administered to turkeys is excreted into the litter via their manure, is extracted from the litter by two inch rainfall after litter is spread on the fields, and enters into water run-off), the estimated water run-off concentration of fenbendazole is 56 ppb as previously calculated. This would be the highest concentration of fenbendazole in any aquatic environment since it assumes six (6) treatment periods per year, does not account for dilution as it enters bodies of water such as streams, rivers, ponds and lakes (secondary aquatic environments), does not account for the fact that fenbendazole and fenbendazole metabolites are bound tightly to the soil and do not migrate into surface waters, and that upon entry into these secondary aquatic environments, fenbendazole and fenbendazole metabolites rapidly decompose through the process of photodegradation. The half-life in water is less than one day. Dilution and photochemical decomposition in the secondary aquatic environments reduces the environmental concentrations of fenbendazole and its metabolites such that the effects from fenbendazole on vertebrate and invertebrate populations are expected to be transient and would not be considered to be significant.

Aquatic Levels

- Daphnia Toxicity >> LC₅₀ (48 hr.) = 12 ppb
- Trout Toxicity >> LC₅₀ (96 hr.) = H₂O solubility Limit (40 ppb)
- Bluegill Toxicity >> LC₅₀ (21 d. continuous exposure) > 19 ppb

Terrestrial Environment

Under "worst case" conditions (assuming that all fenbendazole administered to turkeys is excreted via their manure, accumulates over a year in the litter, and the litter is mixed into the top six inches of soil at the rate of 9,200 kg litter/acre of land) the total initial concentration of fenbendazole is calculated to be 13 ppb. The comparison of the calculated environmental concentrations of fenbendazole in the terrestrial environment in conjunction with the effects levels below is not expected to have a significant impact on the environment.

Terrestrial Effect Levels

• Microorganisms	>>	NOEC	> 100,000 ppb
• Seedling Growth (tomato most sensitive)	>>	NOEC	= 36,000 ppb
		LOEC	= 64,000 ppb
• Seed Germination/ Root Elongation	>>	NOEC	≥ 970,000 ppb
• Earthworm Toxicity	>>	NOEC (28 d.)	= 56,000 ppb
		LOEC (28 d.)	= 120,000 ppb
		LC ₅₀ (28 d.)	= 180,000 ppb
• Dung Beetle Toxicity	>>	NOEC (7 d.)	= 770,000 ppb
		LD ₅₀ (7 d.)	> 770,000 ppb

Environmental risks can be estimated from the relationship between concentrations expected in the environment and the highest concentrations of fenbendazole at or below which no toxicological effects have been observed in laboratory studies. Quotients (Q) representing the relationship between the CEC or calculated environmental concentration and the NOEC or no-observed-effect concentration are presented below where $Q = \text{CEC}/\text{NOEC}$. The Q values below illustrate a considerable margin of safety across a range of microbial, insect, invertebrate and plant species of importance to the terrestrial compartment of the environment. Typically, where $Q < 0.10$, a 10 fold margin of safety, minimal risk to the environment is expected (USEPA 1994)³. Based on margins of safety ranging between about 2,500 and 100,000 fold, the introduction of fenbendazole is not expected to impact the terrestrial environment.

Terrestrial organism or category	NOEC (ppb)	CEC (ppb)	Q (CEC/NOEC)
Microorganisms	100,000	13	0.0001
Earthworm	56,000	13	0.0002
Seed Germination	970,000	13	0.00001
Seedling Growth ¹	36,000	13	0.0004
Dung Beetle	770,000	13	0.00002

¹ Based on most sensitive species - tomato.

Summary

Hoechst Roussel Vet has shown that fenbendazole used at the proposed levels will not significantly adversely affect microorganisms, soil biota, plants, fish or mammals exposed to environmental concentrations of the drug that can reasonably be expected to occur. Studies are included as part of original application NADA 128-620 (48 FR 42809, September 20, 1983) and five studies are included in a supplemental application to NADA 128-620 approving the use of fenbendazole in dairy cattle.

9. USE OF RESOURCES AND ENERGY:

Fenbendazole bulk drug, acquired from Hoechst ERG, Frankfurt, Germany, is formulated into a premix using common inert pharmaceutical grade excipients which are recognized in the U.S.P. or N.F. Energy requirements for manufacturing are similar to those which would be used in any conventional pharmaceutical operation involved in the production and packaging of liquid products. No irreversible or irretrievable commitment of resources will be involved if the proposed action should be implemented.

This action will not require any significant use of the environment. There are no expectations or evidence to expect short-term or long-term effects. Therefore, there is expected to be no effect upon the depletion of natural resources due to manufacture of the drug.

Environmental impact of manufacturing process

No measurable effluents will result from the manufacturing process and no pollutants are expected. The manufacturing facilities in Frankfurt, Germany, comply with local regulations. A statement by Hoechst AG to that effect is in NADA 137-600 (Fenbendazole for Dairy Cattle, 61 FR 29477, June 11, 1996).

10. MITIGATION MEASURES:

In light of the data presented above, no such considerations are necessary.

Probable adverse affects which cannot be avoided

No adverse effects are expected from the use of fenbendazole.

Relationship between local short-term uses of the environment and the maintenance and enhancement of long-term productivity

There is no conceivable effect on the environment from either short- or long-term production.

Risk benefit analysis

The manufacture and distribution of the new drug demonstrates no risk or potential for risk to the environment.

11. ALTERNATIVES TO THE PROPOSED ACTION:

Irreversible and ir retrievable commitments resulting from the proposed action

Substances which constitute fenbendazole suspension are taken from natural resources which are either replaceable or are derived from the most commonly existing substances and are logically viewed as insignificant.

Alternatives to the Proposed Action

The only alternative to approval of the New Animal Drug Application is non-approval. This would mean that the turkey industry would not have the choice of the use of this drug. The drug will have the effect of providing an alternative means for deworming turkeys.

Objections raised by other agencies, organizations, or individuals

Hoechst Roussel Vet knows of no objections raised regarding the proposed action.

Hoechst Roussel Vet believes that an environmental impact statement (E.I.S.) is not required for the proposed action.

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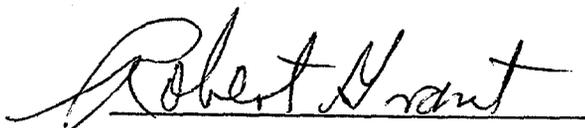
12. LIST OF PREPARERS:

Robert J. Grant, Ph.D.
Director, Regulatory Affairs & Compliance
Hoechst Roussel Vet

13. CERTIFICATION

The undersigned petitioner certifies the information furnished in this Environmental Assessment Report is true, accurate, and complete to the best of his knowledge.

Date March 30, 2000



Robert J. Grant, Ph.D.

Director, Regulatory Affairs & Compliance

14. REFERENCES

Summaries of studies are included in the original NADA 128-620 (48 FR 42809, September 20, 1983), the supplemental NADA 128-620 (53 FR 40058, October 13, 1988), and NADA 137-600 (61 FR 29477, June 11, 1996) approving the use of Fenbendazole Type A Medicated Article in dairy cattle.