ENVIRONMENTAL ASSESSMENT

NADA 137-600

FENBENDAZOLE TYPE A MEDICATED ARTICLE (PREMIX) IN DAIRY CATTLE OF BREEDING AGE

1. **DATE:**
May 1995

2. **NAME OF APPLICANT/PETITIONER:**

Hoechst-Roussel Agri-Vet Company

In the United States, Hoechst-Roussel Agri-Vet Company will be the distributor of the product and will control the suspension manufacture.

3. **ADDRESS:**

P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876-1258

4. **DESCRIPTION OF THE PROPOSED ACTION:**

Hoechst-Roussel Agri-Vet Co. is requesting approval to expand the use of fenbendazole (supplemental filing to NADA 137-600) Type A Medicated Article (premix) as an oral dewormer to lactating dairy cattle (dairy cattle of breeding age) at a dose level of 5 mg fenbendazole/kg body weight. The recommended dose is given once. Retreatment after 4-6 weeks may be necessary if the treated dairy cattle continue to be exposed to worms. There is no milk withdrawal period following treatment. However, the treated dairy cattle can not be slaughtered for human consumption for a period of 13 days after treatment.

Fenbendazole Safe-Guard® Type A Medicated Article (premix), Safe-Guard® 0.5% Cattle Top Dress Pellets (Type B Feed), and Safe-Guard® 35% Free-Choice Mineral (Type C Feed) will be used in lactating dairy cattle at any time during the lactation period and dry period. Safe-Guard® Type A Medicated Article (premix), Safe-Guard® 0.5% Cattle Top Dress Pellets (Type B Feed), and Safe-Guard® 35% Free-Choice Mineral (Type C Feed) will be used as partial replacement for exisitng agents, morantel tartrate and thiabendazole, intended for the same purpose. Safe-Guard® Type A Medicated Article (premix), Safe-Guard® 0.5% Cattle Top Dress Pellets (Type B Feed), and Safe-Guard® 35% Free-Choice Mineral (Type C Feed) will provide an alternative means for deworming lactating dairy cattle.

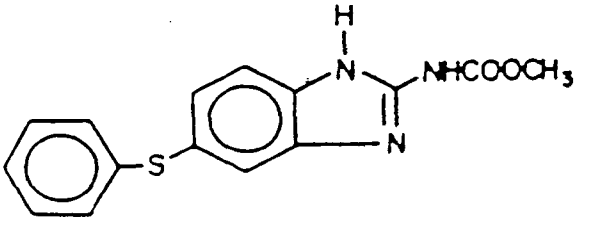
Populations

The number of lactating dairy cattle is projected to be 9 million. Of that number, 17% or about 1.5 million are projected to receive fenbendazole as Safe-Guard® Type A Medicated Article (premix) admixed in feed, Safe-Guard® 0.5% Cattle Top Dress Pellets (Type B Feed), or Safe-Guard® 35% Free-Choice Mineral (Type C 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. Both thiabendazole and mebendazole 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)-1H-benzimidazol-2-y1]-carbamic acid methyl ester.
Also: methyl 5-(phenylthio)-2-benzimidazol-carbamate.
Structural Formula:



Molecular Formula:	$C_{15}H_{13}N_3O_2S$
Molecular Weight:	299.4
Description:	White to light brownish or grayish powder essentially odorless.
Melting Point:	Approximately 233° (with decomposition)
Solubility:	Insoluble in water (approx. 10-40 ppb.) Insoluble or only slightly soluble in the usual solvents. Freely soluble in DMSO.
Octanol/Water Partition Coefficient:	Log K_{ow} 3.9
U.V. Absorption Spectrum:	Representative spectrum with maximum absorptivity at 296 nm is presented in Appendix 1.
Mode of Administration:	Oral

PRODUCT DESCRIPTION

Fenbendazole is sold as Safe-Guard® Type A Medicated Article (premix) which has an active ingredient concentration of 200 grams fenbendazole per kilogram, Safe-Guard® 0.5% Cattle Top Dress Pellets (Type B Feed) which has an active ingredient concentration of 5 grams fenbendazole per kilogram, and Safe-Guard® 35% Free-Choice Mineral (Type C Feed) which has an active ingredient concentration of 1.90 gram fenbendazole per pound (4.19 gm/kg).

MODE OF ACTION

Anthelmintic spectrum: fenbendazole is active against gastrointestinal nematodes and lungworms. Efficacy against the following worms has been demonstrated in the United States:
Lungworm: *Dictyocaulus viviparus*
Stomach Worm (adults): Brown Stomach worm *(Ostertagia ostertagi)*.
Stomach Worm (adults & 4th stage larvae): Barberpole Worm *(Haemonchus contortus/placei)*, Small Stomach Worm *(Trichostrongylus axei)*.
Intestinal Worms (adults & 4th stage larvae): Hookworm *(Bunostomum phlebotomum)*, Threadneck Intestinal Worm *(Nematodirus helvetianus)*, Small Intestinal Worm *(Cooperia oncophora, Cooperia punctata)*, Bankrupt Worm *(Trichostrongylus colubriformis)*, Nodular Worm *(Oesophagostomum radiatum)*.

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 are presented in Appendix 2. Fenbendazole bulk drug substance will be shipped to the United States to Feed Specialties Company, Inc., 1977 NE 58th Avenue, Des Moines, Iowa 50313 for manufacturing and packaging of fenbendazole (Safe-Guard®) Type A Medicated Article (premix). The drug will be distributed in the United States for use in lactating dairy cattle.

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. Dairy facilities and other cattle environments receiving residues of the drug contained in animal wastes.
4. Agricultural lands potentially receiving residue containing wastes.
5. Aquatic systems potentially receiving runoff from dairy facilities and 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 is attached as Appendix 3.

A current manufacturing Environmental Assessment is attached as Appendix 4 for Feed Specialties Company, Inc., manufacturer of the finished dosage form at the facility in Des Moines, IA (USA).

The manufacturing process of fenbendazole suspension consists of carefully controlled weighing and mixing operations conducted in a premix 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.

Target animals excrete quantities of the drug as parent compound and metabolites. The excretion of fenbendazole plus metabolites was measured in studies with cattle treated with radiolabeled fenbendazole. The studies showed that practically the entire dose, as measured by radioactivity, is excreted within a few days as presented in Appendix 5[1]. For the purpose of this evaluation, we assume that 100% of the administered dose is excreted within 7 days. We assume, that a 1,500 lb. dairy cow will be treated at a dose level of 5 mg fenbendazole/kg body weight resulting in a total dose of 3,400 mg (3.4 g) per animal given three times each year. This is the maximum introduction scenario based on labeled recommendations.

A 1,500 lb. dairy cows voids as manure 8% of her body weight each day (Principles of Dairy Science, G. H. Schmidt, L. D. Van Vleck, M. F. Hutjens, page 430, (1988)). This equals 120 lbs. or 54.4 kg manure per day. Because the total fenbendazole dose is voided over seven days, each 380.8 kg (54.4 kg X 7 days) of waste will contain 3.4 g fenbendazole which will equal 8.9 ppm. Assume a maximum of 40 metric tons of cattle excreta is present on one acre of agricultural land.

Concentration in Water Run-Off from Dairy Farm

During the year there will be 2 inches of rainfall over an acre of land. Two inches of rainfall on an acre of land weighs approximately 205,500 kilograms. Assume 10 animals per acre per year. Therefore, the amount of fenbendazole on one acre would equal:

10 dairy cows x 3.4 g/cow x 3 treatments/year = 102 g fenbendazole per acre per year

Fenbendazole is not soluble in water. If we assume that it is possible to have all of the residue in the run-off, the maximum concentration of fenbendazole in the run-off assuming no degradation equals:

$$\frac{\text{102 grams}}{\text{205,500 kg of water}} = .496 \text{ mg/kg (496 ppb) FBZ in runoff}$$

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 and absorbs tightly to soil particles. Therefore, fenbendazole is not expected to migrate from application sites into runoff 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).

Concentration in Soil with Waste from Treated Dairy Cattle

The following assumptions can be made:

- o No degradation in the manure before applying to the soil.
- o Manure is added to the soil at the rate of 40.0 metric tons per acre. Amount of fenbendazole in 40 metric tons equals 0.356 kg.
  (3.4 g fenbendazole/380.8 kg manure per week) X 40,000 kg per acre = 0.356 kg fenbendazole in 40 metric tons manure or 8.9 mg/kg (ppm) manure.
- o The manure will be incorporated into the top 6" of soil (weight of the top 6" of soil in one acre equals 909,000 kg).

The amount of fenbendazole in the top six (6) inches of soil would equal:

$$\text{Drug conc. in soil (mg/kg)} = \text{Drug conc. in manure (mg/kg)} \times \frac{\text{Kg manure applied to soil}}{\text{acre of soil}} \times \frac{\text{acre of soil}}{\text{kgs in top 6" of soil}}$$

$$\text{Drug conc. in soil} = 8.9 \text{ mg/kg} \times \frac{40{,}000 \text{ kg manure}}{1 \text{ acre}} \times \frac{\text{acre}}{9.09 \times 10^5 \text{ kg}} = 0.39 \text{ mg/kg (390 ppb) FBZ in soil}$$

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

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 were stored at 25°C in the dark at pH's of 5, 7 and 9. 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 indicated 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 [14 C] fenbendazole consisted of an extraction method where 4-5 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 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 (T½, days) of fenbendazole at pH 5, 7 and 9 are presented below.

pH	T½ (days)
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 Appendix 6.

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 Runoff Studies with Feces from Animals Treated with Fenbendazole

Studies have shown that the same metabolites are found in the feces of swine and cattle 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.

		Toxic Dose Greater Than
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

An orally administered single dose of fenbendazole is excreted as intact parent compound and several metabolites:

TABLE

	Feces	Urine
Parent Compound	48%	0.5%
SO-Metabolite	8%	-
2-amino-5-Metabolite	-	3%
p-OH-Metabolite	-	6.5%
Not identified	3 metabolites = 17%	2 metabolites = 3%
Total	73%	13%

This is a result of studies in which radiolabeled fenbendazole was given to cattle at a dose 5 mg fenbendazole/kg body weight as presented in Appendix 7[2].

A finite tolerance of 10 ppm in cattle liver was established based on extensive safety studies. Residue levels in the liver fall below the tolerance level before the 7th day after treatment.

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 thetajotaomicron
Sphaerophorus varius
Sphaerophorus freundii
Peptococcus anaerobius and *variabilis*
Peptostreptococcus anaerobius and *variabilis*
Propionibacterium acnes as well as several clostridia strains including *Clostridium erfringens* 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 drug/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 LC_{50} 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 smaller 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 fenbendazole/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 fenbendazole/kg artificial soil was 0, 25, 35, 53, 93, and 100%, respectively. Therefore, earthworm survival was used to establish the LC_{50}, LOEC and NOEC.

The LC_{50} 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 animals would be significantly lower (390 ppb) than the NOEC of 56,000 ppb.

A summary is presented in Appendix 8.

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 LC_{50} (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. LC_{50} 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 ^{14}C fenbendazole with bluegill during 21 days exposure and 7 days depuration under flowthrough conditions. Measured concentrations of ^{14}C fenbendazole in water were prepared at .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 ^{14}C 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, ^{14}C 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 ^{14}C fenbendazole was observed:

LC_{50} in micrograms/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 ^{14}C fenbendazole indicate that the concentration of ^{14}C residues in muscle and carcass were similar with bioconcentration factors of 43X and 92X, respectively. The greatest uptake of ^{14}C residues occurred in the viscera which had a bioconcentration factor of 6600X. The whole body bioconcentration factor for bluegill exposed to 0.0074 micrograms/mL fenbendazole for 21 days was 580X. After 7 days of depuration, 99% of the ^{14}C residues concentrated in the viscera had been eliminated. The average concentration of ^{14}C 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 halflife for ^{14}C fenbendazole in bluegill tissues was >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. 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/mL fenbendazole respectively. The highest mortality of bluegill exposed to 0.040 and 0.080 micrograms/mL fenbendazole 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/ml (95% confidence interval)

Day	4	7	14	21
	0.080[a]	0.0801[a]	0.033[b] (0.028-0.040)	0.028[b] (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:

a. Soluble fenbendazole.
b. Fine particulate - i.e. less than 0.45 micron
c. Course particulate - i.e. greater than 0.45 micron.

However, even the course 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) and 0.0033 mg/L (66%), respectively. In the ^{14}C fenbendazole study, this level could not be measured by the radio carbon ^{14}C assay.

In summary, fenbendazole was tested for toxicity to water flea, bluegill, and rainbow trout. The 48 hour LC_{50} 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 to each appropriately labeled petri dishes containing treated or control filter paper and 15 ml ASTM Type 2 water.

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:

	Germination		Root Elongation	
Species	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 Appendix 9.

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 (controll) 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 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 Appendix 10.

Studies in Plants

Another study was conducted to determine if fenbendazole is accumulated in plants. 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 were continuously exposed to a nominal concentration of .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.

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 halflife 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 cattle 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 LD_{50} 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 ± 2° 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 LD_{50} was empirically estimated to be greater than 770 mg/kg. The No-Observed-Effect Level was determined to be 770 mg/kg. The concentration of fenbendazole in waste manure from treated animals would be significantly lower (8.9 ppm) than the NOEC of 770 ppm.

A summary is presented in Appendix 11.

Environmental Hazard Assessment

Aquatic Environment

Under "worst case" conditions (assuming that all fenbendazole administered to dairy cattle is excreted via their manure, is extracted from the manure by two inch rainfall, and enters into water run-off), the estimated water run-off concentration of fenbendazole is 496 ppb. This would be the highest concentration of fenbendazole in any aquatic environment since it assumes three treatment periods per year which are not consecutive, does not account for

dilution as it enters bodies of water such as stream, 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 >> LC_{50} (48 hr.) = 12 ppb
- Trout Toxicity >> LC_{50} (96 hr.) = Limit of H_2O solubility (40 ppb)
- Bluegill Toxicity >> LC_{50} (21 d. continuous exposure) > 19 ppb

Terrestrial Environment

Under "worst case" conditions (assuming that all fenbendazole administered to dairy cattle is excreted via their manure, accumulates over a year and is mixed into the top six inches of soil at the rate of 40 metric tons per acre of land) the total initial concentration of fenbendazole is calculated to be 390 ppb. The comparison of the calculated environmental concentrations of fenbedazole 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 = CEC/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 100 and 2500 fold, the introduction of fenbendazole is not expected to impact the terrestrial environment.

	NOEC (ppb)	CEC (ppb)	Q
Microorganisms	100,000	390	0.004
Earthworm	56,000	390	0.007
Seed Germination	970,000	390	0.0004
Seedling Growth[1]	36,000	390	0.011
Dung Beetle	770,000	390	0.0005

[1] Based on most sensitive species - tomato.

Summary

Hoechst-Roussel Agri-Vet Company 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 use of fenbendazole in dairy of breeding age and are included in this Environmental Assessment.

9. USE OF RESOURCES AND ENERGY:

Fenbendazole bulk drug, acquired from Hoechst ERG, Frankfurt, Germany, is formulated into an aqueous suspension 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 Section A of Appendix 3.

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 of 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 irretrievable 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.

The only alternative to approval of the New Animal Drug Application is non-approval. This would mean that the dairy cattle 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 dairy cattle.

Objections raised by other agencies, organizations, or individuals: Hoechst-Roussel Agri-Vet Company knows of no objections raised regarding the proposed action.

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

12. LIST OF PREPARERS:

Lawrence E. Deetz, Ph.D.
Research Nutritionist
Product Development & Registration
Hoechst-Roussel Agri-Vet Company

Springborn Laboratories, Inc.
Environmental Sciences Division
790 Main Street
Wareham, Massachusetts 02571-1075

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 5-15-95

Lawrence E. Deetz, Ph.D.
Research Nutritionist

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 five studies are included in the supplemental application to NADA 128-620 approving use of fenbendazole in dairy cattle of breeding age. Results of those five studies are included in this Environmental Assessment. The following references are attached as part of the Environmental Assessment.

1. Fenbendazole Suspension 10% NADA 128-620 submitted June 4, 1981, Volume IX-B of IX, pages 332-358.

2. Fenbendazole Suspension 10% NADA 128-620 submitted June 4, 1981, Volume VIIII-A of IX, pages 782-799.

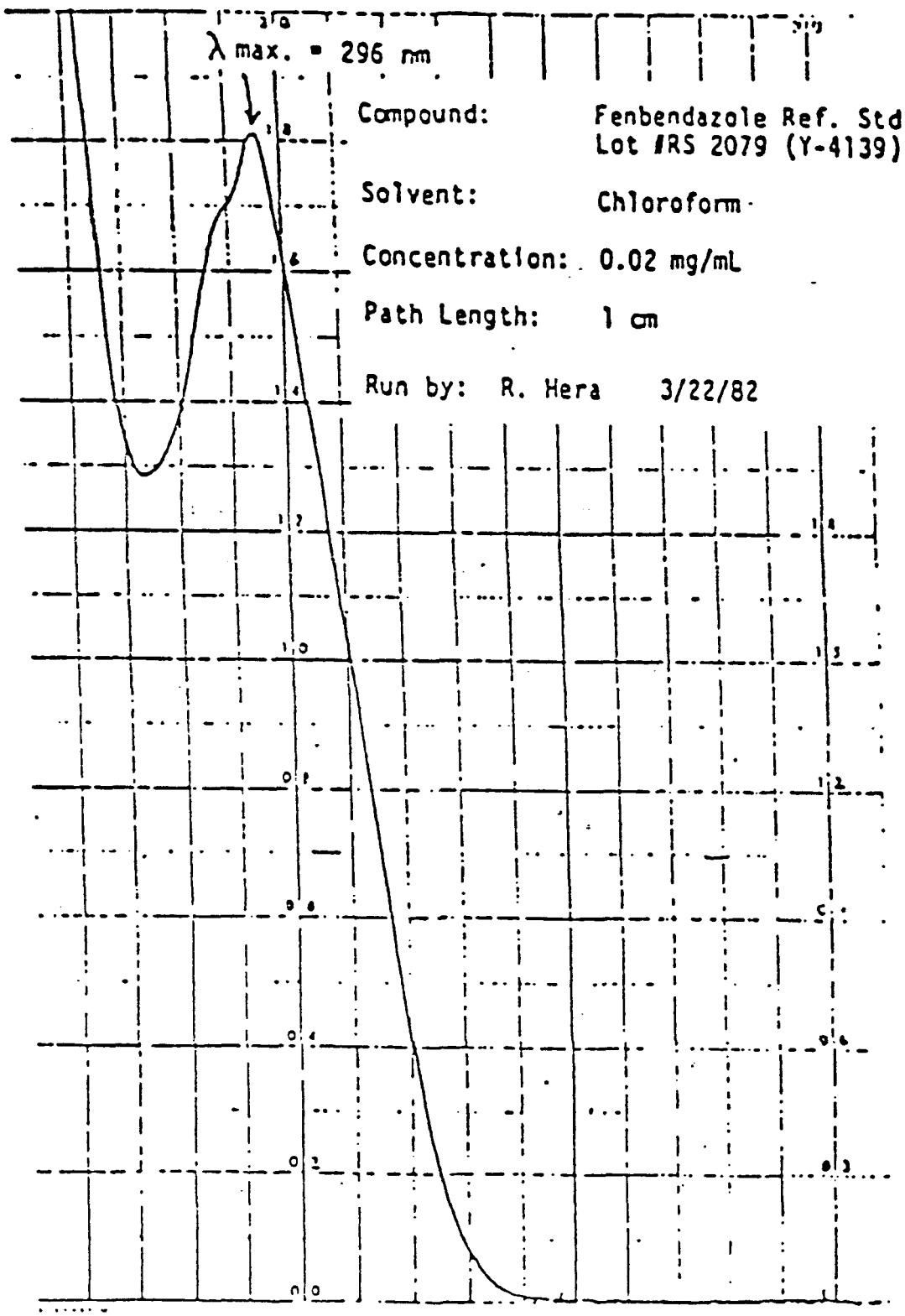
3. Pesticide Registration Rejection Rate Analysis Ecological Effects, EPA 738-R-94-035, December 1994.

15. APPENDICES:

Attached

APPENDIX 1

U.V. Absorption Spectrum: Representative spectrum with maximum absorptivity at 296 nm attached.



APPENDIX 2

Hoechst

Hoechst AG · Postfach 80 03 20 · D-6230 Frankfurt am Main 80

Hoechst Aktiengesellschaft
Pharma-[redacted]
Qualitätssicherung/GMP, D 610

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Dresdner Bank AG, Frankfurt am Main 80
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Commerzbank AG, Frankfurt am Main 80
(BLZ 500 400 00) Kto. Nr. 2570729
Deutsche Bank AG, Frankfurt am Main 1
(BLZ 500 700 10) Kto. Nr. 926006
Hessische Landesbank - Girozentrale -
Frankfurt am Main 1
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Postgiroamt Frankfurt am Main 1
(BLZ 500 100 60) Kto. Nr. 1442-605

TO WHOM IT MAY CONCERN

Ihre Zeichen	Ihre Nachricht vom	Unsere Zeichen	Telefon Durchwahl	Frankfurt am Main
		Dr. Sch/CT	(0 69) 305- 6831	Aug. 17, 1994

Production of Fenbendazole Drug Substance

HOECHST AKTIENGESELLSCHAFT as the producer of Fenbendazole drug substance herewith declares that the estimated increase of production amounts of Fenbendazole is in full compliance with environmental and occupation safety regulations of Germany.

Yours faithfully
HOECHST AKTIENGESELLSCHAFT

ppa. Lehnert ppa. Schwalbe-Fehl

(ppa. Dr. Lehnert) (ppa. Dr. Schwalbe-Fehl)

APPENDIX 3

FENBENDAZOLE SYNTHESIS - ENVIRONMENTAL COMPLIANCE

The purpose of this attachment is to provide a statement that Hoechst AG is manufacturing the bulk drug compound in compliance with the Environmental Regulations of Germany.

Included are:

Section A - English translation of
- o Environmental statement
- o Listing of various German laws/regulations applicable to this submission.

Section B - Signed and Sealed Certification in English and German from the Government of Darmstadt for manufacture of Fenbendazole by Hoechst AG

Section C - Material (DIN) Safety Data Sheet (MSDS) - Bulk Product

MSDS - Safe-Guard® (Fenbendazole) 20% Premix Medicated Dewormer

MSDS - Safe-Guard® (Fenbendazole) 0.5% Cattle Top Dress Pellet Medicated Dewormer

MSDS - Safe-Guard® (Fenbendazole) Free Choice Mineral Medicated Dewormer

SECTION A

Statement from Hoechst AG that Production of Fenbendazole
is in Compliance
with the Environmental Regulations of Germany
[Regulations Included]

May 25, 1993

Hoechst

Hoechst AG · Postfach 80 03 20 · D-6230 Frankfurt am Main 80

Hoechst Aktiengesellschaft
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(BLZ 500 400 00) Kto. Nr. 257 07 29
Deutsche Bank AG, Frankfurt am Main 1
(BLZ 500 700 10) Kto. Nr. 926 006
Hessische Landesbank - Girozentrale -
Frankfurt am Main 1
(BLZ 500 500 00) Kto. Nr. 24 100 000
Landeszentralbank in Hessen, Frankfurt am Main 1
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TO WHOM IT MAY CONCERN

Ihre Zeichen	Ihre Nachricht vom	Unsere Zeichen	Telefon Durchwahl	Frankfurt am Main
		Dr. Bdt./CT	(069) 305- 6831	May 25, 1993

Environmental Assessment

HOECHST AKTIENGESELLSCHAFT, as the producer of drug substances and finished drug products at its factory:

HOECHST AKTIENGESELLSCHAFT
Hoechst Works
Brüningstrasse 50
Postfach 80 03 20
D-6230 Frankfurt/M.-Höchst 80
Federal Republic of Germany

herewith certifies that the above mentioned plant is run in compliance with the existing environmental control laws and regulations of the Federal Republic of Germany.
Environmental protection in the Federal Republic of Germany is subject to a number of laws and regulations which are strictly enforced.
The most important ones are listed below:

- Immissions (Air etc.):

"Gesetz zum Schutz vor schädlichen Umwelteinwirkungen durch Luftverunreinigungen, Geräusche, Erschütterungen und ähnliche Vorgänge ("Bundesimmissionsschutzgesetz"),
(Federal Law for Protection of the Environment against the Adverse Influences Caused by Contamination of the Air, by Noise, Vibration, and Similar Events).
March 15, 1974,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 721,
corrected 1193,
amended May 14, 1990/Federal Law Gazette ("Bundesgesetzblatt") I, 880.

- Water protection:

"Gesetz zum Schutze des Wasserhaushaltes"
("Wasserhaushaltsgesetz"),
(Federal Law for Protection of Water Resources).
October 16, 1976,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 3017,
amended March 28, 1980/Federal Law Gazette ("Bundesgesetzblatt") I, 373.

- Solid Waste:

"Gesetz zur Vermeidung und Entsorgung von Abfällen" ("Abfallgesetz"), (Federal Law for Avoidance and Disposal of Waste).
August 27, 1986,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 1718.

- Technical Directions for Handling of Waste

"Technische Anleitung zur Lagerung, chemisch-physikalischen und biologischen Behandlung und Verbrennung von besonders überwachungsbedürftigen Abfällen"
(Technical Directions for Storage, Treatment and Burning of Waste).
April 10, 1990,
published in Joint Ministerial Gazette ("Gemeinsames Ministerialblatt") no. 11, 170.

- Technical Directions for Maintaining Clean Air:

"Technische Anleitung zur Reinhaltung der Luft" ("TA Luft"),
(Technical Directions for Maintaining Clean Air).
published in Joint Ministerial Gazette ("Gemeinsames Ministerialblatt") 95; February 27, 1986,
amended in Joint Ministerial Gazette ("Gemeinsames Ministerialblatt"), 202; April 4, 1986.

- Technical Directions for Noise Protection:

"Technische Anleitung zum Schutz gegen Lärm" ("TA Lärm"),
(Technical Directions for Protection Against Noise).
July 16, 1968,
published in Enclosure to Federal Register ("Beilage zum Bundesanzeiger") no. 137,
July 26, 1968.

- Chemicals:

"Gesetz zum Schutz vor gefährlichen Stoffen"
("Chemikaliengesetz"),
(Federal Law for Protection Against Dangerous Chemicals).
March 14, 1990,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 521.

Hoechst

- Regulations for Dangerous Goods:

"Gefahrstoffverordnung",
(Regulations for Dangerous Goods).
April 23, 1990,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 790.

- Regulations for Pressurized Systems

"Druckbehälterverordnung",
(Regulations for pressurized systems, e.g. pressurized containers etc.).
April 21, 1989,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 830.

- Regulations for Notifications of Immissions:

"Zwölfte Verordnung zur Durchführung des Bundesimmissionsschutzgesetzes" ("Störfallverordnung"),
(12th Regulation for the Implementation of the Federal Law for Protection of the Environment Against the Adverse Influences Caused by Contamination of the Air, by Noise, Vibration, and Similar Events).
May 19, 1988,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 626.

- Regulations for Storage of Inflammable Liquids:

"Verordnung über Anlagen zur Lagerung, Abfüllung und Beförderung brennbarer Flüssigkeiten zu Lande",
(Regulations for Facilities for Storage, Filling, and Transportation of Inflammable Liquids on Land).
February 27, 1980,

published in Federal Law Gazette ("Bundesgesetzblatt") I, 229, amended May 3, 1982 in Federal Law Gazette ("Bundesgesetzblatt") I, 569.

- Regulations for Transportation of Dangerous Goods (road, rail, sea, river, air):

  -- For Transportation on the Road:
  "Gefahrgutverordnung Straße",
  (Regulations for Transportation of Dangerous Goods on the Road).
  July 22, 1985,
  published in Federal Law Gazette ("Bundesgesetzblatt") I, 1550,
  amended December 21, 1987,
  published in Federal Law Gazette ("Bundesgesetzblatt") I, 2858.

  -- For Transportation by Rail:
  "Gefahrgutverordnung Eisenbahn",
  (Regulations for Transportation of Dangerous Goods by Rail).
  July 22, 1985,
  published in Federal Law Gazette ("Bundesgesetzblatt") I, 1560,
  amended December 21, 1987,
  published in Federal Law Gazette ("Bundesgesetzblatt") I, 2862.

  -- For Transportation by Sea:
  "Gefahrgutverordnung See",
  (Regulations for Transportation of Dangerous Goods by Sea).
  July 5, 1978,
  published in Federal Law Gazette ("Bundesgesetzblatt") I, 1917,
  amended December 21, 1987,
  published in Federal Law Gazette ("Bundesgesetzblatt") I, 2863.

Hoechst

-- For Transportation on Waterways within Germany:
"Gefahrgutverordnung Binnenschiffahrt",
(Regulations for Transportation of Dangerous Goods on Waterways within the Federal Republic of Germany).
March 24, 1983,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 1977,
amended March 16, 1989,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 489.

-- Dangerous Products Regulations of the IATA (International Air Transport Association):
"IATA - DGR" (Dangerous Goods Regulations),
28th edition.

- Regulations for Drinking Water:

"Verordnung über Trinkwasser und über Wasser für Lebensmittelbetriebe",
(Regulations for Drinking Water and for Water to be Used in Food Industries).
May 22, 1986,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 760.

- Feedstuffs (Animal Nutrition):

"Futtermittelgesetz",
(Federal Law on Feedstuffs).
July 2, 1975,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 1745,
and:
"Futtermittelverordnung",
(Regulations on Feedstuffs).
April 8, 1981,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 352.

- Regulations for Work Places:

"Verordnung über Arbeitsstätten" ("Arbeitsstättenverordnung"), (Regulations for Work Places).
May 20, 1975,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 729.

- Drug Law:

"Gesetz über den Verkehr mit Arzneimitteln" ("Arzneimittelgesetz"), (Federal Law for Handling of Drugs).
August 24, 1976,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 2445, 2448,
last amendment April 11, 1990,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 717;
and:

"Betriebsverordnung für pharmazeutische Unternehmer",
(Operations Ordinance for Pharmaceutical Entrepreneurs).
March 8, 1985,
published in Federal Law Gazette ("Bundesgesetzblatt") I, 546,
(and amendments).

Yours faithfully
HOECHST AKTIENGESELLSCHAFT

(Dr. Schütte) (ppa. Dr. Bauerschmidt)

SECTION B

Certification from the Government of Darmstadt (Federated State of Hesse)
Specific for the Manufacture of Fenbendazole by Hoechst AG
at Frankfurt, Germany

Dated August 8, 1994

Regierungspräsidium
Darmstadt

Luisenplatz 2
D-64278 Darmstadt, den 08. August 1994

II 16 e - 18 1 C2/03 (8) - FA 49

Telephon: (06151) 12 62 42
12 53 13
Telefax: (06151) 12 57 89

1. Confirmation

In the Federal Republic of Germany the supreme Health Authority of each individual federal state is responsible for issuing and confirming documents, for signatures to confirm for the production and distribution of medicines, pharmaceutical raw materials, food stuffs and cosmetics.
For the

Hoechst Aktiengesellschaft
Brüngingstr. 50
D-65926 Frankfurt/Main

my office is the responsible authority. A second confirmation of a certificate issued or certified by my office by a superior federal authority is not necessary and will not be carried out for fundamental reasons.

Recipient of this document:

To whom it may concern.

For registration and all official purposes in

United Staates of America.

1. Bestätigung

Für die Ausstellung und Bestätigung von Urkunden und Unterschriften über die Herstellung und den Vertrieb von Arzneimitteln, pharmazeutischen Rohstoffen, Lebensmitteln und Kosmetika sind in der Bundesrepublik Deutschland die Bundesländer zuständig.

Für die Firma

Hoechst Aktiengesellschaft
Brüningstr. 50
D-65926 Frankfurt/Main

ist mein Haus die zuständige Behörde. Eine Überbeglaubigung eines von mir ausgestellten oder beglaubigten Zertifikates scheidet im übrigen aus grundsätzlichen Erwägungen aus.

Zu Registrierungs- und allen amtlichen Zwecken in:

Vereinigte Staaten von Amerika.

2. Statement of Manufacturing/Processing Sales Activities

The Hoechst AG is in the Federal Republic of Germany an acknowledged pharmaceutical and chemical factory. They have permission to produce pharmaceutical products (§ 13 Drug Law).

They are producing chemical and pharmaceutical raw materials for the manufacture of finished pharmaceutical products, cosmetics and food-additives.

They are marketing and selling these products at home and abroad.

3. Certificate

This is to certify that the Hoechst AG holds a manufacturing licence as a pharmaceutical manufacturer according to § 13. of the Drug Law from August 24 th in 1976 (BGBl. I, page 2445).

It is certified, that

a) the manufacturing plant, in which the product is produced is subject to inspections at suitable intervals,

- 2 -

2. Herstell-/Verkaufsbescheinigung Verkaufstätigkeit

Die Firma Hoechst AG ist in der Bundesrepublik Deutschland eine anerkannte pharmazeutische und chemische Fabrik. Sie hat die Erlaubnis zur Herstellung von Arzneimitteln (§ 13 Arzneimittelgesetz).

Sie stellt chemisch-pharmazeutsiche Rohmaterialien zur Fabrikation von Arzneimitteln und Kosmetika sowie Lebensmittelzusatzstoffe her.

Sie verkauft und vertreibt diese Produkte im Inland und im Ausland.

3. Bescheinigung

Hiermit wird der Firma Hoechst AG bestätigt, daß sie als pharmazeutischer Herstellerbetrieb im Besitz einer Herstellungserlaubnis gemäß § 13 des Gesetzes über den Verkehr mit Arzneimitteln vom 24.08.1976 (BGBl. I, S. 2445) ist.

Es wird bestätigt, daß

a) der Herstellerbetrieb, in dem das Produkt hergestellt wird, in angemessenen Abständen überwacht wird,

b) the manufacturer conforms to requirements for good practices in manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

4. Product list

This certificate refers to the following product:

Fenbendazole.

- 3 -

b) der Hersteller hinsichtlich der Produkte, die im Herkunftsland verkauft und vertrieben werden oder für die Ausfuhr vorgesehen sind, den von der Weltgesundheitsorganisation empfohlenen Grundregeln für die Herstellung von Arzneimitteln und die Sicherung ihrer Qualität entspricht.

4. Aufzählung der Produkte

Diese Bescheinigung gilt für folgendes Produkt:

Fenbendazol.

Im Auftrage

REGIERUNGSPRÄSIDIUM DARMSTADT

(Völler)

SECTION C

Material (DIN) Safety Data Sheet (MSDS)

Summary of Physicochemical Properties of Fenbendazole

Procedures for Processing Waste
(incineration, landfill, microbial/chemical treatment)

Environmental Safety Data
(toxicological, ecological)

Dated October 28, 1991

MSDS - Safe-Guard® (Fenbendazole) 20% Premix Medicated Dewormer
Dated January 16, 1995

MSDS - Safe-Guard® (Fenbendazole) 0.5% Cattle Top Dress Pellet Medicated Dewormer
Dated October 12, 1994

MSDS - Safe-Guard® (Fenbendazole) Free Choice Mineral Medicated Dewormer
Dated October 12, 1994

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: FENBENDAZOLE
Product Code: 101870
MSDS Number : 00601
Version Date: 05/16/1995

Material Safety Data Sheet

Print date -- May 17th, 1995 2:05 p.m. PS PSA PSFHV -- 1.1 (1/6)

1. CHEMICAL PRODUCT and COMPANY IDENTIFICATION

Product Name: FENBENDAZOLE
Product Code: 101870
MSDS Number : 00601

SYNONYMS: FENBENDAZOLE
METHYL-5-PHENYLTHIO-2-BENZIMIDAZOLE-CARBAMATE

HOECHST-ROUSSEL AGRI-VET COMPANY
ROUTE 202-206
P.O. BOX 2500
SOMERVILLE, NJ 08876-1258
UNITED STATES

PRODUCT USE:
Fenbendazole is the active ingredient in Panacur(R) and Safeguard(R) products, which are animal dewormers.

2. COMPOSITION / INFORMATION on INGREDIENTS

COMPONENT	CAS NUMBER
FENBENDAZOLE	43210-67-9

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:
Fenbendazole is a solid which is non-reactive, relativley non-toxic, and insoluble in water.

POTENTIAL HEALTH EFFECTS
There are no known adverse health effects associated with this product.

DELAYED/LONG TERM EFFECTS

Product Name: FENBENDAZOLE
Product Code: 101870
MSDS Number : 00601
Version Date: 05/16/1995

Print date -- May 17th, 1995 2:05 p.m. PS PSA PSFHV -- 1.2 (2/6)

3. HAZARDS IDENTIFICATION (Continued)

CARCINOGENIC:

This product is not considered a carcinogen and is not listed by OSHA, IARC or NTP.

4. FIRST AID MEASURES

SKIN:

Wash with soap and water. If irritation develops, get medical attention.

EYES:

Flush with water for 15 minutes. If irritation develops, get medical attention.

INHALATION:

In cases of difficult breathing, remove to fresh air. If not breathing, give artificial respiration and get medical attention immediately.

INGESTION:

If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Contact medical personnel for observation or treatment as needed.

NOTE TO PHYSICIANS:

Fenbendazole is a broad spectrum anthelmintic approved for use in animals. It is non-toxic.

5. FIRE FIGHTING MEASURES

FLAMMABLE PROPERTIES

Spontaneous ignition point: 230°C.

EXTINGUISHING MEDIA:

Water, Water mist, alcohol foam, of dry chemical.

Product Name: FENBENDAZOLE
Product Code: 101870
MSDS Number : 00601
Version Date: 05/16/1995

Print date -- May 17th, 1995 2:05 p.m. PS PSA PSFHV - 1.3 (3/6)

5. FIRE FIGHTING MEASURES (Continued)

FIRE FIGHTING INSTRUCTIONS:

Wear full bunker gear, including SCBA, for fighting fires involving this material. Keep upwind.

6. ACCIDENTAL RELEASE MEASURES

PROCEDURES IN CASE OF SPILL OR LEAK:

Sweep and shovel up spilled material. Place in a secure container for disposal.

7. HANDLING and STORAGE

HANDLING:

Flow of material may generate static electricity. Do not pour contents into vessels containing flammable liquids or vapors.

STORAGE:

Store at room temperature. Keep material dry. Protect containers from damage.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

PROTECTIVE EQUIPMENT

EYES:

Prevent eye contact by wearing appropriate eye protection for handling tasks (safety glasses, goggles, or face shield) and by using good work practices.

INHALATION:

Avoid breathing dust. Wear dust respirator if local exhaust ventilation is not available.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: FENBENDAZOLE
Product Code: 101870
MSDS Number : 00601
Version Date: 05/16/1995

Print date -- May 17th, 1995 2:05 p.m. PS PSA PSFHV - 1.4 (4/6)

9. PHYSICAL and CHEMICAL PROPERTIES

Melting Point: 200 degrees C
Odor: Odorless
Physical Form: Solid
Solubility: Insoluble in water

10. STABILITY and REACTIVITY

CHEMICAL STABILITY:
Stable

HAZARDOUS POLYMERIZATION:
Will not occur.

11. TOXICOLOGICAL INFORMATION

Oral LD50 : rat greater than 10,000 mg/kg
Oral LD50 : mouse greater than 10,000 mg/kg
Skin irritation: negative
Eye irritation: negative

12. ECOLOGICAL INFORMATION

ECOTOXICITY:

Fish Toxicity (LC50): >500 mg/l (Zebrafish) 48 & 96 hrs.
Daphnia Toxicity (LC50): 12 micrograms/l 48 hrs.
Trout Toxicity (LC50): 40 micrograms/l 96 hrs.
Bluegill Sunfish Toxicity (LC50): >19 micrograms/l 21 days.
Earthworm Toxicity (LC50): 180 mg/kg 28 days
Dung Beetle Toxicity (LD50): >770 mg/kg 7 days

Note: Fenbendazole can be eliminated in water treatment plants.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: FENBENDAZOLE
Product Code: 101870
MSDS Number : 00601
Version Date: 05/16/1995

Print date -- May 17th, 1995 2:05 p.m. PS PSA PSFHV -- 1.5 (5/6)

13. DISPOSAL CONSIDERATIONS

Waste should be incinerated.

14. TRANSPORT INFORMATION

DOT proper shipping name :Not regulated by DOT

15. REGULATORY INFORMATION

STATE REGULATIONS

The following chemicals associated with the product are subject to the right-to-know regulations in these states:
No components regulated

U.S. FEDERAL REGULATIONS

SARA 313 : No components listed

16. OTHER INFORMATION

REVISION INDICATORS:

The following sections have been revised:

SECTION 12: ECOLOGICAL INFORMATION
ECOTOXICITY

DISCLAIMER:

These data are based on today's state of the art. They are intended to describe our products with regard to safety requirements and do not therefore have the connotation of guaranteeing certain properties.

The information contained herein is offered only as a guide to the handling of this specific material. Since such information does not relate to use of the material with any other material or in any process, any person using this information must determine for him self its suitability for any particular application. The buyer and user assumes all risk and liability of use, storage and/or handling of this product not in accordance with the

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

DISCLAIMER: (Continued)

terms of the product label.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 20% PREMIX MEDICATED DEWORMER
Product Code: 20405222
MSDS Number : 01008
Version Date: 01/16/1995

Material Safety Data Sheet

Print date – April 8th, 1995 2:57 a.m. 3820 PG1A X0H21001 – 3.1 (8/76)

1. CHEMICAL PRODUCT and COMPANY IDENTIFICATION

Product Name: SAFE-GUARD® (FENBENDAZOLE) 20% PREMIX MEDICATED DEWORMER
Product Code: 20405222
MSDS Number : 01008

SYNONYMS: FENBENDAZOLE
METHYL-5-PHENYLTHIO-2-BENZIMIDAZOLE-CARBAMATE

HOECHST-ROUSSEL AGRI-VET COMPANY
ROUTE 202-206
P.O. BOX 2500
SOMERVILLE, NJ 08876-1258
U.S.A.

PRODUCT USE:
This product is an animal dewormer (anthelmintic).

2. COMPOSITION / INFORMATION on INGREDIENTS

COMPONENT	CAS NUMBER
FENBENDAZOLE	43210-67-9
MINERAL OIL	8012-95-1
ROUGHAGE PRODUCTS	
CALCIUM CARBONATE	471-34-1

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:
Fenbendazole is non-reactive and relatively non-toxic.

POTENTIAL HEALTH EFFECTS
There are no known adverse health effects associated with this product.

DELAYED/LONG TERM EFFECTS

CARCINOGENIC:

This product is not considered a carcinogen and is not listed by OSHA, IARC or NTP.

4. FIRST AID MEASURES

SKIN:

Wash with soap and water. If irritation develops, get medical attention.

EYES:

Flush with water for 15 minutes. If irritation develops, get medical attention.

INHALATION:

In cases of difficult breathing, remove to fresh air. If not breathing, give artificial respiration and get medical attention immediately.

INGESTION:

If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Contact medical personnel for observation or treatment as needed.

NOTE TO PHYSICIANS:

Fenbendazole is a broad spectrum anthelmintic approved for use in animals. It is non-toxic.

5. FIRE FIGHTING MEASURES

EXTINGUISHING MEDIA:

Water, Water mist, alcohol foam, or dry chemical.

FIRE FIGHTING INSTRUCTIONS:

Wear full bunker gear, including SCBA, for fighting fires involving large quantities of this material. Keep upwind.

6. ACCIDENTAL RELEASE MEASURES

PROCEDURES IN CASE OF SPILL OR LEAK:

Clean up spilled material. Place in a secure container for disposal.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 20% PREMIX MEDICATED DEWORMER
Product Code: 20405222
MSDS Number : 01008
Version Date: 01/16/1995

Print date -- April 8th, 1995 2:57 a.m. 3820 PG1A X0H21001 -- 3.3 (10/76)

7. HANDLING and STORAGE

HANDLING:

Do not empty the contents of sacks into vessels containing a combustable mixture of gases. Static discharge may ignite vapors or gases. Equipment used in handling this product should be electrically grounded to prevent possible dust explosion.

STORAGE:

Store at room temperature. Keep material dry. Protect containers from damage.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

PROTECTIVE EQUIPMENT

For Bulk Use:

EYES:

Prevent eye contact by wearing appropriate eye protection for handling tasks (safety glasses, goggles, or face shield) and by using good work practices.

9. PHYSICAL and CHEMICAL PROPERTIES

Bulk Density: 25 lbs/cubic foot

10. STABILITY and REACTIVITY

CHEMICAL STABILITY:

Stable

HAZARDOUS POLYMERIZATION:

Will not occur.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 20% PREMIX MEDICATED DEWORMER
Product Code: 20405222
MSDS Number : 01008
Version Date: 01/16/1995

Print date – April 8th, 1995 2:57 a.m. 3820 PG1A X0H21001 – 3.4 (11/75)

11. TOXICOLOGICAL INFORMATION

Oral LD50 : rat greater than 10,000 mg/kg
Oral LD50 : mouse greater than 10,000 mg/kg
Skin irritation: negative
Eye irritation: negative

12. ECOLOGICAL INFORMATION

ECOTOXICITY:

LC 50: Greater than 500 mg/1 (48 and 96 hrs) (Zebrafish)

13. DISPOSAL CONSIDERATIONS

Waste should be incinerated or disposed of at an approved landfill.

14. TRANSPORT INFORMATION

DOT proper shipping name :Not regulated by DOT

15. REGULATORY INFORMATION

STATE REGULATIONS

The following chemicals associated with the product are subject to the right-to-know regulations in these states:
No components regulated

U.S. FEDERAL REGULATIONS

SARA 313 : No components listed

16. OTHER INFORMATION

DISCLAIMER:

The information contained herein is offered only as a guide to the handling of this specific material. Since such information does not relate to use of the material with any other material or in any process, any person using this information must determine for himself its suitability for any particular application. The buyer and

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 20% PREMIX MEDICATED DEWORMER
Product Code: 20405222
MSDS Number : 01008
Version Date: 01/16/1995

Print date – April 8th, 1995 2:57 a.m. 3820 PG1A X0H21001 – 3.5 (12/76)

DISCLAIMER: (Continued)

user assumes all risk and liability of use, storage and/or handling of this product not in accordance with the terms of the product label.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 0.5% CATTLE TOP DRESS PELLET MED ICATED DEWORMER
Product Code: 20303575
MSDS Number : 01011
Version Date: 10/12/1994

Material Safety Data Sheet

Print date -- November 29th, 1994 1:11 a.m. 3820 PG1A X0H21001 -- 13.1 (60/130)

1. CHEMICAL PRODUCT and COMPANY IDENTIFICATION

Product Name: SAFE-GUARD® (FENBENDAZOLE) 0.5% CATTLE TOP DRESS PELLET MEDICATED DEWORMER
Product Code: 20303575
MSDS Number : 01011

SYNONYMS: FENBENDAZOLE
METHYL-5-PHENYLTHIO-2-BENZIMIDAZOLE-CARBAMATE

HOECHST-ROUSSEL AGRI-VET COMPANY
ROUTE 202-206
P.O. BOX 2500
SOMERVILLE, NJ 08876-1258
UNITED STATES OF AMERICA

PRODUCT USE:
This product is a cattle dewormer (anthelmintic).

2. COMPOSITION / INFORMATION on INGREDIENTS

COMPONENT	CAS NUMBER
FENBENDAZOLE	43210-67-9
DEHYDRATED ALFALFA MEAL	
ROUGHAGE PRODUCTS	
MINERAL OIL	8012-95-1
CALCIUM CARBONATE	471-34-1

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:
Fenbendazole is non-reactive and relatively non-toxic.

POTENTIAL HEALTH EFFECTS
There are no known adverse health effects associated with this product.

DELAYED/LONG TERM EFFECTS

3. HAZARDS IDENTIFICATION (continued)

CARCINOGENIC:

This product is not considered a carcinogen and is not listed by OSHA, IARC or NTP.

4. FIRST AID MEASURES

SKIN:

Wash with soap and water. If irritation develops, get medical attention.

EYES:

Flush with water for 15 minutes. If irritation develops, get medical attention.

INHALATION:

In cases of difficult breathing, remove to fresh air. If not breathing, give artificial respiration and get medical attention immediately.

INGESTION:

If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Contact medical personnel for observation or treatment as needed.

NOTE TO PHYSICIANS:

Fenbendazole is a broad spectrum anthelmintic approved for use in animals. It is non-toxic.

5. FIRE FIGHTING MEASURES

EXTINGUISHING MEDIA:

Water, Water mist, alcohol foam, or dry chemical.

FIRE FIGHTING INSTRUCTIONS:

Wear full bunker gear, including SCBA, for fighting fires involving large quantities of this material. Keep upwind.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 0.5% CATTLE TOP DRESS PELLET MED ICATED DEWORMER
Product Code: 20303575
MSDS Number : 01011
Version Date: 10/12/1994

Print date – November 29th, 1994 1:11 a.m. 3820 PG1A X0H21001 – 13.3 (62/130)

6. ACCIDENTAL RELEASE MEASURES

PROCEDURES IN CASE OF SPILL OR LEAK:

Clean up spilled material. Place in a secure container for disposal.

7. HANDLING and STORAGE

HANDLING:

Do not empty the contents of sacks into vessels containing a combustable mixture of gases. Static discharge may ignite vapors or gases. Equipment used in handling this product should be electrically grounded to prevent possible dust explosion.

STORAGE:

Store at room temperature. Keep material dry. Protect containers from damage.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

PROTECTIVE EQUIPMENT

For Bulk Use:

EYES:

Prevent eye contact by wearing appropriate eye protection for handling tasks (safety glasses, goggles, or face shield) and by using good work practices.

9. PHYSICAL and CHEMICAL PROPERTIES

Bulk Density: 25 lbs/cubic foot

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 0.5% CATTLE TOP DRESS PELLET MED ICATED DEWORMER
Product Code: 20303575
MSDS Number : 01011
Version Date: 10/12/1994

Print date – November 29th, 1994 1:11 a.m. 3820 PG1A X0H21001 – 13.4 (63/130)

10. STABILITY and REACTIVITY

CHEMICAL STABILITY:
Stable

HAZARDOUS POLYMERIZATION:
Will not occur.

11. TOXICOLOGICAL INFORMATION

Oral LD50 : rat greater than 10,000 mg/kg
Oral LD50 : mouse greater than 10,000 mg/kg
Skin irritation: negative
Eye irritation: negative

12. ECOLOGICAL INFORMATION

ECOTOXICITY:
LC 50: Greater than 500 mg/l (48 and 96 hrs) (Zebrafish)

13. DISPOSAL CONSIDERATIONS

Waste should be incinerated or disposed of at an approved landfill.

14. TRANSPORT INFORMATION

DOT proper shipping name :Not regulated by DOT

15. REGULATORY INFORMATION

STATE REGULATIONS
The following chemicals associated with the product are subject to the right-to-know regulations in these states:
No components regulated

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) 0.5% CATTLE TOP DRESS PELLET MED ICATED DEWORMER
Product Code: 20303575
MSDS Number : 01011
Version Date: 10/12/1994

Print date – November 29th, 1994 1:11 a.m. 3820 PG1A X0H21001 – 13.5 (64/130)

15. REGULATORY INFORMATION (continued)

U.S. FEDERAL REGULATIONS

SARA 313 : No components listed

16. OTHER INFORMATION

DISCLAIMER:

The information contained herein is offered only as a guide to the handling of this specific material. Since such information does not relate to use of the material with any other material or in any process, any person using this information must determine for himself its suitability for any particular application. The buyer and user assumes all risk and liability of use, storage and/or handling of this product not in accordance with the terms of the product label.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

Product Name: SAFE-GUARD® (FENBENDAZOLE) FREE CHOICE MINERAL MEDICATED CATTLE DEWORMER
Product Code: 20303573
MSDS Number : 01021
Version Date: 10/12/1994

Material Safety Data Sheet

Print date – November 29th, 1994 1:11 a.m. 3820 PG1A X0H21001 – 14.1 (66/130)

1. CHEMICAL PRODUCT and COMPANY IDENTIFICATION

Product Name: SAFE-GUARD® (FENBENDAZOLE) FREE CHOICE MINERAL MEDICATED CATTLE DEWORMER
Product Code: 20303573
MSDS Number : 01021

SYNONYMS: FENBENDAZOLE
METHYL-5-PHENYLTHIO-2-BENZIMIDAZOLE-CARBAMATE

HOECHST-ROUSSEL AGRI-VET COMPANY
ROUTE 202-206
P.O. BOX 2500
SOMERVILLE, NJ 08876-1258
UNITED STATES OF AMERICA

PRODUCT USE:
This product is a cattle dewormer (anthelmintic).

2. COMPOSITION / INFORMATION on INGREDIENTS

COMPONENT	CAS NUMBER
FENBENDAZOLE	43210-67-9
MOLASSES	68476-78-8
SODIUM CHLORIDE (salt)	7647-14-5
ZINC SULFATE	7446-19-7
RICE HULLS	
CALCIUM CARBONATE	471-34-1
DICALCIUM PHOSPHATE	7789-77-7
POTASSIUM IODIDE	7681-11-0
MAGNESIUM OXIDE	1309-48-4
MINERAL OIL	8012-95-1
SODIUM SELENITE	

Product Name: SAFE-GUARD® (FENBENDAZOLE) FREE CHOICE MINERAL MEDICATED CATTLE DEWORMER
Product Code: 20303573
MSDS Number : 01021
Version Date: 10/12/1994

Print date – November 29th, 1994 1:11 a.m. 3820 PG1A X0H21001 – 14.2 (57/130)

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:

Fenbendazole is non-reactive and relatively non-toxic.

POTENTIAL HEALTH EFFECTS

There are no known adverse health effects associated with this product.

DELAYED/LONG TERM EFFECTS

CARCINOGENIC:

This product is not considered a carcinogen and is not listed by OSHA, IARC or NTP.

4. FIRST AID MEASURES

SKIN:

Wash with soap and water. If irritation develops, get medical attention.

EYES:

Flush with water for 15 minutes. If irritation develops, get medical attention.

INHALATION:

In cases of difficult breathing, remove to fresh air. If not breathing, give artificial respiration and get medical attention immediately.

INGESTION:

If conscious, give water to drink and induce vomiting. Never give anything by mouth to an unconscious person. Contact medical personnel for observation or treatment as needed.

NOTE TO PHYSICIANS:

Fenbendazole is a broad spectrum anthelmintic approved for use in animals. It is non-toxic.

5. FIRE FIGHTING MEASURES

EXTINGUISHING MEDIA:
Water, Water mist, alcohol foam, or dry chemical.

FIRE FIGHTING INSTRUCTIONS:
Wear full bunker gear, including SCBA, for fighting fires involving large quantities of this material. Keep upwind.

6. ACCIDENTAL RELEASE MEASURES

PROCEDURES IN CASE OF SPILL OR LEAK:
Clean up spilled material. Place in a secure container for disposal.

7. HANDLING and STORAGE

HANDLING:
Do not empty the contents of sacks into vessels containing a combustable mixture of gases. Static discharge may ignite vapors or gases. Equipment used in handling this product should be electrically grounded to prevent possible dust explosion.

STORAGE:
Store at room temperature. Keep material dry. Protect containers from damage.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

PROTECTIVE EQUIPMENT
For Bulk Use:

EYES:
Prevent eye contact by wearing appropriate eye protection for handling tasks (safety glasses, goggles, or face shield) and by using good work practices.

Hoechst-Roussel Agri-Vet Company

Hoechst Roussel

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9. PHYSICAL and CHEMICAL PROPERTIES

Bulk Density: 25 lbs/cubic foot

10. STABILITY and REACTIVITY

CHEMICAL STABILITY:
Stable

HAZARDOUS POLYMERIZATION:
Will not occur.

11. TOXICOLOGICAL INFORMATION

Oral LD50 : rat greater than 10,000 mg/kg
Oral LD50 : mouse greater than 10,000 mg/kg
Skin irritation: negative
Eye irritation: negative

12. ECOLOGICAL INFORMATION

ECOTOXICITY:
LC 50: Greater than 500 mg/l (48 and 96 hrs) (Zebrafish)

13. DISPOSAL CONSIDERATIONS

Waste should be incinerated or disposed of at an approved landfill.

14. TRANSPORT INFORMATION

DOT proper shipping name :Not regulated by DOT

Hoechst-Roussel Agri-Vet Company

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15. REGULATORY INFORMATION

STATE REGULATIONS

The following chemicals associated with the product are subject to the right-to-know regulations in these states:
No components regulated

U.S. FEDERAL REGULATIONS

SARA 313 : No components listed

16. OTHER INFORMATION

DISCLAIMER:

The information contained herein is offered only as a guide to the handling of this specific material. Since such information does not relate to use of the material with any other material or in any process, any person using this information must determine for himself its suitability for any particular application. The buyer and user assumes all risk and liability of use, storage and/or handling of this product not in accordance with the terms of the product label.

APPENDIX 4

ENVIRONMENTAL ASSESSMENT

4%, 8%, AND 20% SAFEGUARD TYPE A MEDICATED PREMIX

1. Date: September 9, 1993

2. Company Name: Feed Specialties Company, Inc.

3. Company Address: 1977 NE 58th Avenue
Des Moines IA 50313

4. *DESCRIPTION OF THE PROPOSED ACTION*

The Feed Specialties Company, Inc., facility at Des Moines, Iowa, is located at 41 degrees, 40 minutes, 00 seconds latitude and 93 degrees, 35 minutes, 00 seconds longitude. The plant operations physically consist of a 12,000-ft^2 raw-materials area, 3,000-ft^2 manufacturing area, and a 22,000-ft^2 finished-product area.

The types of environments present at and adjacent to the location where the production will occur:

A. Premix manufacturing areas are enclosed rooms.

5. *IDENTIFICATION OF THE CHEMICALS THAT ARE THE SUBJECT OF THE PROPOSAL*

A. Fenbendazole:
((3-(Phenylthic) - 1H-benzimidazol-2-yl) carbonic acid methyl ester)

CAS No.:	043210-67-9
Molecular Weight:	299.35
Structural Formula:	$C_{15}\ H_{13}\ N_3\ O_2\ S$
Physical Description:	Light Brownish-Gray Odorless, tasteless, water-insoluble crystalline powder

B. Calcium Carbonate:

CAS No.:	000471-34-1
Molecular Weight:	100.09
Structural Formula:	$CaCO_3$
Physical Description:	Odorless, tasteless, water-insoluble powder

C. Mineral Oil:
CAS No.: 000012-95-1
Physical Description: Clear, odorless, tasteless, water white liquid

D. Rice Hulls:
Physical Description: Tan to light brown meal.

6. *INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT FOR THE FEED SPECIALTIES COMPANY, INC., PRODUCTION OF TYPE "A" MEDICATED ARTICLES*

A. List of substances expected to be emitted.

(1) Fenbendazole
(2) Calcium Carbonate
(3) Mineral Oil
(4) Rice Hulls

B. State controls exercised to modify emissions.

Air emissions generated in receiving are controlled by four Rolfes 72W16 filters and one Rolfes 124RA6 filter, with a 99.9+% efficiency. Air emissions generated by handling activities are controlled by one MAC M-Series filter, with a 99.9+% efficiency.

Sanitary wastewaters and warehouse clean-up waters flow to an on-site 1,000-gallon, single-vessel septic tank and with a leach field. Storm-water drainage from under the parking lot and sheet run-off from the facility's property are discharged into the facility's 13,967-ft^2 retention pond.

Solid-waste material is deposited in a permitted sanitary land-fill.

C. The applicable emission requirements and permits obtained at the Federal, State, and Local Levels.

The Iowa Department of Natural Resources has delegated the air pollution control program in Polk County to the Polk County Physical Planning Department Air Pollution Control Division. Feed

Specialties Company, Inc., Air Pollution Control Operating Permit number from Polk County is 00247.

All solid discharges are regulated by EPA 40 CFR 260-272 and Iowa's Solid Waste Rules. The disposal facility Feed Specialties Company, Inc., utilizes is Metro East Sanitary Land-fill with Permit No. 77-SDP-1-72P.

D. **A statement certifying compliance with all applicable emission standards.**

During manufacturing, Feed Specialties Company, Inc., will comply with all emission requirements set by federal, state, and local Agencies.

E. **Discuss the effect the approval of this NADA will have upon compliance with current emissions requirements at Feed Specialties Company, Inc..**

This NADA will not adversely affect our ability to comply with emission requirements. Currently we meet all emission standards on non-generic animal drugs formulated with same/similar active drugs and inactive ingredients.

7. ***REFERENCES***

A. "TOXIC SUBSTANCES CONTROL ACT CHEMICAL SUBSTANCE INVENTORY" TSCA INVENTORY: 1985 edition

B. "THE MERCK INDEX" Tenth Edition, pub. MERCK & CO., INC., Rahway NJ 1983

PREPARED BY Robert L Henricks Date: 9/9/93
Robert L. Henricks, Director of Environmental Compliance

PREPARED BY Randy Sample Date: 9/9/93
Randy Sample, Director of Regulatory Compliance

APPROVED BY Douglas O. Haight Date: 9-13-93
Douglas Haight, Plant Manager