14. ENVIRONMENTAL ASSESSMENT REPORT ON HALOFUGINONE HYDROBROMIDE FOR TURKEYS

The applicant is required to submit an environmental assessment analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the new animal drug pursuant to #25.1 of this chapter. Feeds containing halofuginone hydrobromide are intended to be fed to growing turkeys continuously from one day of age until no more than six days prior to slaughter.

This section of the New Animal Drug Application follows the format as prescribed in 21 CFR 25.1(j).

A. Date: June, 1986

B. Name of applicant:

Sponsor:

Roussel-UCLAF
Division Agro-Veterinaire
163 Avenue Gambetta
75020 Paris, France

Agent:

Hoechst-Roussel Agri-Vet Company
Rt. 202-206 North
Somerville, New Jersey 08876

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

C. Address:

Hoechst Roussel Agri-Vet Company
Rt. 202-206 North
Somerville, New Jersey 08876

D. Environmental Information

1. Describe the proposed action.

a. Purpose of the action. This new animal drug application is submitted for action by the Food and Drug Administration to permit the use of halofuginone hydrobromide in the feed of growing turkeys for the prevention of coccidiosis caused by Eimeria adenoeides, E. meleagrimitis and E. gallopavonis.

The active ingredient will be prepared in France for incorporation into a premix at the concentration of 0.6% in the United States. The premix is intended to be used for the manufacture of finished feeds for growing turkeys. The concentration of halofuginone hydrobromide in the finished feed (complete diet) will be 1.5 to 3 parts per million (ppm). The trade name of the premix is Stenorol^{R}.

The use of the premix, Stenorol^{R}, in feeds will be limited to feed manufacturers who obtain approved medicated feed applications (FD 1900) for receipt and use of the new drug in feeds which they manufacture for growing turkeys.

The use of the new animal drug will be limited to use in feeds for growing turkeys under the approval of this new drug application. The feeds will not contain any other drug substance. Feeds containing halofuginone hydrobromide may be fed continuously to growing turkeys from one day of age until six days prior to slaughter.

The coccidiostat will be used as a partial replacement for existing agents intended for the same purpose. It is the industry practice to incorporate a coccidiostatic agent in feeds fed to growing turkeys, for the first 8 to 12 weeks of life.

b. The environment to be affected if the action is taken.

The active agent, halofuginone hydrobromide, will be manufactured in the Roussel Uclaf factory, Neuville-sur-Saone, France. The premix will be manufactured in one or more of five locations including Lavergne Supplement Company, Nashville, Tennessee; Southern Micro-Blenders, Chattanooga, Tennessee; VMS, Inc., Montgomery, Alabama; Mac-Page Incorporated, Dunn, North Carolina; and/or Merck and Co, St. Louis, Missouri. The premix will be shipped to holders of approved medicated feed applications, for incorporation into growing turkey feed. The feeds will be fed to growing turkeys primarily in southern states (southeastern United States), Atlantic coast states and the north central state of Minnesota. Therefore, the environments affected by the proposed action are:

1. The environment adjacent to the Neuville-sur-Saone manufacturing plant.

2. The environments adjacent to the premix manufacturing plants.

3. The environments adjacent to the feed mills using the drug.

4. The ultimate disposition of the drug would be confined to poultry waste. This may be distributed to soil.

Coccidiosis is an endemic disease, and most of the turkeys grown in the United States are fed feeds containing a coccidiostat. New coccidiostat drugs are developed to be used when existing coccidiostats become less effective because of the development of resistance, to overcome side effects of existing coccidiostats, or because of one or more economic, physical or biological advantages.

2. Discuss the probable impact of the proposed action on the environment, including primary and secondary consequences.

a. Describe probably adverse and beneficial environmental effects of the use, consumption and disposal of the article that is the subject of the action, including but not limited to the following areas of environmental impact.

CHEMICAL/PHYSICAL PROPERTIES

Chemistry structural formula or description for any new animal drug substance.

The new drug is known as Stenorol^{R} (halofuginone hydrobromide) Coccidiostat Premix Medicated

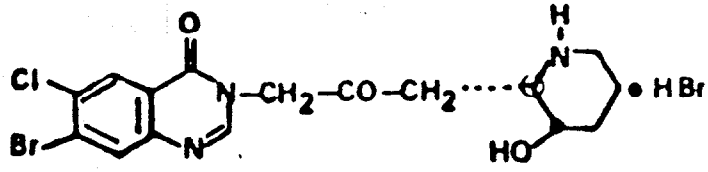
The name of the active ingredient is:

(±)-trans-7-bromo-6-chloro-3-((3-(3-hydroxy-2-piperidyl) acetonyl))-4(3H)-quinazolinone hydrobromide

Generic Name: Halofuginone hydrobromide (Accepted by the United States Adopted Name Council, March 11, 1981).

Chemical Abstract Service Registry No. 64924-67-0.

The structural formula is:



Molecular Formula: $C_{16}H_{18}O_3N_3Clbr_2$

Solubility: Approximately 0.3% in water

Vapor Pressure: approximately 4×10^{-10} mm Hg at 100° C

Molecular Weight: 495.6

Melting Point: 294°C, Melts with decomposition

Ultraviolet Spectrum:

The UV spectrum characterizes the compound exhibiting 5 maxima. The maxima are at 243, 275, 300, 313 and 326 nm, with the respective $E^{1\%}_{1\ cm}$ of about 900, 170, 45, 60 and 55, respectively.

Mode of Administration: Oral (Mixed into complete growing turkey feeds)

Halofuginone hydrobromide belongs to an entirely new chemical type of anticoccidial agent. The active substance was originally derived by modificaiton of a substance isolated from the Asiatic plant, Dichroa febrifuga.

TOXICOLOGICAL/PHARMACOLOGICAL PROPERTIES (Unless otherwise noted all studies in this section were submitted in NADA 130-951, Halofuginone hydrobromide for broiler chickens.)

The acute oral toxicity of halofuginone hydrobromide in mice was determined in a study conducted by the drug sponsor. 120 mice were used in this study and were given doses of 2.5, 3.1, 3.9, 4.9, 6.1 and 7.6 mg halofuginone per kg of body weight in a single dose by oral intubation. During the observation period of 8 days, a record was kept of all mortalities and signs of toxicity. Deaths occurred in mice treated at 3.1 mg/kg body weight and above. Autopsy of the dead animals showed an affected digestion with proliferation of mucous in the stomach and the presence of a yellow liquid in the intestine. Enlargement and hyperplasia of the mesenteric ganglia were also noticed. After 7 days, the surviving mice looked and behaved normally. From this study, the acute median lethal oral dose (LD 50) of halofuginone and its 95% confidence limits to male and female mice were calculated to be 4.9 mg/kg (4.1 - 5.8 mg/kg) and 4.4 mg/kg (3.7 - 5.2 mg/kg) respectively.

The acute oral toxicity of halofuginone hydrobromide to rats was determined by the drug sponsor. 100 rats were used in this study and were given doses of 17.0, 22.1, 28.7, 37.3 and 48.5 mg halofuginone/kg of body weight in a single dose by oral intubation. During the 8 day observation period, mortalities occurred in all treatment levels. After 5 days, wasting in animals of the high dose level was noted. Autopsy of dead animals showed the stomach to be affected by proliferation of mucous and the presence of a yellow liquid in the intestine. Hyperplasia of the mesenteric ganglia was also noted. From this study, the acute median lethal oral dose (LD 50) of halofuginone and its 95% confidence limits to male and female rats were calculated to be 31.0 mg/kg (25.0 - 38.4 mg/kg) and 28.0 mg/kg (23.3 - 33.6 mg/kg) respectively.

The acute oral toxicity of halofuginone hydrobromide in 8 week old turkeys was determined in a study conducted by Dr. David B. Ross, Huntingdon Research Centre,

Huntingdon, England. Forty five (45) turkeys were used in this study and they were given doses of 0.0, 1.0, 2.0, 4.0, 6.0, 7.0, 8.0, 10.0, and 12.0 mg. halofuginone/kg of body weight in a single dose by oral intubation. Turkeys were observed for a 14 day period with mortalities occurring in the group given 7.0 mg halofuginone and above. All mortalities were recorded between days 1 and 5 after dosing. The turkeys became lethargic after dosing. Surviving turkeys recovered within 96 hours after dosing and no further signs of toxicity were observed. All surviving turkeys increased in body weight over the 14 day test period. From this study, the acute median lethal oral dose of halofuginone and its 95% confidence limits to turkeys were calculated to be 6.6 mg halofuginone/kg of body weight (4.2-10.5 mg/kg). The complete report on this study is part of this NADA.

The acute oral toxicity of halofuginone hydrobromide in 5 week old chickens was determined in a study conducted by Huntingdon Research Centre, Huntingdon, England. 35 chickens were used in this study and they were given doses of 0.0, 5.0, 10.0, 15.0, 17.5, 20.0 and 22.5 mg halofuginone/kg of body weight in a single dose by oral intubation. The chickens were observed for a 14 day period with mortalities occurring in the group given 17.5 mg halofuginone and above. All mortalities were recorded between days 9 and 14 after dosing. At doses of 17.5 mg/kg and above the chickens became listless and lethargic and food consumption dropped as the study progressed. All these birds showed signs of emaciation and their crops became very distended. All birds were in poor condition and there was a complete absence of adipose tissue in birds treated at the higher levels. The crops were gas filled with a complete absence of solid material. All other organs appeared normal. From this study, the acute median lethal oral dose (LD 50) of halofuginone and its 95% confidence limits to chickens were calculated to be 17.6 mg halofuginone/kg of body weight (15.7 - 19.7 mg/kg).

The acute oral toxicity of Stenorol^{R} premix to rats was determined in a study conducted by Huntingdon Research Centre, Huntingdon, England. 62 rats were used in this study and were given doses of 0, 1, 1.6, 2.5 and 4 grams Stenorol premix per kg of body weight administered in a single dose by oral intubation. During the observation period of 14 days, a record was kept of all mortalities and signs of toxicity. Death occurred in rats treated at 1.6 grams/kg and above within 21 hours to

7 days after dosing. Autopsy revealed congestion and hemorrhage of the lungs, palor of the liver and kidney and discoloration of the spleen. Recovery of the survivors as judged by external appearance and behavior was apparently complete within 5 days of dosing. From this study, the acute median lethal oral dose (LD 50) and its 95% confidence limits to rats of Stenorol premix were calculated to be: 1.5 (1.3 to 1.8) grams Stenorol premix per kg body weight.

Huntingdon Research Centre, Huntingdon, England, conducted a 24 month oral toxicity study with halofuginone hydrobromide to determine the tumorgenicity to mice in long term dietary administration. The study was conducted in two phases, a reproductive phase dealing with the reproductive performance of an F0 generation covering a period from inception to weaning of the litters of the F0 generation. The main phase of the study dealt with the F1 generation which lasted from weaning until the last group was sacrificed after 100 weeks of treatment. During the reproductive phase, halofuginone was fed at 0, 0.25, 0.5 or 1 ppm. During the reproductive phase, there was no apparent reaction to treatment. The performance of treated mice was similar to that of the controls. During the main phase of the study, halofuginone was fed at levels of 0, 0.03, 0.07, 0.14 mg halofuginone/kg of body weight per day. The high level dosage (0.14 mg/kg/day) was fed during weeks 1-14. The halofuginone level for this high dosage group was increased to 0.24 mg halofuginone/kg body weight/day for the balance of the study after week 14. During the reproductive phase of the study, 80 males and 80 female mice were assigned to each dietary treatment. During the main phase of the study, 52 males and 52 female mice were assigned to each dietary treatment .

At treatment levels of 0.3 and 0.7 mg/kg/day, there was no apparent toxic effect of halofuginone administration during the course of the main phase of the study when compared to the control group. During the 14 weeks that the high dosage group received 0.14 mg/kg/day, there was no apparent reaction to treatment when compared to the control group. Increasing the high dosage group to 0.24 mg/kg/day from 15 weeks to termination of the study lowered body weight gain during this period, impaired food utilization efficiency and increased feed intake by females. No

effect on spontaneous tumor incidence was seen in any of the treatments. Therefore, under the conditions of this study, halofuginone is not a carcinogen. The toxicological no-effect level was established as 0.07 mg halofuginone/kg body weight/day.

A 28 month oral toxicity study in rats was conducted by Huntingdon Research Centre, Huntingdon, England to determine the potential tumorgenicity and toxicity to rats in long term dietary administration. A total of 520 rats were assigned to 4 treatments with 65 males and 65 females being alloted to each treatment group. The dose levels of halofuginone were 0, 2.5, 5.0 and 10.0 ppm given in the feed. The dose level of 2.5 ppm halofuginone produced no detectable changes in clinical signs, growth hematology parameters, urine analysis, nor in gross pathology or histopathology. At the 5 ppm halofuginone level, no detectable changes were noted in any of the parameters except for alopecia in a few females from week 23 and lower values in erythrocytic parameters in females at week 78. At the high level (10 ppm) of halofuginone administration, several observations were made related to the experimental treatment. Reactions to the high level treatment were lower food intake and lower body weight gain during the initial phase of the test period, alopecia in a few females, lower erythrocytic parameters in females, higher SGPT values in some animals, and microscopic examination revealed increased incidence of hepatocyte vacuolation and fat deposition in males and females with associated glycogen depletion in females only. The dosage of drug intake by rats at the low level (2.5 ppm) was approximately equivalent to 0.1 mg halofuginone/kg body weight and approximately the equivalent to 0.2 mg halofuginone/kg body weight at the intermediate level (5 ppm). The no-effect level established for this study is approximately 5 ppm halofuginone in the feed (0.2 mg halofuginone/kg body weight).

A halofuginone toxicity study in beagle dogs was conducted by Huntingdon Research Centre, Huntingdon, England in which 35 beagle dogs were fed halofuginone for 26 weeks at levels of 0.0, 1.25, 2.5 and 5.0 ppm halofuginone in the diet. The results of this study indicated no marked adverse effects on body weight, food consumption, clinical signs, water consumption, ophthalmic examinations, testicular function, blood value and no abnormalities on postmortem examination or organ weights. The high

level of 5 ppm may have resulted in a slight adverse effect on food intake by several animals in that treatment. The mean halofuginone intakes in mg halofuginone/kg body weight/day were approximately 0.08 for the 2.5 ppm level and 0.16 for the 5 ppm level. The toxicological no-effect level in dogs was determined to be 0.08 mg halofuginone/kg body weight/day.

A study was conducted in beagle dogs to determine the potential antifertility effects of halofuginone hydrobromide by Hazelton Laboratories, Vienna, VA. In this study, three groups of 10 male animals each received either 0, 2.5 or 5 ppm halofuginone hydrobromide in the diet. The dogs were fed the diets from the time the dogs were approximately 3 months old through reproductive maturity (breeding age). There were no statistically significant effects upon fertility or sperm count data. In some cases at the high level (5 ppm) there was food refusal and emaciation of the dogs. Because there was a numerically non-significant lowered fertility index for the treated animals compared to the controls, an a numerically non-significant decrease in live - born pups sired by the treated animals when compared with the control animals, a follow-up study was conducted with additional data being collected from 2 control dogs and 3 dogs each from 2.5 and 5 ppm levels. The additional data was collected after the dogs had been receiving a basal diet only (no halofuginone hydrobromide) for a minimum of 27 weeks. The data included semen analysis, testicular measurements and the the results of matings to proven females and gross necropsy findings. No biologically significant necropsy findings were noted. Evaluation of the mating results indicated that all of the males involved were able to sire viable litters. Increased sperm counts were noted for 1 dog each from the control group and the 2.5 ppm treated group. Decreased motility and sperm counts were noted for one 2.5 ppm dog. A trend toward increasing sizes was noted for the testes of all the dogs except one 5 ppm dog which had never produced viable sperm. These results indicate that any possible antifertility effects of feeding halofuginone hydrobromide to male dogs are reversible after halofuginone feeding has been discontinued.

A study to determine the teratogenic effect of halofuginone on rats was conducted by the Institute for Pharmacology and Toxicology, Hannover, West Germany. 100 rats were used in this study in which halofuginone was given in two different tests. In the first test, halofuginone was given in a single dosage at 9.33 mg halofuginone/kg of body weight which was administered by gavage on critical days during pregnancy. The second halofuginone test was a 10 day administration of 6 ppm halofuginone in the feed corresponding to twice the use level of halofuginone in broilers. The fetuses were recovered by section for the investigation of possible damage, x-ray procedures, alinzarin staining of skeletons and the control of organ positions. The halofuginone treated rat fetuses were compared to an untreated control, to a control group whose animals received only a single administration of water and to a group given cyclophosphamide, a known teratogenic substance. A careful study of the individual findings showed no specific teratogenic effect in any of the rats treated with halofuginone. Thus, this study resulted in the determination that halofuginone is not teratogenic. Thus, harmful effects to consumers from possible residues in poultry meat is not to be expected because of the 4-day withdrawal period in broilers and because halofuginone was given at much higher than the 3 ppm dosage level in broilers.

A study was conducted by Huntingdon Research Centre, Huntingdon, England, to determine the effect of halofuginone on reproductive function of the mouse through 3 generations. Halofuginone was given continuously in the feed at levels of 0, 0.25, 0.5 and 1.0 ppm to 4 treatment groups consisting of 15 males and 30 females in each treatment group. This treatment regimen was followed through the 3 generation study. Throughout the 3 generations, the parent animals showed no consistent dosage related effects with respect to reaction to halofuginone, mortalities, food consumption, body weight change, mating performance, pregnancy rate, duration of gestation or findings at terminal autopsy. Additionally, the litter data collected over

the 3 generations which gave values for the incidence of total litter loss, litter size, cumulative pup mortality, incidences of abnormalities and microscopic changes at terminal autopsy were not adversely affected by any treatment at any dosage. Terminal examination of the F3 generation showed no significant differences from control values in respect to organ weights adjusted for body weight or in respect to the incidence of macroscopic or microscopic changes recorded at the pathological examination.

A study on the tolerance of halofuginone hydrobromide by Geese, Muscovy Ducks and Peking Ducks was conducted by the Veterinary College of Hannover, Hannover, West Germany. Halofuginone was given to 56 goslings, 20 Muscovy ducklings and 20 Peking ducklings at the normal dosage for turkeys and broilers of 3 ppm in the feed. Feed intake dropped as soon as the halofuginone containing feed was given leading to depressed growth and extreme emaciation due to feed refusal. Feed refusal was so severe that the first animals died on the fifth day of ingestion of the medicated feed. Aside from advanced cachexia, no other patho-anatomical changes were found. These results suggest that the animals died of starvation. Because of these findings the Stenorol (halofuginone hydrobromide) Premix label contains the CAUTION statement: Do not feed to water fowl. The complete report from this study is attached and labeled as Appendix 1.

The following studies were conducted to determine the phytotoxicity of halofuginone:

Four species of plants (cucumbers, tobacco, tomato and lettuce) were tested in a preliminary toxicity test with the equivalent of halofuginone doses of 480, 240, 120 and 60 grams per hectare. These doses are approximately 0.2, 0.1, 0.05, and 0.03 ppm. While no quantitative measures were taken, observers visually determined that all treatments were similar to controls throughout the 42-day test period. The investigators further studied the effects of manure and bedding from chickens fed 3 and 6 ppm halofuginone on tobacco. Application rates were from 10 to 80 tons manure per hectare. Some leaf curling, other sublethal effects, and mortalities were observed during the 56-day test period in both treatments and controls, which was ascribed to effects of the chicken manure and bedding, rather than to effects associated with halofuginone.

A seed germination and a seedling growth study was conducted using 0, 24, 96, 683, 989 and 1430 ppm halofuginone hydrobromide and corn, cucumbers, wheat and soybeans as test organisms . For the germination trial, 6 replicates of 50 seeds each were germinated for each crop type and the number of seeds germinated by days 2, 3, 5, 10 and 12 were recorded. In the seedling trials, 6 replicates of 25 seedlings were grown and the average shoot length (mm), average root dry weights (mg), and average shoot dry weights (mg) at days 5, 7, 10, 14, 21 were recorded. Only data from the final time period (day 12 for germination and day 21 for seedling) were analyzed.

Seed Germination Trials.

Each crop type was analyzed separately. Percent germination was computed and, because most values were greater than 70%, an arcsine transformation was used on the data. An analysis of variance was computed with effects for blocks, treatment and error.

All main effects for treatment were significant at P .02 for all 4 crops and all had significant linear or quadratic trends. It was in the 24 ppm dose group that most of the departures from the trend occur. The variablity from dose to dose is not consistent, but there is no general pattern of inconsistency. There seems to be no logical basis for the sharp upward jump from the 989 to 1430 dose for cucumber and corn.

Seedling Growth Trials.

Each crop type was analyzed separately. Shoot length at 21 days and dry root and shoot weights at 21 days were all analyzed by analysis of variance with effects for blocks, treatment and error. All main effects for treatment were significant at P .03 except shoot dry weight for corn (P = .56) and (P = .07). However, no consistent, understandable dose response relationship emerged either across crop for any one variable, such as average shoot length, or among variables within a crop. Variability again was erratic.

Summary.

The dose titration data collected for seed germination and seedling growth for corn, cucumbers, soybeans and wheat has highly erratic variability and few consistent, logical relationships between response and dose can be established. There is evidence of a downward linear or quadratic trend for germination for all crops but its credibility is hampered by sharp, upward jumps in germination at the highest dose for corn and cucumbers. There are generally overall significant differences among treatment groups but these differences are difficult to interpret.

Given that the doses of halofuginone applied were far above the expected 0.022 ppm in agricultural soil and the 3 ppm observed in chicken excreta, it is unlikely that adverse effects on the test species will be observed due to the use of manure from halofuginone-treated chickens as soil amendments.

Studies have been conducted in three laboratories to determine the aquatic organism toxicity of halofuginone.

A study of acute toxicity in carp (Cyprinus carpio) in a 72 hour test resulted in determination of median lethal tolerance of 0.3 - 0.7 ppm (mg/liter). This was a static test in 20 liter tanks (at 21 ± 2°C) testing a halofuginone concentration series of 0.01, 0.07, 0.1, 0.3, 0.7, 1.0, 3.0, 7.0 and 10 ppm (mg/liter). The 48-hour TL50 was 0.7 ppm with 95% confidence limits of 0.3 to 1.0 ppm. At 72 hours all doses $\geq$ 0.7 ppm caused 100% mortality and all doses $\leq$ 0.3 ppm showed 0% mortality. Therefore a presumed 72 hour TLm would be between 0.3 and 0.7 ppm.

Halofuginone was used in a comparison of several veterinary drugs in studies conducted at the National Institute of Public Health, Laboratory for Toxicology, the Netherlands. In this study, halofuginone was shown to have a 48 hr LC_{50} in the rainbow trout (Salmo gairdneri) of 2.9 mg/l with 95% confidence limits of 2.1 to 3.8 mg/l, in the guppy (Lebistes reticulatus) the 48 hr LC_{50} was 1.6 mg/l (1.3 -1.9 mg/l) and the 48 hr LC_{50} for Daphnia magna was 0.018 mg/l (0.015 - 0.021 mg/l). The study also included results on the acute toxicity testing using green algae, Chlorella pyrendoidosa, in which the growth inhibition EC_{50} was found to be 46 mg/l. Halofuginone was listed as being very toxic in these studies.

The acute toxicity in the Daphnia magna was confirmed in a recent report of studies conducted at Analytical Biochemistry Laboratories, Inc.,with the 48 hr LC_{50} being reported as 0.020 mg/l. The daphnia test was a static 48-hour LC_{50} test (at 20°C) using halofuginone concentrations of 0.01, 0.018, 0.032, 0.056 and 0.1 mg/l. D.O. and pH measures were within adequate ranges. The 48-hr LC_{50} was 0.02 mg/l and the 95% confidence interval was 0.017-0.023 mg/l. Studies also have been reported for the acute toxicity in the bluegill sunfish giving a 96 hr LC_{50} of 0.12 mg/l . The bluegill (Lepomis macrochirus) test was a static 96-hour LC_{50} test (at 22°C) using halofuginone concentrations of 0.10, 0.18, 0.32,

0.56 and 1 mg/l. The D.O. and pH measures were within adequate ranges. The 96-hour LC_{50} was 0.12 mg/l and the 95% confidence interval was 0-0.18 mg/l. Antimycin A was also used as a reference toxicant and the bluegill results were within the 95% confidence intervals published in the scientific literature. In the rainbow trout the 96 hour LC_{50} was reported as being 1.8 mg/l . The rainbow trout (Salmo gairdneri) test was a static LC_{50} test (at 12°C) using halofuginone concentrations of 0.32, 0.56, 1.0, 1.8 and 3.2 mg/l. The D.O. and pH measures were within adequate ranges. The 96-hour LC_{50} was 1.8 mg/l and the 95% confidence interval was 1.0-3.2 mg/l. Antimycin A was also used as a reference toxicant and the rainbow trout results were within the 95% confidence intervals published in the scientific literature.

Two studies were conducted to determine the LC50 of halofuginone to earthworms (Eisenia foetida) in artifical soil. In the first study, mortality was too high in the controls and too low in the treated groups to determine the LC 50. In the second 28 day study, the determinative test was conducted by adding halofuginone hydrobromide to the artifical soil at concentrations of 0, 1.0, 10.0, 25.0, 50.0, 100.0, 200.0 and 400.0 ppm. This study was conducted using Eisenia foetida (the common dung worm) and the theoretical LC_{50} for the test species exposed to halofuginone hydrobromide for 14 days is 240 ppm with 95 percent confidence intervals of 189-304 ppm. The theoretical LC_{50} for the test species exposed to halofuginone hydrobromide for 28 days is 190 ppm with 95 percent confidence intervals of 148-224 ppm. Individual worms that survived halofuginone exposures greater than or equal to the 28-day LC 50, showed sublethal effects in the form of weight loss. The LC_{50} was calculated using the Litchfield and Wilcoxon method. The 28 day LC_{50} for halofuginone is 8,636 times the highest estimated concentration of halofuginone that will be found in the soil (0.022 ppm) following the use of litter as fertilizer. No differences in mortality over the controls were observed until the soil concentration of halofuginone was over 50 ppm, (2,273 times the highest estimated concentration that will actually be found in the soil).

ANTICOCCIDIAL PROPERTIES

The anticoccidial efficacy of halofuginone hydrobromide has been determined in battery studies and floor pen experiments. These have included studies with negative controls and comparisons with other coccidiostats. Studies included challenge with isolates of all common species of coccidia. Halofuginone hydrobromide was determined to be effective when included in the diet of turkeys at a concentration of 1.5 to 3 ppm.

Included in the studies are coccidia isolated from turkeys having symptoms of infections from coccidia resistant to currently used coccidiostats. Halofuginone hydrobromide has been effective against these organisms.

The new animal drug has been used in commercial applications under investigational approval in the major turkey areas of the United States. It also has been used under practical conditions in countries outside of the United States in the feed of approximately five billion broiler chickens and five hundred million turkeys.

METABOLISM BY TARGET ANIMALS

In studies of the excretion and tissue distribution of radiolabeled halofuginone it has been shown that the highest concentration of radioactivity occurred in the livers and kidneys of treated birds. Tissue depletion studies have been conducted, and compared metabolic fate studies were conducted with the most sensitive experimental animal species used in the life-time feeding studies.

There has been no evidence of build up of residues in the edible tissues of turkeys treated with the drug, and there are no residues of toxicological significance in the tissues of turkeys following the feeding of turkey diets containing the new animal drug, followed by a six day withdrawal from the medicated feed.

Excretion of radioactivity after oral doses of ^{14}C halofuginone to chickens is approximately 50% of the dose during the five days after administration. The liver is the organ with highest concentration of residues of the drug or metabolites of the drug in the chicken or turkey. The depletion of residues from the liver is rapid with a half life of one to two days. Comparison of the total radioactivity and halofuginone in turkey liver shows that halofuginone is the major portion of the total residue . Because halofuginone was the highest single major tissue residue component, it was chosen as the marker residue and the liver the target organ.

Biliary excretion is the major route of disposition of halofuginone from turkeys. A small amount of halofuginone may be disposed of by turkeys via enterohepatic circulation. A major component of the bile is a conjugated form of halofuginone resulting from the addition of an unknown endogenous component. The formation of this conjugated form (metabolite) is considered to be a detoxification process which assists in the elimination of halofuginone residues from tissues. The next largest fraction found in the bile was halofuginone.

The isolated major chicken bile metabolite and halofuginone were derivatized with trifluoroacetic anhydride. The results indicated that the metabolite forms a trifluoroacetyl derivative which is thermally unstable and is converted to N-trifloroacetyl-halofuginone during mass spectroscopic examination. The metabolite may be a ring-opened form of halofuginone which under certain conditions may undergo cyclisation to give the parent compound (see the attached figure of the mass spectral fragmentation of halofuginone and its trifluoroacetyl derivative). The complete report from this study was submitted in NADA 130-951, halofuginone for broiler chickens.

Two major radioactive components were found in chicken excreta, one corresponding to halofuginone (64% extract radioactivity) and another (24% extract radioactivity) which was slightly less polar than halofuginone. These were also the major radioactive components in chicken bile (NADA 130-951).

Based on these studies, and those reported in NADA 130-951, halofuginone for broiler chickens; we have concluded that:

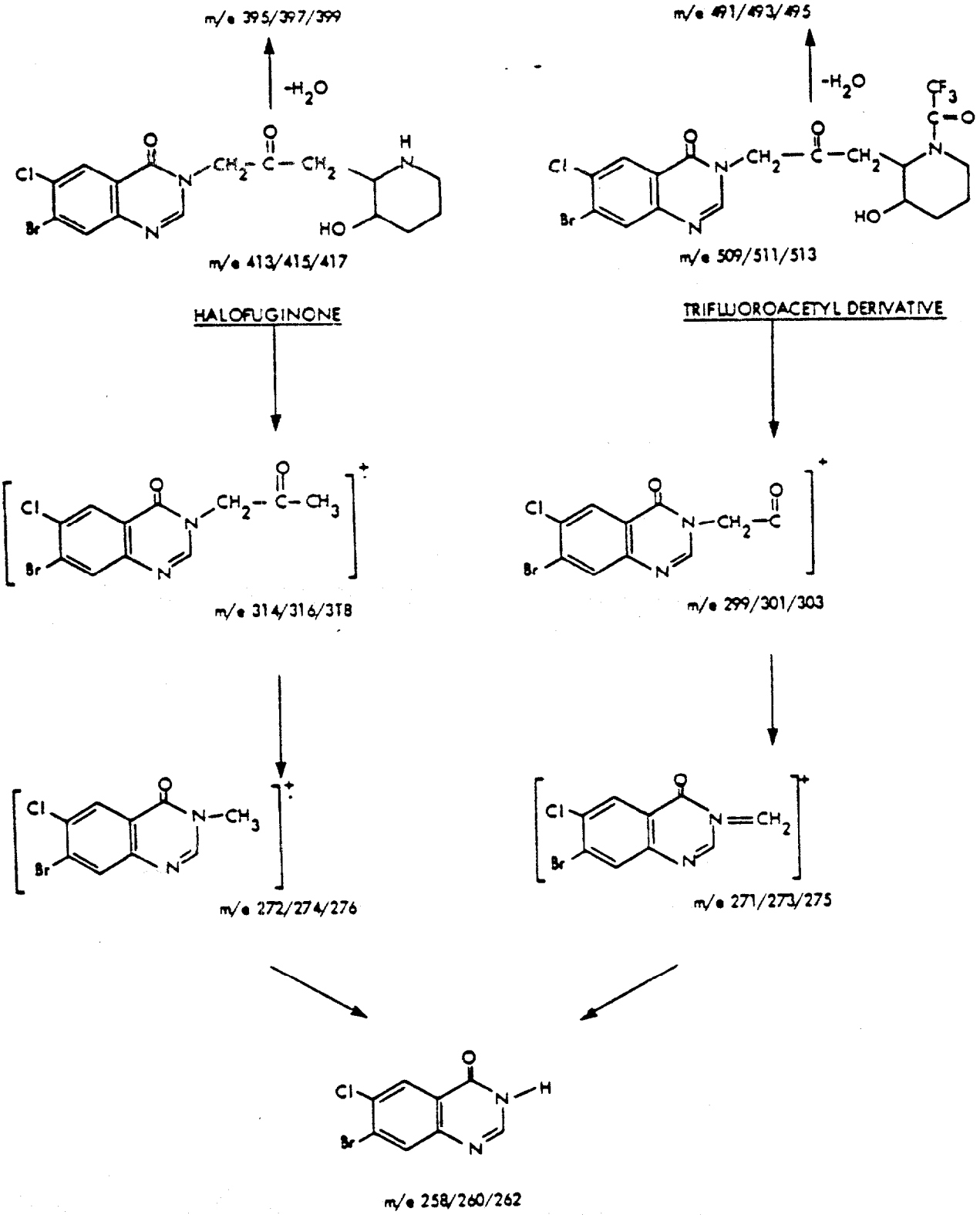
- Halofuginone is essentially not metabolized into component parts, i.e.; piperidine or quinazolinone moietes.

- 60-65% of the radioactive components found in chicken excreta is halofuginone.

- The half-life of halofuginone residues in turkeys is 4-5 days.

FIGURE

Mass spectral fragmentation of halofuginone and its trifluoroacetyl derivative.



- o Halofuginone was the highest single tissue residue component and was chosen as the marker residue. Liver was chosen as the target organ.

- o Halofuginone is excreted from the body through the bile as a conjugated form of halofuginone. Conjugation is a detoxification process rendering the compound less biologically active.

- o Residues of halofuginone do not accumulate in turkey tissue.

Studies were conducted on the metabolism of halofuginone hydrobromide in rats and sheep fed excreta from poultry that had been dosed with the compound. In the rat study, the fate of 14C labeled compound during a 6 day feeding period and a 10 day withdrawal period was observed. The major excretion was by feces with the minor portion being excreted via urine. Accumulation in rat tissues did not occur to any significant degree. Lambs consumed a diet composed of 60% excreta from treated birds for 16 days. Analysis of the tissues for halofuginone was conducted and no edible tissues contained detectable levels immediately after the feeding period, or from 5 to 10 days post-withdrawal. These studies indicate that halofuginone and its metabolites will not accumulate in other species (NADA 130-951).

The potential for halofuginone to bioaccumulate in organisms in the environment was tested by determining the n-Octanol/water partition coefficient of halofuginone. The partition coefficient is expressed as:

$$K_{ow}{}^{1} = \frac{C^{2}\ (\text{n-octanol})}{C\ (\text{water})}$$

$^{1}K_{ow}$= Partition coefficient

^{2} C = Halofuginone concentration

The n-Octanol/water partition coefficient for halofuginone was found to be: K_{ow} = 23.4 (log K_{ow} 1.369). The study was conducted in a PH 5.0 buffered solution. This K_{ow} is further supported by an estimation procedure based on a halofuginone solubility of 3000 ppm. The log K_{ow} is estimated to be 2.622 (Chiou, 1982). Both the experimental K_{ow} and the estimated K_{ow} indicate that halofuginone has a low potential to partition into lipid material. The estimated bioconcentration factor using the method reported by Veith, et al. (1980) is 0.780. Therefore, its bioconcentration potential is expected to be low (NADA 130-951).

References

Chiou, C. T., D. W. schmedding, and M. Manes, 1982. Partitioning of organic compounds in octanol-water systems. Enviroin. Sci. Technol. 16:4-10.

Veith, G. D., et al, 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish, pp. 116-129. In J. C. Eaton, P. R. Parrish, and A. C. Hendricks, Eds. Aquatic Toxicology, ASTM-STP 707. American Society for Testing and Materials, Philadelphia, PA.

ENVIRONMENTAL FATE (Unless otherwise noted all studies in this section were submitted in NADA 130-951; halofuginone hydrobromide for broiler chickens)

Studies reporting the metabolism and migration of the waste products of the drug following feeding to chickens and turkeys have been conducted and are summarized in this Environmental Impact Analysis Report. These reports include the characteristics of radiolabeled halofuginone with respect to soil migration when the radioactive material was applied directly to soil and when excreta collected from chickens dosed with radioactive halofuginone was added to soil. The results of this study indicate that halofuginone hydrobromide elutes very slowly through soil, and there is no significant leaching below the first 5 cm section of the test soil types, a loamy fine sand and a clay loam. When excreta collected from chickens dosed with radiolabeled halofuginone hydrobromide was added to columns and diluted, more than 80% of the radioactivity remained in the top 5 cm, and less than 5% diluted through the 30 cm columns. The elution characteristics were not altered following incubation for 32 days of the excreta from poultry administered radiolabeled compound.

Halofuginone appears to be strongly bound to either loamy fine sand or clay loam soils and therefore does not leach much through soil. $\geq$ 99.5% of the radioactivity stayed in the top 5 cm of the 30 x 4 cm columns after one bed-volume of water (400 ml) was passed through each soil column. Run off of waste to lakes or rivers from application of manure, litter or bedding of medicated birds is not expected to be quantitatively significant.

A soil adsorption/desorption study was conducted with 14C halofuginone hydrobromide. Aqueous solutions of 14C halofuginone hydrobromide were equilibrated with three soil types, adsorption coefficients and adsorption constants were determined by liquid scintillation analysis. The results are summarized below.

Soil Type	Stage of Study	Kd	Koc	n
Silt Loam	Ad	30.3	1515	2.37
	De	389	19450	1.09
Silty Clay Loam	Ad	51.8	7400	1.91
	De	1329	189857	0.906
Silt Loam Loam	Ad	22.0	2651	2.49
	De	199	23976	1.02

The mobility of a chemical through soil can be directly related to its adsorption properties. This relationship is applicable for neutral organic compounds. K_{oc} values can be related to mobility of the test material in the soil. The study shows that, in the three soils tested (at pH's between 6.0 and 7.0), halofuginone mobility in soil is low to very low. Once sorbed to soil, between 1% and 6% could be desorbed, depending on soil type. Based on the ionic nature of halofuginone, higher mobility may be expected as soil pH decreases. Increased organic matter and clay content of soil would be expected to increase the amount of halofuginone sorbed to soils.

Biodegradation studies in soil were conducted in the laboratory and under field conditions. In the laboratory study, the extractable halofuginone residues decreased in time and the half-life was about 15-20 days in these two soils. Degradation products for lower molecular weight compounds, and the portion of these products increased with time. There was slow but continuous evolution of radioactive CO_2 (about 5% in 16 weeks), this indicates a slow but virtually complete degradation of the halofuginone molecules. In the field studies, the initial halofuginone degradation was slower than in the laboratory soils, probably weather related. The field soil half-life was about 43 days. There was no significant leaching of halofuginone and its metabolites through soil. These results indicate that halofuginone and its metabolites in chicken excreta will not be mobilized from the soil environment into the aquatic environment.

Excreta from chickens dosed with radiolabeled halofuginone were incubated with river water stored in the dark at 25°C for 32 weeks. The water soluble residues from chicken excreta were about 35% halofuginone and 30% a major chicken metabolite. The level of water soluble halofuginone (and its major chicken metabolite) declined over a 32 week period. Numerous degradation products were formed and they were generally less polar than halofuginone.

The concentration of halofuginone and metabolites in poultry feces is approximately 3 ppm. Growing turkeys are typically raised on litter, thus further diluting the concentration of drug and metabolites. A conservative estimate is dilution by 33% so as to give a concentration in litter of 2 ppm. Concentration of the drug and metabolites in soil following the use of litter as fertilizer can be estimated by the following formula:

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

For Halofuginone Hydrobromide

$$\text{Drug conc. in soil} = 2 \text{ mg/kg (2 ppm)} \times \frac{10{,}000 \text{ kg litter}}{1 \text{ acre}} \times \frac{\text{acre}}{9.09 \times 10^5 \text{ kg}} = .022 \text{ mg/kg}$$

The estimate of 0.022 mg/kg (22 ppb) addition of halofuginone and metabolites to the soil, with the evidence as stated above that there is no significant leaching (the substance binds to the soil), and the further evidence of biodegradation of the drug and its metabolites, allow for the following conclusions:

- o Levels of halofuginone hydrobromide and its metabolites in soil following fertilizing with fresh litter from birds fed the drug are estimated to be 22 ppb.

- o Soil migration potential for the drug and its metabolites is very small.

- o The drug is biodegradable in soil and in water.

- o Runoff of the drug into bodies of water is not likely because of the low concentration in soil, and the binding properties of the drug and metabolites to soil.

3. Solid and liquid wastes. The active ingredient is to be manufactured overseas in compliance with the laws and regulations of the country of manufacture, France (Appendix 2). Liquid wastes are recovered by distillation, incinerated, or transferred to a biological treatment station. Solid wastes are incinerated or transferred to a waste destruction station. The plants manufacturing the active ingredient, halofuginone hydrobromide, operate under the surveillance of a French Government Agency (Inspection des Installations Classes) which is charged with enforcing the regulations enacted in the field of environmental protection.

In the manufacture of the premix, there is no significant solid or liquid waste produced. The premix manufacturing facilities adhere to the local, state and national environmental laws and regulations (Appendix 2).

Solid or liquid waste from the turkey feeding operations is normally applied to fields as manure mixed with the bedding (litter).

4. Toxic substances. There is no pollution of the environment in the manufacture, processing, and use of the new animal drug with heavy metal, pesticides, or radiation.

The compound halofuginone hydrobromide has an acute oral toxicity of approximately 5 mg/kg in the mouse. This is equivalent to an oral toxicity of greater than 800 mg/kg body weight for the formulated product. Acute oral toxicity of the premix has been determined to be 1.5 (1.3-1.8) grams per kg in the rat.

The toxicity of the compound has been assessed in lifetime feeding studies, in reproduction studies, and in a teratogenicity study. There has been no indication of insidious toxicity of the compound. The toxicological no-effect level in the most sensitive mammalian species (mouse) is 0.07 mg/kg/day.

5. Populations. The intended use of the product is for growing turkeys. Studies have been conducted to demonstrate the safety of use of the product in the diets of turkeys. The product is not intended for use in species other than poultry. The new animal drug does not have antibiotic properties.

Halofuginone residues in plants were not over 35 ppb even when poultry excreta (from animals given approximately seven times the expected dose level) was incorporated into soil at the rate of "80 tons/ha" (32.4 tons/acre).

Halofuginone uptake by plants was very similar whether the drug was directly incorporated into soil or came from poultry excreta incorporated into soil. The only plant part that showed a statistically significant uptake of radioactivity was carrot foliate at 7 ppb halofuginone equivalents. See also the discussion of food contamination in Section D.2.a.(6).

Manure from birds fed diets containing halofuginone hydrobromide may be used as fertilizer for plants. Studies have been conducted to demonstrate the effect of halofuginone hydrobromide, or the waste from animals treated with halofuginone hydrobromide on plants. There have been no serious symptoms of phytotoxicity when the drug is properly used. Also, see the discussion of the phytotoxicity results in Section D.2.a. - Toxicological/Pharmacological Properties.

Test work conducted to determine the effects of halofuginone in other species of farm animals. In the case of the horse, ponies were fed rations containing halofuginone at the level of 3 ppm for four weeks. There were some slight changes in blood composition, but the ponies remained clinically normal at all times. Swine were dosed orally with halofuginone at graded dosage levels. Pigs dosed at 5 mg/kg survived the treatment. The acute toxicity was such that a 30 kg pig would have to ingest approximately 100 kg of poultry diet containing 3 ppm halofuginone to cause mortality.

Halofuginone hydrobromide is a potent antiprotozoal agent against coccidia and has action against other protozoal organisms. Classic in vitro screening tests on protozoa were not conducted; however, several studies in animals have been done to determine if halofuginone is effective against some of the protozoa that are pathogenic in animals. Ten study reports were summarized. Halofuginone was effective against Theileria,

Sarcocystis, Leucocytozoonosis and some species of Babesia at doses of 1-2 mg halofuginone/kg of body weight. Dose levels higher than 2-4 mg/kg of body weight were generally toxic to the host animals. This work demonstrates that halofuginone is effective against protozoa other than chicken coccidia. It has low or no activity against various gram negative and gram positive bacteria. The application of feces from chickens treated with halofuginone did not have any significant effect upon the nitrification process in soil. This study measured the effect of excreta from chickens fed halofuginone at 3 ppm upon soil bacteria nitrogen transformation. NH_4^+ NO_2^- and NO_3^- were followed over 28 days in two soils (a light loam and a heavy clay) with or without excreta (3.5% incorporation rate) kept at R.T. in the dark. In both soils, halofuginone residues appeared to have no significant effect upon the production of NH_4 + and its subsequent conversion to NO_2^- and NO_3^- (measured as micrograms N/g soil).

The acute toxicity of halofuginone on aquatic organisms is discussed in detail in section D.2.a - Toxicological/Pharmacological Properties.

The LC_{50} of halofuginone hydrobromide to earthworms (Eisenia foetida) was determined. The theoretical LC_{50} for the test species exposed to halofuginone hydrobromide for 14 days is 240 ppm with 95 percent confidence intervals of 189-304 ppm. The theoretical LC_{50} for the test species exposed to halofuginone hydrobromide for 28 days is 190 ppm with 95 percent confidence intervals of 148-224 ppm. These findings are discussed in more detail in Section D.2.a. -Toxicological/Pharmacological Properties.

6. Human values. This drug will have the effect of providing an alternative means of control of coccidiosis in poultry. It is well recognized that coccidiosis is an endemic disease and the only suitable methods of control is through drugs. Without use of coccidiostats there is no practical or efficient method of producing turkey meat for human consumption. Turkeys are one of the most efficient producers of high value animal protein.

7. Food contamination. This new animal drug application contains analytical methods for residues, including studies to determine the actual levels of residues in the edible products from birds fed feeds containing halofuginone hydrobromide. It is concluded that the residues of halofuginone are not of toxicological significance when used as labeled.

The analytical methods are adequately sensitive to measure residues of less than 30 parts per billion.

Residues of radioactivity in plants grown in soil treated with radiolabeled halofuginone or excreta from poultry dosed with halofuginone have been investigated. Studies conducted to assess the uptake of residues of radioactivity by root crops and tubers grown in soil treated with excreta from chickens dosed with 14C halofuginone is reported . Application rates representing the maximum likely dose rate with a period of 30 days between applications and sowing of crops were used to provide the maximum uptake of residues. Concentration of halofuginone hydrobromide equivalent were less than 4 ppb in the roots and foliate of sugar beets and 7 ppb in carrots. It was concluded by the authors that halofuginone hydrobromide is not likely to represent an environmental hazard with respect to residues and plants grown in treated soil. Another study was reported on ability of lettuce, tomatoes, tobacco and cucumbers to take up the residues of halofuginone hydrobromide when applied to soil. The results from this study show that at the maximum level of incorporation of residues in soil, the uptake of the residues by plants was negligible.

8. Natural resources. The effect of approval of the NADA will be to provide an alternative medication for prevention of coccidiosis in growing turkeys. The maximum active drug concentration is 3 ppm in the diets of poultry, which is far less than the amount of any drug substance now employed in the prevention of coccidiosis. There is expected to be no effect upon the depletion of natural resources due to manufacture of the drug.

9. Energy. The indirect effect of approval of this NADA will be a saving of energy by prevention of loss of birds due to strains of coccidia which may be resistant to a previously used coccidiostat.

E. Describe measure taken to avoid or mitigate potential adverse environmental effects.

In light of the data presented above, no such measures are necessary except a warning statement on the premix label describing halofuginone as a potential skin irritant to humans and halofuginone's potential toxicity to fish, aquatic life and water fowl.

F. Analyze the environmental impact of the manufacturing process of the article that is the subject of the requested action.

1. An outline of the manufacture of the product is included in Section 5 of the NADA. The synthesis of the new drug substance is contained within the manufacturing facility.

2. The article will be manufactured in FRANCE. Pre-mix operations will be conducted within the United States, and such operations will be in full compliance with federal, state, and local emission requirements. The pre-mixing operation is expected to be contained and there is no waste products produced.

3. The sponsor of this new animal drug application certifies that any emissions resulting from the manufacture of the article will be in full compliance with the appropriate regulations of the country of manufacture. Pre-mix operations will be in full compliance with federal, state, and local emission requirements.

   The pre-mix will be formulated at one or more of the following organizations, Merck and Co., Southern Micro-Blenders, Lavergne Supplement Company, VMS Incorporated, and/or Mac-Page Incorporated. Enclosed as Appendix 2 is a copy of the pollution control procedures and related permits from the individual companies.

G. Specific data. Appendix to this Environmental Impact Analysis Report are reports of studies intended to elucidate the effects of halofuginone on the environment. The attached reports are as follows:

Appendix 1 - Studies on the tolerance of halofuginone by Geese, Muscovy Ducks and Peking Ducks. Behr, K.P., C. Plate. Dtsch. Tierarztl. Wschr. 93, 1-64, Jan, 1986.

Appendix 2 - Supplemental Information Concerning Environmental Impact; Merck & Co., Southern Micro-Blenders, Inc.; VMS, Inc.; Lavergne Supplement Co.; Mac-Page, Inc. and the environmental laws governing the synthesis of halofuginone hydrobromide by Roussel-Uclaf, Paris France.

THE FOLLOWING REPORTS WERE SUBMITTED IN THE EIAR FOR NADA 130-951; HALOFUGINONE FOR BROILER CHICKENS

Appendix D-1 - Fate of 14C halofuginone and its Metabolites Excreted by Chickens in Soil, Huntingdon Research Centre Report, RSL 275/276/78373, 6 June 1978

Appendix D-2 - Uptake of Residues of 14C Halofuginone and its Metabolites in Chicken Excreta, After its Addition to Soil, by Carrots, Sugar Beet and Potatoes, Huntingdon Research Centre Report, RSL 446/81560, 10 September, 1981

Appendix D-3 - Residues of Radioactivity in Plants Grown in Soil Treated with 14C Halofuginone or Excreta from Chickens Dosed with 14C Halofuginone, Huntingdon Research Centre Report, RSL 296/78847, 29 Sept., 1978

Appendix D-4 - The Inclusion of Halofuginone at 3 ppm in the Diet of Horses, Huntingdon Research Centre Report, RSL 258/77991, 9 December, 1977

Appendix D-5 - The Acute Oral Toxicity of Halofuginone to the Domestic Pig, Huntingdon Research Centre Report, RSL 336/78726, 1 August, 1978

Appendix D-6 - The Action in vitro of Halofuginone Hydrobromide on Several Species of Microorganisms, Dr. Lutz, Strasbourg, Roussel UCLAF Laboratories, 18 June, 1974

Appendix D-7 - The Biodegradation in River Water of 14C Halofuginone and its Metabolites in Chicken Excreta, Huntingdon Research Centre Report, RSL 447/81694, 27 November, 1981

Appendix D-8 - The Biodegradation of 14C -Halofuginone and its Metabolites in Chicken Excreta After Application to Soil, Huntingdon Research Centre
Report, RSL 448/81728, 19 March, 1982

Appendix D-9 - The Acute Toxicity of Halofuginone to Carp (Cyprinus carpio), Huntingdon Research Centre Report, RSL 224/FT/5946, 13 January, 1976

Appendix D-10 - The Short-Term Toxicity of Some Feed Additives to Different Freshwater Organisms, Canton, J. H. and G. J. van Esch, National Institute of Public Health, Laboratory for Toxicology, P. O. Box 1, Bilthoven, The Netherlands, Bulletin of Environmental Contamination and Toxicology 15:720-725, 1976

Appendix D-11 - Acute Toxicity of Halofuginone Technical to Daphnia magna, Static Acute Bioassay Report #28808, Submitted to American Hoechst Corporation, 15 March, 1982

Appendix D-12 - Acute Toxicity of Halofuginone Technical to Bluegill Sunfish (Lepomis macrochirus), Static Bioassay Report #28806, submitted to American Hoechst Corporation, 23 April, 1982

Appendix D-13 - Acute Toxicity of Halofuginone Technical to Rainbow Trout (Salmo gairdneri), Static Bioassay Report #28807, Submitted to American Hoechst Corporation, 23 April, 1982

Appendix D-14 - Nitrogen Transformation in Soil, Huntingdon Research Centre Interpretive Comment, April 16, 1982 and full report RSL 445, 3 September, 1981

Appendix D-15 - Supplemental Information Concerning Environmental Impact; Southern Micro-Blenders, Inc.; VMS Inc., Lavergne Supplement Company; and Mac-Page Inc.

Appendix D-16 - Additional information from Roussel Uclaf, Paris, France - Solubility in Water, Vapor Pressure Study, n-Octanol/Water Partition Coefficient Study and Description of Environmental Laws in France, July 1984

Appendix D-17 - Stenorol Phytotoxicity Test, J. C. Reinier, Cent. Res. Sta., Marseille, 11 October 1974 (revised by American Hoechst Corporation Oct. 1984)

Appendix D-18 - The Activity of Halofuginone on Protozoan Species other than Chicken Coccidia - A Review of 10 Published Articles. October 1984

Appendix D-19 - Seed Germination and Seedling Phytotoxicity Study with Halofuginone Hydrobromide, J & S Plant Consultants, Inc., October 1984

Appendix D-20 - Earthworm Toxicity Study of Halofuginone Hydrobromide in Artifical Soil, Biospherics, Inc., August 1984 and October 1984

Appendix D-21 - Soil Adsorption/Desorption with 14C Halofuginone Hydrobromide, ABC Labs, July 1984

H. Describe the probable adverse environmental effects that cannot be avoided.

There are no known significant adverse environmental effects related to the manufacture and use of the new drug. The drug has been produced for use in 44 countries, and over 10,000 tons of the drug have been produced without reported adverse environmental effect.

I. Evaluate alternatives to the proposed action.

The only alternative to approval of the New Animal Drug Application, is non-approval. This would mean that the poultry industry would not have the choice of use of this drug. The drug may be especially useful in those cases where resistance of coccidia to other drugs is of significance. Development of resistance to existing coccidiostats is probable, and it is desirable to have alternative coccidiostats available.

J. Describe the relationship between local and short-term use of the environment with respect to the proposed action and the maintenance and enhancement of long-term productivity.

This action will not require any significant use of the environment. There is no expectations or evidence to expect short term or long term effects.

K. Describe any irreversible and irretrievable commitment of resources that would be involved if the proposed action should be implemented.

None

L. Discuss the objections raised by other agencies, organizations, or individuals that are known by the applicant.

No objections have been raised by an agency, organization, or individual. The drug has a history of safe manufacture and use in France. It has been authorized by that government for manufacture, and has been authorized for use in European Economic Community countries since 1977.

M. If the proposed action should be taken prior to 90 days from this circulation of a draft environmental impact statement or 30 days from the filing of a final environmental impact statement, explain why.

It is the sponsor's position that this action will not require the preparation of an environmental impact statement. If it is determined that an environmental impact statement is required, the petitioner has no objections to the timing as presented above.

N. Risk-benefit analysis.

It is the sponsor's belief that there is no significant risk associated with the proposed action. We have demonstrated in the application the usefulness of halofuginone for the prevention of coccidiosis in turkeys caused by Eimeria adenoeides, E. meleagrimitis and E. galloparonis. The significant benefits of approval of this NADA far outweigh the potential risks.

O. Certification. The undersigned petitioner certifies the information furnished in this Environmental Impact Analysis Report to be true, accurate and complete to the best of his knowledge.

DATE: 6/16/86

Robert J. Grant
Signature

Robert J. Grant, Ph.D.
Manager, Nutritional Research

Capacity

May 1986

TRANSLATION

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BEHR, K.-P., LÜDERS, H.; PLATE, C.: Untersuchungen zur Verträglichkeit von Halofuginon (STENOROL®) bei Gänsen (Anser anser f. dom.), Flugenten (Cairina moschata f. dom.), und Pekingenten (Anas platyrhynchos f.dom.) (Studies on the Tolerance of Halofuginone (STENEROL®) by Geese (Anser anser f.dom.), Muscovy Ducks (Cairina moschata f.dom.), and Peking Ducks (Anas platyrhynchos f.dom.))

From the Hospital for Poultry of the Veterinary College of Hannover (Dir.: Dr. Dr. h.c. O. Siegmann)

Publ.: Dtsch. tierärztl.Wschr.93, 1-64, Jan.7, 1986

Summary

The coccidiostat halofuginone (STENEROL®) was given to 56 goslings, 20 Muscovy ducklings, and 20 Peking ducklings at the normal dosage for broilers and turkeys of 3 mg/kg feed and examined for its tolerance. During preliminary and main tests considerable decreases in feed consumption and subsequently depressed growth rate were observed in the test groups. Goslings which had received halofuginone for 13 days showed extreme emaciation from which they could not recover. On the other hand, the growth inhibition shown by about 4-week-old goslings, Muscovy ducklings, and Peking ducklings after 7 days of halofuginone administration could be partly counterbalanced. But there were also some deadly results in the test groups after seven days of halofuginone administration. Thus, the conclusion is that halofuginone-medicated feed is unfit for waterfowl because of the decrease in feed consumption and the possibility of death.

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As a chlorfebrifugine, the synthetic halofuginone is closely related to the alkaloids of the Chinese Dichroa febrifuga Lour (FAIRBAIRN, 1950) which in China are used against malaria since thousands of years (MOSIG, 1954). The current feed stuff law permits the use of halofuginone (STENEROL®) as a coccidiostatic in broilers and turkeys (SÜLFLOHN, 1985); The manufacturers of mixed feed are adding it to a great extent to the pertinent feed stuffs at t dosage range of 2-3 mg/kg feed, as provided by that law.

Excessive doses lead -- from 12 mg/kg feed on -- to a decrease in feed consumption and consequently to losses in weight gain (YVORE et al., 1974). Only few papers mention data -- and that rather incidentally -- on the tolerance of halofuginone by waterfowl. DORENKAMP (1981) observed in two geese, aged 3-6 weeks, disorders in the general condition after ingestion of halofuginone (3mg/kg feed); however, after reduced feed consumption their conditions improved within days. The efficacy of halofuginone in Eimeria anseris-infected geese proved very beneficial; despite the only very short time of ingestion of halofuginone the animals no longer excreted any oocysts (DORENKAMP, 1981). In view of considerable fluctuations in feed consumption, poor weight gains, and disorders in the general conditions of the geese, DORENKAMP (1981) discontinued his studies with halofuginone in geese. YIN et al. (1983) determined the inefficacy of halofuginone-medicated feed against Tyzeria perniciosa infection in 2-week-old Peking ducks; however, there is still the question whether this inefficacy could have been the result of a decrease in the consumption of the medicated feed. SALYI et al. (1983) observed in nine herds, in ducklings as well as in breeding ducks, nonacceptance of a halofuginone-medicated broiler finisher (3 mg/kg feed). There were no complications later when the same feed was fed to broilers and turkeys.

Various inquiries concerning the possible feeding of waterfowl with feed stuff for broilers and turkeys as well as requests for expert opinions on feed-mixing mistakes or mix-ups with feed stuff made it -- in view of the limited availability of pertinent literature -- seem reasonable to examine the tolerance of halofuginone by waterfowl in a biological study. The following is a report on the results of halofuginone in waterfowl. Feed consumption, weight development, clinical observations, and patho-anatomical findings will be used as evaluation criteria for the tolerance of halofuginone.

Material and Methods

During the preliminary and the main study the animals were kept as day-old chicks in fully air-conditioned dark houses with wire-grated floors in groups of each 14 goslings and 10 ducklings, respectively. After adjustment periods of 14-25 days the "light-day duration" was 14 hours during the actual tests at a light intensity of 20 lux; the room temperature was between 20 and 25°C, and the relative atmospheric humidity between 50 and 60%. For these tests, special feed mixes with equal nutrient contents were used; their only difference was in the halofuginone content. Feed consumption was determined daily at the start of the light day for each individual group. The changes in body weight observed during the main test were determined by weighing the individual animals at the start of the test as well as at the end of it, and also at the end of the follow-up period.

a) Preliminary test

Determination of feed consumption was made in two groups of 14 goslings each who during the preliminary phase from the fifteenth to the twenty-second day of live had received the same feed and after that, during a 13-day testing period, halofuginone-medicated and halofuginone-free feed, respectively.

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Material and methods - cont'd.

b) Main test

Twenty-eight goslings, 20 Muscovy ducklings, and 20 Peking ducklings were available for the main test. After the adjustment period , at the start of the test the goslings were 19 days old, the Muscovy ducklings 24 days, and the Peking ducklings 25 days. During the 4-day preliminary phase as well as during the 10-day follow-up phase the groups received halofuginone-free feed, while between those two phases -- during the 7-day test phase -- they were given halofuginone-medicated and halofuginone-free feed, respectively.

Results and Discussion

a) Preliminary test

Table 1 and Figure 1 demonstrate the average daily feed consumption. During the preliminary phase, clinical observation found no difference between the groups. During the actual test phase, the animals receiving halofuginone-medicated feed showed -- starting on the third day -- clinical signs of retrogression. They became increasingly inert, growth-inhibited, and showed weekness in the legs as well as ataxias. The feather development of these animals stopped at the down stage and their plumage looked quite soiled, whereas the plumage of the control animals remained clean and healthy-looking. Because of the continuing worsening of the clinical picture of these animals and the death of two animals on the twelth feeding day, the test was discontinued after the thirteenth day. Within eight days after test discontinuation, four

Results and discussion, preliminary test - cont'd.

a) animals of the test group died and seven more of that group were in a moribund condition and had to be killed. Thus, 13 out of 14 test animals were available for patho-anatomical examination. All of those animals showed extreme cachexia; other changes in bodies and organs were macroscopically not ascertainable. Results of bacteriological examinations hearts, livers, and spleens were all negative. The behavior of the 14 animals of the control group during the test remained clinically unsuspicious and none of them died.

b) Main test

Table 2 and Figures 2, 3, and 4 show the average daily feed consumption of goslings and ducklings; the average individual weights of the animals are combined in Table 3 and Figure 5. Clinically determinable was -- as already observed during the preliminary test with the goslings -- an inhibition in the goslings and ducklings, starting on the third day of halofuginone medication.

Although these clinical signs had intensified noticeabley, they disappeared within 2-3 days after discontinuation of halofuginone. The affected animals were able to partly make up for the arrested development during the follow-up phase. The first deaths in the test groups occurred on the fifth day of ingestion of the medicated feed: three out of 10 Muscovy ducklings died on the fifth and sixth feeding day, while after discontinuation of the test feed three out of 14 goslings died or had to be killed because of their moribund conditions. Aside from advanced cachexia, no other patho-anatomical changes were found in those animals who had died

Results and discussions (main test) - cont'd.

b) or had to be killed. The results of the bacteriological examination of hearts, livers, and spleens of those animals also were negative.

The results show that halofuginone at the for broilers and turkeys customary dosag of 2-3 mg/kg feed rapidly leads to considerable decrease in feed consumption up to complete refusal of feed intake by geese, Muscovy ducks, and Peking ducks. However, this ist not just a passing symptom, such as for instance the change from a diet to a lesser acceptance; on the contrary, the refusal of feed intake is persistent and the animals may finally die of severe cachexia.

The animals which at the same time had received halofuginone-free feed of the same nutritive composition acted clinically inconspicuously and kept developing their feed consumption increasingly according to age, so that the body weights of these control animals were within the physiological range for animals of that age.

Since none of the dead or (moribund) killed animals showed -- aside from severe cachexia -- any other patho-anatomical changes, it suggests itself that those animals had died of starvation. According to the present results, an additional toxic effect cannot be completely excluded; however, it cannot be proven either. Since the animals injested only very small amounts of halofuginone, it may be assumed that already minute amounts of the substance can cause a toxic effect. Obviously, irreversibly advanced losses in body substance result in lasting damage to the animals as it happened here to the test animals of the preliminary test and to some animals of the main test, which even after discontinuation of the test feed had died. On the other

Results and discussions - cont'd.

hand, short-term feeding of the test feed (2-3 days) leads mainly to reduced feed consumption and poorer weight gains, and consequently to considerable losses in the fattening yield of the animals. Each prolonged halofuginone administration may also lead to the death of goslings, Muscovy ducklings, and Peking ducklings.

Literature

DORENKAMP, B. (1981): Die Wirkung einiger Coccidiostatika auf Eimeria anserina und Eimeria truncata, Vet.-med. Diss. Hann. - FAIRBAIRN, J. W. u. M. (1953): A pharmacognostical study of Dichroa febrifuga Lour, a chinese Antimalarial Plant. J. Pharmacy and Pharmacol. 2, 163–177. - MOSIG, A. (1964): Arzneipflanzen und Drogen in der chinesischen Materia medica. Dtsch. Apoth. Ztg. 94, 887–886. - SALYI, B., F. MAJOROS u. J. SZEMES (1983): (Feed refusal by ducks given compound feeds containing Stenorol [halofuginone]) Magyar Allatorvosok Lapja 38, 101–104. - SULFLOHN, K. (1985): Grüne Broschüre 1986. ASR-Verlag GmbH, Rheinbach. - YIN, P. Y., J. S. JIANG, F. Y. KUNG, K. H. LIN, G. Y. LIN, J. WU u. H. X. YANG (1983): Pathogenicity of Tyzzeria Perniciosa and Wenyonella philipevinei and a comparison of the prophylactic effects of eight anticoccidials against coccidiosis in ducks. Acta Veterinaria et Zootechnica Sinica 14, 263–270. - YVORÉ, P., N. FOURÉ, J. AYCARDI u. G. BENNEJEAN (1974): Efficacité du Stenorol (RU 19110) dans la chimioprophylaxie des coccidioses aviaires. Recueil de médicine vétérinaire 150, 495–503.

Address of authors: Klinik für Geflügel der
Tierärztlichen Hochschule
Bünteweg 17
(D-3000) H a n n o v e r - 71

WEST GERMANY

001437

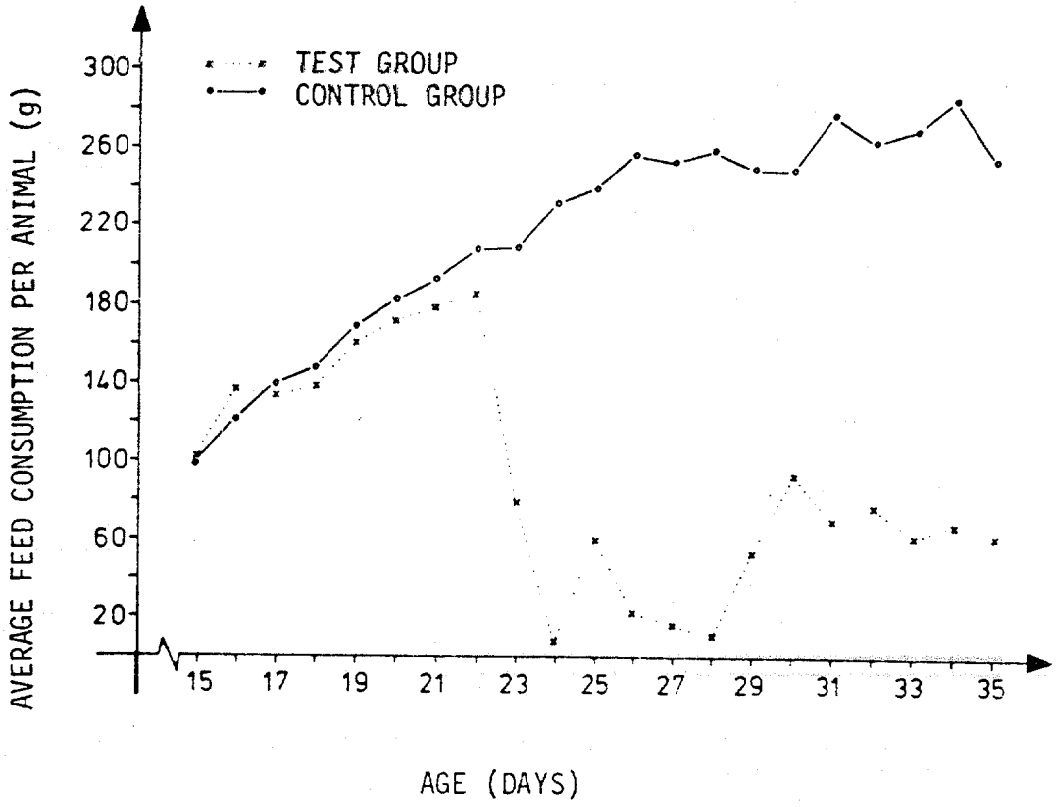

Fig.1: Preliminary test.
Development of the average daily feed consumption (in g) per gosling in test- and control group.
Halofuginone-medicated feed (3 mg/kg feed) in test group

*)

*) Original was cut off here

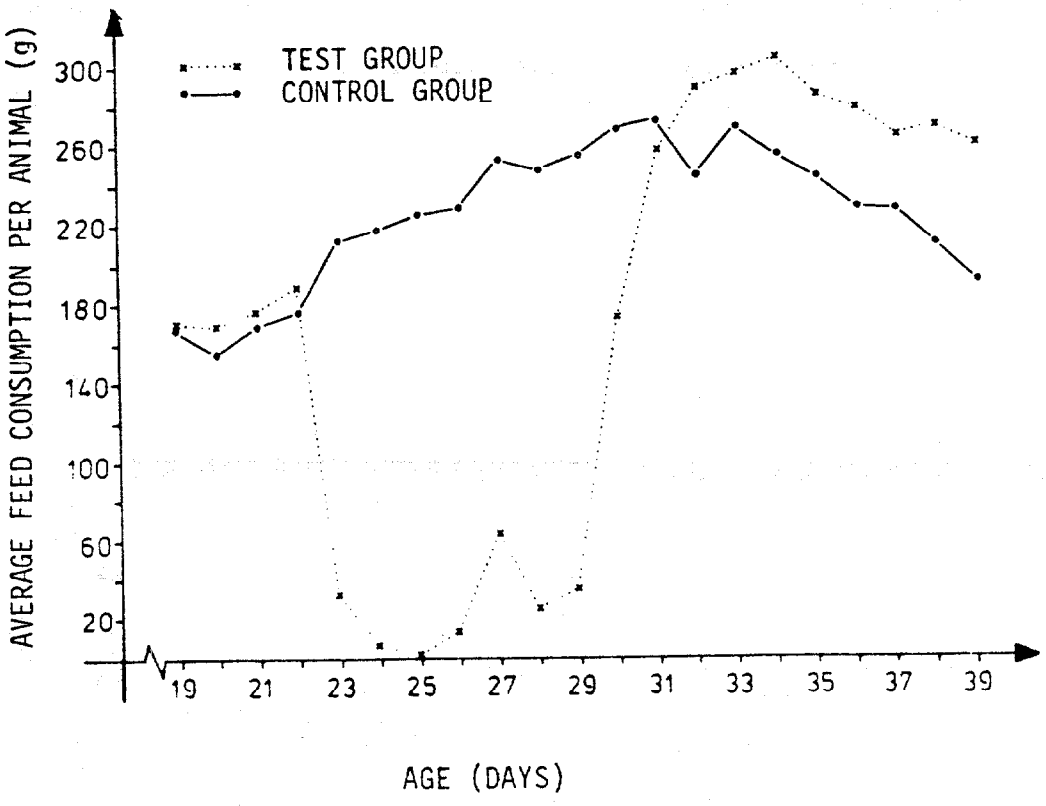

Fig.2: Main test.
Development of the average daily feed consumption (in g) per gosling in test- and control group.
Halofuginone-medicated feed (3 mg/kg) in test group from the 23rd to the 29th day.

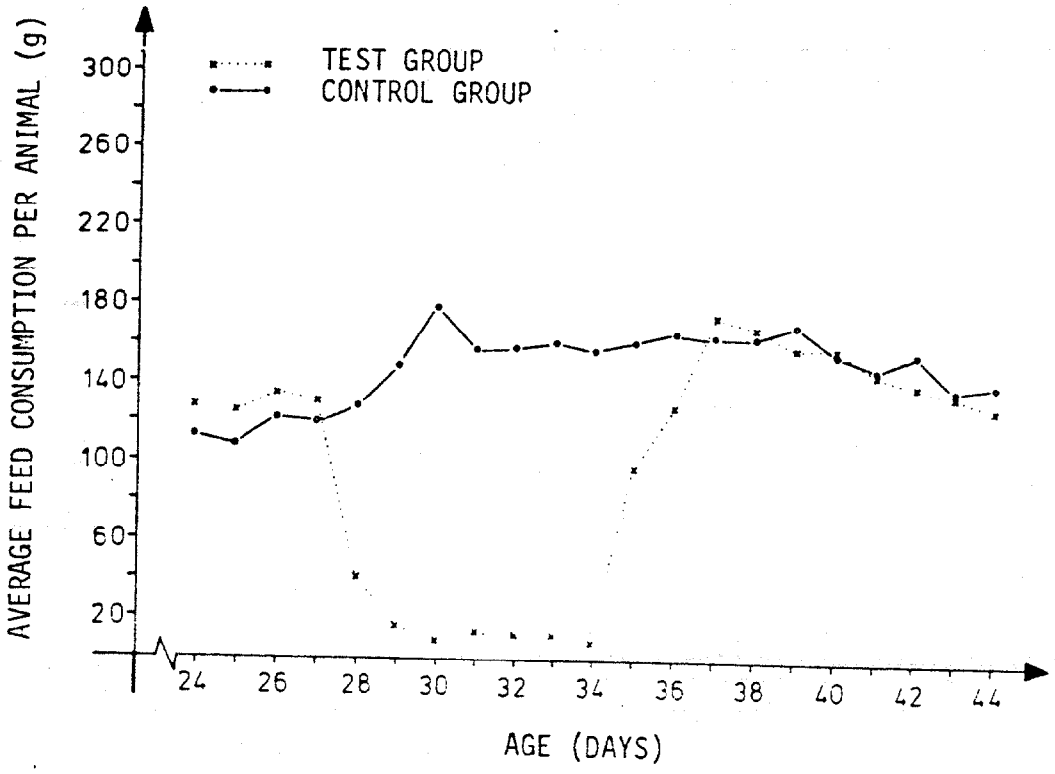

Fig.3: Main test.
Development of the average daily feed consumption (in g) per Muscovy duckling in test- and control group.
Halofuginone-medicated feed (3 mg/kg) in the test group from the 28th to the 34th day.

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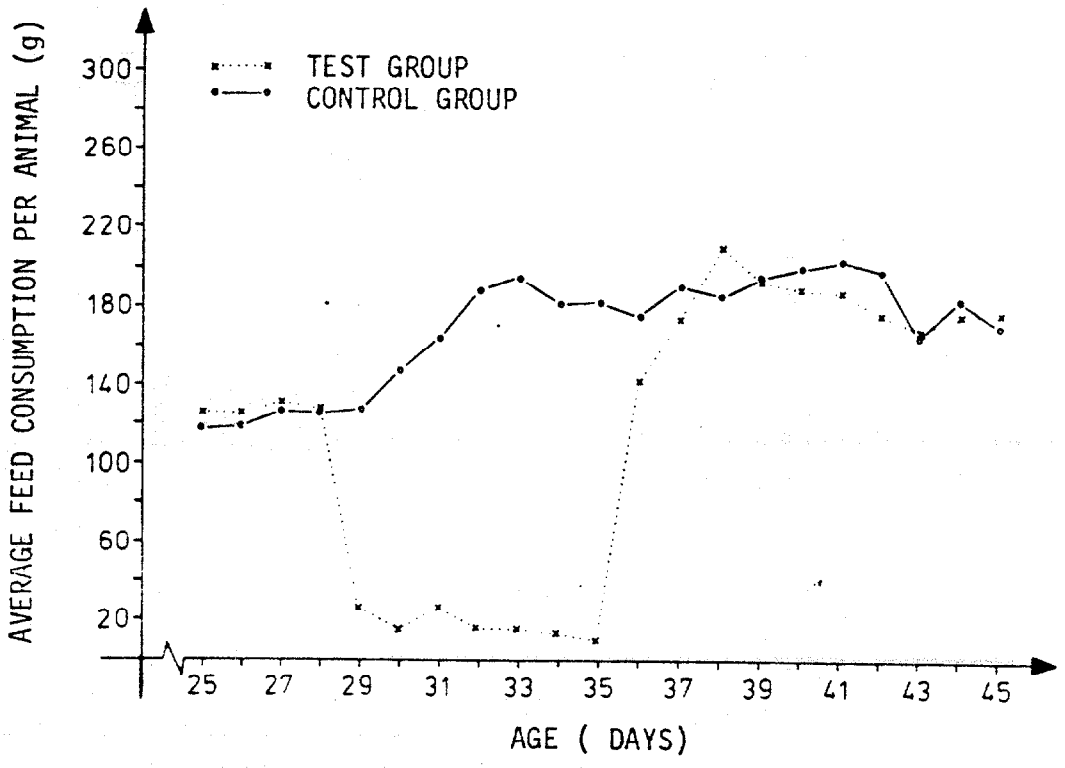

Fig.4: Main test.
Development of the average daily feed consumption (in g) per Peking duckling in test- and control group.
Halofuginone-medicated feed (3 mg/kg) in the test group from the 29th to the 35th day.

060

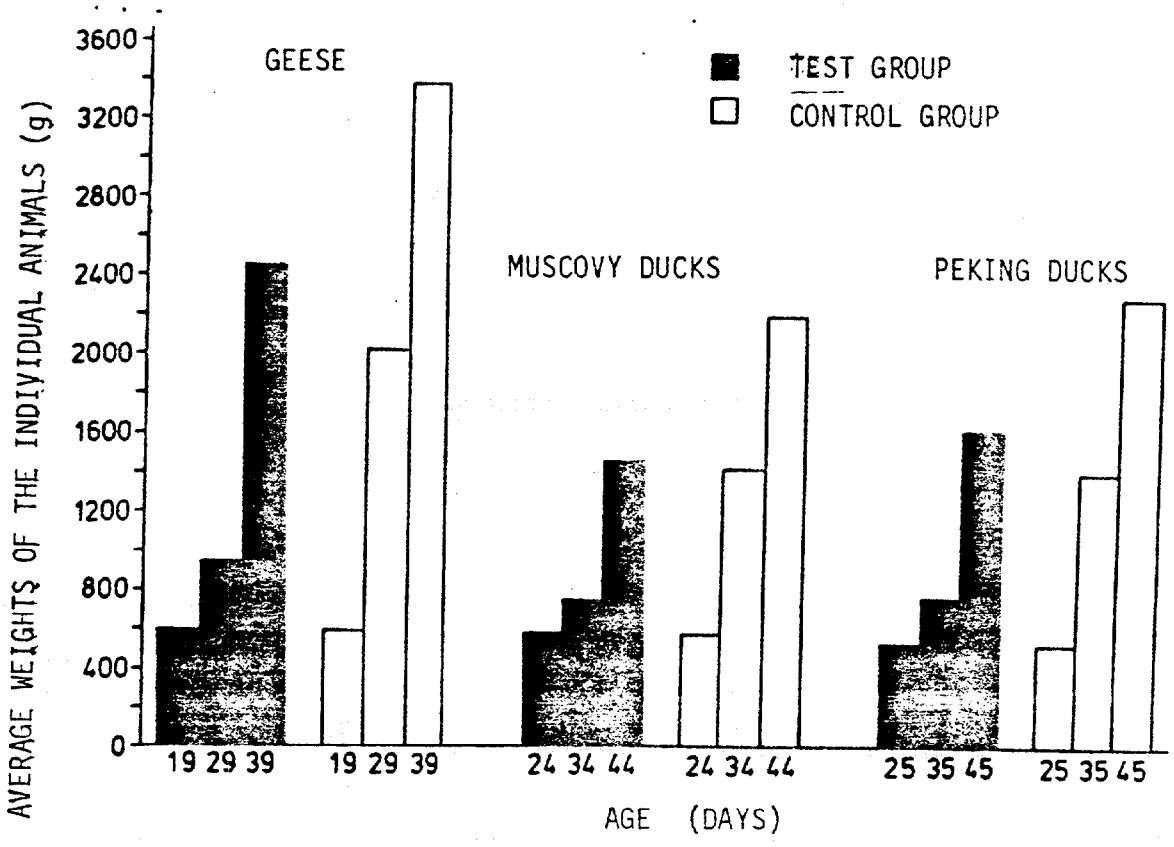

Fig.5: Main test.
Average individual weights of goslings, Muscovy ducklings, and Peking ducklings (in g) at the start of the test, after the test phase, and at the end of the follow-up phase.

TABLE 1: Preliminary test.
Average daily feed consumption per gosling (in g).

Age of Animals (Days)	Test Group Halofuginone (3 mg/kg feed) 23^{rd} - 35^{th} Day	Control Group
15	100,8	98,4
16	135,7	121,3
17	132,5	139,2
18	136,9	146,9
19	159,7	168,5
20	170,9	181,5
21	177,4	191,5
22	183,8	207,5
23	78,7	208,3
24	6,4	230,8
25	59,0	238,2
26	21,8	255,8
27	15,3	252,1
28	10,2	257,9
29	52,4	248,3
30	82,2	247,9
31	69,3	276,9
32	76,0	262,4
33	60,7	268,3
34	66,8	284,6
35	61,1	253,2

TABLE 2: Main test.
Average daily feed consumption (in g) per gosling, Muscovy duckling, and Peking duckling before, during, and after consumption of halofuginone-medicated feed by comparison with the control groups (test groups during test phase with halofuginone 3 mg/kg/feed)

Test Period	Geese			Muscovy Ducks			Peking Ducks		
	Age of Animals (Days)	Test Group	Control Group	Age of Animals (Days)	Test Group	Control Group	Age of Animals (Days)	Test Group	Control Group
Preliminary phase	19	168,9	166,0	24	126,8	111,9	25	125,6	117,6
	20	167,6	154,1	25	124,3	107,8	26	124,8	118,5
	21	175,1	167,8	26	133,3	120,7	27	131,6	126,0
	22	187,6	174,4	27	128,7	119,0	28	127,8	126,5
Test phase	23	32,6	210,4	28	41,4	127,0	29	26,7	127,4
	24	6,4	216,2	29	16,5	148,5	30	15,4	147,2
	25	0,0	224,0	30	9,5	177,5	31	26,5	163,5
	26	12,9	227,1	31	14,0	156,5	32	16,5	188,0
	27	62,9	251,7	32	12,5	157,2	33	16,0	194,6
	28	25,4	246,1	33	12,5	160,0	34	14,0	181,0
	29	35,2	254,3	34	9,0	156,0	35	10,5	181,5
Follow-up phase	30	171,4	267,5	35	96,5	160,5	36	142,0	175,5
	31	257,1	272,1	36	127,5	165,0	37	172,8	190,0
	32	289,9	242,9	37	174,0	163,5	38	210,0	185,0
	33	296,6	270,0	38	167,8	163,0	39	192,0	194,5
	34	304,6	256,0	39	157,4	169,5	40	189,0	200,0
	35	285,7	244,6	40	157,0	155,5	41	187,0	203,5
	36	279,3	229,6	41	147,5	148,0	42	176,5	198,0
	37	264,6	228,2	42	139,5	156,3	43	167,5	166,0
	38	269,6	211,4	43	138,5	136,0	44	176,0	184,5
	39	260,2	192,5	44	127,5	140,5	45	176,7	170,7

001444

Table 3: Main test.
Average individual weights with standard deviations (in g) per gosling, Muscovy duckling, and Peking duckling at the start of the test, after the test phase, and at the end of the follow-up phase.

Test Period	Age of Animals (Days)	Test Group Halofuginone (3 mg/kg feed)	Control Group
a) Geese		23rd to 29th Day	
Start of prel. phase	19	582,4 ±104,2	578,2 ±106,1
End of test phase	29	935,0 ±153,4	2012,5 ±283,9
End of follow-up phase	39	2440,1 ±324,0	3369,1 ±396,9
b) Muscovy ducks		28th to 34th Day	
Start of preliminary phase	24	577,1 ± 94,9	574,5 ± 74,9
End of test phase	34	743,8 ±106,8	1415,5 ±186,4
End of follow-up phase	44	1453,3 ±191,0	2188,7 ±281,9
c) Peking ducks		vom 29.-35. Tag	
Start of preliminary phase	25	532,8 ±87,3	533,7 ±124,0
End of test phase	35	764,0 ±115,2	1402,2 ±178,1
End of follow-up phase	45	1612,1 ±193,5	2287,4 ±257,8

Transl. 3-14-86/Gue

ROUSSEL UCLAF

APPENDIX 2

HALOFUGINONE HYDROBROMIDE

4. DESCRIPTION OF THE ENVIRONMENTAL LAWS GOVERNING THE MANUFACTURE OF HALOFUGINONE IN FRANCE

In France legislation concerning the protection of the environment is based on law N° 76-663 of 19th July, 1976

(modified by 76-1285 of 31st December, 1976)
(" " 77-1468 of 30th December, 1977)

entitled : Law relating to "Classified Installations" for the protection of the environment. (Etablissements classés).

Its range of application is defined in the Article 1 hereunder :

"Subjected to the provisions of this law are factories, workshops, warehouses, work sites, quarries and in general, installations exploited or belonging to any individual or legal entity, public or private, which could endanger or be disadvantageous to : the comfort of the surroundings, health, safety or public health, agriculture, the protection of nature and the environment, or the preservation of sites and monuments".

The decrees concerning the implementation of this law, Decree N° 77-1133 of 21st September 1977,

(modified by Decree 80-813 of 15th October 1980)
(" " Decree 82-752 of 1st September 1982)

and their annexes define these said "classified installations" and the ensemble of general rules to which they must be subjected.

Specific applications, each case considered separately, are the concern of the prefectoral authorities of the department where the installations are located. These authorities, after a public enquiry and different court and courcil hearings, issue a decree called a "Classification".

Thus, the Neuville installations were subject of classification decrees issued by the Rhône Department Prefecture and dated the 2nd February 1970, 23rd October 1978, 21st December 1983 (complementary decrees for rectification and up-date).

In addition, a specialized body called the "Association of Inspectors for Classified Installations", is responsible for the surveillance of these installations and their compliance with the rules in force. These inspectors can at any time (night or day) visit the installations subject to their jurisdiction.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC
P.O. BOX 2000, RAHWAY, NEW JERSEY 07065-0914

R. R. BUCK
ASSISTANT DIRECTOR
REGULATORY AFFAIRS

February 1, 1985

Dr. Lester M. Crawford (HFV-1)
Director
Center for Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Crawford,

We are writing this letter in behalf of:

American Hoechst Corporation
Animal Health Division
Route 202-206 North
Somerville, NJ 08876

who we understood have submitted a New Animal Drug Application for STENOROL (halofuginone) Premix as a poultry coccidiostat.

You are hereby authorized to refer to that section in Drug Master File which describes the manufacturing and control facilities of the St. Louis Blend Plant, St. Louis, Missouri of the MSD Agvet Division, Merck & Co., Inc. in support of the New Animal Drug Application.

It is our understanding that American Hoechst Corporation may wish to use the St. Louis Blend Plant as a manufacturing site for STENOROL Premix. Container and active ingredient will be furnished by American Hoechst Corporation and assays of the active ingredient and final premix will be their responsibility.

An Environmental Impact Statement is attached.

Very truly yours,

Robert R. Buck

RRB:rfg
Attachment

ENVIRONMENTAL IMPACT STATEMENT - HALOFUGINONE PREMIX

The environmental effects resulting from the manufacture of halofuginone (STENOROL) premix at the St. Louis, Missouri plant are summarized below.

Dust is emitted as a result of various diluting, blending, and packaging operations. The dust control system consists of exhaust hoods and a series of filter bags. The control of dust is subject to and in compliance with Title 10, Code of Missouri State Regulations, Chapter 5--Air Quality Standards and Air Pollution Control Regulations for the St. Louis Metropolitan Area.

Water that is used to wash out equipment is discharged to the Metropolitan St. Louis Sewer District. The effluent from the plant contains traces of halofuginone, vitamins, grain and inorganic feed carriers. The discharge of effluent to the sewer is in compliance with Title 10, Code of Missouri State Regulations, Chapter 7--Water Quality, through compliance with the Metropolitan St. Louis Sewer District's Ordinance No. 2289. The code number for the Merck plant in the District is 3112-2369.

Trash and paper resulting from the production process is transported to a local landfill by a licensed disposal company according to Title 10, Division 80, Missouri Solid Waste Rules and Regulations.

Robert R. Buck
Assistant Director
Regulatory Affairs

RRB:rfg

SOUTHERN MICRO-BLENDERS, INC.

"Blenders and Premixers

001448

APR 19 19[illegible]

V.B. ANDERSON

APRIL 13, 1982

MR. BRIAN ANDERSON
AMERICAN HOECHST CORPORATION
ROUTE # 202-206 NORTH
SOMERVILLE, NEW JERSEY 08876

Dear Brian:

We hereby authorize you to use the enclosed revised Environmental Impact Statement dated April 13, 1982 for your Stenorol NADA.

Sincerely,

ROBERT E. RENCH,
PRESIDENT

RER/bd
ENCLOSURE

068

3801 NORTH HAWTHORNE STREET CHATTANOOGA, TENNESSEE 37406 • PHONE 615-629-1469

SOUTHERN MICRO-BLENDERS, INC.
"Blenders and Premixers"

001449

APRIL 13, 1982

AMERICAN HOECHST CORPORATION
ROUTE # 202-206 NORTH
SOMERVILLE, NEW JERSEY 08876

RE: NADA STENOROL
AMERICAN HOECHST CORPORATION
SOLE U. S. A. LICENSEE
SOMERVILLE, NEW JERSEY 0876

AN ANALYSIS OF THE ENVIRONMENTAL IMPACT OF THE MANUFACTURING PROCESS (ES) OF THE ARTICLE THAT IS THE SUBJECT OF THIS REQUESTED ACTION AS SPECIFIED UNDER 21 CFR 25.1 (g).

Southern Micro-Blenders is an existing operation engaged in blending and manufacturing other medicated premixes. The manufacture of Stenorol Premix will not emit pollutants as a result of the proposed operation. Dust will be the only emmision and collection equipment is installed to eleminate discharge of that dust. Dust will be deposited in a hopper or collector, discharged into a container and used in subsequent batches of the product. There are no liquid or gaseous materials evolved from the process.

Southern Micro-Blenders certifies that the facility complies with all local, state and federal requirements, and holds a valid permit NO. 3445-30200799-01C issued by Chattanooga/Hamilton County Air Pollution Control Bureau.

069

3801 NORTH HAWTHORNE STREET · CHATTANOOGA, TENNESSEE 37406 · PHONE 615-629-1469

V M S, INC
Office and Plant Location
1080 Wilbanks Street
Montgomery, Alabama

THE ULTIMATE IN MINERAL VITAMIN NUTRITION MANUFACTURING
FOR LIVESTOCK

RECEIVED
APR 1 ?
001450
V.B. ANDERSON

Mailing Address
P. O. Box 4[illegible]
Montgomery, Alabama 36195-4001
CABLE: VMSINC (205) 834-4518

April 13, 1982

V. Brian Anderson
American Hoechst Corp.
Route 202-206, North
Somerville, New Jersey 08876

Dear Brian:

Responding to your letter of March 22, the following is a brief description of our pollution control procedures at V.M.S., Inc.

Our only emission is in the form of dust from the various ingredients used in formulating mineral supplements and protein blocks for animal consumption. These ingredients are held and passed through a closed system so that the dust is contained within the system.

As air is displaced within the system (ie, mixers, blenders, etc.), dust is trapped in vibrating dust collectors located in the system components and returned to the product.

The product exits the system at one of two points; either (1) as a pressed block or (2) bagged in the form of a loose mineral. Before blocking, cane molasses is applied to the product in such quantities that the product is thoroughly wetted and there is virtually no dust emitted.

Molasses is also applied to the loose mineral before bagging - and in many cases, mineral oil is added as a dust control measure.

Exhaust fans which are located at strategic spots throughout the mill are equipped with filters as a further control measure. These filters are inspected on a scheduled basis and changed as necessary.

V. Brian Anderson
American Hoechst Corp.

April 13, 1982

V.M.S., Inc. is registered with the Environmental Protection Agency (Registration No. 10461-AL) and the Federal Drug Administration as an approved drug establishment (ID. #1019969) - and to my knowledge - is in full compliance with all local, state and federal regulations.

Brian, I hope that this will provide you with the information that you requested. If I might be of further assistance, please do not hesitate to call.

Cordially,

V. M. S., INC.

W. Brent Camp
Executive Vice President

WBC:dma

Lavergne Supplement Company

Vitamins, Minerals & Formula Service
1038 Space Park South ☐ Nashville, Tennessee 37211 ☐ (615) 834 4144

May 13, 1983

AMERICAN HOECHST CORPORATION
Route # 202-206 North
Sommerville, New Jersey 08876

NADA STENOROL
AMERICAN HOECHST CORPORATION
Sole U.S.A. Licensee
Sommerville, New Jersey 08876

An Analysis of the environmental impact of the manufacturing process of the article that is the subject of this requested action as specified under 21 CFR 25.1 (g).

LAVERGNE SUPPLEMENT COMPANY is an existing operation engaged in blending and manufacturing other medicated premixes. The manufacture of Stenorol Premix will not emit pollutants as a result of the proposed operation. To eliminate dust this product will be sprayed with 2 percent mineral oil. There are no liquid or gaseous materials evolved from the process. The Stenorol Premix will be manufactured in our medicated mill. This is a self contained unit consisting of a separate mixer with an elevator leg.

LAVERGNE SUPPLEMENT COMPANY certifies that the facility complies with all local, state and federal requirements. We also hold a valid EPA Registration number 37699-TN-01 .

Sincerely,

Ralph Hurst, Nutritionist

RECEIVED
MAY 16 1983
DR. R. J. GRANT

Challenger

MAC-PAGE, INC.

1600 South Wilson Avenue
DUNN, NORTH CAROLINA 28334

August 12, 1983

Director
Food and Drug Administration
Department of Health, Education and Welfare
Washington, D. C. 20204

Dear Sir:

Following is supplemental information concerning the environmental impact statement to be attached to our F D Form 356 application for Stenorol.

Re: 21 CFR Part 6

1. An identification of pollutants expected to be emitted.

   The only pollutant expected to be emitted would be dust. Our plant has adequate dust control equipment.

2. A citation of applicable federal, state and local emission requirements.

   We are in compliance with all known state, federal and local emission standards, since we are not releasing any pollutants.

3. Certification.

   To the best of my knowledge and belief, the above statements are true.

Signed George M. Herrick
Director of Quality Control

Sincerely,

Mac-Page, Inc.

George M. Herrick, Ph.D.
Director of Quality Control

cc: American Hoechst Corporation

GMH/bbf