ENVIRONMENTAL ASSESSMENT

1. June 1989 (Revised November 23, 1994)*

2. Hoffmann-La Roche Inc.

3. 340 Kingsland Street
Nutley, New Jersey 07110

4. Description of the proposed action.

The proposed action is approval of a supplement to approved New Animal Drug Application 96-298V coded in 21CFR 558.311 which provides for the use of lasalocid as a 20% premix (trade name **Avatec**) for the prevention of coccidiosis in turkeys with a zero day withdrawal time. The use level in feeds remains the same as presently approved for broiler chickens at 68-113 g/ton of feed.

The specific coccidia in turkeys controlled are *Eimeria meleagrimitis, E. gallopavonis* and *E. adenoeides.*

The dose rate needed for prevention was verified in three well-controlled studies conducted under floor-pen conditions using mixed coccidial isolated of *E. meleagrimitis, E. gallopavonis,* and *E. adenoeides.* Laslaocid concentrations in the feed were 0, 75, and 125 ppm (0, 68, and 113 g/ton). Medication with lasalocid was started when poults were one day of age and the coccidial challenge was given at 14 days of age.

The medicated birds had significantly better weights, better feed conversions, lower coccidiosis mortality, and lower lesion scores than the unmedicated control birds.

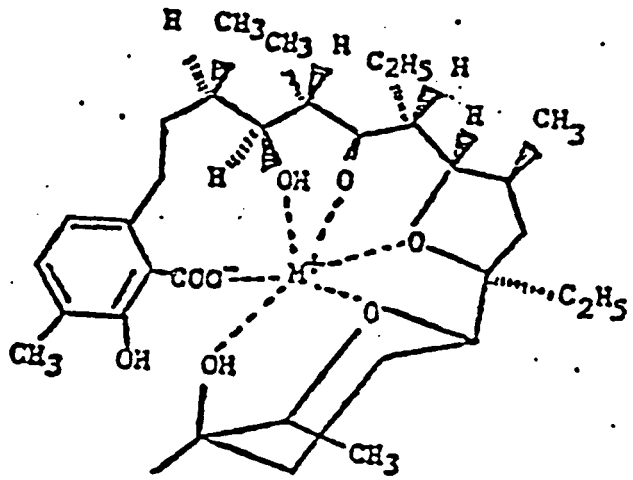
The safety of lasalocid in turkeys was confirmed in a study where day-old poults were medicated continuously for 8 weeks at 0, 125, and 600 ppm lasalocid in the diet. No differences between the treatment groups were noted regarding performance, feathering, leg soundness, and blood clotting times. There were no significant gross or histopathological changes noted

*Reflects current turkey production methods and updates various environmental permits.

5. Identification of chemical substances that are the subject of the proposed action:

The active ingredient in the commercial Bovatec premixes is lasalocid with the inert diluent a grain based product such as rice hulls or wheat middlings.

Lasalocid was first reported in 1951 by J. Berger.



Lasalocid

Lasalocid is classified as an antibiotic having virtually no gram-negative or yeast activity and is limited to activity against gram-positive organisms. The in vitro data presented below confirms the weak gram-positive activity and the lack of activity against yeast.

Organism	ATCC No.	MIC (ug/mL)
Staphylococcus aureus	6538P	1.6
Sarcina lutea	9341	3.1
Bacillus sp. E	27850	0.1
Bacillus subtilis	558	1.6
Bacillus megaterium	8011	3.1
Mycobacterium phlei	355	12.5
Streptomyces cellulosae	3313	6.3
Paccilomyces variota	26820	50.0

5. (cont'd.)

The lasalocid molecules exist in a cyclic configuration with two ends held together by a hydrogen bond between the carboxylic group and a tertiary hydroxyl on the terminal tetrahydropyran ring. The oxygen functions are concentrated in the center of the molecule, and the hydrophobic alkyl groups are all on the surface. This configuration accounts for the unusual solubility properties of the compound. This configuration of the polyether antibiotic salts accounts for their ionophoric activity.

X-ray crystallographic analysis on a number of lasalocid salts revealed that in all cases, two antibiotic molecules exist in a non-symmetrical dimeric conformation. The polar sides of the two lasalocid molecules face each other forming a sandwich structure around a dibasic cation, such as Ba^{+2} and a water molecule or two monobasic cations and two water molecules.

For all of the above cases, the basic solubility profile of the lasalocid salts or free acid doesn't change because the configuration is maintained over the pH range. Lasalocid has an apparent pK of 4.4 as measured in 60% aqueous methanol and an octanol water partition coefficient of 705 for the sodium salt of lasalocid.

The pK indicates that both the salt and the free acid can exist in environmental water samples, but because the configuration doesn't change, neither does the solubility appreciably.

The list of solubilities below was obtained using a 24-hr equilibrium to determine solubility:

5. (cont'd.)

Solvent	% Solubility Lasalocid Na Salt	Lasalocid Free Salt
Chloroform	50	-
THF	> 50	> 50
THF:Water (1 : 1)	5-10	0.3-0.5
Methanol	4.7	5.5
Methanol:Water (3:1)	0.6	0.3
(1:1)	0.5	0.04
(1:3)	0.2	0.03
Water	0.1	0.01

Inspection of the above data shows that the solubility profile is dictated by the configuration of the total molecule and not the polar groups.

The Material Safety Data Sheet for lasalocid prepared by Hoffmann-La Roche Inc. as required by OSHA (Federal Register, 48:53340, November 25, 1983) is included on the following pages.

HOFFMANN-LA ROCHE INC.
CORP. ENVIRONMENTAL & SAFETY AFFAIRS
NUTLEY, NEW JERSEY 07110
(201) 235-2323

FILE NO.	PAGE
E-688	1 of 6

007

MATERIAL SAFETY DATA

ORIGINATED	03/17/81
APPROVED	+
REVISED	09/13/85

CHEMICAL NAME

[6-[7(R)-[5(S)-Ethyl-5-(5(R)-ethyl-tetrahydro-5-hydroxy-6(S)-methyl-2H pyran-2(R)-yl) tetrahydro-3(S)-methyl-2(S)-furyl]-4(S)-hydroxy-3(R),5(S)-dimethyl-6-oxononyl]-2,3-cresotic acid sodium salt]

CODE NO.

51215

CAS NO.	RO NO.
25999-31-9	2-2985

Formula: $C_{34}H_{53}O_8Na$
Formulation/s: AVATEC; BOVATEC
Synonyms: sodium lasalocid; antibiotic X-537A
Chemical Family: Polyether
Molecular Weight: 612.78

I. PHYSICAL PROPERTIES Sources:

Appearance and Odor: White crystalline powder; odorless
Soluble in: Chloroform, THF, methanol, ethyl acetate
Melting Point: 105-107°C
Solubility in Water, % by wt. at 20°C: 0.05%
Optical Rotation: -41/2°

II. CHEMICAL PROPERTIES Sources:

Stability: Unstable
Conditions to Avoid: Acidic conditions; heat plus alkalinity
Materials to Avoid: Ferric sulfate
Hazardous Polymerization: Will not Occur

III. HAZARDOUS INGREDIENTS Sources: CESA

Not Applicable

IV. FIRE AND EXPLOSION HAZARD Sources: CESA

Combustion and dust explosion tests showed that the substance ignites in a match flame ignition source burning to a small char residue with the production of sooty black smoke and flammable vapor, and that the figures in the table below were developed under satisfactory operating conditions.

Vent	Developed Pressure (psig)
Unvented	64
1 sq ft to 180 cu ft	36
1 sq ft to 100 cu ft	30
1 sq ft to 65 cu ft	5
1 sq ft to 35 cu ft	<1

Extinguishing Media: Water spray, dry chemical, carbon dioxide or foam, as appropriate for surrounding fire and materials.
Fire Fighting Procedures: Evacuate personnel to an area of upwind direction and remove unneeded materials; keep fire-exposed containers cool with water spray, and provide fire fighters with self-contained breathing equipment.

V. HEALTH HAZARDS Sources: To

Threshold Limit Value:
TWA: None established
STEL: None established
Toxicity:
Industrial Exposure: May produce slight corneal opacity and conjunctival redness when in contact with eyes.
Experimental: Data obtained with injectable preparation
LD_{50}(mouse, orl) 146 ± 8 mg/kg at 5D
LD_{50}(mouse, ip) 68 ± 4 mg/kg at 5D
LD_{50}(mouse, sc) 140 ± 14 mg/kg at 5D
LD_{50}(rat, orl) 122 ± 7 mg/kg at 5D
LD_{50}(rat, ip) 26 ± 3.5 mg/kg at 5D
LD_{50}(rat,neonates, orl) 33 ± 2 mg/kg at 5D
LD_{50}(rbt, orl) 40 ± 6.7 mg/kg at 5D
LD_{50}(rbt, skn) 14000 mg/kg at 14D (approx.)
[To]
LD_{50}(mouse, iv) 18.5 ± 1.8 mg/kg
LD_{50}(rat, iv) 17.3 ± 0.9 mg/kg
LD_{50}(rbt, iv) 3.6 ± 1.1 mg/kg
LD_{50}(dog, iv) 5.99 ± 0.64 mg/kg
[Po #25755 11/73]

Eye Irritation, rbt: Instillation of .04 g dry powder into the conjunctival sac caused corneal and conjunctival ulceration within 1 hour-7 days of treatment. [Ta 7/15/77]

Instillation of 0.1 ml powder into the conjunctival sac caused the following signs of irritation, whether eyes were irrigated at 5 minutes or 24 hours after treatment: conjunctival redness and chemosis; iritis; corneal opacity, ulceration, necrosis and pannus.
[Bio/Dynamics #4344-77 6/23/77]

Skin Irritation, rbt: No irritation was apparent within 48 hours of application of 500 mg moistened powder to intact or abraded skin patches. [Ha 1/24/77]

Skin Sensitization Tests, gpg: No sign of sensitization was noted in either of 2 studies which tested lasalocid-induced animals against controls as follows: Shaved skin of 10 females was treated with formulated compound intradermally, one week later topically over the injection sites, and 2 weeks later with a challenge application at a remote site. A control group was treated with vehicle alone during the induction phases and with test material during the challenge phase. [Ha et al 10/13/77 and 11/16/77]

Inhalation Study, rat: A 67 minute exposure to a concentration of 13 mg/l caused death in 4/10 animals and symptoms in survivors including body weight loss, excess nasolacrimal discharge; kidney, liver and lung discoloration were evident at necropsy. [Pf 7/27/77]

4-Hour Inhalation Study, rat: LC_{50}(rat, ihl) 2.65 mg/l (1.77-3.98)
Symptoms: lacrimation, salivation, diarrhea, low motor activity. [Pf 1/13/78]

2-Week Toxicity, rat, ihl: 10 rats/sex/dose were exposed to (theoretical) concentrations of 10 or 100 mg/m^3 dust, 6 hours/day 5 days/week for an anticipated schedule of two weeks which was reduced because of early mortality. The following symptoms are outstanding:

14/20 deaths at high dose; corneal opacity, lacrimation, moist rales, dose-dependent decrease in body weight, variations from control clinical chemistry values including changes in tl. and differential WBC, reduced hct; lung discoloration, visceral congestion and hemorrhage apparent at autopsy.
[Jo 8/17/79 via Bio/Dynamics]

Acute Toxicity, gpg, ihl: 5/10 animals died during or shortly after a 1-hour exposure to 11.5 mg/l dust suspension. Symptoms noted prior to death or among survivors include nasal, lacrimal and oral discharge, soft stool, difficult breathing, decreased body weight. Necropsy findings include lung and liver discoloration, urinary- and gall bladder distension. [Bio/Dynamics #77-1911 8/4/77]

Inhalation Study, mouse: A one-hour exposure to an average concentration of 12.5 mg/l dust suspension (tl 10.16 gm test material) caused the following symptoms among 5 males and 5 females from 2 hours to 14 days after exposure: ocular discharge, eyelid swelling, corneal opacity; loss of hair, general poor condition; lung discoloration apparent at necropsy. [Bio/Dynamics #77-1910 8/4/77]

Chronic Toxicity, mouse, orl: Daily administration to 80 mice/sex/dose at levels of 10, 35 or 100 ppm of diet for two years caused no compound-related toxic or carcinogenic effects. [Le 7/25/80 via Hazleton]

13-Week Toxicity, rat, orl: The following dose-dependent changes were seen among groups of 8 rats/sex/dose given 5 or 20 mg/kg/day in diet for 13 weeks: decreased body weight and food consumption, changes in RBC's and in clinical chemistry values. Treatment at 2 mg/kg/day caused no apparent effect. [Pf #26202 11/73]

13-Week Toxicity, rat (weanling), orl: Daily dietary administration of 1, 2, 3 or 10 mg/kg prior to mating and throughout gestation and lactation had no significant effect on the fertility and reproductive performance of parent rats. Reduction in maternal and neonatal weight gain was the only noted sign. 60 weanlings/sex/dose given the same dietary levels as each parent group for 13 weeks showed dose- or sex-dependent symptoms including decreased body weight gain and food consumption, decreased hgb and hct, WBC count change, alterations in clinical chemistry and increased hemosiderin in liver and kidneys. [Ho #23297 11/15/74 and Pf #29981 2/75]

13-Week Toxicity, rat (weanling), orl: The following dose- or sex-dependent symptoms were noted among groups of 40 weanlings/sex/dose given dietary levels of 1, 2, 3 or 10 mg/kg/day for 13 weeks: decreased body weight gain, slightly decreased organ weights, changes in hematology and clinical chemistry, increased levels of hemosiderin in liver and kidneys. [Pf #29982 3/75]

13-Week Toxicity, rat, orl: No deaths or other treatment-related effects were seen among animals given daily doses of 10, 35 or 120 ppm as dietary admix prior to and throughout breeding and during gestation, lactation and after weaning. [Le 11/20/78]

13-Week Toxicity, dog, orl: 4/6 beagles given 10 mg/kg/day as gelatin capsules for 13 weeks showed transient neurological effects including hind limb tremors. Treatment at 2 or 5 mg/kg caused no apparent effects. [Pf #26203 11/73]

Chronic Toxicity, dog, orl: Daily administration to 10 beagles/sex at dietary level of 180 ppm for two years caused slight increase in serum alkaline phosphatase level and decreased prostate weight. Treatment at levels of 35 or 10 ppm caused no significant adverse effect. [Le 7/25/80 via Bio/Dynamics]

Chronic Toxicity, rat, orl: Daily administration to 85 rats/sex/dose at dietary levels of 10, 35 or 120 ppm (equivalent to 0.5, 1.8 and 6.2 mg/kg/day M, 0.6, 2.2, 8.1 mg/kg/day F) for two and one-half years caused no significant compound-related effects. The subject animals were derived from parent rats similarly treated with admix for one week prior to breeding. [Le 4/13/81 via Hazleton]

Reproduction and Teratology Study, rat, orl: Daily dietary administration of 120 ppm (equivalent to 8.3 mg/kg M and 11.4 mg/kg F) to three successive generations caused reduced mean body weight in females of each generation, reduced pregnancy and fertility rates in every generation, lower implantation efficiency in the first filial generation and lower mean offspring weight beginning in second filial generation. Treatment at 35 and 10 ppm diet (equivalent to 0.7 and 2.4 mg/kg M, 0.9 and 3.1 mg/kg F) caused no apparent change in any parameter measured. [Le 7/25/80]

Mutagenicity Testing

Ames Test, substance: Addition of non-toxic concentrations (5, 50, 165, 275 and 400 micrograms/plate) to the growth medium of 4 tester strains of S. typhimurium caused no reversion to histidine independence, either with or without the inclusion of Aroclor-induced rat liver homogenate. [We 6/27/79]

Ames Test, Biomass extract: Addition of non-toxic concentrations of methanol/methylene chloride extracts (25, 250 and 2500 micrograms/plate insoluble residue and 12.5 and 125 micrograms/plate soluble portion) to the growth medium of 4 tester strains of S. typhimurium caused no significant increase in the number of histidine-independent revertants, either with or without the inclusion of enzyme-containing rat liver homogenate. [We 12/3/79]

Ames Test, cattle liver residue: Addition of lasalocid-derived residue (2.5, 25 and 250 micrograms/plate soluble portion and 25, 250 and 2500 micrograms/plate insoluble fraction) to the growth medium of 4 tester strains of S. typhimurium caused no significant increase in the number of revertant colonies, either with or without the inclusion of enzyme-containing rat liver homogenate. [We 9/19/80]

Emergency and First Aid:
Eye contact: Irrigate surfaces with water for 15 minutes. Call physician.
Skin contact: Flush areas with water for 15 minutes. Call physician.

VI. SAFETY MEASURES AND EQUIPMENT Sources: CESA

Ventilation: Local exhaust recommended
Respiratory: NIOSH-approved respirator for toxic dusts
Eyes: Full face shield with safety goggles
Gloves: Rubber
Other Directives:
Precautionary Note: When mixing or handling (AVATEC/BOVATEC) use protective clothing, impervious gloves and a dust mask. Avoid contact with eyes. Wash thoroughly with soap and water after handling.

VII. SPILL CONTROL, WASTE TREATMENT AND DISPOSAL Sources: CESA

Spill Control: Wet down with water spray, shovel into disposable containers and remove to appropriate disposal area.

Waste Treatment and Disposal: Incinerate contained waste in an approved incinerator equipped with afterburner and scrubber.

VIII. REGULATIONS Sources: CESA

DOT: Not regulated

EPA: Not regulated

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The information contained herein is, to the best of Hoffmann-La Roche's knowledge, complete and accurate. Roche, however, uses many sources and references for gathering this information. Thus, Roche cannot guarantee completeness or accuracy and disclaims all liability for its handling or use.

6. Introduction of substance into the environment.

The approval of the lasalocid supplemental claim for the prevention of coccidiosis in turkeys could optimistically result in an increase in usage that would be slightly more than that utilized by the broiler chicken industry in 1988. This increase in USA usage will not affect the amount of lasalocid bulk substance produced at the facility in Belvidere, NJ because the plant is currently at full capacity producing for worldwide consumption. The net effect will be the reduction of export shipment volume as the use in turkeys increases in the USA.

A. Introduction of substances from the manufacturing site.

1. Lasalocid - bulk productions

Bulk lasalocid is produced at the Hoffmann-La Roche manufacturing facility in Belvidere, NJ.

a. Fermentation operations. Lasalocid is produced by standard fermentation at the Roche manufacturing facility in Belvidere, NJ. Lasalocid is extracted from the whole broth using ethyl acetate, evaporated and crystallized, and converted to the sodium salt. The sodium lasalocid crystals are isolated, dried and blended for uniformity to produce the finished product.

The following tables show the material balances for production of one kilogram of lasalocid and one kilogram of sodium lasalocid.

Material balance per 1 kg lasalocid:

	Kilograms
Total input of chemicals	5.1
Output from process	
Product	1.0
Air discharge	1.421[(1)]
Sewer discharge	2.679

[(1)]As CO_2, metabolic product of fermentation

6. (cont'd.)

Material balance per 1 kg sodium lasalocid

	Kilograms
Total input of chemicals	2.247
Output from process	
Product	1.0
Solid disposal	0.061
Air discharge	0.074
Sewer discharge	1.112

b. Wastewater effluent

All wastewaters from the lasalocid process are combined with wastewaters from other manufacturing operations and discharged to the facility's advanced secondary wastewater treatment facility at the plant site. The discharge from the wastewater treatment plant to the Delaware River is covered by NPDES permit no. NJ0004952 which expired on January 31, 1990. The present renewal application was filed 180 days prior to the expiration date of January 31, 1990, with no response from the state to date. The state regulations allow the manufacturer to operate under the existing permit until the state takes the appropriate action.

c. Air emissions

Air emissions from the lasalocid process consist of potentially odorous compounds from the fermentation steps; the organic solvent ethyl acetate, and particulate matter from product drying and blending operations. Air emissions are controlled through the use of an ozonator for odor control, vent condensers and conservation vents for control of organic solvent emissions, a wet scrubber, and various types of fabric filter dust collectors for control of particulate matter.

Air emissions in NJ are regulated under NJAC 7-27-1 et seq., the Bureau of Air Pollution Control petition of New Jersey Administrative Code. These regulations include subchapters governing allowable emissions of particulate matter and volatile organic substances from manufacturing processes, as well as setting forth the requirements for obtaining permits to construct or alter process equipment.

6. (cont'd.)

c. Air emissions (cont'd)

The lasalocid process operates under, and is in compliance with the following New Jersey Department of Environmental Protection (NJDEP) Certificates to Operate: (expiration dates in parentheses)

22840 (11/17/96)	23174 (06/01/96)	23175 (06/01/96)
23176 (06/01/96)	109195 (12/09/94)	116665 (01/02/95)
100449 (02/28/97)		

The level of dust in the processing areas during bulk powder manufacturing operations will be controlled by local exhaust ventilation and general room ventilation. Employee exposure levels are expected to be within safe levels. If necessary, further protection will be provided by the use of personal protective equipment such as respiratory protectors.

d. Solid/liquid wastes

The only solid waste associated with the manufacture of lasalocid is the material removed from the dust collectors in the finishing operations. This material is recycled.

2. Avatec premix production

a. Premix blending operation

Lasalocid is blended with other ingredients to product a feed premix at the Roche facility in Fresno, California. The only pollutant of concern from the premix blending operation is particulate matter. The emission of particulate matter is controlled by a fabric filter dust collector. Emissions of particulate matter are governed by the Rules and Regulations of the Fresno County Air Pollution Control District (FCAPCO) - Regulation II Permits and Regulation IV Prohibitions: Rule 401 Visible Emissions and Rules 404, 405, and 406 concerning allowable quantities. The FCAPCO has issued permit no. 1040007010 to the Fresno facility for emissions from the premix blending plant operation. The facility is in compliance with the provisions of the permit.

6. (cont'd.)

B. Introduction of substance from feed mixing locations.

The bulk of the feed mixing will be done at commercial feed mills or at feed mills of large integrated turkey operations and have to meet Good Manufacturing Practice Standards for feeds. With the required manufacturing controls for feed, inventory accountability and quality assurance procedures, the potential for release of lasalocid sodium into the environment at these locations should be minimal.

C. Introduction of substances into the environment at the use site.

The estimated turkey production in the United States was 287 million birds in 1993. The end use distribution of birds are hens at 13 to 15 pounds (13 weeks old), young toms at 22 to 24 pounds (15 weeks old) and heavy toms at 25 to 30 pounds (18 to 20 weeks old).

Coccidiostats are generally used in turkey production in continuous feeding programs for the first 10 weeks of age. Heavy male and heavy female turkeys will eat approximately 19 pounds and 15 pounds of feed, respectively, through 10 weeks of age. The total feed consumed by 287 million turkeys during this period assuming a 50/50 male/female ratio is 2.44×10^6 tons.

It is estimated that currently 50% of the coccidiostats used in turkeys are ionophores with the remaining 50% divided among amprolium, halofuginone, sulfadimethoxine plus ormetoprim and zoalene. An optimistic projection is that lasalocid could potentially be used for 50% of the ionophore applications or 25% of the total coccidiostat use in turkeys.

The projected annual use of lasalocid in turkeys would therefore be 2.44×10^6 tons of feed x 0.25 pounds of lasalocid per ton (125 ppm highest use rate) x 25% of coccidiostat market, assuming all turkeys receive a coccidiostat. This equates to 76 U.S. tons (69 metric tons).

Avatec will be marketed directly to 20 to 25 integrated companies located in major turkey production areas thus minimizing potential environmental exposure during the product distribution process.

6. (cont'd.)

The management of turkeys is similar to broiler chickens where they are raised from day-old poults to 6-8 weeks of age in the same brooder house. At this point the birds are moved to grower houses for the next 8-16 weeks. Approx. 10-20% of the turkeys will be moved onto the open range pens at 10-12 weeks of age and maintained in the open until they would go to market at 14-24 weeks of age. The use of range pens for growing purposes is decreasing as new complete confinement facilities are built for turkeys.

The litter used in confinement houses is primarily softwood shavings, sawdust straw and rice hulls. The houses are usually cleaned after each growing cycle, and spread on or tilled in the soil as fertilizer, at a rate of 2 tons/acre. The turkey litter is handled in the same fashion as for broiler chicken litter.

Lasalocid is found in the droppings of turkeys at the same concentration found in the droppings of chickens. Metabolism studies with C^{14}-lasalocid comparing the chicken and turkey were done to support the turkey use of lasalocid as a coccidiostat. The percent of intact lasalocid in the turkey and chicken droppings is 10% and 12%, respectively of the total radioactivity present. The lasalocid turkey litter, therefore, will be the same as the lasalocid chicken litter in both concentration and disposition.

The fecal data noted above were obtained from total residue radiolabeled lasalocid studies in turkeys with comparative metabolism C^{14}-lasalocid studies in the chicken, mouse, rat and dog.

The total distribution and elimination of lasalocid-^{14}C administered to turkeys at a concentration of 125 ppm in the feed was determined for 14 days and during a zero day slaughter period. The concentration of total radioactivity and intact lasalocid via hplc was determined in the droppings during treatment, in the whole blood, and the edible tissues at slaughter.

Six B.U.T. Big 6 strain turkeys, 3 male and 3 female, 12-14 weeks old, were individually housed during the 14-day treatment period. The birds were offered a special broiler/turkey diet containing lasalocid-^{14}C sodium at a level of 127 ppm in the feed. The concentrations of radioactivity in the blood and tissues were determined in the 6 birds at industrial zero day time (8 hrs post last dose) and are listed below:

ppm C^{14}-lasalocid equivalents
N = 6

Whole Blood	0.42	Liver	3.38
Abdominal Fat	0.16	Muscle	0.03
Kidney	0.43	Skin & Fat	0.30

6. (cont'd.)

The concentrations of intact lasalocid sodium were determined in the individual daily combined urine and feces samples of treated birds during the 14-day treatment by high performance liquid chromatography. The average daily concentration of intact lasalocid found during the treatment period was 2.45 ± 0.42 ppm. This concentration of intact lasalocid found in the toluene, chloroform extract of fresh homogenized urine and feces, was approx. one-half of the concentration found in the exhaustive methanol extraction of the lyophilized urine and feces samples in the comparative metabolism study.

The metabolic profiles in the feces resulting from the oral administration of lasalocid-^{14}C to 2 target species (turkey, chicken) and 3 species used to assess compound toxicity (mouse, rat, dog) were compared. The method used involved solvent extraction and fractionations, preparative layer chromatography (plc) and high performance liquid chromatography (hplc) analysis of the major fractions obtained. The proportion of radioactivity in the fractions from turkey feces are close to those from the chicken feces, similar to one of the tox species, the mouse.

Intact lasalocid forms the major single component in the feces of all five species in their respective chromatograms. The turkey and chicken have very similar percentages of total activity excreted as intact lasalocid (10.0% and 12.0%, respectively). It forms a larger percent of the feces components in the rat, dog and mouse (43.7%, 32.2% and 22.1%, respectively). With respect to the other components excreted, the pattern in the turkey is very similar to the chicken. In addition, all the significant components present in the turkey are also present in at least one toxicological model species.

7. Fate of emitted substances in the environment.

The utilization of lasalocid by the turkey was studied using C^{14}-lasalocid and metabolically compared at the same time to the utilization in the chicken and the 3 toxicology models (dog, rat, mouse).

The total distribution and elimination of lasalocid-^{14}C administered to turkeys at a concentration of 125 ppm in the feed for 14 days were evaluated in a total residue study. The concentration of total radioactivity and intact lasalocid via hplc was determined in the droppings during treatment and in the whole blood and in the edible tissues at slaughter.

Six B.U.T. Big 6 strain turkeys, 3 male and 3 female, 12-14 weeks old, were individually housed during the 14-day treatment. The birds were offered a special broiler/turkey diet containing lasalocid-^{14}C sodium at a level of 127 ppm in the feed. Average weight of the female birds during treatment was 7.1 kg and the average daily dose was 6.1 mg/kg. The average weight of the male birds was 8.9 kg and the average daily dose was 4.7 mg/kg.

The concentrations of radioactivity derived from lasalocid-^{14}C and its possible metabolites found in the whole blood reached a plateau between days 3-13 of treatment with no cumulative effects.

Samples of blood, muscle, liver, kidney, abdominal fat and skin/subcutaneous fat were taken for assay at 8 hrs. post last dose (industrial practice zero time) and the results for the 6 birds are listed below:

Tissue	Total Radioactivity Lasalocid-^{14}C + Equiv. (ppm) Mean	±	S.D.
Blood	0.035	±	0.018
Kidney	0.43	±	0.05
Liver	3.38	±	0.57
Muscle	0.03	±	0.01
Skin/Fat	0.30	±	0.11
Abdominal Fat	0.16	±	0.06

7. (cont'd.)

The concentrations of intact lasalocid sodium in the tissues were also Determined by hplc. The concentrations were less than the limits of detection at all sacrifice times in the samples of liver (0.025 ppm), muscle (0.025 pp,) and abdominal fat (0.1 ppm). In kidneys, only bird 16, sacrificed at 8 hrs withdrawal, with a concentration of 0.027 ppm, had concentrations greater than the limits of detection of 0.025 ppm. With skin/fat, only bird #17 at 8 hrs withdrawal had a concentration of 0.17 ppm greater than the limits of detection which is 0.1 ppm.

The very low concentrations of lasalocid in all tissues indicate an extensive and complete metabolism in the turkey which is discussed in the next section.

Tissues from the total residue study was used to establish the pattern of metabolites in the excreta and liver of lasalocid-^{14}C treated turkey. The ^{14}C-lasalocid turkey profile was compared to that in an approved species, the chicken, and to the 3 toxicological model species, the dog, rat, mouse. The method used solvent extraction and fractionations, preparative layer chromatography (plc) and high performance liquid chromatography (hplc) analysis of the major fractions obtained.

Intact lasalocid forms the major single feces component in all 5 species with the turkey and chicken having very similar percentages of total activity excreted as intact lasalocid (10.0% and 12.0%, respectively). The data from these studies show that the chicken handles lasalocid in the same manner as the turkey, and that all of the previous environmental studies with lasalocid chicken litter are directly applicable to the turkey. The studies cited below aid the 12 year history of chicken use with no environmental effects support the conclusion that the use of lasalocid in turkeys will not present any environmental concern.

The information on these items has been previously submitted to the Lasalocid NADA 96-298V in previously Environmental Assessments. The following table indexes the relevant information from that EIAR submitted on October 24, 1983 for pasture cattle use:

Topic	Page No.
Metabolism	08A-010A
Methods	015A-016A
Stability - Solid	018A-019A
Stability - Solution	
- pH Effect	019A
- Light Effect	019A-020A
Feedlot Fate	
- Slab and Lagoon	020A-024A
Pasture Fate	024A-024AA
Fecal Stability	024A-027A

7. (cont'd.)

The next table lists relevant information from the environmental information submitted February 11, 1976 for the broiler bird use:

Topic	Page No.
Broiler House Management	2 - 5
Pen Litter Studies w/Method	17 - 38
Aqueous-Chicken Dropping	39 - 40

The last table in this series lists the information from the Environmental section submitted January 30, 1976 for the broiler bird use:

Topic	Page No.
Chicken Litter Stability Studies	208 -218
Soil Stability Studies, Soil Translocation Studies w/ & w/o Chicken Excreta Extracts	219 -232
Initial Aqueous Stability Studies	233-239

8. Environmental effects of released substances.

The information in this area has been previously submitted to the Lasalocid NADA 96-298V in previous Environmental Assessments. The following table indexes the relevant information from that EIAR submitted October 24, 1983 for the pasture cattle use.

Topic	Page No.
Aquatic species toxicity	013A-014A
Plant phytotoxicity	010A-012A
Laboratory animal toxicity	04A-07A
Cattle toxicity	04A
Horse toxicity	05A
Face fly larval toxicity	18 - 37 (EA 10/13/86, NADA 96-298V, Breeding Animal Restriction Removal)
Florida phytotoxicity	1 - 19 (EA 5/13/75, NADA 96-298V, Broiler Applic.)
New Hampshire phytotoxicity	241-256 (EA 1/30/75, NADA 96-298V, Broiler Applic.)

The safety of lasalocid in turkeys was confirmed in a study where day-old poults were medicated continuously for 8 weeks at 0, 125 and 600 ppm lasalocid in the diet. No differences between the treatment groups were noted regarding performance, feathering, leg soundness and blood clotting times. There were no significant gross or histopathological changes noted. This study is fully reported in the FOI for this application.

9. Use of resources and energy.

Manufacturing Avatec will require an amount of energy similar to that used to produce and package any conventional fermentation product for animals. Disposal of waste washwater and materials from the manufacturing process will not require use of unusual amounts of energy or natural resources.

10. Mitigation measures.

The proposed action would not be expected to have any substantial adverse effect on human health or the environmenta. The Avatec label instructs users that if accidental eye contact occurs with Avatec, the eye should be rinsed immediately and thoroughly with water. The label also instructs users to wear protective clothing, impervious gloves, and a dust mask when mixing and handling Avatec. The user is instructed to wash thoroughly with soap and water after handling Avatec. The label will also indicate that horses or other equines must not be allowed access to formulations containing Avatec. Ingestion of Avatec by equines could be fatal. Other than these precautions listed on the label, no mitigation measures are necessary to Avatec.

11. Alternatives to the proposed action.

The proposed action would not be expected to have any substantial adverse effect on human health or the environment. Therefore, alternatives to the proposed action do not need to be considered.

12. List of preparers.

The Environmental Assessment was prepared by Dr. Alexander MacDonald whose CV has been previously submitted to the FDA-CVM.

13. Certification.

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

13 June 1997 _____
(date) (signature of responsible officer)

23 Mar 1998
Revised

Manager, Analytical, Metabolic & Environmental Studies - Animal Science Research
(title)