ENVIRONMENTAL IMPACT ANALYSIS REPORT Page [illegible] 1272:

Date: 6/24/74

Name of Applicant: Hoechst Pharmaceuticals, Inc.

Address: Route 202-206 North, Somerville, New Jersey 08876

1. Describe the proposed action:

This supplemental NADA is a request to allow the marketing of an antibiotic (bambermycins) which will increase the rate of weight gain and improve the feed efficiency of turkeys (see attachment #4).

"It is environmentally and ecologically sound since this use will conserve approximately 3% of the feed used in turkeys and at the same time produce 5-7% more meat, therefore, it is a positive step in the direction of environmental action".

Qualifying statements substantiating the above hypothesis:

(1) Bambermycins are reserved only for use in animals.

(2) The antibiotic is degraded in soil by the natural soil microflora (see attachment #5).

(3) The antibiotic is not taken up by plants (see attachment #6).

(4) There is no evidence of carcinogenicity (see attachment #11).

(5) The antibiotic, if accidentally taken by man is non-toxic (see attachment #7). Also it is non-toxic in mice, rats, or dogs when fed orally at extremely high non-physiologic levels (see attachments 8, 9 and 10).

(6) The antibiotic is not absorbed from the intestinal tract at recommended dosages, therefore, it does not present a food residue problem. (see attachment #19 and #20).

(7) Bambermycins fall in the class of antibiotics which do not transfer "R^+ factor" (transferable antibiotic resistance) - (see attachment 12).

(8) The antibiotic has been shown to be more effective against resistant bacteria (see attachment 13, 14 and 15).

(9) Bambermycins have been shown to drastically reduce the amount of R^+ factor in E. coli in pigs <u>in vivo</u> (see attachment #16, #17), other species <u>in vitro</u> (see attachment #18), and in S. typhimurium <u>in vitro</u> (see attachment #12).

(10) Produced by fermentation in West Germany (see attachments #1, #2 and #3).

ENVIRONMENTAL IMPACT ANALYSIS REPORT

2. Discuss the probable impact of the action on the environment (including primary and secondary consequences:

a. Manufacturing:

Not applicable, manufactured in West Germany

b. Use :

As discussed under question 1 above, so far as the environment is concerned, the use of Bambermycins may have significant beneficial effects in the biological resistance area. At this date we cannot quantitate the benefits which will accrue; however, ecological systems such as wildlife, fish, and other marine life will not be affected by the use of this drug in turkeys as far as we are able to determine.

3. Discuss the probable adverse environmental effects which cannot be avoided:

a. Manufacturing:

see 2a

b. Use:

Although antibiotic resistance to Bambermycins will develop (see attachment #3), the effect of Bambermycins on public health will be limited due to its use restriction in animals.

We are not aware of any adverse effects which would be detrimental to the six environmental goals set forth in section 101 (b) of the National Environmental Policy Act of 1969.

4. Evaluate alternatives to the proposed action:

a. Manufacturing:

see 2a

b. Use:

The only unresolved aspect of this request concerns the biological development of antibiotic resistance. Biological resistance is an acquired process. This will revert to the "normal" state when selection pressures change; therefore, we see this as no problem.

ENVIRONMENTAL IMPACT ANALYSIS REPORT

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

a. Manufacturing:

see 2a

b. Use:

This has been discussed under questions 1, 2, 3, and 4. We would only add that the use of Bambermycins will definitely benefit the maintenance and enhancement of both long and short-term productivity.

6. Describe any irreversible and irretrievable commitment of resources which would be involved in the proposed action should it be implemented:

a. Manufacturing:

see 2a

b. Use:

The use of Bambermycins in swine feeding would have no effect on irreversible and irretrievable commitment of resources other than to conserve and stretch them.

7. Discuss the objections raised by other agencies, organizations, or individuals which are known to the applicant:

a. Manufacturing:

see 2a

b. Use:

The possible detrimental effect of the use of antibiotics in swine feeding (antibiotic resistance question) is being investigated by the FDA antibiotic task force and has been limited in England by the so-called Swann Report; however, in England and, we believe, here in the U.S., both groups welcome the appearance of an antibiotic for use in animals only as the solution to a <u>possible</u> problem.

ENVIRONMENTAL IMPACT ANALYSIS REPORT

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

   a. Manufacturing:

      see 2a

   b. Use:

      Exemption from the 90 day and 30 day provisions is not required.

9. Analyze whether the benefit to the public of the proposed action will outweigh the action's potential risks to the environment:

   a. Manufacturing:

      see 2a

   b. Use:

      Until the U. S. changes to a vegetarian diet, the use of bambermycins (and therefore benefit to the public) will far outweigh any risks to the environment. We do not believe a potential risk exists as discussed in questions 4 and 7. The potential benefits (see question 1) are enormous in terms of conservation and extension of our grain and protein supply.

6/28/74

M. W. Moeller, Ph. D.
Nutritional Section Leader

Personally submitted by: JMC 9/9/81

AMERICAN HOECHST CORPORATION

Animal Health Division

ROUTE 202-206 NORTH, SOMERVILLE, N.J. 08876 • TELEX 833-449 • CABLE: HOECHSTUS SOMERVILLE, N.J. • TELEPHONE (201) 685-2000
MY DIRECT DIAL NUMBER IS 685- 2492

September 8, 1981

Lonnie W. Luther, Ph.D.
Metabolic Branch HFV-147
Division of Drugs for Avian Species
Bureau of Veterinary Medicine
5600 Fishers Lane
Rockville, MD 20857

RE: NADA 44-759 - BAMBERMYCINS FOR TURKEYS

Dear Dr. Luther:

This letter is to advise you that all of the toll manufacturers of Bambermycins premixes have affirmed by letter that they are in conformance with local, state and federal environmental regulations pertaining to their blending of the Bambermycins premixes on behalf of American Hoechst Corporation.

These letters can be found in our approved application NADA 44-759 and its many supplements thereto.

Since this Bambermycins for Turkey label claim makes no changes in our approved premixes, or their ingredients, we are not aware of any manufacturing changes that would affect the environment.

Sincerely,

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

John W. McClain, Manager
Drug Regulatory Affairs

JWM:jk/217

FARBWERKE HOECHST AG vormals Meister Lucius & Brüning

Farbwerke Hoechst AG vormals Meister Lucius & Brüning 6230 Frankfurt (Main) 80 Postf. 80 03 20

Telefon Frankfurt (Main) (0611) 305-1 Vermittlung
Telegramme: [illegible] Frankfurtmain
Telex [illegible]
[illegible] Montag bis Freitag [illegible]-17.00 Uhr

KONTEN
Dresdner Bank AG, Frankfurt (Main) 80
(BLZ 500 801 01) Kto. Nr. [illegible]
Commerzbank AG, Frankfurt (Main) 80
(BLZ [illegible]) Kto. Nr. [illegible]
Deutsche Bank AG, Frankfurt (Main) 1
(BLZ 500 700 10) Kto. Nr. [illegible]
Hessische Landesbank - Girozentrale - Frankfurt (Main) 1
(BLZ 500 500 00) Kto. Nr. 24 100 092
Landeszentralbank in Hessen, Frankfurt (Main) 1
Kto. Nr. 500 03193
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Ihre Zeichen	Ihre Nachricht vom	Unsere Zeichen	Pharma-Fabrik	Telefon (0611) 305-.... Durchwahl

6230 FRANKFURT (MAIN) 80

February 10, 1974

To whom it may concern

Statement

Herewith we state that the production of Flavomycin R (generic name: Bambermycin) at our plant in Frankfurt/Main is carried out in accordance with the pertaining regulations regarding environment control of the Federal Republic of Germany.

FARBWERKE HOECHST AG
vormals Meister Lucius & Brüning

ppa.

Bambermycins - Environmental Impact Profile

Bambermycins, also known as flavomycin, moenomycin, and flavophospholipol, is an antibiotic complex used as a growth promotant in swine and chickens intended for use as food. The action under consideration is the approval of bambermycins for the same use in young hen and tom turkeys. The drug is not used in human medicine.

Physical and Chemical Properties

Bambermycins is a surface-active phosphorus-containing glycolipid antibiotic produced by cultures of the actinomycetes Streptomyces bambergiensis, S. ghanaensis, S. ederensis, S. geysiriensis and related strains. Although the exact structure of the complex is not known, bambermycins contains a UV-chromophore, a lipid portion, a carbohydrate moiety consisting of several sugars, and phosphorus linked in ester form (Figure 1, Huber, 1972). These building blocks are linked together to form four chemically separable bioactive components, A, B_1, B_2, and C. All the components are weak acids containing phosphorus and chemically asscciate into high molecular weight complexes. Component A is present in the largest quantity. Components A and C contain the UV-chromophore (2-amino-cyclo-pentanedione-1,3) absorbing ultraviolet light at 258 µm (Lenoir et al., 1969, Huber et al., 1965).

Purified bambermycins is a colorless, amorphous, acidic substance without a definite melting point. It is readily soluble in water and polar organic solvents (alcohols, dimethylformamide, ether and ethyl acetate) but is almost insoluble in nonpolar solvents (benzene and chloroform). The elemental analysis yields 48.5% C, 7.3% H, 37.3% O, 5.1% N, and 1.8% P. It is stable in neutral aqueous and methanolic solutions, and slowly decomposes in acid and alkaline solutions (Merck Index, 9th Ed., 1977).

Mechanism of Action

Bambermycins interferes with the synthesis of bacterial cell wall material (peptidoglycan). Peptidoglycan synthesis in gram-positive and gram-negative bacteria involves the reaction of a soluble peptide precursor with a lipid C_{55}-isoprenyl phosphate to give a membrane bound intermediate. A disaccharide unit is added to the peptide and the modified disaccharide-peptide unit is transferred to an acceptor with the release of C_{55}-isoprenyl pyrophosphate, which is dephosphorylated to start a new cycle of synthesis. The disaccharide-peptide chains at the acceptor site are cross-linked to form the final cell wall material.

Antibiotics interfere with these pathways at three different places. Bambermycins, vancomycin, ristocetin, ristomycetin, enduracidin, prasinomycin, macarbomycin, and several detergents such as deoxycholate

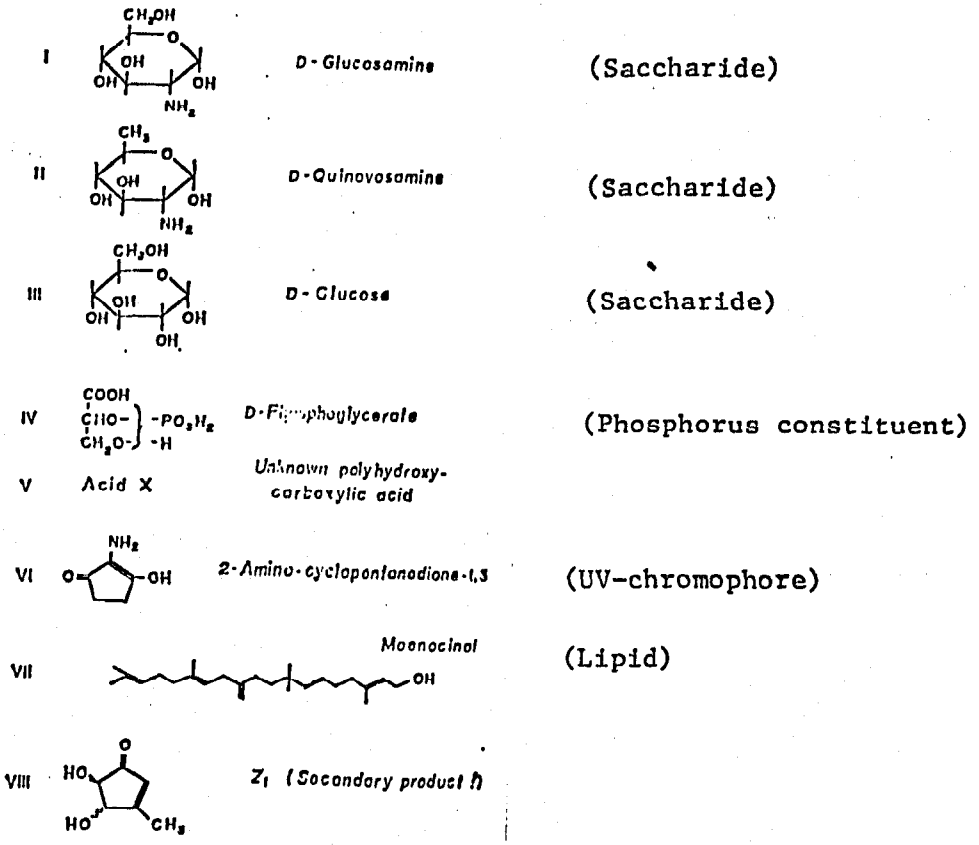

Figure 1. Building Blocks of Bambermycins
(From Huber, 1972)

and n-octanol appear to interfere with the transfer of the disaccharide-peptide unit from the lipid intermediate to the acceptor. Bacitracin inhibits the dephosphorylation of C_{55}-isoprenyl pyrophosphate. The penicillins and cephalosporins inhibit the enzymes (transpeptidase and carboxypeptidase) responsible for cross-linking the disaccharide-peptide units into the final cell wall material (Linnett and Strominger, 1973, Hammes and Neuhaus, 1974).

Spectrum of Antimicrobial Activity

The bambermycins spectrum of activity for bacteria covers staphylococci, streptococci (except for serological group D), diplococci, Corynebacterium, Bacillus subtilis, B. cereus, B. anthracis, B. mesentericus, Neisseria, Brucella, and Pasteurella. Enterobacteria (e.g., E. coli, Aerobacter, Klebsiella) and clostridia are slightly susceptible. See Table 1 (Wasielewski, Muschaweck, and Schutze, 1965). Van Dijck and Van de Voorde (1976) tested bambermycins against functionally important environmental microorganisms, finding Thiobacillus thiooxydans 504DSM and Rhodopseudomonas sp. to be most sensitive (*M.I.C.<1 µg/ml). Mycoplana bullata ATCC 4278, M. dimorpha ATCC 4279, and Flavobacterium sp. were moderately sensitive (M.I.C. = 10 µg/ml). Hydrogenomonas sp., Citrobacter sp., Cythophaga johnsonae 425 DSM, Hyphomycrobium sp., and Nitrobacter sp. proved relatively insensitive (M.I.C. > 100 µg/ml). See Table 2.

Introduction into the Environment

Manufacture

Bambermycins is fermented in bulk at Farbwerke Hoeschst AG in Frankfurt (Main), Federal Republic of Germany. The bulk drug is incorporated into animal feed premixes at three locations in the United States by toll manufacturers: Ralston Purina, St. Louis, MO; Quali-tech, Chaska, MN; and Pfizer, Lee Summit, MO. Hoechst and the toll manufacturers certify that they meet all applicable emissions control requirements.

Metabolism and Excretion by Target Animals

Excretion and tissue distribution studies in chickens (including tracing radioactive bambermycins) demonstrate that oral doses of bambermycins are not absorbed through the gut or metabolized; the antibiotic is eliminated unchanged back into the environment in the feces in 1-2 days (NADA 44-759, Vol. 27; Bauer and Dost, 1965). No bambermycins residues have ever been detected in edible tissues in swine or poultry without massive overdose administration.

*M.I.C. = minimal inhibitory concentration, µg/ml = parts per million

Table 1. Bambermycins antibacterial spectrum

Gram-positive organisms	No. of strains	MIC	Gram-negative organisms	No. of strains	MIC
		µg/ml			µg/ml
Staphylococcus aureus	19	0.03-0.5(0.06)*	Neisseria meningitidis	1	2.4
Sarcina lutea	2	250.0	Pseudomonas aeruginosa	5	62.5-125.0(62.5)
Streptococci, group A	6	0.001-0.01(0.001)	Alcaligenes faecalis	1	39.1
Streptococci, group B	3	0.001-39.1	Escherichia coli	12	62.5-250(125.0)
Streptococci, group C	2	0.03-625.0	Aerobacter cloacae	1	156.0
Streptococci, group D	7	1.6-10,000	Klebsiella spp.	2	5.0-31.5
Streptococci, Viridans group	3	0.001-0.1	Paracolobactrum spp.	3	31.5-156.0
Diplococcus pneumoniae	2	0.3-1.25	Proteus mirabilis	7	31.5-156.0(31.5)
Corynebacterium pyogenes	1	2.5	Salmonella spp.	14	7.8-250.0(156.0)
Listeria monocytogenes	2	0.04-0.3	Shigella spp.	2	31.5-187.7
Erysipelothrix rhusiopathiae	1	0.001	Brucella spp.	2	1.2-2.5
Mycobacterium spp.	4	66.0-500.0	Pasteurella spp.	2	0.15-3.1
Bacilus spp.	4	0.001-0.6(0.07)			
Clostridium spp.	4	313.0-625.0			

*Parenthetical figures give the minimal inhibitory concentration (MIC) of the majority of strains. From Wasielewski, Muschaweck, and Schutze (1965).

Table 2. Sensitivity of environmental microorganisms to bambermycins.

Bacterial Species	Ecological Function	Minimal Inhibitory Concentration µg/ml (ppm)
Mycoplana bullata ATCC 4278	Sediment heterotroph–carbon cycle	10
Mycoplana dimorpha ATCC 4279	" "	10
Hydrogenomonas sp.	Chemolithotroph-hydrogen oxidizer	1000
Citrobacter sp. 1	Sediment heterotroph	1000
Flavobacterium sp.	" "	10
Thiobacillus thiooxydans 504 DSM	Chemolithotroph–sulfur oxidation	<1
Cythophaga johnsonae 425 DSM	Cellulose degradation	>1000
Rhodopseudomonas sp.	Photosynthetic anaerob–carbon fixation	<1
Hyphomicrobium sp.	Multiple mineralization functions	>100
Nitrobacter sp.	Chemolithotroph–nitrification NH_4^+ NO_2^-	1000

Adapted from Van Dijck and Van de Voorde (1976).

In turkeys, bambermycins will be added to complete feed rations at a concentration of 2 grams per ton of feed (2.2 ppm). During its passage through the intestinal tract, part of the feed will be absorbed and utilized by the turkey for growth and respiration, approximately half. However, nearly 100% of the bambermycins will be excreted intact. The result is that the concentration of bambermycins in fresh excreta will be approximately twice the concentration administered in feed. This ratio obviously varies with the digestibility of the feed administered. Subsequent to excretion, the drug residues become admixed with litter material (for housed turkeys) or the soil (for range turkeys).

If one assumes that the bambermycins residues are not degraded during the period they remain in turkey housing litter and that the concentration of drug residues in the liter is 5 ppm (wet weight basis), then the soil concentration expected when these wastes are incorporated into agricultural soil as fertilizer may be calculated:

Weight of 1 acre of soil 6" deep (plow depth): 909,000 kg/acre
Waste application rate: 10,000 kg dry waste/acre
Dry to wet waste conversion factor: 1 kg wet waste = 0.4 kg dry waste

$$\text{Concentration of bambermycins in soil (ppm)} = \frac{5 \text{ mg bamb.}}{\text{kg wet waste}} \times \frac{10{,}000 \text{ kg dry waste}}{\text{acre}} \times \frac{1 \text{ kg wet waste}}{0.4 \text{ kg dry waste}} \times \frac{1 \text{ acre}}{909{,}000 \text{ kgs soil}}$$

$$= \frac{0.138 \text{ mg bambermycins}}{\text{kg soil}} = 0.138 \text{ ppm bambermycins}$$

From these rough estimates and by comparisons with the spectrum of antimicrobial activity, one may conclude that fresh excreta from turkeys fed bambermycins-medicated feed has selective antibacterial effects. After incorporation of these wastes into agricultural soils, the concentration of bambermycins is too low to exert antibacterial effects on the majority of soil bacteria.

Fate in the Environment

Inactivation

In an experiment conducted by the drug sponsor (NADA 44-759, Vol. 26, American Hoechst Corporation, "Soil Moenomycinase"), it was found that 10/48 strains of bacteria, 1/43 streptomycetes, and 2/20 yeast and thread fungi isolated from two West German soil samples were capable of inactivating bambermycins. In an incubated non-sterile soil sample,

bambermycins activity was reduced from 7.4 ppm to 2.48 ppm (33.5% reduction) by soil microorganisms in 21 days. One bacterial strain (B10) was isolated from soil which was capable of inactivating in 18 hours 58%, 56%, 50%, 100% and 100% of bambermycins concentrations of 200, 100, 50, 10, and 1 µg/ml (ppm), respectively. See also "Bioaccumulation" below.

Studies conducted by the drug sponsor on inactivation of bambermycins in swine waste lagoons show that, under both aerobic and anaerobic conditions, the onset of inactivation of bambermycins added in feces is rapid and continuous (NADA 44-759, Vol. 4, p. 073).

Bioaccumulation

Specific partition coefficient data are not available from which potential for bioaccumulation could be estimated. High water solubility and low solubility in nonpolar solvents suggests low probability of bioaccumulation for bambermycins, however.

Hoechst (NADA 44-759, Vol. 26, p. 073) examined bambermycins' potential bioaccumulation in plants. Five kg and 2.8 kg of chicken excreta containing bambermycins were mixed in both sandy and clay types of soil (200 kg lots). The birds had received 128 mg of bambermycins/kg feed. After mixing, the initial bambermycins content of the soil was 2.95 ppm and 1.74 ppm respectively, on a dry weight basis. The 200 kg soil was then replaced in the $2m^2$ patch of soil which had been its source; controls without drug were also included. After one week, normal non-pregerminated barley was sown in 1 m^2 of the two m^2 of the control area and of the test area, the other 1 m^2 of each remained unplanted (Figure 2).

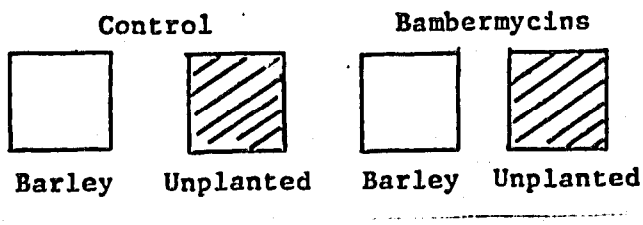

Figure 2. Soil Plot Test for Bambermycins Degradation and Bioaccumulation. (NADA 44-759, Vol. 26)

Both barley and soil were examined for bambermycins content at about weekly intervals for 28 days. Soil and barley plants samples were extracted in 50% methanol at pH 8 with heating for 15 minutes. The diluted extract was tested for its bambermycins content, using

bioassay with Bacillus cereus ATCC 19637. The bioassay indicated that the antibiotic activity of bambermycins in the soil was continuously decreased and that, within 5-6 weeks, 85%-87% of the original quantity of bambermycins was inactivated. Decreased inactivation rates were noted with time, which may have been due to decreased soil microorganism activity in cooler fall weather. No microbiological activity could be found in any of the barley extracts. The sensitivity limit for bambermycins in fresh barley leaves was approximately 0.045 ppm.

Similar results were obtained in studies using wheat and in pot studies with corn, cabbage, soybean, fescue, tobacco, beans and tomato (NADA 44-759, Vol. 4, p. 073). These latter studies were carried out using feces from swine ingesting feed with 2 g/ton bambermycins and using light loam and clay loam soils.

No bioaccumulation studies with soil or aquatic invertebrates, microorganisms, or higher organisms were submitted by the drug sponsor or found in the scientific literature. In view of the rapid inactivation of the drug in the environment and excretion data showing minimal absorption of the drug across intestinal walls of birds and mammals (discussed above), there is small likelihood of extensive bioaccumulation occurring.

Environmental Effects

Toxicity

Administered in oral doses to laboratory and target animals, the maximum applicable doses of bambermycins caused no side effects. According to the Merck Index (1976), the LD50 in mice is greater than 2000 ppm orally. Bambermycins fed to rats in mycelial and semi-purified forms at the high levels of 1,000 and 10,000 mg/kg of feed in a 90-day subacute toxicity test produced no adverse effects in body weight gain, feed consumption, mortality, behavior, functional tests, hematology, urinary findings, organ weights, or histopathology. A diet equivalently diluted with inert plastic performed similarly to the mycelium-diluted diet (NADA 44-759, Vol. 26).

Bambermycins fed to dogs in semi-purified and mycelial form at 400 and 4,000 mg bambermycins/kg of feed in a 90-day subacute toxicity test produced no adverse effects upon body weight, general condition, hematology, blood glucose levels, urinary findings, or histopathology (NADA 44-759, Vol. 26).

Feeding of bambermycins in a semi-purified form at a level of 5000 mg/kg of feed in a 4-week subacute test with chickens produced no adverse effects upon body weight gain, feed consumption, feed efficiency, mortality, liver glycogen, or blood sugar, or necropsy and histological organ examination (NADA 44-759, Vol. 6).

Bambermycins fed in a semi-purified form at 50 mg bambermycins/kg of feed in a two-year rat chronic toxicity test produced no adverse

effects upon body weight, mortality, hematology, liver glycogen, blood sugar levels, urinary findings, organ weights or histopathology (NADA 44-759, Vol. 7).

Fed in a semi-purified form at 50 mg bambermycins/kg of feed in a 2-year chicken chronic toxicity test, bambermycins produced no adverse effects upon body weight, feed utilization, mortality, egg production, egg weight, fertility, hatchability, hematology, blood sugar levels, organ weights, necropsy or histopathology examinations (NADA 44-759, Vol. 6).

Bambermycins fed in a semi-purified form at a level of 100 mg bambermycins/kg of feed in a 20 week swine chronic toxicity test, produced no adverse effect upon body weight, feed efficiency, hematology, histopathology or carcass characteristics (NADA 44-759, Vol. 7).

Bambermycins has been investigated for use in turkeys (Grant et al., 1979), dairy cattle (Ruffo and Valerani, 1977), guinea fowl (Giorgio et al., 1977; Bonomi et al, 1975), Japanese quail (Schulz and Gropp, 1973), rabbits (Schlolaut and Lange, 1973), guinea pigs (Frese and Blobel, 1973) and eels (Hatai, 1973) at levels comparable to or greater than the 2 gram/ton level to be used for turkeys without finding toxic effects. Lal and Schmutterer (1977) found that bambermycins in combination with oxytetracycline and griseofulvin (all at concentrations of 0.2%) reduced the reproduction rate of an aphid (Aphis fabae Scop) by 85% and the weight of the adults produced by 52% when applied foliarly on young broad bean plants (Vicia faba). Bambermycins alone was not as effective as an aphid control agent.

Conclusions

Bambermycins is added at 1 to 4 grams per ton of complete feeds for food-producing animals (turkeys, chickens, and swine) for the purpose of increasing rate of weight gain and improving feed efficiency. It is fed continuously alone or in combination with other animal drugs (e.g., coccidostats). Bambermycins, in the amounts administered, is not absorbed from the intestines of these animals and is excreted unchanged in animal wastes. Soil bacteria, streptomycetes, thread fungi and yeast are capable of inactivating bambermycins in a time period of days to weeks, depending upon the microbial activity of the soil (a factor dependent on weather conditions and soil type). Bambermycins does not appear to bioaccumulate in plants or higher animals.

Based on the antibacterial spectrum of bambermycins, fresh excreta from medicated animals has adequate antibacterial activity to selectively inhibit some bacterial species. However, the rapid biological inactivation of the drug residues (cited above) would preclude any lasting effects. Fresh excreta containing bambermycins does not appear to impair the functioning of animal waste treatment lagoons. The levels of bambermycins present in animal wastes are not adequate to adversely

affect the fish, insect, bird, and mammal species for which literature was cited above.

Therefore, the use of low concentrations of bambermycins in animal feeds does not appear to cause any significant environmental impacts.

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