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6

EEE BRANCH REVIEW

10/5/77

DATE: (2/16/77)
 IN 4/28/77 OUT 10/5/77 IN _____ OUT _____
 FISH & WILDLIFE ENVIRONMENTAL CHEMISTRY EFFICACY

FILE OR REG. NO. 1007-IE

PETITION OR EXP. PERMIT NO. Combined Review Submissions Received

DATE DIV. RECEIVED 2/15/77 and 5/24/77 by Div.

DATE OF SUBMISSION _____

DATE SUBMISSION ACCEPTED _____

TYPE PRODUCT(S): I, D, H, F, N, R, S Agricultural Antibiotic

PRODUCT MGR. NO. Wilson

PRODUCT NAME(S) Myco-Shield - AGRICULTURAL TERRAMYCIN

COMPANY NAME Pfizer, Inc.

SUBMISSION PURPOSE Registration (Data submission - waiver request)

CHEMICAL & FORMULATION Terramycin (oxytetracycline)

1

Environmental Safety Review
Myco Shield

100.0 Label

100.1 Pesticide Use

This material is a non-sterile, suitably denatured antibiotic formulation intended for agricultural use in control of plant diseases. Specifically control of Fire Blight of Pear and Bacterial Spot of Peach.

100.2 Application Directions/Rates

Directions for Use

Application

Pear

Begin spray application at 10% bloom at a dosage rate of 50 to 100 gallons of a 200 ppm solution/acre. This would be 8 oz./50 gallons or 1 lb./100 gallons.

Repeat spray applications at 4 to 6 day intervals. This may involve up to 8 to 10 applications.

Limitations

Do not apply within 60 days of harvest
Use limited to West Coast

Peach

Use on a weekly application schedule starting with shuck split at the rate of 150 ppm active ingredient 0.125 lb. (equivalent to 2 oz. oxytetracycline) per hundred gallons spray solution, or equivalent to 11.33 oz. of Agricultural Terramycin^R per hundred gallons of water (equivalent to 150 ppm active ingredient).

Apply spray solution to point of run off; rate of 3 gallons per tree on basis of 80 trees per acre (240 gallons spray solution per acre). Gallons of spray per acre may be increased for larger trees. Do not exceed 500 gallons per acre. Use pressure sprayer capable of delivering the spray at least 250 lb. pressure per square inch through a hand held single nozzle gun, or 150 lb. pressure per square inch using a wind blast sprayer. For best results with air blast sprayer do not exceed three miles per hour ground speed or 100 miles per hour spray velocity.

2

NOTE: The spray application schedules are based on a definite biological growth period for peaches, the shuck split. Shuck split stage for peaches varies North to South by states, in individual states and by varieties. Applications are weekly after shuck split stage. This may involve up to 8 or 9 applications. Applications to cease three weeks before harvest.

Limitations

Do not apply within 3 weeks of harvest
Use limited to New Jersey, Maryland, North Carolina,
South Carolina, Georgia, Missouri and Illinois

Mixing: To avoid possible pesticide contamination, use only clean metal or plastic containers in preparing all solutions.

Concentration Desired	Quantity Agricultural Terramycin ^R Per Volume of Water		
	50 gals.	100 gals.	500 gals.
ppm*			
100 ppm	4 oz.	8 oz. (½ lb.)	2½ lbs.
150 ppm	6 oz.	12 oz.	3 ¾ lbs.
200 ppm	8 oz. (½ lb.)	16 oz (1 lb.)	5 lbs.

Caution: May cause allergic reactions. Avoid contact with skin and eyes. Do not breathe dust or spray mist. Wear dust mask, chemical goggles and rubber gloves. Wash thoroughly after handling.

Environmental Hazard

Keep out of lakes, ponds and streams. Do not contaminate water by cleaning equipment or disposal of waste.

Storage and Disposal

Storage: Keep tightly closed. Storage should be at a cool temperature when possible, and with minimum exposure to the atmosphere.

Disposal: Do not reuse container or liner. Destroy when empty.

101.0 Chemical and Physical Data

101.1 Chemical Name

Oxytetracycline HCl

Lower indicates active

101.2 Common Name

Terramycin

102.0 Behavior in the Environment

No data submitted

103.0 Toxicity Properties

103.1 Acute Toxicity

103.1.1 Mammal

Test: Acute Mammal LD₅₀

Species: Mice

Result: LD₅₀ - 6700 mg/kg (6124-7656) mg/kg

Chemical: Terramycin HCL

Test: Acute Mammal LD₅₀

Species: Mice

Result: LD₅₀ >4800 mg/kg

Chemical: Terramycin Base

Test: Subacute chronic mammal

Species: Rat

Result: 0.01% (100 ppm) 2 yrs. No adverse effects
0.1% (1000 ppm) related to Terramycin
0.3% (3000 ppm)

Request for Waiver:

The registrant has included the following request for waiver of data requirements for Fish and Wildlife Safety. The Environmental Safety Section will respond to each of the referenced studies and attempt to determine if the body of knowledge is sufficient to allow acceptance of the waiver request.

"A waiver of the formal requirements for Fish and Wildlife Safety is hereby requested pursuant to the provisions of 40CFR, 162.8 relating to data in support of registration and classification.

4

The active ingredient of Agricultural Terramycin^R is oxytetracycline. The safety of oxytetracycline to fish and mammalian species is well documented through both laboratory studies and in its 25 year history of wide and continued usage in medical and veterinary fields for the treatment of diseases. (Pan S. Y., Scaduto L., Cullen M.², Deichmann W. B., Bernal E., Anderson W.A.D., Keplinger M., Landeen K., and MacDonald W.³, Perraud J.⁴, Snieszko S.F.⁸, Branion H.D., Anderson G.W., Hill D.C.⁹, Scott M.L., Holm E.R., Reynolds R.E.¹⁰, Mraz F.R., Boucher, R.V., Callenbach E.W.¹¹, Amschler J.W., Pammer H.¹², and Nowak H.¹³).

It is authorized as an active component of poultry, cattle and fish feeds; CFR title 21, section 121.251¹⁴. The permissible levels in fish and animal feeds are appreciably higher than those that would be added to fish and wildlife diet resulting from application of Agricultural Terramycin^R for control of plant diseases in pear and peach orchards.¹

Oxytetracycline has been shown to be rapidly absorbed onto soil where it is immobilized and degraded (Wong C.K.⁵, Krüger W.⁶, and Martin, N., Gottlieb D.⁷), and in this manner will remain in the target area and not present a hazard to non-target organisms."

"The waiver request for fish and wildlife data requirements (LD₅₀ and LC₅₀ in several species) was based upon feeding trials for up to 16 weeks in many of the same species at levels much higher than those contributed by Agricultural Terramycin to soil, where, in fact, the oxytetracycline is bound and degraded as discussed under the Environmental Chemistry response of February 14, 1977. Thus oxytetracycline would not be expected to reach the fish and wildlife, but if for any reason, it does, its safety has been demonstrated by feeding studies in lieu of LD₅₀ and LC₅₀ studies. Data substitution of this nature would seem appropriate for such a widely used and safe substance as oxytetracycline."

"The question of fish accumulation studies was discussed under their February 14, 1977, response to environmental objection 3.4.8. In the remote chance that oxytetracycline were to enter streams or waterways accidentally before being bound by the soil, data in three varieties of trout show tissue depletion of oxytetracycline within several weeks, and destruction of any residue upon cooking. These data were submitted to and accepted by the Food and Drug Administration as part of New Animal Drug Application No. 38-439 to permit use of oxytetracycline for treating fish diseases. The data are enclosed in duplicate as an addition to Volume 09 of our application together with a resubmission application form."

The following studies were reviewed to determine if they would adequately answer questions related to environmental hazard to non-target organisms.

103.1.2 Bird

Data Review # ES GG 1

Test: Avian Feeding Study

Species: White Pekin Ducks

Results: Ducks were dosed with 25 ppm terramycin Hydrochloride. In addition, in the diet were the following: Aureomycin hydrochloride, penicillin G. Potassium and streptomycin sulphate in experiment #1. In experiment #2 ducks were dosed at 10, 25 and 100 ppm of above compounds in the diet.

The results from experiment #1 indicate no acute toxicity (>25 ppm) present. The test birds did not have stimulated growth nor improved feed efficiency. The addition of terramycin to the diet lowered cecal microbial populations even through an increase in the number of aerobes, aciduric and coliform types of organisms increased.

Experiment #2 had no mortality (>100 ppm) and did not indicate any significant statistical variation in weight gains or food efficiency. The researchers concluded that feeding terramycin at levels of 10, 25 and 100 parts/million did not have any effect upon improving growth and feeding efficiency. They went further and suggested that at certain times this feeding might impair gut flora efficiency by destroying certain microorganisms, and this might impair food utilization in birds up to six weeks of age.

Chemical: Terramycin hydrochloride

Title: Antibiotics and the Growth of Ducks

Accession #: NA

Study Date: 1952

Researcher: Branion, H.D., Anderson, G.W., Hill, D.C.
Poultry Science, 1953, Vol 32, pgs. 335-347

Submission: Pfizer, Inc.

Validation Category: Supplemental

Category Repairability: No. The study does not address the intent and purpose of the guidelines to address environmental hazard. The species tested is not a wild avian species, an LC₅₀ was not determined, and statistical methods were not included.

103.1.2 Bird

Data Review # ES 662

Test: Avian Feeding Study

Species: Ringnecked Pheasant (Phasianus colchicus)

Result: Experiment #2, dosed at 10 mg/lb (22 ppm) Terramycin in basil diet. Growth was increased by addition to a maximum of 27%. Mortality was reduced, feathering was superior.

Chemical: Terramycin hydrochloride

Title: Studies on Pheasant Nutrition: Effect of Antibiotics, Arsenicals and Thyroactive Compounds upon Growth and Feathering in Pheasant Chicks.

Accession #: NA

Study Date: 1954

Researcher: Scott, M.D., Holm, E.R., Reynolds, R.E.
Poultry Science, 1954, Vol 33, pgs. 1261-1265

Submission: Pfizer, Inc.

Validation Category: Supplemental

Category Repairability: No. This study is an efficacy study, in that it reports on the relative effectiveness of terramycin and several other antibiotics for increasing weight gains, reducing mortality and increasing food efficiency. For the intent of the Environmental Safety Section to identify hazard, the dietary level of 22 ppm does not provide adequate information.

103.1.2 Bird

Data Review # ES 663

Test: Avian Feeding Study

Species: Bobwhite Quail (Colinus virginianus)

Result:

Experiment #1: Birds were dosed with varying rates of antibiotic. The rate of Terramycin was 11.4 gm/2000 lbs (12.6 ppm). Each dose level was fed to 2 groups of 60 birds for a 16 week duration. Birds in experiment #1 did not reveal any significant weight gain over control birds for the 16 week period. Birds dosed with terramycin indicated a slightly higher survival over the 16 week period, but this difference was not significantly greater.

Experiment #2: Terramycin was dosed to birds at 5 g/ton (5.5 ppm). The test groups consisted of 60 chicks at each test level. The test was initiated as day old chicks and continued for 6 weeks. Mortality was heavy in both control birds and test birds, but in general terramycin dosed birds exhibited a higher survival, and had slightly increased growth than control birds.

Chemical: Terramycin hydrochloride

Title: The Response of Bobwhite Quail to Antibiotics

Study Date: 1955

Researcher: Mraz F.R., Boucher R.V., Callenbach E.W.
Poultry Science, 1956, Vol 35, pgs. 76-80

Submission: Pfizer, Inc.

Validation Category: Supplemental

Category Repairability: No. This study is an efficacy study in that it reports on the relative effectiveness of terramycin and several other antibiotics for increasing weight gains, reducing mortality and increasing food efficiency. For the intent of the Environmental Safety Section to identify hazard, the maximum dietary level of 22 ppm does not provide adequate information.

103.1.2 Bird

Data Review # ES GG 4

Test: Avian Feeding Study

Species: Pekin Duck

Result: Ducks dosed at 10g/ton terramycin (11 ppm) made better weight gains and better food utilization. Mortality was reduced.

Chemical: Terramycin hydrochloride

Title: Duck Fattening Experiment with Terramycin

Study Date: 1955

Researcher: Amschler J.W., Pammer, H.
Bodenkultur, 1955, Vol 8, pgs. 327-330

Submission: Pfizer, Inc.

Validation Category: Supplemental

Category Repairability: No. This study was presented as a summary of results. Methods were not described. The study presents efficacy data and does not develop an LC₅₀ or provide any real information to use in a hazard evaluation.

103.1.2. BIRD

Data Review # ES GG 5

Test: Avian Feeding Study

Species : Peking Duck

Result : Ducks dosed at 11g/ton (12 ppm);22g/ton (24 ppm) displayed slightly higher weight gains than control birds.

Chemical : Terramycin hydrochloride.

Title: Fattening Ducks With Terramycin and Vigofax.

Researcher: Nowak H.

ARCH GEFLÜGELK

1956 VOL.20 PP. 35-40

Submission : Pfizer Inc.

Validation Category; Supplemental

Category Repairability; No; This study was presented as a summary of results. Methods were not described. The study presents efficacy data and does not develop an LC 50 or provide any real information for use in any hazard evaluation.

103.1.3 Fish

Data Review #: ES GG 6

Test: Fish Feeding Study

Species: Trout

Result: Hatchery trout fed 25 to 75 mg/kg (25-75 ppm) terramycin displayed some growth inhibition. Trout displayed control of systemic bacterial disease. Oxytetracycline was effective in the treatment of fish furunculosis and ulcer disease. In Vitro oxytetracycline was bacteriostatic. Blood levels of oxytetracycline given orally (50 mg/kg - 50 ppm) were detectable, at 100 mg/kg (100 ppm) in a gelatin capsule blood levels were detectable within four hours. Higher levels were detected in the liver and 24 hours after treatment levels in both blood and liver had dropped below detectable levels. (Fish species not identified). Terramycin was noted to have no value as a growth promoting substance.

103.1.5 Phytotoxicity

Efficacy data indicate no phytotoxic response to peach or pear trees (target plants) or chokecherry (non-target plants).

104.0 Hazard Assessment

104.1 Discussion

Myco Shield (Terramycin hydrochloride) will be applied at a maximum application rate of 200 ppm on peach trees. This application may be repeated from 8 to 9 times. For pear trees, the maximum application rate is also 200 ppm and will be repeated every 4-6 days and may involve up to 10 applications. The registrant notes the following tolerance listed: Title 21 CFR - 121.251, Food & Drugs. The permissible levels in chicken feed, 200 ppm, cattle feed 200 ppm, fish feed 55-83 ppm.

104.1.1 Adequacy of Toxicity Data

The data supplied and referenced with this submission is efficacy data. It does not adequately address what rates of application would need to be exceeded before environmental damage could occur (if in fact any rate is possible). The registrant has requested a waiver of the data requirements that would specifically address this area.

104.1.2 Additional Data Required

All of the basic data requirements must be met before the registrant would comply with the intent and purpose of the proposed guidelines, which is to identify if any potential environmental hazard exists from the proposed registration.

104.1.3 Likelihood of Exposure to Non-Target Organisms

Terramycin is an antibiotic substance produced by the growth of Streptomyces rimosus that is used to control a variety of microorganisms, particularly aerobic and anaerobic bacteria, the rickettsiae and certain of the viruses. Terramycin has been used in experimental animals and domestic stock (mammals, birds and fish) and good background information is available concerning its effects at the levels tested and treated. The literature that was cited as evidence for the safe use of this product in the environment is data related to the product's efficacy. The highest dosage level tested in these studies was 100 ppm, and

the test was conducted using domestic pekin ducks that were being maintained on a base diet that included other nutrients and vitamins. This study did not present any information that would indicate any problems with acute toxicity, but it did imply that terramycin is responsible for changing gut flora in test animals, and may in fact cause weight loss at certain times of the year. In other avian studies using bobwhite quail and pheasant, species more applicable to environmental safety, the highest dose level tested was 25 ppm. In these studies, data was presented that indicated slight increases in weight gains and increased survival. These birds were on balanced diets with all the necessary nutrients added, and weight gains were noted to vary with changes in the age of the test animals.

The lab studies that were conducted on mammals did not indicate any serious problem with acute toxicity of this product. Test animals tended to display an increased rate of survival, and this was felt to be due to the protective action of the antibiotic against bacterial infections. The following toxic effects were noted, however: gastroenteric disorders, diarrhea, vomiting, pruritus, drug fever, dermatitis and formation of tumors in the colon. It was not clear if the tumor formation was the result of terramycin or in spite of terramycin, because control animals seemed to have as high an incidence of tumors as test animals. Treated animals appeared to be more vigorous and gained weight faster. A three generation rat study did not produce any adverse effects at dose levels up to 100 mg/kg.

The Environmental Safety Staff does not anticipate any serious aquatic hazard from this use pattern as it is sprayed directly to trees and 90% is expected to be retained as residue. The 10% run off should not result in aquatic exposure because terramycin binds to soil particles and then degrades rapidly. The likelihood of exposure to avian species, however, is very high. The maximum application rate of 200 ppm and the constant reapplication every 4-6 days will result in certain exposure to wild birds at levels higher than those supported by the studies referenced to support this registration (100 ppm on domestic ducks, 25 ppm bobwhite and pheasant). The Environmental Safety Section is concerned about this exposure because of two facts. The registrant does not provide either data on wild birds at the dietary level of 200 ppm, or supply data on the effects of gut flora changes on species that have rather specialized diets.

Terramycin can be a prophylactic, but it could also change the gut flora in some species in such a manner that they might have nutritional difficulties with the diet that they are compelled to utilize as a result of their niche ecology. This prophylactic effect may also alter the wild species' natural resistance to the pathogens that it has evolved with, removing certain micro-organisms that keep others (that might be resistant to terramycin) in check.

Terramycin is at present registered for use in domestic animal feed and as a tree injection antibiotic. It is not registered for a use that would produce the residues mentioned; and therefore fish and wildlife data have never been generated. Human toxicology is not concerned about terramycin because the material degrades rapidly and does not appear as a residue on fruit. The Environmental Safety Section is concerned about this lack of data because residues in the environment are higher than any tested in experiments. The registrant further states that this should be considered as a minor use application. The Environmental Safety Section does not feel that 111,628 acres of pears in the Pacific Northwest, California, New York, Michigan and Pennsylvania and 300,618 acres of peaches in California, Georgia, Michigan, the Pacific Northwest and the Eastern Shore of the U.S. constitute a minor use. We feel that it is a major use and will result in numerous opportunities for avian exposure.

105.0

Conclusions

The Environmental Safety Section cannot concur with this registration or the registrant's request for a waiver of data requirements for Fish and Wildlife Safety. This decision is based upon the following considerations:

- A. Data supplied to support the registration and justify the waiver request was derived during efficacy studies which did not have as their intent the identification of any maximum level of terramycin that could be tolerated before environmental hazard resulted.
- B. The levels tested in the referenced studies for birds are below the level of residue that the registrant has indicated will occur. The Environmental Safety Section therefore does not have sound conclusive proof, based upon studies designed to address wild species of birds, fish and aquatic organisms, that environmental hazard will not occur.

14

- C. The studies referenced in the waiver request do not meet basic data requirements for making an environmental hazard assessment. The bobwhite quail and pheasant studies did not determine an LC₅₀. The highest level tested for these species was 25 ppm. The Environmental Safety Section requires an LC₅₀ test to exceed 5000 ppm to adequately address hazard. The fish feeding study tested levels up to 75 ppm, and this would indicate minimal hazard, but the study is not acceptable as fish and wildlife safety data because the material tested was not properly identified, the species tested was not identified, and the conditions of the study do not meet those required to determine an LC₅₀.
- D. The data supplied with this request were generated to provide efficacy data, and these data indicate that terramycin does have some prophylactic effect and does promote growth during some stages of the life cycle. The data also indicate that changes in gut flora occur, and at some period in the life cycle weight loss can occur. The Environmental Safety Section is concerned that wild avian species that are dependent upon a specific ecological food niche might suffer impairment if terramycin residues were sufficient to impair cecol bacteria and resultant ~~nutritional~~ failure occurred. **NUTRITIONAL**
- E. The Environmental Safety Section is also concerned by the residues that will be present as a result of the repeat applications. The constant exposure during a period of the year may destroy certain micro-organisms that control more virulent pathogens. This may in turn increase wild bird species' susceptibility to disease when terramycin is not present by lowering natural resistance to pathogens. The registrant should resolve these points as well as supply the basic data listed below:
- (1) the avian acute oral LD₅₀ for one species of waterfowl (mallard duck, preferably) or one species of upland game bird (ring-necked pheasant or bobwhite quail);
 - (2) the dietary LC₅₀ for one species of waterfowl (mallard duck) and one species of upland game bird (bobwhite quail or ring-necked pheasant);

- (3) the 96-hour acute LC₅₀'s for a coldwater species (rainbow trout) and a warmwater species (bluegill sunfish) of fish;
- (4) the acute 48-hour LC₅₀ for an aquatic invertebrate (Daphnia sp., preferably). The above basic studies are required for each active ingredient, and the studies should be conducted on the technical grade material.

The registrant should contact the Environmental Safety Staff if there are any questions pertaining to our decision or protocols required for the data requests.

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Fish and Wildlife Section 10/5/77
EEEE-RD WH 567