215B

10-25-91

009093

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.:50534-ROI

From: Lucy D. Markarian, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

To: Susan Lewis, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

Applicant: ISK Biotech Corporation
5966 Heisley Road
P.O.Box 8000
Mentor, Ohio 44061-8000

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Chlorothalonil.....	40.4 %
Inert Ingredient(s):	59.6 %
Total:	100.0 %

INERT INGREDIENT INFORMATION IS NOT INCLUDED

BACKGROUND

ISK Biotech corporation has applied for the registration of the product Tuffgard 404 under EPA symbol 50534-ROI. The formulation is an end use product to be used for the control of surface molds and fungi on wood. The active ingredient is chlorothalonil. A large number of acute toxicological studies have been cited and submitted for review in support. Some of the cited tests are performed using a substantially similar formulation registered under 50534-8 (Bravo 500) and some under 50534- Technical Tuffgard. The compositions of the three products are as follows:

	Tuffgard 404 50534-ROI %	Bravo 500 50534-8 %	Tuffgard Technical 50534- %
Technical (97 %) Chlorothalonil	41.65	41.65	100.0
[redacted]			

The difference between Tuffgard 404 and Bravo 500 is [redacted] Tuffgard technical is the source of the active ingredient.

The cited studies under Bravo 500 were reviewed as of 6/5/90 with the following results:

Test	Accession Number	Result	Tox Category	Rating
Acute Oral	87306	LD_{50} 4.2 g/K	III	Guideline
Acute Dermal	87307	LD_{50} >20 g/K	IV	Guideline
Acute Inh.	87310	LC_{50} >1.072 mg/L		Supp.
Eye Irr.	87177	Clear by day 14	II	Guideline
	87177	Clear by day 7	III	Guideline
Dermal Irr.	87308	PII 0.42	IV	Guideline

Sensitization tests using Technical Chlorothalonil that were cited

MRID	% AI	Results	Type of Test
144112	97.0	not a sensitizer	Open epicutaneous
405460-02	54.0	weak sensitizer	Modified Buehler
405460-01	technical unspecified	weak sensitizer	Maximization

Other cited studies conducted with technical chlorothalonil:

Test	Accession Number	Results	Tox Category	Rating
Acute Oral	94941	LD_{50} >10,000 mg/K	IV	Minimum (reviewed)
Acute Dermal	94940	LD_{50} >10.000 mg/K	IV	Guideline (reviewed)
Acute Inhalation	94942	LC_{50} M 0.094(0.0703-0.1257) F 0.092(0.0795-0.1064)	II	Minimum (reviewed)
Acute (1 hr) Inhalation	100787	LC_{50} 0.225(0.190-0.267)	II	Guideline (EPA one liner)
Eye Irr.	60434			not acceptable
Eye Irr	30350	Corrosive	I	Guideline (EPA one liner)
Dermal Irr.	94939	Nonirritating	IV	Guideline (EPA one liner)

RECOMMENDATION

The reviewed oral toxicity study using the technical Tuffgard is considered core minimum data, because individual data for any group for in life observations are not presented. The reviewer must have this information to be able to draw an independent conclusion.

The rationale for the grading of the inhalation test as core minimum data are as follows:

1- The animals showed an underlying respiratory disease at necropsy. (microscopic examination- murine respiratory mycoplasms) in all groups. This undoubtedly had an effect on the results. These animals should not have been used for testing.

2-LC_{50} calculations for combined sexes were lower than that of the group that showed the lowest values (females). The calculation appears erroneous.

3-MMAD is larger than desirable. No particle size distribution is presented. It is not known what percentage of the aerosol was actually inhalable.

4-It is not clear if deaths were due to underlying disease or to the test material, or a combination of both. The control animals did not die; however this does not mean that the underlying disease had no effect.

The tests conducted with Bravo 500 that are acceptable(all but the inhalation study) support the registration of Tuffgard 404. The inhalation study conducted with the technical Chlorothalonil can support the registration, because the active ingredient in very

small quantities (0.092 mg/L- 50% mortality) proves to have substantial toxicity, enough to place it in category II. This level of active ingredient can be reached with the less concentrated Tuffgard 4C4, and have the same effect regardless of the inerts present. In EPA files there is enough data to confirm that via the inhalation route, chlorothalonil is very toxic. The registration standard for the technical chlorothalonil reiterates this view.

The sensitization tests are not too decisive. The registration standard states that chlorothalonil may induce "temporary allergic side effects characterized by redness of the eyes, mild bronchial irritation and redness or rash on exposed skin". As the reviewed tests echo this by finding the active ingredient to be a week sensitizer, the possibility of sensitization cannot be slighted.

There are two eye irritation studies. One places the eye irritation in category II and the second in category III. PRS usually considers the worst possibility in making a decision; therefore, the eye test showing the product to be in category II toxicity is considered applicable, strengthened by the statement in the registration standard of the technical chlorothalonil that this chemical is corrosive to the eyes.

LABELING

Based on the category II placement of the inhalation and eye irritation tests The signal word is "Warning", as stated on the proposed label.

The Precautionary statement must include:

May be fatal if inhaled. Causes substantial but temporary eye injury. Do not breath dust, vapor or spray mist. Do not get in eyes. Wear a mask or pesticide respirator jointly approved by MSHA and NIOSH. Wear goggles, face shield, or safety Glasses. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.
Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

The statement of practical treatment must include:

If inhaled- Remove victim to fresh air. If not breathing give artificial respiration, Preferably mouth to mouth. Get medical attention.
If in eyes-Hold eyelids open and flush with a gentle steady stream of water for fifteen minutes. Get medical attention.

Category IV placement of the oral toxicity and, dermal toxicity and irritation studies do not require any precautionary labeling in these areas.

4

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1) 009093

roduct Manager: (21)
MRID No.: Acc# 244941
Testing Facility: Bio Research Laboratories, Inc.
Author(s): C.B. Bieu
Species: Rat, Sprague Dawley
Age: 5-7 weeks old
Weight: 176 - 263 g.
Source: Charles River Breeding Laboratories, St Constant, Quebec
Test Material: I-117-7 white crystalline powder (dosed as 20ml/kg) Technical Chemicals
Quality Assurance (40 CFR §160.12): Study conducted before QA + GLP regulations were implemented

Reviewer: L. Markarian
Report Date:
Report No. D-2787
Study 12761

Observation Days (Post Exposure): (14); other ( )

Conclusion:

1. LD_{50} (mg/kg): Males = ; Females = ; Combined =
2. The estimated LD_{50} is > 10,000 mg/kg
3. Tox. Category: IV. Classification: Core minimum

Procedure (Deviations From §81-1): There were 6 phases in the study. Phases I, II & III were conducted using 1.5% Tween 80 as solvent. Phase I & II were two dose levels: 10,000 & 5,000 mg/kg. The responses were inconsistent, because of higher percentage died at 5000 mg/kg. Phase III: 0.000 mg/kg. The phase III part was a range finding study with 2 animals per level 1000, 2000, 2500, 3000, 4000 & 5000 mg/kg 2 animals died at 2500 & 3500 mg/kg and none at 4000 & 5000 mg/kg. Therefore the vehicle was changed to 1% methyl cellulose and at phase IV 3 animals/level were included at 1000, 2000, 2500, 3500, 4000 & 5000 mg/kg level, 1 animal each died at levels 2500 & 4000 mg/kg. At phase V 5 animals per level were included at 10,000 mg/kg. When reanimalized it was decided to include 5 animals per level in methyl cellulose. Observations were frequent on day of treatment and daily thereafter. Body weights were recorded at initiation + days 3, 7 + 14 and at death. Necropsy was performed on all rats.

Reported Mortality

	DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
Phase V →	10,000	0/5	0/5	0/10
	in 1% methyl cellulose dosed at 20 ml/kg			
Phase I (included in new)	10,000 (Tween 80)	1/5	1/5	2/10
Phase IV (included in new)	5,000 (Tween 80)	1/5	2/5	3/10

Symptomology & Gross Necropsy Findings:

No individual data for rat, in any group is given. It is reported cumulatively that "Pharmacotoxicity were evident at all dose levels and in some instances persisted to 13 days". Clinical abnormalities included epistaxis, lacrimation, decreased eyelid tone, urealization, decreased activity, cyanosis, dyspnea, decreased body surface temperature, piloerection, distended abdomen, diarrhea, perianal staining, nervousness, hyperosis

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5

decreased reflex and muscle tone, ataxia (hunchback gait and tremors"

Necropsy of animals according to treatment showed pulmonary congestion; gastric distention, hemorrhage of gastric mucosal. Necropsy of the animals sacrificed at termination showed thickening of the gastric walls, particularly of the fundus. Spleen congested.

The necropsy of the animals were individually presented and it points to the fact that all the observed abnormalities occured in animals that were treated with Tween 80 as suspendy medium. Necropsy of the animals treated at 10,000 mg/kg suspended in 1.5% methyl cellulose showed no gross pathology. The animals that survived to treatment during the range finding study at 2500 & 4000 mg/kg in methyl cellulose did show signs of gastrointestinal distress, congestion of kidneys and congested lungs at necropsy.

009093

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§91-2)

Product Manager: (21) Reviewer: L. Markarian
MRID No.: Acc. 94940 Report Date: ____
Testing Laboratory: Bio-Research Laboratories LTD Report No. DS-3787 Test 12.762
Author(s): Colin B. Brer, Linda Peteet
Species: Rabbit, New Zealand white (West Jersey Biological Supply Farm)
Sex: 6♂ & 6♀ Wt.: 1.9 - 2.6 kg (10 - 13 wks old)
Test Material: T-117-7 white crystalline powder
Quality Assurance (40 CFR §160.12): Study conducted prior to GLP regulation implementation

Summary:

1. LD_{50} (mg/kg): Males = ____; Females = ____; Combined = ____;
2. The estimated LD_{50} is Greater than 10,000 mg/kg
3. Tox. Category: IV. Classification: Guideline

Procedure (Deviations From §81-2): A pretest range finding study was conducted using one male and one female. Abraded skin was treated with 10,000 mg/kg of test material on approximately 10% of the body surface. No deaths occurred. Therefore the main test was performed abraded skin at 10,000 mg/kg applied similarly. Although it is stated that it was done the indented protocol states that solid test material will be slightly moistened with physiological saline prior to application & the trunk will be covered with impervious rubber sheeting. At 24 hrs the sheeting will be removed & site will be wiped. Observations were frequent during the day of application & twice daily thereafter. Body weight were recorded at initiation and on days 3, 7, & 14
Results: Necropsy were performed on all animals.

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
10,000	0/1	0/1	0/10

Symptomology & Gross Necropsy Findings:

There were no mortality. Clinical signs of toxicity included erythema irritation. Diarrhea, nasal discharge and dermal irritation consisting of erythema edema & eschar formation at test sites. Some of the animals & females showed weight loss - and some did not reach their pre Test weight at 14 days. Dermal irritation was still present at 14 days in 4 males & 5 females. Yellow staining on the ears was seen in 5/10

Necropsy revealed seven abnormalities in the lungs of 3/10 as well as foci in discrete areas of firmness. Also rats were yellow / stained around the ears

009093

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (21) Reviewer: L. Markarian
MRID No.: 94942, 505100-17 Report Date: ____
Testing Laboratory: Bio Research Laboratories Ltd Report No. BS2787-0426
Author(s): Charles B. Breckenridge Lab # 9383
Species: Rat, Sprague Dawley
Sex: 10 ♂ & 10 ♀ per level Weight: Batch 1 175-250g Batch 2 210-310g 3 one day
Source: Charles River Breeding Laboratories, Wilmington Mass
Test Material: T-117-17 Chlorothalonil Technical
Quality Assurance (40 CFR §160.12): Study performed prior to QA & GLP regulation implementation

Summary:

1. LC_{50} (mg/kg): Males = 0.0640 (0.0703 - 0.1257) mg/L; Females = 0.0925 (0.0794 - 0.1073) mg/L; Combined = 0.0820 (0.0795 - 0.1064) mg/kg
2. The estimated LC_{50} is ____
3. Mean Concentration: ____
4. Tox. Category: II. Classification: Core minimum

Procedure (Deviations From §81-2): A total of 9 groups were exposed. The first Two groups were discarded immediately after exposure due to an injection problem of the generating system. Two of the remaining 7 groups were not included in the LC_{50} calculations because the chamber concentrations could not achieve the desired level. These were Groups III & IV, however these groups were observed for 14 days, but no necropsy was performed. The remaining five groups, exposed with their 6 days of each other were observed for 14 days with necropsy performed on all animals either at death or at termination

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
Air Control	0/10	0/10	0/20
0.0648	1/10	0/10	1/20
0.0925	4/10	5/10	9/20
0.1010	10/10	7/10	17/20
0.2193	9/10	10/10	19/20

Exposures were in Two 27"3 (400L) chambers. Airflow rate was set at 20Lpm and was measured in the exhaust line Through a magnehelic pressure gauge calibrated with a ball Type flow meter. The chamber was operated at a slightly negative pressure Than the room atmosphere. Chamber air was decontaminated using charcoal hepa filters and a liquid scrubber before release. The aerosol was generated using Wright's Dust Feed Generator supplied with predried compressed air. The grain was generated into the base of a 6cm x 45cm vertical cylinder That had a J shaped tube at the top That conducted the air from the generator into a Tangential head at the Top of the chamber. The proper gear ratio selected at the dust generator adjusted the chamber concentration. Equilibrium was reached in 30 minutes after the start of generation The fan at the end of the exposure 30 minutes were allowed to equilibrate the chamber with room air before removal of the animals.

Chamber concentrations were determined hourly from the breathing zone using Gelman glass fiber filters at the sampling rate of 5 Lpm for 10 minutes. Particle size analysis was made using Andersen 1 ACFM ambient sampler at 30 minute intervals at the sampling rate of 28.4 Lpm for 5 minutes - MMAD were determined by plotting particle size distribution.

All animals were observed hourly during exposure and during the 4 hr post exposure period and twice daily thereafter for 14 days. Body weights were recorded at initiation and on days 7, 3, 4, 7 + 14 as well as at death. At termination, Cage cutaneous tissues, Liver, Kidneys & Lungs were preserved in 10% buffered formalin as well as other gross lesions if present. The organs thus preserved were subjected to histopathological examination.

Results

Chamber Temperatures ranged from 22 - 26°C and relative humidity 30 to 60%.

The following are the MMAD ranges for each concentration (3 values for each concentration)

0.0648 mg/L	Ave MMAD 3.36 um range 1.5 - 5.5 um	Standard Deviation 1.56 - 2.52
0.0935 mg/L	Ave MMAD 3.64 um range 1.35 - 4.7 um	1.66 - 2.21
0.1010 mg/L	Ave. MMAD 3.66 range 1.9 - 4.6 um	1.67 - 2.31
0.2093 mg/L	Ave MMAD 4.36 range 3.1 - 4.7	1.72 - 2.00

The particle size distribution is not presented for any of the concentrations.

Most deaths occurred within 4 days of exposure. The observed signs of toxicity were many as respiratory distress consisting of severe rales, bloody nasal discharge and gasping. It is stated that cause of death were judged to be asphyxiation. There was weight loss in all animals at the end of the first week of observations. Weight loss was observed even in control groups up to day 3 in males and up to day 7 in females

9

Necropsy revealed multiple pinpoint foci scattered on all lobes of lungs of all levels including the controls and were concluded to be none product related

Histological assessment of the presented tissues concluded that There was a high incidence of murine respiratory mycoplasma in all groups including the controls. There was diffuse congestion of the lungs and exudate was present in Trachea. However the incidence of these conditions were higher in the Test groups.

Histological examination also found Treatment related increase in the incidences of lung congestion, as well as congestion of livers & kidneys. There was evidence of hepatotoxicity characterized by loss of glycogen staining & vacuolization of hepatocytes, as well as atrophy of hepatocytes at higher doses. Renal toxicity was manifested as increased accumulation of eosinophilic amorphic material in the convoluted tubules.

The oral Toxicity Test was rated core minimum, because individual data from any group for in life observations was not presented. The erratic pattern of mortality observed during range finding study with methyl cellulose suggests that the dosing solution (suspension) was not homogenous.

1. The Inhalation study is rated core minimum, because all animals showed evidence of underlying respiratory disease (microscopic) (murine respiratory mycoplasma) in all groups. This could have an effect on the results of the tests.
2. LC_{50} calculations for combined sexes is lower than that of the group that showed the lowest values (female). This calculation appears to be erroneous.
3. MMAD is larger than desirable. No particle size distribution is presented. It is not clear if deaths occurred due to underlying disease or actual inhalation as it is not known what percentage of the aerosol was actually inhalable to the test model.