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 %
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:

<table>
<thead>
<tr>
<th></th>
<th>Tuffgard 404</th>
<th>Bravo 500</th>
<th>Technical</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Chlorothalonil</td>
<td>41.65</td>
<td>41.65</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Technical (97 %)

The difference between Tuffgard 404 and Bravo 500 is that 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:

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

Sensitization tests using Technical Chlorothalonil that were cited:

<table>
<thead>
<tr>
<th>MRID</th>
<th>% AI</th>
<th>Results</th>
<th>Type of Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>144112</td>
<td>97.0</td>
<td>not a sensitizer</td>
<td>Open epicutaneous</td>
</tr>
<tr>
<td>405460-02</td>
<td>54.0</td>
<td>weak sensitizer</td>
<td>Modified Buehler</td>
</tr>
<tr>
<td>405460-01</td>
<td>technical</td>
<td>weak sensitizer</td>
<td>Maximization</td>
</tr>
</tbody>
</table>
Other cited studies conducted with technical chlorothalonil:

<table>
<thead>
<tr>
<th>Test</th>
<th>Accession Number</th>
<th>Results</th>
<th>Tox Category</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Oral</td>
<td>94941</td>
<td>( \text{LD}_{50} &gt; 10,000 \text{ mg/K} )</td>
<td>IV</td>
<td>Minimum (reviewed)</td>
</tr>
<tr>
<td>Acute Dermal</td>
<td>94940</td>
<td>( \text{LD}_{50} &gt; 10,000 \text{ mg/K} )</td>
<td>IV</td>
<td>Guideline (reviewed)</td>
</tr>
<tr>
<td>Acute Inhalation</td>
<td>94942</td>
<td>( \text{LC}_{50} \text{ M } 0.094(0.0703-0.1257) )</td>
<td>II</td>
<td>Minimum (reviewed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{F } 0.092(0.0795-0.1064) )</td>
<td></td>
<td>(reviewed)</td>
</tr>
<tr>
<td>Acute Inhalation</td>
<td>100787</td>
<td>( \text{LC}_{50} 0.225(0.190-0.267) )</td>
<td>II</td>
<td>Guideline (EPA one liner)</td>
</tr>
<tr>
<td>Eye Irr.</td>
<td>60434</td>
<td>Corrosive</td>
<td>I</td>
<td>Guideline (EPA one liner)</td>
</tr>
<tr>
<td>Eye Irr</td>
<td>30350</td>
<td></td>
<td></td>
<td>(EPA one liner)</td>
</tr>
<tr>
<td>Dermal Irr.</td>
<td>94939</td>
<td>Nonirritating</td>
<td>IV</td>
<td>Guideline (EPA one liner)</td>
</tr>
</tbody>
</table>

**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- \( \text{LC}_{50} \) calculations for combined sexes are 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 404, and have the same effect regardless of the inert 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 breathe 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.
DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Review者: L. Markarian

MRID No.: 009093

Testing Facility: Bio Research Laboratories, Inc.

Author(s): C. B. Bier

Species: Rat, Sprague-Dawley

Age: 5 - 7 weeks old

Weight: 176 - 263 g.

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

Source: Charles River Breeding Laboratories, Inc., Stoughton, Massachusetts

Test Material: 1 - 117 - 7 with antigenic power (dose of 2 mg/kg) Technical Chemical


Conclusions:

1. LD50 (mg/kg): Males = ; Females =

2. The estimated LD50 is > 10,000 mg/kg

3. Tox. Category: IV

Classification: None

Procedure (Deviations From §81-1): There were 6 phases: Phase I was conducted using 1./3rd lower dose to obtain 1,000 mg/kg as a toxic range. Phase II was conducted using a lower dose range of 1,000 mg/kg.

The responses were inconsistent, because at higher dosages, death at 2,000 mg/kg occurred. Therefore, Phase III was conducted using a 10,000 mg/kg dose range. The animals were then classified as 1/2 methyl cellulose and at Phase IV 1/3rd lower dose was used before death occurred. The animals were then classified as 1/2 methyl cellulose.

Reported Mortality

<table>
<thead>
<tr>
<th>DOSAGE (mg/kg)</th>
<th>NUMBER KILLED/NUMBER TESTED</th>
<th>Males</th>
<th>Females</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,000</td>
<td>1/3rd lower dose</td>
<td>1/3rd</td>
<td>1/3rd</td>
<td>1/3rd</td>
</tr>
<tr>
<td>1,000</td>
<td></td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>1,000 (Phase 3)</td>
<td></td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
</tr>
<tr>
<td>5,000 (Phase 3)</td>
<td></td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

Symptoms and effects for each group are given. It is reported cumulatively.

Pharmacological tests were conducted at all dose levels and in some instances persisted for 13 days. Clinical abnormalities included epistaxis, lacrimation, decreased expiratory respiration, increased activity, conjunctivitis, dyspnea, decreased body surface temperature, pupil reaction, drooling, abdominal distension, prominent diaphragm, pulmonary edema, and others.

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demanded referee and muscle tissue, along with muscle gastrin, gast and

Treatment

Necropsy of animals receiving treatment showed primarily

congestion, gas, necrosis, hemorrhage of gastric mucosa.

Necropsy of the animals sacrificed at termination showed

thickening of the gastric mucosa, particularly of the fundal, antrum, area.

The necropsy of the animals were individually noted and it points to the fact that all three observed abnormalities occurred in animals that were treated with twenty mg. as suspensory medium. Necropsy of the animals treated at 10,000 mg/kg suspended in 0.5% methyl cellulose showed no gross pathology. The animals that received 10,000 mg/kg during the range finding study at 500 mg/kg in methyl cellulose did show signs of gastritis and gastric erosion of kidneys and congestion of lungs at necropsy.
DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§91-2)

Product Manager: (21)  
Reviewer: L. Markarian  
MRID No.: 94 197  
Report Date: 
Testing Laboratory: Bio-Renaissance Ltd  
Report No. 28-177  
Author(s): Colin A. Bee, Linda Peters  
Species: Rabbit, New Zealand white (ANZAC. 2)  
Sex: 6/4  
Wt.: 1.9 - 2.6 kg  
Test Material: T-17-7 white crystals powder  
Quality Assurance (40 CFR §160.12): Study conducted prior to QM and GLP regulations.

Summary:

1. LD50 (mg/kg): Males =  
   Combined =  
   Females =  
2. The estimated LD50 is  
   Classification: 
3. Tox. Category:  

Procedure (Deviations From §91-2): A repeat range-finding study was conducted using one male and one female albino rabbit. Animals were treated with varying 
of test material on approximately 10% of the body surface. No deaths occurred. Therefore this 
material was performed abraded skin of 10 white rabbits applied to the animal's 
material that included the range-finding studies that included material with 
material varied with weight gain and included a number of the material will 
be repeated with weight gain and increased weight gain will be included with 
numbers in the study. At 1 day intervals, animals will be removed and 
will be weighed. Observations were performed during the first 48 hours post 
Results: Necropsy was performed on all animals.

Reported Mortality

<table>
<thead>
<tr>
<th>DOSAGE (mg/kg)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>10,000</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

No mortality. Clinical signs of toxicity included erythema, induration, and edema of the ears and face. 

Test weight at 1 and 7 days. Incidence of necropsy was present at 1, 7 days, and 1, 7 days.

Necropsy revealed some abnormality in the ears of 3/10 animals. Fatty liver was seen in 3/10 animals. 

Legend: 1/10 = one in 10; 3/10 = three in 10; 7/10 = seven in 10; etc.
DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (31)  
Reviewer: L. Markarian  
MPID No.: Q44285  
Report Date:  
Testing Laboratory: Bee Research Laboratories Ltd  
Report No. Q44285-0036  
Author(s): Charles B. Breckenridge  
Species: Rat, Sprague Dawley  
Sex: 10♂ 8♀ 10 g per vent  
Weight: Avg. 175-215 g; R&D Lab No. 20-05726  
Source: Charles River Breeding Laboratories, Wilmington, Mass.  
Test Material:  

Summary:

1. LC50 (mg/kg): Males = 0.09460 (0.0703-0.1257) mg/L; Females = 0.09425 (0.0719-0.1107) mg/L; Combined = 0.09252 (0.0719-0.1106) mg/L
2. The estimated LC50 is
3. Mean Concentration:
4. Tox. Category: Classification: Core minimum

Procedure (Revisions from §81-2): A total of 10 groups were exposed. The first two groups were discarded immediately after exposure was completed. The remaining 8 groups were exposed in the 24 hour LC50 test. The chamber concentrations were adjusted to achieve the desired level. These groups were observed for deaths and narcosis determinations. The remaining 6 groups were exposed for 7 days, with necropsies performed on all animals either at death or at termination.

<table>
<thead>
<tr>
<th>Exposure Concentration (mg/L)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
<th>Males</th>
<th>Females</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Control</td>
<td></td>
<td>%0</td>
<td>%0</td>
<td>%0</td>
</tr>
<tr>
<td>0.0648</td>
<td></td>
<td>%0</td>
<td>%0</td>
<td>%0</td>
</tr>
<tr>
<td>0.0925</td>
<td></td>
<td>%0</td>
<td>%0</td>
<td>%0</td>
</tr>
<tr>
<td>0.1010</td>
<td></td>
<td>%0</td>
<td>%0</td>
<td>%0</td>
</tr>
<tr>
<td>0.3193</td>
<td></td>
<td>%0</td>
<td>%0</td>
<td>%0</td>
</tr>
</tbody>
</table>

Exposures were in two 27"³ (dowel) chambers. Airflow rate was set at 20 LPM and was measured in the exhaust line. Through a magnetic flow system calibrated with a bell type flow meter. The chamber was equipped with a high speed exhaust. The airflow was generated using a centrifugal blower. Chambers were equipped with a high efficiency particulate air filter. The air was filtered in a clean room atmosphere. The air was drawn into the chamber through the top of the chamber. The proper flow rate was determined by adjusting the chamber inlet pressure. Equilibrium was reached in 60 minutes after the start of generation. The air at the end of the exposure chamber was allowed to equilibrate with the chamber with room air before removal of the air males.
Chamber concentrations were determined hourly from the breathing zone using Geotex glass fiber filters at the sampling rate of 5 lpm for 10 minutes.

Particle size analysis was made using Buerker's ACFM and a cascade impactor. MMAD were determined by plotting particle size distribution.

All animals were observed hourly during exposure and during the 5 days post-exposure period and until death. Temperature and relative humidity were measured at initiation and termination.

Results

Chamber temperature ranged from 22-26°C and relative humidity from 35-60%.

The following are the MMAD ranges for each concentration in μm:

- **2.043 mg/L**: Ave. MMAD = 3.26 μm, range 1.8-5.5 μm, 1.56 - 3.52
- **0.935 mg/L**: Ave. MMAD = 3.64 μm, range 1.35-4.7 μm
- **1.010 mg/L**: Ave. MMAD = 3.6 µm, range 1.8-4.6 μm
- **2.013 mg/L**: Ave. MMAD = 4.36 μm, range 3.1 - 4.7

The particle size distribution is presented for only one of the conditions.

Most deaths occurred within 1 day of exposure. The observed signs of toxicity were mainly respiratory distress, coryza, and severe cough, bloody nasal discharge, and conjunctivitis.

It is stated that causes of death were judged to be physiologic.

There was weight loss in all animals at the end of the first week of observation. Weight loss was observed even in control groups up to day 3 in males and up to day 7 in females.

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Necropsy revealed multiple foci of scattered ulcers of the lungs and air sacs at all levels of exposure. These were considered to be product related.

Histological examination of the present tissue concluded that there was a high incidence of mucous respiratory metaplasia in all groups. Pathology of the control and treated groups showed diffuse congestion of the lungs and pulmonary consolidation in the control group. However, the incidence of these conditions was higher in the treated groups.

Histological examination also failed to reveal treatment-related lesions in the incidence of lung congestion, as well as congestion of livers and kidneys. There was evidence of hepatic toxicity characterized by loss of granular staining and vacuolization of hepatocytes, as well as atrophy of hepatocytes at high doses. Renal toxicity was manifested as increased accumulation of eosinophilic amorphous material in the convoluted tubules.
The oral toxicity test was rated as minimum because individual data from any group for in-life parameters were not presented. The acute pattern of mortality observed during course finding study with methylcellulose suggests that the dosing solution (suspension) was not homogeneous.

1. The inhalation study is rated case maximum because all animals showed evidence of underlying respiratory disease, including mucus retention and pleural pneumonia in all groups. This could have an effect on the results of the tests.

2. LC50 calculations for combined sexes is lower than that of the group that showed the lowest value (females). This calculation appears to be erroneous.

3. MMAD is larger than desirable. No particle size distribution is presented. It is not clear if death occurred due to underlying disease or actual inhalation. It is not known what percentage of the aerosol was actually inhalable to the test model.