2-4-83

Memorandum

Date: 4 February 1983

003231

Subject: EPA Reg. No. 59-136 DERMATON II
Caswell #137

From: B. T. Backus
IRB/TSS

To: Mr. George LaRocca
Product Manager 15

Registrant: Wellcome Animal Health Division
Burroughs Wellcome Co.
2000 S. 11th St.
Kansas City, KS 66103

Current Label Declaration:
Active Ingredients:
2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl phosphate...12.25%
Xylene.....10.00%
Mineral Seal Oil.....70.06%
Inert Ingredients:.....7.69%

Proposed Revised Formula Label Declaration:
Active Ingredients:
2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl phosphate...12.25%
Petroleum Solvents.....67.76%
Methylene Chloride.....10.00%
Inert Ingredients:.....9.99%

Background:

The registrant wishes to revise the formula, as indicated above in the current and proposed label declarations. The registrant has sent in acute dermal $LD_{50}$, oral $LD_{50}$, inhalation $LC_{50}$, primary dermal and eye irritation studies on the proposed revised formulation.

Comments and Recommendations:

1. The acute oral $LD_{50}$, primary eye and dermal irritation studies received 12-13-82 are acceptable.

2. The acute dermal $LD_{50}$ study received 12-13-82 is acceptable; however, we doubt that the statistical 95% confidence limits for the reported female $LD_{50}$ value fall in the comparatively narrow range of 1526-1606 mg/kg, particularly as no subjects were tested at dosage levels of between 500 and 1600 mg/L.

3. The inhalation $LC_{50}$ study is also acceptable, although the $LC_{50}$ value should have been reported in terms of actual (gravimetric) concentration rather than nominal. The $LC_{50}$ in terms of actual concentration would be about 0.20 mg/L, which places the product in toxicity category II by this exposure route.

195

003231

4. IRB/TSS would have no objections, on the basis of safety considerations, to the proposed revised formulation with the labeling as proposed by the registrant.

Review:

The following studies were conducted on the proposed revised formulation Studies were conducted at the Department of Toxicology and Experimental Pathology, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709, and were received at EPA 12-13-82. Studies are in Acc. 249462.

1. Acute Dermal $LD_{50}$ - Rabbit. Title: An Acute Dermal Toxicity ($LD_{50}$) Study in the New Zealand White Rabbit with DERMATON® II (BW 0023Z61). Doc. No. TIEP/82/0083; dated 6/2/82.

   Procedure: Groups of 4M, 4F received 24-hr occluded dermal exposure to dosage levels of 500, 1600, 1900, 2200 or 2500 mg/kg, with subsequent 14-day observation.

   Results:

| Dosage Level (mg/kg) | Mortalities/Animals Dosed M | F |
|---|---|---|
| 500 | 0/4 | 0/4 |
| 1600 | 4/4 | 3/4 |
| 1900 | 2/4 | 4/4 |
| 2200 | 4/4 | 4/4 |
| 2500 | 4/4 | 4/4 |

   Mortalities occurred as late as day 10.
   $LD_{50}$ (M) between 500 and 1600 mg/kg.
   $LD_{50}$ (F) reported as 1566 mg/kg with 95% confidence limits of 1526 to 1606 mg/kg (this reviewer doubts that the statistical 95% confidence limits fall in such a comparatively narrow range, especially since no rabbits were dosed at levels between 500 and 1600 mg/kg).
   Symptoms: salivation, ataxia, diarrhea, body tremors, decreased activity, labored breathing, prostration and stains in anogenital region.
   Necropsies of mortalities: not reported.
   Post-sacrifice necropsies of survivors: apparently unremarkable.

   Study Classification: Despite the considerable uncertainty in the dermal $LD_{50}$ value, study is adequate to classify this product. Core Minimum Data.

   Product Classification: Tox. Cat. II

2. Acute Oral $LD_{50}$ - Rat. Title: An Acute Oral Toxicity ($LD_{50}$) Study in the Rat with Dermaton® II (BW 0023Z61). Doc. No. TIEP/82/0109; dated Aug. 17, 1982.

2

Procedure: Groups of 10M were given oral dosages of 30, 60, 90 or 150 mg/kg; groups of 10F were given oral dosages of 50, 65, 80, or 95 mg/kg. Subjects were subsequently observed for 14 days.

Results:

| Dosage Level (mg/kg) | Mortalities/Animals Dosed M | F |
|---|---|---|
| 30 | 0/10 | - |
| 50 | - | 2/10 |
| 60 | 1/10 | - |
| 65 | - | 3/10 |
| 80 | - | 6/10 |
| 90 | 4/10 | - |
| 95 | - | 8/10 |
| 150 | 6/10 | - |

Deaths occurred through day 3.
Oral $LD_{50}$ (M) = 125.9 (99.7 - 187.7) mg/kg
Oral $LD_{50}$ (F) = 74.4 (61.0 - 90.1) mg/kg
Symptoms: salivation, muscular fasciculations, body tremors, ataxia, red material around eyes, rales, prostration and labored breathing.

Study Classification: Core Minimum Data (lack of individual body weight data, lack of data on necropsies of mortalities).

Product Classification: Tox. Cat. II

3. Primary Eye Irritation - Rabbit. Title: An Acute Eye Irritation Study in the New Zealand White Rabbit with Dermaton II (BW 0023Z61). Doc. No. TTEP/82/0073; dated May 13, 1982.

Procedure: 0.1 ml was applied to one eye of each of 6 NZ white rabbits, with no subsequent eyewash.

Results: No corneal opacity. Some conjunctival redness in all eyes, with some chemosis, discharge in some. All eyes clear by 7 days.

Study Classification: Core Minimum Data (no eyewash).

Product Classification: Tox. Cat. III

4. Primary Dermal Irritation - Rabbit. Title: An Acute Primary Skin Irritation Study in the New Zealand White Rabbit with Dermaton II (BW 0023Z61). Doc. No. TTEP/82/0021; dated May 13, 1982.

Procedure: 0.5 ml was applied to each of 4 sites, 2 intact, 2 abraded, on each of 6 rabbits, with 24-hr occluded dermal exposure.

Results: No irritation. PDIS = 0.

Study Classification: Core Guidelines Data

Product Classification: Tox. Cat. IV

The following study was conducted at Bio-Research Laboratories, Ltd. 87 Senneville Rd., Senneville, Quebec H9X 3R3, Canada. Study was received at EPA 12-13-82, and is in Acc.249462.

5. Acute Inhalation $LC_{50}$ - Rat. Title: The Acute Toxicity of Inhaled BW 0023261 (Dermaton II) in the Albino Rat. Sponsor Study No. ACU 247; Project No. 81281; dated June 16, 1982.

Procedure: Groups of 10M, 10F Crl:COBS (CD-SD) rats were exposed for 4 hours to nominal concentrations of from 1.13 to 2.69 mg/L. Four gravimetric measurements were taken during each exposure period. There was a subsequent 14-day observation period.

Results:

| Nominal Conc. (mg/L) | Gravimetric Conc. (mg/L) and S.D. | | Mortalities/Animals Exposed M | F |
|---|---|---|---|---|
| 1.13 | 0.15 | 0.01 | 2/10 | 0/10 |
| 1.55 | 0.21 | 0.01 | 6/10 | 8/10 |
| 1.85 | 0.22 | 0.05 | 8/10 | 6/10 |
| 2.69 | 0.27 | 0.09 | 10/10 | 8/10 |

Mass median diameters ranged from 2.1 to 2.7 um; geometric standard deviations ranged from 2.2 to 2.5 um.

Deaths occurred through day 5.
Inhalation $LC_{50}$ (M) reported as 1.45(1.25-1.68) mg/L (where concentration values are in terms of nominal concentration)
Inhalation $LC_{50}$ (F) reported as 1.47(1.16-1.87) mg/L (where concentration values are in terms of nominal concentration)
While inhalation $LC_{50}$ is not reported in terms of gravimetrically-determined concentrations it would be about 0.20 mg/L.

Symptoms: tremors, salivation, muscular weakness, lethargy, respiratory distress.

Necropsies: Reddening of lungs, slight to severe swelling of lungs, red fluid present in nasal cavities, yellow staining of fur around mouth and nares.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. II

Byron T Backus 12-14-82

Byron T. Backus
IRB/TSS

4

CHLORFENVINPHOS

Page 5 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

X ____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.