3-22-82

Memorandum

Date: 22 March 1982 001534

Subject: EPA File Symbol: 59-ROT DERMATON FLEA COLLAR
Caswell # 187

From: B. T. Backus
IRB/TSS

To: Mr. George LaRocca
Product Manager 15

Applicant: Burroughs Wellcome Co.
3030 Cornwallis Rd.
Research Triangle Park, NC 27709

Active Ingredient:
2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl phosphate.....15%
Inert Ingredients:.....85%

Background:

In response to questions as to possible sensitization potential of this proposed product, the applicant has sent in studies which were conducted on the technical material by Shell Research Ltd. in Great Britain.

Comments and Recommendations:

1. A study on the sensitization potential of the technical material is briefly summarized on p. 76 of the material received 8-18-81.

   According to this summary, the procedure followed was according to "Test Methods in Skin Toxicology Used by Tunstall Laboratory" (Report RIT)-5-64, re-issued as M(T)-2-64). We do not have a copy of this protocol, and should receive it.

2. We do not have information as to the individual observations of each of the animals (presumably guinea pigs) in this study. This material should be submitted.

3. The test material was applied as an 0.1% w/v solution in light liquid paraffin. The product, as proposed for registration, is 15% active in a plastic matrix. However, when the information indicated above has been received and reviewed, we will be able to more adequately assess whether this study is adequate to define the sensitization potential (or lack of it) of this particular proposed product. Observations on skin reactions (or lack thereof) in dogs wearing the proposed collars in cholinesterase studies may be extremely relevant.

Review: 001534

The following studies were conducted at Shell Research, Ltd., Tunstall Laboratory, Sittingbourne, Kent, England, under the title "Some Further Data on the Acute and Sub-acute Toxicities of the Insecticide SD 7859 (GC 4072)." Studies were received from Burroughs Wellcome on 8-18-81, with the title page "Guinea Pig Sensitization." Studies are in Acc. 245714.

1. Acute Oral LD50 - Chicken. Project No. TT.6.10; dated January, 1965.

   Procedure: Groups of 1M, 1F white leghorns were given oral dosage levels of 31.25, 44. 62.5, 94, or 125 mg/kg of active material in gelatin capsules.

   Results: All subjects receiving 62.5 mg/kg or more died within 24 hours; all receiving 44 mg/kg or less survived.

   Study Classification: Core Supplementary Data

2. Acute Oral LD50 - Guinea Pig. Project No. TT.6.10; dated January, 1965.

   Procedure: Groups of 1M, 1F "P" strain guinea pigs received 62.5, 125, 250, or 375 mg/kg of the active, as part of a 10% v/v suspension in 1% aqueous carboxymethyl cellulose.

   Results: Subjects receiving 250 mg/kg or more died within 3 hrs; those receiving 125 mg/kg or less survived. Symptoms: salivation, diarrhea, muscular fasciculations.

   Study Classification: Core Supplementary Data (insufficient number of subjects; no information as to length of observation following dosage).

3. Acute Oral LD50 - Rabbit. Project No. TT.6.10; dated January, 1965.

   Procedure: Groups of 1M, 1F NZ rabbits received oral dosages of 125, 250, 500, or 1,000 mg/kg of the active.

   Results: No mortalities at 500 mg/kg or below. Subjects at 1,000 mg/kg died. Symptoms (all): diarrhea. At highest level there was excessive watery salivation and constriction of pupils before death.

   Study Classification: Core Supplementary Data

4. Acute Subcutaneous LD50 - Guinea Pig. Project No. TT.6.10; dated January, 1965.

   Procedure: A group of 2M, 2F guinea pigs received a subcutaneous injection of 250 mg/kg of active; groups of 1M, 1F received subcutaneous injections of 500 or 1,000 mg/kg of active.

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Results: Mortality

Dosage Level (mg/kg)	Mortalities/Animals Dosed M	F
250	0/2	1/2
500	1/1	0/1
1,000	1/1	1/1

All deaths occurred within 48 hrs of injection. Symptoms:(all) excessive watery salivation, diarrhea, muscular fasciculations.

Study Classification: Core Supplementary Data (insufficient number of subjects; no information as to total observation time following dosage).

5. Cholinesterase (Plasma) - Dermal Absorption - male guinea pig. Project No. TT.6.10; dated January, 1965.

Procedure: Groups of 10M guinea pigs were dermally exposed to 1, 10 or 100 mg/kg/day 7 days a week for 2 weeks. Blood samples were taken 24 hrs after the initial dose and at weekly intervals for 5 weeks, and plasma ChE was assayed. Dosages of 0.01, 0.1 and 1.0 mg/kg/day in olive oil were subsequently administered to groups of 10M guinea pigs, with plasma ChE assayed.

Results: Presented in graph form. Subjects exposed to 100 mg/kg/day averaged less than 10% normal plasma ChE at end of 15 days, recovering to 60% by 36 days. Group at 1 mg/kg/day dropped to an average of about 30% normal plasma ChE at 15 days, recovering to 80% by 36 days. Even when plasma ChE was severely depleted by 100 mg/kg/day exposure the animals were otherwise asymptomatic. No significant effect on plasma ChE was produced by doses of 0.01 or 0.1 mg/kg/day for 15 days.

Study Classification: Core Supplementary Data (only males used, no individual data - only averages - presented, only plasma ChE measured).

6. Cholinesterase - Dog. Project No. TT.6.10; dated January, 1965.

Procedure: 1M, 1F beagles were orally dosed with 5 g/kg of technical. Blood was taken and measured for "plasma acetylcholinesterase" 24 hrs after ingestion and at irregular intervals thereafter.

Results: Dosage level, as reported, is extremely high and it is surprising that death did not occur. Very sharp drop in "plasma acetylcholinesterase" activity in both animals on day 1; at day 2 both were about 10% normal in this respect. Surprisingly little recovery in the male at 28 days (30% normal activity); F was up to 70% normal.

Study Classification: Core Supplementary Data (concern that the reported dosage level is incorrect; too few animals used, not precisely certain what is meant by "plasma acetylcholinesterase." Study is significant in that it indicates a long recovery period may occur after exposure to this material.

7. Sensitization - Guinea Pig (?) - Project No. TT.6.10; dated January, 1965.

Procedure: Apparently 0.1% w/v of active in light liquid paraffin was used following methods described in "Test Methods in Skin Toxicology Used by Turnstall Laboratory."

Results: simply reported as "no evidence of sensitization of the skin was observed."

Study Classification: Core Supplementary Data (no actual report, just a statement that no evidence of skin sensitization was observed. No information as to protocol or individual results).

Byron T Backus 03/22/82

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