Memorandum

Date: 4 November 1982

Subject: EPA File Symbol: 4758-RUU HILL'S HOLIDAY FLEA AND TICK DIP WITH NATURAL INSECTICIDE Caswell #526

From: B. T. Backus
IRB/TSS

To: Mr. William Miller
Product Manager 16

Applicant: Pet Chemicals Inc.
P.O. Box 660656
7781 N.W. 73 CT
Miami Springs, FL 33166

Active Ingredient:
d-Limonene.....78.20%
Inert Ingredients.....21.80%

Background:

Product is proposed for use as a dip, after dilution, on dogs, cats, puppies and kittens over one month of age. This application (without toxicity data) was previously reviewed (B. Backus, Aug. 27, 1982). Toxicity data have now been sent in.

Comments and Recommendations:

1. The acute oral LD50, acute dermal LD50, dermal sensitization, and primary eye and dermal irritation studies received 9-23-82 are adequate and acceptable in defining the potential hazards of these exposure routes.

2. The acute inhalation LC50 study has been classified as supplementary data, since no information is given as to the actual (rather than nominal) concentration of product and/or its active.

3. IRB/TSS would have no objection, on the basis of hazard to humans and domestic animals, to the conditional registration of this product for the proposed uses with the labeling revisions as indicated below.

Labeling:

The following comments are with respect to the proposed label received 9-23-82, and supersede those made in the review of 8-27-82.

1. Based on eye irritation potential, the appropriate signal word for this product is WARNING, as proposed in the labeling received 9-23-82.

2. The referral statement under the signal word should be revised to something like: "Read additional precautions on side panel." or "Read additional warnings on side panel."

3. The potential for dermal sensitization (both in pets and humans coming into contact with the use dilution or concentrate) should be addressed both in the Hazards to Humans and Domestic Animals statement and the Statement of Practical Treatment.

4. The Hazards to Humans & Domestic Animals statement should be revised to something like the following:

   WARNING: DO NOT USE FULL STRENGTH. MIX WITH WATER AS DIRECTED. Concentrate may cause eye and skin irritation; do not get in eyes, on skin, or on clothing. Concentrate is harmful if swallowed. Caution should be exercised when using on nursing animals. Do not use on animals under 1 month of age. Young animals should be towel dried immediately after dipping, to prevent chilling. Some individuals and pets may be sensitive to this product. Discontinue use if irritation develops. Wash hands with soap and water after using.

5. The Statement of Practical Treatment should include the following:

   If on skin - wash off with soap and water. Get medical attention if irritation develops.

6. The if in eyes statement should be revised to something like the following:

   If in eyes - flush with plenty of water. Get medical attention.

7. It would probably be appropriate to indicate in the statement of practical treatment that it is the concentrate, rather than the use dilution, which is of concern. This might be done by using a format something like:

   IF CONCENTRATE:

   is swallowed -

   is on skin -

   is in eyes -

Review:

The following studies were conducted on the product as proposed for registration. Studies were conducted at M B Research Laboratories, Inc. Steinsburg and Wentz Roads, P.O. Box 178, Spinnerstown, PA 18968, and were received at EPA 9-23-82.

1. Acute Oral LD50 - Rat. Project No. MB 82-6185A; dated 9-20-82. In Acc. 248713.

   Procedure: 5M, 5F rats received an oral dosage of 5 g/kg, with subsequent 14-day observation.

   Results: No mortalities. Symptoms included lethargy, piloerection, ptosis, diarrhea, chromodacryorrhea, brown or yellow staining of anogenital area, soiling of body areas, yellow staining of muzzle. Oral LD50 above 5 g/kg.

   Study Classification: Core Guidelines Data

   Product Classification: Tox. Cat. IV

2. Acute Dermal LD50 - Rabbit. Project No. MB 82-6185B; dated 9-20-82. In Acc. 248710.

   Procedure: 5M, 5F albino rabbits received 24-hr occluded dermal exposure on abraded skin to a dosage level of 2 g/kg, with subsequent 14-day observation.

   Results: 1F died day 10, 1M died day 12. Symptoms: diarrhea, lethargy, emaciation. Dermal LD50 above 2 g/kg.

   Study Classification: Core Minimum Data

   Product Classification: Tox. Cat. III

3. Primary Eye Irritation - Rabbit. Project No. MB 82-6185D; dated 9-20-82. In Acc. 248714.

   Procedure: 0.1 ml was placed in the conjunctival sac of one eye of each of 9 rabbits. Three eyes were washed for one minute starting 20-30 seconds after instillation; remaining eyes were unwashed.

   Results: Corneal opacity in 1/6 unwashed, 1/3 washed eyes, clearing by day 4. 5/6 unwashed, 2/3 washed eyes still had some irritation on day 7. Slight conjunctival irritation still present in 3/6 unwashed, 2/3 washed eyes on day 14.

   Study Classification: Core Minimum Data

   Product Classification: Tox. Cat. II

4. Primary Eye Irritation - 1:32 (use) dilution - Rabbit. Project No. MB 82-6185 D-2; dated 9-20-82. In Acc. 248715.

Procedure: 0.1 ml of a 1:32 (use) dilution was placed in the conjunctival sac of one eye of each of 9 rabbits. Three eyes were washed for one minute starting 20-30 seconds after instillation; remaining 6 eyes were unwashed.

Results: Slight conjunctival irritation in 2/6 unwashed, 0/3 washed eyes. Minimal discharge from one unwashed eye at 7 days.

Study Classification: Core Guidelines Data

Product Dilution Classification: Tox. Cat. III

5. Primary Eye Irritation - 1:64 dilution - Rabbit. Project No. MB 82-6185D; dated 9-20-82. In Acc. 248714.

Procedure: 0.1 ml of a 1:64 dilution was placed in the conjunctival sac of one eye of each of 9 rabbits. Three eyes were washed for one minute starting 20-30 seconds after instillation; remaining 6 eyes were unwashed.

Results: 3/6 unwashed, 1/3 washed eyes showed minimal conjunctival irritation (score = 2) with all eyes clear by day 3.

Study Classification: Core Guidelines Data

Product Dilution Classification: Tox. Cat. III

6. Primary Dermal Irritation - Rabbit. Project No. MB 82-6185C; dated 9-20-82. In Acc. 248711.

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

Results: PDIS = 4.84 (average of scores at 4, 24 and 72 hrs). All sites had cleared by 14 days.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. III

7. Primary Dermal Irritation - 1:32 (use) dilution - Rabbit. Project No. MB 82-6185 C-1; dated 9-20-82. In Acc. 248712.

Procedure: 0.5 ml of a 1:32 dilution was applied to each of 4 intact sites (reporting states intact and abraded) on each of 6 rabbits with 4-hr occluded exposure.

Results: PDIS = 1.16 (average of scores at 4, 24 and 72 hrs). All scores zero at 72 hrs.

Study Classification: Core Minimum Data

Product Dilution Classification: Tox. Cat. IV

8. Sensitization - Guinea Pig. Project No. MB82-6185F; dated 9-20-82. In Acc. 248717.

   Procedure: A series of 10 topical 6-hr occluded applications was administered to a group of 10 M guinea pigs over a 4-week period, using a 1% dilution of the test article. Two weeks after the completion of this series, subjects were challenged at the previously exposed application site and a previously unused area. Positive controls were exposed to 0.1% DNCB on the same schedule.

   Results: One subject (#42) began developing an evident sensitization reaction following the 4th treatment; after the 7th application this subject had the maximum possible score (4) at the site at 24 and 48 hrs. It appears that this subject showed a sensitization reaction at challenge. A weaker reaction appeared to be present for subject #50. Other subjects showed no evidence of a reaction. Product, at this dilution, appears capable of causing sensitization.

   Study Classification: Core Minimum Data

   Product Classification: Weakly sensitizing

The following studies were conducted at Cosmopolitan Safety Evaluation Inc. P.O. Box 71, Lafayette, NJ 07848. These studies were received at EPA 9-23-82.

9. Primary Eye Irritation - Rabbit. C.S.E. #S7150-8; dated 8-6-82. In Acc. 248718.

   Procedure: 0.1 ml was placed in the conjunctival sac of one eye of each of 9 rabbits. Three eyes were washed for one minute starting no sooner than 20 seconds after instillation; remaining 6 eyes were unwashed.

   Results: Corneal opacity in 3/6 unwashed, 0/3 washed eyes at 72 and 96 hrs. At 7 days 1/6 unwashed, 0/3 washed eyes showed corneal involvement, while 4/6 unwashed, 0/3 washed eyes showed relatively minor conjunctival irritation. All eyes clear by day 14.

   Study Classification: Core Guidelines Data

   Product Classification: Tox. Cat. II

10. Primary Eye Irritation - 1:32 (use) dilution - Rabbit. C.S.E. #S7150-8; dated 8-6-82. In Acc. 248719.

    Procedure: 0.1 ml of a 1:32 (use) dilution was placed in the conjunctival sac of one eye of each of 9 rabbits. Three eyes were washed for one minute starting no sooner than 20 seconds after instillation; remaining 6 eyes were unwashed.

    Results: No irritation. All eyes scored zero.

    Study Classification: Core Guidelines Data

    Product Dilution Classification: Tox. Cat. IV

11. Acute Inhalation LC50 - Rat. C.S.E. #S7150-8; dated 8-6-82. In Acc. 248720.

Procedure: A group of 5M, 5F SD rats was exposed for 4 hrs to a nominal concentration of 10.2 mg/l. Average mass median diameter was measured on two separate occasions as 1.25 u and 1.35 u. Subjects were subsequently observed for 14 days.

Results: No mortalities. There was a brown stain around muzzles during exposure; otherwise no symptoms. Post-sacrifice necropsies were unremarkable.

Study Classification: Core Supplementary Data (no measurements as to actual concentration to which subjects were exposed).

Byron T Backus 11/04/82

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