Memorandum

Date: 5 May 1982

Subject: EPA File Symbol: 4758-RUR HILL'S HOLIDAY FLEA & TICK SHAMPOO FOR DOGS & CATS
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.....5.0%
Inert Ingredients.....95.0%

Background:

The applicant has sent in, as part of this registration application, acute toxicity studies on the formulation.

Comments and Recommendations:

1. In the acute oral LD50 study on this formulation 3/10 animals died after receiving a dosage level of 5 gm/kg. The probability that only 3 or fewer animals would die if the oral LD50 is 5 gm/kg is slightly greater than 17%. Therefore, it has not been shown within 95% confidence limits that the product is in toxicity category IV, and this product would require toxicity category III labeling with respect to potential oral exposure.

2. The primary eye irritation study shows all subjects had some irritation on day 7, which had not entirely cleared by day 14. On this basis, the product is in toxicity category II with respect to potential eye hazard, and the appropriate signal word for this product is WARNING.

3. We should have, as a part of the record, the amount of material that was injected intradermally in the guinea pig sensitization study. We have assumed it was 0.05 mls in the first induction injection, and 0.1 mls subsequently.

4. In order to adequately evaluate the Acute Inhalation study, we need to have some additional information as to the actual concentration of test material within the chamber. Specifically, we need to know the rate at which the aerosol was pulled through the Anderson Cascade Impactor and the period of time that was required to take the two samples.

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

Labeling:

1. The appropriate signal word is WARNING, based on potential eye exposure effects.

2. There should be a heading PRECAUTIONARY STATEMENTS with the subheading HAZARDS TO HUMANS & DOMESTIC ANIMALS.

3. The statement under HAZARDS TO HUMANS & DOMESTIC ANIMALS should be something like:

> WARNING: Causes eye irritation. Do not get in eyes. Harmful if swallowed. When washing cats, kittens or puppies, avoid getting shampoo in animal's eyes. Do not use on kittens or puppies under 4 weeks of age.

4. There should be a Statement of Practical Treatment (preferably under that heading, but we could accept incorporation of the first aid statements in the HAZARDS TO HUMANS & DOMESTIC ANIMALS statement) something like:

> IF SWALLOWED: Call a Physician or Poison Control Center. Give a glass or two of water and induce vomiting by touching back of throat with finger or, if available, by administration of syrup of ipecac. Never give anything by mouth or induce vomiting in an unconscious person.
>
> IF IN EYES: Flush with plenty of water. Get medical attention.

5. The statement: "...offering safety not found in other flea and tick shampoos." is not acceptable (refer to 162.10(a)(5)(ix)).

6. There appears to be a contradiction in the proposed statement: "When washing cats, kittens or puppies, dry immediately with cloth to prevent chilling." and use instructions which specify: "Allow lather to remain on animal for ten minutes to kill fleas and ticks."

Review:

The following studies were conducted at M B Research Laboratories Inc. Steinsburg and Wentz Roads, P.O. Box 203, Spinnerstown, PA 18968. Studies were conducted on material identified as "citrus shampoo." Studies were received at EPA 1-29-82 and are in Acc. 246739.

1. Acute Oral LD50 - Rat. Project No. MB 81-5736A; dated 1-12-82.

   Procedure: 5M, 5F rats were orally dosed at 5 gm/kg with subsequent 14-day observation.

   Results: 3 males died between days 5 and 8. Symptoms included chromorhinorrhea and chromodacryorrhea (which were presumably responsible for the brown staining around the muzzle), ptosis and lethargy. Animals which died had "abnormalities" of the lungs, thoracic and abdominal cavities. Animals which died showed normal weight gains after receiving the test material. Post-sacrifice necropsies of survivors were unremarkable. Study does not show, with 95% confidence, that this product has an oral LD50 greater than 5 gm/kg, since there is a 17% chance that when a product with an oral LD50 of 5 gm/kg is given to rats at this level 7 or more rats will survive.

   Study Classification: Core Minimum Data

Product Classification: Tox. Cat. III

2. Acute Dermal LD50 - Rabbit. Project MB 81-5736B: dated 1-12-82.

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

Results: 1 male died on day 9 with congested lungs. Symptoms of some subjects included few feces, diarrhea, lethargy, eschar of treated area.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. III

3. Primary Dermal Irritation - Rabbit. Project MB 81-5736C; dated 1-12-82.

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

Results: PDIS = 2.68. (average of scores at 4, 24 and 72 hrs).

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. III

4. Primary Eye Irritation - Rabbit. Project MB 81-5736D; dated 1-12-82.

Procedure: 0.1 mls was applied to one eye of each of 9 rabbits, with three eyes being flushed with water for one minute starting 20-30 seconds after test material instillation.

Results: Irritation in 6/6 unwashed, 3/3 washed eyes on day 7. 5/6 unwashed eyes still had some slight conjunctival irritation on day 14, 1/2 washed eyes (one rabbit with washed eyes died day 14) had slight conjunctival irritation on this day also.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. II

5. Sensitization - Guinea Pig. Project MB 81-5736 F; dated 1-12-82.

Procedure: Each of 10M guinea pigs received a total of 10 induction intradermal injections of 0.1% test material in saline over a period of 22 days (according to the protocol for the positive control, the first injection was 0.05 mls, and subsequent injections were 0.1 ml; it is assumed that this was the protocol for the test material). Two weeks after last induction injection, subjects were challenged at a new site.

Results: No evidence of sensitization. Product is not a sensitizer under these circumstances (Note: Gosselin et al. in Clinical Toxicology of Commercial Products indicates that mild local irritation and skin sensitization have been recorded for limonene).

Study Classification: Core Minimum Data

Product Classification: Not a sensitizer under these conditions

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6. Acute Inhalation LC50 - Rat. Compound No. 81-5736; dated 12-29-81.

Procedure: 5M, 5F rats were exposed for 4 hrs to a nominal concentration of 5 mg/L, with subsequent 14-day observation. Average MMD was measured as 4.78 and 4.85 um, with σ_g = 2.08 and 1.96 um respectively.

Results: No mortalities. Rats exhibited normal exploratory behavior, then huddled for remainder of the exposure period. No symptoms. Post-sacrifice necropsies indicated no abnormalities that would seem to be exposure-related.

Study Classification: Core Supplementary Data (no actual measurements as to concentration of test material within chamber).

Byron T Backus 05/06/82

Byron T. Backus
IRB/TSS

Page 5 is not included with this review. That page consists of draft labeling.