UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

DATE: August 26, 1980

SUBJECT: EPA Registration No. 39159-2 A-200 PYRINATE(R) LIQUID
Caswell # 715, 670

FROM: Cheryl A. Peterson
IRB/TSS

TO: Mr. George LaRocca
Product Manager (15)

Registrant: USV(P.R.) Development Corporation
P.O. Box 345
Manati, Puerto Rico 00701

Active Ingredients: (A-200) Liquid

Pyrethrins	0.17%
Piperonyl butoxide technical [equivalent to 1.6% (butycarbityl)(6-propylpiperonyl) ether and 0.4% related compounds]	2.00%
Inert Ingredients	97.83%

Background:

This registered product is a pediculicide for human head, crab and body lice. The liquid contains 5.00% kerosene. The company is applying for an amended registration which involves a label revision changing the kerosene to an inert ingredient, listing active ingredient percentages to only 2 significant digits to the right of the decimal point, and changes involving additional applications in the Use Directions. The company is using the "alternate" method of support, and has submitted acute oral, primary eye irritation, primary skin irritation, skin sensitization and sub-acute safety studies. There is an accident report in which severe but reversible eye irritation resulted when three children were left unattended following product application.

Recommendations:

1. The primary eye irritation, and primary skin irritation are acceptable and adequate as supporting data.

2. The acute oral, subacute safety and dermal sensitization studies have been classified Core Supplementary Data (See individual test reviews for verification).

3. The proposed Use Directions change (change C, see letter from USV Development Corporation dated 6-27-80) adds two more follow-up applications of the product after the initial application, to be made on Days 5 (optional) and 10. The submitted literature recommends an initial application and a single, subsequent application a week to 10 days later. Based on this information, and since the submitted skin sensitization and subacute safety studies are not adequate, it is recommended that the applications be limited to two in number, with the second application following the first on Day 10.

4. IRB/TSS would have no objection to the adaptation of proposed changes A and B (see letter from USV Development Corporation dated 6-27-80) including the petroleum distillate categorization and the expression of active ingredient percentages with the labeling revision indicated below.

Labeling:

1. The appropriate signal word is WARNING as indicated by the applicant. Place the word WARNING on the front panel below KEEP OUT OF REACH OF CHILDREN.

2. The PRECAUTIONARY STATEMENTS must be revised to something similar to the following:

   WARNING: Not to be used by persons allergic to ragweed. DO NOT USE NEAR EYES OR PERMIT CONTACT WITH MUCOUS MEMBRANES. IF PRODUCT SHOULD GET INTO EYES, DO NOT RUB AND IMMEDIATELY FLUSH WITH PLENTY OF CLEAR WATER. Get medical attention. Harmful if swallowed. Do not inhale. If skin irritation or signs of infection are present consult a physician. Do not leave children unattended with A-200 on their heads.

3. Since the proposed container size is 6 oz., the statements under DIRECTIONS must be similar to the following:

   DIRECTIONS:

   It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

   (Day 1) -- 1st Shampoo: Apply sufficient liquid to completely "wet" the hair and scalp or skin of any infested area. This amount should not exceed 2 oz. or one-third of the contents of this container. Do not add water. Massage thoroughly to allow for even distribution of liquid. Leave on for 10 minute (but no longer). Thoroughly rinse with plenty of warm water. Follow with a regular shampoo. A fine-toothed comb may be used to remove dead lice and eggs from hair.

4. The statement "Anything less invites reinfestation" should be deleted from the label [see CFR 40 162.10(5)(ii)].

Review:

The following studies were conducted by the Pharmacology Dept., USV Laboratories, 1 Scarsdale Rd., Tuckahee, NY on material identified as A-200 Pyrinate Liquid. The tests were received by EPA 7-9-80, and are in Accession No. 242923.

1. Acute Oral LD_{50} - Rat. Dated: May, 1978

Procedure: 4 groups of 6M Charles River rats received via oral intubation 5.0 ml/kg, 6.3 ml/kg, 8.0 ml/kg and 10 ml/kg test material. 1 group of 6 M rats received 12.5, 16 and 20 ml/kg. There was a 14-day observation period. A "control" consisting of the product without pyrethrins or piperonyl butoxicide in the formulation was tested at the same dose levels.

Results: Oral LD_{50} = 8.3 ml/kg (Conf. lim. 6.7 - 10.2 ml/kg).1/6 rats died Day 8 at 5.0 ml/kg; 2/6 rats died one "overnight" and one on Day 8 at 6.3 ml/kg; 2/6 rats died "overnight" at 8.0 ml/kg; 3/6 rats died Day 2 at 10.0 ml/kg; and 6/6/ rats died at the 12.5 ml/kg, 16 ml/kg, and 20 ml/kg from three hours to three days. Treated rats showed a gain in weight when averaged from the beginning to the end of the observation period. The control yielded an LD_{50} of 10.1 ml/kg (Conf. lim. 8.6-11.9 ml/kg).

Study Classification: Core Supplementary Data (No females were tested) LD_{50} of product = 8391.3 mg/kg (Conf. lim. 6773.7 - 10,312.2 mg/kg)

2. Primary Eye Irritation - Rabbit. Dated: May, 1978

Procedure: 6 NZ albino M rabbits received 0.1 ml in the right eye. Observations were made at 24, 48, and 72 hrs two out of six showed corneal opacity at 49 hrs. with clearing by 7 days. Conjunctivitis was present in all animals with clearing by Day 7 in 2/6. 2/6 placebo tested animals had corneal involvement Day 7.

Study Classification: Core Minimum Data

Product Classification: Toxicity Category II

3. Dermal Sensitization - Guinea Pig. Dated: May, 1978

Procedure: 6 white female guinea pig each received an intracutaneous injection of 0.05 ml test material followed by 9 injections of 0.1 ml test material made 3 times weekly for 3 weeks on shaved skin. 2 weeks after the 10th injection, animals were rechallenged with an injection of 0.5 ml test material. Observations were made 24-hrs. following injections. A "placebo" (test material without pyrethrins or piperonyl butoxide) was tested on 6 additional animals.

Results: Both test material and "placebo" were concluded to be nonsensitizing. No response was seen to the ten sensitizing or challenging injections.

Study Classification: Core Supplementary Data (No males used; no positive controls; challenge injection was 0.05 mls. and, rather than 0.1 ml as were 9 of sensitizing injections; only 6 animals used, 10 is preferable. Material tested was 0.1% of formulation in physiological saline; no justification is provided for such a low dilution, particularly as the dermal irritation using undiluted formulation study showed no irritation).

4. Primary Skin Irritation - Rabbit, Dated; May, 1978

Procedure: 6 NZ albino rabbits each received 24-hr occluded dermal exposure on abraded and intact skin areas to 0.5 ml test material. Observations were made at 24 & 72 hrs. 6 animals received similar exposure to the placebo.

Results: Primary skin irritation index = 0.00 for both materials. Neither formulation produced any irritation.

Study Classification: Core Minimum

Product Classification: Toxicity Category IV.

5. Subacute (Dermal) Safety Study-Rabbit. Dated: May, 1978.

Procedure: 4NZ albino M rabbits received dermal exposure on shaved, abraded and nonabraded skin to 1.5 ml test material twice daily 5 days/wk for 2 weeks. Test material was massaged in for 30 sec. at each application. Solution was then left on skin for 5-10 min. and then washed off with warm water; rabbits were towelled dry. 4 additional animals received a total of 20 applications, similar exposure to placebo. There was survivor sacrifice and necropsy at the end of 2 weeks.

Results: Animals showed an average gain in weight from the beginning of the study to necropsy. 4/4 animals exposed to test material exhibited dry,scuffed skin after 6 days, with clearing in 2/4 by Day 12. Necropsy revealed no abnormalities, skin changes were minimal. The "usual" lesions, caused by infectious agents were reported as present in liver and kidney. Reported skin changes were mild acanthosis (slight thickening of the epidermis) without accompanying increased mitotic activity, and occasional focal ulceration in sections from abraded areas.

Study Classification: Core Supplementary Data (Does not meet the protocols outlined in FR43, #163, p. 3766 (Aug 22, 1978) for a 21-day subchronic dermal toxicity study. Occluded exposure should have been at least 6 hours daily).