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

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JUL 24 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: DEET: Review of a dermal absorption study in rabbits
(Acute dermal toxicity in rabbits)

Caswell No. 346 HED Project No. 1-1304
Case No. 027383 Submission No. S396332
EPA ID #: 064583 Littlepoint Insect Repellent (paste)

TO: Richard Mountfort / Joseph Tavano, PM (10)
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. 7/8/91
Pharmacologist
HFAS/Tox. Branch II/ HED (H7509C)

THROUGH: James Rowe, Ph.D. 7/8/91
Section Head
and
Marcia van Gemert, Ph.D. 7/9/91
Branch Chief
HFAS/Tox. Branch II/ HED (H7509C)

The registrant, Dillon, Knowles & Co., represented by RegWest Co. submitted a study with the title, "Acute dermal absorption in rabbits exposed to Deet containing $_{14}C$". This study has been reviewed, and the Data Evaluation Report is attached. The conclusion is as follows:

This report is written in a rather confusing manner. The title of the report indicates that this study should be a dermal absorption study, but the content of the report is more like an acute dermal toxicity study.

As a dermal absorption study, it was designed poorly, and the results derived from this study were of minimal value. The Toxicology Branch II strongly encourages the registrant to contact the reviewer concerning the study design of a dermal absorption study. In general, a dermal absorption study is a specific kind of kinetic study which measures how much chemical passes through a specified area of the skin from dermal exposure; therefore, the dose must be determined on the basis of quantity per unit area of the exposed skin (mg/cm^2). At least 3 doses and 24 animals should be used. Four animals per dose shall be exposed for durations of 1/2, 1, 2, 4, 10, and 24 hrs. The radioactivity in urine, feces,

animals were also observed daily for additional 14 days for any toxic signs. Blood samples were collected prior to the initiation of the study and at 2, 4, 8, and 24 hours following the test article application for determining the plasma radioactivity levels. The body weight of each animals was measured on the day of dosing, weekly thereafter, and at sacrifice.

The test animals were sacrificed on day 14. A gross necropsy consisted of examining the application site, carcass, visceral organs, and the reproductive organs was conducted.

Results

No clinical signs of toxicity were seen in any of the treated animals. No mortality was reported. The test material produced slight irritation on the first day after removal of the test material in all test animals. The irritation was characterized by erythema accompanied by edema. On the third day, 1/5 male and 2/5 female rabbits still showed signs of irritation. By day 7, the affected areas were normal. At necropsy, no abnormality of any organs was seen.

This reviewer crudely graphed the reported results (Figure 1). The plasma ^{14}C levels peaked at 2 hrs after application of the test article for both males and females (Figure 1). At 24 hrs, the radioactivity dropped to a minimum.

Discussion and Conclusion

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As an acute dermal toxicity study, the results indicate the test

article (14C-Deet, 10% [redacted] at 2.0 ~~mg~~ gm/kg caused only slight irritation at the application site. The acute dermal LD_{50} is greater than 2.0 ~~mg~~ gm/kg (Tox. Category III). It fulfills the requirements for an acute dermal toxicity study and is classified as a minimum study.

Reviewer: Whang Phang, Ph.D. Whang Phang 7/8/91
Tox. Branch II/HED
Secondary Reviewer: James Rowe, Ph.D., Section Head James Rowe 7/8/91
Tox. Branch II/HED

DATA EVALUATION REPORT

Chemical: Deet (N,N-diethyl-m-toluamide)

Study Type: Dermal absorption study (rabbit)

Caswell No. 346 HED Project No. 1-1304
Case No. 027383 Submission No. S396332
EPA ID #: 064583 Littlepoint Insect Repellent (paste)
MRID No. 418762-00

Sponsor: Dillon, Knowles, & Co.

Testing Laboratory: Cosmopolitan Safety Evaluation, Inc.
33a, Broad St, Branchville
P.O. Box 71
Lafayette, NJ 07848

Citation: Robbins, G., Acute dermal absorption in rabbits exposed to Deet containing ^{14}C. Unpublished study conducted by Cosmopolitan Safety Evaluation, Inc.: Study No. B3130; March 26, 1991. Submitted to EPA by Regwest Co. (Consultant of Dillon, Knowles, & Co.)

Material and methods

Test article: ^{14}C-Deet, 10% [redacted] a whitish cream. Lot No. 9923-195, 2-27-91'.

Animals: Young adult albino rabbits (NZW) were from the laboratory colony. The body weights were ranged from 2.5-2.8 kg for males and 2.5-2.95 for females at the initiation of the study.

Study design

The trunk of five male and 5 female rabbits was clipped (approximately 20% of the whole animal) approximately 24 hrs (hours) before dosing. The test article (2.0 gm/kg) was uniformly applied onto 10% of the body surface and covered with a gauze pad which was held down with hypoallergenic tapes. The entire trunk of the rabbit was wrapped with non-irritating perforated plastic sheeting secured at each end with masking tape. After 24 hrs of exposure, the plastic sheeting and gauze were removed, and the application site was wiped with "a clean moistened paper towel to remove any test article still remaining".

Immediately after the removal of the test article, the application site was evaluated for any signs of irritation. The test

blood, washes from the skin, in or on the protective device, in or on the washed skin, in selected organs, in the carcass, and in the blood should be determined. The percent of the applied dose found in various samples should be calculated. Therefore it is unacceptable as a dermal absorption study.

As an acute dermal toxicity study, the results indicate the test article (14C-Deet, 10% [redacted] at 2.0 g/kg caused only slight irritation at the application site. The acute dermal LD_{50} is greater than 2.0 g/kg (Tox. Category III). It fulfills the requirements for an acute dermal toxicity study and is classified as a minimum study.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Figure 1. Radioactivity Level in Blood of Rabbits Dermally Applied ^{14}C-DEET (2.0 g/Kg B.W.) (8.917 μCi/g).