DATA EVALUATION RECORD

TWO INSECT REPELLENT SPRAY PRODUCTS (DESIGNATED AS PRODUCT A AND PRODUCT B FOR THIS REVIEW)

STUDY TYPE: PRIMARY DERMAL IRRITATION STUDIES

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Executive Summary:

A series of independent published reports on animal dermal irritation tests for components of Product A and B was provided with summaries of their results. Some of the ingredients in both products are classified into Category III (moderate irritants), but most of the components were classified into Category IV (slight or mild irritants). When classification of products with respect to their skin irritation potential is based on separate animal studies on product components, the studies indicating the most conservative classification (lowest Toxicity Category) for any components, regardless of concentration, defines the product's classification in the absence of a study with the product itself. In this case, Products A and B would be classified into Toxicity Category III for dermal irritation. With the information on product components and composition of the two products, the sponsor of the patch studies concluded that both should be classified as slightly or non-irritating (Toxicity Category IV). The sponsor of the patch test noted that an animal study was not done on either of the repellent products, and because the products are intended for direct application to human skin, a confirmatory irritation assay on human volunteers was initiated.

In classifying pesticide products as irritants, the 72-hour observation is critical in separating moderate irritants from slight or non-irritants, and the human study's last observation was made at 72 hours. Although the results reported an apparent reversal, there were still subjects showing signs of a reaction. These responses were low grade, but the report did not include negative control data for comparisons that could be useful in clarifying interpretation of the 72-hour readings as a response to the test material. Also, observations beyond 72 hours after the application of test substances could possibly add evidence of reversibility. Therefore, the human patch study is considered to be incomplete and can not be used as a critical part of the evidence in classifying the irritancy of Products A and B.

I. Background

A. General Guidance

For insect repellents applied directly to human skin, the most critical acute toxicity testing includes acute dermal toxicity, skin irritation, and testing for dermal sensitization; other product testing typically includes acute oral, inhalation and eye irritation studies which complete the battery of six tests required to define the toxicity profile of any given pesticide product. Evaluation of acute toxicity for pesticides considers the relationship between the exposure of test animals to the test substance and the incidence and severity of responses, the reversibility of observed effects, and any other toxicity that might result from exposure (see OPPTS Test Guideline 870.1000). Data from the acute studies serve as a basis for hazard categorization, labeling, an initial step in establishing a dosage regimen for subchronic and other studies, and may provide information on absorption. To accomplish these purposes, the Agency encourages test methods that address the welfare of laboratory animals in toxicity testing.

The Agency recommends several means to reduce the number of animals used to evaluate acute effects of exposure to a test substance while preserving its ability to make reasonable decisions about safety (see OPPTS Test Guideline 870.1000). In the case of the two insect repellent products considered here, weight-of-evidence approaches to dermal irritation (OPPTS Test Guideline 870.2500) and dermal sensitization (OPPTS 870.2600) were taken by the repellent manufacturer. Human experience and animal data on each component of the two insect repellent products was the first line of analysis, and the human patch studies considered below were performed to confirm that the two products could be classified with respect to skin irritation (single insult patch test) or dermal sensitization (multiple insult patch test). Generally, the sponsor of the patch studies pointed out that each component in the two insect repellents:

- Is discussed in the published literature,
- Has a history of use as intentional additives to food, or in cosmetic products intended for direct application to human skin, and
- Is known to the Agency.

B. Dermal irritation

1. Test methods guidance

In a dermal irritation study (OPPTS 870.2500), the test substance is applied in a single dose to the skin of at least 3 experimental animals, each animal serving as its own control. Test substances are applied to surgical gauze patches which are placed over test sites to maintain skin contact with the test material. Test sites are occluded for at least 4 hours after which the dressings are removed and the skin is rinsed and evaluated for signs of irritation. The degree of irritation is observed and scored at specified intervals to provide a complete evaluation of the effects. The duration of the observation period following exposure should be sufficient to determine the reversibility or irreversibility of the effects but need not exceed 14 days. Liquid test substances such as the insect repellents discussed herein are generally used undiluted. The recommended application rate in animal studies is 0.5 mL or 500mg over an area of approximately 12.5 cm^2 area (40 mg/cm^2), and the recommended minimum duration of exposure is 4 hours with longer periods recommended for substances like insect repellents that are likely to be on human skin for longer periods of time.

2. Test results

Skin reactions are scored according to the following:

Skin Reaction	Value

Erythema and Eschar Formation:	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Necrosis (death of issue)	4
Edema Formation:	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure	4

The Toxicity Categories for skin irritation are defined by the Agency as follows:

Category I	Category II	Category III	Category IV
Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	Mild or slight irritation (no irritation or slight erythema)

II. The Single-Insult Patch Study

A. Products and Testing Objectives

Two types of spray insect repellent product were evaluated using the approach described in Section I. A., above. Product A contains 11 ingredients (including the active ingredient) which are found in 16 previously registered products, and Product B contained 10 ingredients used in the same previously registered products. A series of published reports on animal dermal irritation tests for each product's components was provided with summaries of their results. These results indicated eight of Product A's and seven of Product B's ingredients are classified into Toxicity Category IV (mild or slight irritants) according to the dermal irritation criteria described in Section I. B. 2., above; the remainder of the ingredients in both products are classified into Category III (moderate irritants). The sponsor of the patch test noted that an animal study was not done on either of the finished products, and because the products are intended for direct application to human skin, a confirmatory irritation assay on human volunteers was initiated.

B. Methods

1. Study participants

Male and female volunteers who were selected to participate in the study were at least 18 years of age and in generally good health. They were free of any systemic or dermatologic disorder which would interfere with the results of the study or increase the risk of adverse events. Participants were of any skin type or race, so long as the skin pigmentation allowed discernment of erythema. Those volunteers selected for the study also completed a medical screening procedure and signed an informed consent document.

Volunteers were excluded from participation if they had any visible skin disease which would interfere with the evaluation, if they were receiving systemic or topical medication which would interfere with the study results, or if they had psoriasis or active atopic dermatitis or eczema. Those who were pregnant, planned to become pregnant during the study, or were breast-feeding were not permitted to participate. Finally, volunteers could not participate if they had a known sensitivity to cosmetics, skin care products, insect repellents, or topical drugs as related to the material being evaluated.

Of the 54 participants, one dropped out. The panel of 53 volunteers consisted of 48 females and 6 males. The racial/ethnic distribution was reported to be 50 Caucasian, 3 Hispanic, and one Black. Ages ranged from 19 to 71 with an average of 51 years; 15 were 19-44, 30 were 45-64, and 9 were 65-71.

2. Dosing

For the single-insult patch test, 0.2 mL of the test material was applied to a 2 cm. x 2 cm. Webril pad attached to a non-porous plastic film adhesive bandage which air dried for 30 minutes prior to application to the subject's skin. Patches were secured with hypoallergenic tape to the skin of the infrascapular area of the back, to the right or left of the midline. The application rate on the patch was 0.05 mL/cm^2 (approximately 50 mg/cm^2).

3. Scoring of responses

The scoring system used in the single insult patch study was summarized as follows:

Symbol	Definition	Value
-	No reaction	0
?	Minimal or doubtful response, slightly different from surrounding skin	0.5
+	Definite erythema, no edema	1.0
++	Definite erythema, definite edema	2.0
+++	Definite erythema, definite edema and vesiculation	3.0
D	Damage to epidermis; oozing, crusting and/or superficial erosions.	3.0

On study day 1, patches were applied to designated test sites. Forty-eight hours after the application (study day 3), the patches were removed and the sites were evaluated for reactions.

The highest numerical score for each subject at the 48- or 72-hour observations were summed for all subjects. For example, if 48-hour scores of 0, 0, and 0.5 were reported for subjects *x*, *y* and *z*, respectively (a total score of 0.5) and respective 72-hour scores of 0.5, 0.5, and 0 were reported for subjects *x*, *y* and *z* (total score of 1.0), the 72-hour total score would be used to determine the Primary Irritation Index (PII). The PII would then be the average score for the entire group (i.e., PII = 1.0/3 = 0.33). The results in this example would then be interpreted to indicate an Irritancy Level of "essentially non-irritating" according to the following scale:

PII Range	Irritancy Level

0.50 or less	Essentially non-irritating
0.50 < 1.00	Virtually non-irritating
> 1.00 to 2.00	Minimally irritating
> 2.00	Moderately irritating

C. Reported Results

The results for Products A and B are summarized as follows:

Scores* (Number of Subjects)				
	Product A		Product B	
Grade (Score)	48-hour	72-hour	48-hour	72-hour
- (0) ? (0.5) + (1.0)	0 (22) 13.5 (27) 4 (4)	0 (35) 9 (18) 0 (0)	0 (25) 12.5 (25) 3 (3)	0 (40) 6.5 (13) 0 (0)
Totals	17.5 (53)	9 (53)	15.5 (53)	6.5 (53)
PII**	0.34		0.30	
* Scores are determined by multiplying the grade score (0, 0.5, or 1.0) by the number of subjects with that score (e.g., 0.5 x 27 = 13.5). ** Primary Irritation Index = total score for entire panel divided by the number of subjects in the panel (e.g., (13.5 + 4)/53 = 0.34.				

These results led the investigators to conclude that Products A and B are essentially non-irritating.

D. Discussion

As indicated in Sections I. B. 2. and II. B. 3. above, the scoring systems are considerably different. For example, the animal scoring system separates erythema and edema, while the scoring of responses in human skin combines the two responses. The human scoring system also focuses on substances which are likely to be slightly or, at worst, moderately irritating, whereas the animal scoring system accommodates a range of irritancy including corrosive, severe, moderate and slight irritants. For classification purposes, the 72-hour observation is critical in separating moderate irritants from slight or non-irritants, and the human study's last observation was made at 72 hours. Although the results reported an apparent reversal, there were still subjects showing signs of a reaction. These responses were low grade, but the report did not include negative control data for comparisons that could be useful in clarifying interpretation of the 72-hour readings. Also, observations beyond 72 hours after the application of test substances could possibly add evidence of reversibility. Therefore, the human patch study is considered to be incomplete and can not be used as part of the evidence in classifying the irritancy of Products A and B.