pc 080301

1-6-92

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.: 62337-R Sun & Bug Stuff

From: Mark J. Perry, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

MJP 12-15-91

To: Richard Mountfort, PM 10
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

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Applicant: Reflect, Inc.
3100 Kerner Blvd.
San Rafael, CA 94901

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s):	
N,N-diethyl-m-toluamide	19.0
Other isomers	1.0
Ethylhexly-p-methoxycinnamate	7.5
Oxybenzone	5.0
Inert Ingredient(s):	67.5
Total:	100%

BACKGROUND

Reflect Inc., submitted acute oral, acute dermal, acute inhalation, eye irritation, dermal irritation, and dermal sensitization studies for review. the product is Sun & Bug Stuff, a sunscreen/insect repellent lotion, and the active ingredients are as follows:

N,N-diethyl-m-toluamide	19.0%
Other isomers	1.0%
Ethylhexly-p-methoxycinnamate	7.5%
Oxybenzone	5.0%

All studies were performed by Cosmopolitan Safety Evaluation and the MRID numbers are 416447-01 through 416447-06.

RECOMMENDATION

The acute oral, acute dermal, and skin irritation studies are acceptable and have been graded core guideline. The eye irritation and dermal sensitization studies are acceptable as core minimum data, and the acute inhalation study is unacceptable.

(1) The eye irritation study received a core minimum grade because discharge was not reported at any evaluation period.

(2) The dermal sensitization study received a core minimum grade for the following reasons:

a. Since a group of naive control animals was not included in the positive control study, the results for all three induction periods should be reported. The mean induction score is not appropriate for comparison to the challenge results, since skin irritation increases with each exposure at the same induction site. Only the results of the initial induction and the challenge should be considered when determining if sensitization has occurred.

b. The study failed to include a group of naive animals. According to Buehler (1,2) "a group of previously unexposed control animals are challenged" and "the significance of reactions in the experimental group is based on intensity and incidence relative to reactions in the {two} control group{s}."

c. The range-finding study should be performed with the same animal species as is the sensitization study. The sensitization study used the results of the primary skin irritation study, performed with rabbits, to determine the appropriate doses for induction and challenge.

(3) Since the acute inhalation study was performed on a 10% w/w preparation, the study data does not sufficiently characterize the inhalation hazard posed by the subject product. However, since the subject product cannot be aerosolized, a repeat study is not required. The registrant MAY ELECT TO submit a waiver request based on the inability to aerosolize the undiluted test material. This request should include any additional data resulting from attempts to generate an acceptable test atmosphere or other difficulties encountered during the inhalation study.

LABELING

(1) The appropriate signal word is CAUTION. The signal word must appear on a separate line and with sufficient prominence relative to other front panel text (see 40 CFR, 156.10 "Placement and Prominence").

(2) The statements of Practical Treatment should read as follows:

"IF ON SKIN: Wash with plenty of soap and water. Get medical attention."

(3) The precautionary statements should read as follows:

"Harmful if absorbed through skin. Avoid contact with skin, eyes, or clothing. Wash thoroughly with soap and water after handling."

NOTE TO PM: In reference to dermal contact, the precautionary labeling language contradicts the directions for use of this product. The language is a result of the acute dermal toxicity study which employed a dose of 2g/kg (category 3) rather than a dose of 5g/kg (category 4). The PM should decide how to resolve this problem.

ACUTE TOXICITY PROFILE

Acute Oral	Category 4/Guideline
Acute Dermal	Category 3/Guideline
Acute Inhalation	Supp/ Waiver ~~requested~~ MAY BE APPROP
Eye Irritation	Category 4/Minimum
Dermal Irritation	Category 4/Guideline
Dermal Sensitization	Negative /Minimum

REFERENCES

[1] Buehler, E.V. and Griffith, J.F. Experimental Skin Sensitization in the Guinea Pig and Man. Animal Models in Dermatology [H.I. Maibach, ed.] [1975] p. 56.

[2] Ritz, H.L. and Buehler, E.V. Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests. Current Concepts in Cutaneous Toxicity, [Drill, V.A. and Lazar, P.] Academic Press, NY, NY. [1980] p. 25.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1)

Product Manager: 10
MRID No.: 416447-01
Testing Facility: CSE
Author(s): G. Robbins
Species: Rat
Age: Young adult
Weight: 200-297 g
Source: Lab bred
Test Material: Sun & Bug Stuff
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 4-4-90
Report No.: A2077

Conclusion:

1. LD_{50} (mg/kg): **Males** = --
   Females = --
   Combined = --
2. **The estimated** LD_{50} **is** > 5 g/kg
3. **Tox. Category:** 4 **Classification:** Guideline

Procedure: The test material was administered by gavage to ten fasted test animals. The animals were observed for mortality and signs of toxicity daily during the fourteen day study period.

Results:

Dosage g/kg	(Number Killed/Number Tested)		
	Males	Females	Combined
5.0	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings: No signs of clinical toxicity were observed during the study period. No abnormalities were observed during gross necropsy.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: 10
MRID No.: 416447-02
Testing Laboratory: CSE
Author(s): G. Robbins
Species: Rabbit
Weight: 2.55-2.85 kg
Source: Lab colony
Test Material: Sun & Bug Stuff
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 4-16-90
Report No.: B2077

Summary:

1. LC_{50} (mg/kg): **Males** = --
Females = --
Combined = --

2. **The estimated LD_{50} is** > 2.0 g/kg

3. **Tox. Category:** 3 **Classification:** Guideline

Procedure: The test material was applied to the shaven backs of ten test animals and occulded for a period of twenty-four hours. Body weights were recorded weekly, and observations were performed daily for signs of toxicity and for mortality.

Results:

Reported Mortality

DOSAGE g/kg	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2.0	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings: No signs of toxicity were observed during the study period, and gross necropsy failed to reveal any abnormalities.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: 10
MRID No.:416447-03
Testing Laboratory: CSE
Author(s): G. Robbins
Species: Rat
Weight: 212-306 g
Source: Lab bred
Test Material: Sun & Bug Stuff
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date:5-4-90
Report No.:C2077

Summary:

1. LC_{50} (mg/kg): **Males** = --
   Females = --
   Combined = --

2. **The estimated LC_{50} is** --

3. **Mean Concentration:** --

4. **Tox. Category:** -- **Classification:** Supp (See recommendations)

Procedure: Since the test material was tested as a 10% w/w concentration (in H_2O) and the concentration was determined gravimetrically, this study does not accurately characterize the inhalation hazard posed by the subject product.

Results:

Reported Mortality

Exposure Concentration mg/L	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
5.8 (10% dilution)	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: 10
MRID No.: 416447-04
Testing Laboratory: CSE
Author(s): G. Robbins
Species: Rabbit
Sex: --
Weight: --
Source: Lab bred
Dosage: 100 mg
Test Material: Sun & Bug Stuff
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 3-24-90
Report No.: D2077

Summary:

1. **Toxicity Category:** 4
2. **Classification:** Minimum (see recommendations)

Procedure: The undiluted test article was placed into the everted lower lid of each animal. The lids were then held together for one second. Treated eyes were observed at 1, 24, 48, and 72 hours for response.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	0/6	0/6	0/6	0/6				
Iris	2/6	0/6	0/6	0/6				
Conjunctivae								
Redness	0/6	0/6	0/6	0/6				
Chemosis	2/6	0/6	0/6	0/6				
Discharge	—	—	—	—				

Comments: All positive signs of irritation cleared by twenty-four hours following dose administration.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: 10
MRID No.: 416447-05
Testing Laboratory: CSE
Author(s): G. Robbins
Species: Rabbit
Age: adult
Sex: --
Weight: --
Dosage: 500 mg
Test Material: Sun & Bug Stuff
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 3-26-90
Report No.: E2077

Summary:

1. **The Primary Irritation Index = --**
2. **Toxicity Category:** 4
3. **Classification:** Guideline

Procedure: The undiluted test material was applied to the shaven dorsal surface of the test animals. Following a four hour occluded exposure, dermal responses were evaluated at 1, 24, 48, and 72 hours.

Results: No irritation was present during the 72 hour evaluation period.

Special Comments:

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: 10
MRID No.: 416447-06
Testing Laboratory: CSE
Author(s): G. Robbins
Species: Guinea pig
Weight: 384-402 g
Source: Camm Res. Labs.
Test Material: Sun & Bug Stuff
Positive Control Material: p-phenylenediamine
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 3-24-90
Report No.: F2077

Method: Buehler

Summary:

1. According to this study, the test material is not a dermal sensitizer.
2. **Classification:** Minimum (See recommendations)

Procedure: The undiluted test material was applied to the clipped backs of ten male albino guinea pigs once a week for three weeks. The sites were occluded and contact was maintained for six hours. Following a two week rest period the test animals were exposed to the undiluted test material at a naive clipped site also for six hours. Dermal reactions were evaluated at twenty-four and forty-eight hours.

Results: The first induction resulted in grade one erythema in eight of ten animals at twenty-four hours and six of ten at forty-eight hours. The naive site challenge resulted in grade one erythema in eight of ten animals at twenty-four and forty-eight hours. No edema was present in any animals during these evaluation periods.

Tox Chem. No. : 346 File Last Updated Current date 12-10-91

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
Acute Oral: Rat, CSE, A2077, 4-4-90	"Sun + Bug Stuff" DEET (19.0%), Ethylhexyl-p-methoxy-cinnamate (7.5%) Oxybenzone (5.0%)	416447-01	LD_{50} > 5g/kg	4	Guideline
Acute Dermal: Rabbit, CSE, B2077, 4-16-90	"	416447-02	LD_{50} > 2g/kg	3	Guideline
Acute Inhalation: Rat, CSE, C2077, 5-4-90	"(10% conc)	416447-03	performed with 10% concentration	—	Supp
Eye Irritation: Rabbit, CSE, D2077, 3-24-90	"	416447-04	No irritation at [redacted] 24 hrs	4	Minimum
Dermal Irritation: Rabbit, CSE, E2077, 3-26-90	"	416447-05	No irritation at 72 hrs	4	Guideline
Dermal Sensitization; Guinea Pig, CSE, F2077, 3-24-90	"	416477-06	Not a sensitizer	—	Minimum