3-4-91

346

008907

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 58007-E
Safetygard Insect Repellent

FROM: William S. Woodrow WSW 6-19-90 E 6/20/90 3/4/91
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

TO: Hutton / Tavano (PM 17)
Insecticide - Rodenticide Branch
Registration Division (H7505C)

APPLICANT: Personal Care Products
Consumer Specialties Division/3M
3M Center
St. Paul, Minnesota, 55144-1000

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
N,N-Diethyl Meta-Toluamide	9.02
other Isomers	0.53
Inert Ingredient(s):	90.00
Total	100.0%

1

008907

BACKGROUND

The 3M Company submitted an eye irritation, a skin irritation, and a dermal sensitization study in support of 3M Safetyguard Insect Repellent (58007-E) MRID NOS. used were 412465-02, 412465-03, and 412465-04. Also older acute studies were cited in support, found under the following Accession NOS.: 00001080, and 00001085. The Dect Reg. Std. also cited.

RECOMMENDATION

1) The three acute toxicity studies submitted concurrently with the 3M Sept. 22, 1989 letter are acceptable to RSB/PRS:

	MRID/Acc.#	Tox. Cat.	Grade
a. Skin irritation	412465-03	IV	Guidelines
b. Eye irritation	412465-02	II	Guidelines
c. Dermal sensitivity	412465-04	Not a sensitizer	Guidelines

2) The acute oral study cited by the 3M Co.-performe by Woodard Res. Corp. is acceptable to RSB/PRS:

	Acc.#	Grade
Acute oral study	00001080	Tox. Cat. III Guidelines

3) An acute oral toxicity study (Acc.# 00001085) was graded Supplementary Data due to gross inaccuracy in LD_{50} estimation/no clinical report.

4) An eye irritation study (Acc.# 00001085), generated 3-7-75, was graded Guidelines - Tox. Cat. III, but was not selected as principal supporting data.

5) An acute inhalation study (Acc.# 00001055) was graded Supplementary Data: Nominally calculated aerosol concentration only; no gravimetric or chemical analytical aerosol concentration measurements, no particle size/size distribution study.

6) A skin irritation study (Acc.# 00001085) was acceptable to RSB/PRS; but was not selected as principal supporting data.

008907

7. Requirements for acute dermal and acute inhalation toxicity studies remain to be satisfied. The DEET Registration Standard does not satisfy these requirements for two reasons: A) This product does not fall within the percentage active ingredient range covered by the Registration Standard (12-75% a.i.) and B) the Registration Standard covers only products within the 12-15% a.i. range which were existing at the time the Standard was completed. This product does not meet either of these qualifiers. Acute dermal and acute inhalation toxicity studies must be submitted.

8. Current acute toxicity profile for 3M Safety-gard Insect Repellent (58007-E):

008907

	study #	Tox. Cat.	Grade
Acute oral LD_{50}	00001080	III	Guideline
Eye irritation	412465-02	II	Guideline
Skin irritation	412465-03	IV	Guideline
Dermal sensitization (not a sensitizer) † 412465-04	-		Guideline

9. Additional acute toxicity studies reviewed:
   a. Acute oral # 00001085 LD_{50} >2ml, <5ml/kg Supplementary (nominal chamber value only, no clinical information).
   b. Acute inhalation # 00001085 LC_{50}: Supplementary: no particle size info., no chamber conc. info.
   c. Primary eye irritation: # 00001085, Tox. Cat. III Guideline.
   d. Primary skin irritation # 00001085, Tox. Cat. IV Guideline.

LABELING

1) The WARNING signal word is appropriate
2) Change the content and appearance order of Precautionary Statements as follows:

"Causes temporary eye injury. Do not get into eyes or on lips. ....."

3) The statement of Practical Treatment is acceptable.

PM NOTE #1 Study NO. 1051, Acute dermal toxicity was graded Core Minimum Data due to only 5 days of animal observation post-treatment, and the use of different animal sexes was not explained.

PM Note #2: See March 2, 1985 amendment to the 1985 DEET Registration Standard below:

Toxicity Category Acceptability

Toxicology Category

	I	II	III	IV
Acute Oral Toxicity	No	No	Yes	Yes
Acute Dermal Toxicity	No	No	Yes	Yes
Acute Inhalation Toxicity	No	No	Yes	Yes
Primary Dermal Irritation	No	No	Yes	Yes

Additionally, end-use products must not be corrosive to the eye (cause irreversible destruction of ocular tissue) or cause corneal involvement or irritation persisting for 21 days or more.

Thus, it is possible to utilize eye irritation data that a) does not indicate corrosiveness, or b) does not indicate corneal or irritation involvement persisting for 21 days or more.

PM Note #3: Upon receipt of acceptable acute dermal and acute inhalation toxicity studies, Precautionary Labeling may require revision.

008907

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

Product Manager: (17)
MRID No.: 0000 1080
Testing Facility: Woodard Res. Corp.
Author(s): D. J. Woward
Species: Rat, CF,
Age: young adult males
Weight: 351-378 g
Source: Carworth Farms
Test Material: Formulation 3369D135-1
Quality Assurance (40 CFR §160.12): none

Reviewer: ~~M. Waller~~ Woodrow 3-7-75
Report Date: 6-19-90
Report No. none

Observation Days (Post Exposure): (14); other ( )

sp. gr. = 0.8158 g

Conclusion:

1. LD_{50} (mg/kg): Males = ——— ; Females = ; Combined ———
2. The estimated LD_{50} is 2.61 ml/kg (2.13 g/kg)
3. Tox. Category: III. Classification: Guidelines

Procedure ~~(Deviations From §81-1)~~: Groups of 5M + 5F rats received different doses of test material by oral intubation. Treated rats observed frequently day of dosing and daily to 14 days for toxic signs & mortality. All rats later to gross necropsy.

Results:

Reported Mortality

DOSAGE (ml/g kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
1.0 ml/0.82 g/kg	0/5	0/5	0/10
1.47 ml/1.20 g/kg	0/5	1/5	1/10
2.15 ml/1.75 g/kg	0/5	4/5	4/10
3.16 ml/2.58 g/kg	5/5	5/5	10/10
4.64 ml/3.79 g/kg	5/5	5/5	10/10

Symptomology & Gross Necropsy Findings:

Clinical: Rats at higher dosage levels prostrate 5 min after dosing/ showed decreased respiration. Survivors showed lacrimation, prostration, labored respiration.

Necropsy: All dying rats showed hemorrhagic areas in stomach and/or intestines. Scattered incidence of pale liver, pale areas on kidneys, bright red lungs at higher doses.

00890

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

Product Manager: (17)
MRID No.: 412465-02
Testing Laboratory: Hazleton, Labs, WI.
Author(s): N.A. Randen
Species: Rabbit, NZ White
Sex: not stated
Weight: 2000-2360 g
Source: Hazleton Res. Products
Dosage: 0.1 ml
Test Material: Safety-guard Insect Repellent, liquid (used undiluted)
Quality Assurance (40 CFR §160.12): adequate

Reviewer: ~~Mr. Waller~~ Woodrow
Report Date: 6-12-90
Report No. 3m/PCP 2100661104

Summary:

Tox. Category: II Classification: Guidelines

Procedure (~~Deviation From §81-4~~): 9 rabbits received 0.1 ml placed in the rested lower lid of 1 eye for each of the 9 rabbits. Upper and lower lids held gently together for 1 second. Treated eyes of 3 rabbits were flushed for 1 minute, beginning 30 sec. after installation. Treated eyes of both groups observed & scored for irritation

Results: @ 1, 24, 48, 72 & 96 hours, & at 7 & 14 days post treatment. Body weights recorded at weekly intervals.

Observations (number "positive"/number tested)

	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	9/9 1/2	8/9 1/2	7/9 1/2	7/9 1.0	8/9 2.0	4/9 1/2	0/9	
Iris	9/9 1.0	8/9 1.0	9/9 1.0	9/9 1.0	8/9 1.0	1/9 1.0	0/9	
Conjunctivae Redness	9/9 2/3	9/9 2/3	9/9 2/3	9/9 2/3	9/9 2.0	9/9 1/3	0/9	
Chemosis	9/9 2/3	9/9 2/1	8/9 2/1	8/9 1/2	6/9 1/2	8/9 1.0	0/9	
Discharge	9/9 2.0	9/9 1.2	8/9 2/1	7/9 1.0	3/9 1.0	0/9	0/9	

washed/unwashed approx. the same

"

"

eyeshed-slightly less irritating

"

Comments: Corneal opacity present through day 7, absent by day 14. The same finding for all conjunctival irritation, and also iris involvement.

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

Product Manager: (17)
MRID No.: 412465-03
Testing Laboratory: Hazleton, labs
Author(s): N. A. Rainden
Species: Rabbit, NZ white
Age: young adult
Sex: not stated
Weight: 2008 – 2278 g.
Dosage:
Test Material: Safety gard Insect Repellent
Quality Assurance (40 CFR §160.12): adequate

Reviewer: Woodrow
Report Date: 6-12-90
Report No.: 3in/PCP 2100661104

008907

Summary:

The Primary Irritation Index = 0.83

Toxicity Category: IV

Classification: Guidelines

Procedure (~~Deviations From §81-5~~): 0.5ml undiluted test material applied to clipped backs of each of 6 rabbits - Sites covered with 2.5 cm² Gauze patches secured ∴ Tape; trunks were overwrapped ∴ Saran Wrap secured ∴ Tape - 4 hour exposure. Test sites were observed and scored for erythema 30 minutes after ~~Results:~~ wrappings removal, and again at 24, 48, 72 and 96 hours. Body weights recorded at weekly intervals.

Av. Primary Irritation Scores

observation Period	Av. score*
4 hrs	0.7
24 hrs	1.0
48 hrs	.7
72 hrs	.7
96 hrs	.7
day 7	.7
day 14	0.0

Special Comments:

* Total irritation score for all animals (erythema+edema) ∴ No. of test sites.

008907

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

Product Manager: (17)
MRID No.: 412465-04
Testing Laboratory: Keyline Res. Cin. Ohio
Author(s): N.A. Randen
Species: humans
Sex : _____ Weight: _____
Source: _____
Test Material: T-4286 insect repellent
Positive Control Material: _____
Quality Assurance (40 CFR §160.12): _____

Reviewer: ~~K. Waller~~ Woodrow
Report Date: 6-13-90
Report No.: M/PCP 2/006611 04

Method: Modified Draize Skin Sensitization Test (Repeat human insult patch test).

Summary:
1. This product is / ~~is not a dermal sensitizer~~.
2. Classification: Guidelines

Procedure (~~Deviation From §81-6~~): Keyline Research conducted the study at its test sites in Kentucky; Latonia NOS. 1-130, and at Florence - NOS. 131-230. 230 human subjects began the test, while 208 humans ~~Results~~: completed the study. People ranged in age from 16-17 (approx. (5%), remainder 18 years of age or older; men and women, without regard to race, color. Twenty two people dropped out of the test for various reasons; 208 people completed the test, of 230 who began the study. Subjects were tested by patch test at different sites / subject to include eight different materials; including the T-4286 (5% Deet products, various vehicle Controls, etc.

Induction: All subjects received 3 patch tests per week to total 9 induction applications using same site. Induction application contact was 24 hours & secured w/ tape.

Challenge: 12 to 24 day rest between last induction application and challenge; challenge applications made to naive sites, also simultaneous applications made to induction sites.

Grading system: 0= no visible response
1= mild erythema
2= Papular response
3= Edema c or ̄c out papules
4= Vesicular/bulbous eruption.

Patches: 3/4 x 3/4" cotton containing 0.3ml test material, exposed to dryness for 1/2 hour, held to test site by 1 1/2 x 1 1/2" adhesive.
Challenge sites examined and scored 48 to 96 hours after application.

Results: 208 human subjects completing the test.
The response throughout the study was negligible; 7/208 people challenged exhibited a score of 1.0 (mild erythema).

Conclusions: Off! Pressurized Insect Repellent (EPA 4822-10), containing 15% A.I. Deet, did not sensitize 208 human volunteers, when tested using a modified Draize repeated patch insult test.

008907

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

Product Manager: (17)
MRID No.: 00001085
Testing Facility: WARF Inst. Inc.
Author(s): J.A. Beisemier et
Species: Rat, Sprague Dawley
Age: adult
Weight: 150-250
Source: not stated
Test Material: 3872 D102 (sample)
Quality Assurance (40 CFR §160.12): none

Reviewer: Goodrow ~~Waller~~
Report Date: 6-19-90
Report No. 41222920

Observation Days (Post Exposure): (14); other ( )

Conclusion: no clinical information, very inaccurate estimation of LD_{50}

1. LD_{50} (mg/kg): Males = >5ml, <10ml/kg. ; Females = >2ml, <5ml/kg. ; Combined =
2. The estimated LD_{50} is >2ml, <5ml/kg = 1.63g, or 1630 mg
3. Tox. Category: II. Classification: Supplementary

Procedure ~~(Deviations From §81-1)~~: Groups of 6M + 6F rats were dosed by oral intubation with various doses of test material. Animals were observed only for mortality.

Results:

Reported Mortality

DOSAGE (ml/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
2 ml/kg	0/6	0/6	0/12
5ml/kg	1/6	6/6	7/12
10 ml/kg	6/6		6/6

Symptomology & Gross Necropsy Findings:

Sp. gr. = 0.8158 g/ml 2ml = .8158
× 2
1.6316 g.

1.63g = 1630 mg

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

Product Manager: (17)
MRID No.: 00001085
Testing Laboratory: WARF INST., INC.
Author(s): J.A. Beismiet
Species: Rat, Sprague Dawley
Sex: Not given
Source: Not stated
Test Material: 8872
Quality Assurance (40 CFR §160.12): none
only nominal conc. (no gravimetric conc. no alternative

Reviewer: W. Woodrow
Report Date: 6-1990
Report No. 41229200
Weight: 200 g. (approx.)

Summary: no particle size distrib.

1. LC_{50} (mg/kg): Males = —— ; Females = —— ; Combined = ——
2. The estimated LC_{50} is not determined
3. Mean Concentration: ——
4. Tox. Category : ——. Classification: Supplementary

Procedure (~~Deviations From §81-3~~): Pressurized cans of product sprayed for 5 seconds, every minute, for the 1 hour aerosol exposure period. The nominal concentration only was used to determine dosed concentration. Treated

Results: animals were observed for mortality.

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
dose inaccurate	0/5	0/5	0/10
Controls (air only)	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

Animals (some) occasionally rubbed their noses. Necropsies ~~apparently~~ apparently did not reveal any gross abnormalities!!

Product Manager: (17)
MRID No.: 00001085
Testing Laboratory: WARF INST., INC.
Author(s): J. A Beismier
Species: Rabbit, NZ White
Sex: not given Weight: not stated
Source: not stated
Dosage: 0.1ml (81.6 mg.)
Test Material: 3872 Dilo
Quality Assurance (40 CFR §160.12): none

Reviewer: ~~H. Walker~~
Report Date: 6-19-90
Report No. 41722920

Summary:

Tox. Category: III Classification: Guidelines

Procedure (~~Deviation From §81-4~~): 0.1ml instilled into 1 eye of each of 6 rabbits. Eyes were examined and scored for irritation @ 24, 48 & 72 hours post instillation.

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		0/6	0/6	0/6		0/6		
Conjunctivae Redness		6/6	6/6	6/6		0/6		
Chemosis		6/6	6/6	6/6		0/6		
Discharge		6/6	6/6	6/6		0/6		

2.0 scores
2.0 scores
2.0-1.0 scores

Comments: No corneal or iris involvement. Conjunctival irritation through day 3, absent by day 4.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5) 008907

Product Manager: (17)
MRID No.: 00001085
Testing Laboratory: WARF INST., INC.
Author(s): J.A. Beisemier
Species: Rabbit
Age: not stated
Sex: not given
Weight: not given
Dosage: 0.5ml (.408g, or 408mg)
Test Material: 3872 Dust (sample)
Quality Assurance (40 CFR §160.12): none

Reviewer: ~~H. Walter~~
Report Date: 6-19-90
Report No. 41229.20

Summary:

The Primary Irritation Index = P.I. Index = 0.00

Toxicity Category: IV

Classification: Guidelines

Procedure (~~Deviations From §81-5~~): One abraded and one intact skin area on clipped backs of 6 rabbits each received 0.5ml (0.408g, or 408mg) of test material. Treated areas covered with gauze patches and tape. 24 hours contact. Treated sites examined and scored for erythema & edema @ 24 and 72 hours. An average of the 24 and 72 hour readings was used to determine the P.I. Index.

Results: NO erythema or edema was recorded at any of the (each) time periods for examination - for any of the rabbits.

Special Comments:

008907

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

3-27-75

Product Manager: (17)
MRID No.: 00001086
Testing Laboratory: WARF Institute
Author(s): John A. Bleasemeter
Species: Rat, Sprague Dawley
Sex: male
Source: not given
Test Material: Sample: 4235-0111-1
Quality Assurance (40 CFR §160.12): None

Reviewer: W. Woodrow
Report Date: 2-5-91
Report No. 5030701
Weight: approx. 200g.

Summary: nominal concentration (200.9 mg/L

1. LC_{50} (mg/kg): Males = —; Females = —; Combined = —
2. The estimated LC_{50} is —
3. Mean Concentration: —
4. Tox. Category: —. Classification: Supplementary

Procedure ~~(Deviations From §81-3)~~: 10 male rats exposed in a "portable test chamber" (similar to those developed by F.W. Sexton in Cincinnati). Exhaust fan to provide adjustable flow thru chamber (flow calculated by pressure drop thru critical orifice) - test material sprayed thru - into entering airstream before ~~Results:~~

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
200.9 mg/L ? (nominal)	0/10		0/10

~~Symptomology & Gross Necropsy Findings:~~

"entering circular head of chamber". Note: no description of aerosol generating device, no particle size distribution study. Correction sheet states that "test material sprayed into air stream directly from pressurized container 5 seconds/hour." Chamber concentration = subject amount recovered from

upper chamber from total amount sprayed into chamber ÷ by total L air passing through chamber; this is an approximate assumed concentration.

14 day observation of animals: 4 animals sacrificed & autopsied. Only clinical observation: animals huddled in corners. No gross abnormalities observed during necropsy.

No acceptable description of how animal counted.

No pretest significance study.

Unacceptable ~~sampling~~ means of calculating or estimating chamber concentration.

DATA REVIEW FOR ACUTE ...

Reviewer: ~~H. Walter~~ 1959 Wordeen
Report Date: 7-5-91
Report No. —

Product Manager: (17)
MRID No.: 1051
Testing Laboratory: Published data - see below
Author(s): Anthony Ambrose
Species: Rabbit AV = .9974
Sex: not stated Wt.: 3-4 kg
Test Material: Deet: N,N-diethyl-m-toluamide : m-DET SP. gr. = .9962 - .9986
Quality Assurance (40 CFR §160.12): none (100% AI)
5 day observation, use of different sexes not explained.

Summary:

1. LD_{50} (mg/kg): Males = ______; Females = ______; Combined = ______;
2. The estimated LD_{50} is ≥ 3.99 g/kg
3. Tox. Category: III. Classification: Core minimum

Procedure (~~Deviations From §81-2~~): 2 groups of 6 rabbits; closely clipped. ½ of rabbits - skin was abraded "lightly." One group of rabbits each received 2 ml/kg, the other group, each rabbit received 4 ml/kg; dosage spread evenly over entire depilated trunk area. - Trunk

~~Results:~~ of each rabbit covered lightly with elastic cotton bandage, rabbits restrained for 24 hours.

Reported Mortality

DOSAGE (/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
2 ml/kg × = 2 × .9974 = 1.99 g/kg	0/3	0/3	0/6
4 ml/kg = 4 × .9974 = 3.99 g/kg	? 0/3	? 0/3	0/6
SP. Gr. = .9974			

~~Symptomology & Gross Necropsy Findings:~~

Bandage removed; slightly more erythema observed on abraded skins than not abraded. On 5th post-treatment day, no difference between intact and abraded. NOTE: The post-treat observation period was 5 days only.

Study performed in 1959.

Toxicology & Applied Pharmacology Vol. 1, NO. 1, January, 1959