2-12-91

008870

346

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DEET

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 58007-G
3M ULTRATHON Insect Repellent

FROM: William S. Woodrow WSW 2-12-91
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

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

APPLICANT: 3M Consumer Specialties Division
Personal Care Products
3M Center, Bldg 235-3E-06
St. Paul, MN 55144-1000

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
N,N-Diethyl Meta-Toluamide	22.56
Other isomers	1.19
Inert Ingredient(s):	76.25
Total	100.00

1 of 18

BACKGROUND

The 3M Company submitted eye and skin irritation, and a dermal sensitization study to support registration of 3M ULTRATHON Insect Repellent (EPA Reg. NO. 58007-G). MRID NOS. used were 412465-02, 412465-03, and 412465-04. Older studies were also cited to support registration: 00001085, 00001080, 00001051, and 00001086. The Oct Registration Standard was also cited.

RECOMMENDATION

1) The three acute toxicity studies submitted concurrently with the 3M Oct. 27, 1989 letter are acceptable to RSB/PRS. The acute oral study cited by 3M and performed by Woodard Res. Corp. is also acceptable:

	MRID/Acc #	Tox Cat.	Grade
a. skin irritation	412465-03	IV	Guideline
b. eye irritation	412465-02	II	Guideline
c. dermal sensitivity	412465-04	Not a sensitizer	Guideline
d. acute oral	00001080	III	Guideline

008870

2) Acute oral study # 00001085 was graded Supplementary Data due to gross inaccuracy in LD_{50} estimation, and no clinical report.

3) Eye irritation study # 00001085 generated 3-7-75 was graded Guideline Data - tox. Cat. III, but was not selected as principal supporting data.

4) Inhalation study # 00001085 was graded Supplementary Data; Nominal chamber concentration only, no particle size/distribution information.

5) Skin irritation study # 00001085 was acceptable, but was not selected as principal supporting data (3-7-75).

6) Acute dermal and acute inhalation studies; citation of the Deet Registration Standard: Pages 43 and 45 of the Deet Std.

Quotation:

" 2 Acute Dermal Toxicity (163-81-2)

(2) Pressurized Liquid (PrL)

No data were available to assess the acute dermal toxicity of the existing PrL product. Because technical Deet is placed in Toxicity Category III, and because the inert ingredients in PrL products are not expected to increase the acute dermal toxicity potential, all existing PrL products between 12% and 75% concentrations, except those that incorporate from propellants, are classified in Toxicity Category III. Toxicity Category III corresponds to a low acute dermal toxicity potential.

008870

Acute Inhalation Toxicity (163-81-3)

(2) Pressurized Liquids (PrL)

The available data were invalid to assess the acute inhalation toxicity of the 15% PrL product. Because technical Deet is placed in Toxicity Category IV, and because the inert ingredients in PrL products are not expected to increase the acute inhalation toxicity potential, all existing PrL products between 12% and 75% concentrations, except those that incorporate freon propellants, are placed in Toxicity Category IV. Toxicity Category IV, corresponding to a very low acute inhalation Toxicity potential. 11

Unquote

According to the above quotations from the Deet Registration Standard, the requirement for acute dermal and acute inhalation toxicity studies has been satisfied.

7) Current acute toxicity profile for 3M ULTRATHON Insect REPELLENT (58007-G):

	Study #	Tox-Cat.	grade
Acute oral	00001080	III	Guideline
Acute dermal (Deet Std.)		III	—
Acute inhalation (Deet std.)		IV	—
Eye irritation	412465-02	II	Guideline
Skin irritation	412465-03	IV	Guideline
Dermal sensitization (not a sensitizer)	412465-04	—	Guideline

8) Additional acute toxicity studies reviewed:

a. Acute oral # 00001085 $LD_{50} > 2ml_t < 5ml/kg$. Supplementary - Nominal Chamber conc. only, no clinical information.

b. Acute inhalation # 00001085 LC_{50} - Supplementary - no particle size info., no chamber conc. info.

c. Eye irritation # 00001085, Tox. Cat. III, Guideline.

d. Skin irritation # 00001085, Tox. Cat. IV Guideline.

LABELING

1) The WARNING signal word is appropriate

2) Change the order and content 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.

P.M. NOTE: The March 2, 1985 amendment to the 1985 DEET Registration Standard changes the acute irritation eye

conditions for acceptability somewhat; see below:

	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.

As stated above to be acceptable (eye irritation study) for DEET products an acute eye irritation study should not show the product to be corrosive to the eye, or should not demonstrate corneal involvement or irritation persisting for 21 days or more.

008870

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

Product Manager: (17)
MRID No.: 00001095
Testing Facility: WARF Inst., Inc.
Author(s): J. A. Beisemier
Species: Rat, Sprague Dawley
Age: adult
Weight: 150-250
Source: not stated
Test Material: 3872 D102 (sample)
Quality Assurance (40 CFR §160.12): none

3-7-75 Woodrow
Reviewer: ~~M. Waller~~
Report Date: 6-19-90
Report No. 41122970

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
2ml/kg	0/6	0/6	0/12
5ml/kg	1/6	6/6	7/12
10ml/kg	6/6		6/6

Symptomology & Gross Necropsy Findings:

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

1.63g = 1630 mg

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2) 00880

Product Manager: (17)
MRID No.: 1051
Testing Laboratory: published data - see below
Author(s): Anthony Brabrese
Species: Rabbit
Sex: not stated
Test Material: Deet: N,N-diethyl-m-toluamide; m-DET
Quality Assurance (40 CFR §160.12): none (acc. AI)

Reviewer: 1959 Wardell ~~M. Waller~~
Report Date: 7-5-91
Report No. —
Wt.: 3-4 kg
Av. = .9974
Sp. gr. = .996 - .9956
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; dorsally 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; dosages spread evenly over entire depilated trunk area - Trunk of each rabbit covered lightly with elastic cotton bandage, rabbits restrained for 24 hours.

Results:

Reported Mortality

DOSAGE (/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
2 ml/kg x .9974 = 1.995 g/kg	0/3	0/3	0/6
4 ml/kg = 4 x .9974 = 3.99 g/kg	? 0/3	? 0/3	0/6
Sp. Gr.: .9974			

~~Symptomology & Gross Necropsy Findings~~:

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

Study performed in 1958.

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

BEST AVAILABLE COPY

00887

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

Aug 23, 1971

Product Manager: (17)
MRID No.: 00001080
Testing Facility: Woodard Res. Corp.
Author(s): D.J. Urward
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. Walker~~ Woodrow
Report Date: 6-19-90
Report No. None

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

Conclusion: sp. gr. = 0.8158 g

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 for 14 days for toxic signs & mortality. All animals had gross necropsy.

Results:

Reported Mortality

DOSAGE (ml/g kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
1.0 ml/0.32 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 livers, enlarged kidneys, discolored lungs at higher doses.

9

008870

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

3-27-75

Product Manager: (17)
Reviewer: W. Woodrow
MRID No.: 00001026
Report Date: 2-5-91
Testing Laboratory: WILF Institute
Report No. 5030701
Author(s): John A. Bleasmeister
Species: Rat, Sprague-Dawley
Sex: male
Weight: approx. 200g.
Source: not given
Test Material: Sample: 4235-0111-1
Quality Assurance (40 CFR §160.12): None

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 §81-2)~~: 10 male rats exposed in a "portable test chamber" (similar to those developed by F.D. Sawyer in Cincinnati). Exhaust fan to provide adjustable flow thru chamber (flow calculated by pres. drop thru calibrated 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 end of chamber". Note: no description of aerosol generating device, no particle size distribution study. Comment: test states that "T. material sprayed into air stream directly from pressurized container 5 seconds/hour". Chamber Concentration = ~~?~~ subtract amount recovered from

10

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 aerosol generated.

No particle size distribution study.

Unacceptable ~~simplistic~~ means of calculating & extrapolating chamber concentration.

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

Product Manager: (17)
MRID No.: 00001085
Testing Laboratory: WARF INST, Inc.
Author(s): J.A. Beismier
Species: Rat Sprague Dawley
Sex: Wet given
Source: Int state
Test Material: B,872
Quality Assurance (40 CFR §160.12): none

Reviewer: W. Woodrow
Report Date: 6-19-90
Report No. 41229200

Weight: 200 g. (approx.)

only nominal conc. (no gravimetric determine. no alternative

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 conc of product sprayed for 5 seconds, every minute, for 4 hr exposure period. The nominal concentration only was used to determine blood concentration. Treated animals were observed for mortality.

Results:

Reported Mortality

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

Symptomology & Gross Necropsy Findings:

Animals (some) occasionally exhibited tremors. Necropsies apparently did not reveal any gross abnormalities.

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4) 008870

Product Manager: (17) 10-18-89 Reviewer: Woodrow ~~H. Waller~~
MRID No.: 412465-02 Report Date. 6-12-90
Testing Laboratory: Hazleton, Labs, WI. Report No. 3m/PCP 2100661104
Author(s): N.A. Randen
Species: Rabbit, NZ White
Sex: not stated Weight: 2000g, 2360 g
Source: Hazleton Labs. Products.
Dosage: 0.1 ml
Test Material: Safety guard Insect Repellent, liquid (used undiluted).
Quality Assurance (40 CFR §160.12): adequate

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		washed/unwashed approx. the same
Iris	9/9 1.0	8/9 1.0	9/9 1.0	8/9 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 1/3/3	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		washed-slightly less irritating
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		"

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

A REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4) 3-7-75 Woodrow 00887

Manager: (17)
: 00001085
Laboratory: WARF INST., INC.
): J. G. Beismier
Rabbit, NZ White
not given Weight: not stated
: not stated
0.1ml (81.6 mg.)
erial: 3872 D10
Assurance (40 CFR §160.12): none

Reviewer: ~~M. Waller~~
Report Date: 6-19-90
Report No. 41229-20

ategory: III Classification: Guidelines

e ~~(Deviation From §81-4)~~: 0.1ml installed into 1 eye of each albits. Eyes were examined and scored for irritation 4, 48 & 72 hours post instillation.

Observations
(number "positive"/number tested)

	Hour	Days						
	1	1	2	3	4	7	14	21
		0/6	0/6	0/6		0/6		
		0/6	0/6	0/6		0/6		
vae		6/6	6/6	6/6		0/6		
s		6/6	6/6	6/6		0/6		
ge		6/6	6/6	6/6		0/6		

2-0 scores
2-0 scores
2-0-1-0 scores

No corneal or iris involvement. Conjunctival ~~fation~~ through Day 3, absent by Day 4.

DATA REVIEW FOR SKIN IRRITATION TEST

Product Manager: (17) 3-7-75
MRID No.: 00001085
Testing Laboratory: WARF INST., INC.
Author(s): J. L. Boisemier
Species: Rabbit
Age: Not stated
Sex: Not given
Weight: Not given
Dosage: 0.5ml (.402g, or 402mg)
Test Material: 3877 DIO's (sample)
Quality Assurance (40 CFR §160.12): none

Reviewer: ~~H. Walter~~
Report Date: 6-19-90
Report No. 4122920

008870

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 (0.402g, or 402mg) of test material. Treated areas covered with gauze patches and tape. 24 hours contact. Treated sites examined and scored for erythema & edema @
Results: 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:

DATA REVIEW FOR SKIN IRRITATION TESTS — Woodrow

duct Manager: (17) 10-18-89 — Reviewer: [redacted]
) No.: 412465-03 — Report Date: 6-12-90
ting Laboratory: Hazleton, Labs — Report No.: 3M/PCP 2100661104
nor(s): N.A. Randem
cies: Rabbit, NZ white — 000270
ge: young adult
ex: not stated
eight: 2008 - 2278 g.
ge:
Material: Safety gard Insect Repellent
ity Assurance (40 CFR §160.12): adequate

ary:

e Primary Irritation Index = 0.83

xicity Category: IV

assification: Guidelines

edure (~~Deviations From §81-5~~): 0.5ml undiluted test material plied to clipped backs of each of 6 rabbits - Sites covered h 2.5 cm² Gauze patches secured w/ tape; Trunkes were wrapped w/ Saran Wrap secured w/ tape - 4 hour exposure. sites were examined and scored for erythema 30 minutes after ~~its~~ wrappers removal, and again at 24, 48, 72 and 96 hrs. Body weights recorded at weekly intervals.

IV. 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

ial Comments:

otal irritation score for all animals (erythema+edema) - No. of test sites.

BEST AVAILABLE COPY

16

000370

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

Product Manager: (17) 4-6-89 Reviewer: Woodrow ~~K. Walker~~
MRID No.: 412465-04 Report Date: 6-13-90
Testing Laboratory: Keyline Res. Cin. Ohio Report No.: 3m/PCP 2/00661:04
Author(s): N.L. Reuden
Species: humans
Sex: _____ Weight: _____
Source: _____
Test Material: T-4236 insect repellent
Positive Control Material: _____
Quality Assurance (40 CFR §160.12): _____

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 volunteers 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-4236 (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 application made to naive sites, also simultaneous application made to induction sites.

BEST AVAILABLE COPY

17

Grading system: 0: no visible response
1: mild erythema
2: Papular response
3: Edema & coalescent papules
4: Vesicular/bullous eruption.

Patches: 3/4 x 3/4" cotton containing 0.3ml test material expanded to 4 square for 1/2 hour, held to test site by 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; 2/208 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 produce 208 human volunteers, when tested using a modified Draize repeated patch insult Test.