

2-12-91

008870

346



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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.
<u>N,N-Diethyl Meta-Toluamide</u>	<u>22.56</u>
<u>Other Isomers</u>	<u>1.19</u>
<u>Inert Ingredient(s):</u>	<u>76.25</u>
Total	100.0%

BEST AVAILABLE COPY

1-18

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 Dect 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 Woodward 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

BEST AVAILABLE COPY

- 2) Acute oral study # 00001085 was graded Supplementary Data due to gross inaccuracy in LD₅₀ 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.

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. //

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 REPELLEND (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	412465-04	—	Guideline
(not a sensitizer)			

BEST AVAILABLE COPY

- 8) Additional acute toxicity studies reviewed:
- a. Acute oral # 00001085 $LD_{50} > 2ml, < 5ml/kg$.
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.

BEST AVAILABLE COPY

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

008870

Product Manager: (17)

3-7-75 ^{Woodrow}

Reviewer: ~~M~~ Waller

MRID No.: 0001095

Report Date: 6-19-90

Testing Facility: WAFI Inst., Inc.

Report No. 4122970

Author(s): J.A. Beisemier

Species: Rat, Sprague Dawley

Age: adult

Observation Days (Post

Weight: 150-250

Exposure): (14); other ()

Source: not stated

Test Material: 3872 D102 (sample)

Quality Assurance (40 CFR §160.12): none

Conclusion:

no clinical information, very inaccurate estimation of LD50

1. LD50 (mg/kg): Males = $> 5 \text{ ml}$, $< 10 \text{ ml/kg}$; Females = $> 2 \text{ ml}$, $< 5 \text{ ml/kg}$; Combined =

2. The estimated LD50 is $> 2 \text{ ml}$, $< 5 \text{ ml/kg}$ = 1.63g, or 1630 mg

3. Tox. Category: II. Classification: Supplemental

Procedure (Devia ~~as from §81-1~~): Groups of 6 M & 6 F rats were used 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
5 ml/kg	1/6	6/6	7/12
10 ml/kg	6/6		6/6

Symptomology & Gross Necropsy Findings:

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

1.6316 g.

1.63g = 1630 mg

BEST AVAILABLE COPY

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

008810

Product Manager: (17)

1959
Reviewer: ~~Waller~~
Report Date: 7-5-91
Report No.

MRID No.: 1051

Testing Laboratory: Published data - see below

Author(s): Anthony Ambrose

Species: Rabbit

Sex: not stated

Wt.: 3-4 kg

AVC-9974

Test Material: Dext-Nutritional-m-tolamide: M-DET. SP. GRI-9962-9956

Quality Assurance (40 CFR §160.12):

NONE (see AT) 2

5 day observation, use of different sexes not explained.

Summary:

- LD50 (mg/kg): Males = ; Females = ; Combined = ;
- The estimated LD50 is > 3.99 g/kg
- Tox. Category: III. Classification: Low minimum

Procedure (Deviations From §81-2): 2 groups of 6 rabbits; loosely clipped. 1/2 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 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 x .9974 = 1.995/kg	0/3	0/3	0/6
4 ml/kg = 4 x .9974 = 3.99 g/kg	0/3	0/3	0/6
SP. GRI-9974			

Symptomatology & Gross Necropsy Findings:

Bandages removed; slightly more erythema observed on abraded skins than not abraded. On 5th post-treatment day, no reference lesions intact and abraded. NOTE: The post-treatment observation period was 5 days only.
Study performed in 1959.

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

BEST AVAILABLE COPY

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

00887

Product Manager: (17) Aug 23, 1971 Reviewer: M. Waller
 MRID No.: 00001080 Report Date: 6-19-90
 Testing Facility: Woodward Res. Corp. Report No. None
 Author(s): D. J. Howard
 Species: Rat, CF
 Age: Young Adult males Observation Days (Post Exposure): (14); other ()
 Weight: 351-378 g
 Source: Catworth Farms
 Test Material: Emulsion 3369 D135-1
 Quality Assurance (40 CFR §160.12): None

Conclusion: 51.5% = 0.8158 g

- LD₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
- The estimated LD₅₀ is 2.61 ml/kg (2.13 g/kg)
- Tox. Category: III. Classification: Gul. Delines

Procedure (~~Deviations From §81-1~~): Dropped 5 males & 5 females received different doses of test material for oral intubation. Treated rats observed frequently for 14 days and daily for 14 days for toxic signs & mortality.
 Results: All subjects began necropsy.

Reported Mortality

DOSAGE (ml/g kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
<u>1.0 ml / 0.32 g / kg</u>	<u>0/5</u>	<u>0/5</u>	<u>0/10</u>
<u>1.47 ml / 1.20 g / kg</u>	<u>0/5</u>	<u>1/5</u>	<u>1/10</u>
<u>2.15 ml / 1.75 g / kg</u>	<u>0/5</u>	<u>4/5</u>	<u>4/10</u>
<u>3.16 ml / 2.58 g / kg</u>	<u>5/5</u>	<u>5/5</u>	<u>10/10</u>
<u>4.64 ml / 3.79 g / kg</u>	<u>5/5</u>	<u>5/5</u>	<u>10/10</u>

Symptomology & Gross Necropsy Findings:

Clinical: Rats at higher doses had prostrate soon after dosing / showed decreased respiration. Accidents showed locomotion, prostration, labored respiration.
Necropsy: All dying rats showed hemorrhagic areas in stomach and/or intestines. No other incidence of pale liver, pale spleen or kidneys, bright red lungs at higher doses.

008870

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (S81-3)

3-27-75

Product Manager: (17)
 MRID No.: 00001026
 Testing Laboratory: WAF Institute
 Author(s): John A. Biesemeyer
 Species: Rat, Sprague-Dawley
 Sex: male
 Source: not given
 Weight: approx. 200g.
 Test Material: sample: 4235-011-1
 Quality Assurance (40 CFR 160.12): none

Reviewer: W. Woodrow

Report Date: 2-5-91

Report No. 5030701

Summary: nominal concentration (200.9 mg/L)

1. LC₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated LC₅₀ is _____
3. Mean Concentration: _____
4. Tox. Category: ____ Classification: Supplementary

Procedure (~~Deviations From S81-2~~): 10 male rats exposed in a "portable test chamber" (similar to those developed by P.H. Sauer in Cincinnati). Effort was to provide slightly flow thru chamber (flow calculated by press. drop thru critical orifice).
~~Results:~~ test material? sprayed thru into inhaled airstream before

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
200.9 mg/L ? (nominal)	9/10		9/10

~~Symptomology & Gross Necropsy Findings:~~

"entering circular head 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: unknown amount, recovered from

10

BEST AVAILABLE COPY

upper chamber from total amount of gas into chamber =
by total L air passing through chamber; this is an
approximate normal concentration.

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

No acceptable description of how air was
generated.

No particle size distribution study.

Unacceptable principles means of calculating or
estimating chamber concentration.

008870

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (S81-3)

Product Manager: (17)
 MRID No.: 00001085
 Testing Laboratory: WARE INST., INC.
 Author(s): J. A. Beismiet
 Species: Rat Sprague Dawley
 Sex: Not stated
 Source: Not stated
 Test Material: B. 8.72
 Quality Assurance (40 CFR §163.12): none
 Summary: only nominal conc. (no gravimetric data conc. no alternative no particle size data)

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

1. LC50 (mg/kg): Males = _____; Females = _____
 2. The estimated LC50 is not determined
 3. Mean Concentration: _____
 4. Tox. Category: ____ Classification: Supplemental

Procedure (~~Deviations From S81-2~~): Pressurized can of product sprayed for 5 seconds, every minute, for 1 hour around exposure point. The nominal concentration only was used to determine blood concentration. Treated
 Results: Animals were observed for mortality.

Exposure Concentration (mg/L)	Reported Mortality (NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
<u>None in air only</u>	0/5	0/5	0/10
<u>Controls (air only)</u>	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

Animals (none) occasionally, exhibited thinness.
Necropsies apparently did not reveal any gross abnormalities.

BEST AVAILABLE COPY

008876

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

Product Manager: (17) 10-18-89 Reviewer: Woodrow
MRID No.: 412465-02 Report Date: 6-12-90
Testing Laboratory: Hazleton, Labs, WI. Report No. 3m/PCP 2100661104
Author(s): N.A. Renden
Species: Rabbit, N2 White
Sex: not stated Weight: 2000g, 2360g
Source: Hazleton Res. Products
Dosage: 0.1 ml
Test Material: Safety and Insect Repellent, liquid (used undiluted).
Quality Assurance (40 CFR §160.12): Adequate

Summary:

Tox. Category: 11 Classification: Guidelines

Procedure (Deviation From §81-4): 9 rabbits received 0.1 ml placed in the washed 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 instillation. 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.

	(number "positive"/number tested)								
	Hour	Days							
	1	1	2	3	4	7	14	21	
Cornea Opacity	9/9 1/2	8/9 1/8	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	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	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 2/5	9/9 1/2	8/9 2/1	7/9 1/0	7/9 1/0	0/9	0/9		

washed/flushed approx. the same
"
"
washed - 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.

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

Manager: (17)

3-7-75

Reviewer: W. Waller

Report Date: 6-19-90

Report No. 4122920

Code: 00001085

Laboratory: WARP INST., INC.

Tested by: J. A. Belmick

Rabbit: NZ White

Sex: not given

Weight: not stated

Age: not stated

Dose: 0.1 ml (81.6 mg)

Serial: 3872 D102

Assurance (40 CFR §160.12): none

Category: III Classification: Guidelines

(Deviation From §81-4): 0.1 ml installed into 1 eye of each rabbit. 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 irritation through Day 3, about Day 4.

BEST AVAILABLE COPY

DATA REVIEW FOR SKIN IRRITATION TEST

Product Manager: (17) 3-7-75
 MRID No.: 00001085
 Testing Laboratory: WARR INST., INC.
 Author(s): J. A. Balsemier
 Species: Rabbit
 Age: Not stated
 Sex: Not given
 Weight: Not given
 Dosage: 0.5 ml (0.408g, or 408mg)
 Test Material: 3872 D10 (sample)
 Quality Assurance (40 CFR 9160.12): none

Reviewer: H. Waller
 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 §81.57): One abraded and one intact skin area on clipped backs of 6 rabbits each received 0.5 ml (0.408g, or 408mg) of test material. Treated areas covered with gauze patches and tapes 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:

AVAILABLE COPY

Product Manager: (17) 10-18-89 Reviewer: ~~W. W. Miller~~
 Product No.: 412465-03 Report Date: 6-12-90
 Testing Laboratory: Hazleton, labs Report No.: 31m/PCP210066/1104
 Director(s): N. A. Randen
 Species: Rabbit, N 2 white
 Sex: young adult
 Age: not stated
 Weight: 2008 - 2278 g
 Material: Safety rated Insect Repellent
 Quality Assurance (40 CFR §160.12): adequate

Primary:

Primary Irritation Index = 0.83

Toxicity Category: IV

Classification: Guidelines

Procedure (Deviation from §15): 0.5ml undiluted test material applied to clipped backs of each of 6 rabbits - sites covered by 2.5 cm² gauze patches secured w/ tape; dressings were wrapped - Secum wrap secured w/ tape - 4 hour exposure. Sites were examined and scored for erythema 30 minutes after test: wrappings removal, and again at 24, 48, 72 and 96 hrs. Body weights recorded at weekly intervals.

Observation Period	AV. Primary Irritation Scores
4 hrs	0.7
24 hrs	1.0
48 hrs	7
72 hrs	7
96 hrs	7
day 7	7
day 14	0.0

Additional Comments:

Final irritation score for all animals (erythema/teloma)
 - No. of test sites.

BEST AVAILABLE COPY

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

Product Manager: (17) 4-6-89 Reviewer: ~~W. Walter~~ Woodrow
 MRID No.: 412465-04 Report Date: 6-13-90
 Testing Laboratory: Keyline Res. Cen. Ohio Report No. 3M/PCP 2100661104
 Author(s): N.H. Renden
 Species: humans
 Sex: _____ Weight: _____
 Source: _____
 Test Material: T-4286 insect repellent
 Positive Control Material: _____
 Quality Assurance (40 CFR §160.12): _____

Method: Modified Draize Skin Sensitization Test

Summary: (Repeat human insult patch test).

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 / subjects to include eight different materials; including the T-4286 insect 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 & taped)

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

2.

Grading system:

- 0: no visible response
- 1: mild erythema
- 2: Papular response
- 3: Edema & or erect papules
- 4: Vesicular/bulbous eruption

Patches: $3/4 \times 3/4$ " cotton containing 0.3ml test material, suspended in hexane for 1 hour, held to test site by $1/2 \times 1/2$ " adhesive

Challenging 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 papula challenged exhibited a score of 1.0 (mild erythema).

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