

11-1-91

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.: [4822-GAA] OFF! Insecticide Repellent 1990 #1 and [4822-GAI] OFF! Insecticide Repellent 1990 #3

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

To: Phil Hutton, PM 18
Insecticide-Rodenticide Branch
Registration Division (H7505C)

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

E 11/1/91

Applicant: S.C. Johnson & Son, Inc.
1525 Howe St.
Racine, WI 53403

FORMULATION FROM LABEL: [4822-GAA]

	<u>% by wt.</u>
<u>Active Ingredient(s):</u>	
N,N-diethyl-meta-toluamide [DEET].....	6.65
Related Isomers.....	0.45
<u>Inert Ingredient(s):</u>	93.0
Total:	100%

FORMULATION FROM LABEL: [4822-GAI]

	<u>% by wt.</u>
<u>Active Ingredient(s):</u>	
N,N-diethyl-meta-toluamide [DEET].....	6.65
Related Isomers.....	0.45
<u>Inert Ingredient(s):</u>	93.0
Total:	100%

BACKGROUND S.C. Johnson & Son, Inc., submitted an acute inhalation toxicity waiver request as well as acute oral toxicity, acute dermal toxicity, eye irritation, dermal irritation, and dermal sensitization studies for review. The products, which are considered substantially similar, are OFF! Insecticide Repellent 1990 #1 [4822-GAA] and OFF! Insecticide Repellent 1990 #3 [4822-GAI], and the active ingredients [in both products] are as follows:

	<u>% by wt.</u>
<u>Active Ingredient(s):</u>	
N,N-diethyl-meta-toluamide [DEET].....	6.65
Related Isomers.....	0.45
<u>Inert Ingredient(s):.....</u>	93.0
 Total:	 100%

Since the two products are considered substantially similar by PRS, this submission supports the acute toxicity data requirements for OFF! Insecticide Repellent 1990 #1 and OFF! Insecticide Repellent 1990 #3. All studies were performed at Hill Top Biolabs, Inc., and the MRID numbers are 418443-03 through 418443-07.

RECOMMENDATION The acute oral, acute dermal, eye irritation, skin irritation, and dermal sensitization studies are unacceptable and have been graded supplementary.

[1] The material tested in the acute studies was not identified, therefore, these studies do not currently support the registration of [4822-GAA] OFF! Insecticide Repellent 1990 #1 or [4822-GAI] OFF! Insecticide Repellent 1990 #3. The registrant must identify the materials [6731D152-6 & 6731D152-6 Insect Repellent #351] tested in the acute studies [MRID# 418443-03 through 418443-07]. If the test materials are satisfactorily identified the studies will be considered for upgraded status.

[2] The review of the acute inhalation toxicity waiver for OFF! Insecticide Repellent 1990 #1 and OFF! Insecticide Repellent 1990 #3 is pending HED's response to a technical assistance request by PRS. The request concerns the use of vapor pressures in acute inhalation waivers (see attachment 1). The subject waiver request will receive priority upon the completion of HED's investigation.

LABELING

[1] The appropriate signal word is CAUTION

[2] The first three sentences of the precautionary statements should be replaced with the following:

Harmful if absorbed through skin. Causes eye irritation. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Avoid contact with skin, eyes, or clothing. Wash thoroughly with soap and water after handling.

[3] The statements of practical treatment should read as follows:

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

IF IN EYES: Flush with plenty of water. Call a physician if irritation persists.

[4] Further label revisions may be required.

*NOTE TO PM: In reference to dermal contact, the precautionary labeling language contradicts the directions for use of this product. Since the product was tested only at the category three level [2.0 g/kg], the dermal hazard has not been fully determined and the dermal precautions may or may not be appropriate. The PM should decide how to resolve this problem.

ACUTE TOXICITY PROFILE

Acute Oral.....	Category 4/Supplementary
Acute Dermal.....	Category 3/Supplementary
Acute Inhalation.....	Not Determined
Eye Irritation.....	Category 3/Supplementary
Dermal Irritation.....	Category 4/Supplementary
Dermal Sensitization.....	Positive /Supplementary

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

Product Manager: 18
MRID No.: 418443-03
Testing Facility: Hill Top Biolabs
Author(s): J. Kreuzman
Species: Rat
Age: Young Adult
Weight: 221-286g
Source: Harlan Sprague Dawley, Inc.
Test Material: 6731D152-6
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 5-30-91
Report No.: 90-406621A

Conclusion:

1. LD₅₀ (mg/kg): Males = --
Females = --
Combined = > 5 g/kg
2. The estimated LD₅₀ is > 5 g/kg
3. Tox. Category: 4 Classification: Supplementary

Procedure (Deviations from §81-1):

Results:

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

Symptoms & Gross Necropsy Findings: All animals surpassed their pre-dose weight by study termination. Labored breathing was observed in most animals shortly after dose administration. No abnormalities were observed upon necropsy.

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ORAL TOXICITY DATA SHEET

EPA REG. # 4822-GAA

MRID # 418443-03

ANIMAL [RAT]	✓	
AGE [YOUNG ADULT]	✓	
5/SEX/DOSE LEVEL	✓	
LIMIT TEST	✓	5g/kg
FASTED	✓	
METHOD OF ADMINISTRATION	✓	Gavage
DOSE CONC & DOSE LEVELS	✓	
OBSERVATION PERIOD & FREQUENCY	✓	2x, 14 days
BODY WEIGHT FREQUENCY & RESULTS	✓	All gained days 0, 7, 14
MORTALITY CHART & LD-50	✓	All survived
CLINICAL EXAM RESULTS	✓	
NECROPSY RESULTS	✓	None

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

Product Manager: 18

MRID No.: 418443-04

Testing Laboratory: Hill Top Biolabs, Inc.

Author(s): J. Kreuzman

Species: Rabbit

Weight: 2313-3110g

Source: Hasenpfeffer Hill

Test Material: 6731D1522-6

Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry

Report Date: 5-30-91

Report No.: 90-406621B

Summary:

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

Procedure (Deviation From §81-2):

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: All animals surpassed their pre-dose weight by study termination. No clinical signs of toxicity were observed. Necropsy revealed reddish-brown kidneys in one animal.

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DERMAL TOXICITY DATA SHEET

EPA REG.# 4822-GAA

MRID# 418433-04

ANIMAL [RABBIT]	✓	
TEST MATERIAL PREPARATION	✓	
5/SEX/DOSE LEVEL	✓	2 g/kg
LIMIT TEST	✓	
CLIPPED	✓	
METHOD OF APPLICATION	✓	
METHOD OF OCCLUSION	✓	rubber dental dam
BODY WEIGHT FREQUENCY & RESULTS	✓	days 0, 7, 14
DOSE CONC & DOSE LEVELS	✓	
EXPOSURE TIME	✓	24 hrs
REMOVAL OF EXCESS MATERIAL	✓	post exp wash
MORTALITY CHART & LD-50	✓	All survived
CLINICAL EXAM RESULTS	✓	None
NECROPSY RESULTS	✓	

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

Product Manager: 18

MRID No.: 418443-06

Testing Laboratory: Hill Top Biolabs, Inc.

Author(s): J. Kreuzman

Species: Rabbit

Sex: 3 female, 3 male

Weight: --

Source: King's Wheel Rabbitry

Dosage: 0.369ml [0.318g]

Test Material: 6731D152-6 Insect Repellent #351

Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry

Report Date: 5-30-91

Report No.: 90-413821A

Summary:

1. Toxicity Category: 3
2. Classification: Supplementary

Procedure (Deviations From §81-4): Dose administered by a one second aerosol spray from a distance of 10 cm.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	5/6	5/6	0/6	0/6				
Iris	6/6	3/6	2/6	0/6				
Conjunctivae								
Redness	1/6	5/6	3/6	0/6				
Chemosis	6/6	5/6	0/6	0/6				
Discharge								

Comments: All signs of irritation cleared by day four of the study.

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EYE IRRITATION DATA SHEETEPA REG.# 4822-6AAMRID# 418433-06

ANIMAL [RABBIT]	✓	
DOSE VOLUME [0.1ml]	→	0.369 ml
TEST MATERIAL DESCRIPTION	✓	Aerosol spray
METHOD OF ADMINISTRATION	✓	One second burst from 10 cm
DOSE CONC	✓	undiluted
OBSERVATION PERIOD & FREQUENCY	✓	4 days, daily
OBSERVATION METHOD	✓	
EVALUATION RESULTS	✓	Corneal involvement cleared by day 2

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

Product Manager: 18

MRID No.: 418443-05

Testing Laboratory: Hill Top Biolabs, Inc.

Author(s): J. Kreuzman

Species: Rabbits

Age: Young Adult

Sex: 3 females, 3 males

Weight: --

Dosage: 0.5 ml

Test Material: 6731D152-6

Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry

Report Date: 5-30-91

Report No.: 90-406621C

Summary:

1. The Primary Irritation Index = 1.0
2. Toxicity Category: 4
3. Classification: Supplementary

Procedure (Deviations From §81-5):

Results: Grade 1-2 erythema was present at the 24 and 48 hour evaluation periods. By 72 hours only one animal exhibited grade 1 erythema.

Special Comments:

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SKIN IRRITATION DATA SHEET

EPA REG.# 4822-GAA

MRID# 418433-05

ANIMAL [RABBIT]	✓	
DOSE VOLUME [0.5ml]	✓	
DOSE CONC	✓	undiluted
CLIPPED	✓	
TEST MATERIAL DESCRIPTION	✓	liquid.
EXPOSURE TIME	✓	4 hrs
EXPOSURE SITE AREA	✓	
OCCLUSION	✓	
POST-EXPOSURE WASH	✓	
OBSERVATION PERIOD & FREQUENCY	✓	7 days
EVALUATION RESULTS	✓	slightly irritating irritating

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

Product Manager: 18

MRID No.: 418443-07

Testing Laboratory: Hill Top Biolabs, Inc.

Author(s): J. Kreuzman

Species: Guinea Pig

Weight: 333-612g

Source: Murphy Breeding Labs.

Test Material: 6731D152-6

Positive Control Material: DNCB

Quality Assurance (40 CFR §160.12): Present

Method: Buehler

Summary:

1. This Product is a dermal sensitizer.
2. Classification: Supplementary

Procedure (Deviation From §81-6):

Results: Following primary challenge 12 of 20 test animals and 0 of 10 naive control animals exhibited +/- responses.

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DERMAL SENSITIZATION DATA SHEET

EPA REG.# 4822-GAA

MRID# 418433-07

ANIMAL [GUINEA PIG]	✓	
POSITIVE CONTROL DESCRIPTION	✓	Positive test
TEST METHOD	✓	Buehler
PRE-SCREEN RESULTS	✓	0.5, 1, 2.5, 5.0, 10, 25, 50, 100% tested
INDUCTION DESCRIPTION	✓	one exposure per week / 3 wks of undiluted material
EXPOSURE TIME	✓	6 hrs
EXPOSURE SITES & PREP	✓	
OCCLUSION	✓	
CHALLENGE DESCRIPTION	✓	25% at naive site
NAIVE CONTROLS	✓	
INDUCTION RESULTS	✓	
CHALLENGE RESULTS	✓	

Tox Chem No: 346

File Last Updated _____

Current Date 6-4-91

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	Tox. Conc Grade/ Cnt, Doc. No.	
Acute Oral Tox Rat/ 4-25-90/90-4066-21A Hill Top Biolabs	7% Deet OFF! Repellent	48443-03	LD50 > 5g/kg	4 [redacted] Supplemental	
Acute Dermal Tox Rabbit/5-9-90/90-4066-21B Hill Top Biolabs	"	48443-04	LD50 > 2g/kg	3 [redacted] Supplemental	
Primary Eye Irr Rabbit/ 5-9-90 /90-438-21A 7-28-90 Hill Top Biolabs	"	418443-06	LD50 > 2g/kg Corneal opacity cleared by day 2	3 [redacted] Supplemental	
Dermal Irritation Rabbit/4-24-90/90-4066-21C Hill Top Biolabs	"	418443-05	slightly irritating	4 [redacted] Supplemental	
Dermal Sensitization Guinea pig/5-17-90/90-4066-21E Hill Top Biolabs	"	418443-07	Is a sensitizer	1 [redacted] Supplemental	