CASWELL FILE 8

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

PC 081301

JUL 12 1989

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Blockade Acute Inhalation Study

TO: Mr. George LaRocca, PM 15
Registration Division (H7505C)

FROM: Byron T. Backus, Toxicologist Byron T. Backus 6/30/89
Fungicide/Herbicide/Antimicrobial Toxicology Branch
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 7/5/89
Acting Section Head, Review Section II
Fungicide/Herbicide/Antimicrobial Toxicology Branch
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 7/7/89
Fungicide/Herbicide/Antimicrobial Toxicology Branch
HED (H7509C)

EPA Record No. 239776, 239777

Project No. 9-0804

EPA Registration Nos. 2596-114, 2596-115

Caswell No. (346) 77A

Action Requested:

Examine additional data submitted in response to a previous HED review (memorandum of 5/17/88) of this inhalation study which stated in part: "Unless it can be demonstrated that the rats actually received an exposure to DEET of 0.5 mg/L...the study is classified as core supplementary data."

Additional data:

The registrant has essentially repeated the study using sample collection pads in the breathing zone instead of animals. Two test runs were conducted, and the sample pads (each with a surface area of 1.67 inches^2) were extracted and quantitatively analyzed for fenvalerate and DEET (the two actives in the Blockade formulation). The results (see appended page 1)

indicate means of 5.09 mg of DEET and 0.063 mg fenvalerate per inch^2 surface area of pad were absorbed. Since the area of the breathing zone was 625 inches^2, the overall amounts (residues?) of Deet and fenvalerate were respectively 3181 and 39.38 mg; dividing these values by 4800 liters (the amount of air passing through the chamber) yields 0.662 and 0.0082 mg/L of these two components respectively.

Comments and Recommendations:

1. The data received 2/2/89 adequately demonstrate that the rats in the previous inhalation study were receiving a sufficient exposure to the components of the test material. The assays conducted during the original study, as well as the measurements made in the repeat study, demonstrate that exposure was to a concentration of 5 mg/L of the formulated product.

2. As noted by the registrant, there is an approximately 1:100 ratio of DEET:fenvalerate in the Blockade formulation. The appropriate value for fenvalerate then needs to be only about 0.005 mg/L, rather than the 0.05 mg/L specified in the review of 5/17/88.

3. Based on the information received 2/2/89, classification of this study is upgraded to Core Minimum.

APPENDED P. 1

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TABLE II

CONCENTRATIONS OF FENVALERATE AND DEET FOUND AT THE BREATHING ZONE USING SUPPORT PADS FOR SAMPLE COLLECTION

	Run #1	Run #2	Average
Support Pads			
Fenvalerate (mg/sq. in. On Pads)	0.060	0.066	0.063
DEET (mg/sq. in. On Pads)	5.37	4.81	5.09
Breathing Zone			
Fenvalerate (mg in Entire Breathing Zone)	37.50	41.25	39.38
DEET (mg in Entire Breathing Zone)	3356	3006	3181
Concentration			
Fenvalerate (mg/Liter of Air)	0.0078	0.0086	0.0082
DEET (mg/Liter of Air)	0.699	0.626	0.662

TOXCHEM NO. 077A- Benzeneacetic acid, 4-chloro(A-1-ethyl)-cyano(3-phenoxyphenyl) methyl ester FILE LAST PRINTED: 04/10/89

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Mutagenic-dominant lethal test Species: mice	Pydrin Tech		Negative at 100 mg/kg (HDT).		
Mutagenic- host med. Species: mice	Pydrin tech.		Negative at 50 mg/kg (HDT).		
Mutagenic-Ames Species:	Pydrin tech.		Negative		
Mutagenic-bone marrow cells Species: CHO	Pydrin Tech.		Negative at 25 mg/kg		
Acute Dermal LD50 Species: cat [redacted] 6/28/88	Blockade (0.11% fenvalerate 10% Deet; 89.9% inert).	407040-01	No deaths at dose of 4X. The material was sprayed onto the cats.		Supplementary 006906 Minimum 006986
Acute Dermal LD50 Species: dog [redacted] 6/28/88	Blockade (0.11% fenvalerate; 10% Deet; 89.9% inert) sample # 8340	407040-02	LD50 > 4.1 gm/kg		Supplementary 006906 Minimum 006986
Acute oral LD50 Species: cat 3/24/88 [redacted]	DEET 8.55% other isomers 0.45% Pydrin 0.09%	405734-0	4/12 cats dosed by gavage with 250 mg/kg of Blockade concentrate showed effects , including emesis. In 3 cats emesis occured within 1 hr. of dosing, no further symptoms ;1 cat , vomiting occured 6 hrs after dosing, cat did not eat the following day. Full recovery for cat day 2. No symptoms in cats which received 125 mg/kg (NOEL).		Acceptable 006720
/ oral LD50 Species: dog 3/23/88 [redacted]	DEET 8.55% other isomers 0.45% Pydrin 0.09%	405735-01	4/12 dogs orally dosed at 250 mg/kg (as well as 1/2 at 500 mg/kg ; 4/4 750 mg/kg) showed emesis and/or salivation within 2 hrs of dosing, no further effects. No effects observed in dogs dosed at 125 mg /kg. NOEL = 125 mg/kg; LEL = 250 mg/kg.		Acceptable 006720
Acute inhalation LC50 Species: rat Leberco Labs 1004; 3/9/88	DEET & other isomers 9% Pydrin 0.09%	405735-01 40786-01	No mortalities among 5M, 5F rats which ostensibly received a 4-hr exposure to >5 mg/l concentration of product. Reduced weight gain (F) in period from 0-7 days; (M) tended to be some what less active than normal following exposure. Reported concentration measurements of DEET ranged from 5.48 - 10.6 mg/m3 and for Pydrin from 0.05 -0.24 Values for DEET are about 1 - 2% of what they should have been if rats had received exposure to 5 mg/l of Blockade formulation.		Supplementary 006720 Minimum xxxxxx

Additional analytical information: Sample collection pads in breathing zone indicate exposure to 0.662 and 0.0082 mg/L DEET and fenvalerate respectively.

Commercial/financial information may be entitled to confidential treatment

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Acute inhalation LC50 Species: rat Leberco Labs 1004; 3/9/88	DEET & other isomers 9.0%; Pydrin 0.09%	405735-01	No mortalities among 5 M, 5 F rats which ostensibly received a 4 hr. exposure to > 5 mg/L conc. of product. reduced wt. gain (F) in period from 0-7 days; (M) tended to be somewhat less active than normal following exposure. Reported conc. measurements of DEET ranged from 5.48-10.6 mg/m3 & for Pydrin from 0.05-0.24 mg/m3. values for DEET are about 1-2% of what they should have been if rats had received exposure to 5 mg/L of Blockade formulation.		Supplementary 006720
Acute oral LD50 Species: cat [redacted] Texas [redacted] 24/88	DEET 8.55%; other isomers 0.45%; Pydrin 0.09%	405734-0	4/12 cats dosed by gavage with 250 mg/kg of Blockade concentrate showed effects, including emesis. In 3 cats emesis occurred within 1 hr. of dosing, no further symptoms; 1 cat, vomiting occurred 6 hrs. after dosing, cat did not eat the following day. Full recovery for cat Day 2. No symptoms in cats which received 125 mg/kg (NOEL).		Acceptable 006720

change to for 077A

Commercial/financial information may be entitled to confidential treatment

DER FROM ME, MEMORANDUM OF 5/17/88

Reviewed by: Byron T. Backus Byron T. Backus 05/13/88
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D. M. van Gemert 5/13/88
Section 3, Tox. Branch (TS-769C)

006720

DATA EVALUATION REPORT III

STUDY TYPE: Acute inhalation - rat

TOX. CHEM. NO.: 346, 77A

ACCESSION NUMBER: 405712-01

MRID NO.:

TEST MATERIAL: Blockade

SYNONYMS: Deet + Pydrin

STUDY NUMBER(S): Hartz Test No. 1004

SPONSOR: Hartz Mountain Corporation

TESTING FACILITY: Leberco Testing, Inc.
Roselle Park, NJ 07204

TITLE OF REPORT: Acute Inhalation Toxicity in Rats

AUTHOR(S): Levy, E.

REPORT ISSUED: March 9, 1988

CLASSIFICATION: Core Supplementary Data

CONCLUSION:

There is a question as to whether the test animals received an exposure that was equivalent to 5 mg/L of the product. According to table VII (p. 30) DEET concentration ranged from 5.48 to 10.6 mg/m^3 in the chamber, and the fenvalerate concentration was from 0.05 to 0.24 mg/m^3. These data are consistent with one another in that Blockade contains about 100 times as much DEET as fenvalerate. However, since about 10% of the formulation consists of DEET, the DEET concentration should have been about 10% of 5 mg/L which is equal to 0.5 mg/L, which in turn (since 1 m^3 = 1000 liters) would be equal to 500 mg/m^3. The actual reported values (table VII) are about 1-2% of this. Unless it can be demonstrated that the rats actually received an exposure to DEET of 0.5 mg/L, and to fenvalerate of about 0.05 mg/L, the study is classified as core supplementary data.

A. MATERIALS:

1. Test compound: Test sample #8340, obtained from a pallet of product manufactured 13 March 1987, production lot No. MR10727. An analysis showed that the material contained the label declaration of 10.0% Deet and 0.10% Fenvalerate.

2. Test animals: 8-week old Sprague-Dawley rats of both sexes. At the time of exposure males weighed 250-294 grams; females 201-207 grams.

B. STUDY DESIGN:

1. Animal assignment:

From p. 9: "Animals placed on test were randomly assigned to dose groups. Only rats with body weight within ± 20% of the mean body weight of rats of the same age, strain and sex were used."

2. Exposure to the test material:

Five male and 5 female rats were placed in the exposure chamber ("a 200-liter, non-porous, airtight, square with glass viewing window."). From p. 11: "Operating parameters and test conditions were established prior to the exposure or use of test animals." "The test material was manually introduced into the chamber as a 1-second burst every 60 seconds. Only 175 grams of test material was evacuated from each 200 grams aerosol can. The aerosol can was weighed after every ten bursts." The exposure was for 4 hours, with subsequent 14-day observation.

From p. 14: "Immediately after exposure the animals were rinsed with warm water to remove any residual test material from their body to avoid toxicity by oral route."

3. Quality assurance: there is a Good Laboratory Practice Statement on p. 3 of the report, as well as a Quality Assurance Unit Statement signed and dated on 3/4/88.

C. METHODS AND RESULTS:

1. Observations: From p. 37: "All test animals are observed fo signs of toxicity...and mortality during the exposure period, once an hour for four hours following exposure, twice daily 5 days a week for the first week after exposure and once daily thereafter. Test animals are observed for a total of 14 days after exposure."

Results: From p. 14: "All ten animals spent the first hour preening themselves. At one and two hours post exposure the males had a slight decrease in spontaneous motor activity and at three hours all ten animals appeared normal and remained so throughout the 14 day observation period.

2. Animal weights:

Individual animals were weighed on the day of dosage, and at 7 and 14 days afterwards.

Results:

From data presented on p. 29 one female lost weight in the period from day 0 to day 7. All others gained, although it is noteworthy that weight gains for most females were less during the period from day 0 to day 7 than from day 7 through 14. For males the converse was true. From p. 29:

		Weight change (grams)	
Rat #	Sex	day 0 to 7	day 7 to 14
1	F	16	18
2	F	-7	12
3	F	4	31
4	F	20	23
5	F	11	28
6	M	33	27
7	M	35	22
8	M	50	25
9	M	44	26
10	M	45	24

3. Necropsy:

"A gross necropsy was performed on all test animals 14 days after exposure. The gross necropsy included examination of the adnexa, eyes, thoracic and visceral organs. Emphasis was placed on examination of the respiratory tract. Animals were sacrificed by CO_2 overdose." From p. 11: "At the request of the Hartz Mountain Corporation, tissue samples of the lungs were sent to independent pathologists for review." Slides were prepared and evaluated by two different pathologists.

Results:

According to individual data (p. 114) 4/5 females and 3/5 males had slightly or moderately mottled lungs on necropsy. According to one pathologist who examined slides prepared from these animals (see p. 154): "The changes seen in the lungs and bronchioles of rats...are of trace severity and are commonly seen in experimental rats. They are interpreted as being unrelated to treatment." The other pathologist (see p. 160) made no statement as to whether or not these findings might have been related to treatment. One of the males is reported as having foamy macrophages in the alveoli by one pathologist and as having a granuloma with foamy macrophages in wall of the bronchus by the other.

4. Analysis of test substance concentration:

From p. 11: "Representative air samples were removed from the "breathing zone" of the inhalation chamber via a probe attached to a vacuum system with a flow rate of 5 L/min. The samples were taken 30 minutes into the test...and every half hour thereafter throughout the 4 hour test period... The samples were measured gravimetrically to assure that the average concentration in the breathing zone was 5 mg/L or greater."

Results:

Gravimetric samplings indicated a range of 5.06 to 6.75 mg/L. From table VII (p. 30) the fenvalerate (combined isomers) concentration ranged from 0.05 to 0.24 mg/L; the DEET concentration ranged from 5.48 to 10.60 mg/m^3.

5. Particle size analysis:

From p. 12: "During the generation of the test material three air samples were taken at the breathing zone for particle size analysis by a California Measurements, Inc. 6 stage Cascade Impactor Model PC-5S. Samples were taken at 75 minutes, 190 minutes and 225 minutes into the four hour exposure period."

Results:

Most of the measured particulate matter was in the range of 0.26 to 1.7 microns (see table IV, p. 27). The cumulative amount collected at any one time is given in terms of mg/m^3 (concentration?), and ranges from a total of about 0.3 mg/m^3 at 225 minutes to about 0.6 mg/m^3 at 75 minutes.

D. DISCUSSION:

The major concern of this reviewer is whether, in fact, the test animals received an exposure that was equivalent to 5 mg/L of the product. According to table VII (p. 30) DEET concentration ranged from 5.48 to 10.6 mg/m^3 in the chamber, and the fenvalerate concentration was from 0.05 to 0.24 mg /m^3. These data are consistent with one another in that blockade contains approximately 100 times as much DEET as fenvalerate. However, since about 10% of the formulation consists of DEET, the DEET concentration should have been about 10% of 5 mg/L which is equal to 0.5 mg/L, which in turn (since 1 m^3 = 1000 liters) would be equal to 500 mg/m^3. The actual reported values (table VII) are about 1-2% of this. Unless it can be demonstrated that the rats actually were exposed to a concentration of about 0.5 mg/L DEET, and to about 0.05 mg/L fenvalerate, the study is classified as core supplementary data.

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R025103

Chemical:	**Diethyl toluamide**
PC Code:	**080301**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/12/89 12:00:00 AM**
File ID:	**00000000**
Accession Number:	**412-04-0045**

HED Records Reference Center
02/12/2004