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

006696

APR 29 1988

OFFICE OF
PESTICIDES ANL TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Rat Acute Oral Toxicity Study - Blockade

TO: Mr. George LaRocca, PM 15
Registration Division (TS-767C)

FROM: Byron T. Backus, Toxicologist /Byron T. Backus 04/29/88
Toxicology Branch (TS-769C)

THROUGH: Marcia van Gemert, Ph.D.
Section Head, Review Section III M. van Gemert 4/29/88
Toxicology Branch (TS-769C)

and

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Branch Chief
Toxicology Branch (TS-769C)

EPA Record No. 219028/219029

Project No. 8-0643

Tox. Chem. 346, 77A

Action Requested:

Review a rat oral toxicity study conducted on Blockade.

Background:

An acute oral toxicity study on this formulation was previously reviewed (TB memorandum dated September 24, 1987). In that study a rat oral LD_{50} value of 6.7 g/kg was calculated for combined data from both sexes. However, the TB review noted that data from females (2/5 mortalities at 5 g/kg; 3/5 at 6 g/kg; and all dying at 7 g/kg) indicated that this sex was probably more susceptible, and that the 95% confidence limits associated with the oral LD_{50} level for females would probably be such that category III labeling for the oral hazard potential would be appropriate. A subsequent oral toxicity study has now been submitted and is the subject of this review. This study was conducted at the same laboratory (Leberco Testing, Inc.) as that which did the previous study.

Comments and Recommendations:

1. The findings of this study confirm that female rats are more sensitive to this formulation than are males, at least with respect to the oral LD_{50} value. The female oral LD_{50} is reported as 5420 mg/kg with 95% confidence limits of 4517 to 6504 mg/kg; the male oral LD_{50} is reported as 9250 mg/kg with 95% confidence limits of 8259 to 10360 mg/kg. The lack of overlap between these ranges is significant. It is also noted (p. 14) that those males which became cataleptic but subsequently recovered did so more rapidly than females, despite being dosed with more material.

2. Since the 95% confidence limits for the female oral LD_{50} include values less than 5 g/kg, the Toxicology Branch recommends toxicity category III labeling for this product with respect to its oral hazard potential.

3. The study adequately defines an acute oral dose NOEL in rats (both sexes) at 2 g/kg.

4. Overall, the study and its findings are acceptable. The study is classified as core minimum data.

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Reviewed by: Byron T. Backus Byron T. Backus 04/29/88
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M. van Gemert 4/29/88

DATA EVALUATION REPORT I

STUDY TYPE: Acute oral toxicity - rat TOX. CHEM. NO.: 346, 77A

ACCESSION NUMBER: 405713-01 MRID NO.:

TEST MATERIAL: Blockade

SYNONYMS: Deet + Pydrin

STUDY NUMBER(S): Hartz Test No. 1003

SPONSOR: Hartz Mountain Corporation

TESTING FACILITY: Leberco Testing, Inc.
Roselle Park, NJ 07024

TITLE OF REPORT: Oral Toxicity Study in Rats Ranging from No-Effect Level Through Acute Oral LD_{50}

AUTHOR(S): Platt, C. M.

REPORT ISSUED: February 19, 1988

CLASSIFICATION: Core Minimum Data

CONCLUSIONS:

1. The findings of this study confirm that female rats are more sensitive to this formulation than are males, at least with respect to the oral LD_{50} value. The female oral LD_{50} is reported as 5420 mg/kg with 95% confidence limits of 4517 to 6504 mg/kg; the male oral LD_{50} is reported as 9250 mg/kg with 95% confidence limits of 8259 to 10360 mg/kg. The lack of overlap between these ranges is significant. It is also noted (p. 14) that those males which became cataleptic but subsequently recovered did so more rapidly than females, despite being dosed with more material.

2. Since the 95% confidence limits for the female oral LD_{50} include values less than 5 g/kg, the Toxicology Branch recommends toxicity category III labeling for this product with respect to its oral hazard potential.

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4. Overall, the study and its findings are acceptable. The study is classified as core minimum data.

A. MATERIALS:

1. Test compound: Aerosol Sample 8340; active ingredients Diethyltoluamide (DEET) and Fenvalerate. The material tested was spray collected in a beaker. This is described as a clear colorless liquid with a pH of 4.63. At the end of the study this material was analyzed and was found to contain 0.13% Fenvalerate and 14.2% DEET.

2. Test animals: Male and female Sprague-Dawley derived rats from Taconic Farms, Inc. Germantown, NY. Rats were 7 weeks old when received. When dosed, males weighed between 220 and 280 grams; females between 152 and 193 grams.

B. STUDY DESIGN:

1. Test material administration: "The test material was administered as a single oral dose by syringe and intubation tube." The test material was apparently administered undiluted.

2. Animal assignment: "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."

3. Dosage groups:

Females:

Material Administered	Nominal Dosage (mg/kg)	No. of Animals	Animal Numbers	Date of Administration and page reference
Water	2500	10	11-20	2/5 (p. 276)
Blockade	1500	4	107-110	1/14 (p. 248)
"	2000	3	151-153	1/19 (p. 256)
"	2000	10	161-170	2/2 (p. 269)
"	2500	6	101-106	1/14 (p. 262)
"	3500	10	41-50	1/5 (p. 146)
"	4000	10	71-80	1/12 (p. 154)
"	5000	10	1-10	12/30 (p. 161)
"	6000	10	61-70	1/5 (p. 169)
"	6300	10	131-140	1/19 (p. 177)
"	6400	10	171-180	2/2 (p. 184)
"	6450	10	201-210	2/9 (p. 192)
"	6500	10	111-120	1/14 (p. 199)
"	7000	10	81-90	1/11 (p. 205)

Males:

Material Administered	Nominal Dosage (mg/kg)	No. of Animals	Animal Numbers	Date of Administration and page reference
Water	2500	10	31-40	2/5 (p. 312)
Blockade	2000	3	184-186	2/2 (p. 284)
"	2000	10	191-200	2/5 (p. 305)
"	2500	3	187-189	2/2 (p. 291)
"	3000	3	181-183	2/2 (p. 298)
"	7000	10	21-30	12/30 (p. 211)
"	9500	10	51-60	1/5 (p. 219)
"	10500	10	91-100	1/11 (p. 226)
"	10700	10	141-150	1/19 (p. 233)
"	11000	10	121-130	1/14 (p. 241)

Since the test material was administered undiluted, and to the nearest 0.1 ml, the doses were not as accurate as suggested by the dose values reported. Also, there was considerable variation between groups with respect to mean weights. The following is calculated for females in the nominal 6450 and 6500 mg/kg groups:

Nominal dosage 6450 mg/kg - calculated from data on p. 193:

Animal Number	Weight (grams)	Dose administered (g)	Dose in mg/kg
201	189	1.2	6349
202	193	1.2	6218
203	178	1.1	6180
204	189	1.2	6349
205	178	1.1	6180
206	192	1.2	6250
207	177	1.1	6215
208	192	1.2	6250
209	183	1.2	6557
210	184	1.2	6522
Mean	185.5		6307
S.D.	6.31		136

Nominal dosage 6500 mg/kg - calculated from data on p. 200:

Animal Number	Weight (grams)	Dose administered (g)	Dose in mg/kg
111	163	1.1	6748
112	170	1.1	6471
113	165	1.1	6667
114	164	1.1	6707
115	168	1.1	6548
116	170	1.1	6471
117	153	1.0	6536
118	154	1.0	6494
119	169	1.1	6509
120	160	1.0	6250
Mean			6540
S.D.			143

Another consideration is that there were probably additional slight errors (± 0.05 g) in individual dosing.

3. Quality assurance: there is a "Good Laboratory Practice Statement" dated 3/24/88 on p. 3. It is noted that the signature appears to be from a rubber stamp, but perhaps the lines next to this signature are initials. There is a signed and dated "Quality Assurance Unit Statement" on p. 17.

C. METHODS AND RESULTS:

1. Observations: "All test animals were observed for signs of toxicity and mortality continuously during dosing, 0.5 to 1.5 hours and hourly for four hours post dosing. The animals were checked a minimum of twice daily 5 days a week thereafter. Test animals were observed for a total of 14 days after exposure..."

Results:

Mortality:

The lowest dosage level at which mortality occurred was 4000 mg/kg (only females were tested at this level). The following is a summary of the number of animals dying at dosage levels of 3500 mg/kg and above:

Nominal Dosage Level (mg/kg)	Females No. dying/dosed	Males No. dying/dosed
3500	0/10	-
4000	3/10	-
5000	6/10	-
6000	5/10	-
6300	6/10	-
6400	6/10	-
6450	6/10	-
6500	10/10	-
7000	10/10	2/10
9500	-	6/10
10500	-	6/10
10700	-	9/10
11000	-	10/10

Deaths usually occurred 0-3 days after dosage. The oral LD_{50} values reported are (males) 9250 mg/kg with 95% C.L. of 8259 to 10360 mg/kg; and females: 5420 mg/kg with 95% C.L. of 4517 to 6504 mg/kg. The data for males utilized the findings from 7000 to 10700 mg/kg and for females the findings from 4000 to 6450 mg/kg.

Symptoms:

Females at 3.5 to 7 g/kg (from p. 14): "In all dose levels, the animals' respiration exhibited some degree of change in depth or rate. The animals also exhibited varying degrees of ataxia at all dose levels. By day one...the ataxia had cleared in most of the surviving animals."

"As the dose level increased, the animals began to respond in a more uniform manner for each dose...all animals in a dose group were severely ataxic or cataleptic... (At) 7 g/kg, all animals were cataleptic within 45 minutes."

For males at 7 to 11 g/kg (p. 14): "As with the females, the males' respiration exhibited some degree of change in depth or rate."

"At all dosing levels, the animals exhibited ataxia immediately post dosing. At the higher dose levels, the animals progressed from ataxia to catalepsy. With catalepsy came clear ocular discharge and deep breathing. The males exhibiting catalepsy were less likely to survive than the females (12.9% male survival rate verses 19.3% female survival rate of cataleptic rats). This was not an unexpected response since the males were dosed with almost twice as much test material at all dose levels. However, it should be noted that the males that did survive recovered faster."

NOEL:

At 2500 mg/kg 6/6 females and 2/3 males exhibited ataxia which developed immediately after dosage and persisted for 1-5 hours. No symptoms or indications of toxicity are reported for any animal dosed at 2000 mg/kg.

2. Body weights:

Animals were weighed before dosing, and at 7 and 14 days.

Results:

With the exception of one female at 6450 mg/kg, all 14-day survivors gained weight. Weight gains were generally comparable with those of the negative controls.

3. Necropsy:

"A gross necropsy was performed on all test animals when found dead or 14 days after dosing. The gross necropsy included examination of the adnexa, eyes, thoracic and visceral organs. Animals were sacrificed by CO_2 overdose."

Results:

From p. 15: "Animals...necropsied at the end of the fourteen day observation period had either no gross abnormalities or a slight mottling of the lungs. Those animals which died during the observation period had from one to all the following abnormalities observed: mottled lungs, reddened and or blood filled gastrointestinal tract, and blanching of the liver, kidney and spleen."

D. DISCUSSION:

The findings of this study confirm that females are more sensitive to this formulation than are males, at least with respect to the oral LD_{50} value. The female oral LD_{50} is reported as 5420 mg/kg with 95% confidence limits of 4517 to 6504 mg/kg; the male oral LD_{50} is reported as 9250 mg/kg with 95% confidence limits of 8259 to 10360 mg/kg. The lack of an overlap between these 95% confidence limits is significant. It is also noted (from p. 14) that those males which became cataleptic but subsequently recovered did so more rapidly than females, despite being dosed with more material.

Since the 95% confidence limits for the female oral LD_{50} include values less than 5 g/kg, the Toxicology Branch recommends toxicity category III labeling for this product with respect to its oral hazard potential.

The findings of this study also suggest that younger females may be more susceptible to this formulation than are older ones, although the data are open to more than one interpretation. At 6.45 g/kg, 4/10 females survived, but at 6.5 g/kg all died. The mean weight of the females at the slightly lower dose was 185.5 g; at 6.5 g/kg it was 163.6 g. This suggests that the females at the higher dose level were somewhat younger than those at the lower (those dosed at 6.45 g/kg were dosed on 2/9/88; those at 6.5 g/kg were dosed on 1/14/88, or nearly 4 weeks earlier). However, the dose difference was slightly greater than that suggested by the nominal values given; doses were adjusted only to the nearest 0.1 ml per individual rat. When this is taken into account the mean dose received by females at the 6.45 g/kg dose level was actually 6.31 g/kg, while at 6.5 g/kg the mean dose was 6.54 g/kg. Because of this it can only be stated that younger females might be more susceptible to this formulation than are older ones.

The study does adequately define an acute oral dose NOEL in rats (both sexes) at 2 g/kg.

Overall, the study and its findings are acceptable. The study is classified as core minimum data.