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

C09461

APR 27 1992

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCESMEMORANDUM

SUBJECT: Blockade Domestic Animal Safety Study in Dogs

TO: Lemaster/LaRocca, PM 13  
RD (H7505C)FROM: Byron T. Backus, Ph.D., Toxicologist  
Toxicology Branch 2  
HED (H7509C)Byron T. Backus  
4/22/92THROUGH: K. Clark Swentzel  
Section Head, Review Section 2  
Toxicology Branch 2  
HED (H7509C)K. Clark Swentzel  
4/22/92

and

Marcia van Gemert, Ph.D., Branch Chief  
Toxicology Branch 2  
HED (H7509C)Marcia van Gemert  
4/23/92

Tox. Chem. 77A, 346

Background:

An unreviewed study titled: "Domestic Animal Safety: In Vivo Toxicology Estimation of the Safety Factor of an Aerosol Product in Dogs by Assay of Blood Levels of the Insecticides," was found in the Toxicology Branch 2 files. There was no indication of any action associated with it. This study has now been reviewed, and is being returned to the Product Manager for whatever actions may be appropriate.

Comments and Recommendations:

1. It is noted that this study was not requested by the Agency, and Agency toxicologists had no opportunity to review and/or comment on the protocol before this study was initiated.



2. In this study, dogs were dosed intravenously with Fenvalerate (cumulative dose of 3 mg/kg), DEET (30 and 100 mg/kg) and a combination of the two actives (Fenvalerate at 3 mg/kg and DEET at 30 mg/kg). Blood level measurements of Fenvalerate and/or DEET were then made, and the animals were observed for symptoms of toxicity, and an attempt was made to correlate symptoms with blood levels of DEET and/or Fenvalerate. Subsequently, dogs were dermally exposed to Blockade and blood samples were taken and analyzed for the two actives (no Fenvalerate was detected in any sample; the highest level of DEET observed in a dog exposed to Blockade was 3.27 ppm in an animal receiving approximately 4.5 g Blockade/kg body weight); no symptoms of toxicity were observed in dogs sprayed with Blockade.
3. In animals dosed IV with Fenvalerate, symptoms occurred in 2/4 receiving 3 mg/kg. In those dosed IV with DEET, 0/4 showed symptoms at 30 mg/kg, while 4/4 had symptoms at 100 mg/kg. 4/4 dosed IV with the combination of 3 mg/kg Fenvalerate and 30 mg/kg DEET showed symptoms (ataxia and/or fasciculations and/or tremors).
4. The data are difficult to interpret, particularly with respect to the "safety" of Blockade. Among the conclusions given in the report (p. 8) is: "A more than adequate safety factor exists for an aerosol spray employing 10% DEET and 0.1% Fenvalerate as its active ingredients." However, there is nothing in the text that gives even an approximation of the quantitative value that would constitute "a more than adequate safety factor." In addition to this, there is a question as to the validity of the assumptions made in the protocol of this study that the toxic signs correlate with blood levels of Fenvalerate and/or DEET, and that the findings from IV administration of these actives can be used to calculate a safety factor for dermal exposure, particularly as there appeared to be considerable individual variation in blood levels associated with responses (dog 868, injected with 3 mg/kg Fenvalerate, had no significant symptoms with a maximum blood concentration of 4.31 ppm; dog 903 treated the same way still had symptoms 60 minutes after the last injection with a Fenvalerate blood level of 0.11 ppm).
5. There is no Good Laboratory Practice and/or Quality Assurance Statement within the text of the final report. According to the study protocol (Appendix IV-1, page 9-10, although the pages are not numbered) [REDACTED], will inspect this study during its progress. Data will be examined for completeness, consistency and proper documentation and adherence to protocol." and "Deviations from Good Laboratory Practice Regulations, applicable guidelines and Standard Operating Procedures will be immediately reported to the Study Director."

6. While the study provides some rather intriguing data, it leaves too many unanswered questions. In particular, the study provides no information as to the mechanism(s) involved (Metabolism? Excretion? Deposition in fatty tissues?). Overall, the study is classified as core supplementary data. This study does not satisfy the guideline requirements for either a metabolism (85-1) or domestic animal (86-1) study.

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Reviewed by: Byron T. Backus, Ph.D.  
Section 2, Toxicology Branch 2 (H-7509C)

*Byron T. Backus*  
*4/22/92*

Secondary Reviewer: K. Clark Swentzel  
Section 2, Toxicology Branch 2 (H-7509C)

*K. Clark Swentzel* *4/22/92*

DATA EVALUATION REPORT I

STUDY TYPE: Metabolism (85-1) and Domestic Animal Safety (86-1)

TOX CHEM NO. 77A, 346

MRID NO:

TEST MATERIALS: DEET, Fenvalerate, Blockade formulation

SYNONYMS:

STUDY NUMBER(S): Hartz Test No. 1022

SUBMITTER: Hartz Mountain Corporation  
700 Frank E. Rodgers Blvd.,  
South Harrison, NJ 07029

TESTING FACILITY: [REDACTED]

TITLE OF REPORT: Domestic Animal Safety: In Vivo Toxicology  
Estimation of the Safety Factor of an Aerosol  
Product in Dogs by Assay of Blood Levels of the  
Insecticides

AUTHOR(S): [REDACTED]

REPORT ISSUED: November 1, 1988

CLASSIFICATION: This study is classified as supplementary data.  
It does not satisfy the guideline data requirements  
for either a metabolism (85-1) or domestic animal  
safety (86-1) study.

COMMENTS AND CONCLUSIONS:

1. It is noted that this study was not requested by the Agency, and Agency toxicologists had no opportunity to review and/or comment on the protocol before this study was initiated.

CONFIDENTIAL BUSINESS INFORMATION

2. In this study, dogs were dosed intravenously with Fenvalerate (cumulative dose of 3 mg/kg), DEET (30 and 100 mg/kg) and a combination of the two actives (Fenvalerate at 3 mg/kg and DEET at 30 mg/kg). Blood level measurements of Fenvalerate and/or DEET were then made, and the animals were observed for symptoms of toxicity, and an attempt was made to correlate symptoms with blood levels of DEET and/or Fenvalerate. Subsequently, dogs were dermally exposed to Blockade and blood samples were taken and analyzed for the two actives (no Fenvalerate was detected in any sample; the highest level of DEET observed in a dog exposed to Blockade was 3.27 ppm in an animal receiving approximately 4.5 g Blockade/kg body weight); no symptoms of toxicity were observed in dogs sprayed with Blockade.
3. In animals dosed IV with Fenvalerate, symptoms occurred in 2/4 receiving 3 mg/kg. In those dosed IV with DEET, 0/4 showed symptoms at 30 mg/kg, while 4/4 had symptoms at 100 mg/kg. 4/4 dosed IV with the combination of 3 mg/kg Fenvalerate and 30 mg/kg DEET showed symptoms (ataxia and/or fasciculations and/or tremors).
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A. MATERIALS:

1. Test compounds: Propylene glycol (vehicle), Fenvalerate, Deet, and "an aerosol spray containing 10% Diethyl Toluamide (DEET) and 0.1% Fenvalerate." There is nothing in the report as to the purities, sources, batch numbers or physical characteristics of these test substances. The commercial product is identified in the report text (p. 12) as "A commercially manufactured lot of Blockade containing 10% DEET and 0.1% Fenvalerate as active ingredients." The "Sample No." (Lot No?) is reported as 8340.
2. Test animals: From p. 9: "The test animal group consisted of mongrel canines which had been with the animal colony for a period of time or newly acquired animals which had been vaccinated and quarantined for at least 30 days before testing. Each test group consisted of four animals, two male and two female. Two had been previously exposed themselves to the test substances (DEET and Fenvalerate) and two which (sic) had never been exposed to the test materials." From information in the report, there were 9 test groups. From data in Appendix IV-2 the dogs ranged in age from 1 to 7 years, and in weight (on day 0) from 17 to 67 lbs.

B. STUDY DESIGN:

1. Study purpose: It is stated (p. 7) that in response to the reports of adverse reactions of cats and dogs to Blockade: "the manufacturer decided to undertake studies to determine what, in fact, is the toxic level of each of the active ingredients as well as their combination in the product. It was our recommendation that the best way to develop this information was to establish how much chemical must be introduced into the bloodstream of the animal in order to produce distinct neurological signs. Since the effects on any organ require that the potential toxicant be in the bloodstream for distribution throughout the body, the intravenous route was selected as the best way of determining actual toxicity. Measurements were also necessary to compare the levels reached in the animal treated topically with the aerosol product, and the experimentally determined toxic blood levels in order to assess the true measure of safety."

"Further, since some conflicting literature exists with respect to the transdermal enhancement properties of DEET when used with certain corticosteroids, it was recommended that the potential enhancement of FV by DEET be studied in the dog."

2. Dose selection: From p. 9: "Several range-finding experiments were conducted in the development of the techniques for the method and in the selection of the doses to be employed during the actual test. These experiments revealed:
  - 1) Injection Quantity - All injections were standardized at a total of 0.5 ml/kg. Concentrations of active ingredients were varied within the injectable solution so as to achieve the dosage desired. This injection quantity was well tolerated by the animal and provided ease of handling to the clinician. The actual injection was divided into 5 equal portions each administered 10 minutes apart (total 40 minutes). This was done to keep injection quantity at manageable levels and to maintain a reasonably constant blood level within the animal.
  - 2) Propylene glycol was well tolerated by the animal in the quantities used during the injection. It produced no symptoms nor did it interfere with the assay of either of the active ingredients in the blood.
  - 3) Fenvalerate - 2 mg/kg did not produce any neurological signs. This observation is based upon an I.V. administration in which a low level of DEET (20 mg/kg) was also present in the injection. Since that injection produced no toxic signs, 2 mg/kg was selected as the no effect level while 3 mg/kg was found to be the first effect level.
  - 4) DEET - It was found that 30 mg/kg DEET was the no effect level and 100 mg/kg was the first effect level. 50 mg/kg was equivocal. No other concentrations between these levels were evaluated.
  - 5) Topical Administration - Topical administration was performed in an identical manner to that employed during a recent dermal exposure test submitted to the EPA... A normal application provided that the animal was sprayed until its coat was damp... A heavy application was one in which the animal's coat was visibly wet. For the purpose of this study these two levels were standardized at 1.5 g/kg for the normal application and 4.5 g/kg for the heavy application. Where multiple applications were employed, they were applied at one-hour intervals so as to allow the animal to dry and to allow the active ingredients to accumulate.



6) Some data obtained during method development was actually in the test. The first replicate contains testing performed prior to the actual completion of the test protocols. The data was, however, performed in accordance with draft protocols. The further refinements to the final test protocol did not impact the method of application or the validity of this data."

3. Dose groups: The following were the dose groups:

1. 5 IV injections (10 minutes apart), each injection containing 0.1 ml/kg propylene glycol. Blood samples were analyzed for DEET and Fenvalerate.
2. Five 0.1 ml/kg IV injections (10 minutes apart) of 0.6% Fenvalerate in propylene glycol (cumulative dosage of 3 mg/kg Fenvalerate). Blood samples were analyzed for Fenvalerate.
3. Five 0.1 ml/kg IV injections (10 minutes apart) of 6% DEET in propylene glycol (cumulative dosage of 30 mg/kg DEET). Blood samples were analyzed for DEET.
4. Five 0.1 ml/kg IV injections (10 minutes apart) of 20% DEET in propylene glycol, with a cumulative dosage of 100 mg/kg DEET. Blood samples were analyzed for DEET.
5. Five 0.1 ml/kg IV injections (10 minutes apart) of a mixture of 6% DEET and 0.6% Fenvalerate, with cumulative dosages of 30 mg/kg DEET and 3 mg/kg Fenvalerate. Blood samples were analyzed for DEET and Fenvalerate.
6. A "normal dose" (topical spray application) of Blockade, at a reported rate of approximately 1.5 g/kg (which, in terms of the active ingredients, would be 150 mg/kg DEET and 1.5 mg/kg Fenvalerate). Blood samples were analyzed for DEET and Fenvalerate.
7. A 4X "normal dose" (topical spray application) of Blockade, with a cumulative dose of approximately 6 g/kg (equivalent to 600 mg/kg DEET and 6 mg/kg Fenvalerate). Blood samples were analyzed for DEET and Fenvalerate.
8. A single "heavy dose" of Blockade, applied at approximately 4.5 g/kg (equivalent to about 450 mg/kg DEET and 4.5 mg/kg Fenvalerate). Blood samples were analyzed for DEET and Fenvalerate.
9. Four "heavy dose" applications of Blockade, with a cumulative dosage of about 18 g/kg (equivalent to 1800 mg/kg DEET and 18 mg/kg Fenvalerate). Blood samples were analyzed for DEET and Fenvalerate.



2. Symptoms of Acute Toxicity: The data for individual dogs are presented as "toxicity graphs," using the following scoring classification:

<u>Level</u>	<u>Reaction</u>	<u>Level</u>	<u>Reaction</u>
0	None	4	Fasciculation/Tremor
1	Anxiety	5	Ataxia
2	Salivation	6	Seizures
3	Emesis	7	Death

It is not clear, from the way these scores are reported, whether a dog with a score of 4 ("fasciculations and/or tremors) had exhibited salivation (a score of 2) and/or emesis (a score of 3) before the fasciculations and tremors became evident.

The highest score in this study is a "6" (seizures) for a dog injected with 100 mg/kg DEET; from examination of the graph (Figure V-17) it appears that this occurred following the third injection (so that the dog had received, at that time, a cumulative dose of 60 mg/kg DEET).

The following is derived from Figure VI-1 (the page is not numbered):

<u>Dog #</u>	<u>IV Treatment</u>	<u>Lowest Blood Concentration With Symptoms (+2 or Greater)</u>
868	Fenv. 3 mg/kg	No reaction (Max. blood conc.=4.31 ppm)
903	"	0.11 ppm
992	"	No reaction (Max. blood conc.=2.42 ppm)
982	"	0.5 ppm
948	DEET 30 mg/kg	No reaction (Max. blood conc.=21.23 ppm)
856	"	No reaction (Max. blood conc.=20 ppm)
994	"	No reaction (Max. blood conc.=13.27 ppm)
981	"	No reaction (Max. blood conc.=17.4 ppm)
978	Combination*	0.11 ppm Fenv. (0.69 ppm DEET)‡
865	"	0.22 ppm Fenv. (1.93 ppm DEET)‡
965	"	0.08 ppm Fenv. (0.24 ppm DEET)‡
873	"	0.23 ppm Fenv. (1.07 ppm DEET)‡

\*3 mg/kg Fenvalerate and 30 mg/kg DEET

‡Level of DEET at the time symptoms associated with lowest level of Fenvalerate occurred.

855	DEET 100 mg/kg	18.63 ppm
859	"	29 ppm
888	"	30.95 ppm
984	"	21 ppm

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3. Drop in DEET and Fenvalerate Blood Levels: From p. 6: "It was found that the intravenous first effect toxicity level for FV is 3 mg/kg and for DEET 100 mg/kg. The biphasic half-life for FV in the bloodstream is approximately 15 minutes until it falls below toxic levels. At that point the half-life becomes approximately 2 hours. The half-life for DEET in the bloodstream is approximately 30 minutes at the NOEL and one hour at the first effect level. Assay sensitivities were 10 ppb for FV and 0.2 ppm for DEET... Blood levels were below detection limits after several hours. IV injections of a combination of the two ingredients did not reveal any enhancement of reactions or change in elimination patterns."

The following is derived from Figure V-3:

Dogs Injected IV with 3 mg/kg Fenvalerate		
Minutes after 5th Injection	Average Blood Level of Fenvalerate (ppm)	Half-life
1	2.89	-
10	0.75	4.6 minutes
60	0.11	18.1 minutes

Half-life in the period 1 to 10 minutes after 5th injection.  
 Half-life in the period 10 to 60 minutes after 5th injection.

The following is derived from Figure V-8:

Dogs Injected IV with 30 mg/kg DEET		
Minutes after 5th Injection	Average Blood Level of DEET (ppm)	Half-life
1	17.94	-
10	12.85	18.7 minutes
60	4.46	32.8 minutes

Half-life in the period 1 to 10 minutes after 5th injection.  
 Half-life in the period 10 to 60 minutes after 5th injection.

The following is derived from Figure V-13:

Dogs Injected IV with 100 mg/kg DEET		
Minutes after 5th Injection	Average Blood Level of DEET (ppm)	Half-life
1	55.20	-
10	48.27	46.5 minutes
60	27.01	59.7 minutes
120	14.60	67.6 minutes
180	8.36	74.6 minutes

Half-life in the period 1 to 10 minutes after 5th injection.  
 Half-life in the period 10 to 60 minutes after 5th injection.  
 Half-life in the period 60 to 120 minutes after 5th injection.  
 Half-life in the period 120 to 180 minutes after 5th injection.

The following is derived from Figure V-18:

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Dogs Injected IV with 3 mg/kg Fenvalerate and 30 mg/kg DEET

Minutes after 5th Injection	Average Blood Level of Fenvalerate (ppm)	Half-life
1	3.51	-
10	0.83	4.33 minutes
60	0.32	36.4 minutes

Half-life in the period 1 to 10 minutes after 5th injection.  
 Half-life in the period 10 to 60 minutes after 5th injection.

Dogs Injected IV with 3 mg/kg Fenvalerate and 30 mg/kg DEET

Minutes after 5th Injection	Average Blood Level of DEET (ppm)	DEET Half-life
1	14.30	-
10	8.14	11.1 minutes
60	1.97	24.4 minutes
120	0.61	35.5 minutes

Half-life in the period 1 to 10 minutes after 5th injection.  
 Half-life in the period 10 to 60 minutes after 5th injection.  
 Half-life in the period 60 to 120 minutes after 5th injection.

4. Blood Levels of DEET and Fenvalerate after Blockade Exposure:

No symptoms were observed. No Fenvalerate (detection limit: 0.01 ppm) was found in the blood of any dog. The following maximum blood levels of DEET were observed following topical application of Blockade (from Figure VI-7):

Dog #	IV Treatment	Highest Measured Concentration of DEET in the Blood (ppm)
308	1X ("Normal")	0
986	"	0
991	"	0.38 (60 minutes after treatment)
899	"	0
762	4X "Normal"	1.15 (45 min. after 4th treatment)
993	"	0.72 (30 min. after 4th treatment)
941	"	0
977	"	0.35 (5 min. after 4th treatment)
907	1X "Heavy"	3.27 (3 hr. after treatment)
987	"	0.26 (4 hr. after treatment)
954	"	0
980	"	0.20 (15 min. after treatment)
945	4X "Heavy"	2.20 (30 min. after 4th treatment)
988	"	0.66 (5 min. after 4th treatment)
957	"	0
983	"	1.12 (6 hr. after 4th treatment)



in dogs given 30 mg/kg DEET alone), as all four dogs receiving this combination showed either "level 4" (fasciculations and/or tremors) and/or "level 5" (ataxia) reactions, with symptoms present at 60 minutes in all 4 dogs, and still evident at 3-4 hours in one. This observation suggests that synergism can occur when both Fenvalerate and DEET are administered.

The data indicate that, following IV injection, blood levels for both DEET and Fenvalerate drop fairly rapidly. However, the study provides no information as to the mechanism(s) involved (Metabolism? Excretion? Deposition in fatty tissues?).

A noteworthy observation is that the highest blood level of DEET (3.267, 2 hours after treatment) observed in animals that were sprayed with Blockade was in dog #907, which was in the "1X heavy" group (rather than in the "4X heavy" group). The range in maximum blood levels of DEET in this "1X heavy" group was 0 to 3.27 ppm, suggesting possible differences in individual absorption rates (in the "4X heavy" group it was 0 to 2.20 ppm). It is also puzzling that 907 (see Appendix IV-2) is reported as having been intravenously injected with 20% DEET in propylene glycol on 6/30/88 (with ataxia as a reaction), and yet this dog is not listed among the 4 which received the 100 mg/kg IV dose of DEET.

Overall, the study is classified as core supplementary data. This study does not satisfy the guideline data requirements for either a metabolism (85-1) or domestic animal (86-1) study.

Tox. Chem. No. 77A-346

File Last Updated

Current Date

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, MOEL, LEL	Tox. Cat.	Core-Grade/DOC #
86-1 Domestic Animal Safety Species: Dog Hartz Mountain; Hartz Test No. 1022 11/17/88	Fenvalerate and Deet in Propylene Glycol (administered IV) Hertz Blockade (administered dermally)	not given	Dogs were dosed IV with Fenvalerate (3 mg/kg), DEET (30 mg/kg and 100 mg/kg) and with combination of Fenvalerate & DEET (3 mg/kg and 30 mg/kg respectively). 2/4 dogs dosed IV with Fenvalerate alone showed symptoms; 0/4 dosed IV with 30 mg/kg DEET had symptoms, but 4/4 dosed with 100 mg/kg DEET showed signs of toxicity. 4/4 dogs dosed with the combination showed signs of toxicity (ataxia and/or tremors and/or fasciculations) and symptoms lasted longer than in those receiving 3 mg/kg Fenvalerate alone. Symptoms were observed in one dog with concurrent blood levels of 0.08 ppm Fenvalerate and 0.24 ppm DEET. There was considerable variation between individual dogs with respect to correlation of toxic signs and blood levels of the actives (one dog dosed IV with 3 mg/kg Fenvalerate had symptoms associated with 0.11 ppm blood level of this active; another dog in the same group had no symptoms and a maximum blood level of 4.31 ppm). No Fenvalerate was observed (detection limit: 0.01 ppm) in blood of dogs sprayed with Blockade; highest value for DEET in blood of a dog sprayed with Blockade was 3.27 ppm. No toxicity was observed in dogs sprayed with Blockade (highest dose: 6 g/kg).		Supplementary

Dogs were dosed IV with Fenvalerate (3 mg/kg), DEET (30 mg/kg and 100 mg/kg) and with combination of Fenvalerate & DEET (3 mg/kg and 30 mg/kg respectively). 2/4 dogs dosed IV with Fenvalerate alone showed symptoms; 0/4 dosed IV with 30 mg/kg DEET had symptoms, but 4/4 dosed with 100 mg/kg DEET showed signs of toxicity. 4/4 dogs dosed with the combination showed signs of toxicity (ataxia and/or tremors and/or fasciculations) and symptoms lasted longer than in those receiving 3 mg/kg Fenvalerate alone. Symptoms were observed in one dog with concurrent blood levels of 0.08 ppm Fenvalerate and 0.24 ppm DEET. There was considerable variation between individual dogs with respect to correlation of toxic signs and blood levels of the actives (one dog dosed IV with 3 mg/kg Fenvalerate had symptoms associated with 0.11 ppm blood level of this active; another dog in the same group had no symptoms and a maximum blood level of 4.31 ppm). No Fenvalerate was observed (detection limit: 0.01 ppm) in blood of dogs sprayed with Blockade; highest value for DEET in blood of a dog sprayed with Blockade was 3.27 ppm. No toxicity was observed in dogs sprayed with Blockade (highest dose: 6 g/kg).

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