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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id No.: 002596-RGT. Hartz One Spot Repellent for Dogs. Review of a domestic animal safety study.

TOX CHEM No.: 652BB
PC No.: 109701
Barcode No.: D210681
Submission No.: S479497

FROM: John Doherty, Ph.D., D.A.B.T. 4/10/96
Section IV, Toxicology Branch I
Health Effects Division (7509C)

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Product Manager #13
Registration Division 7509C

THROUGH: Marion Copley, DVM 4/11/96
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CONCLUSION/DISCUSSION

The series 86-1 domestic animal safety study with dogs (MRID No.: 43137201 and 43447101) with the product Hartz Mountain One Spot Repellent for Dogs (a.i. 45% permethrin) as reviewed and determined to be SUPPLEMENTARY. Several serious study deficiencies preclude upgrading this study. A new series 86-1 domestic animal safety study will have to be conducted and presented and determined to be ACCEPTABLE in order to support the registration of this product. It is suggested that the protocol for this study be submitted to the Agency for review.

II. Background and Action Requested

The Hartz Mountain Corporation (refer to letter from Pat Bieler dated February 22, 1994) has submitted a domestic animal safety study with their product Hartz One Spot Repellent for Dogs. This study is identified in Part IV below and was reviewed and determined to be SUPPLEMENTARY. A DER is attached. The following comments apply.

III. Toxicology Branch Comments

1. Study Deficiencies. The following study deficiencies were noted.

a. This study report is poorly organized and there are no summary tables verifying that there were hourly and daily assessments of the conditions of the dogs. There is only one set of actual data that displays the body weight data.

b. There were no control dogs included.

c. The study follows an unconventional method in attempting to attain a 4X application that was actually not a 4X dose but a 1X dose at weekly intervals. In domestic animal safety studies, a 4X the label usage rate is applied in a single dose. For example, if the usage rate is 1 ml/dog, a 4X application is 4 ml/dog applied as a single dose.

d. The study uses some "puppies" of 4 or 5 months of age. There were also only 3 "puppies" of each sex. The optimal number for subjects in a dose group for a domestic animal safety study is considered to be 6/sex for each age group assessed (i.e. adults or puppies and a specified age). TB-I does not consider that this study actually assessed puppies. It is also noted that "puppies" are considered distinct from adults and when a study is conducted to assess for the effects on puppies (or kittens), each dose group is supposed to have 6 subjects/sex. Thus, a study that includes one or two "puppies" in the group of 4-6 total is not really assessing "puppies".

2. Replacement Study. A replacement study that assesses controls, 1X, 3X and 5X the label dosage rate will have to be conducted in order to support the registration of this product. This study needs to consist of 6 dogs/sex/dose group for each age group assessed. If the registrant wants to register this product for use on puppies a second study using puppies (6/sex/dose group) of a defined age (i.e. 8 weeks) that is consistent with the label instructions will also need to be submitted.

The registrant is welcome to submit the protocol for this study to the Agency for review prior to initiation of the study.

In the design of this study, the registrant should be advised of the following "general guidance" provided by the recently created HED domestic animal safety study workgroup.

> The workgroup considers the optimum number of animals for Domestic Animal Safety Studies to be six/sex/age group. This will be formalized when the guidelines are approved. It should be noted that puppies and kittens should be considered as separate groups/sex from adults. Adult dogs and cats are considered 6 months of age or greater.
>
> The groups should be treated with doses adequate to assure that there is a 5X margin of safety (eg. control, 1X, 3X, 5X). **All** treatment groups should have adequate numbers of animals, not just the 5X group. An alternative dosing regimen (**Limit Dose**) with only control (6/sex) and 5X (6/sex) treated groups can be used in lieu of the 1, 3, and 5X dose study. The same treatment procedures should be used as indicated on the label. The retreatment interval will depend on the labelled use of the product and the expected margin of safety. If a 5X margin of safety is determined, no retreatment is necessary for products with retreatment intervals greater than 14 days. Protocols may be submitted to EPA for review prior to initiation of the study.

2. Additional note. TB-I also notes that the registrant may change the product to be packaged as a 25 cc container. This larger container would not assure that the product was being applied at the proper dosage since for most pet owners there is no sure way to measure the 1 cc needed for a dog < 30 pounds. TB-I advises against packaging this product in a 25 cc container since it could lead to application rates that are inconsistent with the study demonstrating this products safety to dogs.

* Claimed confidential by submitter*

IV. Studies Reviewed

Study Identification	Material	MRID No.:	Results	Classification
86-1. Domestic animal safety study-dogs. [redacted] Study No.: 1219, February 1, 1993.	Hartz One Spot Repellent for Dogs (45% permethrin)	43137201 and 43447101	In a domestic animal safety study (MRID No. 43137201 and 43447101) a group of 30 (4 months to 13 years) dogs (14 males and 16 females) of mixed breeds were given a single application of 1 ml/dog if the dog was < 35 lbs and 2 ml/dog if the dog was > 35 lbs of the product Hartz One Spot Repellent for Dogs (a.i. 45% permethrin) weekly for 12 applications and after a three week interval were again treated with 2 ml and 4 ml/dog as a single application. This protocol is considered inappropriate for a series 86-1 domestic animal safety study because untreated controls were not included and the dose levels were not applied as 4X the label usage rate based on a single application. Treatment of dogs under this protocol did not result in reactions of any kind when compared to the pretreatment condition of the dogs. This study is SUPPLEMENTARY.	SUPPLEMENTARY

EPA Reviewer: John Doherty, Ph.D., D.A.B.T., Date 4/8/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copey, DVM, Date 4/10/96
Review Section IV, Toxicology Branch I 7509C)

DATA EVALUATION RECORD

STUDY TYPE: Domestic Animal Safety Study - dogs (mixed breed) [§86-1]

DP BARCODE: D210681 SUBMISSION CODE:S479497
P.C. CODE: 109701 (others) TOX. CHEM. NO.: 652BB (others)

TEST MATERIAL (PURITY): Hartz One Spot Repellent for Dogs. (~45% permethrin formulation).

CITATION: [redacted] (1993) "Effect of a 4X Plus a 2X Dose Treatment of Dogs and Puppies", [redacted] Study No.: 1219, February 1, 1993. MRID No. 4337201 and 43447101. Unpublished.

SPONSOR: Hartz Mountain, Corporation, Harrison, N.J.

EXECUTIVE SUMMARY: In a domestic animal safety study (MRID No. 43137201 and 43447101) a group of 30 (4 months to 13 years) dogs (14 males and 16 females) of mixed breeds were given a single application of 1 ml/dog if the dog was < 35 lbs and 2 ml/dog if the dog was > 35 lbs of the product Hartz One Spot Repellent for Dogs (a.i. 45% permethrin) weekly for 12 applications and after a three week interval were again treated with 2 ml and 4 ml/dog as a single application. This protocol is considered inappropriate for a series 86-1 domestic animal safety study because untreated controls were not included and the dose levels were not applied as 4X the label usage rate based on a single application.

Treatment of dogs under this protocol did not result in reactions of any kind when compared to the pretreatment condition of the dogs.

Classification. This domestic animal safety study is classified as SUPPLEMENTARY because of numerous deficiencies noted (refer to below for discussion) cannot be upgraded. This study does not satisfy the series 86-1 guideline requirement for a domestic animal safety study for the product Hartz One Spot Repellent for Dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality (some restrictions to confidentiality were stated) were provided.

* Claimed confidential by submitter*

011887

[Hartz One Spot/1993] Domestic Animal Safety (86-1)

Review

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:
Description: Hartz One Spot Repellent for Dogs
Lot/Batch #: 10009
Purity: 48.11% a.i. (permethrin)

3. Test animals: Species: dogs
Strain: mixed breeds
Age at dosing: 24 adults (between 1 and 13 years), 6 puppies (3, 4 months and 3, 5 months)
Weight at dosing: 4.2 to 70 lbs.
Source: [redacted]
Acclimation period: None
Diet: Commercial dog food (feeding schedule not described).
Water: Not specified, ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: Approximately Late September, 1992; end: Approximately January 18, 1993.

2. Animal assignment and treatment -

TABLE 1. Dose levels and treatment schedule

Dose (ml/dog)[1]	males	Females	Dose (ml/dog)[2]
2 > 35 lbs	6	6	4
1 < 35 lbs	5	7	2
1 (pups)[3]	3	3	2

[1] Dose level applied weekly for with 1 or 2 ml of the test material for a total of 12 applications. Dogs were dosed with 2 ml if they weighed more than 35 lbs and 1 ml if they weighed less than 35 lbs.
[2] Dose level applied three weeks after the last weekly application of the lower dose rate.
[3] Pups were 4 or 5 months of age.

The dose levels of 2 or 1 ml/kg are reportedly based on the label usage rate. The dogs < 35 lbs were treated by applying 1 ml between the shoulder blades. Dogs > 35 lbs were treated with an additional 1 ml applied directly above the base of the tail. Although the label actually specifies that 30 lbs is the cutoff for the application of 1 or 2 ml, this difference in 30 and 35 lbs is not considered meaningful.

Three weeks after the last weekly application of 1 or 2

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ml, the dogs greater than 35 lbs were dosed with a total of 4 ml and the dogs less than 35 lbs were dosed with a total of 2 ml. It was stated that each of the dogs was fasted for 13 hours prior to application of the test material. This probably means that the dogs were treated in the morning before they were fed.

Following treatment the dogs were said to be continuously observed for signs of intoxication or adverse reactions for a minimum of 8 hours (at least once per hour). The dogs were then assessed daily. Each dog was reportedly given a "thorough physical examination, including body weight" prior to dosing nd at weeks 4, 8, 12 and 17.

3. Statistics - No statistical assessments were made.

II. **RESULTS AND DISCUSSION:**

A. Mortality. All dogs survived the scheduled experimental period.

B. Clinical observations - No reactions to treatment were noted. The physical exams were unremarkable except for one dog with a non-compound related infection. TB-I bases its conclusion on inspection of the individual animal physical examination data sheets which did not report any significant reactions to treatment.

C. Body Weight - No effects of treatment on body weight were noted. A data table was presented.

D. Deficiencies -

1. This study report is poorly organized and there are no summary tables verifying that there were hourly and daily assessments of the conditions of the dogs. There is only one set of actual data that displays the body weight data. The results of the periodic physicals are handwritten.

2. There were no control dogs included.

3. The study follows an unconventional method in attempting to attain a 4X application that was actually not a 4X dose but a 1X dose at weekly intervals. In domestic anmial safety studies, a 4X the label usage rate is applied in a single dose. For example, if the usage rate is 1 ml/dog, a 4X application is 4 ml/dog applied as a single dose.

4. The study uses some "puppies" of 4 or 5 months of age. There were also only 3 "puppies" of each sex. The optimal number

is considered to be 6/sex. TB-I does not consider that this study actually assessed puppies.

DISCUSSION. This study is being classified as SUPPLEMENTARY because of the deficiencies listed above. The study is considered to contain some useful information in that the dogs were demonstrated to tolerate 13 doses of the test material without any apparent signs of reaction. A repeat study which assesses controls, 1X,, 3X and 5X the label usage rate is required to support the registration of this product.

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Chemical:	**Permethrin, mixed cis,trans**
PC Code:	**109701**
HED File Code	**13000 Tox Reviews**
Memo Date:	**04/12/96**
File ID:	**TX011887**
Accession Number:	**412-02-0280**

HED Records Reference Center
04/09/2002