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

Office of Prevention, Pesticides
and
Toxic Substances

MEMORANDUM

~~August 10, 2001~~

SUBJECT: **Review of Incident Data for Four Hartz Mountain Flea and Tick Control Products (2596-146, -147, -148 and -150)**

DP Barcodes: D276262 (Registration # 2596-150)
D276263 (Registration # 2596-148)
D276274 (RF 9804 Topical)
D276701 (Registration # 2596-147)
D276720 (Registration # 2596-146)
D277612 and D277613 (label amendments for 2596-148 and 2596-151)

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EXECUTIVE SUMMARY

Detailed incident reports for Categories D-A (death) and D-B (major events) on four Hartz Mountain products [**2596-146** Control One-Spot for Dogs (2.9% methoprene and 45% permethrin), **2596-147** Control One-Spot for Cats (2.9% methoprene), **2596-148** Advanced Care Flea and Tick Drops for Cats (85.7% d-phenothrin and 2.9% methoprene) and **2596-150** Advanced Care Flea and Tick Drops

for Dogs (85.7% d-phenothrin and 2.9% methoprene) were reviewed. Data were available from 3rd quarter 1998 through 4th quarter 2000 for products 2596-146 and 2596-147 and from 1st quarter 2000 through 4th quarter 2000 for 2596-148 and 2596-150. The detailed data were requested due to large numbers of incidents reported in the quarterly aggregate reports for these products. The registrant, Hartz Mountain, maintains that the following number of incidents should have been classified as D-C (minor events): 3 for 2596-146, 30 for 2596-147 and 46 for 2596-148.

The incidents (number of affected animals) were categorized as to whether the product was responsible for the adverse event using the following categories: definite, probable, possible, unlikely, unrelated and unknown. If an incident report was from the ASPCA/National Animal Poison Control Center, their causality category was used. For product **2596-146**, the majority of deaths (141/239, 59%) involved cats which were accidently or intentionally treated with the product. In addition, 17/239 (7%) cats exposed to treated dogs died. Permethrin toxicosis was the cause of death in the majority of cats. Clinical signs of toxicity prior to death included tremors, seizures and ataxia, which were reported in a majority of cats exposed to 2596-146. One death in dogs was categorized as probable and another as possible. The majority of the D-B (major events) cases [316/346 (91%)] were reported in cats treated directly (294/316, 93%)with 2596-146 or exposed to treated dogs (22/316, 7%). Clinical signs of toxicity included those reported for the D-A cases, i.e., tremors, seizures and ataxia. Only 30/346 (9%) of the D-B incidents were reported in dogs. Six cases in dogs were categorized as probable or possible.

For product **2596-147,** there were a total of 202 deaths reported for 2596-147, 75 (37%) of which were considered unlikely due to product exposure, using NAPCC categorization. A total of 109/202 (54%) were unknown, mostly due to lack of detailed information. NAPCC toxicologists appear to have been convinced that cats reported to have neurological clinical signs of toxicity prior to death were either: 1) exposed to another insecticide used for adulticide control (methoprene is only an insect growth regulator); 2) accidently or intentionally treated with 2596-146; or 3) exposed to dogs treated with 2596-146 or another concentrated permethrin product. In the NAPCC reports, there are notations in the narrative sections where the toxicologists repeatedly questioned owners and veterinarians about such exposure. Even if owners insisted that a cat was exposed only to 2596-147, an incident was still categorized as doubtful (unlikely using EPA categories). However, 5 cases were categorized as probable or possible. Nine cases of liver failure, including two cats from one household, were diagnosed in the D-A incidents with 2596-147. Findings of liver failure were supported in one of two companion animal safety studies in which 2/5 kittens treated at 5x the recommended dose had elevation of liver enzymes. However, in another companion animal safety study, there was no elevation in liver enzymes when kittens were treated at 5x the recommended dose for four weekly intervals.

The majority (109/169, 64%) of the D-B incidents were categorized as unlikely caused by 2596-147. As with the D-A cases, NAPCC toxicologists were reluctant to conclude that a methoprene-only product could be responsible for the incidents. In 128/169 (76%) of the cats, the clinical signs of tremor and/or seizures were reported. The incidents in three cats were categorized as probable or possible.

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There were multiple cases in the D-A and D-B incidents in which cats experienced possible dermal hypersensitivity. Clinical signs observed in 2 hours or less of product application included hyperactivity, nervousness, trying to bite at application site, hissing, agitation, tachycardia, dyspnea and panting.

For product **2596-148**, the majority of the incident reports in cats for the D-A category were from Hartz Mountain and did not contain sufficient information to establish a cause of death. Of the total 35 cats involved, 13 were reported to have the neurological signs of tremors and/or seizures prior to death. One cat may have had an anaphylactic reaction to the product. Of the 104 total cats which experienced major events, the product was definitively associated with the reaction in 8 cats, probably associated in 10 cats and possibly associated in 46 cats. Of the 104 cats, 91 were reported to have tremors and/or seizures.

For product **2598-150**, there were five reports of deaths involving 4 dogs and 1 cat. The cat had seizures six hours after application and died possibly as a result of the seizure control treatment. In three of the dog cases, there was not enough information to categorize the cause of the death. In the fourth dog, the case was categorized as unlikely. There were two D-B reports involving 1 dog and 3 cats. The dog was reported to have seizures 11 hours after product application. The three cats had neurological signs and breathing difficulties.

There was some evidence of **possible packaging mix-up** in the incident data. Based on internal communication, it is possible that the dog product 2596-146 was accidently placed into packaging for the cat product 2596-147.

Five **companion animal safety studies** were reviewed. In two studies (MRIDs 45410906 and 45435901) conducted with a 3.0% methoprene, cats or kittens were administered 5x the recommended dose. Both studies were classified as unacceptable because they did not meet guideline requirements. In one study, signs of toxicity were observed at 5x the recommended dose; therefore, a 3x level should have been tested. In the other study, animals were not observed for clinical signs of toxicity immediately after product application.

A study conducted in adult cats and kittens with a 95.7% d-phenothrin and 3.09% methoprene product (MRID 44864007C) was also unacceptable. Adult cats treated at 5x the recommended dose had excessive salivation, restlessness and scratching. There was decreased body weight gain and food consumption in adult cats and male kittens. A full study using 3 dose levels should have been conducted instead of the limit test since there was evidence of toxicity at the 5x dose. Companion animal safety studies in puppies (45006402C) and adult dogs (45006403C) with this product were acceptable and demonstrated no evidence of toxicity at 5x the recommended dose.

Acute toxicity studies (MRIDs 45410901 through 45410905) conducted with Hartz Test Sample #11146 (3% methoprene) demonstrated that it is has low acute oral and dermal toxicity, is not a dermal or eye irritant and is not a dermal sensitizer in laboratory animals.

Proposed **label amendments** for products 2596-148 and 2596-150 (85% d-phenothrin for use on dogs and cats) were reviewed. Hartz Mountain is proposing adding the following to the label. "Cats don't like to get wet and can try to remove moisture by licking or rubbing the area, twitching, running away or shaking. They can send ripples down their back which may look like tremors. After treatment with this product, your pet may exhibit these normal behavior patterns. You will need to differentiate these patterns from an adverse reaction by considering whether they are similar to your experience when your cat's back gets wet with plain water or are more serious. This product is oil based and your pet may sense the moisture from it until it dries in about 24 hours."

RECOMMENDATIONS

1. The EPA Office of Enforcement and Compliance Assurance should be asked to sample available product 2596-147 from market outlets across the country, especially those likely to have old product on hand (e.g., hardware and garden stores) and have the product tested for composition.

2. The possibility of packaging problems should be thoroughly explored to determine if and when it occurred, which products were involved, how much product was mixed up and what actions Hartz Mountain took to rectify the situation. EPA laboratory audits of manufacturing facilities should be included in this effort. Until OPP knows if contamination occurred, it is not possible to clearly determine if any of the D-A or D-B incidents in cats with 2596-147 were due to the registered product (methoprene only).

3. It is recommended that product 2596-148 be re-evaluated for its safety in cats. There is significant evidence from the incident data that some cats develop neurological signs of toxicity after exposure. A margin of safety was not been established in the companion animal safety studies. Therefore, studies should be repeated. It is unclear how the stripe-on method of application contributes to the toxicity, i.e., whether the toxicity observed in some cats and not others is due to ingestion, along with dermal absorption, of the product. However, other pyrethroids, such as permethrin, are extremely toxic in cats at a lower percentage of active ingredient.

4. It is strongly recommended that the proposed labeling for products 2596-148 and 2596-150 not be accepted. Many incidents for 2596-148 from the NAPCC in which tremors were reported were categorized as high, medium or low suspicion that the product was the cause of the adverse reaction. The proposed labeling revisions may cause owners to delay treatment of potentially fatal neurological signs of toxicity. Early, aggressive treatment of pyrethrin/pyrethroid toxicity often results in full recovery but pets not receiving aggressive care may die.

5. The registrant has misintepreted the 6(a)(2) regulations in classification of D-B and D-C categories. Surviving animals which experience seizures should be classified as D-B (major events). (Tremors would not normally be considered life-threatening; however, they may progress to seizures in many cases.) The registrant should be notified, that until further notice, separate reports should be filed on

each case involving seizures, tremors or other significant signs (D-A, D-B, D-C) as a condition of continued registration.

6. Label revisions of concentrated permethrin products to warn pet owners about the dangers of permethrin toxicity in cats directly treated or exposed to treated dogs should be required.

7. Incidents with product 2596-147 should continue to be monitored for evidence of liver failure and dermal hypersensitivity reactions. As a condition of continued registration, the registrant should be required to submit detailed reports on all such reactions.

8. The registrant should submit the missing reports listed on page 20 of this review.

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I. BACKGROUND

In a March 13, 2001 letter from the Office of Pesticide Programs' 6(a)(2) Officer, detailed incident data were requested on four Hartz Mountain flea and tick control products for use on dogs and cats. The products, registration numbers, active ingredients and registration dates are as follows:

Reg. No. 2596-146: Control One-Spot for Dogs
2.9% methoprene and 45% permethrin
Registered 7/29/97

Reg. No. 2596-147: Control One-Spot for Cats
2.9% methoprene
Registered 5/14/98

Reg. No. 2596-148: Advanced Care Flea and Tick Drops for Cats
85.7% D-phenothrin and 2.9% methoprene
Registered 12/10/98

Reg. No. 2596-150: Advanced Care Flea and Tick Drops for Dogs
85.7% D-phenothrin and 2.3% methoprene
Registered 1/23/00

Under the current 6(a)(2) summary reporting practices, incidents of adverse reactions in domestic animals may be accumulated for three months and submitted to EPA two months later.[1] Incidents are categorized according to severity as follows:

D-A: Domestic Animal Death (death or euthanasia)
D-B: Domestic Animal Major (clinical signs which may have been life-threatening or resulted in residual disability)
D-C: Domestic Animal Moderate (clinical signs which are more pronounced, more prolonged or of a more systemic nature than minor signs)
D-D: Domestic Animal Minor (clinical signs which are minimally bothersome)
D-E: Signs Unknown, Unspecified or May Appear in Future (clinical signs are unknown or not specified)

Registrants are required only to report the number of animals in each category. Neither the species of animal nor the nature of the alleged adverse reaction is included. However, if OPP has concern about the number of incidents reported for a product, detailed information on the incidents may be requested.

The March 13 letter requested detailed information on the incidents in categories D-A and D-B with the above four products due to the large numbers in the aggregate reports. The letter also noted that

[1] PR Notice 98-3

thousands of minor incidents have been reported by the sponsor. Additional information requested included any data on the safety of the active ingredients (methoprene, permethrin and d-phenothrin) or products containing these chemicals registered for use on dogs and cats. Data submitted to the Food and Drug Administration on these chemicals was also requested. (An oral methoprene product is approved for use in dogs.)

II. DATA SUBMITTED

The registrant has submitted the following data:

1) Detailed reports on the alleged adverse incidents for the four products, along with the company's assessment of causality categories and incident rates of the adverse events based on product sales

2) MRID 45435901 - Companion Animal Safety Study in Juvenile Cats with RF 9804 Topical (methoprene), conducted by Wellmark International

3) MRID 45410906 - Companion Animal Safety Study in Kittens with Hartz Test Sample #11146 (methoprene)

4) MRID 44864007C - Companion Animal Safety Study in Kittens with Liquid Once-a-Month Stripe-on Product (methoprene and d-phenothrin)

5) MRID 45006402C - Companion Animal Safety Study in Puppies with TS 11506 (methoprene and d-phenothrin)

6) MRID 45006403C - Companion Animal Safety Study in Dogs with Product 11506 (methoprene and d-phenothrin)

7) Five acute studies (MRIDs 45410901 through 45410905) with Test Sample #11146 (methoprene)

8) Freedom of Information Summary for New Animal Drug Application (NADA 141-162), oral methoprene product for use in dogs

9) Label amendment for products 2596-148 and 2596-150

III. INCIDENT DATA REVIEW

A. Overview of Registrant's Submission and Categorization

Hartz Mountain has conducted a review of the incident data on the four products and assigned the following codes:

Misuse/Misapplication
Multiple Products Use
Non Product Related
No Confirming Information
Misclassified (using EPA's D-A, D-B, etc.)
Other
Possible Product Involvement

No criteria for assigning the codes were submitted. Hartz's assessment of the number of incidents in each EPA category (i.e., D-A and D-B) for the 4 products is presented in Attachment Table 1. Incidents for 4th quarter 2000 are included, whereas the March 13 letter from OPP only requested data from 3rd quarter 1998 through 3rd quarter 2000. According to the registrant's categorization, the majority of D-A [142/219 (65%)] and D-B [272/304 (89%)] incidents for **2596-146** were due to misuse of the product. Only 16/219 (7%) of the D-A and 11/304 (4%) of the D-B incidents were possible product involvement. With **2596-147**, only 19/209 (9%) of the D-A and 19/162 (12%), of D-B cases were possible product involvement. The most represented categories were non product involvement [60/209 (29%) for D-A and 26/162 (16%) for D-B] and no confirming information [83/209 (40%) for D-A and 42/162 (26%) for D-B]. For **2596-148**, the majority of the incidents in the D-A category were no confirming information [20/37 (54%)], while in the D-B category, most of the incidents were either misclassified [46/93 (49%)] or no confirming information [30/93 (32%)]. Only 3/37 (8%) D-A and 5/93 (5%) D-B were categorized as possible product involvement. For **2596-150**, only 1/5 (20%) D-A incident was categorized as possible product involvement.

Misclassification was used mostly for incidents in the D-B category which the registrant thought should be in the D-C category. The only criteria offered as a basis for the misclassifications were hand-written statements on some of the incident reports that animals did not suffer life-altering effects.

The majority of the incident reports on some of the products are from the ASPCA/National Animal Poison Control Center (NAPCC), which is a 24-hour emergency hotline for animals similar to human poison control centers. It is staff by veterinary toxicologists who provide diagnostic and treatment recommendations. Complete records on each call, including follow-up conversations to determine the outcome of a case are maintained in a database. Causality categories are assigned to cases considering assessments such as assurance of exposure and identity of alleged agent, time between exposure and reaction and consistency of reaction with known mechanism of toxicity of a chemical. The major causality categories are high suspicion, medium suspicion, low suspicion, doubtful and unknown assessment.

Other incident reports came from data collected by Hartz Mountain in the form of Consumer Relations telephone record forms or email messages. Some of this information is very brief and does not give enough detail to assign a causality category while others are detailed. If a consumer complains about a product harming a pet, the company requires submission of a

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letter describing the event, a statement from the veterinarian(s) involved and return of used packaging for the product. Reimbursement for product and/or veterinary expenses is based on this information. This type of report often includes a very detailed history of clinical signs, treatment and outcome.

B. Incident Rates Calculated by Hartz Mountain

Based on the sales of the four products, Hartz Mountain has reported the following total incident rates.

Product	D-A	D-B
2596-146	0.0008%	0.001%
2596-147	0.001%	0.0009%
2596-148	0.001%	0.003%
2596-150	0.0001%	0.00005%

The ratios are calculated based on the amount of product sales (denominator). The number of incidents (numerator) is not provided so it is unclear if the calculations were done subtracting those incidents which Hartz Mountain thinks are misclassified as D-B and should be D-C.

C. EPA Review of the Incident Data

The detailed incident data were reviewed and the following EPA causality categories assigned to the cases: definite, probable, possible, unlikely, unrelated and unknown. In general, the EPA reviewer relied on the professional judgment and experience of the NAPCC veterinary toxicologists in assigning causality categories for those incident reports prepared by the NAPCC. EPA causality categories were translated from those of NAPCC as follows:

High Suspicion = Definite
Medium Suspicion = Probable
Low Suspicion = Possible
Doubtful Suspicion = Unlikely
Unknown = Unknown

Cases where an animal's health problems were clearly due to another disease condition, toxin, trauma, etc., were classified as unrelated. Reports prepared by Hartz Mountain were categorized as best possible based on the level of detail in the information provided. **The number of animals (as opposed to number of cases) were considered in categorizing incidents**. It should be emphasized that the number of animals in each category is an estimate.

In some reports, multiple animals were treated with the products: the number affected and the final outcome were not always clear.

1. Product 2596-146 (Control One-Spot for Dogs)

D-A

The EPA causality categorization of the D-A incidents for product 2596-146 is presented in Attachment Table 2. Although the product is registered for use on dogs, the majority of deaths (141/239, 59%) involved cats which were accidently or intentionally treated with the product. In addition, 17/239 (7%) cats exposed to treated dogs died. Permethrin toxicosis was the cause of death in the majority of cats. Clinical signs of toxicity prior to death included tremors, seizures and ataxia, which were reported in a majority of cats exposed to 2596-146. (See Discussion/Conclusions section for additional information on permethrin toxicity in cats.)

Permethrin is usually well-tolerated by dogs. In the analysis of the D-A cases for 2596-146, one incident in dogs was categorized as probable and one as possible. A 7 year-old Bichon Frise was vocalizing and crying 1 hour after product application with erythema of the skin at 18 hours and vomiting at 20 hours. The signs progressed to tremors, shock, tachycardia and death 2½ days after application. A necropsy was performed but no cause of death could be established. The NAPCC categorized the death as low suspicion (possible using EPA categories). In another case, a 3-month old unknown breed dog had anorexia, vomiting and depression 5-6 hours after product application. It was found dead at 20 hours. Although the dog may have been exposed to other insecticidal products, NAPCC classified this incident as medium suspicion (probable using EPA categories).

Unfortunately, many of the dog cases (39/81, 48%) did not have sufficient detail to assess causality. Missing details included information such time course of the reaction, examination by a veterinarian and necropsy if the cause of death was unknown.

D-B

The EPA causality categorization of the D-B incidents for product 2596-146 is presented in Attachment Table 3. The majority of cases of major events [316/346 (91%)] were reported in cats treated directly (294/316, 93%)with 2596-146 or exposed to treated dogs (22/316, 7%). Clinical signs of toxicity included those reported for the D-A cases, i.e., tremors, seizures and ataxia. Only 30/346 (9%) of the D-B incidents were reported in dogs. Clinical signs associated with the cases categorized as probable or possible included the following:

dog possible: poodle- tremor, cyanosis, dyspnea 1 hr after application
Australian shepherd - seizures 2 days after application
Jack Russell terrier - convulsions, vomiting 12 hrs after application
Jack Russell terrier - ataxia, dilated eyes, seizures 20 minutes after application

dog probable: Boston terrier - tremor, dyspnea, nystagmus 2 hrs after application
Chihuahua - tremors, pruritis 14 hrs after application

2. Product 2596-147 (Control One-Spot for Cats)

D-A

The EPA causality categorization of the D-A incidents for product 2596-147 is presented in Table 4. There were a total of 202 deaths reported for 2596-147. 75 (37%) of which were considered unlikely due to product exposure. A total of 109/202 (54%) were unknown, mostly due to lack of detailed information.

As indicated previously, the EPA reviewer relied on the causality categorization assigned by the NAPCC. The active ingredient in 2596-147, methoprene, is generally considered to be nontoxic. The only expected toxicity is mild gastrointestinal upset with small ingestion.[2] Therefore, NAPCC toxicologists appear to be convinced that cats reported to have neurological clinical signs of toxicity prior to death were either: 1) exposed to another insecticide used for adulticide control (methoprene is only an insect growth regulator); 2) accidently or intentionally treated with 2596-146; or 3) exposed to dogs treated with 2596-146 or another concentrated permethrin product. In the NAPCC reports, there are notations in the narrative sections where the toxicologists repeatedly questioned owners and veterinarians about such exposure. Even if owners insisted that a cat was exposed only to 2596-147, an incident was still categorized as doubtful (unlikely using EPA categories). However, 5 cases were categorized as probable or possible. The clinical signs observed in these animals included:

Probable: salivation, panting, hypothermia 6 hrs after application, seizures and death later
Probable: weakness, depression, bradypnea 2 hrs after application, died during treatment
Possible: tremors 15 minutes after application, seizures at 16 hours, euthanasia due to poor response to treatment, applied product to open sore
Possible: convulsions, bleeding from mouth 2 hrs after application, death
Possible: seizure and paresis 2 hrs after application, death

Eight cases were noted to have immediate reactions possibly indicative of dermal hypersensitivity. Clinical signs observed in 2 hours or less of product application included hyperactivity, nervousness, trying to bite at application site, hissing, agitation, tachycardia, dyspnea and panting. These animals later developed other signs which lead to their death or euthanasia. The product may have caused the immediate reaction but the death was categorized as unlikely.

It is noted that 9 cases of liver failure, including two cats from one household, were diagnosed in the D-A incidents with 2596-147. Necropsy was performed on two animals with a diagnosis

[2] Notation on case report form from NAPCC

of hepatic lipidosis. On one pathology report, it is stated that hepatic lipidosis can be caused by prolonged anorexia, which did occur with this cat, but anorexia alone does not usually cause this degree of severity. Although there are many causes of liver failure in cats, elevation of liver enzymes was reported in 2/5 kittens treated with 5x the recommended dose of 2596-147 in a companion animal safety study (MRID 45410906). However, there was no elevation in liver enzymes when kittens were treated at 5x the recommended dose for four weekly intervals (MRID 45435901).

D-B

The EPA causality categorization of the D-B incidents for product 2596-147 is presented in Attachment Table 5. The majority (109/169, 64%) of the incidents were categorized as unlikely caused by 2596-147. Again, the EPA reviewer relied on the NAPCC categorization. As with the D-A cases, NAPCC toxicologists were reluctant to conclude that a methoprene-only product could be responsible for the incidents. In 128/169 (76%) of the cats, the clinical signs of tremor and/or seizures were reported. The toxicologists assumed that cats must have been exposed to a neurotoxic product instead of or in addition to 2596-147. However, one cat that had tremors 19 hours post-application was categorized as medium suspicion (EPA=probable). Another two cats with clinical signs of salivation, seizures and hyperthermia were categorized as low suspicion (EPA=possible). It is unclear why these cases were so categorized when others with similar clinical signs were doubtful (EPA=unlikely).

The EPA reviewer classified six cases as probable based on immediate signs of hypersensitivity as described under D-A. These cases were clearly different from those in which tremors and/or seizures were reported a significant time after application (as long as 24-48 hours later).

3. Product 2596-148 (AdvancedCare Flea and Tick Drops for Cats)

D-A

The EPA causality categorization of the D-A incidents for product 2596-148 is presented in Attachment Table 6. The majority of the incident reports for the D-A category were from Hartz Mountain and did not contain sufficient information to establish a cause of death. Five animals were found dead without prior clinical signs and necropsies were not performed. There were 10 of the 35 animals for which the product was definitively, probably or possibly the cause of death. Of the total 35 cats involved, 13 were reported to have the neurological signs of tremors and/or seizures prior to death. One cat may have had an anaphylactic reaction to the product. The cat had trouble breathing and died 1 hour after application. On necropsy, there was suggestive but not definitive diagnostic evidence of hypertrophic cardiomyopathy. The pathologist noted the most likely scenario was that the cat had chronic hypertrophic cardiomyopathy resulting in some passive congestion and alveolitis secondarily in the lungs.

He stated that he could not entirely rule out the possibility of anaphylactic shock associated with the flea product but would not expect the lesions identified in the samples received.

D-B

The EPA causality categorization of the D-B incidents for product 2596-148 is presented in Attachment Table 7. Of the 104 total cats which experienced major events, the product was definitively associated with the reaction in 8 cats, probably associated in 10 cats and possibly associated in 46 cats. Of the 104 cats, 91 were reported to have tremors and/or seizures. The neurological signs were not observed immediately but were delayed. It was often reported that the product was applied at night and the tremors and/or seizures were observed in the morning, approximately 12 hours later. Also, in many cases, it was noted that the product was applied to multiple cats but only one reacted.

4. Product 2596-150 (AdvancedCare Flea and Tick Drops for Dogs)

D-A

There were five reports of deaths for 3rd quarter 2000 involving 4 dogs and 1 cat. The cat had seizures six hours after application and died possibly as a result of the seizure control treatment. In three of the dog cases, there was not enough information to categorize the cause of the death. In the fourth dog, the case was categorized as unlikely.

D-B

There were two D-B reports for the 3rd quarter 2000 involving 1 dog and 3 cats. The dog was reported to have seizures 11 hours after product application. No other information was available. The three cats had neurological signs and breathing difficulties.

IV. POSSIBLE PRODUCT PACKAGING PROBLEMS

There are several notations in the incident reports from Hartz Mountain which suggest possible packaging problems with at least two of the four products.

A. In the 1st quarter 2000 data on 2596-146 D-A, first report, there is a statement from the owner (Barba) in a compliant letter to the company which says, "My first call resulted in an operator telling me to go to the store and look at the product to see which color tube was used. The following is a direct quote from the operator, 'You're not hearing this from me, but if you had a dog product in a cat package then it is manufacturing error, and it has happened before and there was a recall because of it!' (Owner claimed there was an orange tube in the box for the cat product, 2596-147, which is supposed to be purple.) There is a hand-written statement

on this letter assumed to be by the registrant which says, "Statement would not have been made - there has not been any recall."

B. In a D-B incident report for 2596-147 dated 7/18/00, a cat was reported to have salivation, seizures and dilated pupils after product application, which are typical signs of permethrin poisoning. There is a note on the incident that the consumer thought the product had been tampered with because yellow tubes (dog product) were sold in a box for the cat product (purple tubes). Included with the report are several internal email messages between Hartz personnel. One says the following:

"On Tuesday 12/7/99 at 9:35am the One Spot packaging line changed over from Cat One Spot, 97557 to One Spot f/Dogs<15 lbs, 97835. It appears that an improper line clearance was performed (line clearance procedure went into effect June of '99) resulting in the product coming onto the line (97835) while packaging materials for 97557 were still in the machines."

C. The National Pesticide Telecommunications Network (NPTN) database was searched for domestic animal calls involving permethrin, methoprene and d-phenothrin. In a call on July 24, 2001, a caller reported that several months ago she applied what she thought was Hartz One Spot for Cats on her cats. The cats developed seizures and one died. The caller reviewed the packing materials and the vial of the product. The materials stated the product was for cats but the vials were marked for dogs as Hartz One Spot for Dogs.

D. OPP recently received an incident report (IDS 11940) from USP Veterinary Practitioners'Reporting Program for Hartz Advanced Care Flea and Tick Drops for Cats (2596-148). The product label read "Hartz Advanced Care Once-a-Month Flea and Tick Drops for Cats and Kittens Over 10 lbs" but the product inside contained three 1-ml "Hartz Control Pet System Once-a-Month for Dogs and Puppies (15 lbs and under)" containing 45% permethrin, Lot/Serial number 622002, EPA Reg. Number 2596-137, EPA est. number 2596-NJ-1. The caller submitted digital photographs of the product packaging and product tubes.

V. Review of Companion Animal Safety Studies

Executive Summaries of the DERs for the studies are provided below. The full DERs are attached.

A. Companion Animal Safety Study for 2596-147

In a companion animal safety study (MRID 45435901), RF 9804 Topical (Lot/Batch No. ED 134: 3.66% methoprene; Lot/Batch No. ED 160: 19.5% methoprene) was applied topically to groups of 6 male and 6 female kittens in 1.0 mL dose volumes containing 35 mg/mL (the recommended dose) or 182 mg/mL (5 times the recommended dose) of methoprene. Controls were not treated. Animals were treated on study days 0, 7, 14, and 21. Animals were observed for clinical signs once daily throughout the study (the time of observation relative to the

treatment time was not indicated). Clinical pathology parameters were evaluated only after the second and third treatment.

Possible treatment-related clinical signs included excessive salivation by one female from the 1X group following the first application of the test material and the scabbing noted in the chin area of one male and one female from the 5X group during weeks 4 and/or 5. However, because clinical observations were not conducted hourly for at least 4 hours following treatment, and not twice daily for the remainder of the study, as required by the guidelines, it is possible that treatment-related clinical signs were missed. There were no treatment-related effects on body weight, food consumption or clinical pathology parameters, with the possible exception of increased WBC counts in treated males (1x and 5x) and neutrophil counts in males (5x) during Week 4.

This study is classified as **Unacceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats due to the lack of hourly observations following the treatments.

B. Companion Animal Safety Study for 2596-147

In a companion animal safety study (MRID 45410906), IGR One Spot Flea Control (TS#11146, 3.0% w/w (S)-Methoprene) was topically applied (at the base of the neck) to 12- to 14-week old cats two times (14 days apart) at 5X the clinical dose. On day 0 and day 14, five male and five female cats were administered a 1X dose (1.25 mL) on the dorsal aspect of the neck. This material was allowed to disperse, and the application was repeated approximately every 30 minutes until a 5X dose was administered. The untreated control group (5 males and 5 females) was not removed from the cages on day 0; however, on day 14 a "sham dosing" was performed to assess any possible effect from the dosing procedure.

Observed clinical signs included vocalization and restlessness and attempts to scratch and lick the application site in 3/5 treated males and 1/5 treated females; vomiting in 1/5 treated males and 1/5 treated females; clear ocular discharge in 2/5 treated females; and reddening of the skin in 2/5 treated males. There were no biologically-significant treatment-related effects on hematology and coagulation parameters. Two treated males had elevations in the liver enzymes SGOT (AST) and SGPT (ALT) 4-5 times the pretest values on Day 15.

Numerous deficiencies were noted in the conduct of this study. Only 5 cats/sex/group were used and the guidelines specify 6 animals/sex/group. Body weight and food consumption were not measured. More importantly, the authors attribute the clinical signs to wetness from treatment and excitement from handling; however, due to the absence of a vehicle control, these assumptions cannot be verified. In addition, two treated animals had elevations in liver enzymes. Therefore, the required 5X margin of safety has not been proven and the study is classified as **Unacceptable (Non-Upgradable)/Guideline** for a companion animal safety study [OPPTS 870.7200] in kittens.

C. Companion Animal Safety Study with 2596-148

In a companion animal safety study (MRID 44864007C). Liquid Once-a-month Stripe-on Product [Active Ingredients: 95.2% Sumithrin (d-phenothrin): 3.09% (S)-Methoprene: Lot no. 11401] was topically applied (as a stripe along the animal's back) to groups of 6 male and 6 female cats or 6 male and 6 female kittens at dose volumes of 1.0 mL for a total of 5 doses given approximately 60 minutes apart (5 times the recommended dose). Controls were dosed at the same intervals with 1.0 mL of safflower oil.

One male from the 5X adult group had reddened skin at the base of the skull 1 hour after the fourth treatment which lasted for 27 hours and was considered treatment-related. Other clinical signs that may have been related to treatment included the following: excessive salivation of up to 12 minutes duration exhibited by two animals from the 5X adult group on day 0 and restlessness with signs of discomfort and occasional scratching exhibited by one animal from the 5X group which lasted for 37 minutes following the last treatment. The study author attributed the salivation to the animals licking the test substance. There were no treatment-related clinical signs exhibited by animals from the 5X kitten group. During the Day 0-7 interval, the 5X male adult and female kitten groups had significant ($p<0.05$) mean body weight losses compared to mean body weight gains by their respective control groups (adult males: -0.10 vs. +0.05 kg for controls; female kittens: -0.02 vs. +0.07 kg for controls), and body weight gain by the 5X male kitten group was significantly decreased and compared to controls (0 vs. 0.12 kg; $p<0.05$). During the Days 1-5, food consumption by 5X male and female adults and 5X male kittens were decreased as compared to their respective control groups. There were no treatment-related effects on hematology, coagulation or clinical chemistry parameters.

This study is classified as **Unacceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats and kittens. The observed toxicity at the 5X treatment level indicates that a full study using 3 dose levels should have been done instead of a limit test, and a repeat treatment should have been included.

D. Companion Animal Safety Study in Puppies with 2596-150

In a companion animal safety study (MRID 45006402C), a stripe-on formula [Active Ingredients based on two analyses: Sumithrin (d-phenothrin), 84.154 and 84.487% w/w; (S)-methoprene, 2.323 and 2.319%] was topically applied (as a stripe along the back) at a 5X dose (1.3 mL every 60 min until a 5X dose was achieved) to a group of 6 male and 6 female beagle dogs, 84-90 days old at study initiation. Controls were treated with safflower oil. Treatments were applied to the skin of the back from a point midway between the shoulder blades to the base of the tail. Blood samples were obtained on the Days -7, 2 and 7 for hematology and clinical chemistry measurements. Animals were observed for 14 days.

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology. Several statistically-significant clinical chemistry differences were observed between treated and control groups; however, these were within the pre-test reference ranges (mean ± two standard deviations) for the animals included in the study, and are therefore not considered toxicologically significant.

This study followed the pertinent guidelines for a companion animal safety study (OPPTS 870.7200). The package labeling and application instructions were not provided. It is assumed that the intended use would be for only one application per month of 1.3 mL as stated in the study report. If this is the case, then the required 5X margin of safety has been demonstrated and the study is **Acceptable/Guideline.**

E. Companion Animal Safety Study in Adult Dogs with 2596-150

In a companion animal safety study (MRID 45006403 C), a stripe-on formula [Active Ingredients: Sumithrin (d-phenothrin), 95.22% w/w; (S)-methoprene, 2.41%) was topically applied (from the neck to the base of the tail) at a 5X dose (1.3 mL every 60 min until a 5X dose was achieved) to a group of 6 male and 6 female beagle dogs, each at least 6 months old. Controls were treated with safflower oil. Treatments were applied to the skin of the back from the neck to the base of the tail. Blood samples were obtained on the Days -7, 2 and 7 for hematology and clinical chemistry measurements. Animals were observed for 14 days.

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical chemistry, or hematology. Several statistically-significant clinical chemistry and hematology differences were observed between treated and control groups; however, these were within normal limits, and are not considered toxicologically significant.

This study followed the pertinent guidelines for a companion animal safety study (OPPTS 870.7200). The package labeling and application instructions were not provided. It is assumed that the intended use would be for only one application per month of 1.3 mL as stated in the study report. If this is the case, then the required 5X margin of safety has been demonstrated and the study is **Acceptable/Guideline.**

VI. Acute Toxicity Studies with Hartz Test Sample #11146 (3% methoprene)

The acute studies with the 2596-147 (3% methoprene) product demonstrated that it is has low acute oral and dermal toxicity, is not a dermal or eye irritant and is not a dermal sensitizer in laboratory animals. The study reports are presented in the table below.

Study (species)	Results	Toxicity Category
Acute oral toxicity (rats)	LD_{50} >5000 mg/kg	IV
Acute dermal toxicity (rabbits)	LD_{50} >5000 mg/kg	IV
Primary eye irritation (rabbits)	minimally irritating	IV
Primary dermal irritation (rabbits)	slightly irritating	IV
Dermal sensitization (guinea pigs)	non-sensitizing	N/A

N/A = not applicable

VII. Freedom of Information (FOI) Summary for Oral Methoprene Product

An oral methoprene product for use in dogs has been approved by the Food and Drug Administration under the trade names Zodiac® Fleatrol™ Caps™ and Hartz® Flea Control Capsules™. The products were approved on January 24, 2000, for dogs nine weeks of age and older and 4 pounds body weight or greater. There are different size capsules for seven different weight ranges based on a dose of 22 mg/kg. In Target Animal Safety Studies discussed in the FOI Summary, 6 week-old beagle puppies were administered doses of 1, 3, 5 the recommended dose once weekly for 13 weeks. Another group was administered 10x the recommended dose once weekly for 4 weeks. Clinical signs of toxicity included depression, ataxia and tremors in all dose groups. The signs decreased with each additional weekly dosing as the puppies aged. It was concluded that the methoprene capsules were safe for administration to puppies 9 weeks of age and older and 4 pounds body weight or greater.

A reproduction study demonstrated that methoprene capsules, administered up to 3x the recommended dose, were safe for male and female breeding dogs.

In another safety study, methoprene was administered at 5x the recommended dose in combination with several adulticidal flea products containing fipronil, permethrin/piperonyl butoxide, phosmet or carbaryl. It was concluded that the methoprene capsules are safe for administration in combination with commercially available flea adulticides.

In clinical field trials, a total of 246 dogs ranging in age from 6 months to 16 years and weighing between 4 and 130 pounds were administered the methoprene capsules once weekly for five months. AdamsÔ Flea and Tick Mist (active ingredients not stated) was applied once per week for the first eight weeks to eliminate adult flea burdens. Adverse reactions included vomiting, diarrhea, lethargy/depression and nervousness.

VIII. Label Amendments

Hartz Mountain has submitted revised labeling for products 2596-148 and 2596-151 (85% d-phenothrin for use on dogs and cats). The registrant states that a large number of reported incidents involving cats have resulted from misuse of permethrin-based dog products on cats. However, it is their position that even when products registered for use on cats are used correctly, the consumer is sometimes confused by the cat's normal reaction to the product. Most cats do not like water or other liquids on their body and will react in odd ways to remove the moisture from their bodies or to try to escape from it. Since spot-on products are oil-based, they remain on the cat's coat for up to 24 hours before they dry. Therefore, the cat may act in an unnatural manner for that period of time. Many owners believe that the pet's actions are the result of an adverse incident.

Hartz Mountain is proposing revised labeling to: 1) educate the consumer so they are not concerned if their cat reacts in this manner; 2) ensure that adverse incident reports are actually a reaction to the product and not a physical manifestation of the cat's displeasure. The adverse reaction reports would therefore be a more accurate account of the number of actual incidents resulting from the product. The registrant is proposing adding the following:

"Cats don't like to get wet and can try to remove moisture by licking or rubbing the area, twitching, running away or shaking. They can send ripples down their back which may look like tremors. After treatment with this product, your pet may exhibit these normal behavior patterns. You will need to differentiate these patterns from an adverse reaction by considering whether they are similar to your experience when your cat's back gets wet with plain water or are more serious. This product is oil based and your pet may sense the moisture from it until it dries in about 24 hours."

The registrant is also proposing to delete the phrase ".... such as a slight transitory redness of the skin at the site of application,..." from the precautionary statements and substitute the EPA required statement "Sensitivity may occur after using ANY pesticide product for pets."

IX. DISCUSSION/CONCLUSIONS

A. Hartz Mountain Classification of D-B Incidents

Hartz Mountain has indicated that the following number of D-B incidents have been misclassified and should have been D-C (moderate event) cases: 3 for 2596-146, 30 for 2596-147 and 46 for 2596-148. The basis for changing the classification appears to be that the cases were not life-altering. The 6(a)(2) regulations state that an incident should be categorized as D-B if the animal exhibited or was alleged to have exhibited symptoms that may be life-

threatening or resulted in residual disability.[3] Examples of life-threatening effects include, massive or internal hemorrhage, loss of consciousness, grand mal seizures and paralysis. As discussed above, seizures and tremors were reported for the majority of these cases. NAPCC noted on several incident reports that seizures are a life-threatening problem which must be controlled. Clearly, these incidents should have been categorized as D-B and not D-C. If the registrant applied the "life-altering" criteria for these four products and other Hartz Mountain products, there are likely D-C cases in their summary reports which should be D-B.

B. Missing Incident Reports

The following incidents are listed in the summary page provided at the beginning of the quarter but are not included with the detailed reports:

4596-146 - D-B, 2nd quarter 2000 - reports with owners' name Dorathy (involving a 10-month old Chihuahua) and Thomas (email message)

4596-147, D-B, 3rd quarter 2000 - report with owner's name Darroch

4596-147, D-B, 4th quarter 2000 - last five reports

C. Product 2596-146

Intentional or accidental misapplication of Control One-Spot for Dogs to cats or exposure of cats to dogs treated with the product resulted in the majority of deaths (158/239) and major events (316/346). Permethrin toxicosis in cats has been recognized since the introduction of concentrated (45-65%) products. Numerous articles on recognition, treatment and prevention of permethrin toxicity have appeared in the veterinary literature.[4,5,6] Treatment of permethrin toxicosis can be very difficult for the veterinarian and expensive for the pet owner. Cats with seizures may not respond to standard anticonvulsants and must be repeatedly treated with a muscle relaxant or anesthesized until the permethrin is metabolized in 24-72 hours. The dermal application of 1 ml of a 45% permethrin to a 4.5 kg cat (100 mg/kg) can result in life-

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[3]PR Notice 98-3

[4] Meyer KE (1999). Toxicosis in cats erroneously treated with 45 to 65% permethrin products. JAVMA 215(2): 198-203.

[5] Richardson JA (2000). Permethrin Spot-on Toxicoses in Cats. Vet Emergency Crit Care 10: 103-106.

[6] Volmer PA, Khan SA, Knight MW and Hansen, SR (1998). Permethrin spot-on products can be toxic to cats. Vet Med 93(12): 1039.

threatening toxicosis.[7] Cats, as compared to other domestic animals, are relatively deficient in their ability to conjugate xenobiotics with glucuronic acid, which is the most important step in the metabolism of certain substances.[8] Therefore, they metabolize many chemicals more slowly than other species.

In a December 7, 2000 letter from the Registration Division, OPP, nine registrants of concentrated permethrin products were requested to revise their labeling to make warnings about use on cats more prominent, including adding icons (graphic of cat crossed out). In addition, the statement, "May be toxic and potentially fatal if applied to or ingested by cats" after the warnings to not use on cats was suggested. EPA also asked that labels contain the statement, "Cats which actively groom or engage in close physical contact with treated dogs may be at risk of serious harmful effect. Do not use this product in households with both dogs and cats." This statement was requested because there are no data demonstrating a safe period to reunite cats with dogs after treatment. The registrants were reluctant to add the last statement. In a meeting on December 7, 2000, the Consumer Specialty Products Association representing the registrants agreed they would generate data on the safe period for isolation of cats from treated dogs. To date, no data have been submitted. However, Hartz Mountain has agreed to make the label revisions requested in the December 2000 letter.

D. Product 2596-147

Assignment of causality categories to the incidents with 2596-147 was complicated by the uncertainty about product exposure. It was not always clear if a cat was exposed to 2596-147 containing only methoprene or the dog product containing methoprene and permethrin. A cat could be exposed to the dog product in three ways. First, the owner could have accidently or intentionally applied the dog product to a cat. In households where there are both dogs and cats, owners could have treated both species and gotten the products mixed up. Or they could have intentionally applied the dog product to cats, thinking it wouldn't hurt them. Second, cats could have been exposed to dogs treated with product 2596-146 or an other permethrin product. Third, based on possible packaging problems, as discussed above, owners could have applied dog product with cat labels.

There was evidence that some cats may have experienced immediate hypersensitivity reactions to the product. Clinical signs observed in 2 hours or less of product application included hyperactivity, nervousness, trying to bite at application site, hissing, agitation, tachycardia, dyspnea and panting.

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[7] Hansen SR. Pyrethrins and Pyrethroids. *In* ME Peterson and PA Talcott (eds) Small Animal Toxicology. Philadelphia: WB Saunders, 2001; 687-694.

[8] Wilke JR. Principles of Drug Therapy. *In* RG Sherding (ed) The Cat: Diseases and Clinical Managment. New York: Churchill Livingstone, 1991; 1401.

Nine cases of death due to liver failure were reported: two cases were diagnosed with hepatic lipidosis. Although there are many cases of liver failure in cats, elevation of liver enzymes in 2/5 kittens treated with 5x the recommended dose in one companion animal safety study. However, in another study with 4 weekly treatments of 5x the recommended dose, there was no increase in liver enzymes.

E. Product 2596-148

There is evidence in the incident data that some cats exposed to 2596-148 may have develop neurological signs of toxicity, i.e., tremors and seizures and possibly die as a result of the exposure. Of 35 deaths, 10 cases were categorized as definitive, probable or possible evidence that the product was the cause of the death. Another 22 cases were unknown, mainly because detailed information on the incident was not provided. Of 104 major events (D-B), 63 were categorized as definitive, probable or possible evidence that the product was the cause of the reaction.

This product and 2596-150 (dog product) are applied as a stripe down the animal's back from the base of the skull to the tail, whereas other spot-on products are only applied at the base of the skull. This stripe method of application increases the possibility that cats will ingest the product and have a toxic reaction. Also, the percentage of active ingredient (85.7% d-phenothrin) in the product is very high in comparison other spot-on products.

F. Product 2596-150

There is insufficient detailed information from the incident reports to form any conclusions about causality for this product. However, it is noted that neurological clinical signs were reported in both dogs and cats. In the companion animal safety studies, dogs (MRID 450006403C) and puppies (MRID 450006402C) treated with 5x the recommended dose of this product had no evidence of toxicity.

G. Labeling

The proposed label revisions are confusing, poorly written and require the pet owner to distinguish "ripples down their back which may look like tremors" on their cat from tremors which are a clinical sign of neurotoxicity. This is very difficult for a lay person, even one who is an experienced pet owner, and may delay treatment for an animal which does have an adverse reaction to the product. It is the registrant's assertion that cats react abnormally when any liquid is applied to their skin. This was not exhibited in the companion animal safety study (MRID 44864007C) in cats/kittens with the Liquid Once-a-Month Stripe-on Product (d-phenothrin and methoprene). Control cats were treated with 1 ml of safflower oil five times at hourly intervals. One control animal was observed licking the dose site; none were observed to have tremor-like reactions. Tremor-like reactions were also not observed in control animals

in the companion animal safety study (MRID 45410906) in cats with the methoprene-only product. The study report indicates that "sham dosing" was performed on the control animals; it does not state exactly what material was applied to the control cats.

Many incidents for 2596-148 from the NAPCC in which tremors were reported were categorized as high, medium or low suspicion that the product was the cause of the adverse reaction. The proposed labeling revisions may cause owners to delay treatment of potentially fatal neurological signs of toxicity. Early, aggressive treatment of pyrethrin/pyrethroid toxicity often results in full recovery but pets not receiving aggressive care may die.[9]

[9] Hansen, ibid

ATTACHMENT

Table 1: Categorization of Incident Reports by Registrant

Product	Number Analyzed	MU	MPU	NPR	NCI	MC	Other	PPI
2596-146*								
D-A	219	142	5	23	23	0	10	16
D-B	304	272	3	6	9	3	0	11
2596-147*								
D-A	209	25	13	60	83	1	8	19
D-B	162	27	15	26	42	30	3	19
2596-148**								
D-A	37	0	0	12	20	0	2	3
D-B	93	1	2	6	30	46	3	5
2596-150**								
D-A	5	1	0	1	2	0	0	1
D-B	2	1	0	0	1	0	0	0

MU = misuse/misapplication; MPU= multiple products used; NPR = non product related; NCI = no confirming information; MC = misclassified; PPI = possible product involvement

* data from 3rd quarter 1998 through 4th quarter 2000

** data from 1st quarter 2000 through 4th quarter 2000

Table 2: EPA Categorization of Deaths (D-A) Associated with 2596-146

	Dogs						Cats		
Quarter	No. affected	Probable	Possible	Unlikely	Unrelated	Unknown	No. affected	Applied directly	Exposed to treated dog
3rd quarter '98	8			5		3	26	25	1
4th quarter '98	5			1		4[a]	19	19[b]	
1st quarter '99	7		1	1		5[c]	5	4	1
2nd quarter '99	6			5		1[d]	18	17	1
3rd quarter '99	18[e]			16		2[f]	32	25	7
4th quarter '99	4				1	3	7	7	
1st quarter '00	1					1	6	6	
2nd quarter '00	11	1[g]		4		6	17	16	1
3rd quarter '00	16			5		11[h]	21	16	5
4th quarter '00	5			2		3	7	6[i]	1
Total	81	1	1	39	1	39	158	141	17

a includes 1 ferret that died after exposure to a treated dog
b includes 1 cat misclassified by Hartz Mountain as D-B and two classified as D-A for 2596-147
c decreased pups in litters when product applied to two pregnant dogs; counted as 2 dogs
d includes one dog that was misclassified as D-B
e includes 5 puppies from 1 incident
f includes 1 dog that was misclassified as D-B
g product applied to 3 month-old dog; label restricts product to dogs 6 months or older
h includes 1 female dog with a litter of puppies born dead, counted a 1 animal
i includes 1 case that recovered from permethrin poisoning but then died as mast cell tumor; is an unrelated case

Table 3: EPA Categorization of Major Events (D-B) Associated with 2596-146

	Dogs						Cats		
Quarter	No. affected	Probable	Possible	Unlikely	Unrelated	Unknown	No. affected	Applied directly	Exposed to treated dog
3rd quarter '98	3			1		2	53	49	4[a]
4th quarter '98	5			2		3	58	52[b]	6
1st quarter '99	0						19	18	1
2nd quarter '99	4	1	1	1		1	23	23	
3rd quarter '99	2			1		1	35	33	2
4th quarter '99	3	1	1	1			35	31	4[c]
1st quarter '00	1			1			15	14	1
2nd quarter '00	3		1	1		1	30	27	3
3rd quarter '00	7		1	3		3	42	41	1
4th quarter '00	2					2	6	6	
Total	30	2	4	11	0	13	316	294	22

a includes cat that was exposed by playing with an open product container
b includes cat exposed when owner applied by mouth
c includes 1 incident where cat licked spilled product

Table 4: EPA Categorization of Deaths (D-A) Associated with 2596-147

	Cats					
Quarter	No. affected	Probable	Possible	Unlikely	Unrelated	Unknown
3rd quarter '98	12			3		9
4th quarter '98	13			3		10[a]
1st quarter '99	9			4		5
2nd quarter '99	23	1		6	3	13
3rd quarter '99	30			16	3	11
4th quarter '99	26		1	12	4	9
1st quarter '00	8			1	3	4
2nd quarter '00	26	1	1	9		15
3rd quarter '00	37		1	17[b]		19[a]
4th quarter '00	18			4		14[a]
Total	202	2	3	75	13	109

a includes cats misclassified as D-B for 2596-147
b includes 14 kittens counted as 1 animal

Table 5: EPA Categorization of Major Events (D-B) Associated with 2596-147

	Cats					
Quarter	No. affected	Probable	Possible	Unlikely	Unrelated	Unknown
3rd quarter '98	16	1		11		4
4th quarter '98	25	2		16		7
1st quarter '99	8	1		4		3
2nd quarter '99	13	1	1[a]	9		2
3rd quarter '99	34			24		10
4th quarter '99	3			2		1
1st quarter '00	5			4		1
2nd quarter '00	6			5		1
3rd quarter '00	55	2	1	33	2	17
4th quarter '00	4			1		3[a]
Total	169	7	2	109	2	49

a includes cat misclassified as D-A

Table 6: EPA Categorization of Major Events (D-A) Associated with 2596-148

	Cats						
Quarter	No. affected	Definitive	Probable	Possible	Unlikely	Unrelated	Unknown
1st quarter '00	1						1
2nd quarter '00	6	1		1			4
3rd quarter '00	17		2	3			12
4th quarter '00	11		1	2	1	2	5
Total	35	1	3	6	1	2	22

Table 7: EPA Categorization of Major Events (D-B) Associated with 2596-148

	Cats						
Quarter	No. affected	Definitive	Probable	Possible	Unlikely	Unrelated	Unknown
1st quarter '00							
2nd quarter '00	7	3	2		1		1
3rd quarter '00	90[a]	5	7	43	3	1	30
4th quarter '00	7		1	3	1		2
Total	104	8	10	46	5	1	33

a There was also one animal in which the product was misused.

DATA EVALUATION RECORD

DOMESTIC ANIMAL SAFETY STUDY OF IGR ONE SPOT FLEA CONTROL IN YOUNG CATS

STUDY TYPE: Companion Animal Safety - Kittens (OPPTS 870.7200)
MRID 45410906

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
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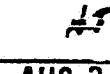
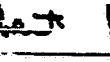
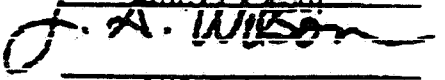
Task No. 01-130F

Primary Reviewer: Cheryl B. Bast, Ph.D., D.A.B.T.	Signature: Date:	 AUG 3 1 2001
Secondary Reviewers: H. Tim Borges, Ph.D., D.A.B.T.	Signature: Date:	 AUG 3 1 2001
Robert H. Ross, M.S., Group Leader	Signature: Date:	 AUG 3 1 2001
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	 AUG 3 1 2001

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy Date: 9/4/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart Date: 9/17/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/ Kittens [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D276701; MRID NUMBER: 45410906; SUBMISSION: S598364

TEST MATERIAL: IGR One Spot Flea Control, Hartz Test Sample #11146 (methoprene)

STUDY NUMBER: WEL Study No. 98797

TESTING FACILITY: White Eagle Toxicology Laboratories, 2003 Lower State Road, Doylestown, PA

SPONSOR: The Hartz Mountain Corporation, 400 Plaza Drive, Secaucus, New Jersey 07094

TITLE OF REPORT: Domestic Animal Safety Study of IGR One Spot Flea Control in Young Cats

AUTHOR: Juliann Ehrhart, B.S.

REPORT ISSUED: April 23, 1998

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 45410906), IGR One Spot Flea Control (TS#11146, 3.0% w/w (S)-Methoprene) was topically applied (at the base of the neck) to 12- to 14-week old cats two times (14 days apart) at 5X the clinical dose. On day 0 and day 14, five male and five female cats were administered a 1X dose (1.25 mL) on the dorsal aspect of the neck. This material was allowed to disperse, and the application was repeated approximately every 30 minutes until a 5X dose was administered. The untreated control group (5 males and 5 females) was not removed from the cages on day 0; however, on day 14 a "sham dosing" was performed to assess any possible effect from the dosing procedure.

Observed clinical signs included vocalization and restlessness and attempts to scratch and lick the application site in 3/5 treated males and 1/5 treated females; vomiting in 1/5 treated males and 1/5 treated females; clear ocular discharge in 2/5 treated females; and reddening of the skin in 2/5 treated males. There were no biologically-significant treatment-related effects on hematology and coagulation parameters. Two treated males had elevations in the liver enzymes SGOT (AST) and SGPT (ALT) 4-5 times the pretest values on Day 15.

Numerous deficiencies were noted in the conduct of this study. Only 5 cats/sex/group were used and the guidelines specify 6 animals/sex/group. Body weight and food consumption were not measured. More importantly, the authors attribute the clinical signs to wetness from treatment and excitement from handling; however, due to the absence of a vehicle control, these assumptions cannot be verified. In addition, two treated animals had elevations in liver enzymes. Therefore, the required 5X margin of safety has not been proven and the study is classified as **Unacceptable (Non-Upgradable)/Guideline** for a companion animal safety study [OPPTS 870.7200] in kittens.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: IGR One Spot Flea Control, Hartz Test Sample #11146

   Description: not provided
   Lot No.: Test sample #11146
   Active Ingredients: (S)-Methoprene (3.0% w/w)
   Storage Conditions: at room temperature

2. Administration: Topical (spot-on)

3. Vehicle and/or positive control: not stated

4. Test animals

   Species: Cat
   Breed: Mixed
   Age and weight at study initiation: 12-14 weeks; weights not given
   Source: White Eagle Laboratories, Inc., 2003 Lower State Road, Doylestown, PA 18901
   Housing: Individually in elevated metal cages
   Diet: Purina Feline Diet #5003, 200 g/day
   Water: Potable water, *ad libitum*
   Environmental conditions: "maintained according to currently acceptable practices of good animal husbandry"
   Temperature: not reported
   Humidity: not reported
   Air changes: not reported
   Photoperiod: not reported
   Acclimation period: 1 week

II. STUDY DESIGN

A. IN LIFE DATES

Start: February 2, 1998; end: March 17, 1998

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

Cats were assigned to dose groups using a random permutation table. On day 0 and day 14, five male and five female cats were administered a 1X dose (1.25 mL) of test material at the base of the neck between the shoulders. This material was allowed to disperse, and the application was repeated approximately every 30 minutes until a 5X dose was administered. The untreated control group (5 males and 5 females) was not removed from the cages on day 0; however, on day 14 a "sham dosing" was performed to assess any possible effect from the dosing procedure. However, no description of the sham dosing was given and it is unclear what, if any, substance was applied.

TABLE 1. Study design

Treatment	Number of animals	
	Male	Female
Control (untreated)	5	5
5X One Spot Flea Control	5	5

Data taken from text p. 5, MRID 45410906.

C. DOSE SELECTION RATIONALE

Although not stated in the study report, it is assumed that the 5X dose was selected to target the required 5X margin of safety.

D. EXPERIMENTAL DESIGN

All cats were observed twice daily (once/day on weekends and holidays) for signs of mortality and moribundity. On day 0 and day 14, all cats were observed for clinical signs (such as abnormal posture, loss of appetite, vocalization) at 1, 2, 3, 4, and 6 hours following the completion of dosing. Further observations were made as warranted according to severity and/or frequency of clinical signs. All animals were also observed for clinical signs once/day on days 1 to 13 and 15 to 28. The study was terminated following the final observation on day 28.

E. PATHOLOGICAL PARAMETERS

Blood samples were collected during the week prior to dosing and on day 15 via jugular venipuncture. It was not stated whether the animals were fasted overnight prior to blood collection. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count	X	Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)*		
X	(Activated partial thromboplastin time)*		
X	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
		X	Total and direct bilirubin*
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase(ALK)*	X	Triglycerides
	Cholinesterase(ChE)		Serum protein electrophoresis
	Creatine kinase		Albumin/Globulin ratio
	Lactic acid dehydrogenase(LDH)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase(also SGOT)*		
X	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

Group means with standard deviations were analyzed by a two-tailed t-test.

G. DISPOSITION OF ANIMALS

The disposition of animals was not reported.

H. COMPLIANCE

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The treated group was exposed at the 5X limit dose two times, 14 days apart.

B. MORTALITY

There were no deaths during the study.

C. CLINICAL SIGNS

Clinical observations are summarized in Table 2 and include vocalization and restlessness, attempts to scratch and lick the application site, vomiting, soft mucoid feces, clear ocular discharge, and reddening of the skin. It is unknown if the vocalization and restlessness and attempts to scratch the application site are due to test material toxicity or a result of discomfort due to wetness. Unfortunately, no vehicle control group was included in this study to answer this question. The authors attributed the vomiting to excitement from handling. Since the control animals were not handled on day 0, this statement cannot be verified. The reddening of skin was attributed to test material administration, and the cause of the abscess in one male was not determined.

TABLE 2. Clinical observations of cats treated with IGR One Spot Flea Control[a]

Clinical observations	Group	Incidence	Comments
Vocalization and restlessness	Control male	0/5	
	5X male	3/5	Study day 0, following the fourth or fifth applications continuing intermittently for 2 to 3 hours and study day 14 following the final application
	Control female	0/5	
	5X female	1/5	Study day 0, following the third application continuing intermittently for 2 to 3 hours and study day 14 following the final application
Licking and scratching of application site	Control male	0/5	
	5X male	2/5	Study days 0 and 14 (these cats also exhibited vocalization and restlessness)
	Control female	0/5	
	5X female	1/5	Study days 0 and 14 (this cat also exhibited vocalization and restlessness)
Vomiting	Control male	0/5	
	5X male	1/5	Study day 0, following the second application
	Control female	0/5	
	5X female	1/5	Study day 0, following the second and third applications
Soft and/or liquid mucoid feces	Control male	3/5	1 to 3 intermittent occurrences
	5X male	1/5	1 to 3 intermittent occurrences
	Control female	1/5	1 to 3 intermittent occurrences
	5X female	0/5	
Slight, clear ocular discharge	Control male	0/5	
	5X male	0/5	
	Control female	0/5	
	5X female	2/5	Observed after the fifth application on day 0 and persisting through day 5 in one female and observed from day 3 through day 7 in another female
Reddening and/or scabbing of skin	Control male	0/5	
	5X male	2/5	Observed after the third application on day 14 and resolved on one cat by day 15. Persisted on the other cat through day 21, and on day 28 this cat had an abscess ventral to the lower mandible which healed after antibiotic treatment.
	Control female	0/5	
	5X female	0/5	

a Extracted from text on page 7 of 36 of the study report

D. BODY WEIGHT AND WEIGHT GAIN

Body weight data were not reported.

E. FOOD CONSUMPTION

Food consumption data were not reported.

F. HEMATOLOGY

There were no biologically-significant treatment-related effects on hematology and coagulation parameters. There were some statistical ($p \leq 0.05$) differences between control and treated groups, but the mean values were reported to be within reference ranges. Observed differences included a decrease in white blood cell count in treated males at day 15, a decrease in neutrophil count in treated males on day 15, and an increase in lymphocyte count in treated males on day 15 compared to controls. No other effects were noted in males and no effects were noted in females. Selected hematology data are presented in Table 3.

TABLE 3. Selected Hematology Values (mean ± SD) in Cats Treated with IGR One Spot Flea Control

	Males				Females			
	Control (untreated)		5X One Spot Flea Control		Control (untreated)		5X One Spot Flea Control	
	Pretest	Day 15	Pretest	Day 15	Pretest	Day 15	Pretest	Day 15
WBC x 10^3	9.68±1.43	12.35± 0.47	9.39±1.96	9.00*±1.92	13.51±4.23	13.09±2.84	10.98±0.78	10.49±1.57
Neutrophils (%)	49.1±2.8	59.4±3.8	53.8±6.1	51.2*±6.6	56.4±8.8	62.5±5.4	57.6±7.4	60.9±6.7
Lymphocytes (%)	33.8±8.6	25.4±6.5	34.1±8.0	36.5*±5.3	31.0±9.8	25.5±5.6	29.6±5.8	25.6±7.3

Data taken from Table 1. pp. 11-12 & pp. 18-19. MRID 45410906. *$p \leq 0.05$.

G. CLINICAL CHEMISTRY

Glucose was slightly increased ($p \leq 0.05$) in treated males and females compared to controls on day 15. SGOT and SGPT were elevated 4-5x the pretest values in two treated males; the values for these enzymes were as follows:

	SGPT		SGOT	
	Pretest	Day 15	Pretest	Day 15
Male #3	56	314	18	72
Male #5	40	205	14	69

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Mean glucose measurements are presented in Table 4.

TABLE 4. Selected Clinical Chemistry Values (mean ± SD) in Cats Treated with IGR One Spot Flea Control

	Males				Females			
	Control (untreated)		5X One Spot Flea Control		Control (untreated)		5X One Spot Flea Control	
	Pretest	Day 15	Pretest	Day 15	Pretest	Day 15	Pretest	Day 15
Glucose (mg/dL)	93±6	81± 4	92±4	96*±4	87±9	83±5	88±4	92*±4

Data taken from Table 2, pp. 27-28 & 33-34 , MRID 45410906. *p≤0.05.

H. NECROPSY FINDINGS

Necropsies and histopathological examinations were not performed.

IV. DISCUSSION

A. Clinical signs included vocalization and restlessness and attempts to scratch and lick the application site, vomiting, clear ocular discharge, and reddening of the skin. The study author states that it is not known if the vocalizations, restlessness, licking, and scratching are due to the test material or to discomfort as a result of the large area of wetness from treatment. It was not clear what the Day 14 "sham control" involved. However, if a vehicle control had been included in this study, it might have been possible to determine whether or not these effects were signs of toxicity. The author also attributes the vomiting on day 0 to be a result of handling the animals during dosing. However, it is not possible to confirm this hypothesis since the control animals were not handled on day 0. There were no biologically-significant treatment-related effects on hematology and coagulation parameters. The liver enzymes SGOT (AST) and SGPT (ALT) were increased 4-5x the pretest values in two treated males.

Due to the lack of proper controls and evidence of effects in the treated animals, it is not possible to establish the required 5X margin of safety. This study is classified as **Unacceptable (NON-UPGRADABLE)/ Guideline** for a companion animal safety study [OPPTS 870.7200] in kittens.

B. STUDY DEFICIENCIES

The following deficiencies were noted:

There were only 5 animals/sex/group. The guidelines state that 6 animals/sex/group are required.

No vehicle control was included in this study. Animals were not even sham treated until day 14, and the sham control procedure was not defined.

No body weight or food consumption data were provided.

The liver enzymes in the two treated males that were elevated on Day 15 should have been repeated on Day 28 to determine if they had returned to pretest values. The 870.7200 guidelines state that clinical pathology measurements should be repeated if the values are altered.

DATA EVALUATION RECORD

RF9804

STUDY TYPE: Companion Animal Safety - Cat (OPPTS 870.7200)
MRID 45435901

Prepared for

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Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

Chemical Hazard Evaluation Group
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Task Order No. 01-126

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EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy Date: 9/10/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn E Stewart Date: 9/12/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/kittens [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D276274; MRID NUMBER: 45435901

TEST MATERIAL: RF 9804 Topical

STUDY NUMBER: 2521

TESTING FACILITY: Toxicology and Metabolism, Ricerca, Inc., 7528 Auburn Road, P.O. Box 1000, Painesville OH 44077-1000

SPONSOR: Wellmark International, 1000 Tower Lane, Suite 245, Bensenville, IL 60106

TITLE OF REPORT: A target animal safety evaluation study in juvenile cats with RF 9804 Topical.

AUTHOR: J. Bassett, B.S. and M. Watson, B.Sc.

REPORT ISSUED: March 31, 1999

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 45435901), RF 9804 Topical (Lot/Batch No. ED 134: 3.66% methoprene; Lot/Batch No. ED 160: 19.5% methoprene) was applied topically to groups of 6 male and 6 female kittens in 1.0 mL dose volumes containing 35 mg/mL (the recommended dose) or 182 mg/mL (5 times the recommended dose) of methoprene. Controls were not treated. Animals were treated on study days 0, 7, 14, and 21. Animals were observed for clinical signs once daily throughout the study (the time of observation relative to the treatment time was not indicated). Clinical pathology parameters were evaluated only after the second and third treatment.

Possible treatment-related clinical signs included excessive salivation by one female from the 1X group following the first application of the test material and the scabbing noted in the chin area of one male and one female from the 5X group during weeks 4 and/or 5. However, because clinical observations were not conducted hourly for at least 4 hours following treatment, and not twice daily for the remainder of the study, as required by the guidelines, it is possible that treatment-related clinical signs were missed. There were no treatment-related effects on body weight, food consumption or clinical pathology parameters, with the possible exception of

increased WBC counts in treated males (1x and 5x) and neutrophil counts in males (5x) during Week 4.

This study is classified as **Unacceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats due to the lack of hourly observations following the treatments.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. Test material: RF 9804 Topical

Description: slightly oily, clear liquid with a faint, alcohol-like odor
Lot/Batch Nos.: ED 134, ED 160
Active Ingredients:
Lot/Batch No. ED 134: Methoprene 3.66% (35 mg/mL)
Lot/Batch No. ED 160: Methoprene 19.15% (182 mg/mL)
Storage Conditions: refrigerated in amber glass bottles

B. Administration: Topical (spot-on)

C. Vehicle and/or positive control: none

D. Test animals

Species: Cat
Breed: Domestic shorthair
Age and weight at study initiation: 8 weeks; males: 688-986 g., females: 692-981 g.
Source: Liberty Research, Food and Drug Research Laboratories, Waverly, New York
Housing: Individually in cages
Diet: PMI Feeds, Inc.,™ Feline Diet™ (No. 5003), *ad libitum*, except for when the animals were fasted prior to blood collection and during a 2-day period when the animals were fed commercial Purina Cat Chow
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 64-84 ° F.
Humidity: 30-70%
Air changes: at least 10/hour
Photoperiod: 12-hour light/dark cycle
Acclimation period: 5 days

II. STUDY DESIGN

A. In life dates: Start: September 30, 1998; End: November 4, 1998

B. Animal assignment/dosage and administration

Kittens were assigned to the groups in Table 1 by means of a computer-generated process utilizing random numbers so that the group mean body weights for each sex differed by no more than 10 percent. Group 1 did not receive any treatment; Group 2 (1X) received a test formulation containing a 35 mg/mL concentration of methoprene; and Group 3 (5X) received a test formulation containing a 182 mg/mL concentration of methoprene. The dose volume of both treated groups was 1 mL. Treatments were applied to the base of the hair on the neck area using a syringe. Animals were dosed weekly for a total of 4 applications. The study report does not explicitly state when the treatments were given. Data were reported for weeks -1, 0, 1, 2, 3, 4, 5, and the reviewer is assuming that the first treatment was given during week 0.

TABLE 1. Study design

Group	Number of animals		Dose level (mg methoprene/mL)	Dose volume (mL)	Number of applications[a]
	Male	Female			
1. Untreated control	6	6	0	n/a[b]	0
2. 1X	6	6	35	1	4
3. 5X	6	6	182	1	4

Data taken from text and text table, p. 12, MRID 45435901.

[a] Animals were dosed at weekly intervals.

[b] Not applicable.

C. Dose selection rationale

Treatment levels were chosen by the sponsor. The product is intended to be applied monthly as a 1 mL volume of a 35 mg/mL formulation. The 5X exaggerated dose was achieved by using a formulation containing an increased amount of the active ingredient. Although the product is intended for once a month use, and a single repeated treatment 4 weeks after the first treatment would have been acceptable, the study included repeated treatments at weekly intervals for a total of four treatments. No explanation was provided for the absence of 3X and vehicle control groups.

D. Experimental design

The cats were observed for mortality or moribundity twice daily during the acclimation, treatment, and observation periods. After the initiation of dosing, animals were observed once daily for clinical signs. Complete physical examinations were conducted and the animals were weighed one week prior to initiation of dosing and weekly thereafter until study termination. Beginning one week prior to initiation of dosing, food consumption was calculated weekly using the amounts of food given to and left by each cat each week.

E. Pathological parameters

1. Blood samples were collected from fasted, anesthetized animals via jugular venipuncture once prior to initiation of dosing, 24 hours after the third application of the test material, and 24 hours after the fourth application of the test material. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)*		
	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
		X[a]	Total and direct bilirubin*
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase(ALK)*		Triglycerides
	Cholinesterase(ChE)		Serum protein electrophoresis
X	Creatine kinase	X	Albumin/Globulin ratio
	Lactic acid dehydrogenase(LDH)		
X	Serum alanine amino- transferase (also SGPT)*		
X	Serum aspartate amino- transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
X	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

[a]Total bilirubin was evaluated but direct bilirubin was not.

2. Urine samples were obtained at the time of blood collection by placing clean litter boxes filled with glass beads in the cages the prior afternoon. The CHECKED (X) parameters were examined.

a. Urinalysis*

X		X	
X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)	X	Nitrate
X	Protein	X	Urobilinogen
			Osmolality

* Not required for companion animal safety studies

F. Statistics

Body weights, body weight gains, food consumption, hematology, blood chemistry, and urinalysis parameters were subjected to statistical analysis as follows, with data from males and females being analyzed separately. Bartlett's test was used at the 1% significance level. If Bartlett's test was not significant, Bonferroni's t-test was used to compare the treated groups to the control group. If Bartlett's test was significant, Dunn's summed-rank test was used to compare the treated groups to the control group. Regression analysis was used to test for a linear trend; however, for parametric data the test for trend was only performed if the test for lack of fit was not significant at the 1% level. Two-sided tests were used at the 1% and 5% significance levels for comparison of means and at the 1% significance level in the tests for trend.

G. Disposition of animals

The cats were returned to the test facility stock at the end of the study.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Each 1.0 mL of the 1X formulation contained 35 mg of methoprene, and each 1.0 mL of the 5X formulation contained 182 mg of methoprene. Therefore, the 5X group received 5.2 times the recommended dose.

B. Mortality

There were no deaths during the study.

C. Clinical signs

Abnormal clinical signs observed during the study are given in Table 2. Clinical observations were not conducted at hourly intervals following application of the test material, and the study report only included which week of the study a particular clinical sign was exhibited by a particular animal. Excessive salivation by one female from the 1X group following the first application of the test material and the scabbing noted in the chin area of one male and one female from the 5X group are considered possibly treatment-related. The colored material around the eyes of the same female from the 5X group, and lacrimation from the left eye of one female from the 5X group are considered potentially treatment-related. The observations of soft or few/no feces are unlikely to be treatment-related as they were observed in the control groups and, in one case were first noted during the week prior to the first application of the test formulation; however, since there was insufficient data provided as to when the observations were made with respect to the test material applications, it is impossible to definitely rule out that some of the observations of soft feces may have been treatment-related.

TABLE 2. Abnormal clinical signs exhibited by kittens treated with RF 9804 Topical (Number of animals exhibiting the sign/the week that the sign was observed)[a]

Observation	Treatment group					
	Untreated controls		1X		5X	
	Male	Female	Male	Female	Male	Female
Excessive salivation	0	0	0	1 kitten Week 0	0	0
Scabbing chin area	0	0	0	0	1 kitten[b] Weeks 4, 5	1 kitten[c] Week 4
Colored material around eyes	0	0	0	0	0	1 kitten Week 1
Lacrimation (left eye)	0	0	0	0	0	1 kitten[d] Week 0
Soft feces	2 kittens Week 3 Week 4	2 kittens Week 2 Weeks 3, 4	3 kittens Weeks -1 to 5 Weeks 0 to 2, 4 Week 4	3 kittens Weeks 1, 2 Weeks 2, 4 Week 4	3 kittens Week 1 Week 1 Week 3	4 kittens Weeks 1, 2 Week 3 Week 4 Week 4
Few or no feces	0	0	1 kitten[e] Week 3	0	0	0

Data taken from Tables 1, 2, A-1, and A-2, pp. 23, 24, 65-67, and 68-70, respectively. MRID 45435901.

[a] The study only reported that a particular clinical sign was observed during a particular week of the study.

[b] This kitten also had soft feces during week 3.

[c] This kitten also had colored material around its eyes during week 1.

[d] This kitten also had soft feces during week 4.

[e] This kitten also had soft feces during weeks -1 through 5.

D. Bodyweight and weight gain

The group mean body weights and mean body weight gains (with respect to week 0) of the treated groups were similar to those of their respective controls for all intervals. The majority of the kittens gained weight every week, with the only exceptions being one male from the 1X group and one female from the control group that both lost weight between weeks 1 and 2 but gained weight during all other intervals.

E. Food consumption

There were no significant differences between the mean amounts of food consumed per week of the treated groups as compared to those of their respective controls.

F. Hematology

There were no treatment-related effects on hematology and coagulation parameters as assessed 24 hours following the third and fourth treatments (15 and 22 days after the first treatment). There were occasional statistically significant differences between the treated and control groups, but none were of sufficient magnitude to be considered biologically significant, with the possible exception of WBC counts in treated males at Week 4. WBC counts were statistically significantly increased in both the 1x and 5x groups as compared to controls. No laboratory reference values were provided so it is unknown if these levels exceeded normal WBC counts for kittens of this age. The percentage of neutrophils was also significantly increased in the 5x males.

G. Clinical chemistry

There were no treatment-related effects on clinical chemistry parameters as assessed 24 hours following the third and fourth treatments (15 and 22 days after the first treatment). There were occasional statistically significant differences between the treated and control groups, but none were of sufficient magnitude to be considered biologically significant.

H. Urinalysis

There were no statistically significant differences in the urine specific gravity, pH, or urobilinogen concentrations of the treated groups as compared with their respective controls 24 hours following the third and fourth treatments (15 and 22 days after the first treatment). The results for urine occult blood and urine protein were not compared statistically. Small, moderate, or large amounts of occult blood and/or urine protein concentrations of $\geq$100 mg/dL were noted in the urine of one or more animals from most groups at most intervals. These findings are not treatment-related as they were observed in the control groups and were noted during the week prior to the first application of the test formulation as well as at the later two measuring intervals, and there was no clear dose-response pattern seen.

G. Necropsy findings

Necropsies and histopathological examinations were not performed, as all animals survived until termination of the study.

IV. DISCUSSION

A. Discussion

Possible treatment related clinical signs included excessive salivation at the 1X treatment level and scabbing on the chin area at the 5X treatment level. Additional clinical signs noted at the 5X treatment level that may have been treatment-related included colored material around the eyes and lacrimation at the 5X treatment level. However, clinical observations were not conducted hourly for at least 4 hours following treatment, and were only conducted once daily for the remainder of the study rather than twice daily as recommended in the guideline. It is therefore possible that there were additional treatment-related clinical signs on the day of dosing that were missed. There were no treatment-related effects on body weights, food consumption, or clinical pathology parameters, with one possible exception. WBC counts were increased in the 1x and 5x males at Week 4; the percentage of neutrophils was also increased in the 5x males. However, individual WBC counts were extremely variable.

B. Study deficiencies

Clinical observations were conducted only once daily, including the days of treatment. The time of observation, relative to the treatment time was not indicated. The guideline recommends that clinical observations be conducted hourly on the day of treatment for at least 4 hours following treatment, and twice daily thereafter. It is, therefore, possible that there were treatment-related clinical signs on the days of dosing that were missed. In addition, the data did not include the time of each abnormal sign and its subsequent course, but only reported which week of the study a particular clinical sign was exhibited by a particular animal. It was, therefore, impossible to correlate the onset of clinical signs with treatment days.

The study design did not include 3X or vehicle control groups. As this study attained a 5X exaggerated dose by using a formulation containing an increased amount of the active ingredient, the reviewer considers the inclusion of a group treated with the inert ingredients at the maximum levels that would appear in the 5X formulation as particularly important.

Other, minor deficiencies include the following. The protocol stated that urine protein values were verified by sulfosalicylic acid test, but these data were not included in the study. Individual food consumption was measured weekly rather than daily. The study report did not mention whether the animals were dewormed. Activated partial thromboplastin time and direct bilirubin were not evaluated.

C. Study Acceptability

Due to the lack of hourly observations following treatments, this study is classified as **Unacceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats.

DATA EVALUATION RECORD

LIQUID ONCE-A-MONTH STRIPE-ON PRODUCT

STUDY TYPE: Companion Animal Safety - Cat [OPPTS 870.7200]
MRID 44864007C

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 01-129

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Date: AUG 2 9 2001

Disclaimer

This review may have been altered subsequent to the contractors signatures above.

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy Date: 9/4/01
Reregistration Action Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart Date: 9/17/2001
Toxicology Branch , Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Cats and kittens [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D276263; MRID NUMBER: 44864007C

TEST MATERIAL: Liquid Once-a-month Stripe-on Product

STUDY NUMBER: 99879

TESTING FACILITY: White Eagle Toxicology Laboratories, 2003 Lower State Road, Doylestown, PA 18901

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

TITLE OF REPORT: Domestic animal safety study of a monthly stripe-on formula in domestic shorthair cats and kittens

AUTHOR: C. Godin

REPORT ISSUED: June 9, 1999

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 44864007C), Liquid Once-a-month Stripe-on Product [Active Ingredients: 95.2% Sumithrin (d-phenothrin); 3.09% (S)-Methoprene; Lot no. 11401] was topically applied (as a stripe along the animal's back) to groups of 6 male and 6 female cats or 6 male and 6 female kittens at dose volumes of 1.0 mL for a total of 5 doses given approximately 60 minutes apart (5 times the recommended dose). Controls were dosed at the same intervals with 1.0 mL of safflower oil.

One male from the 5X adult group had reddened skin at the base of the skull 1 hour after the fourth treatment which lasted for 27 hours and was considered treatment-related. Other clinical signs that may have been related to treatment included the following: excessive salivation of up to 12 minutes duration exhibited by two animals from the 5X adult group on day 0 and restlessness with signs of discomfort and occasional scratching exhibited by one animal from the 5X group which lasted for 37 minutes following the last treatment. The study author attributed the salivation to the animals licking the test substance. There were no treatment-related clinical signs exhibited by animals from the 5X kitten group. During the Day 0-7 interval, the 5X male adult and female kitten groups had significant ($p<0.05$) mean body weight losses compared to

mean body weight gains by their respective control groups (adult males: -0.10 vs. +0.05 kg for controls; female kittens: -0.02 vs. +0.07 kg for controls), and body weight gain by the 5X male kitten group was significantly decreased and compared to controls (0 vs. 0.12 kg; $p<0.05$). During the Days 1-5, food consumption by 5X male and female adults and 5X male kittens were decreased as compared to their respective control groups. There were no treatment-related effects on hematology, coagulation or clinical chemistry parameters.

This study is classified as **Unacceptable /Guideline** for a companion animal safety study (OPPTS 870.7200) in cats and kittens. The observed toxicity at the 5X treatment level indicates that a full study using 3 dose levels should have been done instead of a limit test, and a repeat treatment should have been included.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. Test material: Liquid Once-a-month Stripe-on Product

Description: liquid
Lot No.: TS 11402
Active Ingredients: 95.22% Sumithrin; 3.09% (S)-Methoprene
Storage Conditions: ambient temperature and humidity

B. Administration: Topical

C. Vehicle and/or positive control: none; however, the negative control group was treated with safflower oil

D. Test animals

Species: Cat
Breed: Domestic shorthair
Age and weight at study initiation: Adults: 7-8 months; males: 3.7-5.5 kg., females: 2.6-3.4 kg.; Kittens: approximately 10-11 weeks; males: 1.4-1.8 kg., females: 1.2-1.7 kg.
Source: Liberty Research, Waverly, New York
Housing: Individually in cages
Diet: Purina Lab Feline Diet #5003, approximately 200 g. per animal
Water: *ad libitum*
Environmental conditions:
Temperature: 58-82° F.
Humidity: 1-64%
Air changes: not reported
Photoperiod: not reported
Acclimation period: 13 or 14 days

II. STUDY DESIGN

A. In life dates: start: February 23, 1999; end: March 23, 1999

B. Animal assignment/dosage and administration

The animals were assigned to the groups in Table 1 based on body weight by means of a random permutation table. The adult and kitten control groups received safflower oil, and the adult and kitten 5X groups received the test article. The dose volume for all groups was 1 mL, and treatments were repeated approximately every 60 minutes for a total of 5 applications. Treatments were administered using a syringe with no needle as a stripe along the back of each animal from the base of the skull to the base of the tail. The syringe was kept at skin level, and the samples were dispensed as evenly as possible.

TABLE 1. Study design

Group	Number of animals		Dose volume (mL)	Number of applications[a]
	Male	Female		
1. Adult control	6	6	1	5
2. Adult 5X	6	6	1	5
3. Kitten control	6	6	1	5
4. Kitten 5X	6	6	1	5

Data taken from text and text table, p. 11, MRID 44864007C.
[a] Treatments were given approximately 60 minutes apart.

C. Dose selection rationale

The dose selection rationale was not stated in the study report.

D. Experimental design

The animals were observed for mortality or moribundity twice daily during the week and once daily on the weekends. Physical examinations were conducted during acclimation. On Day 0 clinical observations were made prior to dosing and 0.5, 1, 2, 3, 4, and 6 hours post dosing, with additional observations if warranted by frequency or severity of clinical signs, and on Days 1-14 clinical observations were made twice daily. The animals were weighed on Days -7, 0, 7, and 14. Individual food consumption was measured qualitatively daily from Day -7 through the end of the study by estimating whether the animal had eaten 0, 1-25, 26-50, 51-75, or 76-100% of an approximately 200 g portion of food.

E. Pathological parameters

Blood samples were collected from fasted anesthetized animals via jugular venipuncture on Days -7, 1 (approximately 24 hours after treatment), and 7. The CHECKED (X) parameters were examined.

1. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)*		
X	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

2. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
	ENZYMES	X	Total and direct bilirubin*
		X	Total serum protein (TP)*
X	Alkaline phosphatase(ALK)*		Triglycerides
	Cholinesterase(ChE)		Serum protein electrophoresis
	Creatine kinase	X	Albumin/Globulin ratio
	Lactic acid dehydrogenase(LDH)		
X	Serum alanine amino- transferase (also SGPT)*		
X	Serum aspartate amino- transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

[a] Total bilirubin was evaluated but direct bilirubin was not.

F. Statistics

Group means and standard deviations were calculated. Clinical pathology data from days 1 and 7 were compared to pretest values using paired Student's two-tailed t-test.

G. Disposition of animals

One kitten was adopted. The remaining kittens and all adult cats were euthanized.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Adult males and females from the Adult 5X group received 1058.4-1401.6 mg/kg and 1571.5-1920.7 mg/kg of the test article, respectively. Male and female kittens from the Kitten 5X group received 2881.1-3704.3 mg/kg and 3241.3-3989.2 mg/kg of the test article, respectively.

B. Mortality

There were no deaths during the study.

C. Clinical signs

Selected abnormal clinical signs observed during the study are given in Table 2. The observation of reddened skin at the base of the skull of one 5X adult is considered treatment-related. Other clinical signs that may have been treatment-related included excessive salivation and restlessness with signs of discomfort and occasional scratching.

TABLE 2. Selected abnormal clinical signs exhibited by cats and kittens treated with Liquid Once-a-month Stripe-on Product or safflower oil
[Number of animals (Number of occurrences)/Time observed (duration, if applicable)]

Observation	Adult control	Adult 5X	Kitten control	Kitten 5X
Reddened skin at base of skull	0	1 m (1) 1 hr after 4th dose (27 hours)	0	0
Excessive licking of dose site	1 m, 1 f (2) ≤7 min. after 1st dose (≤10 minutes)	1 f (2) 15 min after 2nd dose (2 min) [a] 2 min after 5th dose (37 min) [a]	0	0
Excessive salivation	0	2 f (4) 3 min after 1st dose (5 min) [b] 5 min after 1st dose (3 min) [a] 41 min after 4th dose (4 min) [b] 3 hours after 5th dose (12 min) [a]	0	0
Restlessness with signs of discomfort and occasional scratching	0	1 f (1) 2 min after 5th dose (37 min) [a]	0	0
Ongoing soft, mucoid feces with or without red substance present	0	1 m (1) Days -11 to -8	0	0
Single occurrence(s) of soft or liquid/soft feces with or without red substance	0	2 f (3) Day 0 prior to treatment and Day 1 [a]	0	1 f (1) Day 1
Slight wheezing respiration	1 m (1) 1 min. after 1st dose (5.5 hours)	0	0	0
Slightly lethargic	0	0	1 f (1) Day 1	0

Data taken from text, pp. 26-34 and Table 3, pp. 43-45, MRID 44864007C.

[a] These signs were exhibited by the same animal.
[b] These signs were exhibited by the same animal.

D. Body weight and weight gain

Body weight data are given in Table 3. The group mean body weights of the treated groups were similar to those of their respective controls for all intervals. During the Day 0-7 interval, the 5X male adult and female kitten groups had significant ($p<0.05$) mean body weight losses compared to mean body weight gains by their respective control groups, and body weight gain by the 5X male kitten group was significantly ($p<0.05$) decreased compared to controls. These differences are considered treatment-related.

TABLE 3. Mean body weights and body weight changes[a] of cats and kittens treated with Liquid Once-a-month Stripe-on Product or safflower oil (kg)[b]

Study day	Males		Females	
	Controls	5X	Controls	5X
Adults				
-7	4.3±0.4[b]	4.2±0.5	3.0±0.2	3.0±0.3
0	4.4±0.6	4.3±0.4	2.9±0.3	3.0±0.3
7	4.5±0.4	4.2±0.4	2.9±0.3	2.9±0.3
14	4.7±0.5	4.6±0.5	3.0±0.2	3.1±0.2
Body Weight Changes[a]				
-7-0	0.13±0.19	0.10±0.17	-0.07±0.20	-0.02±0.08
0-7	0.05±0.14	-0.10±0.06 *	-0.02±0.13	-0.10±0.06
7-14	0.22±0.12	0.32±0.12	0.12±0.04	0.22±0.12
Kittens				
-7	1.4±0.1	1.4±0.1	1.3±0.2	1.4±0.1
0	1.6±0.1	1.6±0.2	1.5±0.2	1.5±0.1
7	1.7±0.1	1.6±0.2	1.5±0.2	1.4±0.1
14	2.0±0.2	1.9±0.2	1.8±0.2	1.7±0.2
Body Weight Changes[a]				
-7-0	0.18±0.08	0.17±0.05	0.15±0.05	0.08±0.04 *
0-7	0.12±0.04	0±0.11 *	0.07±0.05	-0.02±0.04 *
7-14	0.27±0.05	0.32±0.04 *	0.25±0.05	0.3±0.06

Data taken from Tables 7 and 8, pp. 28-29 and 30-31, respectively, MRID 44864007C.

[a] Calculated by reviewer using data from Tables 7 and 8, MRID 44864007C.

[b] Data expressed as Mean ± Standard deviation.

* Significantly different from control:$p<0.05$. Data were analyzed by reviewer using Bartlett's test followed by either Dunnett's comparison or a non-parametric t-test, as appropriate.

E. Food consumption

Food consumption data are given in Table 4. Food consumption was evaluated qualitatively, using the following scores: 0=no food consumed; 1=1-25% of food consumed; 2=26-50% of food consumed; 3=51-75% of food consumed; and 4=76-100% of food consumed. The study report also provided mean daily scores for each group. It is difficult to evaluate data presented in this manner; therefore, the reviewer calculated and compared the overall mean of the mean daily scores and the range of daily means during the pretreatment interval and each of the two weeks following treatment. The mean scores for days on which the animals were fasted were excluded. During the 5 days following treatment, food consumption by 5X male and female adults and 5X male kittens was decreased as compared to their respective control groups. The overall means of these groups differed from those of their respective controls by 0.6 to 1.0, and differences of these magnitudes were not noted for any group for either of the other two intervals. Food consumption by the 5X female kitten group was only slightly less than controls for Study Days 1-5.

TABLE 4. Food consumption by cats and kittens treated with Liquid Once-a-month Stripe-on Product or safflower oil [Mean of mean daily scores (Range of mean daily scores)][a]

Study day[b]	Males		Females	
	Controls	5X	Controls	5X
Adults				
-6 to -1	3.7 (3.5-4.0)	3.3 (3.0-3.8)	2.7 (2.0-3.5)	2.7 (2.2-3.8)
1-5	3.5 (3.3-4.0)	2.5 (1.8-3.0)	2.2 (1.5-2.8)	1.4 (0.7-1.8)
7-13	3.8 (3.7-4.0)	3.7 (3.3-4.0)	3.0 (2.8-3.3)	3.2 (2.7-3.5)
Kittens				
-6 to -1	3.1 (2.7-3.3)	3.0 (2.8-3.2)	3.2 (3.0-3.7)	2.9 (2.3-3.3)
1-5	3.4 (3.2-3.8)	2.8 (2.2-3.3)	3.0 (2.8-3.2)	2.8 (2.5-3.2)
7-13	3.1 (2.8-4.0)	3.1 (2.5-3.8)	3.0 (2.7-3.8)	3.2 (2.7-3.7)

Calculated by reviewer using data found in Tables 9 and 10, pp. 32-33 and 34-35, respectively, MRID 44864007C.

[a] Food consumption was evaluated qualitatively, using the following scores: 0=no food consumed; 1=1-25% of food consumed; 2=26-50% of food consumed; 3=51-75% of food consumed; and 4=76-100% of food consumed.

[b] Animals were fasted on Days -7, 0, and 6; therefore, the mean food consumption scores for these days were excluded from calculations.

F. Hematology

There were numerous statistically significant differences noted when hematology and coagulation parameters at 1 and 7 days following the final treatment were compared to their pre-treatment values. However, most parameters fell within the reference ranges for the laboratory, the differences between the pre- and post-treatment values for the same group were not of sufficient magnitude to be considered biologically significant, and/or the values for the treated group(s) were similar to those of their respective controls at the same interval. The pretest mean monocytes (%) and basophils (%) of all kitten groups (treated and control, male and female) exceeded the upper limit of the reference range,

but as these increases were only noted prior to treatment, they cannot be treatment-related and are of unknown significance.

G. Clinical chemistry

There were numerous statistically significant differences noted when clinical chemistry parameters at 1 and 7 days following the final treatment were compared to their pre-treatment values. However, most parameters fell within the reference ranges for the laboratory, the differences between the pre- and post-treatment values for the same group were not of sufficient magnitude to be considered biologically significant, and/or the values for the treated group(s) were similar to those of their respective controls at the same interval. The mean alanine aminotransferase activity of the 5X female kitten group was increased above the reference range pretest and on Day 1 and fell within the reference range on Day 7 (Table 5). This is not considered to be treatment-related as it was first noted prior to treatment, and in the absence of elevated aspartate aminotranferase activity, the biological significance of this finding is questionable.

TABLE 5. Alanine aminotranferase activity in kittens treated with Liquid Once-a-month Stripe-on Product or safflower oil (U/L)[a]

Study day	Males		Females	
	Controls	5X	Controls	5X
Pretest	51±10	58±7	58±18	95±36 [b]
1	54±10	51±7	61±22	81±34 [b]
7	50±11	57±6	57±19	60±12

Data taken from Tables 17 and 18, pp. 55-57 and 58-60, respectively, and Appendix B, p. 80, MRID 44864007C.
[a] Data expressed as Mean ± Standard deviation
[b] Value exceeds the laboratory's reference range for kittens (1-67 U/L).

H. Necropsy findings

Necropsies and histopathological examinations were not performed.

IV. DISCUSSION

A. Discussion

Treatment related effects noted in adult cats treated at 5 times the intended recommended dose included clinical signs (reddened skin and possibly excessive salivation and restlessness with signs of discomfort and occasional scratching), body weight loss by males and decreased food consumption by males and females. Treatment-related effects noted in kittens treated at 5 times the intended recommended dose included decreased body weight gains by males, body weight loss by females, and decreased food consumption by males. There were no treatment-related effects on clinical pathology parameters.

B. Study deficiencies

The product is intended to be used monthly, and the study therefore should have included a repeat treatment 28 days after the first treatment. Products with re-treatment intervals of 14-30 days do not require a repeat treatment if there is no toxicity observed at the 5X dose level: however, toxicity was observed at the 5X dose level in this study. In fact, the observed toxicity at the 5X treatment level indicates that a full study using 3 dose levels should have been done instead of a limit test.

The study report mentioned that the animals were vaccinated but did not mention whether they were dewormed. The observation of mucoid feces and/or feces containing a red substance during acclimation and the remainder of the study suggest that the health status of the animals may have been compromised by infectious disease.

There was no vehicle control group. Information on the inert ingredients of the formulation was removed to a Confidential Appendix.

Data were not summarized but instead were presented with individual data and group means together in the same table and printed in a very small font. The made it unnecessarily difficult and time-consuming for the reviewer to evaluate the data.

Body weights were not subjected to statistical analysis, and clinical pathology data for each interval should have been compared to controls.

C. Study Acceptability

This study is classified as **Unacceptable /Guideline** for a companion animal safety study [OPPTS 870.7200] in cats. Toxicity was observed at the 5X treatment level in cats and kittens, and this study therefore should have been conducted as a full study using 3 dose levels, and a repeat treatment should have been included 28 days after the first treatment.

DATA EVALUATION RECORD

TOLERANCE OF A MONTHLY STRIPE-ON FORMULA CONTAINING ADULTICIDE AND IGR IN PUPS

STUDY TYPE: Companion Animal Safety – Dog (OPPTS 870.7200)
MRID 450064-02 C

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Yask Order No. 01-128

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Date: AUG 2 3 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia Dobozy, VMD, MPH Virginia Dobozy Date: 9/4/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart Date: 9/7/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Puppies [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D 276262; MRID NUMBER: 450064-02 C

TEST MATERIAL: TS 11506

STUDY NUMBER: USA004/99-001 (Hartz Test Number 1499)

TESTING FACILITY: Biological Laboratories Europe Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

SPONSOR: Hartz Mountain Corp., 192 Bloomfield Avenue, Bloomfield, NJ 07003

TITLE OF REPORT: Tolerance of a Monthly Stripe-on Formula Containing Adulticide and IGR in Pups

AUTHOR: Geoff Wragg H.N.C., H.T.E.C.

REPORT ISSUED: December 6, 1999 (study completion date)

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 450064-02C), a stripe-on formula [Active Ingredients based on two analyses: Sumithrin (d-phenothrin), 84.154 and 84.487% w/w; (S)-methoprene, 2.323 and 2.319%] was topically applied (as a stripe along the back) at a 5X dose (1.3 mL every 60 min until a 5X dose was achieved) to a group of 6 male and 6 female beagle dogs, 84-90 days old at study initiation. Controls were treated with safflower oil. Treatments were applied to the skin of the back from a point midway between the shoulder blades to the base of the tail. Blood samples were obtained on the Days -7, 2 and 7 for hematology and clinical chemistry measurements. Animals were observed for 14 days.

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology. Several statistically-significant clinical chemistry differences were observed between treated and control groups: however, these were within the pre-test reference ranges (mean ± two standard deviations) for the animals included in the study, and are therefore not considered toxicologically significant.

This study followed the pertinent guidelines for a companion animal safety study (OPPTS 870.7200). The package labeling and application instructions were not provided. It is assumed that the intended use would be for only one application per month of 1.3 mL as stated in the

study report. If this is the case, then the required 5X margin of safety has been demonstrated and the study is **Acceptable/Guideline.**

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. TEST MATERIAL: Liquid Once a Month Stripe-on Product 11506

Description: Liquid
Lot/Batch No.: TS 11506
Active Ingredients: Based on two analyses: Sumithrin, 84.154 and 84.487% w/w; (S)-methoprene, 2.323 and 2.319%
Storage Conditions: 16-18°C, except for one occasion when the temperature dropped to 13°C.

B. ADMINISTRATION: Topical (stripe-on)

C. VEHICLE AND/OR POSITIVE CONTROL

Vehicle: Not reported; the inert ingredients of the product were removed to a Confidential Appendix
Control: Safflower oil
Positive control: none

D. TEST ANIMALS

Species: Dog
Breed: Beagle
Age and weight at study initiation: Males: 84-90 days old on Day 0; 2.1-5.1 kg on Day -1; Females, 84-90 days old on Day 0; 2.8-4.7 kg on Day -1
Source: Biological Laboratories Europe Ltd
Housing: Individually, in 2 m by 0.88 m pens
Diet: Pedigree Chum pup food, at the recommended rates
Water: *ad libitum*; potable water supply.
Environmental conditions:
Temperature: 16-24°C
Humidity: 38-68%
Acclimation period: 7 days

II. STUDY DESIGN

A. IN LIFE DATES

Start: Sept. 15, 1999 (set 1), Sept. 23, 1999 (set 2), Sept. 30, 1999 (set 3); End: Oct. 6, 1999 (set 1); Oct. 14, 1999 (set 2), Oct. 21, 1999 (set 3). Note: Pups used in the study were drawn from more than one litter. As it was not possible to have the full complement of pups available at the same time, the pups were assigned to the study in three sets.

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

Pups in each set were assigned to the treatment group and control groups on Day -1 using random order numbers derived from Fisher and Yates tables. Pups from each set were represented equally in each group. Six pups/sex were topically treated with a 1X dose of TS 11506 (1.3 mL) every 60 min until a 5X total dose was achieved. The test material was applied with a syringe (no needle) directly to the skin of the back from a point midway between the shoulder blades extending to the base of the tail. In the control animals 1.3 mL of safflower oil was applied five times at 60 min intervals.

TABLE 1. Experimental design

Group	No. of animals		Treatment	Number of applications
	Male	Female		
1	6	6	Controls 1.3 mL safflower oil	5
2	6	6	1.3 mL TS 11506	5

Data taken from p. 13, MRID 450064-02 C.

C. DOSE SELECTION RATIONALE

The rationale for the dose level was to establish the margin of safety and potential toxicity of 5X the recommended label dose.

D. EXPERIMENTAL DESIGN

Clinical assessments were carried out prior to dosing, within 30 min of dosing, and at approximately 1, 2, 3, 4, and 6 hours after the last application on Day 1 and twice daily thereafter for the following 14 days. The animals were observed for changes in behavior, signs of effects on the nervous system and muscles, condition of the feces, occurrence of vomiting, and reaction at the application site. Food consumption was recorded from Day -7 to Day 14; body weights were recorded on Days -7 (pretest), -1, 7 and 14.

E. PATHOLOGICAL PARAMETERS

Blood samples were obtained on Day -6 (pretreatment), Day 1 and Day 7. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count	x	Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)*		
x	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total Cholesterol
x	Potassium*	x	Globulin*
x	Sodium*	x	Glucose*
		x	Total and direct bilirubin*
	ENZYMES	x	Total serum protein*
x	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)	x	Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)	x	Albumin/globulin ratio
x	Serum alanine amino- transferase (also SGPT)*		
x	Serum aspartate amino- transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

Group means for hematology and clinical chemistry parameters were compared using analysis of variance (ANOVA), after transformation when appropriate, with sex and treatment group as factors. Baseline values were included as co-variants.

G. DISPOSITION OF ANIMALS

Not reported.

H. COMPLIANCE

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The total amount of product applied was 6.5 mL, and this contained approximately 84.3% w/w sumithrin and 2.3% w/w (s)-methoprene. After five applications, the total dose per animal ranged from 6.66 g to 6.82 g (MRID 450064-02C, p. 38). The total amount of sumithrin applied was therefore 5.61- 5.75 g and that of (S)-methoprene 0.15-0.16 g. The overall mean weight of the treated animals was 3.9 kg (MRID 450064-02C, p. 35); therefore, the total dose of sumithrin ranged from 1.44 g/kg to 1.47 g/kg, and the total dose of (s)-methoprene ranged from 0.038 g/kg to 0.041 g/kg.

B. MORTALITY

No pups died during the study.

C. CLINICAL SIGNS

Clinical observations are presented in Table 2. There were no other reported differences between the control and treatment groups in any of the parameters evaluated, except a male in the treatment group had loose feces in the morning of Day 8. The stools were normal by the afternoon.

TABLE 2. Clinical observations

Treatment group	Sex	Day	Observation
5X- Control	M, F	1-14	No changes
5X- Treatment	M	8	Loose feces

Data taken from p. 31, MRID 450064-02 C.

D. BODYWEIGHT AND WEIGHT GAIN

From Day -1 to Day 14 the mean body weight of the treated males increased by 1.1 kg while the control males increased by 1.3 kg. The weight of both the control and treated females increased by 1.1 kg. The reported differences in body weight gain between control and treated groups was considered by the study authors to be within normal inter-animal variation.

E. FOOD CONSUMPTION

It was reported that there was no evidence of a decrease in appetite after control or test item application. There was no indication that food consumption data were analyzed statistically.

F. HEMATOLOGY

No treatment-related, biologically-significant hematological effects were observed. Individual values outside the normal limits occurred sporadically in both control and treated animals, but there were no reported significant differences in mean values between treated and control groups.

G. CLINICAL CHEMISTRY

There were no statistically significant clinical chemistry differences between control and test groups in the following: ALT, AST, albumin, albumin/globulin ratio, total bilirubin and direct bilirubin, glucose, sodium, potassium, cholesterol, and calcium. Statistically significant differences between control and test groups were seen in the following (see Table 3): alkaline phosphate (ALP), urea, creatinine, total protein, globulin, chloride, phosphorus, and triglycerides; however, in each case the values were reported to be within the reference range for the study animals. The reference ranges were based on the mean ± two standard deviations of the values recorded on Day -6 of the study.

TABLE 3. Selected changes in clinical chemistry[a]				
Parameter /sample time	Males		Females	
	Controls	5X	Controls	5Xx
ALP- Day -6 (u/L)	138.05±16.16	159.61±39.69	160.86±46.84	163.15±60.06
ALP- Day 1 (u/L)	115.98±16.26	155.28[b]±28.97	145.63±52.53	153.87[b]±71.68
ALP- Day 7 (u/L)	125.58±17.20	146.43[b]±39.25	121.25±69.63	147.98[b]±81.94
Urea- Day -6 (mmol/L)	3.08±1.33	4.18±2.00	3.77±1.91	3.60±0.59
Urea- Day 1 (mmol/L)	3.19±0.52	3.62[c]±1.16	4.76±4.82	3.55[c]±0.42
Urea- Day 7 (mmol/L)	3.51±0.99	2.98[c]±1.00	4.92±4.66	3.55[c]±1.00
Creatinine- Day -6 (mmol/L)	16.42±6.92	17.88±11.16	25.14±10.81	25.63±10.69
Creatinine- Day 1 (mmol/L)	35.93±14.53	36.20[d]±17.31	39.80±14.00	31.54[d]±16.63
Creatinine- Day 7 (mmol/L)	22.88±5.00	21.82[d]±6.31	23.94±5.89	17.87[d]±7.09
Total protein- Day -6 (g/L)	49.85±1.92	47.06±3.65	51.34±2.47	49.57±4.23
Total protein- Day 1 (g/L)	48.09±2.07	47.71[e]±4.67	52.63±2.74	48.17[e]±4.46
Total protein- Day 7 (g/L)	50.13±2.60	49.09[e]±5.63	52.43±1.26	48.97[e]±4.45
Globulin- Day -6 (g/L)	25.65±1.95	24.76±1.71	25.76±1.99	24.89±2.40
Globulin- Day 1 (g/L)	24.48±1.93	24.26[f]±1.78	25.49±1.64	23.00[f]±3.20
Globulin- Day 7 (g/L)	24.74±3.52	24.87[f]±3.83	23.69±2.81	22.33[f]±4.61
Chloride- Day -6 (mmol/L)	110.75±1.83	111.92±3.00	109.30±3.40	109.87±5.23
Chloride- Day 1 (mmol/L)	108.75±2.59	110.19[g]±2.88	108.33±0.99	110.68[g]±1.67
Chloride- Day 7 (mmol/L)	110.05±0.97	111.20[g]±2.08	109.62±0.90	111.30[g]±0.68
Phosphorus- Day -6 (mmol/L)	3.13±0.36	3.09±0.24	3.07±0.26	3.00±0.25
Phosphorus- Day 1 (mmol/L)	3.07±0.20	3.15[h]±0.20	3.03±0.24	3.08[h]±0.21
Phosphorus- Day 7 (mmol/L)	3.02±0.26	3.02[h]±0.19	2.92±0.18	3.10[h]±0.18
Triglycerides- Day -6 (mmol/L)	0.33±0.13	0.33±0.17	0.35±0.10	0.39±0.11
Triglycerides- Day 1(mmol/L)	0.38±0.14	0.37[i]±0.05	0.39±0.12	0.30[i]±0.07
Triglycerides- Day 7 (mmol/L)	0.44±0.06	0.37[i]±0.06	0.40±0.07	0.35[i]±0.04

Data taken from Tables 27- 29, MRID 450064-02C

[a] Mean values and ± SD

[b] p = 0.0227; p. 33 of Appendix 5 of MRID 450064-02C

[c] p = 0.0022; p. 35 of Appendix 5 of MRID 450064-02C

[d] p = 0.0469; p. 37 of Appendix 5 of MRID 450064-02C

[e] p = 0.0474; p.38 of Appendix 5 of MRID 450064-02C

[f] p = 0.0341; p. 41 of Appendix 5 of MRID 450064-02C

[g] p = 0.0068; p. 48 of Appendix 5 of MRID 450064-02C

[h] p = 0.0148; p. 52 of Appendix 5 of MRID 450064-02C

[i] p = 0.0208; p. 53 of Appendix 5 of MRID 450064-02C

H. NECROPSY FINDINGS

No necropsies were performed.

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IV. DISCUSSION

A. DISCUSSION

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical chemistry, or hematology. Several statistically-significant clinical chemistry differences were observed between treated and control groups: however, these were reported to be within the normal reference ranges, as defined by the mean ± two standard deviations of the Day -6 values for the animals included in the study.

B. STUDY DEFICIENCIES

Several minor deficiencies were identified. The guidelines recommend that the vehicle alone, without active ingredients, be used as the control; however, in this case the inert ingredients (presumably including the vehicle) were classified as Confidential, and the controls were tested with safflower oil. It was not indicated whether safflower oil was a component of the formulated product..

C. STUDY ACCEPTABILITY

This study followed the pertinent guidelines for a companion animal safety study (OPPTS 870.7200). The package labeling and application instructions were not provided. It is assumed that the intended use would be for only one application of 1.3 mL as stated in the study report. If this is the case, then the required 5X margin of safety has been demonstrated and the study is **Acceptable/Guideline.**

DATA EVALUATION RECORD

DOMESTIC ANIMAL SAFETY STUDY OF A MONTHLY STRIPE-ON FORMULA IN ADULT BEAGLES

STUDY TYPE: Companion Animal Safety – Dog (OPPTS 870.7200)
MRID 450064-03 C

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
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Oak Ridge National Laboratory
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Task Order No. 01-128

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia Dobozy, VMD, MPH Virginia A Dobozy Date: 9/4/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart Date: 9/7/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Dog [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D 276262; MRID NUMBER: 450064-03 C

TEST MATERIAL: Liquid Once a Month Stripe-on Product 11506

STUDY NUMBER: 5310-99

TESTING FACILITY: Stillmeadow, Inc., 12852 Park One Drive, Sugar Land TX, 77478

SPONSOR: Hartz Mountain Corp., 192 Bloomfield Avenue, Bloomfield, NJ 07003

TITLE OF REPORT: Domestic Animal Safety Study of a Monthly Stripe-on Formula in Adult Beagles

AUTHOR: Janice O, Kuhn, Ph.D., D.A.B.T.

REPORT ISSUED: November 5, 1999

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 450064-03 C), a stripe-on formula [Active Ingredients: Sumithrin (d-phenothrin), 95.22% w/w; (S)-methoprene, 2.41%) was topically applied (from the neck to the base of the tail) at a 5X dose (1.3 mL every 60 min until a 5X dose was achieved) to a group of 6 male and 6 female beagle dogs, each at least 6 months old. Controls were treated with safflower oil. Treatments were applied to the skin of the back from the neck to the base of the tail. Blood samples were obtained on the Days -7, 2 and 7 for hematology and clinical chemistry measurements. Animals were observed for 14 days.

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical chemistry, or hematology. Several statistically-significant clinical chemistry and hematology differences were observed between treated and control groups; however, these were within normal limits, and are not considered toxicologically significant.

This study followed the pertinent guidelines for a companion animal safety study (OPPTS 870.7200). The package labeling and application instructions were not provided. It is assumed that the intended use would be for only one application per month of 1.3 mL as stated in the study report. If this is the case, then the required 5X margin of safety has been demonstrated and the study is **Acceptable/Guideline.**

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

Dogs were randomly distributed within the experimental and control groups (Table 1) in an effort to equalize mean body weight and sex. Six dogs/sex were topically treated with a 1X dose of product (1.3 mL) every 60 min until a 5X total dose was achieved. The test material was applied with a syringe (no needle) by parting the hair and applying the liquid directly to the skin of the back from the neck to the base of the tail. In the control animals 1.3 mL of safflower oil was applied five times at 60 min intervals.

TABLE 1. Experimental design

Group	No. of animals		Treatment	Number of applications
	Male	Female		
1	6	6	1.3 mL	5 (60 min apart)
2	6	6	Controls (1.3 mL of safflower oil)	5 (60 min apart)

Data taken from p. 8, MRID 450064-03 C.

C. DOSE SELECTION RATIONALE

The rationale for the dose level was to establish the margin of safety and potential toxicity of 5X the recommended label dose.

D. EXPERIMENTAL DESIGN

Clinical observations were conducted at 0.5, 1, 2, 3, 4, and 6 hours following the last dose on Day 1 and twice daily thereafter for the following 14 days. The animals were observed for signs of abnormal posture, loss of appetite, or vocalization indicative of pain or distress. Food consumption was recorded daily; body weights were recorded on Days -7 (pretest), 7 and 14.

E. PATHOLOGICAL PARAMETERS

Blood samples were obtained by venipuncture of the jugular vein on Day -7 (pretreatment), Day 2 and Day 7. The CHECKED (X) parameters were examined.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. TEST MATERIAL: Liquid Once a Month Stripe-on Product 11506

Description: Clear yellow liquid
Lot/Batch No.: Not reported
Active Ingredients: Sumithrin (95.22%), (S)-Methoprene (2.41%)
Storage Conditions: Room temperature

B. ADMINISTRATION: Topical (stripe-on)

C. VEHICLE AND/OR POSITIVE CONTROL

Vehicle: Information concerning the inert ingredients was placed in a Confidential Appendix
Control: Safflower oil
Positive control: None

D. TEST ANIMALS

Species: Dog
Breed: Beagle
Age and weight at study initiation: At least 6 months (males: 9.1-13.5 kg; females, 6.7-10.8 kg)
Source: Ridglan Farms
Housing: Individually, in 3' by 4' cages
Diet: PMI High Density Canine Diet 5L18; once per day
Water: *ad libitum*; municipal water supply.
Environmental conditions:
Temperature: 22±3°C
Humidity: 30-80%
Acclimation period: Not given

II. STUDY DESIGN

A. IN LIFE DATES

Start: 09/09/99; End: 9/22/99

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)*		
x	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*		Total Cholesterol
x	Potassium*	x	Globulin*
x	Sodium*	x	Glucose*
		x	Total and direct bilirubin*
	ENZYMES	x	Total serum protein*
x	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)	x	Albumin/globulin ratio
x	Serum alanine amino- transferase (also SGPT)*		
x	Serum aspartate amino- transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

Group mean values with standard deviations were calculated and compared by two-tailed t-Test, with the exception of food consumption data (most group means were reported to be equivalent).

G. DISPOSITION OF ANIMALS

Not reported.

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H. COMPLIANCE

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The total amount of product applied was 6.5 mL, and this contained 95.22% w/w sumithrin and 2.41% w/w (s)-methoprene. The mean male and female dose rate was 557.6 and 767.4 mg/kg of the product, respectively.

B. MORTALITY

No dogs died during the study.

C. CLINICAL SIGNS

Clinical observations are presented in Table 2.

TABLE 2. Clinical Observations

Treatment group	Sex	Day	Observation
5X- Control	F	2-4	Bilateral ocular discharge
5X- Treatment	M, F	1-14	No adverse effects observed

Data taken from p.9, MRID 450064-03 C.

D. BODYWEIGHT AND WEIGHT GAIN

No significant differences occurred in the group body weight gains for treated and control groups. The mean body weight of the treated group increased 0.1 kg and that of the controls 0.2 kg.

E. FOOD CONSUMPTION

Food consumption was consistent between the two groups throughout the study.

F. HEMATOLOGY

No treatment-related, biologically-significant hematological effects were observed. There were statistically significant hematological differences between control and test groups in the following (Table 3): on Day 2 platelet count in females was lower in the treated group than in the controls; on Day 7 total leukocyte count was slightly but significantly higher in females in the treated group than in the controls.

TABLE 3. Selected changes in hematology[a]				
Parameter / sample time	Males		Females	
	Controls	5X	Controls	5X
Platelet Count- Day 2 (x 10^3/uL)	317±124	213±111	360±25	203*±158
WBC- Day 7 (x 10^3/uL)	10.8±2.1	9.6±2.3	9.5±1.7	11.6*±1.3

Data taken from Table 5, pp. 21-23, MRID 450064-03C
[a]Mean values and ± SD
* p =<0.05

G. CLINICAL CHEMISTRY

Serum chemistry parameters were within normal limits. There were statistically significant clinical chemistry differences between control and test groups in the following (Table 4): mean alkaline phosphatase was increased in treated females on Days -7, 2 and in treated males on Day 7; glucose was increased in treated females on Days -7 and 2; albumin/globulin ratio was decreased in treated females on Day 7; and potassium was decreased in treated females on Day 2. However, the alterations were minor and not toxicologically significant.

TABLE 4. Selected changes in clinical chemistry[a]				
Parameter / sample time	Males		Females	
	controls	5X	controls	5X
ALP- Day -7 (U/L)	98±22	104±19	87±16	108*±13
ALP- Day 2 (U/L)	88±12	100±12	81±12	106*±23
ALP- Day 7 (U/L)	76±9	95*±15	74±13	101*±19
Glucose- Day -7(mg/dL)	106 ±6	96±9	91±4	101*±7
Glucose- Day 2(mg/dL)	104±7	107±5	94±5	103*±8
Glucose- Day 7(mg/dL)	101±6	102±4	96±5	97±10
Albumin- Day -7(g/dL)	3.6±0.1	3.6±0.1	3.5±0.1	3.7±0.2
Albumin- Day 2(g/dL)	3.4±0.2	3.7*±0.2	3.5±0.2	3.4±0.1
Albumin- Day 7(g/dL)	3.1±0.1	3.2±0.1	3.3±0.3	3.2±0.1
Albumin/globulin - Day -7	1.6±0.1	1.5±0.1	1.7±0.2	1.8±0.2
Albumin/globulin- Day 2	1.4±0.1	1.5±0.1	1.4±0.1	1.4±0.2
Albumin/globulin- Day 7	1.0±0.1	1.1±0.1	1.4±0.3	1.1*±0.1
Potassium- Day -7(mEQ/L)	4.9±0.3	4.8±0.2	4.6±0.1	4.7±0.2
Potassiumn- Day 2(mEQ/L)	4.7±0.2	4.7±0.3	4.7±0.2	4.4*±0.1
Potassium- Day 7(mEQ/L)	4.6±0.2	4.6±0.3	4.6±0.3	4.5±0.3

Data taken from Table 4, pp. 18-20, MRID 450064-03C
[a]Mean values and ± SD
* p =<0.05

H. NECROPSY FINDINGS

No necropsies were performed.

IV. DISCUSSION

A. DISCUSSION

No mortality was observed and there were no treatment-related, biologically-significant effects on body weight, clinical chemistry, or hematology. Several statistically-

significant clinical chemistry and hematology differences were observed between treated and control groups: however, the authors reported these to be within normal limits. Reference values were not provided; however, the author's contention was suppported by comparison with reference data listed in the "CRC Handbook of Toxicology" (1995) and "The Clinical Chemistry of Laboratory Animals" (1989)]. Therefore, the reported changes are not considered toxicologically significant.

B. STUDY DEFICIENCIES

Several minor deficiencies can be identified in this study. The acclimation period was not specified, and the normal ranges (historical and/or laboratory) for the hematological and clinical chemistry parameters were not given.

C. STUDY ACCEPTABILITY

This study followed the pertinent guidelines for a companion animal safety study (OPPTS 870.7200). The package labeling and application instructions were not provided. It is assumed that the intended use would be for only one application of 1.3 mL as stated in the study report. If this is the case, then the required 5X margin of safety has been demonstrated and the study is **Acceptable/Guideline.**

DATA EVALUATION RECORD

METHOPRENE
(HARTZ TEST SAMPLE #11146)

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [870.1100 (81-1)]
MRID 45410901

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
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Task Order No. 01-130A

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy, Date 9/10/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart, Date 9/5/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat [OPPTS 870.1100 (§81-1)]

DP BARCODE: D276701 SUBMISSION CODE: S598364
P.C. CODE: 105402 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Acute oral toxicity limit test. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5971, March 26, 1998. MRID 45410901. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 45410901) five male and five female fasted young adult Sprague-Dawley rats were given a single oral 5000 mg/kg dose of One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported] and observed for 14 days.

No rats died during the study. Four males and one female had anogenital staining and/or diarrhea four hours after dosing. All other rats were active and healthy during the study. All rats had normal body weight gains. No test material-related gross abnormalities were noted at necropsy.

The oral LD_{50} for males, females, and combined was > 5000 mg/kg (Limit Test).

One Spot - IGR Only, Hartz Test Sample #11146 is in TOXICITY CATEGORY IV based on the LD_{50}.

This acute oral study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for an acute oral study [870.1100 (81-1)] in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: One Spot - IGR Only, Hartz Test Sample #11146

   Description: clear yellow liquid
   Lot/Batch #: not reported; PSL Code No. E80211-2R
   Purity: approximately 3% (S)-methoprene in an isoparafinic hydrocarbon
   CAS No.: 65733-16-6 for methoprene

2. Vehicle and/or positive control

   None

3. Test animals

   Species: rat
   Strain: Sprague-Dawley derived
   Age and/or weight at dosing: young adult; males: 191-210 g, females: 159-188 g
   Source: Ace Animals, Inc., Boyertown, PA
   Acclimation period: 9 days
   Diet: Purina Rodent Chow No. 5012
   Water: filtered tap water, *ad libitum*
   Housing: individually in suspended stainless steel cages with mesh floors
   Environmental conditions:
   Temperature: 63-69°F
   Humidity: not reported
   Air changes: not reported
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: February 12, 1998; end: February 26, 1998

2. Animal assignment and treatment

   The study was conducted as a limit test. Following an overnight fast, five rats/sex were given a single 5000 mg/kg dose of the test material by gavage. The animals were observed for clinical signs of toxicity at 1, 3, and 4 hours post dosing and at least once daily thereafter for 14 days. They were weighed prior to dosing and on study days 7 and 14. All rats were sacrificed and necropsied.

3. Statistics

Calculation of the oral LD_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

None of the rats died as a result of One Spot - IGR Only, Hartz Test Sample #11146 toxicity.

The oral LD_{50} for males, females, and combined was > 5000 mg/kg. This places One Spot - IGR Only, Hartz Test Sample #11146 in TOXICITY CATEGORY IV.

B. CLINICAL OBSERVATIONS

Four males and one female had anogenital staining four hours after dosing. This female also had diarrhea at 4 hours after dosing. All other rats were active and healthy during the study.

C. BODY WEIGHT

All rats had normal body weight gains during the study.

D. NECROPSY

No test material-related gross abnormalities were noted.

E. DEFICIENCIES

The humidity and air change frequency of the animal room were not reported. These would not affect the study results.

DATA EVALUATION RECORD

METHOPRENE
(HARTZ TEST SAMPLE #11146)

STUDY TYPE: ACUTE DERMAL TOXICITY - RABBIT [870.1200 (81-2)]
MRID 45410902

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 01-130B

Primary Reviewer:
Susan Chang, M.S.

Signature: Susan Chang
Date: SEP 0 5 2001

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H T Borges
Date: SEP 0 5 2001

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: SEP 0 5 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: SEP 0 5 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy. Date 9/10/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart. Date 9/12/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit [OPPTS 870.1200 (§81-2)]

DP BARCODE: D276701
P.C. CODE: 105402

SUBMISSION CODE: S598364
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Acute dermal toxicity limit test. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5972, March 26, 1998. MRID 45410902. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 45410902) an approximate 4 inch x 8 inch area on the clipped back of five male and five female young adult New Zealand albino rabbits was dermally exposed to 5000 mg/kg One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported] for 24 hours. The animals were observed for 14 days.

No rabbits died during the study. One male and four females lost or did not gain weight during the first week. Two males lost weight during the second week. Two females that lost weight during the first week regained their original weight. All other rabbits gained weight and all rabbits were active and healthy during the study. Erythema, edema, and desquamation were noted on all rabbits with clearance by day 13. All tissues/organs appeared normal at necropsy.

The dermal LD_{50} for males, females, and combined was > 5000 mg/kg.

One Spot - IGR Only, Hartz Test Sample #11146 is in TOXICITY CATEGORY IV based on the LD_{50}.

This acute dermal study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for an acute dermal study [870.1200 (§81-2)] in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: One Spot - IGR Only, Hartz Test Sample #11146

   Description: clear yellow liquid
   Lot/Batch #: not reported; PSL Code No. E80211-2R
   Purity: approximately 3% (S)-methoprene in an isoparafinic hydrocarbon
   CAS #: 65733-16-6 for methoprene

2. Vehicle and/or positive control

   None

3. Test animals

   Species: rabbit
   Strain: New Zealand albino
   Age and/or weight at dosing: young adults; males: 2.3-2.5 kg, females: 2.3-2.5 kg
   Source: Davidson's Mill Farm, South Brunswick, NJ
   Acclimation period: 8 days
   Diet: pelleted Purina Rabbit Chow No. 5326
   Water: filtered tap water, *ad libitum*
   Housing: individually in suspended stainless steel cages with mesh floors
   Environmental conditions:
   Temperature: 64-70°F
   Humidity: not reported
   Air changes: not reported
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: February 19, 1998; end: March 5, 1998

2. Animal assignment and treatment

   Five male and five female rabbits were given a single 5000 mg/kg dose of One Spot - IGR Only, Hartz Test Sample #11146 applied to a 4 inch x 8 inch (approximately 10% of body surface) area on the clipped skin on the dorsal trunk. The application

site was covered with a gauze pad and wrapped with Durapore tape. Elizabethan collars were placed on the rabbits. After 24 hours, the dressing and the collars were removed. The excess test material was wiped with acetone, water, and clean towels. The animals were observed for clinical signs of toxicity 1 and 3.5 hours after treatment and at least daily thereafter for 14 days. They were weighed prior to test material application, and on study days 7 and 14. All rabbits were sacrificed and necropsied.

3. Statistics

Calculation of the dermal LD_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

None of the rabbits died during the study.

The dermal LD_{50} for males, females, and combined was > 5000 mg/kg. This places One Spot - IGR Only, Hartz Test Sample #11146 in TOXICITY CATEGORY IV.

B. CLINICAL OBSERVATIONS

All rabbits were active and healthy during the study. Erythema, edema, desquamation were noted on all rabbits with clearance by day 13.

C. BODY WEIGHT

One male lost weight during the first week and did not gain weight during the second week. Another male lost weight during the second week. Two females lost weight during the first week and gained back their original weight during the second week. One female lost weight and another female did not gain weight during the first week, but gained weight during the second week. All other rabbits gained weight by the end of the study.

D. NECROPSY

The necropsy of all rabbits appeared normal.

E. DEFICIENCIES

The humidity and air change frequency of the animal room were not reported. These would not affect the study results.

EPA Reviewer: Virginia Dobozy, ~~Ph.D.~~ VMD, MPH _____, Date _____
Reregistration Branch 1 (7509C), HED
EPA Work Assignment Manager: Joycelyn Stewart, Ph.D. _____, Date _____
Toxicology Branch (7509C), HED

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit [OPPTS 870.1200 (§81-2)]

DP BARCODE: D276~~263~~ SUBMISSION CODE: S~~600258~~
P.C. CODE: 105402 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Acute dermal toxicity limit test. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5972, March 26, 1998. MRID 45410902. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 45410902) an approximate 4 inch x 8 inch area on the clipped back of five male and five female young adult New Zealand albino rabbits was dermally exposed to 5000 mg/kg One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported] for 24 hours. The animals were observed for 14 days.

No rabbits died during the study. One male and four females lost or did not gain weight during the first week. Two males lost weight during the second week. Two females that lost weight during the first week regained their original weight. All other rabbits gained weight and all rabbits were active and healthy during the study. Erythema, edema, and desquamation were noted on all rabbits with clearance by day 13. All tissues/organs appeared normal at necropsy.

The dermal LD_{50} for males, females, and combined was > 5000 mg/kg.

One Spot - IGR Only, Hartz Test Sample #11146 is in TOXICITY CATEGORY IV based on the LD_{50}.

This acute dermal study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for an acute dermal study [870.1200 (§81-2)] in the rabbit.

DATA EVALUATION RECORD

METHOPRENE
(HARTZ TEST SAMPLE #11146)

STUDY TYPE: PRIMARY EYE IRRITATION - RABBIT [870.2400 (81-4)]
MRID 45410903

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 01-130C

Primary Reviewer:
Susan Chang, M.S.

Signature: Susan Chang
Date: SEP 0 5 2001

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H T Borges
Date: SEP 0 5 2001

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: SEP 0 5 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: SEP 0 5 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia Dobozy, VMD, MPH Virginia A Dobozy. Date 9/10/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, Ph.D. Joycelyn Stewart. Date 9/13/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit [OPPTS 870.2400 (§81-4)]

DP BARCODE: D276701
P.C. CODE: 105402

SUBMISSION CODE: S598364
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Primary eye irritation. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5973, March 26, 1998. MRID 45410903. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 45410903) 0.1 mL of One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported] was instilled into the right conjunctival sac of two male and four female adult New Zealand albino rabbits. The contralateral eye of all rabbits served as control. The eyes were scored for ocular irritation according to the Draize method 1, 24, 48, and 72 hours after instillation and the irritation classified according to the method of Kay and Calandra.

No corneal opacity or iritis were found on any rabbit. The test material induced positive conjunctival irritation on 6/6 rabbits one hour after test material instillation. By 24 hours, all rabbits had conjunctival vessels that were definitely injected above normal. There were no effects at 48 hours. The highest maximum mean total score was 8.0, recorded one hour after test material instillation.

In this study, One Spot - IGR Only, Hartz Test Sample #11146 was minimally irritating and is in TOXICITY CATEGORY IV for primary eye irritation.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a primary eye irritation study [870.2400 (§81-4)] in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: One Spot - IGR Only, Hartz Test Sample #11146

   Description: clear yellow liquid
   Lot/Batch #: not reported; PSL Code No. E80211-2R
   Purity: approximately 3% (S)-methoprene in an isoparafinic hydrocarbon
   CAS #: 65733-16-6 for methoprene

2. Vehicle

   None

3. Test animals

   Species: rabbit
   Strain: New Zealand albino
   Age and weight at dosing: adult; weight of male and females not reported
   Source: Davidson's Mill Farm, South Brunswick, NJ
   Acclimation period: 11 days
   Diet: pelleted Purina Rabbit Chow No. 5326
   Water: filtered tap water, *ad libitum*
   Housing: individually in suspended stainless steel cages with mesh floors
   Environmental conditions:
   Temperature: 64-68°F
   Humidity: not reported
   Air changes: not reported
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: February 23, 1998; end: February 26, 1998

2. Animal assignment and treatment

   The test material (0.1 mL) was instilled into the right conjunctival sac of two male and four female rabbits and the eye lids held together for approximately 1 second. The contralateral eye of all rabbits served as control. The animals were scored for

ocular irritation 1, 24, 48, and 72 hours after instillation according to the Draize method and the degree of irritation classified according to the method of Kay and Calandra.

II. RESULTS AND DISCUSSION

A. No corneal opacity or iritis were found on any rabbit. The test material induced positive conjunctival irritation on 6/6 rabbits one hour after test material instillation. By 24 hours, all rabbits had conjunctival vessels that were definitely injected above normal. There were no effects at 48 hours. The highest maximum mean total score was 8.0, recorded one hour after test material instillation.

This classifies the test material as minimally irritating. One Spot - IGR Only, Hartz Test Sample #11146 is in TOXICITY CATEGORY IV.

B. DEFICIENCIES

The humidity and air change frequency of the animal room were not reported. These would not affect the study results.

DATA EVALUATION RECORD

METHOPRENE
(HARTZ TEST SAMPLE #11146)

STUDY TYPE: PRIMARY DERMAL IRRITATION - RABBIT [870.2500 (81-5)]
MRID 45410904

Prepared for
Antimicrobials Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 01-130D

Primary Reviewer:
Susan Chang, M.S.

Signature: S. Chang
Date: SEP 0 5 2001

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H T Borges
Date: SEP 0 5 2001

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: SEP 0 5 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: SEP 0 5 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy Date 9/10/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart. Date 9/17/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit [OPPTS 870.2500 (§81-5)]

DP BARCODE: D276701
P.C. CODE: 105402

SUBMISSION CODE: S598364
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Primary skin irritation. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5974, March 26, 1998. MRID 45410904. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 45410904) three male and three female adult New Zealand white rabbits were dermally exposed to 0.5 mL One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported] for 4 hours on the dorsal trunk. The animals were observed for 10 days. Irritation was scored by the method of Draize.

Very slight to well defined erythema with very slight to slight edema was noted on all rabbits one hour following patch removal that resolved to very slight erythema with or without very slight edema by 24 hours. By 48 hours, three rabbits had very slight erythema with resolution by 72 hours. The primary dermal irritation index was 1.3.

In this study, One Spot - IGR Only, Hartz Test Sample #11146 was slightly irritating and is in TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a primary dermal irritation study [870.2500 (§81-5)] in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: One Spot - IGR Only, Hartz Test Sample #11146

   Description: clear yellow liquid
   Lot/Batch #: not reported; PSL Code No. E80211-2R
   Purity: approximately 3% (S)-methoprene in an isoparafinic hydrocarbon
   CAS No.: 65733-16-6 for methoprene

2. Vehicle

   None

3. Test animals

   Species: rabbit
   Strain: New Zealand albino
   Age and weight at dosing: adult; weight of males and female not reported
   Source: Davidson's Mill Farm, South Brunswick, NJ
   Acclimation period: 6 days
   Diet: pelleted Purina Rabbit Chow No. 5326
   Water: filtered tap water, *ad libitum*
   Housing: individually in suspended stainless steel cages with mesh floors
   Environmental conditions:
   Temperature: 65-70°F
   Humidity: not reported
   Air changes: not reported
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: February 18, 1998; end: February 21, 1998

2. Animal assignment and treatment

   Three male and three female animals were given a single 0.5 mL dose of One Spot - IGR Only, Hartz Test Sample #11146 applied to a 6 cm^2 clipped intact site on the dorsal trunk. The application sites were covered with gauze and wrapped with semi-occlusive tape. Elizabethan collars were placed on each rabbit. The dressings were left in place for 4 hours, after which they were removed and the application sites

wiped with acetone, water, and a towel. The sites were scored for erythema and edema according to the Draize method 1, 24, 48, and 72 hours after patch removal.

II. RESULTS AND DISCUSSION

A. Very slight to well defined erythema with very slight to slight edema was noted on all rabbits one hour following patch removal that resolved to very slight erythema with or without very slight edema by 24 hours. By 48 hours, three rabbits had very slight erythema with resolution by 72 hours. The primary dermal irritation index was 1.3.

One Spot - IGR Only, Hartz Test Sample #11146 was slightly irritating and is in TOXICITY CATEGORY IV.

B. DEFICIENCIES

The humidity and air change frequency of the animal room were not reported. These would not affect the study results.

EPA Reviewer: Virginia Dobozy, ~~Ph.D.~~ A UMD MIA _____, Date _____
Reregistration Branch 1 (7509C), HED
EPA Work Assignment Manager: Joycelyn Stewart, Ph.D. _____, Date _____
Toxicology Branch (7509C), HED

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit [OPPTS 870.2500 (§81-5)]

DP BARCODE: D276263 701
P.C. CODE: 105402

SUBMISSION CODE: ~~S600258~~
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Primary skin irritation. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5974, March 26, 1998. MRID 45410904. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 45410904) three male and three female adult New Zealand white rabbits were dermally exposed to 0.5 mL One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported] for 4 hours on the dorsal trunk. The animals were observed for 10 days. Irritation was scored by the method of Draize.

Very slight to well defined erythema with very slight to slight edema was noted on all rabbits one hour following patch removal that resolved to very slight erythema with or without very slight edema by 24 hours. By 48 hours, three rabbits had very slight erythema with resolution by 72 hours. The primary dermal irritation index was 1.3.

In this study, One Spot - IGR Only, Hartz Test Sample #11146 was slightly irritating and is in TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a primary dermal irritation study [870.2500 (§81-5)] in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

DATA EVALUATION RECORD

METHOPRENE
(HARTZ TEST SAMPLE #11146)

STUDY TYPE: DERMAL SENSITIZATION - GUINEA PIG [870.2600 (81-6)]
MRID 45410905

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 01-130E

Primary Reviewer:
Susan Chang, M.S.

Signature: Susan Chang
Date: SEP 0 5 2001

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H T Borges
Date: SEP 0 5 2001

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: SEP 0 5 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: SEP 0 5 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Virginia A. Dobozy, VMD, MPH Virginia A Dobozy . Date 9/12/01
Reregistration Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: Joycelyn Stewart, PhD Joycelyn Stewart . Date 9/12/2001
Toxicology Branch, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pig [OPPTS 870.2600 (§81-6)]

DP BARCODE: D276701
P.C. CODE: 105402

SUBMISSION CODE: S598364
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene]

SYNONYMS: None

CITATION: Wnorowski, G. (1998) One -Spot - IGR Only, Hartz Test Sample #11146: Dermal sensitization test- Buehler method. Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816. Laboratory project identification number 5975, March 30, 1998. MRID 45410905. Unpublished.

SPONSOR: The Hartz Mountain Corporation, 192 Bloomfield Avenue, Bloomfield, NJ 07003

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 45410905) with One Spot - IGR Only, Hartz Test Sample #11146 [~3% (S)-Methoprene, a.i., Lot No. not reported], 10 young adult male Hartley guinea pigs were tested using the Buehler method. Five animals served as naive controls. An additional ten male guinea pigs were treated with 1-chlor-2,4-dinitrobenzene (DCNB), the positive control; five animals served as naive controls. Based on preliminary irritation testing, a 50% w/w solution of the test material in mineral oil and a 0.04% w/w DNCB solution in acetone were selected for the challenge phase. Approximately 24 and 48 hours after each induction and challenge dose, the animals were scored for erythema.

After three weekly inductions, dermal irritation suggestive of sensitization was not observed on the test animals after challenge. Very faint usually nonconfluent erythema was noted on 6/10 test animals 24 hours following challenge with resolution on five animals by 48 hours. Very faint usually nonconfluent erythema was noted on 3/5 naive control animals 24 hours following challenge with resolution on two animal by 48 hours. The results of DNCB positive control study were appropriate.

In this study, One Spot - IGR Only, Hartz Test Sample #11146 was not a dermal sensitizer.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a dermal sensitization study [870.2600 (§81-6)] in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: One Spot - IGR Only, Hartz Test Sample #11146

   Description: clear yellow liquid
   Lot/Batch #: not reported; PSL Code No. E80211-2R
   Purity: approximately 3% (S)-methoprene in an isoparafinic hydrocarbon
   CAS #: 65733-16-6 for methoprene

2. Vehicle and positive control

   Vehicle: mineral oil (challenge); positive control: 1-chloro-2,4-dinitrobenzene (DNCB)

3. Test animals

   Species: guinea pig
   Strain: Hartley
   Age and weight at start of treatment: young adult; males: 301-404 g
   Source: Davidson's Mill Farm, South Brunswick, NJ
   Acclimation period: 6 days
   Diet: pelleted Purina Guinea Pig Chow No. 5025
   Water: filtered tap water, *ad libitum*
   Housing: individually in suspended stainless steel cages with mesh floors
   Environmental conditions:
   Temperature: 63-73°F
   Humidity: not reported
   Air changes: not reported
   Photoperiod: 12 hour light/dark

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: February 19, 1998; end: March 20, 1998

2. Animal assignment and treatment

   The animals were induced and challenged according to the method of Buehler. In a preliminary irritation test, 50% w/w test material in mineral oil was selected for challenge of the test animals. The study report states that preliminary irritation testing

for DCNB are re-evaluated every 12 months. Based on the most current evaluation, the highest non-irritating concentration was 0.04% w/w solution in acetone. The dorsal area and flank of ten guinea pigs were clipped free of hair on the day prior to each treatment. For each of the three weekly inductions, 0.4 mL of undiluted test material was applied using an occlusive 25 mm Hill Top Chamber on the left side of ten male test animals for six hours. Fourteen days after the last induction, the test animals were challenged with 0.4 mL of 50% w/w test material in mineral oil on naive sites in a manner identical to the induction. A naive control group of five male animals was treated with 50% w/w test material in mineral oil at challenge only. Ten positive control males were induced with 0.4 mL of 0.08% DNCB in 80% aqueous ethanol and challenged with 0.4 mL of 0.04% DNCB in acetone using the identical procedure. In addition, five naive positive control males were treated with 0.4 mL of 0.04% DNCB in acetone at challenge. Reactions were scored 24 and 48 hours post exposure.

II. RESULTS AND DISCUSSION

A. INDUCTION REACTIONS AND DURATION

Very faint usually nonconfluent erythema (score = 0.5) and faint usually confluent erythema (score = 1) were noted on 5/10 and 4/10 animals, respectively, 24 hours after the first induction. By 48 hours, very faint usually nonconfluent erythema and faint usually confluent erythema were noted on 5/10 and 1/10 animals, respectively. All animals had very faint usually nonconfluent to faint usually confluent erythema 24 and 48 hours after the second and third inductions.

B. CHALLENGE REACTIONS AND DURATION

Very faint usually nonconfluent erythema was noted on 6/10 test animals 24 hours following challenge with resolution on five animals by 48 hours. Very faint usually nonconfluent erythema was noted on 3/5 naive control animals 24 hours following challenge with resolution on two animal by 48 hours. No positive reactions were noted from any of the test animals.

One Spot - IGR Only, Hartz Test Sample #11146 was not a dermal sensitizer.

C. POSITIVE CONTROL

The results of DNCB positive control study were appropriate. Severe erythema was observed in 1/9 animals, moderate erythema in 3/9 animals and faint erythema in 5/9 animals at 24 hours. One animal died prior to scoring. By 48 hours, there was moderate erythema in 2/9, faint erythema in 5/9 and very faint erythema in 2/9 animals.

D. ADDITIONAL TESTING

It is the reviewer's opinion that the study was conducted in a manner suitable to detect the sensitization potential of the test material. No additional testing is needed.

E. DEFICIENCIES

The humidity and air change frequency of the animal room were not reported. These would not affect the study results.

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