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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: December 14, 2005

MEMORANDUM

Subject: EPA File Symbol: 2596-RLU HARTZ REFERENCE 121
DP Barcode: D318634
Decision No.: 357507
PC Codes: 109701 (Permethrin), 044312 (Dinotefuran) and 129032 (Sumilarv)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
12/14/2005

To: Rita Kumar/Daniel Kenny, RM 1
Insecticide Branch
Registration Division (7505C)

Registrant: THE HARTZ MOUNTAIN CORP.

FORMULATION DECLARATION FROM LABEL:

Chamber A:

Active Ingredient(s):	% by wt
Permethrin (CAS #52645-53-1)	45.00%
Inert Ingredients:	55.00%
Total:	100.00%

Chamber B:

Active Ingredient(s):	% by wt
Dinotefuran (CAS #165252-70-0)	14.85%
Sumilarv (CAS #96737-68-1)	1.48%
Inert Ingredients:	83.67%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

> "Please review acute toxicity data to support registration of this new dog spot-on with multiple active ingredients. This is a new use for dinotefuran. A copy of the proposed label and CSF is enclosed. MRID#s 465527-02 to -06..."

BACKGROUND: This product is proposed as a topical spot-on (application rate: once a month) for control of fleas, ticks and mosquitoes on dogs and puppies of over 7 weeks of age. It consists of 2 chambers; Chamber A and Chamber B, the contents of which would be mixed in the application process. Chamber A would represent approximately 70% of the end-use mixture, while Chamber B would represent approximately 30%.

This package includes acute oral LD50 (MRID 46552702), acute dermal LD50 (MRID 46552703), primary eye irritation (MRID 46552704), primary dermal irritation (MRID 46552705) and dermal sensitization (MRID 46552706) studies.

COMMENTS AND RECOMMENDATIONS:

1. While the material submitted for this review did not include studies conducted on the individual components (contents of Chamber A and those of Chamber B), but on the end-use mixture, it is noted that the registrant does have two existing registrations containing 45% Permethrin (EPA Reg. No. 2596-137, which contains 45% Permethrin as sole active, and EPA Reg. No. 2596-146, which contains 45% Permethrin and 2.9% S-Methoprene), as well as an existing registration (EPA Reg. No. 2596-155) containing14.85% Dinotefuran as sole active. These 3 registrations have labels with the signal word "CAUTION." It would probably be appropriate for the registrant to cite (by MRID numbers) the acute toxicity studies conducted on these formulations as additional supporting data for the contents of Chamber A and Chamber B.

2. The five acute toxicity studies submitted for review (conducted on the use-mixture of the two components) have been classified as acceptable.

3. There is no acute inhalation toxicity study. The requirement for an acute inhalation toxicity study is normally waived for a product of this type and packaging. However, the registrant should request this waiver.

4. Based on the results of the acute toxicity studies the following is the acute toxicity profile for EPA File Symbol 2596-RLU HARTZ REFERENCE 121:

Study Type	Tox. Cat.	Classification & MRID #
Oral LD_{50} (rat)	Tox. Cat. III	Acceptable (MRID 46552702)
Dermal LD_{50} (rat)	Tox. Cat. IV	Acceptable (MRID 46552703)
Inhalation LC_{50}(rat)	-	Not submitted
Eye Irritation (rabbit)	Tox. Cat. III	Acceptable (MRID 46552704)
Dermal Irritation (rabbit)	Tox. Cat. IV	Acceptable (MRID 46552705)
Dermal Sensitization	Not a Sensitizer	Acceptable (MRID 46552706)

5. Based on the acute toxicity profile indicated above, the following is the precautionary labeling for this product, as obtained from the Label Review System:

PRODUCT ID #: **002596-00154**

PRODUCT NAME: **HARTZ REFERENCE 121**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Harmful if swallowed. Causes moderate eye irritation. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Avoid contact with eyes or clothing.

First Aid:

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Byron T. Backus, Ph.D.
Risk Manager (EPA): 01

Date: December 2, 2005
DP Barcode: D318634

STUDY TYPE: Acute Oral Toxicity Up and Down Procedure - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL (% a.i.): A mixture (2.5 mL TS#12516 & 1.0 mL TS#12517, both clear liquids) with a specific gravity of 1.082 as determined by the test laboratory. From the proposed label for this product the TS#12516 corresponds to the material in Chamber A, with a declaration of 45% Permethrin. The TS#12517 corresponds to the material in Chamber B, with a declaration of 14.85% Dinotefuran and 1.48% Sumilarv. From these percentages and the mix proportions, the test material contained approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv.

SYNONYMS: The test material description is consistent with the mixture that would be obtained by mixing 0.7 mL of the contents of Chamber A with 0.3 mL of the contents of Chamber B.

CITATION: Merkel, D.J. (2005) Acute Oral Toxicity (Up and Down Procedure) of Hartz TTE (Samples 12516/12517). Study ID Numbers: Product Safety Laboratories No. 16390; Hartz Mountain No. 1771. Unpublished study prepared by Product Safety Laboratories, Dayton, NJ. 15 p. Study Completion Date: 21 March, 2005. MRID 46552702.

SPONSOR: The Hartz Mountain Corporation

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46552702), fasted (overnight) young adult female Sprague-Dawley derived albino rats (Source: Ace Animals, Inc., Boyertown, PA; Age: 9-12 weeks of age; Weight: 173-235 g;) were orally gavaged with a liquid obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517. The test material (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv) had a specific gravity of 1.082. Initially, the test material was administered to a single female at 5000 mg/kg (limit dose); when this rat died a second was dosed at 175 mg/kg; when this rat survived another was dosed at 550 mg/kg; and when this survived another was dosed at 1750 mg/kg and this rat also survived. The remaining 6 rats were dosed at 5000 and 1750 mg/kg.

On the day of dosage rats were observed several times for mortality and signs of toxicity. They were then observed at least once a day for the remainder of the 14-day observation period. Individual body weights were recorded just prior to dosing (Day 0) and on days 7 and 14.

There was no mortality or signs of toxicity in rats dosed at 175, 550 and 1750 mg/kg. At 5000 mg/kg 4/5 rats died within 24 hours of dosage; signs of toxicity noted prior to death included hypoactivity, hunched posture and tremors. The one survivor at this dose also showed signs which included hypoactivity, tremors, diarrhea, ano-genital staining and a reduced fecal volume, with recovery by Day 5. All survivors (including the one at 5000 mg/kg) gained weight in the period from Day 0 to 7 and again from Day 7 to 14. All survivors (including the one rat surviving a dose of 5000 mg/kg) had normal necropsy results. The four rats which died following dosage

at 5000 mg/kg had red or slightly red intestines, and one also had a discolored liver and red lungs.

Estimated Oral LD_{50} in female rats > 1750 mg/kg but < 5000 mg/kg (EPA Tox. Cat. III)

The test material (specific gravity of 1.082, and containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv) is in EPA Toxicity Category III in terms of oral toxicity based on the results of this study.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Friday, December 02, 2005, 3:05:40 PM
Data file name: HARTZ_TTE.dat
Last modified: 12/2/2005 3:05:21 PM

Test/Substance: HARTZ_TTE
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	8661	5000	X	
2	8815	175	O	O
3	8819	550	O	O
4	8850	1750	O	O
5	8912	5000	O	O
6	9173	5000	X	
7	9302	1750	O	O
8	9400	5000	X	
9	9433	1750	O	O
10	9463	5000	X	

(X = Died, O = Survived)

Dose Recommendation: Stop dosing animals. Observe the previously dosed animals for 14-days and record the long-term outcomes.

WARNING:
Please review the data for accuracy.
Starting the Main Test above the likely LD50 will induce bias toward the starting dose. See OECD Guideline 425.
At least one dose is much greater than the limit dose.
The doses are not completely consistent with the recommended doses.

Stopping criteria met: 5 reversals in 6 tests.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
175	1	0	1
550	1	0	1
1750	3	0	3
5000	1	4	5
All Doses	6	4	10

Statistical Estimate based on long term outcomes:

Estimated LD50 = 5000 (The one dose with partial response).
95% PL Confidence interval is 1963 to 6290.

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
175	-	0/1	-
550	-	0/1	-
1750	-	0/3	-
5000	-	4/5	-

Statistics - See the summary above for the LD_{50} value. This reviewer notes that if the oral LD_{50} value is 5000 mg/kg, then the cumulative probability that there would be an outcome of 1/5 survivors or worse (0/5 survivors) is 6/32, or 18.75%, indicating there is an 81.25% probability

that the LD_{50} value is less than 5000 mg/kg.

A. Mortality - Four out of 5 rats dosed at 5000 mg/kg died, with all 4 deaths occurring within one day of test material administration. None of the other rats (including the three at 1750 mg/kg, the next lower dose from 5000 mg/kg) died.

B. Clinical observations - No abnormal physical signs were noted during the observation period for rats dosed up to and including 1750 mg/kg. At 5000 mg/kg toxic signs noted prior to death included hypoactivity, hunched posture and tremors. The one survivor at this dose also showed signs which included hypoactivity, tremors, diarrhea, ano-genital staining and a reduced fecal volume, with recovery by Day 5. All survivors (including the one at 5000 mg/kg) gained weight in the period from Day 0 to 7 and again from Day 7 to 14

C. Gross Necropsy - All survivors (including the one rat surviving a dose of 5000 mg/kg) had normal necropsy results. The four rats which died following dosage at 5000 mg/kg had red or slightly red intestines, and one also had a discolored liver and red lungs.

D. Reviewer's Conclusions: The study is acceptable. As 4/5 rats died following dosage at 5000 mg/kg, and all survived at 1750 mg/kg, the test material is considered to have an LD_{50} value of less than 5000 mg/kg but greater than 1750 mg/kg. This defines an EPA Toxicity Category III category for oral exposure.

E. Deficiencies - The study protocol did not strictly adhere to the recommended up-and-down procedure dosing recommendations.

Reviewer: Byron T. Backus, Ph.D. **Date:** December 1, 2005
Risk Manager (EPA): 01 **DP Barcode:** D318634

STUDY TYPE: Acute Dermal Toxicity - Sprague-Dawley derived albino rats - OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): A mixture (2.5 mL TS#12516 & 1.0 mL TS#12517, both clear liquids) with a specific gravity of 1.082 as determined by the test laboratory. From the proposed label for this product the TS#12516 corresponds to the material in Chamber A, with a declaration of 45% Permethrin. The TS#12517 corresponds to the material in Chamber.B, with a declaration of 14.85% Dinotefuran and 1.48% Sumilarv. From these percentages and the mix proportions, the test material contained approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv,

SYNONYMS: The test material description is consistent with the mixture that would be obtained by mixing 0.7 mL of the contents of Chamber A with 0.3 mL of the contents of Chamber B.

CITATION: Merkel, D.J. (2005) Acute Dermal Toxicity of Hartz TTE (Samples 12516/12517). Study ID Numbers: Product Safety Laboratories No. 16391; Hartz Mountain No. 1774. Unpublished study prepared by Product Safety Laboratories, Dayton, NJ. 14 p. Study Completion Date: 21 March, 2005. MRID 46552703.

SPONSOR: The Hartz Mountain Corporation

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46552703) a group (5M & 5F) of young adult Sprague-Dawley derived albino rats (source: Ace Animals Inc., Boyertown, PA; age: 9-10 weeks; Males: 278-312 g; Females: 190-205 g) received a 24-hr dermal occluded exposure to a dose of 5000 mg/kg of a liquid obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517. The test material (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv) had a specific gravity of 1.082.

Rats were observed several times on the day of application (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing (day 0) and on days 7 and 14.

There was no mortality and no signs of systemic toxicity. There were no indications of dermal irritation. All rats gained weighed in the period from Day 0 to 7 and again from Day 7 to 14.

Post-sacrifice necropsy results were normal.

Dermal LD_{50} Males > 5000 mg/kg (0/5 died)
Females > 5000 mg/kg (0/5 died)
Combined > 5000 mg/kg (0/10 died)

The liquid obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517, containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity of 1.082 is in EPA toxicity category IV in terms of dermal toxicity based on the results of this study.

This acute dermal study is classified as acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

Statistics - Not necessary to compute the dermal LD_{50}.

A. Mortality - None, as noted in the table above.

B. Clinical observations - There were no signs of systemic toxicity. There were no indications of dermal irritation. All rats gained weighed in the period from Day 0 to 7 and again from Day 7 to 14.

C. Gross Necropsy - No gross abnormalities were observed at post-sacrifice necropsy.

D. Reviewer's Conclusions: The study is acceptable. The liquid (specific gravity of 1.082) obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517 (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv) is in EPA toxicity category IV in terms of dermal toxicity with a rat $LD_{50} > 5000$ mg/kg.

E. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** December 5, 2005
Risk Manager (EPA): 01 **DP Barcode:** D318634

STUDY TYPE: Primary Eye Irritation - NZW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL (% a.i.): A mixture (2.5 mL TS#12516 & 1.0 mL TS#12517, both clear liquids) with a specific gravity of 1.082 as determined by the test laboratory. From the proposed label for this product the TS#12516 corresponds to the material in Chamber A, with a declaration of 45% Permethrin. The TS#12517 corresponds to the material in Chamber B, with a declaration of 14.85% Dinotefuran and 1.48% Sumilarv. From these percentages and the mix proportions, the test material contained approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv,

SYNONYMS: The test material description is consistent with the mixture that would be obtained by mixing 0.7 mL of the contents of Chamber A with 0.3 mL of the contents of Chamber B.

CITATION: Merkel, D.J. (2005) Primary Eye Irritation of Hartz TTE (Samples 12516/12517). Study ID Numbers: Product Safety Laboratories No. 16392; Hartz Mountain No. 1772/1782. Unpublished study prepared by Product Safety Laboratories, Dayton, NJ. 20 p. Study Completion Date: 21 March, 2005. MRID 46552704.

SPONSOR: The Hartz Mountain Corporation

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46437606), 0.1 mL of undiluted liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517 was instilled into the conjunctival sac of one eye of each of 3 young adult male New Zealand White Rabbits (weights: not reported; age: not reported; source: Robinson Services, Inc. Clemmons, NC), with observations and scoring at 1, 24, 48 and 72 hours and days 4 and 7 after instillation. Sodium fluorescein dye was used at the 24 hour evaluation and as needed at subsequent scoring times to evaluate corneal damage or to verify reversal of effects.

At 24 and 48 hours corneal opacity was present in 3/3 eyes. This had cleared in 2/3 eyes at 72 hours, and in the remaining eye by day 7. At 24 hours all eyes were also positive for iridial irritation and conjunctival effects; overall, 3/3 eyes were still positive for irritation effects (corneal opacity and/or iridial effects and/or conjunctival irritation scores > 2) on day 4. All scores were zero by day 7.

This liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517, is in EPA Toxicity Category III for eye irritation, based on the presence of eye irritation effects at 24 hours with clearing by Day 7.

In a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) the resulting test material (containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv) caused corneal opacity in 3/3 male rabbits at 24 hours; all eyes were also positive for iridial and conjunctival irritation effects at this time. All eyes had

completely cleared (all scores zero) by Day 4, indicating this mixture is also in EPA Toxicity Category III for eye irritation (one minor difference in response: all eyes scored "1" for corneal opacity at one hour, while all eyes exposed to the other mixture scored "0" for corneal opacity at this time).

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

In a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) the resulting test material (containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv) caused corneal opacity in 3/3 male rabbits at 24 hours; all eyes were also positive for iridial and conjunctival irritation effects at this time. All eyes had completely cleared (all scores zero) by Day 4, indicating this mixture is also in EPA Toxicity Category III for eye irritation (one minor difference in response: all eyes scored "1" for corneal opacity at one hour, while all eyes exposed to the other mixture scored "0" for corneal opacity at this time).

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested					
	1 hr	24 hrs[2]	48 hrs	72 hrs[2]	4 days	7 days
Corneal Opacity	0/3	3/3	3/3	1/3	1/3	0/3
Iritis	3/3	3/3	2/3	1/3	1/3	0/3
Conjunctivae:						
Redness[1]	3/3	3/3	3/3	1/3	1/3	0/3
Chemosis[1]	3/3	3/3	1/3	1/3	1/3	0/3
Discharge[1]	3/3	3/3	1/3	0/3	0/3	0/3

[1]Score of 2 or more considered positive
[2]Fluorescein staining was used to determine the extent of or verify the absence of corneal opacity.

A. Observations - No systemic effects were observed. Corneal opacity was observed in all 3 exposed eyes at 24 and 48 hours, and all eyes were also positive for conjunctival effects at these readings. All eyes had completely cleared (all scores zero) by Day 7. In a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) the resulting test material (containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv) caused corneal opacity in 3/3 male rabbits at 24 hours; all eyes were also positive for iridial and conjunctival irritation effects at this time. All eyes had

completely cleared (all scores zero) by Day 4, indicating this mixture is also in EPA Toxicity Category III for eye irritation (one minor difference in response: all eyes scored "1" for corneal opacity at one hour, while all eyes exposed to the other mixture scored "0" for corneal opacity at this time).

B. Reviewer's Conclusions: The study adequately defines a Toxicity Category III hazard potential for eye irritation for a formulation (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12516 (45% Permethrin) & 1.0 mL TS#12517 (14.85% Dinotefuran and 1.48% Sumilarv)

based on the presence of positive eye irritation effects (including corneal opacity) at 24 hours with clearing by Day 7.

C. Comment - While the contents of Chamber A (TS#12516: 45% Permethrin) and Chamber B (TS#12517: 14.85% Dinotefuran and 1.48% Sumilarv) were not tested separately, the erroneous mixing and subsequent testing of a 3:7 (rather than a 7:3) TS#12516:TS#12517 mixture also gave toxicity category III results. Additionally, it is noted that the registrant two existing registrations containing 45% Permethrin (EPA Reg. No. 2596-137, which contains 45% Permethrin as sole active, and EPA Reg. No. 2596-146, which contains 45% Permethrin and 2.9% S-Methoprene), as well as an existing registration (EPA Reg. No. 2596-155) containing14.85% Dinotefuran as sole active. These 3 registrations have labels with the signal word "CAUTION," indicating they are no worse than toxicity category III with respect to eye irritation potential.

D. Deficiencies: None

Reviewer: Byron T. Backus, Ph.D.
Risk Manager (EPA): 01

Date: December 13, 2005
DP Barcode: D318634

STUDY TYPE: Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL (% a.i.): A mixture (2.5 mL TS#12516 & 1.0 mL TS#12517, both clear liquids) with a specific gravity of 1.082 as determined by the test laboratory. From the proposed label for this product the TS#12516 corresponds to the material in Chamber A, with a declaration of 45% Permethrin. The TS#12517 corresponds to the material in Chamber B, with a declaration of 14.85% Dinotefuran and 1.48% Sumilarv. From these percentages and the mix proportions, the test material contained approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv,

SYNONYMS: The test material description is consistent with the mixture that would be obtained by mixing 0.7 mL of the contents of Chamber A with 0.3 mL of the contents of Chamber B.

CITATION: Merkel, D.J. (2005) Primary Skin Irritation of Hartz TTE (Samples 12516/12517). Study ID Numbers: Product Safety Laboratories No. 16393; Hartz Mountain No. 1773/1783. Unpublished study prepared by Product Safety Laboratories, Dayton, NJ. 17 p. Study Completion Date: 21 March, 2005. MRID 46552705.

SPONSOR: The Hartz Mountain Corporation

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46552705), 0.5 mL aliquots of a liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517 together were applied to single dermal sites on each of 3 (2 male & 1 female) adult New Zealand White albino rabbits (weights: not reported; age: young adult; source: Robinson Services, Inc. Clemmons, NC) with 4-hour semioccluded exposure.

After 4 hours, the gauze pad and holding tape were removed. The test sites were scored (Draize) at 1, 24, 48 and 72 hrs and at 7 days.

At 24 hours scores for erythema ranged from "1" to "2" and scores for edema from "0" to "1." At 72 hours 2 sites scored "1" and one scored "0" for erythema, while all edema scores were "0." All scores were "0" at 72 hours. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.42

The test liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517 is in EPA Toxicity Category IV for dermal irritation effects, based on the low score for dermal irritation (PII at 72 hrs = 0.67) following 4-hr semi-occluded exposure.

In a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) dermal exposure to the test material (containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv) resulted in similar dermal irritation scores (at 24 hours scores for erythema were all "2" while scores for edema were all "1"; at 72 hrs all scores for erythema and edema were "0." The PII = 1.17), indicating this mixture is also in EPA

Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

A. Observations - At 24 hours scores for erythema ranged from "1" to "2" and scores for edema from "0" to "1." At 72 hours 2 sites scored "1" and one scored "0" for erythema, while all edema scores were "0." All scores were "0" at 72 hours.

B. Results - The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.42

C. Reviewer's Conclusions -The test liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12516 & 1.0 mL TS#12517 is in EPA Toxicity Category IV for dermal irritation based on the low score for dermal irritation (PII at 72 hrs = 0.67) following 4-hr semi-occluded exposure and the PII at 72 hours (=0.67)

While the individual components of this mixture were not tested, there was a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) dermal exposure to the test material (containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv), and this mixture gave similar dermal irritation scores (at 24 hours scores for erythema were all "2" while scores for edema were all "1"; at 72 hrs all scores for erythema and edema were "0." The PII = 1.17), indicating this mixture is also in EPA Toxicity Category IV.

D. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D.
Product Manager (EPA): 01

Date: December 14, 2005
DP Barcode: D318634

STUDY TYPE: Dermal Sensitization - albino Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL (% a.i.): A mixture (2.5 mL TS#12567 & 1.0 mL TS#12568, both clear liquids), presumably with a specific gravity of 1.082. From the proposed label for this product the TS#12567 corresponds to the material in Chamber A, with a declaration of 45% Permethrin. The TS#12568 corresponds to the material in Chamber B, with a declaration of 14.85% Dinotefuran and 1.48% Sumilarv. From these percentages and the mix proportions, the test material contained approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv,

SYNONYMS: The test material description is consistent with the mixture that would be obtained by mixing 0.7 mL of the contents of Chamber A with 0.3 mL of the contents of Chamber B.

CITATION: Merkel, D.J. (2005) Dermal Sensitization (Buehler Method) of Hartz TTE (Samples 12567/12568). Study ID Numbers: Product Safety Laboratories No. 16394; Hartz Mountain No. 1775/1784. Unpublished study prepared by Product Safety Laboratories, Dayton, NJ. 27 p. Study Completion Date: 21 March, 2005. MRID 46552706.

SPONSOR: The Hartz Mountain Corporation

EXECUTIVE SUMMARY: In a Buehler protocol dermal sensitization study (MRID 46552706) a liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12567 & 1.0 mL TS#12568 was tested using a group of 20 young adult male Hartley albino guinea pigs (weights: 356-445 g at first exposure; source: Elm Hill Breeding Labs, Chelmsford, MA). Each received a once-a-week 6-hr occluded dermal exposure to a 0.4 mL aliquot of undiluted test material. Twenty-seven days after the first induction dose, each was challenged (at a previously unexposed site) for 6 hours with 0.4 mL undiluted test material. An additional 10 (all male) previously unexposed guinea pigs were similarly treated at this time. Challenge sites on all 30 guinea pigs were evaluated and scored for erythema at 24 and 48 hours after the application.

Following challenge, the maximum score observed for erythema at 24 hours was 0.5, seen in 8/20 previously exposed and 3/10 previously unexposed guinea pigs. At 48 hours all scores were zero.

The report includes results from a positive control study (PSL Study #15590, completed on August 12, 2004; the dates of the testing with Hartz TTE were from November 22, 2004 to February 16, 2005) conducted with alpha-Hexylcinnmaldehyde Technical (HCA). The results (a positive response in 6/10 previously induced and 0/5 naive guinea pigs) were appropriate.

In this study **there were no indications that the test material (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv; obtained by mixing 2.5 mL TS#12567 and 1.0 mL TS#12568) is a dermal sensitizer.**

There was a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) and a Buehler study was conducted on material containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv. The results at challenge (maximum score following challenge: 0/5, present at 24 hours in 6/20 previously induced and 4/10 naive guinea pigs) were similar and indicated there was no evidence that this test material is a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

I. PROCEDURE

A. Induction - Each of 20M young adult Hartley albino guinea pigs was treated once a week for 3 consecutive weeks to a 6-hour exposure to 0.4 mL undiluted test material (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12567 & 1.0 mL TS#12568.

B. Challenge - Approximately fourteen days after the last induction exposure 0.4 mL undiluted test material (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12567 & 1.0 mL TS#12568. was applied to a naive (previously unexposed) dermal site on each guinea pig. These sites were evaluated and scored for erythema at 24 and 48 hours after the challenge application.

C. Naive Controls - At the time the 20 previously induced guinea pigs were challenged, 10M previously unexposed (negative control) guinea pigs were similarly challenged.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Following challenge, the maximum score observed for erythema at 24 and/or 48 hours was 0.5, seen in 8/20 previously exposed guinea pigs. The remaining 12 guinea pigs scored zero. The maximum score observed in the naive controls was also 0.5, seen in 3/10 guinea pigs. All other scores in the naive group were zero.

B. Positive control -The report includes results from a positive control study (PSL Study #15590, completed on August 12, 2004; the dates of the testing with Hartz TTE were from November 22, 2004 to February 16, 2005) conducted with alpha-Hexylcinnmaldehyde Technical (HCA). The results (a positive response in 6/10 previously induced and 0/5 naive guinea pigs) were appropriate.

C. Reviewer's Conclusions: Based on the results of this study **the test material (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv; obtained by mixing 2.5 mL TS#12567 and 1.0 mL TS#12568) is not a dermal sensitizer.**

While the individual components of this mixture were not tested, there was a preliminary study in which a mixing mistake was made (2.5 mL TS#12517 was mixed with 1.0 mL TS#12516) dermal exposure to the test material (containing approximately 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv), and the results for this mixture also indicate no dermal sensitization potential.

D. Deficiencies - None

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D318634
2. **PC CODES:** 109701 (Permethrin), 044312 (Dinotefuran) and 129032 (Sumilarv)
3. **CURRENT DATE:** December 14, 2005
4. **TEST MATERIAL:** A liquid (containing approximately 32.1% Permethrin, 4.24% Dinotefuran and 0.42% Sumilarv, with a specific gravity = 1.082) obtained by mixing 2.5 mL TS#12567 (45% Permethrin) & 1.0 mL TS#12568 (14.85% Dinotefuran and 1.48% Sumilarv).

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity up-an-down procedure/rat/Product Safety Labs, Dayton, NJ/PSL No. 16390; Hartz Mountain No. 1771/MAR-21-2005	46552702	LD_{50}>between 1750 (0/3 died) and 5000 (4/5 died) mg/kg. No signs of toxicity in rats dosed at 175, 550 and 1750 mg/kg. At 5000 mg/kg 4/5 rats died within 24 hrs of dosage; signs of toxicity prior to death included hypoactivity, hunched posture and tremors. The one survivor at this dose also showed signs including hypoactivity, tremors, diarrhea, ano-genital staining and reduced fecal volume, with recovery by Day 5. All survivors gained weight from Day 0 to 7 and again from Day 7 to 14. All survivors had normal necropsy results; the four rats which died after dosage at 5000 mg/kg had red or slightly red intestines, and one also had discolored liver and red lungs.	III	A
Acute dermal toxicity/rat/Product Safety Labs, Dayton, NJ/PSL No. 16391; Hartz Mountain No. 177/MAR-21-2005	46552703	LD_{50} > 5000 mg/kg. 5M & 5F Sprague-Dawley derived albino rats were dermally exposed to 5000 mg/kg for 24 hrs; no mortality and no signs of systemic toxicity. All gained weight in the period from Day 0 to 7 and again from Day 7 to 14. Post-sacrifice necropsy results were normal.	IV	A
Primary eye irritation/rabbit/ Product Safety Labs, Dayton, NJ/PSL No. 16392; Hartz Mountain No. 1772/1782/ 21-MAR 2005	46552704	At 24 and 48 hrs corneal opacity was present in 3/3 eyes. This had cleared in 2/3 eyes at 72 hrs and in the remaining eye by day 7. All scores were zero by day 7. In a preliminary study a mixing mistake was made and the resulting test material contained approx. 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv. Corneal opacity was observed in 3/3 eyes at 24 hrs with clearing by day 7. This material was also in toxicity category III for eye irritation.	III	A
Primary dermal irritation/rabbit/ Product Safety Labs, Dayton, NJ/PSL No. 16393; Hartz Mountain No. 1773/1783/ 21-MAR-2005	46552705	Max. scores: 2 for erythema and 1 for edema. At 72 hrs 2/3 sites scored "1" for erythema and zero for edema. In a preliminary study a mixing mistake was made and the resulting test material contained approx. 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv. This material was also in toxicity category IV for dermal irritation.	IV	A

Dermal sensitization/guinea pig/ Product Safety Labs, Dayton, NJ/PSL No. 16394; Hartz Mountain No. 1775/1784 /21-MAR-2005	46552706	Buehler: Once a week induction treatments with undiluted test material for 3 weeks, followed by challenge with undiluted test material two weeks after last induction. At challenge maximum score for erythema was 0.5, seen in 8/20 previously exposed male guinea pigs and in 3/10 previously unexposed guinea pigs. No indications of a dermal sensitization reaction from this formulation. In a preliminary study a mixing mistake was made and the resulting test material contained approx. 12.9% Permethrin, 10.6% Dinotefuran and 1.06% Sumilarv. This material also gave no indications of a dermal sensitization reaction. Positive control study (with HCA) was conducted within 6 months of this study and gave appropriate results.	Not a sensitiz er	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**