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

008202

DEC 17 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Hartz Flea & Tick Repellent for Cats III
Hartz Flea & Tick Repellent for Dogs III

TO: Mr. George LaRocca, PM 15
Registration Division (H7505C)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 12/10/90
Herbicide/Fungicide/Antimicrobial Support Branch
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section Head, Review Section II
Herbicide/Fungicide/Antimicrobial Support Branch
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief M van Gemert 12/12/90
Herbicide/Fungicide/Antimicrobial Toxicology Branch
HED (H7509C)

DP Barcode: D157198, D157196

Case No. 033469, 016287

Project No. 1-0038

EPA Reg. No. 2596-REN (cats), 2596-RER (dogs)

Tox. Chem. 346, 268J

Action Requested:

Review a series of acute toxicity studies (oral $LD_{50}$, dermal $LD_{50}$, inhalation $LC_{50}$, primary eye irritation, primary dermal irritation, dermal sensitization) and domestic animal safety studies on this formulation.

Comments and Recommendations:

1. The oral $LD_{50}$, dermal $LD_{50}$, primary eye irritation, primary dermal irritation, and dermal sensitization studies have been

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classified as core minimum data. This formulation is in toxicity category IV in terms of its oral $LD_{50}$ and primary dermal irritation potentials, and in toxicity category III in terms of its dermal $LD_{50}$ and primary eye irritation potentials. There was no indication of any dermal sensitization reaction in guinea pigs which received induction and subsequent challenge exposure to undiluted test material.

2. The two domestic animal safety studies have been classified as acceptable. In both studies the lack of evident toxicity indicates a reasonably high expectation of at least a 4X safety factor between a normal use application to healthy animals and a level of exposure at which signs of toxicity might develop. Labeling for the existing Blockade products includes the following: "Do not use this or any other pesticide on sick, old or debilitated pets. Some animals may be sensitive to ingredients in this or other pesticide products. Pets should be observed following treatment. If any unusual symptoms occur, immediately bathe pet with a non-pesticidal shampoo." Similar statements should appear on the labels of these proposed products.

3. Largely because of uncertainties associated with measurement of the actual chamber concentrations of the two actives, the inhalation $LC_{50}$ study is currently classified as core supplementary data. This classification can be upgraded with sufficient additional information and/or justification for measurement of the chamber concentration from amount of actives collected by the pads. However, in addition to the question as to whether pads from locations 1 and 2 should be used in computation of the averages, any product chamber concentration calculation might also have to be adjusted to take into consideration the amount of product available in respirable sizes. Also, from the report presentation, it is not evident how the percentage value for DME (as reported on p. 20) was converted into an average chamber concentration. Because of questions as to whether or not the mottled lungs observed on necropsy were related to exposure, the method of animal sacrifice should also be stated.

4. Since the primary eye irritation study and the two domestic animal safety studies were conducted on the aerosol formulation, these studies are acceptable in support of an aerosol formulation (not a formulation with a hand-pump delivery system). It is noted that the eye irritation study was conducted on a formulation containing 4.0% Deet (in all other studies the content was 4.2%); this minor difference is of no toxicological significance.

5. Copies of the attached data evaluation reports should be supplied to the registrant.

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 12/10/90
Section 2, HFASB (H-7509C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

DATA EVALUATION REPORT I

STUDY TYPE: Acute oral $LD_{50}$ - rats (81-1)

TOX CHEM NO. 346, 268J

MRID NO: 416394-02

TEST MATERIAL: Hartz Flea & Tick Repellent for Dogs III; Hartz Flea and Tick Repellent for Cats III; Sample # 8985-3

STUDY NUMBER(S): Assay # 903817

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: Leberco Testing, Inc.
123 Hawthorne St.
Roselle Park, NJ 07204

TITLE OF REPORT: Acute Oral Toxicity Testing of Hartz Mountain Corporation Sample # 8985-3

AUTHOR(S): Barbera, Joanne

REPORT ISSUED: 13 June 1990

CLASSIFICATION: Core Minimum Data. This study satisfies the data requirements (81-1) for an acute oral LD50 study on this formulated product.

CONCLUSIONS:

1. The study adequately demonstrates an oral $LD_{50}$ > 5 gm/kg (no mortalities among 10 rats at this dose level) for the proposed product, which is then in toxicity category IV in terms of oral exposure hazard.

2. The weight loss in the two females over the first 7 days following dosage may have been entirely or partly due to water deprivation (it is not immediately apparent from the reporting whether there were only these two females in one cage, or whether other females were also present with them).

A. MATERIALS:

1. Test material: Sample #8953-3, identified by the laboratory as a cloudy liquid, which was stored in the container in which it was received. According to information on the attached dosing sheet the density of the test material was 1.02 g/ml. From information on p. 16 the active ingredients by weight were Asana (84% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Test animals: "Sprague Dawley derived" male and female rats from Harlan Sprague Dawley, Inc., Indianapolis, IN. The males weighed 213-242 grams and the females 200-209 grams on the day they were given a single oral dose.

B. STUDY DESIGN:

1. Administration of test material: From p. 8: "The test material was administered as a single oral dose by syringe and suitable intubation tube." The test animals had been fasted for 14 hours before being dosed. "A dose of 5 g/kg body weight was administered for the limit test." According to the attached dosing sheet: "Test material was shaken thoroughly prior to dosing each animal."

2. Observations: According to information on p. 8 body weights were recorded just prior to administration of the test material and 7 and 14 days later. The animals were observed for signs of toxicity and mortality twice a day for the entire 14-day post-dosing period, after which they were sacrificed with $CO_2$. Gross necropsies were performed,

3. Quality assurance: There is a signed and dated "Quality Assurance Unit Statement" giving dates on which study operations, records and the final report were reviewed on p. 4 of the report. There is also a "Good Laboratory Practice Statement" on p. 3 of the report.

C. RESULTS:

Mortality and symptoms: There was no mortality, as all 10 rats survived the 14-day observation period. According to information on p. 9 one female exhibited rales 4 hours after dosage; two females were thin and dehydrated on day 7 and "a water bottle was added to the cage." On day 8 and 9 these two rats were no longer dehydrated but appeared thin. These were the only two rats which lost weight in the period from day 0 to day 7; all rats had gained between 18 and 89 grams from their initial (day 0) weight by day 14. At necropsy, no gross abnormalities were observed in any of the animals.

D. DISCUSSION:

The study adequately demonstrates an oral $LD_{50}$ of > 5 g/kg for the test material, which is in toxicity category IV by this exposure route. The weight loss in the two females over the first 7 days following dosage may have been entirely or partly due to water deprivation (it is not immediately apparent from the reporting whether there were only these two females in one cage, or whether other females were also present with them). The study is classified as core minimum data.

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus
Section 2, HFASB (H-7509C) 12/10/90

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

DATA EVALUATION REPORT II

STUDY TYPE: Acute dermal $LD_{50}$ - rabbits (81-2)

TOX CHEM NO. 346, 268J

MRID NO: 416394-03

TEST MATERIAL: Hartz Flea & Tick Repellent for Dogs III; Hartz Flea and Tick Repellent for Cats III; Sample # 8985-1

STUDY NUMBER(S): Assay # 903818

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: Leberco Testing, Inc.
123 Hawthorne St.
Roselle Park, NJ 07204

TITLE OF REPORT: Acute Dermal Toxicity of Hartz Mountain Corporation Sample # 8985-1

AUTHOR(S): Barbera, Joanne

REPORT ISSUED: 22 June 1990

CLASSIFICATION: Core Minimum Data. This study satisfies the data requirements (81-2) for an acute dermal LD50 study on this formulated product.

CONCLUSIONS:

1. The study adequately demonstrates a dermal $LD_{50}$ > 2 gm/kg (no mortalities among 10 rabbits dermally exposed to this dose) for the proposed product. The formulation is in toxicity category III in terms of dermal toxicity hazard.

2. The study is classified as core minimum data.

A. MATERIALS:

1. Test material: Sample #8953-3, identified by the laboratory as a white liquid with a density of 1.02 g/ml which was stored in the container in which it was received. From information on p. 17 the active ingredients by weight were Asana (84% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Test animals: Identified (p. 6) as New Zealand white rabbits, from Gingrich Animal Supply, Fredericksburg, PA 17026. Males weighed 2.27-2.55 kg and females 2.33-2.61 kg on the day they were dosed topically.

B. STUDY DESIGN:

1. Exposure to the test material: From p. 8: "The test material was applied as a uniform film covering approximately 10% of the total body surface area and covered with gauze. The gauze was held in place with non-irritating tape and covered with an occlusive dressing. The skin was exposed to the test material for a period of 24 hours. After the 24 hour exposure period the patches and residual test material were removed."

2. Observations: According to the text (p. 8) body weights were recorded just prior to application of the test material, at 7 days, and at sacrifice (day 14). Rabbits were observed for signs of toxicity and mortality once a day for the entire 14-day post-dosing period, and then were sacrificed with sodium pentobarbital. Gross necropsies were performed,

3. Quality assurance: There is a signed and dated "Quality Assurance Unit Statement" (giving dates on which study operations, records and the final report were reviewed) on p. 5 of the report. There is also a "Good Laboratory Practice Statement" which appears on p. 3 of the report.

C. RESULTS:

Mortality and symptoms: There was no mortality, as all 10 rabbits survived the 14-day observation period. The effects observed (see p. 9) included minor dermal irritation with clearing by day 4. Three animals showed possible effects, which included bloat, loose stool and/or diarrhea, thinness, dehydration, and slight weight loss in the period from day 0 to 7. All rabbits had either gained weight or had recovered to their initial (day 0) weight on day 14. At necropsy, one female (which had shown bloat and/or diarrhea throughout the 14-day observation period) was noted as having "soft material in gastrointestinal tract." No gross abnormalities were observed in any of the other animals.

D. DISCUSSION:

The study adequately demonstrates that the dermal $LD_{50}$ of the test material is > 2 g/kg. The formulation is in toxicity category III in terms of its potential dermal toxicity hazard. Indications of systemic toxicity were equivocal, as they occurred (in one rabbit) throughout the observation period, and in two other rabbits were noted a few days after exposure took place. The study is classified as core minimum data.

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Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 12/10/90
Section 2, HFASB (H-7509C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

DATA EVALUATION REPORT III

STUDY TYPE: Acute inhalation $LC_{50}$ - rat (81-3)

TOX CHEM NO. 346, 268J

MRID NO: 416394-06

TEST MATERIAL: Hartz Flea & Tick Repellent for Dogs III; Hartz Flea and Tick Repellent for Cats III; Sample # 8986, aerosol

STUDY NUMBER(S): Assay # 905487

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: Leberco Testing, Inc.
123 Hawthorne St.
Roselle Park, NJ 07204

TITLE OF REPORT: Acute Inhalation Toxicity Testing Hartz Mountain Corporation Sample # 8986

AUTHOR(S): Barbera, Joanne

REPORT ISSUED: 5 September 1990

CLASSIFICATION: Core Supplementary Data. This study does not currently satisfy the data requirements (81-3) for an acute inhalation LC50 study for this formulated product.

CONCLUSIONS:

1. No mortality occurred among 5 male and 5 female rats as a result of 4-hour exposure to an aerosol of the formulated product.

2. One of the major problems in evaluating this study is that it is not evident that the laboratory actually measured the atmospheric concentrations of either of the two active ingredients. The report states that average concentrations for Asana and Deet were 0.0191 and 4.5 mg/liter of air in the

breathing zone, corresponding to levels of 4.42 and 6.5 mg product/liter. However, these values were obtained by analyzing filter pads which had been in open cassettes, and it is not immediately apparent that these filters were anything other than passive collectors. If a justification can be made for measuring the chamber concentration of product on the basis of amount of actives collected by these filters, there would still be a question as to whether the results from pads at locations 1 and 2 should be included in computation of averages.

3. While the chamber concentration of product based on dimethyl ether concentration measurements corresponds reasonably well with the nominal concentration of 13.23 mg/liter, dimethyl ether is a gas at normal temperatures. Other components of the formulation may have more readily settled out, or the dimethyl ether may have been retained longer within the exposure chamber. Also, from the report presentation, it is not evident how the percentage value for DME (as reported on p. 20) was converted into an average chamber concentration.

4. Largely because of the uncertainties associated with measurements of the actual chamber concentrations of the two actives the study is currently classified as core supplementary data. This classification can be upgraded with sufficient additional information and/or justification for measurement of the chamber concentration from amounts of actives collected by the pads. However, in addition to the question as to whether pads from locations 1 and 2 should be used in computation of the averages, any product chamber concentration calculation might also have to be adjusted to take into consideration the amount of product available in respirable sizes. Because of questions as to whether or not the mottled lungs were related to exposure, the method of animal sacrifice should also be stated.

5. A copy of this DER should be sent to the registrant.

A. MATERIALS:

1. Test material: Sample 8986, an aerosol, identified (p. 55) as containing 0.030% Asana (86% active) and 4.2% N,N-diethyl toluamide. From information on p. 55 the active ingredients by weight were Asana (86% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Test animals: "Sprague Dawley derived" male and female rats from Harlan Sprague Dawley, Inc., Indianapolis, IN. Males weighed 260-300 grams, and females 256-280 grams on the day of exposure to the test material.

B. STUDY DESIGN:

1. Description of test chamber and measured parameters: For particle size analysis (see p. 10): "Five air samples were taken at the breathing zone...using a 6 stage Cascade Impactor... Samples were taken at 30, 50, 100, 145 and 200 minutes into the four hour exposure period." Also from p. 10: "Filter pads were placed in open cassettes attached to wooden dowels. The dowels were placed near the four corners of each cage in which the animals were held. The filter pads remained in place during the entire length of the test to collect representative samples of the test material. Filter pads were analyzed to determine the concentration of ASANA and DEET...in the breathing zone." Refer to appended page 1 for a description of the test chamber, and some of the other parameters (including concentration of dimethyl ether, used as a propellant) that were measured during the course of the exposure.

2. Exposure to the test material: From p. 9: "The test material was introduced into the chamber as one second bursts every 60 seconds, with a flow rate of 40 liters of air per minute." From p. 10: "The length of time required to establish a concentration of 99% of the maximum attainable dose level...was determined to be 30 minutes." The animals were exposed for 4 hours.

3. Observations: From p. 9: "Body weight was recorded in grams for each animal just prior to test substance exposure, seven days after exposure, and just prior to necropsy." "All animals were checked a minimum of twice daily during the 14 day observation period." No information is provided as to the method of sacrifice. "A gross necropsy was performed on all test animals at the end of the study... Emphasis was placed on examination of the respiratory tract."

4. Quality assurance: On p. 5 there is a signed and dated "Quality Assurance Statement" giving dates on which study operations, records and the final report were reviewed. There is also a "Good Laboratory Practice Statement" on p. 3 of the report.

C. RESULTS:

1. Exposure parameters: From 40.8 to 67.8% of the particles by weight (mean: 52.6%) were $\leq$ 1.7 $\mu$m. Refer to appended pages 2 and 3. From the information presented on p. 22, the nominal concentration of test material was 13.23 mg/liter (142.93 gm in 10,800 liters).

According to the report (page 20), the average concentration of product was 16.43 mg/liter, based on measurements of dimethyl ether (an inert in the formulation). It is not possible to determine from the data, as presented on p. 20 (DME is presented as a %, but there is nothing to indicate what value 100% is or would represent) how this value was reached.

From p. 12: "Analysis for the active ingredients of the test sample resulted in exposure concentrations of 4.4 mg Product/Liter of air and 6.5 mg Product/Liter of air." The following is from p. 20 (Table V):

| Location | ASANA Concentration (mg/pad) | DEET Concentration (mg/pad) |
|---|---|---|
| 1 | 0.0921 | 19.22 |
| 2 | 0.0838 | 21.28 |
| 3 | 0.0144 | 3.38 |
| 4 | 0.0141 | 3.38 |
| 5 | 0.0184 | 3.68 |
| 6 | 0.0118 | 3.08 |
| 7 | 0.0104 | 3.05 |
| 8 | 0.0102 | 3.05 |
| Avg mg/pad | 0.0319 | 7.5 |
| mg/liter of air in breathing zone | 0.0191 | 4.50 |
| mg product/liter of air in breathing zone | 4.42 | 6.50 |

According to the report (p. 20): "The concentration of ASANA and DEET determined at locations 1 and 2 were considerably higher than the other six locations. Locations 1 and 2 were closest to the air exhaust and this probably accelerated precipitation of the spray onto those filter pads."

Without results from locations 1 and 2, averages were 0.0132 mg ASANA/pad, and 3.27 mg DEET/pad, or 0.414 and 0.436 respectively of the averages presented in the report. Multiplying 0.414 and 0.436 by the values given for mg product/liter of air in breathing zone (4.42 and 6.50 respectively) would give 1.83 and 3.25 mg product/liter of air respectively.

2. Mortality and symptoms: There was no mortality, as all 10 rats survived the 14-day observation period. There is no indication as to whether or not animals were observed during the exposure period, and it is not stated whether or not symptoms occurred during exposure (p. 26 of the report lists

only pre- and post-exposure observations). From p. 12: "At the conclusion of the exposure period all animals appeared wet. During the PM observation period all animals appeared normal. All animals appeared normal throughout the remainder of the 14 day observation period."

On necropsy, it is reported (p. 12): "All animals exhibited mottled lungs." However, the significance of this finding is unclear, particularly as no information is given as to how the animals were sacrificed.

D. DISCUSSION:

The report states (p. 6) that based on analytical results for the two actives, the rats were exposed to 4.42 or 6.5 mg/liter of the product for 4 hours. However, one of the problems in evaluating this study is that it is not immediately apparent that the laboratory actually measured the atmospheric concentrations of either of the two active ingredients. The report states that average concentrations for ASANA and DEET were 0.0191 and 4.5 mg/liter of air in the breathing zone; however, these values were obtained by analyzing filter pads which had been in open cassettes, with no indication as to how much chamber atmosphere actually went through any pad.

It appears (p. 11: "The chamber utilized in this study was a 200 liter, non-porous, airtight square..." - perhaps "cube" would have been a better word than "square") that the chamber measured about 2 feet on a side (200,000 $cm^3$ would be the capacity of a cube measuring about 58.5 cm - or 23 inches - on a side). Each pad had an exposed surface area of 1.67 $inches^2$ (0.0319 mg ASANA/pad is reported as being equivalent to 0.0191 mg ASANA/$inch^2$ in the breathing zone). 1 $in^2$ = 6.45 $cm^2$, so 0.0191 mg ASANA/$inch^2$ equals 0.00296 mg ASANA/$cm^2$. The amount of ASANA/liter of chamber atmosphere is reported as 0.0011 mg/liter, implying that the amount of chamber atmosphere going (?) through a filter was 2.7 liters/$cm^2$ (or 29 liters/filter). This reviewer assumes that the 2.7 liters/$cm^2$ value is related to the distance to the top of the chamber above the filter (approximately 50 cm) times the number of chamber atmosphere changes (10,800 liters ÷ 200 liters = 54). However, it is not immediately apparent that these filters were anything other than passive collectors. If the 29 liters/filter value is justified, there still remains the question as to whether the results from pads at locations 1 and 2 should be included in computation of averages of actives deposited on these pads.

While the chamber concentration of product based on dimethyl ether concentration measurements corresponds fairly closely to

the nominal concentration value, dimethyl ether is a gas at normal temperatures. Under the conditions of this study, the active components of the product may have more readily settled out, or the dimethyl ether may have been retained longer within the exposure chamber. It is noted that the fact that dimethyl ether is a component of this formulation occurs within the text of a supposedly non-confidential report (it is stated on p. 2 that information claimed confidential has been removed to a confidential appendix) and, from the information on p. 20, it is fairly easy to determine its percentage in the formulation.

Largely because of the uncertainties associated with measurements of the actual chamber concentrations of the two actives the study is currently classified as core supplementary data. The study classification can be upgraded with additional information and/or justification for the 29 liters/filter value. There is also a question as to whether it is appropriate to include the findings for the pads at locations 1 and 2 in computation of the averages. The product chamber concentration may also have to be adjusted to take into consideration the amount of product available in respirable sizes. Information should also be given as to how the percentage value obtained for DME (as reported on p. 20) was converted into an average chamber concentration. Because of questions as to whether or not the mottled lung findings were related to exposure, the method of animal sacrifice should also be indicated.

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Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 12/10/90
Section 2, HFASB (H-7509C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

DATA EVALUATION REPORT IV

STUDY TYPE: Primary eye irritation - rabbits (81-4)

TOX CHEM NO. 346, 268J

MRID NO: 416394-04

TEST MATERIAL: Hartz Flea & Tick Repellent for Dogs III; Hartz Flea and Tick Repellent for Cats III; Sample # 8894

STUDY NUMBER(S): Assay # 899790

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: Leberco Testing, Inc.
123 Hawthorne St.
Roselle Park, NJ 07204

TITLE OF REPORT: Primary Eye Irritation Hartz Mountain Sample # 8894

AUTHOR(S): Reilly, C.

REPORT ISSUED: 1/2/90

CLASSIFICATION: Core Minimum Data. This study satisfies the data requirements (81-4) for a primary eye irritation study on this formulated product.

CONCLUSIONS:

1. The study adequately demonstrates that reversible (within 7 days) eye irritation (without corneal involvement) occurs as a result of exposure to the test material. The formulation is in toxicity category III in terms of eye hazard potential.

2. The study is classified as core minimum data.

A. MATERIALS:

1. Test material: Sample #8894, identified by the laboratory as a liquid in an aerosol can which "was stored at ambient temperature and humidity in the container in which it was received." From information on p. 15 the active ingredients by weight were Asana (86% active) 0.029% and N,N-diethyl toluamide 4.0%.

2. Test animals: New Zealand White rabbits, from Gingrich Animal Supply, Fredericksburg, PA 17026. "Prior to administration of the test material the eyes were examined with sodium fluroescein. Animals with corneal injury or ocular irritation were eliminated from the study."

B. STUDY DESIGN:

1. Administration of test material: From p. 8: "Each animals' test eye was gently held open, and a one second burst of the test material from a distance of ten centimeters was sprayed onto the corneal surface of the test eye. The contralateral eye was not dosed and served as a control." "The treated eyes of all rabbits remained unwashed."

2. Observations: From p. 9: "The treated eye of each rabbit was examined for irritation of the cornea, iris and conjunctivae using the contralateral eye as a control at one hour, twenty-four, forty-eight, seventy-two hours after exposure."

3. Quality assurance: On p. 5 of the report there is a signed and dated "Quality Assurance Unit Statement" giving dates on which study operations, records and the final report were reviewed. There is also a "Good Laboratory Practice Statement" on p. 3 of the report.

C. RESULTS:

Eye irritation: There was no corneal or iridial irritation. It is reported (p. 8) that at one hour 6/6 rabbit eyes showed redness and chemosis, while discharge was present in 4 eyes. Redness was still present in 2/6 eyes on day 1 and in 1/6 on day 2, with all eyes clearing by day 3. No Draize scores are provided.

D. DISCUSSION:

The study adequately demonstrates that reversible (within 7 days) eye irritation (without corneal involvement) occurs as a result of exposure to the test material. The formulation is in toxicity category III in terms of eye irritation hazard potential.

The study is classified as core minimum data.

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 12/10/90
Section 2, HFASB (H-7509C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

DATA EVALUATION REPORT V

STUDY TYPE: Primary dermal irritation - rabbit (81-5)

TOX CHEM NO. 346, 268J

MRID NO: 416394-05

TEST MATERIAL: Hartz Flea & Tick Repellent for Dogs III; Hartz Flea and Tick Repellent for Cats III; Sample # 8985-1

STUDY NUMBER(S): Assay # 903819

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: Leberco Testing, Inc.
123 Hawthorne St.
Roselle Park, NJ 07204

TITLE OF REPORT: Primary Dermal Irritation Hartz Mountain Sample # 8985-1

AUTHOR(S): Barbera, J.

REPORT ISSUED: 6/13/90

CLASSIFICATION: Core Minimum Data. This study satisfies the data requirements (81-5) for a primary dermal irritation study on this formulated product.

CONCLUSIONS:

1. The study adequately demonstrates a low dermal irritation potential (toxicity category IV) for this product formulation.

2. The study is classified as core minimum data.

A. MATERIALS:

1. Test material: Sample # 8985-1, identified by the laboratory as a white liquid, which was stored refrigerated prior to use. From information on p. 13 the active ingredients by weight were Asana (84% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Test animals: Female New Zealand White rabbits, from Gingrich Animal Supply, Fredericksburg, PA 17026. "Animals were acclimated to the testing facility at least seven days prior to the start of testing."

B. STUDY DESIGN:

1. Administration of test material: According to the text (p. 8) one application of 0.5 ml test material was applied to one intact skin site (from which fur had been clipped) on each of 6 rabbits, with subsequent 4-hour occluded exposure.

2. Observations: From p. 9: "Animals were examined within thirty to sixty minutes after patch removal and then daily for three days." Application sites were scored at 4, 24, 48 and 72 hours.

3. Quality assurance: On p. 5 of the report there is a signed and dated "Quality Assurance Unit Statement" giving dates on which study operations, records and the final report were reviewed. There is also a "Good Laboratory Practice Statement" on p. 3 of the report.

C. RESULTS:

Dermal irritation: 2/6 animals showed minimal erythema/eschar at 4 and 24 hours; 1/6 showed slight edema at 4 and 24 hrs. All sites had cleared by 72 hours. The primary irritation index is reported as 0.20.

D. DISCUSSION:

The study adequately demonstrates a low dermal irritation potential (toxicity category IV) for this product formulation.

The study is classified as core minimum data.

903820

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus
Section 2, HFASB (H-7509C) 12/7/90

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel, 12/11/90
Section 2, HFASB (H-7509C)

**DATA EVALUATION REPORT VI**

STUDY TYPE: Dermal Sensitization - guinea pig

TOX CHEM NO. 346, 268J

MRID NO: 416394-07

TEST MATERIAL: Hartz Flea & Tick Repellent for Dogs III; Hartz Flea and Tick Repellent for Cats III; Sample # 8985

STUDY NUMBER(S): Assay # 903820

SPONSOR: Hartz Mountain Corporation
700 S. 4th St.
Harrison, NJ 07029

TESTING FACILITY: Leberco Testing, Inc.
123 Hawthorne St.
Roselle Park, NJ 07204

TITLE OF REPORT: Delayed Contact Hypersensitivity in Guinea Pigs of Hartz Mountain Corporation Sample # 8985

AUTHOR(S): Barbera, J.

REPORT ISSUED: 7/2/90

CLASSIFICATION:

CONCLUSIONS:

1. There was no indication of any dermal sensitization reaction in guinea pigs which received induction and subsequent challenge exposure to undiluted test material, in a dermal sentization study using the "Modified Buehler Method." The positive control material (0.1% DNCB dissolved in 50% aqueous ethanol) elicited the appropriate reaction.

2. The study is classified as core minimum data.

A. MATERIALS:

1. Test material: Sample # 8985-1, 8985-2, 8985-4, 8985-5 and 8985-6, identified by the laboratory as a cloudy, white liquid. From p. 7: "a fresh sample of the test material was provided for each week's dose application" (presumably this is why several sample numbers are reported). "The test material was stored refrigerated in the container in which it was received." From information on p. 31 the active ingredients by weight were Asana (84% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Positive control compound: dinitrochlorobenzene (DNCB). Purity and source not reported.

3. Test animals: Male Hartley-derived guinea pigs, from Gingrich Animal Supply, Fredericksburg, PA 17026. "Animals were acclimated to the testing facility at least 7 days prior to the start of testing."

B. STUDY DESIGN:

1. Method: The study procedure is identified (p. 7) as a "modified Buehler Method." No reference is given.

2. Primary irritation screening: From p. 8: "Three concentrations of the test material in water were used. These were 100%, 50% and 20%. Three guinea pigs were exposed to the 100%, 50% and 20% concentrations..." On the basis of findings in this part of the study, the test material was applied undiluted for induction and challenge.

3. Induction: Two groups, each containing 10 guinea pigs (with hair on their backs closely clipped) were used, one group being exposed to the positive control material, the other receiving the test material.

   The positive control animals received three 0.5 ml occluded applications of 0.1% DNCB dissolved in 50% aqueous ethanol. Applications were made at one-week intervals to a flank of each animal. "Test sites were evaluated for degree of erythema and edema at 24 and 48 hours post application."

   For the animals exposed to the test material: "Five tenths of a millilter of the test material as supplied was placed on a patch and applied to the clipped backs of each of the 10 guinea pigs exactly as described for the positive control group."

4. Challenge: "After a two week rest period the test and the positive control groups were challenged on naive sites with 0.5 ml of the appropriate suspension...skin evaluations were made at 24, 48 and 72 hours post application." "One group of

five guinea pigs not previously exposed to the test or positive control material, was exposed to the positive control material, a second group of five animals was exposed to the test material at the time of the challenge application..."

5. Post-challenge observations: From p. 9: "Approximately 18 hours following removal of the patches which remained in place for six hours, reading were made for erythema and edema. Additional readings were taken at 48 and 72 hours post challenge application... The site reactions are graded on a scale of 1 (slight erythema) to 4 (marked erythema)."

6. There is a signed and dated Quality Assurance Unit Statement (giving the dates when study operations, records and the final report were reviewed) on p. 4 of the report. There is a Good Laboratory Practice Statement on p. 3 of the report.

C. RESULTS:

1. Primary irritation screening: Minimal (score of 1) erythema at 24 hours (but not subsequently) was observed in 1/3 guinea pigs at the application site receiving undiluted test material. No other irritation was noted.

2. Induction and sensitization: The only animals which showed any irritation following either induction exposures or challenge were in the positive control group which had received induction exposures to the 0.1% DNCB solution. At challenge, all of these guinea pigs showed erythema (scores of 1 or 2) at 24 hours. One of the animals in the test material group died within 24 hours of challenge (p. 12: "Gross necropsy observations included congested lungs, white adhesions through abdominal cavity, stomach inflated, large intestine impacted, caecum empty.").

D. DISCUSSION:

There was no indication of any dermal sensitization reaction in guinea pigs which received induction and subsequent challenge exposure to undiluted test material. The positive control material (0.1% DNCB dissolved in 50% aqueous ethanol) elicited the appropriate reaction.

The study is classified as core minimum data.

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus 12/10/90
Section 2, HFASB (H-7509C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

**DATA EVALUATION REPORT VIII**

STUDY TYPE: Domestic Animal Safety - dog (85-2)

TOX CHEM NO. 346, 268J

MRID NO: 416394-09

TEST MATERIAL: Hartz Flea and Tick Repellent for Dogs III

STUDY NUMBER(S): Hartz Test No. 1086 CONFIDENTIAL BUSINESS INFORMATION

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: [redacted]

TITLE OF REPORT: Domestic Animal Safety: Effect of High Dose Treatment on Dogs

AUTHOR(S): [redacted]

REPORT ISSUED: 9/18/90

CLASSIFICATION: Acceptable. This study satisfies the data requirements (85-2) for a dermal application study on dogs for this formulated product.

CONCLUSIONS:

1. The lack of evident toxicity in this study indicates a reasonably high expectation of at least a 4X safety factor between a normal use application (4.5 g/kg dog weight) on healthy dogs and a level of exposure at which signs of toxicity might develop. Some dogs may be more sensitive to this formulation than the dogs in this study. Labeling for the existing Blockade product includes the following: "Do not use on young (less than three months old) puppies. Do not use this or any other pesticide on sick, old or debilitated pets. Some animals may be sensitive to ingredients in this or other pesticide products. Pets should be observed following treatment. If any unusual symptoms occur, immediately bathe pet with a non-pesticidal shampoo." A similar statement should appear on the label of this proposed product.

[redacted]

2. This study is acceptable in support of an aerosol product formulation (not a formulation with a hand-pump spray delivery mechanism).

A. MATERIALS:

1. Test material: Sample #8986, identified by the laboratory as an aerosol product (in a can). From information on p. 10 the active ingredients by weight were Asana (86% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Test animals: Twelve dogs (6M, 6F), of a variety of breeds. Eleven of these animals were from 2 to 9 years of age; one was 8 months old. Six had short hair and the remainder had long hair. The source of the dogs is not reported.

B. STUDY DESIGN:

1. Administration of test material: From p. 5: "The dogs were fasted for approximately four hours prior to dosing. Treatment consisted of four applications of the product. The spray nozzle was held from 6 to 10 inches from the animal, and the spray covered all the body except the face. Extra care was taken to protect the eyes from the spray mist."

"The aerosol can was weighed before and after each application and at several intervals during the application in order to determine when the target dose of approximately 4.5 g/kg b.w. had been reached. This high dose leaves the hair coat completely saturated with the product and visibly wet."

"The repeat treatments were not applied until the dog's hair coat had completely dried. This period of time was approximately one hour..."

2. Observations: "The animals were observed continuously during four treatments (approximately 3 1/2 hours), hourly during during the first 8 hours following the last treatment and at least once a day for 14 days after treatment."

"The weight of each test animal was determined immediately before treatment as well as one and two weeks after treatment..."

3. Quality assurance: On p. 19 of the report there is a signed and dated "Quality Assurance Unit Statement" giving dates on which study operation, records and the final report were reviewed. There is also a "Good Laboratory Practice Statement" on p. 3 of the report.

C. RESULTS:

From p. 6: "No treatment related toxicity of any kind was observed in any of the test animals. A very significant observation is that the appetite of each dog remained normal starting at the first feeding four hours after the last test material application and continuing throughout the test period." Note by reviewer: since these dogs had been fasted for 4 hours before testing and for 3 1/2 hours during testing and were not fed for an additional 4 hours (4 + 3 1/2 + 4 = 11 1/2 hrs) it isn't surprising they were hungry!

Body weights were apparently measured in lbs, and the weights were evidently converted to kg by multiplying lbs by 0.454. All dogs either gained or maintained weight over the two-week observation period.

D. DISCUSSION:

The lack of evident toxicity in this study indicates a reasonably high expectation of at least a 4X safety factor between a normal use application of this product on healthy dogs and the level of exposure at which signs of toxicity might develop. Some dogs may, of course, be more sensitive to this formulation than the dogs in this study. The reference labeling for the existing Blockade product registration includes the following: "Do not use on young (less than three months old) puppies. Do not use this or any other pesticide on sick, old or debilitated pets. Some animals may be sensitive to ingredients in this or other pesticide products. Pets should be observed following treatment. If any unusual symptoms occur, immediately bathe pet with a non-pesticidal shampoo." The labeling for this proposed product should include this or a similar statement.

This study is acceptable in support of an aerosol product formulation (not a formulation with a hand-pump delivery system).

Reviewed by: Byron T. Backus, Ph.D. Byron T. Backus
Section 2, HFASB (H-7509C) 12/10/90

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/11/90
Section 2, HFASB (H-7509C)

DATA EVALUATION REPORT VII

STUDY TYPE: Domestic Animal Safety - cats (85-2)

TOX CHEM NO. 346, 268J

MRID NO: 416394-08

TEST MATERIAL: Hartz Flea and Tick Repellent for Cats III

STUDY NUMBER(S): Hartz Test No. 1087

SPONSOR: Hartz Mountain Corporation
700 S. 4th Street
Harrison, NJ 07029

TESTING FACILITY: [redacted]

TITLE OF REPORT: Domestic Animal Safety: Effect of High Dose Treatment on Cats.

CONFIDENTIAL BUSINESS INFORMATION

AUTHOR(S): [redacted]

REPORT ISSUED: 9/18/90

CLASSIFICATION: Acceptable. This study satisfies the data requirements (85-2) for a dermal application study on cats for this formulated product.

CONCLUSIONS:

1. The lack of evident toxicity in this study indicates a reasonably high expectation of at least a 4X safety factor between a normal use application to healthy cats and a level of exposure at which signs of toxicity might develop. Some cats may be more sensitive to this formulation than the cats in this study. Labeling for the existing Blockade product includes the following: "Do not use this or any other pesticide on sick, old or debilitated pets. Some animals may be sensitive to ingredients in this or other pesticide products. Pets should be observed following treatment. If any unusual symptoms occur, immediately bathe pet with a non-pesticidal shampoo." A similar statement should appear on the label of this proposed product.

2. This study is acceptable in support of an aerosol product formulation (not a formulation with a hand-pump spray delivery mechanism).

A. MATERIALS:

1. Test material: Sample #8986, identified by the laboratory as an aerosol product. From information on p. 10 the active ingredients by weight were Asana (86% active) 0.03% and N,N-diethyl toluamide 4.2%.

2. Test animals: Twelve cats (6M, 6F). Eleven of these animals were 7 to 9 months of age; one was 2 years old. All are described as having "short" hair coats. The source of the cats is not reported.

B. STUDY DESIGN:

1. Administration of test material: From p. 5: "The cats were fasted for approximately 13 hours prior to dosing. Treatment consisted of four applications of the product. The spray nozzle was held from 6 to 10 inches from the animal, and the spray covered all the body except the face. Extra care was taken to protect the eyes from the spray mist."

"The aerosol can was weighed before and after each application and at several intervals during the application in order to determine when the target dose of approximately 4.5 g/kg b.w. had been reached. This high dose leaves the hair coat completely saturated with the product and visibly wet."

"The repeat treatments were not applied until the cat's hair coat had completely dried. This period of time was approximately one hour..."

2. Observations: "The animals were observed continuously during the first four treatments (approximately 3 1/2 hours), hourly during the first 8 hours following the last treatment and at least once a day for 14 days after treatment."

"The weight of each test animal was determined immediately before treatment as well as one and two weeks after treatment..."

3. Quality assurance: On p. 19 of the report there is a signed and dated "Quality Assurance Unit Statement" giving dates on which study operation, records and the final report were reviewed. There is also a "Good Laboratory Practice Statement" on p. 3 of the report.

C. RESULTS:

From p. 6: "No treatment related toxicity of any kind was observed in any of the test animals. A very significant observation is that the appetite of each cat remained normal starting at the first feeding four hours after the last test material application and continuing throughout the test period." Note by reviewer: since these cats had been fasted for 13 hours before testing and for 3 1/2 hours during testing and were not fed for an additional 4 hours (13 + 3 1/2 + 4 = 20 1/2 hrs) this observation is not surprising!

Body weights were apparently measured in lbs, and to the nearest 0.5 lb (the cat weights reported in kg on p. 9 of the report apparently represent conversions from the day 0 weights given on p. 7). All cats either maintained or gained weight during the 2-week observation period.

D. DISCUSSION:

The lack of evident toxicity in this study indicates a reasonably high expectation of at least a 4X safety factor between a normal use application of this product to healthy cats and a level of exposure at which signs of toxicity might develop. Some cats may, of course, be more sensitive to this formulation than the cats in this study. The reference labeling for the existing Blockade product registration includes the following: "Do not use this or any other pesticide on sick, old or debilitated pets. Some animals may be sensitive to ingredients in this or other pesticide products. Pets should be observed following treatment. If any unusual symptoms occur, immediately bathe pet with a non-pesticidal shampoo." The labeling for this proposed product should include this or a similar statement.

This study is acceptable in support of an aerosol product formulation (not a formulation with a hand-pump delivery system).