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

SEP 19 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTAI

MEMORANDUM

SUBJECT: High-Dose Blockade Studies on Cats and Dogs

TO: Mr. George LaRocca, PM 15
Registration Division (TS-769C)

FROM: Byron T. Backus 9/19/88
Toxicologist, Section II
Toxicology Branch 2, HED (TS-769C)

THROUGH: Marcia van Gemert, Ph.D., Section Head
Review Section II
Toxicology Branch 2, HED (TS-769C) 9/19/88

and

William Burnham, Acting Chief 9/19/88
Toxicology Branch 2
Hazard Evaluation Division (TS-769C)

EPA Record No. 227788/227789

Project No. 8-0984

EPA Reg. Nos. 2596-114, 2596-115

Tox. Chem. 77A, 346

Action Requested:

Review "high-dose" application studies of Hartz Blockade on cats and dogs. These studies were "voluntarily under by Hartz" to determine the potential effect of a magnified dose of the product if the consumer did not follow...directions."

Comments and Recommendations:

1. Examination of the xeroxed laboratory sheets leads to concern over the adequacy of the observations. In any group of these many healthy dogs or cats it is anticipated that over a 2-week period there would be a few instances of vomiting, loose feces and/or diarrhea and possibly some (at least occasionally) behavioral patterns worth commenting on. Yet, the only observation that is present on these sheets in "NR" for "no reaction."

2. Although the registrant has claimed that the Blockade formulations were applied at something like 12X normal dosage on both dogs and cats, the dose levels suggested in the first data submitted to the Agency (reviewed by the Toxicology Branch in September, 1987) indicate adult cats received a cumulative dosage of 2-3X, while adult dogs received 3-4X the levels indicated in the original study.

3. From the data, the puppies received a somewhat lower dosage on a body weight basis than adult dogs, and kittens received a lower dose on the same basis as adult cats. One would normally assume that since puppies and kittens are smaller than adults (the weights reported are consistent with this) then their surface-to-volume ratios would be greater, so dermal application dosages would be higher when expressed in terms of body weight.

4. In summary, although these studies report no adverse effects in dogs and cats following exposure to a "heavy dosage" of the test material, both have been classified as core supplementary data. For these two studies it has been concluded that it has not been adequately demonstrated that a sufficient margin of safety exists with respect to use of the Blockade formulation on household pets.

Reviewed by: Byron T. Backus
Section 2, Tox. Branch 2 (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 2, Tox. Branch 2 (TS-769C)

Byron T. Backus 9/19/88
Marcia van Gemert 9/19/88

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DATA EVALUATION REPORT I

STUDY TYPE: Domestic animal safety - cat TOX. CHEM. NO. 346, 77A

ACCESSION NUMBER: 407040-01 MRID NO.:

TEST MATERIAL: Blockade CONFIDENTIAL BUSINESS INFORMATION

SYNONYMS: Deet + Pydrin

STUDY NUMBER(S): Hartz Test No. 1015

SPONSOR: Hartz Mountain Corporation

TESTING FACILITY: NOTE: The name of the testing facility, as well as the names of personnel at this laboratory, have been claimed to be confidential by the registrant

[redacted]

TITLE OF REPORT: Domestic Animal Safety: Effect of High Dose Dermal Treatments on Cats

AUTHOR(S): [redacted] (note: claimed as confidential information by the registrant) and Perlberg, W.

REPORT ISSUED: 6/28/88 (last date appearing in document, on page 2, relating to statements of confidentiality claims).

CLASSIFICATION: Core Supplementary Data

CONCLUSIONS:

1. In a Toxicology Branch review of September, 1987 of a report issued 9/29/86 the following was noted:

"No adverse reactions were observed in two cats which were sprayed once with the Blockade formulation. One cat was sprayed with 38 gms of formulation, the other with 39.4 grams. However, no further information (body weights, sex, approximate age) is reported for these two animals...the test material was applied only at what was presumably a "normal" use exposure level..."

In this most recently submitted study the range of total dosage per adult cat was from 75.6 to 120.3 grams. On this basis, the cumulative exposure to the test material was 2-3X the level reported in the original study, rather than the 12X claimed by

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the registrant. As reported, the test material was sprayed from a cannister 6-10 inches from the animals; there is some uncertainty as to how much of the material actually reached the fur (dosage was measured by weighing cans before and after spraying) and how much may have dissipated.

2. Examination of the xeroxed laboratory sheets leads to concern over the adequacy of the observations. In any group of this many healthy cats it is anticipated that over a 2-week period there would be a few instances of vomiting from furballs, loose feces and/or diarrhea and possibly some behavioral patterns worth commenting on. Yet, the only observation that is written down is "NR" for "no reaction."

3. It is concluded that the report leaves too many unanswered questions for it to be regarded as authoritatively demonstrating an adequate margin of safety for normal use of the Blockade formulation on cats. The report is therefore classified as core supplementary data.

A. MATERIALS:

1. Test material: Identified as sample #8340. This is the same sample number as was reported in the study reviewed 9 May 1988. According to that review this sample was obtained from a pallet of product manufactured 13 March 1987, production lot no. MR10727. In the review of 9 May 1988 it was noted (p. I-2) that: "Analysis showed an average of 10.16% Deet 0.095% Fenvalerate." According to the test sample identification (on p. 8) in the more recent study the actives were Fenvalerate (90% Active) 0.110% and N,N-diethyl toluamide 10.000%. This appears to be a label declaration rather than an analysis.

2. "The test was performed on twelve cats ranging in age from four months to four years." Nine cats were adults (4M, 5F) ranging in ages from 1 to 4 years (and in weight from 5-10 lbs), while the remaining 3 (2M, 1F) were 4 months old and ranged from 4.5 to 5 lbs at the initiation of the study. There is no information as to the source of these cats, as the supplier's name (p. 19) is the same as the laboratory where the studies were conducted.

B. STUDY DESIGN:

1. Animal assignment: Not reported.

2. Test material exposure: The cats were sprayed with the test material from a distance of 6 to 10 inches "until the coat was visibly wet." "The next treatment was applied when the cat's coat was dry. Approximately one hour elapsed between treatments." A total of 4 treatments was applied to each of the cats.

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3. Quality assurance: There is a signed and dated Good Laboratory Practice Statement on p. 3 of the report, and a signed Quality Assurance Unit Statement on p. 15, along with a Sponsor Inspection Statement on p. 16.

C. METHODS AND RESULTS:

1. Amount of material applied: From p. 10: "Careful records of dosage amounts were maintained." Apparently containers were weighed before and after each spraying.

Results:

	Mean Applications of Test Material (grams)				
	1st	2nd	3rd	4th	Total
Adults:	21.2	22.9	20.9	23.6	88.7
Kittens:	14.4	13.5	11.8	13.7	53.5
All cats:	19.5	20.6	18.7	21.2	79.9

The dosages are also presented (p. 14) on a body weight basis:

	Mean Applications of Test Material (grams)/kg Body Weight				
	1st	2nd	3rd	4th	Total
Adults:	6.62	7.17	6.56	7.48	27.83
Kittens:	6.54	6.18	5.41	6.27	24.41
All cats:	6.60	6.93	6.27	7.18	26.98

2. Observations:

"The animals were carefully observed during the 4X treatment period (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."

Results:

There were no mortalities. All of the animals are reported as showing no reactions during the 14-day observation period. On a few dates individual cats are reported as showing "good appetite," but no quantitative food consumption data are given.

3. Body weights:

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

Results:

"None of the animals lost weight and 5 of the 12 cats on the study had slight weight gains over the two week test period."

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D. DISCUSSION:

The registrant has, on the basis of the results of this study stated (p. 9) that: "the product has a safety factor greatly in excess of 4 times a single heavy dose."

In a Toxicology Branch review of September, 1987 of a report issued 9/29/86 the following was noted:

"No adverse reactions were observed in two cats which were sprayed once with the Blockade formulation. One cat was sprayed with 38 gms of formulation, the other with 39.4 grams. However, no further information (body weights, sex, approximate age) is reported for these two animals...the test material was applied only at what was presumably a "normal" use exposure level..."

In this most recently submitted study the range of total dosage per cat was from 48 to 58.2 grams for the kittens, and from 75.6 to 120.3 grams for the adults. On the basis of the adult dosages, the cumulative exposure to the test material was 2-3X the level reported in the original study, rather than the 12X claimed by the registrant. As reported, the test material was sprayed from a cannister 6-10 inches from the animals; there is some uncertainty as to how much of the material actually reached the fur, and how much may have dissipated before then.

From the data, the kittens received a somewhat lower dosage on a body weight basis than adults. One would normally assume that since kittens are smaller than adults (the weights reported are consistent with this) then their surface-to-volume ratios would be greater, so dermal application dosages would be higher when expressed in terms of body weight. Within the group of 9 adults, this relationship seems to be present (the 3 heaviest cats received a mean dose of 25.57 g/kg of test material, while the remaining 6 received 28.97 g/kg). The significance of this is unknown.

Examination of the xeroxed laboratory sheets leads to concern over the adequacy of the observations. In any group of this many healthy cats it is anticipated that over a 2-week period there would be a few instances of vomiting from furballs, loose feces and/or diarrhea and possibly some behavioral patterns worth commenting on. Yet, the only observation that is written down is "NR" for "no reaction."

In summary, the report leaves too many unanswered questions for it to be regarded as demonstrating an adequate margin of safety exists for normal use of the Blockade formulation on cats.

The report is classified as core supplementary data.

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Reviewed by: Byron T. Backus
Section 2, Tox. Branch 2 (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 2, Tox. Branch 2 (TS-769C)

Byron T. Backus 9/19/88
Marcia van Gemert 9/19/88

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DATA EVALUATION REPORT II

STUDY TYPE: Domestic animal safety - dog TOX. CHEM. NO. 346, 77A

ACCESSION NUMBER: 407040-02 MRID NO.:

TEST MATERIAL: Blockade CONFIDENTIAL BUSINESS INFORMATION

SYNONYMS: Deet + Pydrin

STUDY NUMBER(S): Hartz Test No. 1007

SPONSOR: Hartz Mountain Corporation

TESTING FACILITY: NOTE: The name of the testing facility, as well as the names of personnel at this laboratory, have been claimed to be confidential by the registrant

[redacted]

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

AUTHOR(S): [redacted] (note: claimed as confidential information by the registrant) and Perlberg, W.

REPORT ISSUED: 6/28/88 (last date appearing in document, on page 2, relating to statements of confidentiality claims); study completion date is reported as 6/27/88

CLASSIFICATION: Core Supplementary Data

CONCLUSIONS:

1. In this most recently submitted study the range of cumulative dosage per dog was from 84.4 to 111.3 grams for the puppies, and from 217.9 to 325.6 grams for the adults. On the basis of the adult dosages, the exposure to the test material was 3-4X the level reported originally in an efficacy study, compared to the 12X claimed by the registrant.

2. From the data, the puppies received a somewhat lower dosage on a body weight basis than adults. One would normally assume that since puppies are smaller than adults (the weights reported are consistent with this) then their surface-to-volume ratios would be greater, so dermal application dosages would be higher when expressed in terms of body weight.

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3. Examination of the xeroxed laboratory sheets leads to concern over the adequacy of the observations. In any group of this many healthy dogs it is anticipated that over a 2-week period there would be a few instances of vomiting, loose feces and/or diarrhea and possibly some behavioral patterns worth commenting on. Yet, the only observation that is written down is "NR" for "no reaction."

4. It is concluded that the report leaves too many unanswered questions for it to be regarded as demonstrating an adequate margin of safety for normal use of the Blockade formulation on dogs.

A. MATERIALS:

1. Test material: Identified as sample #8340. This is the same sample number as was reported in the 4X dog study reviewed 9 May 1988. According to that review this sample was obtained from a pallet of product manufactured 13 March 1987, lot no. MR10727, and "Analysis showed an average of 10.16 Deet; 0.095% Fenvalerate." According to the test sample identification (on p. 8) of the subject study the actives were Fenvalerate (90% Active) 0.110% and N,N-diethyl toluamide 10.000%. This appears to be a label declaration rather than an actual analysis.

2. "The test was performed on twelve dogs ranging in age from four months to five years." Nine dogs were puppies (2M, 7F) from 4 to 6 months old (weight range: 10-17 lbs at the start of the study), while the remaining 3 dogs (1M, 2F) were 3-5 years old and ranged from 29 to 42 pounds. The supplier's name (p. 10) for these dogs is the same as the laboratory where the studies were conducted.

B. STUDY DESIGN:

1. Animal assignment: Not reported.

2. Test material exposure: The dogs were sprayed with the test material from a distance of 6 to 10 inches until the coat was visibly wet." "The next treatment was applied when the animal's coat was dry. Approximately one hour elapsed between treatments." A total of 4 treatments was applied to each of the dogs.

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3. Quality assurance: There is a signed and dated Good Laboratory Practice Statement on p. 3 of the report, and a signed Quality Assurance Unit Statement on p. 15, along with a Sponsor Inspection Statement on p. 16.

C. METHODS AND RESULTS:

1. Amount of material applied: From p. 10: "Careful records of dosage amounts were maintained." Apparently containers were weighed before and after each spraying.

Results:

Mean Applications of Test Material (grams) from table 2, p. 13

	1st	2nd	3rd	4th	Total
Puppies:	25.8	22.1	22.8	26.9	101.6
Adults:	60.4	62.3	70.3	81.5	274.5
All dogs:	34.4	32.2	34.6	40.6	141.8

The dosages are also presented (p. 14) on a body weight basis:

Mean Applications of Test Material (grams)/kg Body Weight

	1st	2nd	3rd	4th	Total
Puppies:	4.19	3.61	3.71	4.35	15.86
Adults:	3.62	3.77	4.32	5.04	16.75
All dogs:	4.04	3.65	3.86	4.52	16.08

2. Observations:

"The animals were carefully observed during the 4X treatment period (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."

Results:

There were no mortalities. All of the animals are reported as showing no reactions during the 14-day observation period. On some dates the dogs are reported as having "good appetite," but there is no indication that food consumption was measured.

3. Body weights:

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

Results: "The pups gained an average of one pound and the adult dogs gained an average of two pounds over the two week test period." None of the dogs lost weight.

D. DISCUSSION:

The registrant has, on the basis of the results of this study stated (p. 9) that: "the product has a safety factor greatly in excess of 4 times a single dose."

In a Toxicology Branch review of September 21, 1987 of a report issued 4/20/86 the following was noted:

"In this study 50 dogs were sprayed a total of 136 times with the contents of 50 cans. If each can contained 7 ounces of spray then the average application was 2.57 ounces (= 73.0 grams)."

In this most recently submitted study the range of total dosage per dog was from 84.4 to 111.3 grams for the puppies, and from 217.9 to 325.6 grams for the adults. On the basis of the adult dosages, the cumulative exposure to the test material was 3-4X the level reported in the original study, compared to the 12X claimed by the registrant. As reported, the test material was sprayed from a cannister 6-10 inches from the animals; there is some uncertainty as to how much of the material actually reached the fur, and how much may have dissipated before then, but presumably the dissipation was similar in the original (efficacy) studies.

From the data, the puppies received a somewhat lower dosage on a body weight basis than adults. One would normally assume that since puppies are smaller than adults (the weights reported are consistent with this) then their surface-to-volume ratios would be greater, so dermal application dosages would be higher when expressed in terms of body weight.

Examination of the xeroxed laboratory sheets leads to concern over the adequacy of the observations. In any group of this many healthy dogs it is anticipated that over a 2-week period there would be a few instances of vomiting, loose feces and/or diarrhea and possibly some behavioral patterns worth commenting on. Yet, the only observation that is written down is "NR" for "no reaction."

Overall, the report leaves too many unanswered questions for it to be regarded as authoritatively demonstrating an adequate margin of safety for normal use of the Blockade formulation on dogs.

The study is classified as core supplementary data.

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