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

005704

FEB - 2 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sergeant's Flea and Tick Collar (9% Baygon, 7% DDVP)

TO: Mr. George LaRocca, PM 15
Registration Division (TS-767C)

FROM: Byron T. Backus Byron T. Backus
Toxicologist 1/14/87
Toxicology Branch (TS-769C)

THROUGH: Marcia van Gemert, Ph.D. Marcia Gemert 1/16/87
Section Head, Section III
Toxicology Branch (TS-769C)

and
Theodore Farber, Ph.D. W. Farber 1/28/87
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Chemical no. 508, 328

Project No. 2128 Record No. 176589

Action Requested:

The Registration Division has requested a review of several acute toxicity studies, a dermal sensitization study, and a cholinesterase inhibition submitted in support of registration of a dog collar with (label declaration) 9% Baygon and 7% DDVP (Vapona).

Comments and Conclusions:

1. In the discussion attached to the oral LD50 study the male oral LD50 is estimated as 2945 mg/kg, with 95% confidence limits of 1510 to 3818 mg/kg. It has been assumed there was an inadvertant error from using an erroneous lower C.L. of 199 mg/kg (rather than the correct value of 299 mg/kg). The lower confidence limit has therefore been raised to 2270 mg/kg. The female oral LD50 of 1237 (95% C.L. 614-2482) mg/kg is acceptable.

   Additionally, the proportions of Vapona and Baygon in the active part of the dry blend were 44.3 and 55.7% respectively (in table 2 of the discussion the second column is erroneously labeled as "Vapona" rather than "Sendran" or "Baygon"). However, in the 2.2% extracted by simulated gastric fluid the proportions were were 0.6/2.2 and 1.6/2.2 (or 27.3 and 72.7%) respectively.

1/23

However, an increase in the proportion of Baygon should result in a higher oral LD50 value for the collar, as Baygon is somewhat less toxic than Vapona (typical literature values for LD50's of Vapona and Baygon are 56 and 83 mg/kg respectively).

The estimated oral LD50 values provided (as well as the study) are therefore acceptable.

2. The primary eye irritation study conducted on a saline extract of the collar has been classified as Core Supplementary Data since there was no analysis for the actives within the formulation, and there is a question as to the applicability of this study to potential collar exposure.

3. In the cholinesterase study, the presentation of the data is a bit shaky in places (for example: control dog 542 is reported as having had 80.6% RBC ChE inhibition on day 98 relative to its preexposure level when it had 19.4% less; there is a minor error in table 6 where the S.D. associated with the RBC ChE activity for 5 collar females on day 3 should be 0.12 instead of the 0.16 reported, and with the lower S.D. the mean RBC ChE activity for the 5-collar females would be significantly lower than that of controls). Another annoyance is that there is no explanation in the text as to why in table 6 relatively minor percentage differences between the 1 collar group and control means for RBC ChE should be statistically significant. The conclusion finally made is that it partly relates to preexposure values obtained for the 1-collar group (which averaged about 18.5% less RBC ChE activity than controls for the three preexposure readings).

   However, what is demonstrated in the study (mean plasma ChE inhibitions of approximately 30, 55 and 65% for 1, 3 and 5-collar dogs respectively on days 7-28, but no evidence for RBC ChE inhibition, along with lack of any symptoms of cholinesterase inhibition) is fairly conclusive. Additionally, the rapid drop during the first week in plasma ChE activities correlates with the rate of release of actives. The cholinesterase study is therefore acceptable.

4. The remaining studies (acute dermal LD50, primary dermal irritation, primary eye irritation on the powder and the dermal sensitization) are acceptable.

5. The proposed label copy includes a statement that under conditions of severe infestation and where continued rapid kill is desired, collar may be replaced more often than every 6 months. Considering the levels of plasma ChE depression occurring in this study, and the "burst" of Vapona given off by the collar during the first week it is worn by the dog, there should be a statement that collars should not be replaced sooner than 60 days. Additionally, the statement "Atropine is antidotal." should be revised to something like "Atropine is antidotal only if symptoms of cholinesterase in-

hibition are present."

6. In the cholinesterase study one dog wearing a single collar developed exudative dermatitis around the neck necessitating removal of the collar. A similar (but not as severe) reaction occurred in a control dog. Additionally, some of the guinea pigs in the dermal sensitization study had a slight (but non-allergenic) reaction to 24-hour exposure. The registrant has included a statement ("Some animals may become irritated by any Collar. If this occurs, remove Collar. If condition persists, consult a veterinarian") on the proposed label that addresses this problem, and the Toxicology Branch accepts this, particularly as this collar is similar, in terms of its inerts, to many other registered collars currently being marketed.

Data Evaluation Reports (attached):

The following is a listing of the individual data evaluation reports, along with the study classification. Copies should be supplied to the registrant.

I. Costello, B. A. and Moore, G. Acute Oral Toxicity, LD50 - Rats. Study no. 85-4850A, conducted by Biosearch Inc. for the A. H. Robins Co. Report issued 12/31/85; in Acc. 263653.

II. Costello, B. A. and Moore, G. Acute Dermal Toxicity, Single Level - Rabbits. Study no. 86-4962A, conducted by Biosearch Inc. for the A. H. Robins Co. Report issued 4/28/86; in Acc. 263653.

III. Hershman, R. J. and Moore, G. Primary Eye Irritation (powder) - Rabbit. Study no. 86-4962A, conducted by Biosearch Inc. for the A. H. Robins Co. Report issued 4/28/86; in Acc. 263653.

IV. Hershman, R. J. and Moore, G. Primary Eye Irritation (saline extract) - Rabbit. Study no. 86-4962A, conducted by Biosearch Inc. for the A. H. Robins Co. Report issued 4/28/86; in Acc. 263653.

V. Costello, B. A. and Moore, G. Primary Skin Irritation - Rabbits. Study no. 86-4962A, conducted by Biosearch Inc. for the A. H. Robins Co. Report issued 4/28/86; in Acc. 263653.

VI. Costello, B. A. and Moore, G. Guinea Pig Dermal Sensitization - Modified Buehler Method. Study no. 86-4962A, conducted by Biosearch Inc. for the A. H. Robins Co. Report issued 4/28/86; in Acc. 263653.

VII. Hall, H. F., McCall, J. W., Dzimianski, M. T. and Lewis, R. E. Toxicology Evaluation of AHR 4781(3), Sergeant's Vapona/ Sendran Flea and Tick Collar for Dogs. Study #85-275, conducted by TRS Labs, Inc. for the A. H. Robins Co. Report issued 5/27/86; in Acc. 263653.

3

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005704

DATA EVALUATION REPORT I

STUDY TYPE: Acute oral LD_{50} - Rat TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653 MRID NO.: not given

TEST MATERIAL: [redacted] Blend containing 9.3% Baygon & 7.4% DDVP Material used to formulate Baygon-DDVP Flea & Tick collar

SYNONYMS: (Sendran is a synonym for Baygon)

STUDY NUMBER(S): 85-4850A

SPONSOR: A. H. Robins Company

TESTING FACILITY: Biosearch Incorporated, Philadelphia, PA.

TITLE OF REPORT: Acute Oral Toxicity, LD50 - Rats

AUTHOR(S): Costello, B. A. and Moore, G.

REPORT ISSUED: 12/31/85

CLASSIFICATION: Core Minimum

CONCLUSIONS:

1. The study is acceptable. It was conducted on pre-extruded material [redacted] blend" - a mixture of all ingredients before fusing the insecticide within the matrix system), and the LD50 values obtained (388 mg/kg for males and 163 mg/kg for females) were subsequently used to obtain estimated oral LD50 values for the collar.

2. In the discussion of determination the collar male oral LD50 is estimated as 2945 mg/kg, with 95% C.L. of 1510 to 3818 mg/kg. It has been assumed that there was an inadvertant error from using an erroneous C.L. of 199 mg/kg (rather than the correct value of 299 mg/kg), and that the estimated male oral LD50 95% C.L. should have been 2270 to 3818 mg/kg. The female rat oral LD50 of 1237 (95% C.L. 614-2482) mg/kg is acceptable.

3. The proportions of vapona and baygon in the active part of the dry blend were 44.3 and 55.7% respectively (in table 2 of the discussion the second column is erroneously labeled as "Vapona" rather than "Sendran" or "Baygon"). However, in the 2.2% extracted by simulated gastric fluid from the collar the proportions were 0.6/2.2 and 1.6/2.2 (or 27.3 and 72.7%) respectively. However, an increase in the proportion of Baygon should increase the estimated oral LD50 value of the collar (typical literature values for LD50's of Vapona and Baygon are 56 and 83 mg/kg respectively).

005704

A. MATERIALS:

1. Test compound: Dog Collar Blend, Lot Number 80935-51, AHR No. 4781(3). From analysis (see the copy of the A. H. Robins memorandum dated April 4, 1986) the material contained 7.4% Vapona (DDVP) and 9.3% Sendran (Baygon). The test material was administered as a 5% w/v suspension in corn oil.

2. Test animals: outbred Sprague-Dawley rats, from Ace Animals Inc., Boyertown, PA.

B. STUDY DESIGN:

1. Animal assignment: not stated. Fasted groups containing 5 males and/or 5 females received (by gavage) the following dose levels of test material:

Test Group	Dose level administered (mg/kg)	Number of animals males	female
1	70.0	-	5
2	138.9	5	5
3	197.2	5	-
4	277.8	5	5
5	393.5	5	-
6	555.6	5	5
7	1111.1	-	5

2. Following dosage the rats were allowed food and water ad libitum for the subsequent 14-day observation period.

3. Statistics - "The LD50 was calculated employing the Litchfield & Wilcoxon Method."

4. Quality assurance: There is a "Good Laboratory Practice Compliance Statement" signed by R. B. Murray, Quality Assurance Officer on 1-2-86.

C. METHODS AND RESULTS:

1. Observations

Animals were "observed frequently" on the day of dosing, and afterwards twice (morning and afternoon) on weekdays and once per day on weekends and holidays for signs of toxicity and mortality.

Toxicity/Mortality (survival)

All mortalities occurred within 48 hrs of dosage, with most within 4 hrs.

005704

Test Group	Dose level administered (mg/kg)	Mortalities/Number of animals dosed males	female
1	70.0	-	1/5
2	138.9	0/5	2/5
3	197.?	0/5	-
4	277.8	1/5	4/5
5	393.5	3/5	-
6	555.6	4/5	4/5
7	1111.1	-	5/5

Oral LD50 (male) = 388 (95% C.L. 299-503) mg/kg.
Oral LD50 (female) = 163 (95% C.L. 81-327) mg/kg.
Oral LD50 (combined) = 280 (187-422) mg/kg.

Symptoms: an initial "increased responsiveness to external stimuli" was followed by hypoactivity. Tremors were observed in at least some animals at all dosage levels; salivation was observed at higher dosages. All survivors appeared normal at 72 hours.

2. Body weight

Animals were weighed on the day of dosage, at week 1, and again at week 2.

Results: Individual weight data are not reported, only group means. No marked dose-related effect seems to have occurred in overall weight gains.

3. Sacrifice and Pathology -

All animals that died and that were sacrificed at two weeks were subjected to gross necropsy.

Results: No gross abnormalities were found in animals which were sacrificed at two weeks. One male and one female which died had distended stomachs and congested lungs; no gross abnormalities were noted in any of the other mortalities.

D. DISCUSSION:

In a discussion submitted by the registrant this study is used to estimate LD50 values for the finished collar. According to this discussion, it was found that corn oil (the vehicle used in dosing the rats) extracts 100% of the insecticidally active components of the dry blend (pre-extruded) mixture (or 16.7% of the total mixture, with 7.4% vapona + 9.3% Baygon). Simply placing extruded collar (the finished product) for 6 hrs in simulated gastric fluid resulted in extraction of 2.2% (the summation of 0.6% vapona and 1.6% Baygon) of the contents of the collar.

From this the registrant calculates the male oral LD50 value for the collar as 388 (95% C.L. 299-503) mg/kg x 0.167/0.022 = 2945 (95% C.L. 2270-3818) mg/kg. (Note: in Table 1 of the discussion of determination the 95% confidence limits are given as 1510 to 3818 mg/kg. I believe that this was an inadvertant error from using a lower - and erroneous - C.L. of 199 mg/kg (x 0.167 ÷ 0.022 = 1510 mg/kg) rather than the correct lower C.L. of 299 mg/kg). The female oral LD50 is estimated as 163 (95% C.L. of 81-327) mg/kg x 0.167/0.022 = 1237 (615-2482) mg/kg. Although not reported in the discussion the combined oral LD50 can be calculated as 280 (95% C.L. 187-422) mg/kg x 0.167/0.022 = 2125 (95% C.L. of 1420-3203) mg/kg.

The proportions of vapona and baygon ("Sendran") in the insecticidally active part of the dry blend were 44.3 and 55.7% respectively (note in table 2 of the discussion the second column is erroneously labeled as "vapona" rather than "Sendran" or "Baygon"). However, in the 2.2% total amount extracted by simulated gastric fluid from the collar the proportions were 0.6/2.2 and 1.6/2.2 (or 27.3 and 72.7%) respectively. However, an increase in the proportion of baygon would probably increase the oral LD50 (typical literature values for LD50's of vapona and baygon are 56 and 83 mg/kg respectively), assuming a lack of synergism between the two actives.

This study is acceptable in demonstrating a rat male LD50 of 388 (299-503) mg/kg, and a rat female LD50 of 163 (81-327) mg/kg for the test (pre-extruded) material. The subsequently calculated oral LD50 values for the extruded collar material are reasonable estimates placing it in toxicity category III by this exposure route.

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DATA EVALUATION REPORT II

STUDY TYPE: Acute dermal LD_{50} - Rabbit TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653 MRID NO.: not given

TEST MATERIAL: Dog Flea and Tick Collar (7% Vapona, 9% Baygon)

SYNONYMS: (Sendran is a synonym for Baygon)

STUDY NUMBER(S): 86-4962A

SPONSOR: A. H. Robins Company

TESTING FACILITY: Biosearch Incorporated, Philadelphia, PA.

TITLE OF REPORT: Acute Dermal Toxicity, Single Level - Rabbits

AUTHOR(S): Costello, B. A. and Moore, G.

REPORT ISSUED: 04/28/86

CLASSIFICATION: Core Minimum

CONCLUSIONS:

1. The study is acceptable in demonstrating a low degree of hazard potential (no worse than toxicity category III, with a dermal LD50 > 2 g/kg) for this product by this exposure route.

A. MATERIALS:

1. Test compound: Dog Flea and Tick Collar, Lot # F-190-162-163 AHR No. 4781(3). According to a copy of the proposed label, the collar contains 7% Vapona (DDVP) and 9% Sendran (Baygon).

2. Test animals: New Zealand white rabbits, weighing from 2-3 kg. from Ace Animals Inc., Boyertown, PA.

B. STUDY DESIGN:

1. Animal assignment: not stated. Five males and 5 females with intact skin (but with clipped fur) were each exposed to 2.0 g/kg of the test material "applied with the white side toward the skin." The collar was moistened with 3 ml of NaCl solution, and there was 24 hr occluded exposure.

2. Wayne 15% Rabbit Ration and tap water were provided ad libitum.

3. Statistics - There is no indication that the data were analyzed statistically (or that there was any need to do this).

4. Quality assurance: There is a "Good Laboratory Practice Compliance Statement" signed by R. B. Murray, Quality Assurance Officer, on 4-29-86.

C. METHODS AND RESULTS:

1. Observations

Animals were "observed for a 14 day period for signs of toxicity (systemic and topical) and for mortalities" with frequent observation during the first day of dosing and twice a day thereafter (except for weekends and holidays when they were observed only once).

Toxicity/Mortality (survival).

There was no indication of any systemic or dermal toxic effects. One female was found dead on day 2. This is reported as "most likely attributable to a respiratory infection."

2. Body weight

Animals were weighed on the day of dosage, at week 1, and again at week 2.

Results: Individual weight data are not reported, only group (by sex) means. There was a slight increase in mean weights for both males and females.

3. Sacrifice and Pathology -

All animals that died and that were sacrificed at two weeks were subjected to gross necropsy.

Results: In the one female which died on day 2 findings were hemorrhagic lungs, pale kidneys, a dark liquid in the stomach and no formed fecal material in the lower intestine. No gross abnormalities were found in the animals which survived the 14 day observed period.

D. DISCUSSION:

The report's statement that the death of one rabbit was most likely attributable to a respiratory infection can be accepted as there was no indication of any symptoms (tremors, salivation) of cholinesterase inhibition in these animals.

The study is acceptable in demonstrating a low degree of hazard potential (rabbit dermal LD50 > 2 g/kg, toxicity category III) in terms of its dermal toxicity potential.

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DATA EVALUATION REPORT III

STUDY TYPE: Primary eye irritation - Rabbit TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653 MRID NO.: not given

TEST MATERIAL: Dog Flea and Tick Collar (7% Vapona, 9% Baygon)

SYNONYMS: (Sendran is a synonym for Baygon)

STUDY NUMBER(S): 86-4962A

SPONSOR: A. H. Robins Company

TESTING FACILITY: Biosearch Incorporated, Philadelphia, PA.

TITLE OF REPORT: Primary Eye Irritation - Rabbit

AUTHOR(S): Hershman, R. J. and Moore, G.

REPORT ISSUED: 04/28/86

CLASSIFICATION: Core Minimum

CONCLUSIONS:

1. The study is acceptable. The test material is in toxicity category III in terms of its eye irritation potential.

A. MATERIALS:

1. Test compound: Powder scraped from Dog Flea and Tick Collar, Lot # F-190-162-163, AHR No. 4781(3). According to a copy of the proposed label the collar contains 7% Vapona (DDVP) and 9% Sendran (Baygon).

2. Test animals: New Zealand white rabbits, weighing from 2-3 kg. from Ace Animals Inc., Boyertown, PA.

B. STUDY DESIGN:

1. Animal assignment: A group of 9 rabbits which had shown no evidence of "pre-existing injury" (presumably to the eyes) were used.

2. Wayne 15% Rabbit Ration and tap water were provided ad libitum.

3. Quality assurance: There is a "Good Laboratory Practice Compliance Statement" signed by R. B. Murray, Quality Assurance Officer, on 4-29-86.

C. METHODS AND RESULTS:

1. Procedure: 0.1 g of test material was applied to one eye of each of 9 rabbits. Three treated eyes were washed out with tap water for one minute starting 30 seconds after instillation of the test material. The remaining eyes were unwashed.

2. Observations: Eyes were scored (Draize) at 1 hr, and at 1, 2, 3, 4, 7, 14 and 21 days (if irritation persisted).

Results: Except for conjunctival effects all eyes were clear at day 1. At day seven 5/6 unwashed eyes were clear except for a low degree (maximum score of 1) of redness and/or chemosis and/or discharge. Two unwashed eyes still had minimal redness with minimal discharge on day 21. All washed eyes were clear by day 4.

D. DISCUSSION:

The study defines a toxicity category III classification of the test material in terms of eye irritation potential, as redness, chemosis and/or discharge scores of 1 are not considered "positive" - perhaps "conclusive" would be a better term - effects (refer to the Subdivision F Hazard Evaluation Guidelines, p. 54) of exposure to the test material.

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005704

DATA EVALUATION REPORT IV

STUDY TYPE: Primary eye irritation - Rabbit TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653 MRID NO.: not given

TEST MATERIAL: Dog Flea and Tick Collar (7% Vapona, 9% Baygon) (saline extract).

SYNONYMS: (Sendran is a synonym for Baygon)

STUDY NUMBER(S): 86-4962A

SPONSOR: A. H. Robins Company

TESTING FACILITY: Biosearch Incorporated, Philadelphia, PA.

TITLE OF REPORT: Primary Eye Irritation - Rabbit

AUTHOR(S): Hershman, R. J. and Moore, G.

REPORT ISSUED: 04/28/86

CLASSIFICATION: Core Supplementary

CONCLUSIONS:

1. While the test material used (a saline extract of the collar) is in toxicity category III in terms of its eye irritation potential, there are some questions as to this material's exact composition (there was no analysis for the actives within the saline extract) and how applicable this study is to potential collar exposure.

A. MATERIALS:

1. Test compound: A 60 cm^2 portion of the Dog Flea and Tick Collar, lot # F-190-162-163, AHR No. 4781(3), was cut into 5 x 0.3 cm strips which were placed in an extraction tube with 20 mls sterile saline solution. The mixture was heated to 70° C for 24 hrs, allowed to cool, and was then decanted. The extract was used within 24 hrs of decanting.

2. Test animals: New Zealand white rabbits, weighing from 2-3 kg. from Ace Animals Inc., Boyertown, PA.

B. STUDY DESIGN:

1. Animal assignment: A group of 9 rabbits which had shown no evidence of "pre-existing injury" (presumably to the eyes) were used.

2. Wayne 15% Rabbit Ration and tap water were provided ad libitum.

3. Quality assurance: There is a "Good Laboratory Practice Compliance Statement" signed by R. B. Murray, Quality Assurance Officer, on 4-29-86.

C. METHODS AND RESULTS:

1. Procedure: 0.1 ml of test material was applied to one eye of each of 9 rabbits. Three treated eyes were washed out with tap water for one minute starting 30 seconds after instillation of the test material. The remaining eyes were unwashed.

2. Observations: Eyes were scored (Draize) at 1 hr, and at 1, 2, 3, 4, 7, and, if irritation persisted, at 14 and 21 days.

Results: Except for conjunctival effects all eyes were clear at day 1. At day seven 1/6 unwashed, 3/3 washed eyes still showed low degree (maximum score of 1) of conjunctival redness. All washed eyes were completely clear by day 14, and the one unwashed eye was clear by day 21.

D. DISCUSSION:

The study defines a toxicity category III classification of the test material in terms of eye irritation potential, as redness, chemosis and/or discharge scores of 1 are not considered "positive" - perhaps "conclusive" would be a better term - effects (refer to the Subdivision F Hazard Evaluation Guidelines, p. 54) of exposure to the test material.

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005704

DATA EVALUATION REPORT V

STUDY TYPE: Primary dermal irritation - rabbit

TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653

MRID NO.: not given

TEST MATERIAL: Dog Flea and Tick Collar (7% Vapona, 9% Baygon)

SYNONYMS: (Sendran is a synonym for Baygon)

STUDY NUMBER(S): 86-4962A

SPONSOR: A. H. Robins Company

TESTING FACILITY: Biosearch Incorporated, Philadelphia, PA.

TITLE OF REPORT: Primary Skin Irritation - Rabbits

AUTHOR(S): Costello, B. A. and Mocre, G.

REPORT ISSUED: 04/28/86

CLASSIFICATION: Core Minimum

CONCLUSIONS:

1. The study is acceptable in demonstrating that the product is in toxicity category IV in terms of its dermal irritation potential.

A. MATERIALS:

1. Test compound: Dog Flea and Tick Collar, Lot # F-190-162-163 AHR No. 4781(3). According to a copy of the proposed label the collar contains 7% Vapona (DDVP) and 9% Baygon.

2. Test animals: New Zealand white rabbits, weighing from 2-3 kg. from Ace Animals Inc., Boyertown, PA.

B. STUDY DESIGN:

1. Animal assignment: "Animals with healthy intact skin were used." There were a total of six subjects which had been previously clipped over a wide area on their backs.

2. Wayne 15% Rabbit Ration and tap water were provided ad libitum.

005704

3. Statistics - There is no indication that the data were analyzed statistically (or that there was any need to do this).

4. Quality assurance: There is a "Good Laboratory Practice Compliance Statement" signed by R. B. Murray, Quality Assurance Officer, on 4-29-86.

C. METHODS AND RESULTS:

1. Procedure: A 1 inch square of collar material was moistened with saline and applied to the test site with the white side towards the skin. There was 4-hr occluded exposure.

2. Observations: The skin at the application site was scored (Draize) for erythema and edema 30-60 minutes after patch removal and at 24, 48 and 72 hrs.

Results: All scores were zero.

D. DISCUSSION:

The study adequately defines a toxicity category IV classification of the test material in terms of its primary dermal irritation potential.

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005704

DATA EVALUATION REPORT VI

STUDY TYPE: Dermal sensitization (Buehler) - Guinea pig

TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653

MRID NO.: not given

TEST MATERIAL: Dog Flea and Tick Collar (7% Vapona, 9% Baygon)

SYNONYMS: (Sendran is a synonym for Baygon)

STUDY NUMBER(S): 86-4962A

SPONSOR: A. H. Robins Company

TESTING FACILITY: Biosearch Incorporated, Philadelphia, PA.

TITLE OF REPORT: Guinea Pig Dermal Sensitization - Modified Buehler Method.

AUTHOR(S): Costello, B. A. and Moore, G.

REPORT ISSUED: 04/28/86

CLASSIFICATION: Core Minimum

CONCLUSIONS:

1. It is concluded from this report that the collar has an acceptably low level of dermal sensitization potential. However, the results following 24 hour exposure to the collar suggest that it can elicit some dermal irritation, which has been addressed in the proposed product labeling.

A. MATERIALS

1. Test compound: Dog Flea and Tick Collar, Lot # F-190-162-163 AHR No. 4781(3). According to a copy of the proposed label the collar contains 7% Vapona (DDVP) and 9% Baygon.

2. Test animals: Hartley guinea pigs, 300-500 g, obtained from Ace Animals Inc., Boyertown, PA.

B. STUDY DESIGN:

1. Animal assignment: Not stated. Twelve animals were exposed to the collar material, and twelve were exposed to the positive control.

2. Wayne guinea pig formula and tap water were provided ad libitum.

3. Quality assurance: There are two "Good Laboratory Practice Compliance Statements" (one for the collar, and one for the simultaneous study utilizing the positive control). Both were signed by R. B. Murray, Quality Assurance Officer, on 4-29-86.

C. METHODS AND RESULTS:

1. Procedure

A one inch square portion of the test material was applied to a test site on each of 12 guinea pigs, with 6-hr occluded exposure. The animals were then allowed to rest for at least one day, and then were exposed again. There were 3 exposures per week for 3 weeks (total of 9 weeks). Following the ninth exposure guinea pigs were rested for a two week period, and then were challenged at a previously unexposed skin site. The challenge application remained on for 24 hrs. Five naive animals were also challenged. Because some skin responses were noted test animals were rechallenged, along with a second group of five naive animals.

Positive control animals were exposed to 0.5 ml aliquots of 0.15% w/v solutions of the positive control in 25% EtOH - saline, using the same exposure time and probably the same application schedule as those guinea pigs exposed to the test material.

2. Observations

"After each induction stage application and 24 and 48 hours after the challenge and rechallenge applications, the sites were examined for irritation...using the Draize method of scoring to grade reactions."

Results:

6/12 of the previously exposed guinea pigs showed slight irritation at 24 hrs following the first challenge application. In five cases this consisted of minimal (score of 1) erythema only; in the other case there was a score of 2 for erythema. No edema was observed. 3/5 of the naive controls had minimal erythema.

At rechallenge (it is not indicated how long this occurred after the initial challenge, however, it was presumably about 2 weeks, as this part of the study was completed 4/17/86, and the positive control part of the study was completed 4/4/86) 10/12 of the previously exposed guinea pigs and 5/5 of the naive controls showed some reaction. From the data, as presented, the following are the mean reaction total (erythema + edema) scores:

	Challenge		Rechallenge	
	24 Hrs	48 Hrs	24 Hrs	48 Hrs
Previously exposed (collar)	0.58	0.08	1.25	0.67
Naive group #1 (to collar)	0.60	0.17	-	-
Naive group #2 (to collar)	-	-	2.00	0.80
Positive control (DNCB)	1.92	0.83	-	-

D. DISCUSSION:

According to the report of the laboratory conducting the study: "The Test Article...may possibly be a fatiguing agent and a primary skin irritant in albino guinea pigs. It does not appear to be a skin sensitizer."

The term "fatiguing agent" in this context is used to denote a substance not producing primary irritation but capable of eliciting a severe skin reaction after a number of exposures. However, the material is not a sensitizer as the skin, after a 10-14 day rest period, recovers its original resistance to injury by this substance.

However, it is noted that, for the schedule used (6-hr exposure, 3 days a week for 3 weeks) there was no indication of an increase in incidence or degree of dermal irritation following the later applications, which appears to rule out the collar (at least for this exposure schedule) being a fatiguing agent. The higher incidence (and degree) of dermal irritation following challenge and rechallenge were probably due to the longer (24-hr) exposure period at these times. At both times, results for previously exposed guinea pigs were essentially the same as those for "naive" animals.

This reviewer concludes from this report that the collar has an acceptably low level of dermal sensitization potential. However, the results from 24 hour exposure to the collar suggest that it can elicit some dermal irritation, and this has been addressed in the proposed product labeling ("Some animals may become irritated by any Collar. If this occurs, remove Collar. If condition persists, consult a veterinarian").

Reviewed by: Byron T. Backus Byron T. Backus 1/14/87
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Section 3, Tox. Branch (TS-769C) Marcia van Gemert 1/16/87

005704

DATA EVALUATION REPORT VII

STUDY TYPE: Cholinesterase (98 day collar exposure) - dog

TOX. CHEM. NO.: 508, 328

ACCESSION NUMBER: 263653

MRID NO.: not given

TEST MATERIAL: 9% Baygon - 7% DDVP dog collar

STUDY NUMBER(S): 85-275

SPONSOR: A. H. Robins Company

TESTING FACILITY: TRS Laboratories, Inc.

TITLE OF REPORT: Toxicology Evaluation of AHR 4781(3), Sergeant's Vapona/Sendran Flea and Tick Collar for Dogs.

AUTHOR(S): Hall H. F., McCall, J. W., Dzimianski, M. T. & Lewis, R. E.

REPORT ISSUED: 05/27/86

CLASSIFICATION: Core Minimum

CONCLUSIONS:

1. Although the presentation of the data is a bit shaky in places, with some minor inaccuracies, what is demonstrated is fairly definite. A considerable drop in plasma ChE activity the first 7 days of exposure (in one-collar dogs by about 30%: in 3-collar dogs by about 57%, and in 5-collar dogs by about 63%) correlates with release rate data showing approximately 25% of the total Vapona, and about 11% of the total Baygon being released during this period. During the second week an additional 10% of the total initial amount of Vapona is released, along with perhaps 3% of the Baygon, and these rates of release continue through weeks 3 and 4. During this period of time the plasma ChE activity recovered somewhat in all exposure groups.

2. In the one-collar exposure group there was essentially complete plasma ChE recovery by day 56, and there was no further statistically significant plasma ChE inhibition in this group. However, in the 3 and 5-collar females there was still significant plasma ChE inhibition (about 35 and 43% respectively) on day 98 (when the last ChE measurements were made).

3. There was no evidence of any RBC ChE inhibition in any group at any time during this study, even on day 7 when the greatest plasma ChE depressions were noted. Additionally, no symptoms of cholinesterase depression were noted.

4. The most serious effect was what was probably a non-allergenic

dermatitis occurring in one dog, which reached the exudative state and required removal of the collar. This problem is addressed in the proposed labeling.

5. Overall, the study is acceptable.

A. MATERIALS:

1. Test compound: Dog Collar, Lot Number F-190-162-163, AHR No. 4781(3). The nominal percentages for the actives were Baygon 9% and Vapona (DDVP) 7%.

2. Test animals: 14 Mixed-breed and 10 "distinct-breed" dogs, half males, half females, ages and source(s) not specified. All dogs were examined and judged to be in good health at the start of the study.

B. STUDY DESIGN:

1. Animal assignment: Serum cholinesterase data from 3 pretest blood collections were used to establish 4 groups, each with 3 males and 3 females:

	Males		Females	
Group	N	Pre-exposure mean serum ChE	N	Pre-exposure mean serum ChE
5 Placebo collars	3	2.3 IU/ml	3	2.5 IU/ml
1 Test collar	3	2.2 IU/ml	3	2.4 IU/ml
3 Test collars	3	2.3 IU/ml	3	2.4 IU/ml
5 Test collars	3	2.2 IU/ml	3	2.3 IU/ml

"Groups were placed in the kennel in relation to the major air flow pattern... The flow of air was from the placebo group to the one collar, three collar, and finally the five test collar group."

2. Statistics - "Biochemical data were analyzed using Bartlett's test for homogeneity of variance and analysis of variance (one way classification). Treatment groups were compared to the control group, by sex, using the appropriate t-statistic (equal or unequal variance)... Dunnett's multiple comparison tables were used to determine significance. All statistical tests were two-tailed, with $p < 0.05$ and $p < 0.01$ used as levels of significance."

3. Quality assurance: There is a "Quality Assurance Attestation" signed and dated May 1, 1986.

C. METHODS AND RESULTS:

1. Administration - When received, each collar was sealed in foil. The collars were stored at room temperature until immediately

prior to application on November 11 (Day 0), when all collars were applied. The study was terminated on day 98 (February 17, 1986).

2. Observation - Dogs were observed daily for changes in general appearance and behavior, including an examination of any irritation in the neck area.

Results:

On day 49 a female (dog #555) in the 1 test collar group had a reddish patch of bare skin on the back of the neck. By day 56 this lesion had spread around the neck beneath the collar, and by day 65 had developed into an exudative moist dermatitis. At this time the collar was removed. Because of the animal's scratching, the condition became worse and on day 80 therapy with prednisolone and lincocin was initiated. Although there was subsequent improvement it did not reach the point where the collar could be reapplied.

In the individual clinical findings (see appendix D) a control male is reported as having "focal hair loss and dermatitis on neck" on day 28. It is not indicated anywhere whether or not treatment was initiated; it is only stated that this condition had resolved by day 56.

A male in the 5 test collar was lethargic on day 39. The condition was diagnosed as probable cholestasis; appropriade therapy was initiated and the dog had recovered by day 48. This event was considered to be unrelated to collar exposure.

2. Body weight

Individual body weights were taken and recorded on days 1, 49 and 98 of the study.

Results: Most of the dogs gained a few kg or remained at about the same weight throughout the study. However, dog #555 (with the neck lesion) showed a weight drop from 20.2 to 16.5 kg (3.7 kg, or 18.3%) in the period from day 49 through 98 (presumably associated with the development of the neck lesion).

3. Cholinesterase Measurements:

Blood was taken from the cephalic vein of each dog on days -7, -4, 0, 3, 7, 14, 28, 42, 56, 70, 84 and 98. Samples were shipped to Vetpath (Teeterboro, NJ) where serum (plasma) and RBC ChE activities were measured using a variation of the Ellman method.

Results:

Dogs wearing the test collar had exposure-related reduced (both with respect to control and their own pre-exposure values) plasma ChE activity by day 7, followed by at least some recovery:

Sex	Number of collars	% Depression in mean serum ChE relative to control value Day 3	7	14	28	42	70	98
M	1	-24.1	-28.6	-23.8**	-14.3	-29.2	0	0
M	3	-41.4**	-57.1**	-52.4**	-33.3*	-50.0	-15.8	-14.3
M	5	-37.9**	-61.9**	-57.1**	-52.4**	-50.0	-26.3	-33.3
F	1	-20.0	-34.8**	-32.0**	-32.1**	-13.6	-8.3	-25.0
F	3	-33.3*	-56.5**	-56.0**	-46.4**	-36.4	-29.2**	-35.7**
F	5	-50.0**	-65.2**	-64.0**	-60.7**	-54.5*	-50.0**	-42.9**

*Significantly different from control group at $p \leq 0.05$
**Significantly different from control group at $p \leq 0.01$

From the group means (tables 4 and 6) there is no indication that any RBC ChE inhibition occurred. However, there do appear to be some minor errors in table 6 (for example, the S.D. associated with the RBC ChE activity for 5 collar females on day 3 should be 0.12 instead of the 0.16 which is reported, and with the lower S.D. the mean RBC ChE activity for the 5 collar females would be significantly lower than that of controls). Another minor annoyance is that "percent deviations" were calculated from cholinesterase activities after the latter had been rounded off.

Additionally, there is no immediate explanation as to why why the "percent deviation" for the 1-collar dogs on day 3 (as well as for some subsequent values for this group) is reported as being significantly different from controls, but the tentative conclusion of this reviewer is that it partially relates to the pre-exposure values obtained for this group (this group averaged 18.5% less mean RBC ChE than controls during the preexposure period).

4. Sacrifice and Pathology

There was no sacrifice, and none was necessary.

5. Release rate data

In addition to cholinesterase data, there is a page (after the report proper) titled "Analysis of Collars Before and After Application," followed by a page titled "Release Data of Insecticides From Collars on Dogs." These indicate that something like 90-100% of the Vapona and about 30% of the Sendran (Baygon) are released from the collar over a period of 140 days under the anticipated use exposure, with about 25% of the Vapona and 11% of the Baygon being released during the first week.

Since the collar weight is 23 grams this means approximately 0.44 grams of Vapona and 0.24 grams of Sendran (Baygon) are released during the first week.

Another point of interest is that collars in the 3-collar and 5-collar group had released less Vapona (although the release of Baygon was essentially the same) so that the exposures of dogs in these groups were not really 3X and 5X those of controls respectively for this ingredient:

	% VAPONA	% SENDRAN	% RELEASED VAPONA	% RELEASED SENDRAN
Initial Assay	7.4	9.2	-	-
At 140 days:				
1-collar	0.85	6.40	88.5%	30.4%
3-collar	1.55	6.45	79.1%	29.9%
5-collar	1.94	6.20	73.8%	32.6%

Since no standard deviations are reported, it is assumed that only one collar was analyzed from each of the 3 groups.

D. DISCUSSION

Overall, the presentation of the data is a bit shaky in places (for example: control dog 542 is reported, under individual biochemical values, as having had 80.6% RBC inhibition on day 98 relative to its "preexposure" level, when in fact it had only 19.4% less, but in this case it is fairly obvious how the mistake was made).

However, what is shown is fairly definite. There is a rapid release of what is mostly Vapona during the first week, and this correlates with the plasma ChE activity (maximum inhibition on day 7, followed by recovery in the 1X group in the period between days 42 and 56, but continuing on, particularly in females of the 3X and 5X groups). There is no evidence for any RBC ChE inhibition in any of the dosage groups.

From the occurrence of exudative dermatitis in a dog in the one-collar group, the collar has been shown to have some irritation potential. The collar is similar in composition (both with respect to its actives and inerts) to collars which have been previously registered and which are being marketed. This potential is addressed in the proposed product labeling ("Some animals may become irritated by any Collar. If this occurs, remove Collar. If condition persists, consult a veterinarian").