10/31/78

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: October 31, 1978

003691

SUBJECT: Sergeant's Flea and Tick Collar for Cats; Sergeant's Sentry IV Flea & Tick Collar for Dogs. Caswell #506 & (508), EPA#778-UE, 778-UR

FROM: William Dykstra, Ph.D
TOX/HED TS-769

10/31/78 id 4/10

TO: William Miller
Product Manager#16

Registrant: Miller-Morton Co.
2007 North Hamilton St.
P.O. Box 6235
Richmond, Va. 22230

Action Type: Resubmission with Data.

Recommendations:

1. Previously requested toxicological information has been submitted by the registrant. The toxicology studies submitted are acceptable as core-minimum data. No additional toxicology studies are required for registration.

2. The request by the registrant to increase width of dog & cat collars from 0.375 inches to 0.45 inches is toxicologically supported. No additional toxicology studies are required for this requested change in collar size.

*No RPAR criteria have been exceeded in these studies.

Sergeant's Flea and Tick Collar for Cats

Ingredient	Percent Weight
Naled (Dibrom)	7.0
Sendran (Baygon)	2.4
Inerts	90.6
	100.0

Sergeant's Flea and Tick Collar for Dogs

Ingredient	Percent Weight
Naled (Dibrom)	15.0
Sendran (Baygon)	4.2
Inerts	80.8
	100.0

1/7

EPA FORM 1320-6 (REV. 3-76)

Review:

1. Memos of 10/31/77 and 3/21/78 from W. Greear regarding toxicology requirements for registration and review of delayed neurotoxicity of Naled (Dibrom).

2. Memo of 9/10/77 from W. Greear with review of IRDC report#77-25, 3/7/77 of EPA Reg.#778-UE.

3. Baygon is a methyl carbamate and is exempt from requirement for delayed neurotoxicity in 8/22/78 Federal Register EPA Subpart F Guidelines.

4. Memo of 2/3/78 from W. Dykstra on Chevron teratology validation of Naled (Dibrom).

5. Memo of 6/5/78 from R. Gessert relating to Naled teratology.

6. Memo of 10/26/77 from K. Bailey on delayed neurotoxicity, teratology, reproduction with Baygon, core minimum data/supplementary data.

7. Additional Data on teratology of Baygon technical, requested in memo 10/26/77 from K. Bailey, submitted by Bayvet in letter (with data) dated Oct. 6, 1978; Acceptable.

8. Review of Data Submitted:

A. Sergeant's Sentry IV Flea & Tick Collar for Cats & Dogs (EPA#778-UE)

a. VRR. 77-25

1. Toxicological Evaluation of Antiflea Collar in Cats (TRDC Report No. 259-140, March 11, 1977). 16 Week Subacute Dermal Toxicity Study.

Test Material: The antiflea collars and placebo collars were received from A.H. Robins Company, Richmond, Virginia as July 27, 1976.

The collars were identified as:

No. 21	Placebo
D-2882	D-2873
LS 26422	LS 26414
Cat	6-14-76
6-18-76	

Twelve male (1.90-5.25 kg) and twelve female (2.35 - 3.30 kg) mixed breed cats were used in this study. The antiflea collars were applied as indicated below:

(continue on next page)

2

Group	No. of Cats Male	Female	No. of Cats with Short Hair	Long Hair	No. of Collars
I	3	3	4	2	1 (placebo)
II	3	3	2	4	1
III	3	3	3	3	2
IV	3	3	3	3	4

The cats, housed individually in metal metabolism cages, were observed daily for changes in generally behavior and appearance and the neck area was examined for local irritation. Individual body was examined for local irritation. Individual body weights were recorded weekly. Twice in the control period and at 2, 4, 8, 12 and 16 weeks of study, blood and urine samples were obtained from all cats for analysis. Hematological studied included Hg, Ht, RBC, WBC and Diff. WBC.

Biochemical studies included: glucose, BUN, SGOT, SAP. Plasma and RBC cholinesterase activities were determined for all cats, 3 times in the control period, at 3 and 7 days of study, and at 2, 3, 4, 5, 6, 7, 8, 12, and 16 weeks of study. Urinanalysis included measurement of volume, pH, sp. gr., color, appearance, glucose, albumin, bilirubin, occult blood and microscopic examination of sediment. Appropriate statistical evaluation was performed. At the termination of the 16 week experimental period, all cats were anesthesized with ketamine HCl, sacrificed by exsanguination and necropsied. Representative tissues from cats from each group were examined for histopathological lesions. Included are organ weights of pituitary, thyroids, adrenal, heart and gonads.

Results: None of the cats died during the study. Flaky skin on the neck was noted most frequently as occurring in both the controls and treated cats but occurred to the greatest extent in Group IV cats (4 collars). No changes in body weights considered related to the antiflea collars were seen. No compound related effects in hematological, biochemical, or urinanalyses were seen in the treated groups in comparison to controls. Decrease (slight) in plasma cholinesterase activity were seen at 3 and 7 days for cats in Group II, at 7 days for cats in Group III and through 5 weeks of study for cats in Group IV. No changes were seen in the RBC cholinesterase activities. No compound-related lesions were seen at necropsy. Organ/body weight data revealed no meaningful differences which could be related to compound administration. Examination of tissues of brain and spinal cord of cats exposed to compound revealed no lesions of the central nervous system related to treatment. Also, other tissues examined histologically were unremarkable.

Conclusion: Transient depression in plasma cholinesterase was seen, especially in cats wearing four collars. No RBC cholinesterase inhibition was seen during treatment. No compound related changes due to exposure were seen in hematological, biochemical, urinanalysis, necropsy, organ weights or histologic examination of tissues. Flaky skin on the neck of cats wearing four collars (Group IV) occurred more frequently than in the other groups.

Classification: Core-Minimum Data

b. VRR 78-57. Histopathology for 16 Week Study. Part of VRR-77-25.

Classification: Core-Minimum Data

c. VRR-77-115. Daily records of VRR 77-25; animal behavior and dermal irritation.

Classification: Core-Minimum Data

d. VRR 78-4. Acute Oral LD_{50} Study of Cat Flea and Tick Collar Pellets (A.H. Robbins, Report No. T-10-014-78, Feb. 24, 1978)

Test Material: Naled (7.6%); Sendran (2.7%) pellets Lot No. V-15-70.

One group (2M & 2F), 2.9-3.8 kg BW, of four cats was used. The test material was mixed in the diet of the cats and fed ad libitum. The cats were observed daily for seven days, after which the above described procedure was repeated until the animals had received a total of three doses (464, 1000 and 2150 mg/kg) of the cat collar pellets. At the conclusion of the study the cats were weighed and then sacrificed by intravenous injection of T-61 Euthanasia. Gross examination of the viscera was performed on all animals.

Results: No deaths, $LD_{50} > 2150$ mg/kg

Toxic Signs: none were noted

Body Weight: gain in weight

Necropsy: not remarkable

Classification: Core-Minimum Data, TOX Category III: CAUTION

e. VRR 78-56. Skin Irritation Acute Dermal Irritation Study of Cats Flea and Tick Collar #21B and Dog Flea and Tick Collar #18G (A.H. Robbins) Report #T-10-108-78, March 31, 1978

Test Material: Cat Flea and Tick Collar #21B (7.38% Naled, 2.4% Dibrom); Dog Flea and Tick Collar #18G (15.9% Naled, 4.48% Dibrom); placebo collar (a colorless, odorless material)

One group of Six NZW rabbits, 2.5-2.8 kg BW, were used in this study. The backs of rabbits were fur clipped. On the back of each rabbit 3 tests sites were abraded and three sites of equal size were left intact. Each test substance and placebo of one inch strips, cut from each collar, were applied to one intact and one abraded test site on each rabbit under an impervious cuff for 24 hours. Scoring at 24 and 72 hours was done according to Draize.

Results: None of the intact skin sites were irritated. The abraded skin sites were irritated in 1/6 control, 3/6 dog collar sites, and 2/6 cat collar sites. The primary irritation scores for the collar materials were: (continue on next page)

4

	P.I. Score
Placebo	0.17
Dog #18G	0.67
Cat 21B	0.42

Conclusion: The dog collar & cat collar are not considered primary irritants.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

B. Sergeant;s Sentry IV Flea & Tick Collar for Dogs (EPA#778-UR)

a. VRR 77-26. Toxicological Evaluation of Antiflea Collar in Dogs (IRDC Report No.259-141, March 11, 1977)

Test Material: The antiflea collars and placebo collars were received from A.H. Robins Co., Richmond, Va. on July 27, 1976. The collars were identified as follows:

No. 18	Placebo
D-2878	D-2873
LS 26419	LS 26414
Dog	6-14-76
6-14-76	

Twelve male (5.0 to 30.3 kg BW) and twelve female (3.0 to 20.8 kg BW) mixed breed dogs were used in this study. The smaller dogs were housed individually in metal metabolism cages throughout the study. The dogs listed below were housed in metal metabolism cages during the control period and during the first 9 weeks of study. Thereafter, these dogs were housed in indoor pens.

Group I	Group II	Group III	Group IV
76-312	76-313	76-291	76-290
76-416	76-310	76-295	76-292
		76-314	76-307

The dogs were housed in temperature and humidity controlled rooms during the study. During the conditioning period, stool flatation studies were conducted and followed by appropriate vermifuge therapy. All of the dogs were vaxxinated against canine distemper, hepatitis, leptospirosis and rabies. The antiflea collars were applied as indicated below:

Group	No. of Dogs Male	No. of Dogs Female	No. of Dogs Short Hair	No. of Dogs Long Hair	No. of collars
I	3	3	3	3	1(placebo)
II	3	3	3	3	1
III	3	3	4	2	2
IV	3	3	3	3	4

The dogs were observed daily for changes in general behavior and appearance and the neck area was examined for local irritation. Individual body weights were recorded weekly. Twice in the control period and at 2, 4, 8, 12 and 16 weeks of study, blood and urine samples were obtained from all dogs for analysis. Hematological studies included: Hg, Ht, RBC, WBC and diff. WBC.

Biochemical studied included: glucose, BUN, SGOT, SAP.

Urinanalysis included measurement of: volume, pH, sp. gr., color, appearance, albumin, glucose, bilirubin, occult blood and microscopic examination of the sediment.

Plasma and RBC cholinesterase activities were determined, for all dogs, 3 times in the control period, at 3 and 7 days of study, and at 2, 3, 4, 5, 6, 7, 8, 12 and 16 weeks of study. All statistical analyses compared the treatment groups with control groups. At termination of the 16 week experimental period, all dogs were sacrificed and necropsied. Organ weights of pituitary, thyroids, adrenal, heart and gonads were determined. Representative tissues from dogs of the control and high-dose group were examined for histopathological lesions.

Results: None of the dogs died having the study. No changes considered to be related to the antiflea collars were seen in general behavior or appearance. Two dogs in Group IV showed dry flaky skin on the neck area during week 10 of study but not thereafter. No changes in body weight considered to be related to compound-administration were seen. No changes considered to be related to treatment were seen in hematological, biochemical values or urinanalyses. Plasma cholinesterase was lower for dogs in Group IV through the first four weeks of study. No changes were seen in RBC cholinsterase activities. No compound related changes were seen in gross pathology, organ weights or histopathological examination of tissues.

Conclusion: Plasma cholinesterase was lower for dogs in Group IV through the first four weeks of study. No RBC cholinesterase inhibition was seen during treatment. Two dogs in Group IV showed dry flaky skin on neck area during week 10 of study but not thereafter. No compound-related changes due to exposure were seen in hematological, biochemical, urinanalysis, necropsy, organ weights or histological examination of the tissues.

Classification: Core-Minimum Data

b. VRR 78-68 Histopathology of dogs as part of VRR 77-26.

Classification: Core-Minimum Data

c. VRR 77-114 Daily records with respect to test animal behavior and dermal irritation as part of VRR 77-26.

Classification: Core-Minimum Data

003691

d. VRR 78-3 Acute Oral LD_{50} study of Dog Flea and Tick Collar Pellets (Naled (15:5%); Sendran (4.6%) in dogs (A.H. Robbins Report#T-10-060-78, 2/24/78)

Test Material: Pellets (2mm length X2mm diameter) of dog collars (Naled 15.5%; Sendran - 4.6%)

One group (2M & 2F), 8.2-11.9 kg BW, of four mongrel dogs was used. The test material was mixed in the diet of the dogs and administered ad libitum. After administration of the initial dose of 464 mg/kg, the dogs were observed daily for six days.

The procedure of dosing described above was then repeated (using the same animals) but administering a dose of 1000 mg/kg of the dog collar pellets. After a 10-day observation period the dogs received a final dose of 2150 mg/kg. 7 days following administration of the third and final dose, the dogs were weighed, sacrificed and examined grossly.

Results: No deaths occurred. Emesis occurred in one male dog at the 1000 mg/kg level and in all animals at the 2150 mg/kg level. An acute oral LD_{50} cannot be determined due to emetic properties of the test substance $LD_{50} > 1000$ mg/kg (emesis above this dose)

Toxic Signs: emesis, no other signs

Body Weight: Dogs gained weight

Necropsy: not remarkable

Classification: Core-Minimum Data

TOX Category III: CAUTION

e. VRR 78-56 Skin Irritation review for EPA#778-UE.

TOX/HED:th:REngler:10-30-78

11/3/78

7