UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: August 2, 1977

SUBJECT: Sendran Tick and Flea Dip Concentrate for Dogs and Cats 003709
EPA File Symbol 11556-AO
Caswell #568

FROM: Toxicology Branch
Registration Division

TO: Frank Sanders
Product Manager # 12

Recommendations:

The following toxicity data must be referenced or submitted for review:

1) Hen Neurotoxicity Study - Technical

At the time of registration the following label changes will be required:

1) Change the Human Hazard Signal Word from "Caution" to "Warning" due to ocular effects.

2) Add the precautionary statements "Causes eye irritation" and "May cause allergic skin reaction."

3) Add the first aid statements "In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician."

Review:

1) Acute Oral LD_{50} of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 54521, 12/17/76, Acc. # 228023, submitted by Cutter Laboratories).

Twenty male Sprague Dawley rats, weighing 189-253g, were divided into 4 equal groups and dosed at 600 mg/kg, 780 mg/kg, 1000 mg/kg or 1290 mg/kg. Twenty-five female Sprague Dawley rats, weighing 168-215g, were divided into 5 equal groups and dosed at 360 mg/kg, 470 mg/kg, 600 mg/kg, 780 mg/kg or 1000 mg/kg. The compound was diluted in Lutrol and administered to rats fasted 20 hours. Rats were observed 14 days for symptoms and mortality. Necropsies were performed.

Results

Symptoms included tremors, lethargy, and muscular fasciculations. The duration and severity of the symptoms were close related. No gross lesions attributed to the compound were seen at necropsy.

EPA Form 1320-6 (Rev. 3-76)

179

LD_{50} (male) = 884(739-1058)mg/kg

LD_{50} (female) = 548(432-695)mg/kg

Classification

Core-Minimum Data

1) Individual body weight and food consumption were not determined daily.

2) Eye Irritancy of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 47065, 3/2/76, Acc. # 228023, submitted by Cutter Laboratories).

Eleven mature New Zealand rabbits, weighing at least 2 kg, were divided into 2 groups containing 5 rabbits in the "eye wash" study and 6 rabbits in the "unwashed eye" study. One-tenth milliliter of the formulation was instilled into the eye of each rabbit. Five of the animals were exposed to the substance for 5 minutes after which the eyes were washed for 2 minutes with 300 ml of water. Six other rabbits were exposed to the formulation for 24 hours prior to washing. Readings were made at 1, 2, 3, 7, 14 and 21 days after treatment (with the exception of 3 rabbits in the "unwashed eye" study whose eyes were read at 1, 2, 3 and 7 days).

Results

Rabbits in both groups displayed very mild conjunctivitis which was absent by day 7. One rabbit in the "unwashed eye" study exhibited corneal opacity on day 1. In general, washing did reduce the amount of irritation observed.

Classification

Core-Guideline

3) Acute Dermal LD_{50} of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 54522, 12/17/76, Acc. # 228023, submitted by Cutter Laboratories).

Four male and 4 female New Zealand white rabbits, weighing 2.3-2.7 kg were used to assay the dermal toxicity of the

formulation. Backs of the animals were shaved and abrasions made. The formulation was applied undiluted at a rate of 5000 mg/kg to the rabbits' backs, and the test area was wrapped with plastic. After 24 hours exposure, wrappings were removed and the area washed with water. Animals were observed for 14 days for signs of toxicity. Necropsies were performed.

Results

No symptoms were observed during the 14-day observation period. No gross lesions attributable to the compound were seen at necropsy. Deaths failed to occur.

LD_{50} (males) > 5000 mg/kg

LD_{50} (females) > 5000 mg/kg

Classification

Core-Minimum Data

1) Although only one dose level was tested on animals with abraded skin the study is acceptable since the toxicity is low and abrading the skin would lead to greater absorption of the material. Testing of the formulation on intact skin is not necessary.

4) Dermal Irritancy of Sendcan 8% Dip Concentrate - (Bayvet Corp., Report # 54525, 8/26/76, Acc. # 228023, submitted by Cutter Laboratories).

Six rabbits were utilized to determine the dermal irritancy of the formulation according to 21CFR191.11.

Results

No erythema or edema was observed at any time during the test.

P.I. = 0.0/8.0

Classification

Core-Minimum Data

1) Readings were made on 1 intact and 1 abraded skin site.

5) Cholinesterase Determinations in Dogs Following a Use Rate Application of Senc an 8% Dip Concentrate - (Bayvet Corp., Report # 50520, 12/6/76, Acc. # 228023, submitted by Cutter Laboratories).

Six dogs (3 male and 3 female) of various breeds, ranging in age from 3 months to adult, were subjected to use dilutions of the formulation (2 oz/gal). The material was applied by completely submerging and saturating the animals for 1 minute except for eyes, nose and mouth. Blood samples were obtained 24 hours pretreatment and again immediately prior to the dip application. Post-treatment samples were collected at 1, 4, 24 and 48 hours. Observations were made for clinical signs of toxicity throughout the study.

Results

No clinical signs of carbamate toxicity were observed. The following average ChE values were observed:

Time	% Cholinesterase Inhibition	
(Post-treatment)	Plasma	RBC
1 hr	29	33
4 hr	28	43
24 hr	8	4
48 hr	1	0

Classification

Core-Minimum Data

6) Cholinesterase Determinations in Cats Following Use Rate and 10 x Application of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 50521, 12/9/76, Acc. # 228023, submitted by Cutter Laboratories).

Twelve cats (6 male and 6 female) of mixed breeding, ranging in age from 6 months to adult, were subjected to 1Ø (2 oz/gal) and 10 x (20 oz/gal) use-dilution concentrations of the formulated product. The dip application was applied by completely submerging

and saturating the animals for 1 minute except for eye, nose and mouth. Blood samples were obtained 24 hours pretreatment and again immediately prior to the dip application. Post-treatment samples were collected at 24 and 48 hours. Observations were made for clinical signs of toxicity throughout the study.

Results

One animal (male) in the 10 x study group developed the following signs of intoxication following exposure: unilateral miosis at 1 hour; salivation, trembling and lateral recumbancy at 3 hours; slight salivation at 4 hours. The following average ChE values were observed:

		% Cholinesterase Inhibition	
Time	Treatment	Plasma	RBC
24	1 x	+10	+19
24	10 x	30	+11
48	10	+14	+16
48	10 x	26	6

Classification

Core-Minimum Data

7) Cholinesterase Determinations in Dogs Following a 10 x Application of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 54500, 11/18/76, Acc. # 228023, submitted by Cutter Laboratories).

Six adult dogs (3 male and 3 female), of various breeds, were subjected to 10 x (20 oz/gal) the use-dilution concentration. The dip application was applied by completely submerging and saturating the animals for 1 minute except for eye, nose and mouth. Blood samples were obtained 24 hours pretreatment and again immediately prior to the dip application. Post-treatment samples were collected at 1/2, 1, 3, 6, 24 and 48 hours. Observations were made for clinical signs of toxicity throughout the study.

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Results

One male terrier received an unknown quantity of the solution in the mouth and eyes. The animal was uncoordinated and salivating 30 minutes post-treatment. Forty minutes after treatment the animal was convulsing and expired. One male English Pointer developed moderate clinical signs of toxicity, but was normal within 6 hours. Only slight transient signs were observed in the remaining animals. The following average ChE values were observed:

	% Cholinesterase Inhibition	
Time	Plasma	RBC
30 min.	43	41
1 hr.	50	60
3 hr.	45	52
6 hr.	41	48
24 hr.	32	41
48 hr.	33	48

Classification

Core-Minimum Data

8) Subacute Dermal Toxicity of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 54523, 1/17/77, Acc. # 228023, submitted by Cutter Laboratories).

Twenty New Zealand white rabbits, weighing 2.34-2.51 kg, were divided into two groups of 5 animals/sex/treatment. Five hundred mg/kg of material was applied to the shaven backs of rabbits for 6-8 hrs/day, 5 days/week for 3 weeks. The test group received 500 mg/kg of the formulation, whereas the control group received an equivalent amount of blank formulation (material without active ingredients). At the end of each exposure period, the material was washed from the back. Animal were shaved weekly and abrasions were made. Daily observations were made for signs of toxicity, behavioral changes and skin reactions. Animals were weighed on days 0, 7, 14 and 21. The following

tests were conducted on all animals prior to initiation of the study and on Day 22 (one day after the final treatment).

Cholinesterase Activity

Plasma
Erythrocyte
Brain (Day 22)

Hematology

PCV	MCV	WBC
RBC	Hb	Differential WBC
Platelet Count		

Blood Chemistry

Glucose	SGPT	BUN
SAP	SGOT	

Urinalysis

Protein	Bilirubin	pH
Glucose	Blood	Specific Gravity
Urobilinogen	Ketones	Microscopic Exam

Complete gross necropsies were performed on all animals. The following organs were weighed:

Thyroid	Spleen	Liver
Heart	Adrenals	Gonads
Lungs	Kidneys	Brain

The following tissues were subjected to histological examination:

Lymph Node Submaxillary	Esophagus	Lungs
Salivary Gland	Trachea	Pancreas
Thyroid	Dorsal Aorta	Spleen
Parathyroid	Heart	Adrenals
Kidneys	Small Intestine (duodenum, jejunum and ileum)	Colon
Stomach (cardia, fundus and pylorus)	Caecum	Liver

Urinary Bladder	Ovaries	Gall Bladder
Testes	Prostate	Uterus
Skeletal Muscle (gastrocnemius)	Sciatic Nerve	Spinal Cord (lumbar)
Bone Marrow	Skin (from application site)	Bone (femur)
Optic Nerve		Eye
Pituitary		Brain (cerebrum, cerebellum, pons)

Results

Survival and body weights were unaffected. No appreciable, consistent differences between the control and treated rabbits were demonstrated in blood chemistry, hematology, urinalysis, and organ body weight ratios. Plasma, brain and RBC cholinesterase were insignificantly affected by application of the test material. Neither the gross necropsy report nor the histopathology report revealed any lesions which could be related to treatment.

N.E.L. = 500 mg/rabbit over a 3-week period (15 applications)

Classification

Core-Minimum Data

1) Less than 3 dosage levels were employed in the study.

9) Skin Sensitization of Sendran 8% Dip Concentrate - (Bayvet Corp., Report # 54524, 1/18/77, Acc. # 228023, submitted by Cutter Laboratories).

Fifteen male white guinea pigs, weighing 330-385g, had their backs and flanks shaved and the test material injected intradermally every other day (3x/week) for a total of 10 injections. The material injected was a 0.1% solution of the formulation in physiological saline. The first injection was 0.05 ml and the remaining 9 injections were 0.1 ml. The challenge injection was given 2 weeks after the last sensitizing injection and consisted of 0.05 ml of freshly prepared 0.1% solution. Twenty-four hours after each injection, readings were made for the diameter, edema and erythema of the associated reaction.

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Results

Of the 15 animals evaluated for an erythematous reaction 4 of the group showed a challenge reaction greater than their highest sensitizating reaction, 2 showed a challenge reaction smaller than their highest sensitizing reaction, and 9 showed a challenge equivalent to their highest sensitizing reaction. When evaluated for an edematous reaction, 3/15 animals showed a challenge reaction greater than their highest sensitizing reaction, 5/15 showed a challenge reaction smaller than their highest sensitizing reaction and seven showed a challenge reaction equivalent to their highest sensitizing reaction. When reaction diameter was measured, 8/15 animals showed a greater reaction than their highest sensitizing reaction, 4/15 showed a reaction smaller than their highest sensitizing reaction and 3/5 showed a challenge reaction equivalent to their highest sensitizing reaction. The average challenge reaction was greater than the average sensitizing reaction. Under the conditions of test the material may be considered a potential sensitizer.

William Greear
William Greear
for OEP 8/26/77