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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Precautionary Labeling for Rabon Dog Collar

TO: George LaRocca (PM-15)
Registration Division (TS-767)

FROM: Byron T. Backus B.T. Backus 02-24-84
Toxicology Branch
HED (TS-769)

THROUGH: William Butler, Head William M. Butler 3-2-84
Review Section III
and
William Burnam, Chief
Toxicology Branch

Product: Rabon dog collar
13.7% active ingredient

Registration # 2596-62

Tox Chem # 217A

Registrant: Hartz Mountain Corp.

Action

There is a question as to whether current precautionary labeling for this product is adequate, particularly in relation to its use on pregnant bitches, and exposure involving newborn and nursing puppies.

Conclusion

Current precautionary labeling for this product is inadequate. Labeling should be revised to state that pregnant bitches and newborn and nursing puppies should not be exposed to this collar. It would also be appropriate to state that cholinesterase inhibitors should not be used on dogs wearing this collar.

If the data received 11-25-83 are all that are available for this product, then there is insufficient information to demonstrate an acceptably low level of risk to dogs associated with even normal use exposure.

Background

An incident has been reported in which a collar was placed on a pregnant cocker spaniel bitch. Two days later she had five puppies, two of which subsequently died two days after birth with symptoms similar to cholinesterase inhibition. The incident was reviewed at FDA, and the comment was made that the labeling seems deficient in warnings concerning neonatal exposure.

The registrant has taken the position that current precautionary labeling is adequate, and has submitted a number of dog exposure studies.

Discussion

The registrant has submitted studies which have been reviewed and classified as follows:

Albert, J.R. Long-Term Repeat Exposure of Dogs to 10% Stirofos Flea Collars. Core Supplementary Data.

Shwartzman, R.M. Laboratory Test Report. Core Invalid Data.

Zaret, E.H. Effect of Exposure to Rabon® Insecticide Pet Collars of Dog Blood Cholinesterase. Core Supplementary Data.

Albert, J.R. Effect of the 10% Stirofos Flea Collar on Reproductive Capacity of the Bitch Dog. Core Supplementary Data.

D'ver, A.S. Interim Report - Effects of the Use of An SD-8447 Collar on Puppies. Core Supplementary Data.

In addition to these studies, two one-page summaries entitled: "Distribution of Ages of Puppies During Field Tests of 10% Stirofos Collars" and "Rabon® Insecticide Tick and Flea Collar Summary of Field Investigations Overall" were received. These are more in the nature of testimonials than toxicological data.

A major deficiency in the studies is that collars were tested only at a normal use exposure level, and there is no information then as to what safety factor exists between normal exposure and that at which effects may occur.

In the study titled Effect of the 10% Stirofos Flea Collar on Reproductive Capacity of the Bitch Dog there is a suggestion of body weight depression in puppies exposed to this collar, as all 4 control bitches which raised 6 or more surviving pups had litters averaging at least 0.98 kg/pup at 4 weeks, while of 7 test litters with 6 or more surviving pups 4 averaged less than 0.95 kg/pup at 4 weeks. One test group

litter of 6 surviving pups averaged 0.77 kg/pup at 4 weeks, while another test group with only 5 averaged 0.86 kg/pup. There were no significant differences between placebo and test collar groups for birth weights of pups which survived.

Even if the study had been completely negative, it is doubtful whether data generated using a collar containing 10% Rabon would be adequate to demonstrate the safety of a collar containing 13.7% of this active ingredient.

There may be considerable variation in the susceptibilities of different dog breeds to pesticides, as well as the possibility of idiosyncratic reactions. It is extremely likely that newborn pups are at a higher risk than older animals for whatever adverse effects may occur. The circumstances of this reported incident (collar applied only two days before whelping, puppies affected with symptoms similar to cholinesterase inhibition) in conjunction with the lack of appropriate precautionary labeling are cause for concern.

Data Evaluation Report

Compound: Rabon dog collar

Citation:

Albert, J.R. Long-Term Repeat Exposure of Dogs to 10% Stirofos Flea Collars. TIR-72-012-73. Study conducted at the Galesburg facility of Laboratory Research Enterprises (LRE) at Kalamazoo, MI; undated. Received at EPA 11-25-83; in Acc. 251920.

Reviewed by:

Byron T. Backus
Toxicologist

Core Classification: Supplementary

Tox. Category: N/A

Conclusions:

There are a number of deficiencies in this study. These include the following:

The dogs were only exposed at one level (normal use-exposure level). The resulting data give no indication as to what sort of safety factor exists between normal exposure to this collar and the level at which adverse effects might occur.

There is no information as to the weight of the collar used in the testing, or how much (either on an average or individual basis) was cut off when it was fitted to dogs.

There are no units reported for cholinesterase activity measurements.

Materials:

Placebo dog collars identified as lot no. 06XPPL.
Stirofos dog collars (10%) identified as lot no. 06XPR2.

A total of forty male and female beagles, four, five and six months of age.

Methods:

All dogs went through a 10 or 11 day "adaptation period" during which they were fitted with (presumably wore) a placebo collar. Animals were then divided into two groups of 20, each containing "equal numbers of males and females" One group subsequently wore placebo collars; the other group wore Stirofos collars. Dogs were housed two (same sex and treatment group) per hanging wire cage, except for dogs which removed (and sometimes ate) their cagemate's collar. These dogs were caged individually.

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Animals were weighed on days 0 to 2, and had either a placebo or test collar placed on them. Collars were changed on a regular basis every 30-32 days. If dogs succeeded in removing collars these were either refitted on the animal or a new collar was put on. Collars were fitted so that they were able to rotate freely around the dog's neck. Excess collar material was cut off. It is reported that collar weights were taken for possible future correlations with dog size and collar weight loss; however, these data are not reported.

Individual body weights were taken on days 0, 30, 60, 90, 130, 150 and 180.

Blood samples were taken from all dogs during the adaptation (pre-exposure) period. Blood samples were subsequently taken from 10 animals per group on days 45, 90, 135 and 180, (same 10 animals/group were bled each of these days). Samples were anticoagulated with EDTA-Na, and the following determinations were made:

Hematology	Clinical Chemistry	
red blood cell counts	RBC ChE	
white blood cell counts	plasma ChE - determined by	method of Williams
hematocrit	total protein	glucose
hemoglobin	blood urea nitrogen	cholesterol
cell size	total bilirubin	uric acid
white blood cell differential (by microscopic examination of stained preparations).	SGOT	calcium
	alkaline phosphatase	inorganic phosphorus

Animals were observed daily. There were additional 3-time weekly observations and 30-day physicals with emphasis on dermatologic, otologic and opthalmalogic conditions. On day 90 observers evaluated not only dogs in the study but 20 similarly aged dogs.

On day 90 samples of rump fur were obtained from 4 dogs. Each of these dogs was then put in a tub, flushed with water for 4-5 minutes, then allowed to shake itself and dry normally. Repeat samples of dry fur were taken at 18 hrs and again 48 hrs. These samples were analyzed for "SD 8447" (which is not further identified). It is stated that results of these analyses are discussed (and presumably given) in another report.

At study termination, 5 randomly-selected animals/group were used to assess kidney function by a phenolsulphophthalein injection method. Five others for each group were used to assess liver function by a brosulphthalein method. Two days after these determinations, half the animals in each group were premedicated with acetylpromazine maleate, 0.25 mg/kg, administered intramuscularly, and 30 minutes later were infused with Na thiamylal (Surital) to determine if exposure to the collar resulted in prolonged anesthesia. It is stated that the data from this study is reported elsewhere.

Results:

Animals are reported as appearing healthy and unaffected during the 6-

month period. However, at the 30-day interval the room in which dogs were kept was noted to have poor ventilation and a high ammonia level, the latter from the nearness of the fecal trays. Lacrimation and injection of the sclera vessels of the eyes (occurring through the duration of the study) were interpretated as being due to exposure to vapors. According to data as presented, an average of 3.17 dogs with placebo collars had lacrimation at any one time, while 7.83 of the dogs with the test collar showed this symptom.

No individual body weight are presented, only means $\pm$ S.E. for the sexes and groups. Females in the test collar group consistently weighed more (on the average) from day zero than those in the control group; males in the placebo collar group consistently weighed more on the average than those in the test collar group.

Hematology: no significant differences are readily apparent between placebo and test collar groups with respect to any parameter. On day 45 test collar group had a higher average WBC count than that of controls ($17.05 \times 10^3/mm^3$ to $14.94 \times 10^3/mm^3$).

Cholinesterase: subjects not identified by sex; also it is not indicated what units are associated with numerical values presented. The numbers given indicate no differences between placebo and test groups. Plasma ChE activities are lower on day 90 for both controls and test group; this is ascribed to failure of the buffers used in the study on that date.

Clinical Chemistry: no significant differences seen between animals in placebo and test group for any parameter. One animal in test group had a high alkaline phosphatase reading (>350 mU/ml) on days 0 and 45, but this subsequently decreased. Since animals were fairly young at start of the study, initial alkaline phosphatase readings were fairly high and generally declined over the 6-month period.

Data Evaluation Report

Compound: Rabon dog collar

Citation:

Shwartzman, R. N. Untitled. No study number. Study conducted at the University of Pennsylvania School of Veterinary Medicine, 3800 Spruce St, Philadelphia 19104. Study dated July 23, 1976. Received at EPA 11-25-83; in Acc. 251920.

Reviewed by:

Byron T. Backus
Toxicologist

Core Classification: Invalid. (No controls used).

Tox. Category: N/A

Conclusions:

The study is invalid as there was no concurrent control group. Additional deficiences were that only males were used and there was only one exposure group.

Since no information is given as to collar weight, how much of the collar was trimmed for each dog during fitting, and what the release rate of active is from this collar, it is not possible to determine what safety factor exists between normal use exposure and that at which adverse effects might be expected to occur.

Materials:

14.5% Rabon dog collars

Ten adult male beagles, 1 year old, each approximately 10 kg in weight.

Methods:

On day 0 one collar was fitted around the neck of each of the ten beagles. Excess collar length was removed and disposed. Blood samples were taken from each dog on days -1 and 0, the second drawing being just before collars were fitted. Blood was subsequently drawn from each dog on days 1, 2, 3, 5, 7, 9, 12 and 14; plasma and RBC cholinesterase activities were determined by the Upjohn Clinical Labs, Philadelphia, PA using Che-Tel and A-Che-Tel kits produced by Charles Pfizer Inc.

Results:

No information other than cholinesterase activities is provided.

There was no evidence of any possible plasma or RBC cholinesterase inhibition. Individual activities for days 1 through 14 were essentially identical to those obtained for days -1 and 0. There were considerable variations in RBC cholinesterase activities that were caused by sporadically

observed low values (i.e., 0.1 for dog #SHQ1 on day 0, 0.3 for #JK4 on day 0, 0.3 for #L11 on day 1, 0.4 for #LA1 on day 2) before and during exposure.

There was no concurrent control (unexposed group). Since there may be considerable fluctuations in cholinesterase activities, a concurrent control group is an essential part of this type of study.

Data Evaluation Report

Compound: Rabon dog collar

Citation:

Zaret, E.H. Effect of Exposure to Rabon® Insecticide Pet Collars on Dog Blood Cholinesterase. Project No. 74-61756.00; study conducted by the Shell Development Co. at the Biological Sciences Research Center, Modesto, CA. Protocol sheet dated July 7, 1976. Received at EPA 11-25-83; in Acc. 251920.

Reviewed by:

Byron T. Backus
Toxicologist

Core Classification: Supplementary

Tox. Category: N/A

Conclusions:

Cholinesterase data are presented only from controls and dogs wearing one collar (normal use exposure). No information is provided on individual animals (sexes, body weights) other than they were mature beagles of both sexes.

There is a suggestive trend with respect to plasma ChE activities. Dogs in the 14.5% Rabon collar group showed higher mean plasma ChE activities with respect to controls on days -3, 0, 1 and 2 (11.6, 5.8, 0.6 and 2.5% respectively). On days 3, 5, 7, 9 and 11 the same group had less mean plasma ChE activity (on day 9 9.4% less) than did controls. While this difference is not statistically significant, it may be that there is a mild (5-15%) plasma ChE inhibition effect which is masked by inherent variation in the data. On day 14 dogs wearing the Rabon collar had slightly higher mean plasma ChE activity than controls.

There was no evidence of any effect on "whole blood" cholinesterase activity.

Materials:

Placebo dog collars.
14.5% Rabon dog collars (no lot number given).

Thirteen mature beagles of mixed sexes.

Methods:

Seven dogs wore placebo collars; the remaining six wore 14.5% Rabon collars. Collars were placed on the animals on day 0. Dogs were caged individually. Blood was drawn from each dog on days -3, 0 (whether before or after collars were placed on animals is not noted), 1, 2, 3, 5, 7, 9, 11 and 14. EDTA was the anticoagulant. Tubes of blood were put in ice immediately after drawing. Determination

of plasma and whole blood cholinesterase activities (measurements in SH units) was by the thiocholine method, using an autoanalyzer.

The only computations were determination of means for plasma and whole blood ChE activities for the placebo and test groups for any given drawing date.

Results:

Dogs in the 14.5% Rabon collar group showed higher mean plasma ChE activities (11.6 and 5.8% respectively) on days -3 and 0 (before collar was fitted) and slightly higher mean plasma ChE activities (0.6 and 2.5% respectively) on days 1 and 2 with respect to the control group. On days 3, 5, 7, 9 and 11 dogs wearing the Rabon collar showed less plasma ChE activity than controls; on day 9 they had 9.4% less mean plasma ChE activity. However, it is doubtful that these figures are statistically significant, although the trend is suggestive. On day 14 dogs wearing the Rabon collar had slightly higher mean plasma ChE activity than controls.

Dogs in the 14.5% Rabon collar group consistently (days -3 through 14) had more whole blood cholinesterase activity than did controls.

Data Evaluation Report

Compound: Rabon dog collar

Citation:

Albert, J.R. Effect of the 10% Stirofos Flea Collar on Reproductive Capacity of the Bitch Dog. No study number given. Study conducted at the facilities of Laboratory Research Enterprises (LRE), at Kalamazoo, MI; undated (but the study was apparently conducted July-October 1972). Received at EPA 11-25-83; in Acc. 251920.

Reviewed by:

Byron T. Backus
Toxicologist

Core Classification: Supplementary

Tox. Category: N/A

Conclusions:

The results of this study suggest body weight depression in puppies whose mothers wore the collar. All 4 control bitches which raised 6 or more surviving pups had litters averaging at least 0.98 kg/pup at 4 weeks, while of 7 test litters with 6 or more surviving pups four averaged less than 0.95 kg/pup at 4 weeks. One test group litter of 6 surviving pups averaged 0.77 kg/pup at 4 weeks , while another test group with only 5 averaged 0.86 kg/pup. There were no significant differences between placebo and test collar groups for birth weights of pups which survived.

The reported cholinesterase values are of little value, as no pre-exposure measurements were made, and the buffers failed. The clinical chemistry and hematologic values reported are likewise of dubious value as only averages are given, and no pre-exposure measurements were made.

Even if findings in this study had been completely negative, it is doubtful that data obtained from a study on a collar containing 10% Rabon could be used to demonstrate the safety of a collar containing 13.7% of this active ingredient.

Materials:

Placebo dog collars identified as from lot no. 06XPP1.
10% Stirofos dog collars identified as from lot no. 06XPP2.

Twenty proven bitches (each with at least two, but no more than 3, previous whelpings).

Methods:

Ten bitches were assigned to a control (placebo collar) group and ten were assigned to the test collar group. According to the methods and materials section of the report placebo collars were fitted on all bitches as soon as assignments were made, each bitch was bred to a different stud, and a new placebo collar was fitted immediately after breeding. Thirty days after breeding the collars were removed and the dogs were refitted with a second placebo or test collar. During whelping the collar was removed and immediately following whelping a new collar was fitted. This third collar was left on the bitch until the pups were 4 weeks old. Any collars that came off were refitted if possible, and any that were lost were replaced by new collars.

It is reported that bitches were observed daily for "overall care" and weekly for "gross effects of the collar on the eyes, ears and skin. Each bitch was examined for opthalmologic, otologic and dermatologic effects before breeding, 30 days after breeding, and when the pups were 4 weeks old. Birth weights of the individual pups were recorded. Health of the pups was assessed at 28-30 days of age, and body weights were taken.

Blood samples were taken from all bitches 30 days after breeding and four weeks after parturition. The following determinations were made:

Hematology	Clinical Chemistry	
hemoglobin	RBC ChE	
hematocrit	plasma ChE - method of Williams	
cell size estimates	SGOT	total bilirubin
white cell differentials	urea nitrogen	cholesterol
	alkaline phosphatase	uric acid
	glucose	calcium
	total protein	inorganic phosphorus

Results:

One control bitch failed to conceive. There were 58 pups born to 9 control bitches (average of 6.44) and 65 pups were born to the 10 test bitches (average of 6.5). In the control group 43 were weaned; in the test group 55 were weaned. All litters in placebo group at 4 weeks averaged at least 0.98 kg/pup, but six of the litters in the test group averaged less than this figure. The statement is made that it could be expected that the average body weight of pups at four weeks in the test collar group would be less than that of controls because of the larger number in each litter (that were weaned?).

However, there were 2 bitches in the control group that lost all of their offspring (2 pups were transferred to one of these bitches), leaving 7 bitches that raised 41 offspring (average of nearly 6 per bitch) while average in test group was 5.5. All 4 control bitches which raised 6 or more surviving pups had litters averaging at least 0.98 kg/pup at 4 weeks, while of 77 test litters with 6 or more surviving pups four averaged less than 0.95 kg/pup at 4 weeks. One test group litter with 6 surviving pups averaged 0.77 kg/pup. Another test group with only 5 pups averaged 0.86

kg/pup at 4 weeks. There were no significant differences in average birth weights between placebo and test collar groups.

Same-day plasma and RBC cholinesterase activities (reported on an individual basis) for placebo and test group animals were similar, but the data are of little value as no pre-exposure measurements were made on these animals and it is noted that the buffers had failed during this period.

Blood chemistry and hematologic determinations are reported only on a group basis. Again, data are of limited value as no pre-exposure measurements were taken. Data, as presented, indicate only slight (and probably not significant) differences between animals wearing the test collar and those with the placebo.

The typewritten data sheets (presumably copies of records) do not indicate adequate records were kept. For example, dog IW60 is reported as being fitted with a placebo collar on day -4, and subsequently (no date given) a test collar fitted. This collar was replaced on day 20, but there is no record of any subsequent collar change. Dog AR69, ostensibly a member of the test group, is reported as having a placebo collar fitted on day -4, but there is no record of any test (Stirofos) collar being placed on this dog. It seems surprising that no mention is made of routine collar changes for individual bitches after day zero.

Data Evaluation Report

Compound: Rabon dog collar (no percentage of active given)

Citation:

D'Ver, A.S. Interim Report. Effects of the Use of An SD-8447 Collar on Puppies. Study No. 137; Nov. 15, 1983. Study conducted at White Eagle Laboratories, Inc. 2000 Lower State Road, Doylestown, PA. Received at EPA 11-25-83; in Acc. 251920.

Reviewed by:

Byron T. Backus
Toxicologist

Core Classification: Supplementary

Tox. Category: N/A

Conclusions:

It is not anticipated that this study, even when completed, will provide significant data. Maximum exposure is to a single collar. No cholinesterase activity measurements are being made, and no weight data (either group or individual) have been reported. There is also a question as to whether the data in table 14 are for aluminum (as stated) or albumin.

Materials:

Placebo dog collars.
SD-8447 dog collars (no percentage of active given).

Eighteen beagle puppies, one month old.

Methods:

Blood samples were taken from 3 four-week old beagle puppies in each of 6 litters. Each of the 3 puppies in 4 of the litters was fitted with an SD-8447 collar, while the 3 puppies in each of the remaining 2 litters was fitted with a placebo collar. All other puppies in the placebo and test group litters were also fitted with a placebo collar.

Blood samples were taken from the same dogs again 30 days later. The following individual blood chemistry determinations are reported as having been made on both samples:

Glucose	"Anongap" (an electrolyte balance?)	Cholesterol
Blood Urea Nitrogen	Alkaline Phosphatase	Triglycerides
Creatinine	Calcium	Total Bilirubin
BUN/CREA Ratio	Phosphate	Uric Acid
Sodium	Prothrombin	Aspartate Aminotransferase
Potassium	Aluminum (Albumin?)	Alanine Aminotransferase
Chloride	Globulin	Creatine Phosphokinase
Carbon Dioxide		Lactate Dehydrogenase

Results:

Mortalities in the first month were one control pup, one test pup, as well as a littermate (not being used in the study) of the dead test pup. Cause of deaths reported as pneumonia. Several other pups were medicated with Chloramphicol and recovered.

Although no statistical tests were run, there appear to be no significant differences between test and control animals with respect to blood chemistry parameters.