3-12-84

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

003686

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Hercon Flea & Tick Dog and Cat Collar

TO: Jay Ellenberger (PM-12)
Registration Division (TS-767)

FROM: Byron T. Backus
Toxicology Branch
HED (TS-769)

THROUGH: William Butler, Head
Review Section III
and
William Burnam, Chief
Toxicology Branch

Product: Baygon dog and cat collar
10% active ingredient

Registration # 8730-UG

Tox Chem # 508

Applicant: Hercon Division
Health-Chem Corp.

Action

Product is proposed for use as a dog and cat collar. Acute oral LD_{50}, dermal LD_{50}, primary eye and dermal irritation studies have been submitted, along with 44-day exposure dog and 30-day exposure cat cholinesterase activity studies.

Conclusion

The data received is inadequate to assess the potential risks which might be associated with the proposed product uses.

No information is provided as to the dermal sensitization potential of this product.

The material tested in the acute studies is not adequately described, as no information is provided as to how it was prepared (by grinding collars?), or why it is reported in the oral LD_{50} study as "a bicolored granular solid material which was sieved through a #40 mesh and wire screen" and as [redacted] requiring cutting with scissors) in the other acute studies. It should be confirmed that the material(TARC #G2039) tested in the oral LD_{50}

INFORMATION WHICH MAY REVEAL AN INERT INGREDIENT IS NOT INCLUDED

study is the same as that (Lot #G2039) used in the other acute studies.

The product as proposed for registration is 10.0% Baygon, but according to the analytical results the material tested in the acute toxicity studies assayed only 9.61% Baygon.

The dog cholinesterase study involved only 44 days exposure, while the product claims activity for up to 6 months. Since the study shows little or no cholinesterase depression, it can be accepted provided additional data are submitted demonstrating that the greatest rate of release of (highest level of exposure to) active ingredient occurs during the first 6 weeks the collar is worn. This can be done by measuring the Baygon content of 12 collars, 4 worn by dogs for 2 weeks, 4 for 4 weeks, and 4 for 6 weeks, and by samples of collars worn by dogs for a period of 4 to 6 months. There should also be analytical data as to the initial Baygon content of these collars.

There are a number of problems associated with the 30-day cat cholinesterase study. These include the following:

In the 3X and 5X groups the dose was calculated by measuring subjects' neck circumferences, and multiplying by 3 or 5. This amount of total collar length was applied as one continuous loop. The first loop was secured with a non-slip buckle, while the remaining length was wrapped ("stacked") on top of the first loop and held in place with a small amount of adhesive tape. With this collar arrangement it is unlikely that 3X and 5X subjects were receiving these exposure levels compared to one-collar animals. One-collar cats showed significant plasma ChE depression on days 7 and 30, and significant RBC depression on day 7. Since there was no significant depression noted for 3X or 5X cats, there is a question as to whether or not the higher dosage groups were even receiving as much exposure to Baygon as one-collar animals. Rate of release data from "stacked" collars as well as single collars would be needed to make this determination.

The study involved only 30-day exposure. The product has a 6-month efficacy claim, and the one-collar group is reported as showing significant plasma ChE inhibition at 30 days.

Although it is stated that significant ChE depressions occurred in the one-collar group, the percentages associated with these depressions are not reported. One subject (#104) in the one-collar group showed lower plasma ChE activities than other animals; it is not certain whether the statistically significant plasma ChE depressions in the one-collar group were due to this one subject.

One of the subjects in the control group developed an ear infection. Plasma ChE activities for this subject were lower than normal on days 7 and 14, but are nevertheless included as part of the control values. This may have had the effect of lowering

control values for plasma ChE activities on these dates.

Two of the subjects in the one-collar group were found to be positive for feline leukemia virus after the exposure period. No cholinesterase activities are presented for these subjects. The immediate question is whether in fact these animals showed any ChE depression relative to the other 4 animals in this group. The data should be reported.

Data Evaluation Report

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Compound: 10% Baygon dog and cat collar

Citation:

Morgan, J.M. Acute Oral LD_{50} in the Rat. Sample #G 2039. #112.001. Study conducted at Inhausen Research Institute, Inc. 111 East Drake, Suite 7111, Fort Collins, CO 80525. Dated 12-01-83. Received at EPA 01-11-84; in Acc. 252196.

Reviewed by:

Byron T. Backus 03-14-84
Toxicologist

Core Classification: Supplementary (upgradable). No information is reported as to how the test material was prepared from the proposed product.

Tox. Category: III

Conclusions:

The results of this study indicate a toxicity category III hazard potential by the oral exposure route. However, additional information is needed as to how the test material was prepared from the product, and why material designated TARC #G2039 is described as a bicolored granular material in this study while material designated as from Lot #G2039 is described as composed of [redacted] in the dermal LD_{50}, primary eye and dermal irritation studies.

With the additional information indicated above the study can be upgraded to core minimum data.

Materials:

Young adult Sprague-Dawley rats of both sexes, obtained from Charles River Breeding Labs, Wilmington, DE.

Test material identified as TARC #G2039, a bicolored granular solid material which was sieved through a #40 mesh.

Procedure:

Following a range-finding study, groups of 5M, 5F rats which had been fasted overnight were orally intubated with the test material in a corn oil suspension. Each dosing volume less than 2.26 ml was brought up to that volume by additional corn oil. Rats were observed for 14 days and then sacrificed. Body weights were taken prior to fasting, immediately prior to dosing, and on days 7 and 14. Necropsies were performed on animals which died, and on all others following sacrifice.

LD_{50} values for males, females and combined sexes were calculated by the method of Litchfield and Wilcoxon.

Results:

Dose (g/kg)	Mortalities/Rats Dosed M	F
1.00	0/5	0/5
1.26	1/5	0/5
1.59	1/5	1/5
2.00	0/5	3/5
2.52	2/5	4/5

All deaths occurred on the day of dosing.

Oral LD_{50} (M) reported as 3.00 g/kg with 95% C.L. of 2.56-3.51 g/kg
Oral LD_{50} (F) reported as 1.94 g/kg with 95% C.L. of 1.66-2.27 g/kg
Oral LD_{50} (combined) reported as 2.43 g/kg with 95% C.L. of 1.90-3.11 g/kg

Symptoms: all rats reported as showing excessive salivation, uncontrolled tremors and prostration. Most showed a decrease in motor activity. Additional observations included rails (sic), gasping, diarrhea, clonic and tonic convulsions (both together and separate), ruffled hair, fine body tremors, excessive bleeding from cut toenail, and squealing when touched.

Necropsies: findings in animals which died included dark and/or mottled lungs, fluid filled stomach, test material in stomach or small intestines. Findings in rats which were sacrificed at 14 days included small nodules on kidneys, black foci or dots on lungs, raised nodules on lungs. It is stated that findings for rats which were sacrificed at 14 days are commonly occurring in the Sprague-Dawley rat.

Data Evaluation Report 003686

Compound: 10% Baygon dog and cat collar

Citation:

Walter, M.K., Hansen, K.L. & Perry, J. Acute Dermal Toxicity Study Hercon Collar. Project No. 1980-C; dated 11-07-83. Study conducted at Elars Bioresearch Laboratories, Inc. 225 Commerce Drive, Fort Collins, CO 80524. Received at EPA 01-11-84; in Acc. 252196.

Reviewed by:

Byron T. Backus 03-14-84
Toxicologist

Core Classification: Supplementary (upgradable). No information is presented as to how the test material was prepared from the proposed product.

Tox. Category: III

Conclusions:

The dermal LD_{50} of the material tested is greater than 2 g/kg, indicating the dermal toxicity hazard potential is no worse than toxicity category III. Additional information is needed as to how the material tested was prepared from the proposed product.

Materials:

NZ white rabbits, M and F, from L.I.T. Rabbitry, Whitehall, Montana.

Test material, identified as Hercon Flea and Tick Collar 10%, Lot #G2039, composed of [redacted] Prior to testing, the [redacted] was cut into very small pieces with scissors, then mixed with ground-up particulate matter to form as homogeneous a mixture as possible.

Procedure:

A group of 5M, 5F received a 24-hr occluded dermal exposure to 2 g/kg. Test material was mixed with physiological saline solution. A concurrent control group was exposed to physiological saline only. All rabbits were observed for 14 days and then sacrificed. Necropsies were performed on all animals.

Results:

No mortalities. No systemic effects were observed. Erythema noted at application site for all animals; more pronounced in those exposed to the collar. All animals gained weight during the 14-day observation period. Necropsies indicated mild bronchopneumonia in lungs of 3/5 males in test group, 2/5 males in control group. One female in test group had light reddish-brown spots on skin at test site at 14 days.

Data Evaluation Report

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Compound: 10% Baygon dog and cat collar

Citation:

Walter, M.K., Hansen, K.L. & Rivoire, B.L. Primary Eye Irritation Study Hercon Flea and Tick Collar 10%. Project No. 1980-B; dated 10-12-83. Study conducted at Elars Bioresearch Laboratories, Inc. 225 Commerce Drive, Fort Collins, CO 80524. Received at EPA 01-11-84; in Acc. 252196.

Reviewed by:

Byron T. Backus 03-14-84
Toxicologist

Core Classification: Supplementary (upgradable). No information is presented as to how the test material was prepared from the proposed product.

Tox. Category: III

Conclusions:

The material tested is in toxicity category III by eye irritation potential. How this relates to the actual product hazard is unknown. No information is provided as to how the material tested was prepared from the product.

Materials:

NZ white rabbits from L.I.T. rabbitry, Whitehall, Montana.

Test material, identified as Hercon Flea and Tick Collar 10%, Lot #G2039, composed of [redacted] Prior to testing, [redacted] was cut into very small pieces with scissors, then mixed with ground-up particulate matter to form as homogeneous a mixture as possible.

Procedure:

100 mg of test material was instilled into the conjunctival sac of one eye of each of 9 rabbits. Three eyes were washed for one minute with lukewarm water starting 20-30 seconds after instillation. The remaining eyes were not washed.

Results:

Some irritation in 3/6 unwashed, 0/3 washed eyes. One unwashed eye showed some corneal opacity through 48 hrs. All eyes clear by 72 hrs.

Data Evaluation Report

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Compound: 10% Baygon dog and cat collar

Citation:

Walter, M.K., Hansen, K.L. & Rivoire, B.L. Primary Dermal Irritation Study Hercon Flea and Tick Collar 10%. Project No. 1980-A; dated 10-12-83. Study conducted at Elars Bioresearch Laboratories, Inc. 225 Commerce Drive, Fort Collins, CO 80524. Received at EPA 01-11-84; in Acc. 252196.

Reviewed by:

Byron T. Backus 03-14-84
Toxicologist

Core Classification: Supplementary (upgradable). No information is presented as to how the test material was prepared from the proposed product.

Tox. Category: IV

Conclusions:

The material tested is in toxicity category IV by dermal irritation potential. Additional information is needed as to how the material tested was prepared from the actual product.

Materials:

NZ white rabbits from L.I.T. Rabbitry, Whitehall, Montana.

Test material, identified as Hercon Flea and Tick Collar 10%, Lot #G2039, composed of [redacted] Prior to testing, [redacted] was cut into very small pieces with scissors, then mixed with ground-up particulate matter to form as homogeneous a mixture as possible.

Procedure:

0.5 g test material mixed with physiological saline solution was applied to 1 x 1 inch gauze patches back with occlusive wrapping. Four of these patches were applied to each of 6 rabbits, with 4-hr exposure.

Results:

All scores zero (no erythema and/or edema) at 5, 24 or 72 hrs.

Study Classification: Core Supplementary Data (no information as to how test material was prepared from the proposed product).

Product Classification: Tox. Cat. IV

Data Evaluation Report 003686

Compound: 10% Baygon dog and cat collar

Citation:

Schafer, J.H., Heimbichner, D.L. & Hansen, K. Hercon Flea and Tick Collar Test for Cholinesterase Depression in Dogs. Project No. 1981, dated 12-20-83. Study conducted at Elars Bioresearch Laboratories, Inc. 225 Commerce Drive, Fort Collins, CO 80524. Received at EPA 1-11-84; in Acc. 252196.

Reviewed by:

Byron T. Backus Byron T Backus 03-17-87
Toxicologist

Core Classification:

Core Supplementary Data (can be upgraded with additional data demonstrating that the greatest release rate occurs during the first six weeks).

Product Classification: N/A

Conclusions:

Under the conditions of this study, there was no indication of RBC cholinesterase depression observed in dogs wearing 1, 3 or 5 collars during a 44-day period. Dogs wearing 5 collars showed statistically significant plasma plasma ChE depression (approximately 12%) on day 3. Statistically significant 7% plasma ChE depression on day 30 may be indicative of a continuing slight effect, although no inhibition was observed on days 7, 14 or 44.

No behavioral or physical symptoms were observed indicative of ChE inhibition.

This study involved only 44-day exposure. The proposed product has a claim of 6 months. Since no cholinesterase inhibition was evident at 44 days, the study can be accepted provided rate of release data are submitted demonstrating that the highest exposure to Baygon (greatest release from the proposed product) occurs during the first six weeks. This can be done by measuring the Baygon content of 12 collars, 4 worn by dogs for 2 weeks, 4 worn for 4 weeks, 4 worn for 6 weeks, and by samples of collars worn by dogs for a period of 4 to 6 months. There should also be analytical data as to the initial Baygon content of these collars.

Materials:

Hercon flea and tick collars, lot #E3012, ostensibly 10% Baygon, assaying 11.08%.

Young mongrel dogs of both sexes "obtained from available sources."

Procedure:

Groups of 6 dogs (either 2M and 4F, or 4F and 2M) served either as controls (no collar), wore 1 collar, 3 collars, or 5 collars. All dogs were individually caged.

Dogs were observed from day -21 through day 44. There were four instances in which a dog removed a collar and it was refastened. On two other occasions the collar was chewed and had to be replaced.

All dogs were physically examined and body weights taken on days -14, 0 and 30.

Blood was collected from all dogs on days -14, -7, 0, and, following collar fitting, on days 1, 3, 7, 14, 30 and 44.

Cholinesterase determinations were performed the same day as blood was collected using an automated version of the Ellman method on a MCA centrifugal analyzer. This method was tested using a single oral dose (3.5 mg/kg) of parathion in one 12.35 kg healthy male beagle, with blood sampling at 0, 15, 30 and 45 minutes, and at 1, 2, 3, 4 and 6 hrs, and analyses for both RBC and plasma ChE activity on each sample.

Results:

There were no symptoms noted indicative of cholinesterase inhibition or any other toxicity. Emesis was observed in 3 dogs (1 control and 2 in the 1-collar group) on day 23, and diarrhea was observed in 1 dog in the 3 collar group on the same day.

With the exception of one dog in the control group, all dogs gained weight, although there were considerable variations as might be expected with mongrels.

Statistical analysis indicated significant differences (variations) in preexposure cholinesterase activities. Use of only day 0 values as a covariant adjustment provided the best fit with exposure data.

There was no evidence of any RBC ChE inhibition. There was slight (approximately 12%) but statistically significant plasma ChE depression in the 5-collar group on day 3, and another slight (about 7%) statistically significant plasma ChE depression in the same group on day 30.

Data Evaluation Report

003686

Compound: 10% Baygon dog and cat collar

Citation:

Schafer, J.H., Heimbichner, D.L., & Hansen, K. Hercon Flea and Tick Collar Test for Cholinesterase Depression in Cats. Project No. 1983, dated 01-04-84. Study conducted at Elars Bioresearch Laboratories, Inc. 225 Commerce Drive, Fort Collins, CO 80524. Received at EPA 01-11-84, in Acc. 252196.

Reviewed by:

Byron T. Backus 03-1787
Toxicologist

Core Classification: Supplementary Data

Product Classification: N/A

Conclusions:

There are a number of problems with this study.

In the 3X and 5X groups the normal length of one collar was determined by measuring subjects' neck circumferences, multiplying by 3 or 5, and applying the total collar length as one continuous loop. The first loop was secured with a non-slip buckle, while the remaining length was wrapped ("stacked") on top of the first loop and held in place with a small amount of adhesive tape. With this type of collar fitting it is unlikely that 3X and 5X subjects were respectively receiving these exposure levels. Statistically significant plasma ChE depression was noted in 1-collar animals for all readings taken in the period from day 7 through day 30, and there was statistically significant RBC ChE depression in this same group for day 7. Since there was no significant depression noted for 3X or 5X cats, there is a question as to whether or not the higher dosage groups were even receiving as much exposure to Baygon as one-collar animals. Rate of release data from "stacked" collars as well as normal proposed-use collars would be needed to make this determination.

Two cats in the 1 collar group were found to be infected with feline leukemia virus at termination. The cholinesterase activities from these two subjects are not reported, reducing the number of animals in this group to four. The immediate question is whether the data from these two animals was that different from the other members of this group.

One subject (#104) in the 1 collar group showed considerably lower plasma plasma ChE activity than the remaining 3 members during the exposure period. It is not certain whether the statistically significant plasma ChE depressions were due to the values obtained from this single animal.

The control group consisted of 5 females and 1 male; all exposure groups consisted of either 2 males and 4 females or 3 males and 3 females. One of the subjects in the control group (#105) is reported as suffering from an inner ear infection from days 10 through 30. This particular individual showed

comparatively low plasma ChE activitities on days 7 and 14.

There was an outbreak of ringworm infection involving nine of the 24 cats, requiring treatment with Tinavet and Benzospore (noted as not being cholinesterase inhibitors). With the exception of the one cat most severely affected with feline leukemia virus lesions were minor and regressing by day 30.

The study involved only 30-day exposure. The product has a 6 month efficacy claim. Animals in the 1X group were apparently still showing a statistically significant plasma ChE depression at 30 days. It is not reported what this level of plasma ChE depression was.

Materials:

Hercon flea and tick collars, lot #E3012, assaying 11.08% Baygon.

Twenty-four cats, with both sexes represented, "obtained from available sources."

Procedure:

Groups of 6 cats served either as controls (no collar), wore 1 collar, or wore the equivalent of 3 or 5 collars fastened around the neck. Smaller animals were used as controls or in the 1-collar group; larger animals were used in the ostensibly 3X and 5X groups.

Because of the physical limitations of neck size, measurements were made of the cats' neck circumferences. This length was multiplied by 3 or 5, and the total length was applied as a continuous strip around the neck. The first loop was secured with a non-slip buckle, while the rest of the collar was wrapped on top of the first loop and secured with adhesive tape.

Collars were fitted on day 0 and were worn for 30 days. Animals were physically examined and weights recorded for days -14, 0 and 30. Cats were observed daily. When individual cats managed to loosen or remove a collar it was refastened.

Blood samples were taken from all animals on days -14, -7, 0, 1, 3, 7, 14 and 30, and plasma and RBC cholinesterase activities were assayed using an automated version of the Ellman method of a MCA III centrifugal analyzer.

Results:

No symptoms of toxicity were observed which could be ascribed to exposure to the collars.

There was an outbreak of ringworm infection in 9/24 animals requiring treatment with Tinavet and Benzospore, noted as not being cholinesterase inhibitors. With the exception of one subject (see below) these lesions were regressing or had resolved by day 30.

Two cats in the one-collar group were tested and found to be positive for feline leukemia virus shortly after study termination. Both had weight losses

Propoxur Toxicology Reviews

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Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

X A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

___ The document is a duplicate of page(s) _____