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

009403

APR 3 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id Nos.: 000059-00195 (EXPAR 3.2% EC), 000059-205 (Expar Creme Rinse For Dogs), 000059-00231 (EXSPOT For Dogs). Permethrin: Submission of a domestic animal safety study.

TOX CHEM No.: 652BB
PC No.: 109701
TOX PROJECT No.: 1-1999, 1-2289, 1-2390
Submission No.: S401066, S400694, S402720

FROM: John Doherty 3/31/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: George LaRocca
Product Manager #15
Registration Division (H7505C)

THROUGH: Marion Copley, DVM, Section Head 3/31/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

No additional domestic animal safety studies are required at this time for the products EXSPOT For Dogs (EPA Id# 000059-00231), EXPAR 3.2% EC (EPA Id No.: 000059-00195) and EXPAR 3.2% EC (EPA Id No.: 000059-00195).

Issues related risk assessment for humans handling these products and possible carcinogenicity to domestic animals will be addressed separately.

II. Action Requested

The Cooper's Animal Health Company has submitted a domestic animal safety study with their product EXSPOT For Dogs (EPA Id No.: 000059-00231). The registrant proposes to use this study to support the registration of two other products designed for use on dogs to control fleas and ticks. The study was reviewed and a copy of the DER is attached. Each of the three products is addressed as follows.

III. Toxicology Branch Comments

1. EXSPOT For Dogs (EPA Id# 000059-00231).

The domestic animal safety study (see below and attached DER) was conducted with this product. Thus, the study can be used to support the registration of this product.

2. EXPAR Cream Rinse for Dogs (EPA Id No.: 000059-00205).

This product is a shampoo like product containing only 0.5% permethrin. The product was tested in cats and no adverse effects were noted when the product was applied at a rate of 4 and 16 ml/cat (MRID No.: 413638-01, refer to HED document No.: 8216). TB-I does not consider that additional testing to demonstrate the safety of this product to dogs is required. The study with cats and the study attached with 65% permethrin support the safety of this product to domestic animals.

The product labelling will have to be changed to state more clearly the amount that should be applied to dogs per treatment. This should be derived from the formula 4 ml/cat or one teaspoon/cat. For example, if a cat weighs 2 kg (about 5 lbs), the instructions for dogs should be apply at a rate of one teaspoonful for every five pounds of dog weight.

The label for dogs must also clearly state that the product should not be applied more frequently than once every seven days.

3. EXPAR 3.2% EC (EPA Id No.: 000059-00195).

This product is an emulsifiable concentrate which will be diluted at a rate of 2 fluid ounces per gallon of water. The dogs will either be dipped into the solution or the solution will be swabbed or sponged onto the dog. The amount of permethrin in contact with the dogs is substantially less than the amount that was applied for the EXSPOT product (DER attached). Since the product will be applied in water, TB-I does not consider it necessary to conduct additional safety demonstrations in dogs for

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This issue was addressed in a 8/12/91 memo for this product. The conclusions in the 8/12/91 memo are appropriate. The product labelling need not have to be changed as suggested in the 4/3/92 (this) memo. Adm Petter 4/7/92

this product.

4. Study Reviewed

Study Identification	TB-I Comments
85-2. Domestic animal safety study - dogs. Coopers/Pitman-Moore, Study No.: P151-53-91, May 21, 1991. MRID No.: 419532-0[illegible] ACCEPTABLE	Treatment with 4X the recommended usage rate did not result in effects in treated pregnant dogs or puppies of different breeds. Note: The registrant should be advised of the deficiencies listed on page 3 of the DER so that future domestic animal safety studies will be conducted in a more appropriate manner.

Reviewed by: John Doherty 11/7/91 009403
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: William Greear 11/7/91
Section IV, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 85-2. Domestic animal safety study - dogs (pregnant and puppies)

MRID NO.: 419532-0[illegible] TOX. CHEM. NO.: 652BB
PC. No.: 109701

TEST MATERIAL: EX-spot (Permethrin 65% w/w)

STUDY NUMBER(S): P151-53-91

SPONSOR: Coopers/Pitman-Moore, Inc. (Coopers Animal Health, Inc.)

TESTING FACILITY: Coopers/Pitman-Moore, Inc, Neely Kennel and Reynolds Kennel.

TITLE OF REPORT: "Target Animal Safety Study of a 65% Permethrin Spot-On Formulation in Pregnant Bitches and Nursing Puppies".

AUTHOR(S): D.L. Salsbury and J.E. Dyer

REPORT ISSUED: May 21, 1991

STUDY DATES: December 13, 1990 to May 21, 1991. (Note: The Quality Assurance report (page ii) incorrectly states the date of the "final study" inspection as "05/21/90" but the report was signed 5/21/91. Since the study was initiated on 12/13/90, the correct date should be 05/21/91.

CONCLUSIONS:

Treatment with 4x the recommended usage rate did not result in effects in treated pregnant dogs or puppies.

Classification: ACCEPTABLE. No additional domestic animal safety study on dogs is required for the product EXSPOT for Dogs at this time.

Quality Assurance Statement: Provided. Signed by J.E. Dyer dated 5/21/91.
Good Laboratory Practice Statement: Provided

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REVIEW

The basic study design consisted of dosing a total of 17 supposedly pregnant dogs (ages ranging from 3 to 7 years old and weighing generally from 47 to 93 pounds) with either the test material applied at 4x the recommended usage rate or with the formulation inerts of the product (control group). No information regarding prior treatment such as vaccinations and flea treatment was provided. Three dogs were dropped from the study (two in the control group and 1 in the EXSPOT treated group) because they were either not pregnant or dystocia/poor mothering resulted in loss of litter. Application of the test material was conducted by applying 4 ml along the shoulder midline for dogs under 33 pounds. For dogs over 33 pounds, an additional 4 ml were applied at the midline at the hips. The control animals (treated with formulation inerts) were similarly dosed with either 1.4 ml or an additional 1.4 ml in the region of the hips. It should be noted that the pups (which weighted 1.7 to 4.4 pounds) all received 4 ml of the test material or 1.4 ml of the inerts solution. It is also noted that this application rate is consistent with treatment at 4x the label usage rate which states 1 ml for dogs less than 33 pounds and 2 ml for dogs greater than 33 pounds. The number and breed of pregnant dogs and puppies used in this study for the EX-spot treated group and for the control treated group is illustrated in Table 1 below.

Table 1. Distribution of dogs.

Breed	Group 1 (EX-spot)	Group 2 (Controls)
Collie		1/8[1]
Coonhound	1/3	1/7
Foxhound	2/16	1/11
Greyhound	5/24	2/12
Labrador		1/9
Total	8/43	6/47

1. Numerator = number of bitches/denominator = number of puppies.

The pregnant females were treated 4 to 21 days prior to whelping (with the exception of one Collie dog which was treated only one day prior to whelping). The exact day of breeding was not available for all dogs. The puppies and bitches were treated at days 10-19 following the whelping date. Following treatment the bitches and puppies were monitored for signs of reaction including dermal irritation by the kennel operators or caretakers or owners. Treatments and weekly observations were conducted by the attending veterinarians. For some dogs individual

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observations were made. For others, the observations were made as a group.

Results.

No signs of dermal irritation were noted in the treated dogs or puppies. Body weight for the bitches only was reported as normally maintained. Inspection of the individual animal data sheets indicated that most dogs were only weighted twice (at the time of compound application). Thus the comments provided by the study report on maintaining body weight are not actually backed by weighings. There were no effects reported on food or water intake or bowel movement conditions. There were no indications that the treatment initiated delivery or that the puppies were affected by the treatment on delivery. No signs of irritation in the pups were reported.

Conclusion.

This study is ACCEPTABLE.

Discussion. This study was conducted by dog owners and not all the observations were made by a single individual to assure a uniform comparison. The individual animal observations are presented in handwritten form. The dogs were not all treated during the same periods of gestation. The potential for permethrin to cause fetal toxicity or developmental toxicity is not an issue in this study since there are developmental toxicity studies in rats and rabbits on file in the Agency. The body weight of the bitches was not monitored except at time of application of the material so that the comments on maintaining body weight are subjective observations. The study used the inerts in the formulation to treat the control dogs. This is not considered an appropriate procedure since the the inerts in the formulation may cause irritation or effects when the active ingredient is know to be of low toxicity. It is also noted that the person signing the Quality Assurance Statement was also an author of the paper.

Although there are deficiencies in the study as noted above, the study, however, did not indicate that the pregnant dogs or their puppies developed adverse effects due to permethrin treatment (as EX-spot). Thus, the study is considered ACCEPTABLE for regulatory purposes.

The registrant, however, should be advised of the deficiencies listed above so that future domestic animal safety studies will be conducted in a more appropriate manner.