



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

February 9, 1999

MEMORANDUM

SUBJECT: Secondary Review of DERs for Companion Animal Safety Studies

DP Barcodes: D252334; D252474

PC Codes: 109701, 129032, 069001, 128722, 067501, 057001, 106201

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer
Reregistration Branch I, Health Effects Division (7509C)

Virginia A. Dobozy 2/9/99

TO: John Redden, Branch Senior Scientist
Technical Review Branch, Registration Division (7505C)

Action Requested: Provide secondary review of DERs for MRIDs 44128307C, 44128308C and 44527902

Recommendation: The HED Companion Animal Safety Committee met on February 3, 1999, to discuss the above DERs. See attached minutes of that meeting.

Memorandum of Companion Animal Safety Committee Meeting - February 3, 1999

The following DERs prepared by the Technical Review Branch, RD, were discussed.

1) DP Barcode: D249947; MRID Number: 44128307C; PC Codes 109701, 129032

Study Title and Number: Safety - INS 48 2; PLRS 9560

A permethrin-pyriproxyfen shampoo (permethrin, 1.006%; pyriproxyfen, 0.252%) was applied one time (contact time of 5 minutes) to a group of 2 male and 4 female mixed breed puppies approximately 9 weeks old. The mean dose rate was 37.7 g/kg equivalent to 379.5 mg/kg permethrin and 95.1 mg/kg of pyriproxyfen. With a target safety factor of 5x, this dose rate would support a maximum label rate of 7.5 g/kg or 0.6 fl oz/lb body weight of the formulated product. Controls were treated with water. Hematology and clinical chemistry parameters were measured at Days -14, 1 and 7. Animals were observed for 7 days post-treatment. There were no treatment-related changes in any of the parameters.

The DER notes that the study was conducted before the publication of the Companion Animal Safety Study Guidelines. It does not meet the guideline requirements in the number of animals and in the timing and length of post-treatment observations. However, these deviations are not considered to be critical and the study was classified as Acceptable.

CAS Committee Comments/Recommendations

The CAS Committee agrees with the DER and study classification. However, the Committee noted that there were subtle clinical signs indicating that some of the animals may not have been healthy prior to treatment. Three of six puppies in Group A (treated) were reported to have ocular discharges. Three of six Group B puppies had loose feces; one of these also had an ocular discharge. See additional comments about the health of animals from this laboratory in the review of the kitten study below.

A label for the tested product was not included with the DER. Therefore, no conclusions can be made about the correlation between the study and the product label. The label which was included is for a single ingredient pyriproxfen (0.01 a.i.), whereas the tested product contained a combination of permethrin (1.006% a.i.) and pyriproxfen (0.252%). Assuming that the label for the combination product will be the same as the single ingredient product, the study did not mimic the treatment in that the label recommends the lather stay in contact with the skin for 10 minutes, whereas a 5 minute contact period was used in the study. The dose on the single ingredient product label is 1 tablespoon for each 5 lbs (7.5 g/kg), which is supported by the study. The label for the combination product should not exceed this dose. The combination label should also follow PR Notice 96-6.

2) DP Barcode: D249947; MRID Number 44128308C; PC Codes: 069001, 129032, 128722, 067501, and 057001

Study Title and Number: Safety - INS 54.3; PLRS 9561

A combination pyrethrin-pyriproxyfen shampoo (pyrethrins, 0.15%; pyriproxyfen, 0.25%; prallethrin, 0.15%; piperonyl butoxide, 1.5%; n-octyl bicycloheptene dicarboximide, 1.5%) was applied one time to a group of 2 male and 3 female kittens (= 9 weeks old) at a dose rate of 50 g/kg, reported to be equivalent to 5x the recommended label rate of 10 g/kg. Controls were treated with water. Hematology and clinical chemistry parameters were measured at Days -14, 1 and 7. Animals were observed for 7 days post-treatment. There were no treatment-related changes in any of the parameters. One kitten in the treated group was observed shaking its hind leg at 2 hours after treatment, otherwise there were no treatment-related changes in the parameters.

The DER notes that the study was conducted before the publication of the Companion Animal Safety Study Guidelines. It does not meet the guideline requirements in the number of animals and in the timing and length of post-treatment observations. These deviations were not considered critical. However, the kittens were treated with a medication for a *Coccidia* infection prior to and on the day of the shampoo application. The DER concludes that the study is unacceptable because of this concomitant exposure.

CAS Committee Comments/Recommendations

1. The CAS Committee agrees with the DER study classification. Page 159 of the study report shows that the anthelmintic medication was given on December 12, 1995, the day of treatment with the shampoo.
2. The shaking of the hind leg two hours after treatment was dismissed as a possible clinical sign of toxicity in the DER. However, this behavior has been reported in association with pyrethrin exposure in cats. In an article from the National Animal Poison Control Center, it was reported that cats occasionally exhibit ear flicking, paw shaking and repeated contractions of the superficial cutaneous muscles after treatment with pyrethrins.¹ These clinical signs may result from agitation or from topical stimulation of peripheral sensory nerves in the skin. Therefore, a 5X Margin of Safety may not have been established in this study.
3. As noted in the DER, there is a question about whether the tested formulation contained prallethrin or not. It is included in the formulation on pages 8 and 47, but not on page 41.

¹ Hansen SR (1995) Management of Adverse Reactions to Pyrethrin and Pyrethroid Insecticides. In: Bonagura JD (ed) Kirk's Current Veterinary Therapy XII Small Animal Practice. Philadelphia, W.B. Saunders Company, pp. 242-248.

4. No label for this combination product was supplied with the DER. However, since the study is unacceptable, no comments are required.

5. The Committee noted that other studies from this laboratory have been found unacceptable because the animals were not healthy or because concomitant treatment was given during the study.

3) DP Barcode: D247419; MRID 44527902; PC Codes: 106201, 129032

In this study, 1, 3 or 5 Amitraz-pyriproxyfen collars (Active Ingredients: Amitraz, 9%, pyriproxyfen, 0.5%) were fitted to groups of 6 male and 6 female beagle dogs, 11-12 weeks old. Controls were each fitted with 5 collars without active ingredients. Blood samples were obtained on Day -6 (pretreatment) and on Days 1, 7, 14, and 30 for hematology and clinical chemistry measurements. Animals wore the collars for 30 days and the study was terminated after removal of the collars.

No mortality was observed and the only reported clinical sign in any animal receiving the test substances was a yellow nasal discharge in one male in the group wearing 3 collars with the active ingredients. This clinical sign was not considered to be treatment related. There were no treatment-related effects on body weight, food consumption, hematology, or clinical biochemistry, except for a dose-related increase in glucose levels in the test animals. Pretest means for glucose levels were essentially the same for all groups. On Day 1 overall means for the 1X, 3X and 5X groups were respectively elevated by 5.2%, 10.0%, and 17.0% relative to controls. The corresponding elevations on Day 7 were 20.3%, 18.6% and 26.3%. For Day 14: 7.5%, 17.5% and 16.7%; for Day 30: 7.4%, 10.4% and 17.9%. Examination of individual data shows that on Day One 1/6 3X males, 1/6 5X males, and 2/6 5X females had glucose levels > 200 mg/dL, as did 2/6 5X females on Day 7. These were the only occasions when individual glucose values >200 mg/dL were observed in this study.

A search of the tox one-liners indicates that the Agency has previously received studies (MRIDs 00044591, 00040336, 00028716 and 00040345, 00029972 and 00040865, 00030493 and 00040856) in which hyperglycemia was observed in dogs and rabbits following oral or dermal exposure to relatively low levels of Amitraz or Amitraz-containing formulations.

CAS Committee Comments/Recommendations

1. The Committee agrees that a 5X Margin of Safety was not achieved in the study. However, the study is acceptable to support registration provided a statement is added to the label regarding the observed hyperglycemia following the use of the product at five times the recommended dose. Based on the use of appropriate labeling, it would not be necessary to redo the study.

2. Amitraz (19.9%, trade name Mitaban™) is approved by the FDA as a veterinary drug for use

in the treatment of demodectic mange in dogs. The label for this product notes that hyperglycemia was observed four hours post-treatment during the clinical trials at the recommended dose.

Prepared by: Virginia A. Dobozy, V.M.D., M.P.H., RRB1, Health Effects Division