BL-1329
TXB-2282

Memorandum

Date: 15 November 1982

002282

Subject: EPA File Symbol: 2724-EOO ZOECON COLLAR RF-160 FOR CATS
Caswell #219AA

From: B. T. Backus
IRB/TSS

To: Mr. Jay Ellenberger
Product Manager 12

Applicant: Zoecon Industries
12200 Denton Drive
Dallas, TX 75234

Active Ingredient:
Chlorpyrifos.....4.00%
Inert Ingredients:.....96.00%

Background:

Product is a cat collar. A 300-day cholinesterase study was previously reviewed (B. Backus, 14 June 1982). At that time, it was indicated that there was concern about the relatively high level of plasma ChE depression seen, which was apparent even in the animals wearing 1 collar (proposed product use exposure level) which exhibited more than 77% plasma ChE inhibition. Additional data have now been sent in for review, including (received October 4, 1982) information on the subjects and their previous exposure(s) to pesticides.

Comments and Recommendations:

1. Review of the subject ages indicates many fairly young cats. The oldest is designated as 8+ years. Further, some of these subjects had previous exposure to cholinesterase inhibitors, so that there may have been inadvertent selection since, if any of these cats had become sick or ill in these prior studies they might have been discarded and so been unavailable for this study. Given this background, and the high level of plasma ChE inhibition (77%) seen in even subjects at the 1X (use exposure level), this reviewer does not consider the safety of this product proven.

2. The Agency is currently in the process of developing guidelines as to acceptable levels of cholinesterase (both plasma and RBC) inhibition levels in pets that would result from exposure to products containing cholinesterase inhibitors. It is this reviewer's understanding that the 77% plasma ChE inhibition seen in subjects at the use exposure level would be unacceptable.

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3. Cats at the use exposure level showed approximately 14% RBC ChE activity. Although it was previously stated (14 June 1982) that this was acceptable, it may be that even this figure would be considered unacceptable in the eventual guidelines.

4. Given the above considerations, this reviewer cannot recommend for the registration of this proposed product.

Byron T Backus 11/15/82

Byron T. Backus
IRB/TSS

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002282 In 4-14-82

(14)

Memorandum

Date: 14 June 1982

Subject: EPA File Symbol: 2724-EOO ZOECON COLLAR RF-160 FOR CATS In 07-01-82
Caswell #219AA

From: B. T. Backus
IRB/TSS

To: Mr. Jay Ellenberger
Product Manager 12

Applicant: Zoecon Industries
12200 Denton Drive
Dallas, TX 75234

Active Ingredient:
Chlorpyrifos.....4.0%
Inert Ingredients:.....96.0%

Background:

Product is proposed for use on cats. The submission includes a 261-day in progress cat cholinesterase study.

Comments and Recommendations:

1. The 261-day study shows a dramatic reduction in plasma CHE activity in all groups of cats exposed to chlorpyrifos. In the 1X group this reduction was approximately 78% relative to controls. In the 3X and 5X groups plasma CHE was, as expected, reduced even further, and these subjects showed respectively 15.4 and 12.9% of normalized control activity in the period 4-261 days (without days 57 and 64). This activity was reduced even further for these groups in the period from 84 to 261 days (to 9.1% and 8.9% respectively).

2. Although reduction in RBC CHE activity occurred in all exposed groups, it was to an acceptable level (maximum reduction was about 30%, seen in the 5X group).

3. Subjects tested were common variety cats, with no breeds such as Persians or Burmese, which may tend to be more susceptible to cholinesterase inhibitors.

4. Some of the subjects used in the 261-day study (#294, 287 of the controls; #288 of the 1X group; #292 and #295 of the 5X group) had been previously exposed to chlorpyrifos in the kitten dermal toxicity study.

5. The cat consistently showing greatest plasma CHE depression in the 5X group was subject #292, noted to have lesions and hair loss around the neck at day 8, the condition subsiding about day 17. Although stated to be from a litter exhibiting hypersensitivity, this cat had not shown these effects in the kitten dermal toxicity study.

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6. Since the physiological significance of plasma CHE is not fully understood, some caution appears to be appropriate in accepting a product of this nature. What was tested was a 4.4% (label declaration: 4.0%) chlorpyrifos collar; IRB/TSS recommends reduction of the label declaration to 3.2% (which would allow a maximum amount of 3.5% chlorpyrifos in this collar).

7. In the Kitten Dermal Toxicity study it is reported (page 1) that the study was initiated November 13, 1980, and terminated Feb. 19, 1981. However, the data sheet indicates the study began Oct. 13, 1980 and the study is declared to be a 4-month study. This point should be clarified.

8. IRB/TSS would have no objection, on the basis of hazards to humans and domestic animals, to the conditional registration of this product containing no more than 3.5% chlorpyrifos (when overformulated) with the following additional label revisions as indicated below.

Labeling:

1. Labeling should state that the product contains a cholinesterase inhibitor, and that atropine by injection is antidotal only if symptoms of cholinesterase inhibition are present.

2. Labeling should specify that this product is not to be used on nursing cats, or on kittens of less than 3 months age.

Review:

The following studies were conducted at Zoecon Industries R. & D. facilities, 12219 Ford Road, Dallas, TX. Studies were received 4-7-82, and are in Acc. 247202.

1. Subacute Dermal Toxicity - Kitten. Report No. TR-727; dated Feb. 23, 1981.

   Procedure: Groups of 2-3 kittens (4-5.5 months old at start) were either controls (wore no collars), received 2X expected exposure (wore 2 collars), or 3X expected exposure (wore 3 collars), or 3X expected exposure plus a label dose of an anti-helmintic. Cats were observed for a 4-month period, with recollaring every 21 days.

   Results: No symptoms. Kittens remained apparently healthy.

   Study Classification: Core Supplementary Data

2. Acute Oral LD50 - Cat. Report No. TR-811; dated Dec. 21, 1981.

   Procedure: Initially, 3 cats were fed 8 or 9 mineral oil-lubricated pieces of a 5 cm segment of collar. Collar pieces were recovered from cat litter boxes and analyzed to determine how much chlorpyrifos had been absorbed [redacted] Subsequently, groups of 3 cats received, by gelatin capsule, oral dosage levels of either 97 or 45 mg/kg technical chlorpyrifos.

   Results: Initial samples of collar contained 16.3 mg chlorpyrifos/cm; losses ranged from 3.62 to 5.21 (22.2 to 32.0%) mg/cm, with average loss of 4.31 mg/cm

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(= 26.4%). Subjects (1M, 2F) fed a dosage level of 97 mg/kg chlorpyrifos were all dead 3-7 days after dosage, with symptoms (emesis, diarrhea, hypersalivation) characteristic of CHE inhibition. Subjects (3F) receiving 45 mg/kg all survived, but all exhibited symptoms of CHE inhibition. Oral LD50 (cat) = probably between 45 and 97 mg/kg.

Study Classification: Core Supplementary Data (insufficient number of animals, only two dosage levels, mostly females used)

3. Cholinesterase - 261 Day Dermal (Collar) - Cat. (Interim Report).

Procedure: Groups of 2M, 2F cats (except 3X group - 3M, 1F) were exposed to no collars (controls), 1 collar each (1X group), 3 collars each (3X), or 5 collars (5X). Period of exposure was for 261 days (study continuing on past that date). Blood samples were taken at -55, -49, -47, -45, -13 and at 0 days before collars were placed on cats, and at 1, 2, 4, 8, 11, 15, 17, 23, 29, 36, 43, 50, 57, 64, 85, 113, 141, 169, 200, 227 and 261 days after collars were placed on cats. Blood samples from each animal at each time were analyzed for plasma and RBC CHE activity. Electrode errors reported for readings at -55, -49, 57, and 64 days. RBC activities lost at 11 days.

Results:

PLASMA CHE ACTIVITY - NORMALIZED ACTIVITY

GROUP	Av. days 4-261 / Av. days -47 to 0	Av. days 4-261 w/o 57,64 / Av. days -47 to 0	Av. days 84-261 / Av. days -47 to 0
Controls	1.000	1.000	1.000
1X	0.217	0.224	0.215
3X	0.145	0.154	0.091
5x	0.131	0.129	0.089

RBC CHE ACTIVITY - NORMALIZED ACTIVITY

GROUP	Av. days 4-261 / Av. days -47 to 0	Av. days 4-261 w/o 57,64 / Av. days -47 to 0	Av. days 84-261 / Av. days -47 to 0
Controls	1.000	1.000	1.000
1X	0.848	0.863	0.916
3X	0.707	0.737	0.743
5X	0.686	0.712	0.692

Cat in 5X group (#292) developed small lesions and hair loss around neck on day 8, the condition subsiding around day 17. "This cat is of a litter which has exhibited sensitivity and/or skin allergy to any type of collar." This cat had been previously used in the kitten dermal toxicity study, and had not been reported to show any dermal effects in the course of that study. This subject showed the lowest plasma CHE activity in the 5X group in the period after day 15. No other signs of toxicity due to collars noted; no evidence of CHE inhibition (other than plasma, RBC CHE activities).

Study Classification: Core Minimum Data (ongoing; additional data relative to recovery will be sent in later).

Byron T. Backus 9/14/82

Byron T. Backus
IRB SS