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

12/1/83

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MEMORANDUM

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Registration No. I0182-18. Review of a 1 year dog dosing study with the synthetic pyrethroid permethrin.

TO: T. A. Gardner, PM #17  
Registration Division (TS-767)

Tox Chem No. 652EB

Background:

The ICI Americas, Inc. has submitted a 1 year dosing study with the synthetic pyrethroid permethrin. The study was reviewed as below.

Recommendations:

The study was reviewed and found to be CORE GUIDELINES. The NOEL for this study has been set at 5 mg/kg/day. Since the ADI is being determined using a NOEL of 5 mg/kg/day based on a 2 year rat study, no change in the ADI will be required as a result of this new dog oral dosing study.

Review of Study

A. Permethrin: One year oral dosing study in dogs.

ICI, Central Toxicology Laboratory TL #CTL/P/647, February 24, 1982, EPA Accession No. 250845, Tab 43C.

B. The test material used for this study was permethrin (3-phenoxybenzyl (+) cis:trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate). It was supplied by the ICI Co. and was from lot numbers 8-12 and 14-20. It was stated that the "nominal total permethrin content" was 92.5%. The nominal isomer content was stated as being 32.3% cis and 60.2% trans.

C. The test animals used were beagle dogs which were 15-22 weeks old when obtained from the supplier (ICI Alderly Park). They were allowed to acclimatize to the CTL for a period of 4 weeks. The dogs were prepared by vaccinations and wormed. Four groups of 5 males and 6 female dogs were prepared as

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groups receiving either 0, 5, 100 or 1000 mg/kg/day of permethrin in gelatine capsules (10 ml size). The group which received 1000 mg/kg/day was originally dosed with 2000 mg/kg/day for 2 days. The dose level was dropped because of the obvious reactions to the test material. The dogs received varying amounts of corn oil depending upon the dose level. For example, the low and mid-dose group dogs and control dogs received 0.5 ml/kg but the high dose group dogs received at first 3 ml/kg and later 1.5 ml/kg. Sometimes it was necessary to administer two or three capsules per day to the dogs receiving the high dose. The test sample was adjusted to compensate for the 92.5% purity of the test material.

- E. Survival: There were no mortalities. The dogs that were initiated in this study at 2000 mg/kg dose level were reported as showing severe signs of reactions and the dose level was reduced to 1000 mg/kg. The dogs dosed with 1000 mg/kg of permethrin exhibited tremors, incoordinated gait, "nervous" and convulsions, also excessive salivation and vomiting. Four of the dogs receiving the highest test dose showed a generalized loss in condition. No signs of neurological disturbance were reported in the low and mid-dose test group dogs. A NOEL of 100 mg/kg/day was assigned for induction of clinical signs.
- F. The body weight gain was reported as being adversely affected for the dogs in the high dose test group (male and females). The mid-dose test group was occasionally lower in body weight gain. Owing to the differences in initial body weight and small sample size, TB considers that only the high dose test group was affected. Consistent with the reduced body weight gain, there was reduced food consumption in the high dose test group. Water consumption was not measured.

NOEL for body weight loss is 100 mg/kg.

Note: For sections G and H below, blood samples were taken preexperimentally and at weeks 4, 8, 12, 16, 20, 26, 39 and 52. Samples were taken from the jugular vein prior to feeding.

- G. Hematology. The following parameters were assessed at the times indicated above: hemoglobin, hematocrit, and blood cell count, mean cell volume, mean cell hemoglobin, (and concentration), total and differential white cell count, platelet count, kaolin-cephalin and prothrombin time. Also, bone marrow aspirates obtained from the iliac-crest puncture (at weeks 26 and 52) were taken and stained using Romanowsky's stain. Of these parameters the following showed signs of being affected by the test material.

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Red cell count: On one occasion the male or female groups receiving 100 mg/kg were reduced. On one occasion the female group receiving 1000 mg/kg was reduced. Reductions were of the order of 6-8%. Because of a lack of consistency, TB does not conclude that this response is a direct result of the test material.

Mean Cell Volume: The values tended to be slightly increased for the high dose test groups and only on one occasion in the mid-dose test group (2-3%).

Platelet Count: Both the males and females showed rather consistent dose related increases in the platelet counts. For example at week 52 the data for both sexes were +3.3%, +18.6% and +21.5%. Because of the dose response and consistency in the high dose test group being higher, an apparent effect of permethrin on platelet count may be factual. However, inspection of the raw data indicates a wide variation in the individual determinations. Thus, TB considers that at the high dose group only is there a possible effect on the platelets and this effect may be more likely due to the trauma rather than a specific blood effect of the test material.

Prothrombin times were elevated slightly in the high dose test group only 6-7% and the differences are not considered toxicologically significant by TB.

A NOEL of 100 mg/kg is set for hematology. At 1000 mg/kg an increase in platelet count is evident and is conservatively attributed to either a direct or more preferably an indirect effect of permethrin.

H. Clinical Biochemistry: The following parameters were examined: urea, glucose, triglycerides, albumin and total protein, cholesterol,  $Ca^{++}$ ,  $K^+$ , alkaline phosphatase, alanine transaminase, aspartate transaminase, and creatine kinase. Of these parameters the following showed statistically significant possible effects of the test material:

$K^+$  - occasionally depressed especially among the males in the high dose test group (7-8%) not considered by TB to be toxicologically significant.

$Ca^{++}$  - consistently depressed especially for males in the high dose test group ( 5%) and occasionally in the mid dose test group ( 3%). Occasionally, the females were also depressed ( 4%).

Alkaline Phosphatase: was increased for both males and

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females at the mid (216% group, 234% for males and 199% for females), and high dose level (393% group, 477% for males and 320% for females). The low dose test group was also slightly higher but statistical significance was not attained (24% group; -4% for male and +45% for females). Albumin: decreases in the high dose test group for both males and females ( 20%).

Total protein: decreases in the high dose test group ( 9%).

There were other parameters which occasionally showed apparent changes but these were not considered by TB to be significant.

A NOEL for clinical biochemistries is set at 5 mg/kg/day. At 100 mg/kg there are increases in alkaline phosphatase. At 1000 mg/kg there are some possible changes in Ca<sup>++</sup>, albumin and total protein levels.

- I. Urinalysis: Urine was collected pre-experimentally, at weeks 8, 16, 26, 39 and 50. The dogs were placed in metabolism cages and the collection period was reported to be 18 hours. The following parameters were measured glucose, ketones, bilirubin, urobilinogen, pH, specific gravity, and protein.

There were no dose related changes in any of these urinalysis parameters noted.

- J. Gross pathology: The gross necropsy findings are presented in the individual animal pathology sheets together with the microscopic observations.

No table was presented which summarized the gross necropsy findings.

- K. Organ Weights: The left and right organs were weighed separately and individual and combined organ weights were reported. The following organs were weighed: gonads, spleen, adrenals, kidneys, liver, thymus, heart, lungs, brain, pituitary, and thyroids.

The liver was increased in the mid (+25% for males, +25% for females) and high (+30% for males and +36% for females). The low dose group was 7% higher (not significant) for females.

The thyroid showed apparent increases in weight for the males (-27%, +23% and +17%) and the females (-5%, +27% and +33%) for the low, mid and high dose test groups.

Other organs which showed apparent effects were the heart

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and adrenals. The heart weight of the high dose group males was -12% of the controls. The adrenal weights were slightly higher but statistical significance was not attained.

A NOEL for changes in organ weight is set at 5 mg/kg/day. Only the liver is considered to be affected by the test material.

- L. Histopathology: Samples of some 40 tissue types were prepared for histology for all dogs. Special samples of the brain and spinal cord were stained in Luxol fast blue/cresyl violet and toluidine blue. Sections of the right sciatic and posterior tibial nerves from the high dose group and three from each sex from the other groups were imbedded and stained with H&E, solochrome cyanin and by Palmgren's silver impregnation technique. The liver was especially stained with oil Red O.

The data were presented on individual animal pathology sheets together with the gross necropsy observations. There were two summary tables, the first showed lesions which were thought to be related to the test material, the second showed the incidences of "lesions unrelated to treatment."

The first table indicated that the adrenals showed "focal degeneration + necrosis in cortex with variable inflammatory cell infiltration." There were 0, 0, 1, 5 males and 0, 0, 0, 4 females affected for the control, low, mid and high dose groups. The dogs also had increases in "swelling and vacuolation of cells in inner cortex." There were 3 dogs in the male high dose test group affected. Single dogs in the mid dose group (male and female) and high dose group female were also affected.

The liver was also reported as being affected with "swelling". There were 0, 1, 3, 4 among the males and 0, 0, 1, 5 among the female control, low, mid and high dose test groups.

Inspection of the table of "lesions unrelated to treatment" indicated that there were several organs which showed higher incidences of certain lesion types in the high dose group than in the controls. These included: chronic pyelitis of the kidney in males; medullary cysts of the thymus in males; siderofibrotic conditions of the spleen in females; granulomata and medullary hemorrhage of the mesenteric lymph node in males; increased erythiophagocytosis in the females; minor inflammatory changes in the brain of females; cysts of the eyes in females.

TB does not consider that there are sufficient data to

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conclude that the lesions as above (except for those in the liver and adrenals) are related to ingestion of the test material.

Neoplasms: There was a cortical adenoma in the adrenals in a control female. A single male control dog had mesenchymal hamartoma in the kidney. Two papillomata were found in the mouth of one female receiving 5 mg/kg/day.

Note: The pathologist responsible for evaluating the tissue slides was Susan F. Moreland.

Conclusions: This study is CORE GUIDELINES. A NOEL of 5 mg/kg/day is supported. At 100 mg/kg/day there is noted a definite increase in alkaline phosphatase. At 1000 mg/kg/day there were signs of nerve stimulation, body weight loss, possible changes in platelet count, possible changes in  $K^+$  and  $Ca^{++}$  levels. Pathology revealed lesions in the adrenals and in the liver, only the liver was affected at 100 mg/kg.

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