(005100 EXCERPT)

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DATA EVALUATION REPORT

STUDY TYPE: Chronic Toxicity (Dog)

ACCESSION NUMBER: 073205

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)alpha-cyano-3-phenoxybenzyl (±)-cis-3-(Z-2-chloro-3,3,3-trifluoropropyl-enyl)-2,2-dimethylcyclopropane carboxylate, batches Y 00102/010/001 and Y 00102/010/002

STUDY NUMBER(S): Central Toxicology Lab (CTL) CTL No. PDO 395

REPORT NUMBER: CTL/C/1093; Huntingdon Research Centre No. ICI/326/8162

SPONSOR: Imperial Chemical Industries Ltd.

TESTING FACILITY: Huntingdon Research Centre

TITLE OF REPORT: Cyhalothrin Oral Toxicity Study in Beagle Dogs (Repeated Daily Dosing for 26 Weeks)

AUTHOR(S): Harold Chesterman, Ralph Heywood, Thomas R. Allen, Alan E. Street, Donald F. Kelly, Chirukandath Gopinath, David E. Prentice

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IDENTIFYING VOLUME: Volume II, Book 3 of 16 (Tab Reference 9C)

CONCLUSION: This study is classified as CORE GUIDELINE. Although a slight increase in passage of liquid feces was seen in the lowest dose group (7% over controls), this effect at this dose level is not considered to have any particular toxicological significance. Therefore, the NOEL is set at 1 mg/kg/day and the LEL is 2.5 mg/kg/day. Since this study was performed prior to publication of the Subpart F Guidelines, it is accepted as fulfilling the requirement for a chronic dog study.

Toxicity Category: N/A

Classification: CORE GUIDELINE

COMMENTS AND QUESTIONS: The registrant should verify that the test material was technical grade. The registrant should also address the presence of a small amount of cyhalothrin detected in the control solutions during analysis. In addition, a statement should be made as to how soon after collection of the samples were the analyses conducted.

MATERIALS AND METHODS:

Test Compound

Two batches of cyhalothrin were used for the study. Solutions for dosing were prepared at weekly intervals and stored. Concentrations of the chemical in corn oil solutions were measured at weeks 1, 2, 4, 9, 11, 13, 17, 21 and 25 of the study. Stability of cyhalothrin in corn oil was analyzed after 0, 5 and 10 days storage. The stability of cyhalothrin itself was measured at four and six months of dosing.

Animals

Forty-eight pure-bred beagle dogs (24 males and 24 females supplied from the Animal Breeding Unit of ICI Ltd., Alderly Park) were selected for the study. The animals were between four and five months of age and weighed between 7.9 and 12.5 kg.

Administration of Test Compound

The dogs were divided into groups of six males and six females per dose group. Cyhalothrin was administered orally, as a solution in corn oil in gelatin capsules at the following levels for 26 weeks: 0, 1.0, 2.5 and 10.0 mg/kg/day. A constant dosage volume was set at 0.1 ml/kg bodyweight. Individual dosage levels were calculated each week on the basis of bodyweight.

Observations

All animals were checked regularly throughout the working day and up to midday on weekends. Body weights were determined weekly. Food consumption was recorded daily and water consumption was recorded on weekdays during the four weeks prior to commencement of dosing and during weeks 1-3, 5-7, 9-11, 13-15, 17-19 and 21-24 of the dosing period. Eye examinations by means of a Keeler indirect ophthalmoscope were conducted on each animal once before commencement of dosing and again during weeks 6, 12 and 24. Before commencement of treatment and during week six, a neurological examination was performed on all high level and control animals.

Laboratory Examinations

A sample of venous blood was taken from each animal prior to the commencement of dosing and again during weeks 4, 8, 12, 16, 20 and 25. Urine samples were taken prior to commencement of dosing and again during weeks 8, 16 and 25. The urine samples were collected over a 16-hour period, water having been removed from the kennels five hours prior to the start of the collection. The following estimations were performed:

Hematology: erythrocyte sedimentation rate, packed cell volume, hemoglobin, red cell count, MCHC, MCV, WBC, differential blood count, platelet count, prothrombin index, activated partial thromboplastin time.

Biochemistry: BUN, plasma glucose, serum total protein, serum albumin, SAP, SGPT, SGOT, serum bilirubin, Na, K, Cl, Ca, P, serum cholesterol, serum creatinine, LDH, alpha-hydroxy-butyric dehydrogenase, creatinine phosphokinase.

Urinalysis: volume, specific gravity, pH, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen and hemoglobin. Microscopic examinations of the urine sediments were also performed.

Terminal Studies

Bone Marrow

On the day before the first day of autopsy, bone marrow was obtained from each animal by sternal puncture. A smear was prepared and examined.

Gross Pathology

The following organs were examined macroscopically and weighed: brain, pituitary, thyroids, spleen, heart, liver, kidneys, lungs, adrenals, pancreas, testes or ovaries, uterus or prostate and thymus.

Histopathology

The following organs were preserved together with any tissues showing macroscopic abnormalities and were examined microscopically: aorta, trachea, heart, lungs, thymus, lymph nodes, liver, gall bladder, spleen, pancreas, kidneys, spinal cord, ureter, urinary bladder, uterus, prostate, testes, ovaries, epididymides, cervix, thyroids, parathyroids, adrenals, salivary gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, skin, skeletal muscle, mammary gland, tongue, eyes and optic nerves, brain (cerebral cortex, thalamic nuclei, midbrain, medulla, cerebellum), pituitary, sciatic nerve, posterior tibial nerve, bronchi. Bone (sternum) was preserved but not processed.

Statistical Analyses

Statistical analyses were conducted using either the Student's 't' test, Bartlett's test, Williams' test, or the Chi^2 test where appropriate.

Results

No animals died during the course of the study. A dose-related increase in the passage of liquid feces was observed for all test groups throughout the study. This was coupled with the fact that in the highest dose group (10.0 mg/kg/day) there was a statistically significant increase in water consumption during the first four weeks of the study. This continued through week 15, although statistical significance disappeared. Vomiting,

usually within a few hours following dose administration occurred occasionally in the controls and the two lower dose groups and more often in the highest dose group. Occasional disturbances of the nervous system (unsteadiness and/or muscular trembling) were recorded for dogs receiving 10 mg/kg/day. During week two, head shaking and excessive salivation were recorded for several animals at this dose level. These signs were observed only occasionally at this dose level during subsequent test weeks. One male dog at the 10 mg/kg/day dose level exhibited more severe signs. During the second week this dog exhibited excessive salivation and head shaking. On day 14, three hours after dosing, he was found in a state of collapse, stiff limbed and frothing at the mouth with the presence of vomitus. The recovery period was approximately six hours. During the following weeks there were periods of head shaking, salivation and loss of appetite, episodes of collapse, muscular spasms, marked incoordination and vocalization and one episode of convulsive behavior.

With the exception of the one dog discussed above, bodyweight gain for all treated groups was similar to controls. A slight, but significant reduction in food intake was observed for animals in the 10 mg/kg/day group.

No abnormalities of the eye were noted that could be related to administration of the test material. The neurological assessment did not reveal any treatment-related changes.

During the pre-dosing and dosing periods, there were isolated incidences of statistically significant intergroup differences in the laboratory examinations. Since there was no dose-related trend and no consistency in the results, these incidences are not considered to be biologically significant.

No treatment-related effects were noted in either the bone marrow, macroscopic or microscopic examinations for any of the dose groups. In addition, no intergroup differences were noted for organ weights.

Discussion

This study is classified as CORE GUIDELINE. It is a well-run study. There was a dose-related effect on the gastrointestinal tract which appeared immediately during the first week at all dose levels and continued to the end of the study. The clinical sign was the passage of liquid feces. The mean increase in the total number of passages of liquid feces over controls for the entire 26 weeks was approximately 7, 26 and 39 percent for 1.0, 2.5, and 10.0 mg/kg/day respectively. The increase was not due to treatment-related activity in only a few dogs. All of the treated animals exhibited the effect to a greater degree than the controls. However, although the effect was seen at the lowest dose level, since it was only a 7% increase over controls and since no other effects were observed at this dose level, the slight increase in passage of liquid feces in dogs dosed with 1 mg/kg/day is not considered to be of toxicological significance. Therefore, 1 mg/kg/day is considered to be the NOEL for dogs in this study. 2.5mg/kg/day is the LEL.

At selected times throughout the study, samples of the dosing solutions from each dose level were collected for analysis of concentration of cyhalothrin. At weeks one, four and nine, a small amount of cyhalothrin was detected in the control solutions. Although this probably did not affect the outcome of the study, an explanation for the presence of the chemical in the control solution was not addressed in the final report. In addition, a statement should have been made as to how soon after

collection of the samples were the analyses conducted. The stability analyses of cyhalothrin in corn oil were only determined for a storage time of ten days. If the concentration analyses were conducted at a time much greater than ten days, then cyhalothrin degradation may have been an important factor in the concentration determinations.