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005158

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral (82-1) rat

TOX. CHEM. NO.: 271F
725D

ACCESSION NUMBER: 073980

TEST MATERIAL: (RS)alpha-cyano-3-phenoxybenzyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoro-prop-1-enyl)-2,2-dimethylcyclopropane-1-carboxylate and (RS)alpha-cyano-3-phenoxybenzyl (EZ)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-1-carboxylate

SYNONYMS: Cyhalothrin, PP563 (active ingredient of Grenade) for first test chemical and PP564 for second test chemical

STUDY NUMBER(S): PRO337

REPORT NUMBER: CTL/P/1056

SPONSOR: ICI PLC Plant Protection Division, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP563: 28-Day Feeding Study in Rats - Summary Report

AUTHOR(S): Tinston DJ, Banham PB, Chart IS, Core CW, Pratt I, Scales MDC, Weight TM.

REPORT ISSUED: 7/12/84

IDENTIFYING VOLUME: Volume II, Book 1 of 2, Section C, Tab Ref. 9C

CONCLUSION: For male rats effects were noted at the lowest dose level PP563, 20ppm. For females, the NOEL was 20 ppm. PP564 was less toxic than PP563, indicating that the cis isomer is more toxic than the trans isomer.

Classification: Not Core Guideline, but acceptable for the purposes for which it was performed.

MATERIALS AND METHODS:

Chemical:

PP563 was given the following references: CTL - Y00102/006/001 and Plant Protection Batch P5. It had a purity of 89.0% w/w (100% cis isomer). PP564 was given the following references: CTL - Y00102/001/001 and Plant Protection Batch P5. It had a purity of 84.0% w/w (50:50 cis:trans isomers). Both were viscous, pale yellow liquids.

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Animals:

Male and female Alpk/AP (Wistar-derived) rats were obtained from the Animal Breeding Unit at ICI PLC, Alderly Park, Macclesfield, Cheshire, UK. The rats were 3 weeks old and were acclimated for one week. The animals were supplied in two groups, one group arriving a week ahead of the other group.

Protocol:

Six groups of 16 male and 16 female rats were fed the experimental diets at the following dose levels for 28 days: 0, 20, 100, 250, 500, and 750 ppm (PP563); and 500 and 750 ppm (PP564). All rats were observed once daily throughout the experimental period for any clinical signs of toxicity. The eyes of all rats from the control, 500 and 750 ppm groups (PP563) were examined pre-experimentally and during the week prior to termination with an ophthalmoscope with and without a mydriate. Bodyweights were recorded weekly and food consumption was recorded daily for the first week and weekly thereafter.

Clinical Chemistry:

The following clinical chemistry parameters were measured in up to 8 designated male and female rats per group prior to the experimental phase and at termination: plasma urea, glucose, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and triglyceride and plasma cholesterol levels (at termination only).

Urinalysis:

Urinalysis measurements were taken from up to 4 male and 4 female rats prior to the experimental phase and at termination. The rats were given an oral water load at 2.5 ml/100g bodyweight and the urinary volume, pH, specific gravity and urinary sediments were measured. The animals were then deprived of water for 18 hours during which time the urine was collected for analysis of urinary volume, pH, specific gravity, protein, glucose, bilirubin and ketones.

Hematology:

The following hematological measurements were taken pre-experimentally and terminally from up to 8 male and 8 female animals per group: hemoglobin, total white cell count, red cell count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, hematocrit, differential white cell count and platelet count. The morphological appearance of the red cells were also examined. At termination, in addition to the above, prothrombin and kaolin/cephalin time tests were conducted and 2 bone marrow smears from the right femurs of all rats were examined for any cytological abnormalities.

Pathology:

Any rats found dead or moribund during the study received a full post mortem examination and tissues were submitted for histopathological examination. The weights of the following organs were recorded from up to 8 male and females rats per group: gonads (combined), spleen, adrenals (combined), kidneys (combined), liver, thymus, heart, lungs (combined), brain and pituitary. The livers from these animals (except the PP564 livers) were fixed in formol corrosive for histopathological examination. The livers from the PP564 group along with the following tissues from 8 male and 8 female animals per group were fixed in formol saline: salivary glands (parotid, sub-maxillary and sub-lingual), cervical lymph node, mammary tissue, voluntary muscle, testes, epididymides, protate and seminal vesicles or ovaries, uterus and cervix, urinary bladder, spleen, pancreas, stomach, duodenum, jejunum, ileum, mesenteric lymph node, caecum, colon, adrenals, kidneys, liver, thyroid, aorta, trachea, esophagus, thymus, heart, lungs, eyes, sciatic nerves, brain and spinal cord. The left sciatic and posterior tibial nerves from 4 male and 4 female controls and 750 ppm PP563 groups were fixed in formol glutaraldehyde and examined. All remaining animals received a gross post mortem examination and only abnormal appearing tissues were submitted for histopathological examination. Livers from a designated 6 male and 6 female animals from all groups were taken for measurement of hepatic aminopyrine-N-demethylase activity. These livers were the same as those taken for measurement of weight and examination by electron microscope. For the electron microscopy, samples were taken from the median lobes from the preselected male and female animals from control, 20, 100 and 250 ppm groups (PP563). Smooth endoplasmic reticulum (SER) was quantified using the point counting method of Weibel.

RESULTS:

Dietary Concentrations:

Concentrations of PP563 and PP564 were within 10% of the nominal values except for the 500 ppm PP563 and 500 ppm PP564 diets where the mean concentrations were 83% and 89% respectively. PP563 was shown to be stable in the diet for up to 30 days after preparation.

Mortalities:

Three male and three female rats receiving 750 ppm PP563 in the diet were found to be either dead or moribund. As a result, a second batch of animals already scheduled to start one week later were fed 500 ppm instead (this also included a second batch of PP564 animals). At 750 ppm, 2 more female rats died, one after 14 days and one after 27 days. No other deaths occurred during the study.

Clinical Observations:

Clinical observations included high-stepping gait, severe ataxia, hypersensitivity to external stimuli, piloerection and excessive salivation at the 750 and 500 (less severe) ppm (PP563) levels and similar but transient effects at the 250 ppm level. At 100 ppm, one male showed high stepping gait on day 3. Also at the lower levels there was occasional evidence of slight hypersensitivity to external stimuli. The clinical effects observed with PP564 were comparable but less severe: the effects noted at the 750 ppm level were similar to those noted at the 500 ppm level of PP563 and the effects observed at the 500 ppm level were similar to those noted at the 250 ppm level of PP563.

Bodyweight Gain and Food Consumption:

Statistically significant decreases in bodyweight gain were noted for male and female groups receiving either PP563 or PP564 at dietary concentrations of 250 ppm or greater (except for bodyweight gains of males receiving 500 ppm PP564). Statistically significant reductions in food consumption were also observed in both male and female rats fed levels of 250 ppm or greater for both PP563 and PP564.

Clinical Chemistry and Urinalysis:

Reductions in plasma triglyceride levels were noted in males receiving either 500 or 700 ppm PP563 and to a lesser extent in females receiving 750 ppm PP563 and males receiving either 500 or 750 ppm PP564. Dose-related decreases in protein excretion levels in the urine were observed in males receiving either 500 or 750 ppm PP563.

Organ Weights:

Statistically significant increases in liver weights (after adjustments for bodyweights) were observed in the 250 and 500 ppm dose groups (PP563) and in the 750 ppm (PP564) dose group. At 750 ppm 563, the large bodyweight reduction distorted the organ weight analysis. There was some evidence of increased testes weights and decreased ovary weights at the 500 and 750 ppm levels of PP563. There was a dose-related reduction in the heart weight of males fed diets containing PP563 which was statistically significant down to 250 ppm. There was also some evidence for reduction in spleen, brain and thymus weights in groups which grew less than controls.

Histopathology:

Male and female rats dying or killed in extremis showed thymic atrophy, and enlargement, vacuolation and differential staining of the cortical cells of the adrenals. In males, incomplete spermatogenesis and reduction of seminal vesicular secretion was evident. No changes in the nervous system were present. No other changes were noted.

Hepatic Aminopyrine Demethylase Activity:

A dose-related increase in APDM activity was observed in male rats receiving 20 ppm and above (PP563), in females receiving 100 ppm and above (PP563) and in PP564 but to a lesser extent.

Electron Microscopy:

There was a statistically significant increase in SER proliferation (greater in males than in females) which did not show any dose-response effect. The effect was observed in males at dose levels of 20, 100 and 250 ppm PP563 and in females at 250 ppm PP563. One female rat receiving 250 ppm PP563 showed marked vacuolation of hepatocyte cytoplasm, as a consequence of dilatation of endoplasmic reticulum.

DISCUSSION:

The results of this study confirmed the results of another previously submitted 28-day study on cyhalothrin in rats (Moyes et al. 1984) conducted at dose levels of 1 - 250 ppm. Clinical observations indicated signs of neurotoxicity, characteristic of synthetic pyrethroid toxicity. Evidence of decreased bodyweight gain and food consumption was also noted, as well as increased ADPM activity and proliferation of SER. As evidenced by comparing the results from testing PP564 with the results from PP563, it appears that the cis component is the more toxic of the 2 isomers. It should be noted that even at the lethal dose of 750 ppm PP563, no histopathological changes were observed in the peripheral nerves, even when accompanied by neurotoxic signs. The liver hypertrophy accompanied by increases in liver weight, APDM activity and SER proliferation are characteristic of effects due to pyrethroid administration. These effects are considered to be adaptive in this case. The authors stated that the histopathological changes noted in the animals that died were due to stress rather than PP563 toxicity, especially since there was no sign of these changes in the animals that survived.

The purpose of the study was to find the highest dose useful for a longer term study and to compare the toxicity of PP563 with PP564. It was recommended that for longer term studies, dosages higher than 250 ppm should not be used. This study is not Core Guideline because the exposure time was only 28 days and only 8 of the animals per sex per dose group were examined for many of the measurements taken. However, the study is acceptable for the purpose that it was conducted.

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