4/18/1994

Reviewed by: William Dykstra, Ph.D. Toxicologist William Dykstra 9/1/93
Review Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Tox Branch I Roger Gardner 4/18/94

DATA EVALUATION REPORT

STUDY TYPE: 82-7; Exploratory Two Week Dietary Neurotoxicity Study in CD-1 Mice

TOX. CHEM NO: New Chemical; P.C. Code 122806

MRID NO.: 427436-29

TEST MATERIAL: MK-0243 Technical

SYNONYMS: Emamectin

STUDY NUMBER: TT #89-023-0; Lab Project ID: 618-244-TOX26

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: MK-0243 (L-656,748). Exploratory Two-Week Dietary Neurotoxicity Study in Mice. TT #89-023-0

AUTHOR(S): George D. Lankas

REPORT ISSUED: December 18, 1992

CONCLUSION: The NOEL for neurotoxicity is 2.0 mg/kg/day (HDT).

There were no compound-related toxic signs. There were no treatment-related deaths. There were no treatment-related effects in food consumption. Control male mice had a 19% increase in average weight gain, whereas male mice in the 0.6 and 1.2 mg/kg/day groups showed 25 and 37% increases in weight gain. The increased weight gain in male mice in these two groups is considered treatment-related. Body weight gains in treated females were comparable to controls.

There were no treatment-related gross necropsy and microscopic findings. Microscopically, there was one high-dose male with a slight, cellular infiltrate in the meninges of the brain. This change was reported to be occasionally seen in control mice and may indicate an asymptomatic viral infection. There were no characteristic neuronal lesions in the brain, spinal cord and sciatic nerve in CD-1 mice of the high-dose group (2.0 mg/kg/day) as have been previously

observed in CF_1 mice.

Core Classification: **ACCEPTABLE**

1. Quality Assurance Statement: A Compliance Statement by Study Director, Dr. George R. Lankas, stating that the study was conducted in accordance with EPA Good Laboratory Practice Standards was signed and dated December 18, 1992.

2. Test Material: MK-0243 (L-656,748) hydrochloride; Batch Number (L-656,748-0100V003); 96.1% purity by HPLC. Vehicle: Untreated Purina Certified Rodent Chow Meal

3. Animals: Male and female Crl:CD-1™(ICR)BR mice, 37 days old, and weighing 18.9 - 30.4 g (males) and 17.9 - 26.0 g (females) were used in the study. The mice were purchased from Charles River Breeding Labs, Inc., Wilmington, MA, housed 2 or 3 animals per cage, and fed Purina Certified Rodent Chow Meal and tap water ad libitum. Food was withheld approximately 19 to 26 hours prior to scheduled necropsies.

4. Methods: Randomized groups of 10/sex/dose were fed continuously in the diet for 13 days at doses of 0 (unmedicated diet), 0.2, 0.6, 1.2, and 2.0 mg/kg/day of test material. Mice were observed daily for clinical signs, and mortality. Food consumption was measured over a six day interval during week 1 and over a three day interval during week 2. Body weight was taken pretest and at weekly intervals.

RESULTS

TOXIC SIGNS, MORTALITY, BODY WEIGHT, and FOOD INTAKE

There were no compound-related toxic signs. There were no treatment-related deaths. There were no treatment-related effects in food consumption. Control male mice had a 19% increase in average weight gain, whereas male mice in the 0.6 and 1.2 mg/kg/day groups showed 25 and 37% increases in weight gain. The increased weight gain in male mice in these two groups is considered treatment-related. Body weight gains in treated females were comparable to controls.

NECROPSY and HISTOPATHOLOGY

There were no treatment-related gross necropsy and

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microscopic findings. Microscopically, there was one high-dose male with a slight, cellular infiltrate in the meninges of the brain. This change was reported to be occasionally seen in control mice and may indicate an asymptomatic viral infection. There were no characteristic neuronal lesions in the brain, spinal cord and sciatic nerve in CD-1 mice of the high-dose group (2.0 mg/kg/day) as have been previously observed in CF_1 mice.

CONCLUSIONS

The NOEL for neurotoxicity is 2.0 mg/kg/day (HDT).

There were no compound-related toxic signs. There were no treatment-related deaths. There were no treatment-related effects in food consumption. Control male mice had a 19% increase in average weight gain, whereas male mice in the 0.6 and 1.2 mg/kg/day groups showed 25 and 37% increases in weight gain. The increased weight gain in male mice in these two groups is considered treatment-related. Body weight gains in treated females were comparable to controls. There were no treatment-related gross necropsy and microscopic findings. Microscopically, there was one high-dose male with a slight, cellular infiltrate in the meninges of the brain. This change was reported to be occasionally seen in control mice and may indicate an asymptomatic viral infection. There were no characteristic neuronal lesions in the brain, spinal cord and sciatic nerve in CD-1 mice of the high-dose group (2.0 mg/kg/day) as have been previously observed in CF_1 mice.