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DATA EVALUATION REPORT

STUDY TYPE: 81-8; Acute Oral Neurotoxicity Study in Rats #2

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

MRID NO.: 427436-19

TEST MATERIAL: MK-0243 Technical

SYNONYMS: Emamectin; Deoxyavermectin

STUDY NUMBER: TT #89-0129-0; Lab Project ID: 618-244-TOX15

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: MK-0243; (L-656,748-038W): Acute Oral Neurotoxicity Study in Rats #2. TT #89-0129-0

AUTHOR(S): Jeanne M. Manson

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CONCLUSION: Randomized groups of 10/sex/dose young Sprague-Dawley rats received by oral intubation, at a constant volume of 5.0 ml/kg, a single dose of 0, 0.5, 2.5, 5.0, 10.0, or 25.0 mg/kg of MK-0243 dissolved in sterile water. Animals were observed for 21 day for toxic signs and mortality. Toxic signs were noted as a "blind" observation. However, the functional observational battery and motor activity assessments were not performed. Body weight was measured weekly. Survivors were sacrificed by exsanguination and all animals were necropsied with attention placed on brain, spinal cord, optic and sciatic nerves. Brains were weighed. Brain, spinal cord, and nerves were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, stained with H & E, and examined by light microscopy.

The NOEL for the study is 5.0 mg/kg. At 10.0 mg/kg, 4/20 (2M & 2F) rats had tremors and irritation. At 25 mg/kg, all rats displayed toxic signs and had neuronal lesions.

A total of 20 rats (20/20) at 25 mg/kg MK-0243 had very-slight to slight treatment-related white matter degeneration of the brain (5M & 7F), white matter degeneration of the spinal cord (10M & 8F), and degeneration of the sciatic nerve (10 M & 9F).

Core Classification: **SUPPLEMENTARY**

In this study, the required functional observational battery and motor activity measurements were not conducted. In addition, tissues were not prepared according to the 81-8 Guideline requirements for an acute mammalian neurotoxicity study. However, the 14-week rat subchronic neurotoxicity study demonstrated that clinical signs and measurements in the functional observational battery occurred at the same dose level (5.0 mg/kg/day, but not at 1.0 mg/kg/day). Therefore, it is not likely that effects in the functional observational battery and motor activity measurements would be observed at 2.5 mg/kg in the acute toxicity study, thus providing a lower NOEL for neurotoxicity. A new study is not required because it would not provide any additional data.

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1. Quality Assurance Statement: A Certification of Good Laboratory Practice was signed by the Study Director, Dr. Jeanne M. Hanson, and dated December 18, 1992. QUA Inspections and Report Dates were signed by Cindra L. Lohan, and Michelle M. Nace, Quality Assurance Auditors.

2. Test Material: Mk-0243 Technical; L-656,748-038W002; 94.2% purity by HPLC area.

3. Animals: Male and female Crl:CD™(SD)BR strain (Sprague-Dawley) rats, approximately 6 weeks old, and weighing 113-181 grams, were used in the study. The rats were purchased from Charles River Laboratories, Raleigh, NC, housed individually and fed Certified Purina Rodent Chow and tap water ad libitum. Food was withheld approximately 18 hours before oral administration of the test material and until about 3 hours following compound administration.

4. Methods: Randomized groups of 10/sex/dose were orally gavaged by gastric intubation using a metal catheter attached to a syringe with test material in sterile water at the volume of 5 ml/kg. Groups were administered single doses of 0, 0.5, 2.5, 5.0, 10.0, or 25.0 mg/kg of MK-0243 dissolved in sterile water. Animals were observed for 21 day for toxic signs and mortality. Toxic signs were noted as a "blind" observation. However, the functional observational battery and motor activity assessments were not performed. Body weight was measured weekly. Survivors were sacrificed by exsanguination and all animals were necropsied with attention placed on brain, spinal cord, optic and sciatic nerves. Brains were weighed. Brain, spinal cord, and nerves were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, stained with H & E, and examined by light microscopy.

RESULTS

TOXIC SIGNS

Two rats, one at 0.5 and one at 2.5 mg/kg, were killed before the scheduled necropsy due to weight loss and

poor clinical condition. These toxic signs were considered unrelated to MK-0243 and the cause of these toxic signs was not determined at necropsy.

There were no treatment-related deaths. A total of 4/20 (2M & 2F) rats in the 10.0 mg/kg dose group and 20/20 rats in the 25 mg/kg dose group had treatment-related toxic signs, which were tremors and occasionally irritability on the first day. Rats in the treated groups below 10 mg/kg did not display any toxic signs.

BODY WEIGHT

Body weight gains of treated rats were comparable to controls.

NECROPSY, ORGAN WEIGHTS, and HISTOPATHOLOGY

There were no gross treatment-related findings in the brains, spinal cords, and sciatic nerve. Additionally, absolute and relative brain weight in treated rats was comparable to controls. A total of 20 rats (10 M/10 F) at 25 mg/kg MK-0243 had very-slight to slight treatment-related white matter degeneration of the brain (5M & 7F), white matter degeneration of the spinal cord (10M & 8F), and degeneration of the sciatic nerve (10M & 9F). Sciatic nerve degeneration, not considered to be treatment-related, occurred in 2 control males (2M), 2M & 2F at 0.5 mg/kg, no animals at 2.5 mg/kg, 2 M & 1F at 5.0 mg/kg, and 2M & 1F at 10 mg/kg.

CONCLUSIONS

The NOEL for the study is 5.0 mg/kg. At 10.0 mg/kg, 4/20 (2M & 2F) rats had tremors and irritation. At 25 mg/kg, all rats displayed toxic signs and had neuronal lesions. In this study, the required functional observational battery and motor activity measurements were not conducted. In addition, tissues were not prepared according to the 81-8 Guideline requirements for an acute mammalian neurotoxicity study. However, the 14-week rat subchronic neurotoxicity study demonstrated that clinical signs and measurements in the functional observational battery occurred at the same dose level (5.0 mg/kg/day, but not at 1.0 mg/kg/day). Therefore, it is not likely that effects

in the functional observational battery and motor activity measurements would be observed at 2.5 mg/kg if this study were repeated because there were no clinical signs to indicate that this may occur.