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for

DATA EVALUATION REPORT

STUDY TYPE: 82-7; Sixteen-Day Dietary Neurotoxicity Study in the CF-1 Mouse

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

MRID NO.: 427436-30

TEST MATERIAL: MK-0243 Technical

SYNONYMS: Emamectin

STUDY NUMBER: TT #90-101-0

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: MK-0243. Sixteen Day Dietary Neurotoxicity Study in the CF-1 Mouse. TT #90-101-0

AUTHOR(S): Ronald J. Gerson

REPORT ISSUED: December 18, 1992

CONCLUSION: Randomized groups of 10/sex/dose CF-1 mice received continuously via the diet doses of 0 (untreated feed), 0.05, 0.10, 0.30, and 0.90 mg/kg/day of MK-0243 (96.9% purity) for 15 days. All mice were observed at 3 intervals/day for clinical signs of toxicity and mortality. Mice were weighed pretest and once per week thereafter. Food consumption was measured once per week. All mice underwent necropsies limited to removal and examination of the brain, spinal cord, and sciatic nerves. The tissues were fixed in buffered neutral 10% formalin. Weights of brains were recorded. Sections of brain, cervical, thoracic and lumbar spinal cord and sciatic nerves from all mice on study were prepared by routine methods and stained with hematoxylin and eosin.

The NOEL for clinical signs is 0.1 mg/kg/day. At 0.3 and 0.9 mg/kg/day, there were clinical signs and moribund sacrifices. In the treated mice at 0.3 and 0.9 mg/kg/day, 6 mice at 0.3 and 4 mice at

0.9 displayed a range of clinical signs, which always included tremors and/or decreased activity plus other physical signs. Four mice in the 0.3 mg/kg/day group and 4 mice in the 0.9 mg/kg/day group were sacrificed in a moribund condition. There were no gross changes seen at necropsy. There were no deaths in the mice in the 0.05 and 0.1 mg/kg/day groups. With the exception of 1 male in the 0.3 mg/kg/day group which lost 3.0 grams, decreases in body weight gain were only observed in the 0.3 and 0.9 mg/kg/day males which had clinical signs. Food consumption was comparable among control and treated groups.

There were no gross or microscopic lesions in the brains, spinal cords, and sciatic nerves of treated mice in the 0.9 mg/kg/day group in comparison to controls. Brain weights were comparable among the eight treated mice which were killed moribund (control brain weights were not reported).

Core Classification:

SUPPLEMENTARY

This study is not a guideline requirement study.

1. Quality Assurance: A Certification of Compliance with Good Laboratory Practice was signed by the Study Director, Dr. Ronald J. Gerson, and dated December 18, 1992.
2. Test Material: MK-0243; Lot No. L-656,748-038W002; 96.9% purity by HPLC
3. Animals: Fifty male and 50 female Crl:CF-1™BR mice, 51 days old, weighing 21.8 - 32.6 grams (males) and 19.5 - 26.7 grams (females), purchased from Charles River Laboratories, Inc., Kingston, NY, were used in the study. The mice were individually caged and fed Purina Certified Rodent Meal and drinking water.
4. Methods: Randomized groups of 10/sex/dose received continuously via the diet doses of 0 (untreated feed), 0.05, 0.10, 0.30, and 0.90 mg/kg/day of test material for 15 days. All mice were observed at 3 intervals/day for clinical signs of toxicity and mortality. Mice were weighed pretest and once per week thereafter. Food consumption was measured once per week. All mice underwent necropsies limited to removal and examination of the brain, spinal cord, and sciatic nerves. The tissues were fixed in buffered neutral 10% formalin. Weights of brains were recorded. Sections of brain, cervical, thoracic and lumbar spinal cord and sciatic nerves from all mice on study were prepared by routine methods and stained with hematoxylin and eosin.

RESULTS

TOXIC SIGNS, MORTALITY, BODY WEIGHT and FOOD INTAKE

There were no compound-related clinical signs in any of the mice in the groups exposed to 0.05 and 0.1 mg/kg/day. In the treated mice, 6 mice at 0.3 and 4 mice at 0.9 displayed a range of clinical signs, which always included tremors and/or decreased activity plus other physical signs. Four mice in the 0.3 mg/kg/day group (90-2939F, -2926M, -2930M, -2940M) and 4 mice in the 0.9 mg/kg/day group (90-2946M, -2945F, -2949F, -2955F) were sacrificed in a moribund condition during days 2 - 15. There were no gross changes

seen at necropsy. There were no deaths in the mice in the 0.05 and 0.1 mg/kg/day groups. Body weight and food consumption was comparable between controls and mice in the 0.05 and 0.1 mg/kg/day groups, and in all surviving mice which did not have clinical signs in the 0.3 and 0.9 mg/kg/day groups, except male mouse 90-2936 (0.3 mg/kg/day group) which lost 3.0 grams, but did not have any clinical signs. In mice which had clinical signs, mean weight changes were comparable among females, but in males, the 0.3 mg/kg/day group and the 0.9 mg/kg/day group gained less weight than controls (decreases of 94% and 80% in weight gain in comparison to controls, respectively, for the 0.3 and 0.9 mg/kg/day males). Food consumption was comparable between controls and treated mice of both sexes.

NECROPSY, BRAIN WEIGHT and HISTOPATHOLOGY

There were no gross lesions observed at necropsy and brain weights were comparable among the eight treated mice which were killed moribund (control brain weights were not reported). There were no microscopic lesions in the brains, spinal cords, and sciatic nerves of treated mice in the 0.9 mg/kg/day group in comparison to controls. Therefore, there were no neurological lesions in CF₁ mice fed MK-0243 in the diet for 15 days at levels up to 0.9 mg/kg/day.

CONCLUSIONS

This study was a 16-day dietary neurotoxicity study in mice. It is not a Guideline requirement and is thus rated **CORE-SUPPLEMENTARY**. The NOEL is 0.1 mg/kg/day and the LEL is 0.3 mg/kg/day.