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DATA EVALUATION REPORT

STUDY TYPE: 82-7; Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice

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

MRID NO.: 428515-05

TEST MATERIAL: L-695,638 (8,9-Z-isomer); 4"-deoxy-4"-epi-methylamino-avermectin B1a-Delta-8,9-isomer

SYNONYMS: Photoproduct of MK-0244

STUDY NUMBER: TT #92-090-0; Lab Project ID: 618-244-TOX42

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: L-695,638: Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice. TT #92-090-0

AUTHOR(S): Ronald J. Gerson

REPORT ISSUED: March 31, 1993

CONCLUSION: In a previous study, the concentrations of measured doses of L-695,638 administered to female mice were less than 15% of targeted levels due to the low concentrations in the prepared diets. Therefore, the female CF-1 mice (10/dose) were again fed diets continuously for 14 days at targeted levels of 0.0, 0.05, 0.075, 0.10, and 0.30 mg/kg/day.

Randomized groups of 10 female CF-1 mice were fed 4"-deoxy-4"-epi-methylamino-avermectin B1a-Delta-8,9-isomer (L-695,638, 93.7% purity) continuously in the diet for 14 days at targeted levels of 0.0 (control, untreated diet), 0.05, 0.075, 0.10, and 0.30 mg/kg/day. All mice were observed daily for clinical signs of toxicity and mortality. Mice were weighed pretest and once weekly. Food consumption was measured weekly during pretest and the study period, based on 6-day intake amounts. All surviving mice were necropsied and brains were

weighed. Samples of the brain, spinal cord (cervical, thoracic, and lumbar) and sciatic nerve were fixed in neutral buffered 10% formalin. Sections were prepared by routine methods and stained with hematoxylin and eosin. All high-dose and control female mice had the brain, spinal cord, and sciatic nerve examined microscopically.

The NOEL is 0.243 mg/kg/day (HDT, Targeted Dose was 0.30 mg/kg/day) in female CF-1 mice.

There were no treatment-related effects in clinical signs, mortality, body weight and food consumption. The actual concentrations were 0.041, 0.057, 0.086, and 0.243 mg/kg/day for the nominal levels of 0.05, 0.075, 0.10, and 0.30 mg/kg/day, respectively. There were no treatment-related effects in necropsy findings, brain weights, and histopathology.

Core Classification: **SUPPLEMENTARY**

This is not a Guideline requirement study.

1. Quality Assurance: A Certification of Good Laboratory Practice was signed by the Study Director, Dr. Ronald J. Gerson, and dated March 31, 1993. A Quality Assurance Statement was signed by Catherine Masson, Assigned Auditor, Gerald P. McMahon, Senior Quality Assurance Associate, Oksana C. Powzaniuk, Quality Assurance Associate, and Warren D. Ditzler, Associate Director of Nonclinical Quality Assurance and dated March 31, 1993.

2. Test Material: L-695,638-001C001 was used throughout the study. Purity was 93.7% via HPLC.

3. Animals: 50 female CF-1 mice (Crl:CF-1 BR), 40 days old, weighing 19.9-25.8 g, purchased from Charles River Laboratories, Portage, MI, individually housed in polycarbonate cages in a controlled environment, were fed Purina Certified Rodent Chow (meal) and tap water ad libitum. Mice were fasted overnight prior to scheduled necropsy.

4. Methods: Randomized groups of 10 female CF-1 mice were fed continuously in the diet for 14 days at targeted levels of 0.0 (control, untreated diet), 0.05, 0.075, 0.10, and 0.30 mg/kg/day. All mice were observed daily for clinical signs of toxicity and mortality. Mice were weighed pretest and once weekly. Food consumption was measured weekly during pretest and the study period, based on 6-day intake amounts. All surviving mice were necropsied and brains were weighed. Samples of the brain, spinal cord (cervical, thoracic, and lumbar) and sciatic nerve were fixed in neutral buffered 10% formalin. Sections were prepared by routine methods and stained with hematoxylin and eosin. All high-dose and control female mice had the brain, spinal cord, and sciatic nerve examined microscopically.

RESULTS

Clinical Signs and Mortality: There were no deaths and no clinical signs at any dose level during the study.

Body Weight and Food Consumption: No treatment-related changes were observed.

Necropsy, Brain Weights, and Histopathology: There were no treatment-related effects in necropsy results, absolute or relative brain weights, or histopathology.

Discussion: This is a 15-day dietary neurotoxicity study in mice. It is not a Guideline requirement and is therefore classified as a **CORE-SUPPLEMENTARY** study. The NOEL is 0.243 mg/kg/day (HDT) in female mice (Targeted dose was 0.30 mg/kg/day).