7/27/1994

Reviewed by: William Dykstra, Ph.D. Toxicologist William Dykstra 7/27/94
Review Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hurley 7/27/94
for Review Section I, Tox Branch I

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.: 428515-04

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 #92-072-0; Lab Project ID: 618-244-TOX41

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: L-695,638: Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice. TT #92-072-0

AUTHOR(S): Ronald J. Gerson

REPORT ISSUED: March 31, 1993

CONCLUSION: Randomized groups of 10/sex/dose 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 dose levels of 0 (control, untreated diet), 0.05, 0.075, 0.10, and 0.30 mg/kg/day. Mice were examined daily for clinical signs of toxicity and mortality. Mice were weighed pretest and once weekly. Food consumption was measured weekly during the pretest and study period and was based on a 6-day intake period. All mice were necropsied at scheduled sacrifice. The brain, spinal cord, and sciatic nerve were fixed in neutral buffered 10% formalin. Terminal body weights and brain weights were recorded. Sections of the brain, spinal cord (cervical, thoracic, and lumbar) and sciatic nerve were prepared by routine methods from all control and high-dose mice, stained with hematoxylin and eosin, and examined

microscopically.

The NOEL in males is 0.30 mg/kg/day (HDT). However, for females in week 2, the average % claim of all concentrations was less than 10% of the targeted concentrations. Since the dietary concentrations of the test material for females during week 2 fell below acceptable limits, the study was repeated in female CF-1 mice (TT #92-090-0).

There were no reported clinical signs at any dose level and all mice survived the 2 week treatment period. There were no treatment-related effects in body weight or food consumption. There were no compound-related effects in necropsy results, absolute and relative brain weights and histopathology in treated mice of both sexes in comparison to controls.

Core Classification: **SUPPLEMENTARY**
This is not a Guideline requirement.

2

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 Cynthia L. Murphy, Assigned Auditor, Gerald P. McMahon, Senior Quality Assurance Associate, Micelle M. Nace, 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 in the study. Purity was 93.7% by HPLC. Diet mixtures were prepared weekly.

3. Animals: 50 male and 50 female CF-1 mice (Crl:CF-1 BR), 39 days old, weighing 21.3-30.3 g (males) and 17.6-27.2 g (females), purchased from Charles River Laboratories, Portage, MI, were individually housed in polycarbonate boxes in a controlled environment and fed Purina Certified Rodent Chow (meal) and tap water ad libitum. Mice were fasted overnight prior to necropsy.

4. Methods: Randomized groups of 10/sex/dose CF-1 mice were fed the test material continuously in the diet for 14 days at dose levels of 0 (control, untreated diet), 0.05, 0.075, 0.10, and 0.30 mg/kg/day. Mice were examined daily for clinical signs of toxicity and mortality. Mice were weighed pretest and once weekly. Food consumption was measured weekly during the pretest and study period and was based on a 6-day intake period. All mice were necropsied at scheduled sacrifice. The brain, spinal cord, and sciatic nerve were fixed in neutral buffered 10% formalin. Terminal body weights and brain weights were recorded. Sections of the brain, spinal cord (cervical, thoracic, and lumbar) and sciatic nerve were prepared by routine methods from all control and high-dose mice, stained with hematoxylin and eosin, and examined microscopically.

RESULTS

Dietary Analyses and Compound Intake: The test material was shown to be stable for 14 days at room temperature at concentrations from 0.10 to 10 ppm. Analyses of samples for concentration showed that in week 1, for males, the average % claim for all concentrations was 113% with a C.V. of 4.6%. For females in week 1, the average % claim for all concentrations was 101% with a C.V. of 2.4%. For males in

week 2, the average % claim for all concentrations was 92.4% with a C.V. of 4.75%. However, for females in week 2, the average % claim of all concentrations was less than 10% of the targeted concentrations. Since the dietary concentrations of the test material for females during week 2 fell below acceptable limits, the study was repeated in female CF-1 mice (TT #92-090-0).

Clinical Signs and Mortality: There were no reported clinical signs at any dose level and all mice survived the 2 week treatment period.

Body Weight and Food Consumption: There were no treatment-related effects in body weight or food consumption. Body weight gain in males was 3.0, 4.7, 3.8, 4.0 and 3.7 g, respectively, for the control, 0.05, 0.075, 0.10 and 0.30 mg/kg/day groups. In females, body weight gain for the study was 2.2, 2.3, 1.1, 1.0, and 2.1 g, respectively, for the control, 0.05, 0.075, 0.10, and 0.30 mg/kg/day groups.

Necropsy, Brain Weights and Histopathology: There were no compound-related effects in necropsy results, absolute and relative brain weights and histopathology in treated mice of both sexes in comparison to controls.

Dose (mg/kg/day)	Control	0.05	0.075	0.10	0.30
		MALES			
Body Weight, g	28.2	27.4	27.4	27.0	28.0
Brain Weight, g	0.452	0.461	0.472	0.452	0.457
% B.W.	1.61	1.68	1.73	1.68	1.64

Dose (mg/kg/day)	Control	0.05	0.075	0.10	0.30
		FEMALES			
Body Weight, g	22.0	21.8	21.3	21.3	21.0
Brain Weight, g	0.449	0.442	0.452	0.436	0.442
% B.W.	2.05	2.06	2.13	2.05	2.11

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 0.30 mg/kg/day (HDT) for males. A study in females will have to be repeated.