

7/27/1994

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

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.: 428689-01

TEST MATERIAL: L-657,831; 4"-epi-(N-formyl)-amino-4"-deoxy-
avermectin B1

SYNONYMS: Formyl amino derivative of MK-0244

STUDY NUMBER: TT #92-058-0; Lab Project ID: 618-244-TOX40

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: L-657,831: Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice. TT #92-058-0

AUTHOR(S): Ronald J. Gerson

REPORT ISSUED: May 7, 1993

CONCLUSION: Randomized groups of 10/sex/dose CF-1 mice were fed 4"-epi-(N-formyl)-amino-4"-deoxyavermectin B1 (L-657,831, 89.4% purity) continuously in the diet for 14 days at concentrations of 0 (control, untreated diet), 0.050, 0.075, 0.100, and 0.300 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 pretest and weekly based on a 4-6 day intake period. All mice were necropsied and the central nervous system (brain and spinal cord [cervical, thoracic, and lumbar segments]), and sciatic nerve were examined. Brain weight was recorded. Tissues were fixed in neutral buffered 10% formalin. Sections of the brain, spinal cord and sciatic nerve from all high-dose and control mice were prepared by routine methods and stained with hematoxylin and eosin.

The NOEL, based on decreased body weight gain, is 0.07 mg/kg/day (targeted dose was 0.10 mg/kg/day). The LEL is 0.23 mg/kg/day (targeted dose was 0.30 mg/kg/day) and the effect is decreased weight gain in both sexes (17% in males and 43% in females). There were no clinical signs, mortality, effects in food consumption, necropsy findings, absolute and relative brain weights, and histopathology of the brain, spinal cord, and sciatic nerve at doses up to the HDT of 0.23 mg/kg/day.

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 May 7, 1993. A Quality Assurance Statement was signed by Gerald P. McMahon, Senior Quality Assurance Associate, Oksana C. Powzaniuk, Quality Assurance Auditor, Cynthia L. Murphy, Assigned Auditor, and Warren D. Ditzler, Associate Director, Nonclinical Quality Assurance and dated May 7, 1993.
2. Test Material: L-657,831-000S008; purity of 89.4%.
3. Animals: 50 male and 50 female CF-1 mice (Cr1:CF-1 BR), 36 days old, weighing 20.4-28.4 g (males) and 17.0-24.8 g (females), purchased from Charles River Laboratories, Portage, MI, were individually housed in polycarbonate boxes under controlled conditions and fed Purina Certified Rodent Chow and tap water ad libitum. Food was withdrawn overnight prior to scheduled necropsy.
4. Methods: Randomized groups of 10/sex/dose CF-1 mice were fed continuously in the diet for 14 days at concentrations of 0 (control, untreated diet), 0.050, 0.075, 0.100, and 0.300 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 pretest and weekly based on a 4-6 day intake period. All mice were necropsied and the central nervous system (brain and spinal cord [cervical, thoracic, and lumbar segments]), and sciatic nerve were examined. Brain weight was recorded. Tissues were fixed in neutral buffered 10% formalin. Sections of the brain, spinal cord and sciatic nerve from all high-dose and control mice were prepared by routine methods and stained with hematoxylin and eosin.

RESULTS

Dietary Analyses for Stability, Homogeneity and Concentration: The test material was stable in rodent diet for 18 days at room temperature. The results of targeted concentrations at 0.10 and 10.0 ppm over an 18 day period averaged 0.100 and 10.7 ppm (C.V. of 14.2 and 10.6%), respectively. Dietary concentrations of test material were below the desired target concentrations during week 1 (60.0-69.2% of theoretical) and in week 2 (76.3-87.3% of theoretical). The resulting average compound intake,

therefore, was below the desired levels. The corrected compound intake is shown below.

<u>Dose Group</u>	<u>Average Consumed Dose of L-657,831</u>	
	<u>mg/kg/day</u>	
	<u>Males</u>	<u>Females</u>
0.050 mg/kg/day	0.04	0.04
0.075 mg/kg/day	0.06	0.05
0.100 mg/kg/day	0.07	0.08
0.300 mg/kg/day	0.23	0.24

Clinical Signs and Mortality: There were no compound-related clinical signs and no mortalities.

Body Weight and Food Consumption: High-dose male and female mice had 17 and 43% decreases in body weight gain during the 2-week period. Control male mice gained 4.7 g and high-dose male mice gained 3.9 g. For females, control mice gained 3.0 g and high-dose mice gained 1.7 g. Body weight gains for the other treated groups of male and female mice were comparable to controls. Food consumption was comparable between control and treated groups of mice of both sexes.

Necropsy, Brain Weights, and Histopathology: There were no treatment-related findings at necropsy and absolute and relative brain weights were comparable between control and treated groups of both sexes. There were no remarkable findings in the histopathological evaluation of brain, spinal cord, and sciatic nerve in high-dose mice in comparison to controls.

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 0.07 mg/kg/day and the LEL is 0.23 mg/kg/day, based on decreased weight gain.