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DATA EVALUATION REPORT

STUDY TYPE: 82-7; Exploratory Comparative Neurotoxicity Study in Dogs

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

MRID NO.: 427436-26

TEST MATERIAL: MK-0243 (L656,748), L-682,901, L-653,648, L-653,649, L-655,372

SYNONYMS: Emamectin

STUDY NUMBER: TT #88-134-0; Lab Project ID: 618-244-TOX23

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: MK-0243 (L656,748), L-682,901, L-653,648, L-653,649, L-655,372. Exploratory Comparative Neurotoxicity Study in Dogs. TT #88-134-0

AUTHOR(S): George D. Lankas

REPORT ISSUED: December 18, 1992

CONCLUSION: Male and female adult beagle dogs (2/sex/compound) were gavaged once a day at a dose of 1.5 mg/kg/day and a dosing volume of 1.0 mg/kg/day for 14 days with control formulation or emamectin (4" epi-methylamino avermectin), 4" epi-methylamino ivermectin (L-682,901), 4" epi-acetyl avermectin (L-653,648), 4" epi-amino avermectin (L-653,649), or 4" epi-dimethylamino avermectin (L-655,372). All dogs were examined for clinical signs, mydriasis, body weight and food consumption and mortality. All dogs were necropsied and brain, spinal cord and optic and sciatic nerves were processed and examined by routine methods.

Treatment-related clinical signs consisted of mydriasis, tremors, drooling, and loss of righting. Individual animal data were not provided with respect to clinical signs, but the report states that mydriasis was seen in all dogs

receiving L-653,648, and 3/4 dogs receiving L-653,649. Tremors were seen in 2/4 dogs receiving MK-0243, 2/4 dogs receiving L-653,649, and 3/4 dogs receiving L-655,372. Additionally, 1 dog in the L-653,649 group was drooling and was laterally recumbent prior to necropsy. There were no treatment-related deaths. Very slight to slight neuronal degeneration was observed in all dogs receiving either MK-0243, L-653,649, or L-655,372. However, L-682,901 and L-653,648 did not produce the neuronal lesions seen with the other compounds. The neuronal vacuolation seen in one male treated with L-653,648 was a unilateral lesion and was not considered compound-related for this reason and the fact that a control dog in an other study (TT #88-9016) had the same histologic change. Additionally, neuronal vacuolation was not seen in any other treated dogs in other groups.

Core Classification: **SUPPLEMENTARY**

This is not a guideline requirement study.

2

1. Quality Assurance: A Good Laboratory Compliance Statement was signed by Dr. George R. Lankas, Study Director, and dated December 18, 1992.

2. Test Material: MK-0243 (L-656,748; 4" epi-methylamino avermectin); L-682,901 (4" epi-methylamino ivermectin); L-653,648 (4" epi-acetyl avermectin); L-653,649 (4" epi-amino avermectin); L-655,372 (4" epi-dimethylamino avermectin); Vehicle: Formulation B. I.D. #14513-223 (propylene glycol: glycerol formal, 60:40 v/v). The test material was suspended in a small volume of Formulation B by using a tissue grinder for two minutes. The suspended test material was added to an appropriate amount of Formulation B in order to administer the desired dosage in a volume of 1 ml/kg.

3. Animals: Twelve male and 12 female adult beagle dogs, 41-49 weeks old, and weighing between 9.8-14.3 kg (males) and 6.8-11.6 kg (females) were used in the study. The dogs were purchased from three sources (Hazleton Research Animals, Cumberland, VA; Laboratory Research Enterprises, Inc., Kalamazoo, MI; and Marshall Farms, North Rose, NY), individually caged, and fed approximately 350 grams per day of Certified Purina Dog Chow in a single feeding. Food was withdrawn approximately 16.5 to 20.5 hours prior to necropsy. Water was provided ad libitum.

4. Methods: Each dog was dosed by gavage once a day at a dosing volume of 1.0 ml/kg/day. The total number of doses administered was 14 doses for control males and females, 13 doses for males and females receiving L-682,901, and for other compounds, males received 13 doses and females received 14 doses. The Treatment Groups were arranged as shown below:

Group	Dose	Males	Females
Control	(Formulation B)	2	2
MK-0243	1.5 mg/kg/day	2	2
L-682,901	1.5 mg/kg/day*	2	2
L-653,648	1.5 mg/kg/day	2	2
L-653,649	1.5 mg/kg/day	2	2
L-655,372	1.5 mg/kg/day	2	2

* Due to shortage of this compound, the dosage was reduced to 0.5 mg/kg/day on Day 11 and to 0.71 mg/kg/day on Days 12 and 13.

All dogs were examined daily for mydriasis, clinical signs and mortality. Dogs' eyes were examined for mydriasis approximately two hours after each dose. Food consumption was measured daily, Wednesday through Friday in Week 1 and Tuesday through Friday in Week 2. Body weight was measured pretest and at the end of Week 2. In Week 2, all drug-treated dogs were bled at 0 (pre-dose), 1, 2, 4, and 6 hours via jugular venipuncture. At each interval approximately 5 mls of blood were taken into EDTA-containing tubes. Plasma was collected and frozen for possible future drug concentration analysis.

RESULTS

TOXIC SIGNS, BODY WEIGHT AND FOOD INTAKE

Treatment-related clinical signs consisted of mydriasis, tremors, drooling, and loss of righting. Individual animal data were not provided with respect to clinical signs, but the report states that mydriasis was seen in all dogs receiving L-653,648, and 3/4 dogs receiving L-653,649. Tremors were seen in 2/4 dogs receiving MK-0243, 2/4 dogs receiving L-653,649, and 3/4 dogs receiving L-655,372. Additionally, 1 dog in the L-653,649 group was drooling and was laterally recumbent prior to necropsy. Other lesions, unrelated to treatment, consisted of plantar abscesses in two dogs receiving L-655,372. Moderate to severe decreases in food consumption were observed in dogs receiving L-653,648, l-653,649, and L-655,372. These decreases ranged from 100 - 350 grams /day of food in some instances. Body weight losses ranging from 0.2 - 0.6 kg were observed in all groups receiving the various treatments in comparison to control dogs which gained 0.1 kg. The effects in food consumption and body weight are considered treatment-related.

NECROPSY and HISTOPATHOLOGY

There were no treatment-related deaths. Very slight to slight neuronal degeneration was observed in all dogs receiving either MK-0243, L-653,649, or L-655,372.

However, L-682,901 and L-653,648 did not produce the neuronal lesions seen with the other compounds. The neuronal vacuolation seen in one male treated with L-653,648 was a unilateral lesion and was not considered compound-related for this reason and the fact that a control dog in an other study (TT #88-9016) had the same histologic change. Additionally, neuronal vacuolation was not seen in any other treated dogs in other groups. The following table presents the results of the histopathological evaluation.

Group	Control		MK-0243		L-682,901		L-653,648		L-653,649		L-655,372	
	M	F	M	F	M	F	M	F	M	F	M	F
Examined	2	2	2	2	2	2	2	2	2	2	2	2
Brain												
white matter, degeneration	0	0	0	0	0	0	0	0	1	0	1	0
neuron, degeneration	0	0	2	2	0	0	0	0	2	2	2	2
neuron, vacuolation	0	0	0	0	0	0	1	0	0	0	0	0
Spinal Cord												
white matter, degeneration	0	0	1	0	0	0	0	0	1	1	1	1
Sciatic Nerve												
degeneration	0	0	0	1	0	0	0	0	2	2	1	2
Optic Nerve												
degeneration	0	0	0	0	0	0	0	0	1	0	0	0

CONCLUSIONS

This is an exploratory neurotoxicity study in dogs. It is not a guideline requirement and is rated **CORE-SUPPLEMENTARY.**