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DATA EVALUATION REPORT

STUDY TYPE: 81-8; Acute Dermal Neurotoxicity Study in Male Rabbits

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

MRID NO.: 427436-11

TEST MATERIAL: MK-0243 0.16 EC Formulation

SYNONYMS: Emamectin; Deoxyavermectin

STUDY NUMBER: TT #90-024-0; Lab Project No.: 618-244-TOX07

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: MK-0243 0.16 EC Formulation. Acute Dermal Neurotoxicity Study in Male Rabbits. TT # 90-024-0

AUTHOR(S): Walter J. Bagdon

REPORT ISSUED: December 21, 1992

CONCLUSION: The NOEL for neuronal lesions for rabbits treated with MK-0243 EC for 24 hours is 0.5 gm/kg. The NOEL for neuronal lesions for rabbits treated with MK-0243 EC for 4 hours is 2.0 gm/kg.

There were no treatment-related toxic signs observed in any treated rabbit during the study. There were no deaths and no treatment-related effects on body weight gain in treated rabbits in comparison to vehicle EC controls during the study. Individual scores were reported for each rabbit. Dermal effects seen in rabbits at 1.0 and 2.0 gm/kg MK-0243 EC at 4 and 24-hours were similar to the changes seen in the 2.0 gm/kg vehicle control EC rabbits and, therefore, these dermal changes were attributed to vehicle. Rabbits treated with 0.5 gm/kg MK-0243 EC were less severely affected than rabbits treated at higher doses. The dermal changes consisted of progressively worsening very slight to severe erythema (scores of 1 to 4), and very slight to moderate edema (scores of 0 to 3) which appeared as wrinkled and scabby (and occasionally orange, and cracking) skin as the study progressed with some improvement near termination.

MK-0243 EC and vehicle EC are considered to be severe skin irritants in this study.

There were no treatment-related effects in absolute or relative brain weight, and gross necropsy findings. One rabbit at 1.0 gm/kg MK-0243 EC treated for 24 hours had very slight white matter degeneration of the brain. Although there were no rabbits at 2.0 gm/kg MK-0243 EC treated for 24 hours which had this neuronal lesion, this lesion in 1 rabbit at 1.0 gm/kg MK-0243 EC is considered to be compound-related, since the lesion occurred in the cerebellar peduncle and this location was target area for compound-related changes in other studies with rabbits.

Core Classification: **ACCEPTABLE**

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1. <u>Quality Assurance Statement:</u> A Certification of Good Laboratory Practice was signed by the Study Director, Dr. Walter J. Bagdon, and dated 12/21/92. A QAU Inspections and Report Audit Dates document was signed by Cindra L. Lohan, and Nelly P. Sanjuan, Quality Assurance Auditors.

2. <u>Test Material:</u> L-656,748-048A001 (0.16 lb/gal E.C. formulation); L-676,863-126Y014 (vehicle); The test formulation was stable under the conditions of the study (see Appendix). The active cation constituted 1.94% (w/w) of the test formulation. MK-0243 technical grade was 94.2% purity by HPLC.

3. <u>Animals:</u> Thirty male NZW rabbits, weighing 2.85 to 3.37 kg, approximately 20-21 weeks of age, were used in the study. The rabbits were purchased from Hazleton Research Products, Inc., Denver, PA, individually caged and fed Certified Purina High Fiber Rabbit Chow and tap water <u>ad libitum</u>.

4. <u>Methods:</u> The hair from the back of each rabbit was removed with electric clippers, and an intact area, approximately 10 x 10 cm, was selected. The formulation and its vehicle were tested as received. The <u>4-Hour Exposure Group</u> consisted of five males treated with 0.5 gm/kg MK-0243 EC, five males treated with 1.0 gm/kg MK-0243 EC, four males treated with 2.0 gm/kg MK-0243 EC, and two males treated with vehicle EC at 2.0 gm/kg. The <u>24-Hour Exposure Group</u> consisted of five males treated with 0.5 gm/kg MK-0243 EC, five males treated with 1.0 gm/kg MK-0243 EC, and four males treated with 2.0 gm/kg MK-0243 EC. The volume of test material used was 0.55, 1.11, or 2.22 ml/kg corresponding to a dose of 0.5, 1.0 or 2.0 gm/kg, respectively, of MK-0243 EC or vehicle EC. The intact treatment site on each rabbit was covered with a 4" x 4" gauze patch. The site was then wrapped with a clear plastic semi-occlusive dressing. The test material was then injected with a needle and syringe through the gauze patch onto the skin. A plastic collar was placed on each animal to prevent ingestion of test material and the animal was returned to its cage. After a 4 or 24-hour exposure period, the dressings were removed. Rabbits were examined for toxic signs at 1 and 6 hours on Day 1 and daily for 14 days. The treatment sites were examined for dermal changes

at 4 and 24 hours after treatment and daily thereafter, for 14 days and scored according to Draize. Each rabbit was weighed prior to treatment and once weekly.

RESULTS

TOXIC SIGNS

There were no treatment-related toxic signs observed in any treated rabbit during the study.

BODY WEIGHT

There were no deaths and no treatment-related effects on body weight gain in treated rabbits in comparison to vehicle EC controls during the study.

DERMAL CHANGES

Individual scores were reported for each rabbit. Dermal effects seen in rabbits at 1.0 and 2.0 gm/kg MK-0243 EC at 4 and 24-hours were similar to the changes seen in the 2.0 gm/kg vehicle control EC rabbits and, therefore, these dermal changes were attributed to vehicle. Rabbits treated with 0.5 gm/kg MK-0243 EC were less severely affected than rabbits treated at higher doses. The dermal changes consisted of progressively worsening very slight to severe erythema (scores of 1 to 4), and very slight to moderate edema (scores of 0 to 3) which appeared as wrinkled and scabby (and occasionally orange, and cracking) skin as the study progressed with some improvement near termination.

Mk-0243 EC and vehicle EC are considered to be severe skin irritants in this study.

NECROPSY, ORGAN WEIGHTS, AND HISTOPATHOLOGY

There were no treatment-related effects in absolute or relative brain weight, and gross necropsy findings. One rabbit at 1.0 gm/kg MK-0243 EC treated for 24 hours had very slight white matter degeneration of the brain. Although there were no rabbits at 2.0 gm/kg MK-0243 EC treated for 24 hours which had this neuronal lesion, this lesion in 1 rabbit at 1.0 gm/kg MK-0243 EC is considered to be compound-related, since the lesion occurred in the cerebellar peduncle and this location was target area for compound-related changes in other studies with rabbits. Therefore, the NOEL for neuronal lesions for rabbits treated with MK-0243 EC for 24 hours is 0.5 gm/kg. The NOEL for neuronal lesions for rabbits treated with MK-0243 EC for 4 hours is 2.0 gm/kg. There were no treatment-related effects in absolute or relative brain weight, and gross necropsy findings. One rabbit at 1.0 gm/kg MK-0243 EC treated for 24 hours had very slight white matter degeneration of the brain. Although there were no rabbits at 2.0 gm/kg MK-0243 EC treated for 24 hours which had this neuronal lesion, this lesion in 1 rabbit at 1.0 gm/kg MK-0243 EC is considered to be compound-related, since the lesion occurred in the cerebellar peduncle and this location was target area for compound-related changes in other studies with rabbits. Therefore, the NOEL for neuronal lesions for rabbits treated with MK-0243 EC for 24 hours is 0.5 gm/kg. The NOEL for neuronal lesions for rabbits treated with MK-0243 EC for 4 hours is 2.0 gm/kg.

CONCLUSIONS

There were no treatment-related toxic signs observed in any treated rabbit during the study. There were no deaths and no treatment-related effects on body weight gain in treated rabbits in comparison to vehicle EC controls during the study. Individual scores were reported for each rabbit. Dermal effects seen in rabbits at 1.0 and 2.0 gm/kg MK-0243 EC at 4 and 24-hours were similar to the changes seen in the 2.0 gm/kg vehicle control EC rabbits and, therefore, these dermal changes were attributed to vehicle. Rabbits treated with 0.5 gm/kg MK-0243 EC were less severely affected than rabbits treated at higher doses. The dermal changes consisted of progressively worsening very slight to severe erythema (scores of 1 to 4), and very slight to moderate edema (scores of 0 to 3) which appeared as wrinkled and scabby (and occasionally orange, and cracking) skin as the study progressed with some improvement near termination.

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