7/28/1994

Reviewed by: William Dykstra, Ph.D. Toxicologist William Dykstra 7/28/94
Review Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hanley 7/28/94
Review Section I, Tox Branch I

DATA EVALUATION REPORT

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

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

MRID NO.: 428515-07

TEST MATERIAL: L-930,905 (a complex mixture of polar MK-0244 photodegradates which co-elute upon HPLC)

SYNONYMS: Polar photodegradates of MK-0244

STUDY NUMBER: TT #92-082-0

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Research Laboratories

TITLE OF REPORT: L-930,905: Fifteen Day Oral Neurotoxicity Study in CF-1 Mice. TT #92-082-0

AUTHOR(S): Ronald J. Gerson

REPORT ISSUED: April 13, 1993

CONCLUSION: Randomized groups of 10/sex/dose CF-1 mice were administered a complex mixture of polar photodegradates (L-930,905, 100% purity) at doses of 0, 3, 6, 12, or 18 mg/kg/day by gavage, once a day, at a volume of 10 ml/kg for 14 days. All mice were observed daily for mortality and clinical signs. Mice were weighed at pretest, once in week 1, and twice/week in week 2. Food consumption was measured weekly beginning in pretest based on a four-day intake period. All mice received a limited necropsy, terminal body weights and brain weights were recorded, and the brain, spinal cord (cervical, thoracic, and lumbar) and sciatic nerve were fixed in 10% neutral buffered formalin and routinely processed. Hematoxylin and eosin sections from all control and high-dose mice were examined in the brain, spinal cord (cervical, thoracic, and lumbar), and sciatic nerve and all gross findings in all animals.

The NOEL is 18 mg/kg/day (HDT) in both sexes of CF-1 mice for the polar photodegradates. There were no compound-related effects in clinical signs, mortality, body weight, food consumption, necropsy, 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 Dr. Ronald J. Gerson, Study Director, and dated April 13, 1993. A Quality Assurance Statement was signed by Krystyna T. Mancinelli and Louise F. Winski, Quality Assurance Associates, Janet H. McKeon, Assigned Auditor, and Warren D. Ditzler, Associate Director, Nonclinical Quality Assurance.

2. Test Material: L-930,905-00D002; Purity of 100% by HPLC; Vehicle: 0.5% aqueous methyl cellulose (LotMM91081403A). An appropriate amount of L-930, 905 was suspended in 0.5% methylcellulose at a concentration of 1.8 mg/ml. This preparation constituted the high-dose suspension and aliquots were used to prepare the lower dose level suspensions. Stability and concentration analyses showed that the test material was stable, uniformly suspended, and present in the dosing solutions at 89-100% of desired concentrations.

3. Animals: Crl:CF-1™BR mice, approximately 39 days old, weighing 17.8-33.0 g (males) and 18.6 -26.8 g (females), purchased from Charles River Laboratories, Portage, MI, were fed Purina Certified Rodent Chow and tap water ad libitum and housed in polycarbonate boxes (2 to 3 mice/box) under controlled conditions.

4. Methods: The following treatment groups were established:

| | Males | Females |
|---|---|---|
| Control | 10 | 10 |
| L-930,905 | | |
| 3 mg/kg/day | 10 | 10 |
| 6 mg/kg/day | 10 | 10 |
| 12 mg/kg/day | 10 | 10 |
| 18 mg/kg/day | 10 | 10 |

High-doses were used in this study since: (1) the polar fraction contains a complex mixture of degrades and (2) the polar fraction comprises the greatest amount of residue remaining after application. Doses were administered by gavage, once a day, at a volume of 10 ml/kg for 14 days. All mice were observed daily for mortality and clinical signs. Mice were weighed at

pretest, once in week 1, and twice/week in week 2. Food consumption was measured weekly beginning in pretest based on a four-day intake period. All mice received a limited necropsy, terminal body weights and brain weights were recorded, and the brain, spinal cord (cervical, thoracic, and lumbar) and sciatic nerve were fixed in 10% neutral buffered formalin and routinely processed. Hematoxylin and eosin sections from all control and high-dose mice were examined in the brain, spinal cord (cervical, thoracic, and lumbar), and sciatic nerve and all gross findings in all animals.

**RESULTS**

There were no deaths and no compound-related clinical signs. Male mice in the 12 mg/kg/day group gained 6.8 g of weight compared to 4.0 in the control group, but the 18 mg/kg/day group gained only 0.9 g. Since the finding in the 12 mg/kg/day group was not dose-related and did not appear in other male or female groups, it was not considered compound-related. Food consumption was comparable between control groups of male and female mice and their respective treated groups. There were no unusual findings at necropsy.

Brain Weights

| Dose (mg/kg/day) | Control | 3 | 6 | 12 | 18 |
|---|---|---|---|---|---|
| | | **Males** | | | |
| Body Weight (g) | 30.5 | 28.5 | 28.5 | 28.4 | 27.1 |
| Brain (g) | 0.426 | 0.438 | 0.452 | 0.458 | 0.452 |
| % B.W. | 1.40 | 1.54 | 1.60 | 1.63 | 1.67 |

| Dose (mg/kg/day) | Control | 3 | 6 | 12 | 18 |
|---|---|---|---|---|---|
| | | **Females** | | | |
| Body Weight (g) | 21.0 | 22.6 | 22.9 | 22.2 | 21.8 |
| Brain (g) | 0.424 | 0.445 | 0.447 | 0.443 | 0.443 |
| % B.W. | 2.03 | 1.97 | 1.95 | 2.01 | 2.05 |

In male mice, the percent increase in absolute brain weight in treated groups in comparison to controls was 2.8, 6.1, 7.5, and 6.1 in the 3, 6, 12, and 18 mg/kg/day groups, respectively. In female mice, the percent increase in absolute brain weight in treated groups in comparison to controls was 4.9, 5.4, 4.5 and 4.5 in the 3, 6, 12, and 18 mg/kg/day groups, respectively. These slight increases in absolute brain weight in treated males and females in comparison to controls are not considered toxicologically significant. There were no compound-related microscopic changes in the examined brains, spinal cords, and sciatic nerves of treated 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 18 mg/kg/day (HDT).



5