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For PC "005108"

4/9/98

MEMORANDUM

SUBJECT: Fipronil ID# 000264-LTT: Evaluation of Neurotoxicity Positive Control (Validation) Studies in Support of a Rat Acute Neurotoxicity Screening Study on MB46513, a Photodegradate of Fipronil (81-8ss)

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I. CONCLUSIONS

The classification of the rat acute neurotoxicity screening study on the fipronil photodegradate (MRID 44262808, reviewed in TXR No. 012509) is upgraded from unacceptable (guideline) to acceptable (guideline) due to the submission of adequate positive control (validation) studies. There is no other change to the executive summary other that the classification. This document is considered an amendment to the original DER.

The positive control or validation studies (MRIDs 44447801, -02, -03, -04) submitted to support the previously submitted rat acute neurotoxicity screening study on the fipronil photodegradate MB46513, are considered acceptable and satisfy the neurotoxicity guideline requirement for demonstration of proficiency of the testing laboratory in evaluating neurobehavioral effects. Appropriate responses were identified for each of the positive control chemicals tested. The studies demonstrated the capability of the testing laboratory, Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, to conduct adequate functional operational battery, grip strength, motor activity testing and neuropathology evaluations.

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Brief summaries of the results of these studies are attached to this memorandum.

II. ACTION REQUESTED

Rhone-Poulenc submitted four positive control studies conducted at Huntingdon Life Sciences Ltd., England to support the previously submitted neurotoxicity screening study in the rat (81-8ss), MRID 44262808, reviewed in TXR No. 012509. Validation studies are required for guidelines 81-8ss to demonstrate proficiency of the testing laboratory in performing neurobehavioral evaluations.

cc: Copley, Fricke, Doherty, Caswell file, imaging copy

NEUROTOXICITY VALIDATION STUDIES
BUSHY RUN RESEARCH CENTER
(Addendum to MRID 44262808/TXR. No. 012509)

The four neurotoxicity validation studies summarized below were submitted to support a previously submitted rat acute neurotoxicity study on a photodegradate of fipronil (81-8ss, MRID 44262808, reviewed in TXR No. 012509). The studies are considered to satisfy neurotoxicity guidelines requiring demonstration of proficiency of the testing laboratory in conducting neurobehavioral tests. Effects on motor activity and parameters of functional observational battery (FOB) testing in the validation studies were generally consistent with known neurobehavioral effects of the positive control substances.

1) Hughes, E.W. (1996) Acrylamide: Neurotoxicity Screen in Rats Following Treatment (**Functional Observational Battery and Neuropathology**). Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Study No. R&D 91A/01A(4)942639.January 31, 1996. MRID 44447801. Unpublished.

Ten, Crl:CD (SD) BR rats (about 39 days old)/sex/dose group received 0, 12.5, 25 or 50 mg/kg/day of acrilamide, for 7 consecutive days. Doses were administered in 5 ml/kg water by gavage (controls received only water). Each animal was evaluated for clinical signs at least once daily. They were examined weekly for body weight and food consumption, food efficiency. The FOB was performed pre-treatment, about 3 hours after first dose (day 0), and 7 and 14 days after treatment. At term, neuropathology consisted of the following: brain measurements, histologic examination of brains, spinal cords, ganglia and dorsal and ventral root fibres and peripheral nerves.

Clinical Signs - At the **12.5 mg/kg/day** and above, there was decreased body weights and food efficiency (in females). At **25 mg/kg/day** and above, there was decreased body weights (males) food consumption. At **50 mg/kg/day** and above, there were clinical signs including unsteadiness in the cage, reduced muscle tone, distended abdomen and piloerection. There were effects in the **FOB** at all doses starting on day 7. There included increased tremors, increased hindlimb foot splay, and decreased rearing counts at **12.5 mg/kg/day**. At **25 mg/kg/day** there was also swaying/lurching gait. The **50 mg/kg/day** group also had impaired mobility, slow pupil reflex, increased difficulty in handling, increased vocalizations, and decreased fore- and hind limb grip strength. Neuropathology was present at all doses. At **12.5 mg/kg/day** there was trace axonal degeneration in peripheral nerve in one female. At **25 mg/kg/day** there was also trace axonal degeneration in one male and four female rats. The **50 mg/kg/day** group had axonal degeneration in peripheral nerve and a higher incidence and that was more extensive of axonal degeneration in peripheral nerve (trace to marked). In addition there was trace degeneration in spinal nerve roots in several rats (this occurred in one control rat).

2. Hughes, E.W. (1996) Trimethyltin Chloride (TMT): **Neurotoxicity to Rats by Acute Oral Administration**. Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Study No. R&D 91A/01C(2)942873. January 31, 1996. MRID 44447802. Unpublished.

Ten, Crl:CD (SD) BR rats (about 54 days old)/sex/dose group received a single 0, 5, 7.5 or 10 mg/kg dose of TMT. The dose was administered in 1 ml/kg saline by gavage (controls received only saline). Each animal was evaluated for clinical signs at least once daily. They were examined weekly for body weight and food consumption, food efficiency. The FOB and locomotor activity was assessed pre-treatment and on day 28 after treatment. On day 29 animals were sacrificed and designated tissues of the nervous system were underwent histopathological examination.

Clinical Signs - At the **10 mg/kg** dose, two males showed signs of aggressive behavior on handling, hunched posture and piloerection upon handling from week 2 on. There were no changes in bodyweight, food consumption and food efficiency. The FOB changes were observed at 5 and 7.5 mg/kg consisting of unsteady appearance. At **10 mg/kg** a slight sway was observed th the rats. Tremors and a slight difficulty in handling occurred at **7.5 and 10 mg/kg**. In addition at **10 mg/kg** there was a reduced startle response in males. There was a suggestion of increased locomotor activity at **10 mg/kg**. There were no changes in brain parameters. Neuropathology changes included changes in the spinal cord and loss of neurons and gliosis in the hippocampus at all doses. In males at 7.5 and 10 mg/kg there was also effects in the pyriform cortex.

3. Hughes, E.W. (1996) pp DDT: Neurotoxicity Screen in Rats Following Treatment (**Functional Observational Battery**). Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Study No. R&D 91A/01A(5)942737. January 31, 1996. MRID 44447803. Unpublished.

Ten, Crl:CD (SD) BR rats (about 45 days old)/sex/dose group received a single 0, 50, 100 or 200 mg/kg dose of pp DDT. Males received a second dose one month later due to no observed effects observed with the first dose. The dose was administered in 5 ml/kg by gavage in corn oil (controls received only corn oil).Each animal was evaluated for clinical signs at least once daily. They were examined weekly for body weight and food consumption, food efficiency. The FOB was assessed pre-treatment, at 6 hours and 7 days after treatment. Animals were sacrifices after the last FOB and received a macroscopic examination.

Clinical Signs included tremors at all doses, with three high dose females being sacrificed due to the severity of reaction. Body weight gain was decreased at **200 mg/kg** in males (only after the second dose). There were no changes in food consumption or food efficiency. FOB effects occurred **at all doses** including tremors and increased reactivity to sound/movement. There was decreased foot splay in males at **100 mg/kg** and above and in females at **200 mg/kg**. In addition, at **200 mg/kg,** there were tail pinch reactions and decreased forelimb grip strength in

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females. These effects were limited to the 6 hour evaluation. No treatment related effects were observed at macroscopic examination.

4. Hughes, E.W. (1996) Neurotoxicity Screen in Rats Following Treatment With Carbaryl (**Functional Observational Battery**). Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Study No. R&D 91A/01A(6)942779. January 31, 1996. MRID 44447804. Unpublished.

Ten, Crl:CD (SD) BR rats (about 43 days old)/sex/dose group received a single 0, 50, 100 or 200 mg/kg dose of Carbaryl. The dose was administered in 5 ml/kg by gavage in 1% methyl cellulose (controls received only 1% methyl cellulose). Each animal was evaluated for clinical signs at least once daily. They were examined weekly for body weight and food consumption, food efficiency. The FOB was assessed pre-treatment, at 1 hour. and 7 days after treatment. Animals were sacrifices after the FOB and received a macroscopic internal and external examination.

Clinical signs occurred on the day of treatment primarily at **200 mg/kg** and included increased lacrimation/salivation, hunched posture, lethargy and piloerection. They were resolved by the second day. Body weight was decreased at **200 mg/kg**. Food consumption and food utilization were decreased at **100 mg/kg** (females) and **200 mg/kg** (males and females). At 1 hour post treatment FOB effects occurred at **all doses** and included increased urination, tremors, decreased arousal, increased rearing counts, vocalization during the tail pinch and a decrease in body temperature. At **100 mg/kg** and above there were affects to posture. At **200 mg/kg** there was a decrease in activity and in response to touch, slow reaction in righting and reduced grip strength.