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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MAR 15 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPTC---Data Submitted as Potential 6(a)(2) Data Cn
MRID 43039701

ID # 041401

Chemical: 041401 (435)
RD Record: S-456562
HED Projec.: D198372

FROM: Irving Mauer, Ph.D., Geneticist
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03-09-94

TO: Walter Waldrop, PM # 71
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THRU: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I
Health Effects Division (7509C)

3/12/94

Registrant: Zeneca Ag (formerly ICI), Wilmington, DE

Request: Review and evaluate the following toxicity study (GDLN: 81-8-SS) submitted as possible FIFRA 6(a)(2) data:

EPTC: Acute Neurotoxicity Study in Rats, performed at Zeneca's Central Toxicology Laboratory (CTL), Macclesfield (UK), Study No. AR5527 (CTL Report No. 4092) (MRID 430397-01).

TB CONCLUSION: Doses tested: 0, 200, 1000, 2000 mg/kg, by acute gavage; animals observed for 15 days post-dose.

NOEL = 200 mg/kg (females only)
LOEL = 1000 mg/kg (death; decr. bw.; clinical/cholinergic effects; decr brain wt.; neuronal cell necrosis)

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NB: The LDT, 200 mg/kg, is an effect level in males, since the brains of 2 of the 5 animals treated at this level manifested neuronal cell necrosis.

This study is therefore considered CORE-SUPPLEMENTARY DATA, since a NOEL was not established for males.

ATTACHMENT: DER

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (7509C)

08-09-94

3/12/94

DATA EVALUATION RECORD

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MRID No.: 430397-01
PC No.: 041401
RD Record No.: S456562
EPA ID No.: 041401
Tox Chem. No.: 435
Project No.: D198372

I. SUMMARY

STUDY TYPE: (81-8-SS) Acute neurotoxicity screen

CHEMICAL: EPTC (s-ethyl dipropylthiocarbamate)

SPONSOR: Zeneca Ag Products, Wilmington, DE

TESTING FACILITY: (Zeneca) Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield (UK)

TITLE OF REPORT: EPTC: Acute Neurotoxicity Study in Rats

AUTHOR: A. Brammer

STUDY NUMBER: Study No. AR5527 (Report No. CTL/P/4092)

DATE ISSUED: 18 October 1993

EXECUTIVE SUMMARY: Doses tested: 0, 200, 1000, 2000 mg/kg by oral gavage, once; observed for 15 days post-dose. Two high-dose males found dead; one high-dose and one mid-dose female sacrificed *in extremis*. Dose-related reduction in body weight, brain weight, and clinical toxicities found at 1000 and 2000 mg/kg. Neuronal cell necrosis found at all dose levels in males, but only in mid and high-dose females.

NOEL (females) = 200 mg/kg
LOEL (females) = 1000 mg/kg (death;reduced body weight)
LOEL (males) = 200 mg/kg (LDT): Neuronal cell necrosis

TB-I EVALUATION: CORE-SUPPLEMENTARY DATA. No NOEL for treated males provided.

II. DETAILED REVIEW

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A. TEST MATERIAL: EPTC (Zeneca Agrochemicals)

Description: Yellow liquid
Batches (Lots): P4/D7534/10
Purity (%): 98.4
Solvent/carrier/diluent: Corn oil

B. TEST ORGANISM: Rodent

Species: Rat
Strain: Alpk:APfSD
Age: 34-36 days
Weights - males: 163-165 g
females: 131-134g
Source: Zeneca, Macclesfield (UK)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the acute neurotoxic potential of the test when administered in vivo to rats.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Four groups of rats (10/sex/group) were gavaged once at doses of 0 (corn oil vehicle), 200, 1000 and 2000 mg/kg, and sacrificed two weeks later. Animals were observed daily throughout the study period, weighed on Days 1, 8 and 15 of the study, and food consumption recorded continuously. One day before dosing, and subsequently on study days 1, 8 and 15, each rat underwent a battery of functional tests (landing foot splay, tail-flick, fore/hind-limb grip). In addition, each animal was assessed for autonomic functions (e.g. lacrimation, salivation, piloerection, exophthalmus, urination/defecation, pupillary response, ptosis); as well as for convulsion/tremors/ abnormal motor function or abnormal behavior; reactivity to stimuli; changes in arousal; sensorimotor responses; and finally, alterations in respiration. Locomotor activity was monitored on an automated activity recording apparatus.

At study termination (Day-15), one-half the animals per dose group was subjected to a full post-mortem examination. Rats found dead before scheduled sacrifice also underwent a full necropsy as soon as

possible after death (always within 24 hours). Brains from scheduled Day-15 sacrifices were weighed, and length/width recorded.

The following tissues were processed for histological examination: Brain, gastrocnemius muscle, dorsal root ganglia and spinal roots (cervical and lumbar). Twelve levels of brain from one high-dose male and female were examined; from all other dose groups, only six levels were examined.

Data were statistically analyzed, as follows:

Body weights and brain measurements: By analysis of covariance, separately for males and females.

Food consumption, motor activity measurements, and sensory function: By ANOVA, separately for males and females.

After processing (by SAS' GLM-program), least-squares means were calculated, and differences between test and control groups compared by two-sided student's testing.

E. RESULTS: The concentrations of EPTC in the vehicle were within 2% of nominal at all dose levels (Report Table 2), as was chemical stability after storage for 32 days (Report Table 3).

Four animals died before scheduled termination: Two high-dose males found dead on Day-2; one high-dose and one mid-dose female sacrificed *in extremis* on Days 1/2.

Both body weight and food consumption were reduced in both sexes given 1000 and 2000 mg/kg, statistically persistent throughout the observation period in males (Report Tables 4 and 5, attached here). No such effects were evident in 200 mg/kg males or females.

A variety of dose-related clinical toxicities was observed in mid-dose (1000 mg/kg) and high-dose (2000 mg/kg) animals beginning within 5 hours of dosing (*e.g.*, reduced activity/foot withdrawal reflex, lacrimation, salivation, spinal curvature); recovery occurred in most affected rats by Day 4 or 5 (Report Table 6). Transient lacrimation (only) occurred in a few low-dose (200 mg/kg) animals.

There was no evidence of treatment-related landing-foot splay changes (Report Table 7), or time-to-tail flick (Report Table 8), or grip-strength values (Report Table 9). On the other hand, both high-dose and mid-dose

groups (but no low-dose animal) evinced significantly reduced motor activity within five minutes of dosing, which persisted up to 20 minutes post-dose ir females (Report Table 10; Figs 1-4). No such alterations were recorded on Days 8 or 15 of the study.

High and mid-dose brains weighed slightly but significantly less than controls (Report Table 11). attached Brain weight among low-dose animals did not differ from controls. In rats sacrificed on schedule (and the 4 DOS), macroscopically relevant findings were considered unrelated to EPTC-treatment (Report Table 12) attached

On the other hand, treatment-related microscopic findings in the brain were evident. For example, all mid-dose and high-dose rat brains manifested dose-related neuronal necrosis, involving either the pyriform/entorhinal cerebral cortex or the vertical/caudal portion of the dentate gyrus, or both (Report Table 13). attached Among 200 mg/kg animals, only 2/5 males had similar lesions, but of minimal severity, and confined to only occasional neuronal cells; 200 mg/kg females were unaffected.

The investigators concluded that EPTC was clearly acutely toxic at 1000 and 2000 mg/kg, but with no apparent clinical effects at 200 mg/kg. However, dose-related (in severity and incidence) histopathological changes were evident as specific brain lesions (neuronal cell necrosis), with males more affected (even at the lowest dose, 200 mg/kg) than females (0/5 at 200 mg/kg).

Hence the investigators claim the NOEL in females to be 200 mg/kg, and although not clearly established in males, to be considered "... close to 200 mg/kg."

F. TB EVALUATION: CORE-SUPPLEMENTARY, since a firm NOEL was not established for males.

ATTACHMENT: Data Tables

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Pages 9 through 13 are not included in this copy.

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