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

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SEP 25 1986

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Acute Delayed Neurotoxicity Study with trifluralin and 4 amendements to previously submitted studies.

To: Richard Mountfort PM-23
Registration Division, TS-767

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch, HED
M. van Gemert 9.22.86

Thru: Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division
Theodore M. Farber 9/22/86

Chemical: Trifluralin

Accession No.: 262955

Project No.: 2102

Registrant: Industria Prodotti Chimici

IPC has submitted a delayed neurotoxicity study along with several minor amendements to 4 previously submitted studies.

1. Acute Delayed Neurotoxicity Study: DER is attached;

Conclusions:

Dose eliciting Neurotoxicity > 5000 mg/kg body weight

LD_{50} > 5000 mg/kg body weight

Core classification: Minimum

2. Study type: Embryotoxicity study in the rabbit: first amendement to the report.

Hoechst has submitted the following corrections to the original report. They include;
a. Test article identification
b. Statistical methods that were omitted in the original report.

c. Mating schedules that were not included in the original report. 005510

these three items are on appended pages 3,4 and 5, and will be incorporated into the review of the reproduction study when it is reviewed by Dynamac.

3. Study Type: 12-month oral toxicity study in beagle dogs, 1st amendment to the report.

Hoechst has amended their test article description to include some homogeneity and stability information. The new page is appended page 6. The study has been reviewed by Dynamac and the omission of these data had not been considered a problem for the study. Dynamac had classified the study as core guideline.

4. Study type: Multiple generation study in the rat. 1st amendement to the report.

The page concerning diet preparation, analysis of the test article and stability have been amended very slightly. The page is attached on appended page 7. None of the changes in wording would affect the review or conclusions of this study.

5. Study type: Embryotoxicity in Wistar rats: Historical control incidence of wavy ribs in control studies and at dose levels toxic to either dams or embryos.

Hoechst has presented some historical data for "wavy ribs" in their laboratories from 1970 to 1985. These tables are enclosed in appended pages 8-16. "wavy ribs" were observed in 83 of 91 groups examined. Their frequency was between 1 and 21 fetuses equivalent to 0.7- 18.5%. The frequency of affected litters was between 1 and 11, equivalent to 5.0-70.0%. In the control groups up to 1981, with one exception, no more than 10% of the fetuses were spontaneously affected. Data from the study are found on appended pages 17 and 18.

The study authors argue in this submission that they believe they have good reason to assign the number of affected fetuses in the 20 and 100 mg/kg groups to the spontaneous rate, and to evaluate the number of those in the 500 mg/kg group as treatment-related. This argument appears reasonable. However, there are so many other developmental problems associated with this compond at all dose levels tested that a NOEL for developmental toxicity can still not be established. (see Dynamac DER of 8.13.86.

Reviewed by: M. Kramer 9.22.86
Section III Tox Branch (TS-769C)
Secondary Reviewer:
Chief, Toxicology Branch (TS-769C)

005510

DATA EVALUATION REPORT

Study Type: Acute Delayed Neurotoxicity Tox Chem No: 889

Accession No. 262955 MRID NO: ?

Test Material: Trifluralin Project No: 2102

Synonyms: HoeO38474 OH ZD 990002

Study Number: 85: 0742

Sponsor: Hoechst

Testing Facility: Hoechst Aktiengesellschaft
Pharma Forschung Toxikologie

Title of Report: Testing for acute delayed neurotoxicity in white leghorn hens

Author: Dr. M. Kramer

Report Issued: Oct. 10, 1985

Conclusions:

Dose eliciting neurotoxicity > 5000 mg/kg body weight

LD_{50} > 5000 mg/kg body weight

Classification: core minimum

MATERIALS;

1. Test Compound: Trifluralin, Active ingredient technical

   Description: red crystals

   Batch #: HOE 038474

   Purity: 98.4%

   Contaminants: list in CBI appendix

   Administered by gavage or in gelatin capsules in a 50% w/v suspension in sesame oil

2. Test Animals: Species: White leghorn hens

   Strain: Gallus gallus domesticus

005510

Age: 13 months

Weight: 1260-1962 gms.

Source: Bernhard Franzsander, Heustrasse 15
4795 Delbruck-Hagen
Federal Republic of Germany

B. STUDY DESIGN:

1. Animal Assignment:

Animals were assigned randomly to the following groups:

TABLE I

Test Group	Dose	# Animals	Animal Number
1. Sesame Oil	10 ml/kg BW	10	1-10
2. Triortho-cresyl phosphate (TOCP)	500 mg/kg	10	11-20
3. Trifluralin	5000 mg/kg	12	21-32

Acute oral toxicity was determined using sesame oil and gelatin capsules as vehicle.

TABLE II

Group	Dose mg/kg	vehicle	concentration	# of animals
1.	800	gelatin capsules	original	2
2.	2000	" "	original	2
3.	5000	" "	"	2
4.	5000	sesame oil	50% (w/v)	5

3. Animals received food and water ad libitum.

4. Statistics: The LD_{50} was calculated by probit analysis (according to the method of Linder and Weber) and the limits of confidence ($p = 0.05$) according to the method of Fieller (where mortality rate permitted.)

5. Quality assurance was verified with a sign-off sheet. The study was inspected twice during the once after completion of the study.

METHODS AND RESULTS:

1. Observations:

Animals were inspected continuously on the first day for the LD_{50} for signs of toxicity and mortality and daily for 14 days thereafter. For the neurotoxicity portion of the study, ataxia (ataxia assessment was done according to the appended grading scale) was assessed daily and twice weekly during the study.

Results:

LD_{50}: Under the conditions of the study, no deaths occurred. The LD_{50} is greater than 5000 mg/kg body weight.

Neurotoxicity:

Group 1 control: No abnormal signs of toxicity were noted

Group 2- TOCP: Ataxia was noted in 2 animals from day 8 and in all animals from day 12. Between days 19 and 22, 3 of the 10 in the group were in a completely paralytic state and had to be killed intercurrently in stati moribundi and perfused. The remaining animals survived to termination showing ataxia in some cases. No other symptoms were evident.

Group 3- Trifluralin: marginal disturbances in muscle coordination were seen from days 9 to 11 in 4 animals, especially after periods of increased activity. From day 12 post-treatment no further disturbances were noted. Following redosing no signs of ataxia were noted.

2. Body weight:

Animals were weighed on days 1, 8 and 15 for the LD_{50}, and twice weekly for the neurotoxicity portion of the study.

Results: No differences between the treated (500 mg/kg trifluralin and the controls could be seen. Positive control animals (TOCP showed marked body weight reductions from day 11 post treatment.

3. Food Consumption:

Food consumption was measured on days 3,7,9,11,14 and 15 for the LD_{50} portion of the study, and twice weekly for the neurotoxicity

study.

Results: No differences in food consumption were noted between treated (trifluralin) and controls for food consumption. However, the positive control animals showed a marked decrease in food consumption from day 11 post-treatment.

Perfusion: (fixation in situ) Dissection and macroscopic exam.

According to the text, all animals were anesthetized by IV nembutal 20 mg/kg BW and perfused with 8% formaldehyde solution until complete blood replacement.

24 hours after perfusion, the brain and spinal cord in situ and brachial and sciatic nerves were removed and stored in 8% formaldehyde solution for subsequent fixation. The other tissues were examined macroscopically.

Histopathology: The following animals were examined microscopically.

Brain- Medulla, pons, cerebral and cerebellar cortex (motor centers, basal ganglia, hippocampus and other cranial nerves.

Spinal cord- cervical, thoracic and lumbosacral regions (longitudinal and transverse sections)

Sciatic and brachial nerves- Proximal and distal segments (longitudinal and transverse sections)

Results:

Histopathology revealed no treatment-related neurotoxic effects.

There were also no pathological findings in the nervous system in the majority of the positive controls treated with 500 mg/kg body weight TOCP. This could possibly be due to the fact that only 12 to 16 days had elapsed between the first appearance of the ataxia and sacrifice of the animals, according to the study text. This interval may have been too short for the development of the fine tissue changes in the central and peripheral nervous system corresponding to the various grades of ataxia.

Discussion:

It appears that under the conditions tested trifluralin at the highest dose tested, 5000 mg/kg does not produce acute delayed neurotoxicity.

trifluralin

Page_____ is not included in this copy.

Pages 7 through 24 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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X FIFRA registration data.

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