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

JUN 17 1987

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCESMEMORANDUM:

SUBJECT: Trifluralin RS; Supplemental Data to 90-day Special Urinalysis Study in Fischer 344 Rats (Males); [TOX CHEM No. 889].

TO: Carole V. Gray
PM #23 Team
Herbicide/Fungicide Branch
Registration Division (TS-767)

FROM: R. Bruce Jaeger, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

RCJ 6/16/87
WJ 6/17/87

The Registrant (Eli Lilly and Co) submitted the final two phases of the special urinalysis study in Fischer 344 rats in response to our request for demonstrating a NOAEL on the kidneys from exposure to Trifluralin. The first portions of this study were evaluated by Tox Branch 9/26/86 (B. Dementi, Tox Doc. # 005521). The DER for the final phases of this study are reviewed herein.

Recommendation:

The data provided in this special urinalysis study demonstrate a NOAEL of 50 ppm for non-neoplastic nephrotoxic effects in the Fischer 344 rat (male), and satisfies the Tox. Branch's request for additional data in this strain of rat to resolve the adverse effects on the kidney. Although both sexes were not tested in this study, the male is decidedly more sensitive than females to the nephrotoxic effects of trifluralin and therefore, is an adequate model for demonstrating the LOAEL and NOAEL for non-oncogenic effects on the kidney and urinary bladder.

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Reviewed By: R. Bruce Jaeger *RBJ* 6/16/87
Section #1, TOX. Branch (TS-769)

TOX. CHEM. NO. 889
MRID NO. 40138301

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Urinalysis Study in Fischer 344 Male Rats
[4 month oral dosing with 6 week reversibility phase]

ACCESSION NUMBER: 193,395 (record number)

TEST MATERIAL: Trifluralin (Tech. 96.4% purity)

STUDY NUMBER: R04785

SPONSOR: Eli Lilly and Company, Elanco Div.

TESTING FACILITY: Lilly Research Laboratories, Greenfield, Indiana

TITLE OF REPORT: A Supplementary Report of a Special Urinalysis
Study on Fischer 344 Rats Maintained on Diets
Containing Trifluralin (Compound 36352) for Three
Months.

AUTHORS: J.L.Emerson, W.H. Jordan, and R.W. Usher

REPORT ISSUED: August 13, 1986

CONCLUSIONS:

The NOAEL of 0.005% (50ppm) is unchanged from our previous evaluation of the 3 month oral dosing phase (diet). There was evidence of protein excretion (TP, alpha 1, alpha 2, beta globulins) at > 0.02%, after 4 months dosing, which although not statistically significant at 200 ppm was increased in a dose related manner compared to controls. Examination of rats during the reversibility phase (6 weeks) demonstrated that many of the adverse effects were reversible. However, this was dependent upon the dose administered and the effect observed. Protein excretion, for example, was not completely reversible by the 6th week at > 0.08%, although there was no evidence of intracytoplasmic hyaline droplet formation or hyaline casts at doses < 0.32% (3200 ppm).

Special Review Criteria (40 CFR 154.7)

Materials, Methods and Study Design are the same as previously identified in DER reviewed by Dementi (9/26/86) and will not be further listed herein. (See Tox Branch Doc. No. 005521)

The supplemental submission reviewed herein contains additional data on male Fischer 344 rats maintained on diets containing 0, 0.005, 0.02, 0.08, 0.32, or 0.64% trifluralin for an additional month beyond the 3 month portion previously reviewed by B. Dementi. There were 15 control and low dose, and 10 rats in all other groups. These rats received trifluralin for a total of 4 months, placed on control diets for 6 weeks and then necropsied. No rats were necropsied at the end of the 4th month of dosing. Urine samples were collected prior to the end of the 4th month and at 3 and 6 weeks of the reversibility phase of the study.

Results (after 4 months):

Observations: No deaths occurred. No observable symptoms, other than staining of the fur around genital areas in rats at $\geq 0.02\%$.

Body Weight: Significant decrease in body weight and body weight gain at $\geq 0.32\%$.

Food Consumption: No significant difference in food consumption during the 4th month. The efficiency of food utilization (E.F.U.) was significantly lower than controls at 4 months at $\geq 0.32\%$.

Compound Ingested: Time-weighted average daily doses during the 4 months were equivalent to: 0, 2.5, 10.1, 40.1, 164, and 330.1 mg/kg.

Urinalysis: The attached table, extracted from the report, summarizes the urine excretion and urine electrophoresis data. This table is supported by the available individual animal data provided. At 4 months there was increased excretion of Na^+ ($> 0.08\%$) and Cl^- ($> 0.08\%$), and a decrease in K^+ ($> 0.32\%$), which differ somewhat from the data at 3 months. Also, increased total protein (TP) at 4 months was consistent with 3 month data. Excretion of TP at $> 0.02\%$, although not statistically significant, is greater than control and dose related. The registrant indicated that excretion of albumin ($> 0.08\%$) and agamma globulin ($\geq 0.64\%$) at 3 and 4 months suggests glomerular damage.

REVERSIBILITY PHASE:

Data gathered during this phase of the study and highlighted in the attached table (days 148-149, and 168-169), demonstrate the reversibility of many of these changes, dependent upon time and dose:

- o Ca^{++} , Mg^{++} , AST, LDH excretion reversed by 3rd week;
- o increase in urine volume reversed by 6th week;
- o Na^+ , Cl^- not completely reversible by 6th week at $\geq 0.32\%$;
- o protein excretion not completely reversible by 6th week at $\geq 0.08\%$;
- o increased excretion of K^+ at $\geq 0.64\%$;
- o increased excretion of Inorganic phosphorus at $\geq 0.08\%$;
- o changes in color, clarity, and amorphous material content completely reversed.

Histopathology:

Previously reported histopath changes (which were evident after 3 months treatment) had completely reversed at doses $\geq 0.32\%$ after 6 weeks on control diets. However, at $\geq 0.64\%$ there was still increased incidence of hyaline casts. There was also evidence of tubular epithelial regeneration (not completely reversed) demonstrating a trend toward reversal. Either the dose administered or the time for recovery were such that complete reversal was not observed.

CLASSIFICATION: CORE: Minimum

trifluralin

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Pages 5 through 8 are not included.

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