7-10-85

TOXICOLOGY BRANCH: DATA REVIEW

006890

CHEMICAL: Trifluralin

Caswell: 889
EPA Chem.#: 036101

STUDY TYPE: Mutagenicity - Chromosome Aberrations (dominant lethal test) in rats

CITATION: "A Dominant Lethal Study with Technical Trifluralin (Compound 36352) in the Wistar Rat".

ACCESSION No./MRID No.: 250598/00129059

SPONSOR/TESTING LAB.: Elanco/Toxicology Division, Lilly.

STUDY No./DATE: R00283/July, 1983.

TEST MATERIAL: Compound 36352 (technical trifluralin), Lot # 00554AP2 (95.0% ai, with unstated nitrosamine content).

PROCEDURES: Young adult male Wistar rats (357.6 + 2.0 g) were gavaged daily with test material at 0 (vehicle), 0.1 and 1.0 g/kg/day (suspended in 10% aqueous acacia) for 5 days (15 animals per test group), immediately following which each male was mated serially with single untreated females each week for 10 consecutive weeks, according to standard (referenced) procedures. Dose selection was based upon a preliminary rangefinding test in males, showing dose-related depressed food consumption and weight loss at daily doses of 0.5, 1.0 and 2.0 g/kg for 5 days. [A study with triethylenemelamine (TEM) as reference mutagen, was stated to have been conducted concurrently, but no data were given in this report.] Group means and SE were calculated for fertility, pre-implantation loss, and post-implantation deaths. Arcsin square root transformed data were analyzed statistically ($p<0.05$) by a Bonferroni-t computation for dose and mating week, while Dunnett's procedure was used for body weight and implants; chi-square was used to compare fertility rates.

RESULTS: No mortalities were reported, and orange-colored urine was evident for all treated males during the dosing period (indicating the test compound was absorbed). Significant body weight-gain depression was observed (Summary Tables 3,4; Individual Tables 12-15) on test day-5 in high-dose animals (1.0

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g/kg/day). No significant differences between control and test groups were found during any of the 10 mating weeks in mating performance and fertility (Summary Table 5; x Individual Value Tables 16-19), or in reproduction parameters (Summary Tables 6-9; Individual Value Tables 17-19), as evidenced by comparable values for pre- and post-implant losses, total number of implants and/or dead implants. Isolated occurrences of fetal anomalies (omphalocoele, cleft palates and harelip, inter alia) in live fetuses were unrelated to treatment, since these have been observed in control fetuses in other studies conducted by the laboratory.

CONCLUSIONS: The authors conclude that trifluralin administered by gavage for 5 days to males at levels depressing body weight gain (1.0 g/kg/day) had no effect on fertility nor induce dominant lethals.

TB EVALUATION: Since clinically effective doses which were evidently absorbed were employed (up to a total, limit, level of 5.0 g/kg), the negative results appears to have been validly generated. The study is provisionally ACCEPTABLE, pending receipt and review of the stated concurrent study with the reference mutagen, TEM, to assure responsiveness of the test system to a positive control.

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J. Mauer 7-11-85

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006890

TOXICOLOGY BRANCH: DATA REVIEW

CHEMICAL: Trifluralin

Caswell: 889

STUDY TYPE: Mutagenicity - Gene mutation in mammalian cells (L5178Y/TK)

EPA Chem #: 036101

CITATION: "The Effect of Trifluralin (Compound 36352) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells."

ACCESSION No./MRID No.: 249846/00126661

SPONSOR/TESTING LAB.: Elanco/Toxicology Division, Lilly.

STUDY No./DATE: 830201MLA2055/March, 1983.

TEST MATERIAL: Compound 36352 (technical trifluralin), Lot #00554AP2 (95% ai, but nitrosamine content unstated)

PROCEDURES: Following a preliminary cytotoxicity test at concentrations up to 1000 ug/ml, mutant-cleansed mouse lymphoma (L5178Y)-$TK^{+/-}$ (heterozygote) cells of the TK3.7.2C subline were exposed for 4 hr to 8 concentrations of test substance (dissolved in DMSO) ranging from 0.5 to 20 ug/ml, both in the absence and presence of Aroclor 1254 - stimulated microsomal enzymes from the livers of male Fischer-344 rats (S-9), according to standard (referenced) procedures. The reference mutagens, ethylmethanesulfanate (EMS), and 3-methylcholanthrene (3MC), served as positive controls for non-activated (-S-9) and activated (+S-9) assays, respectively. The incidences of mutant colonies ($TK^{-/-}$) in test and control cultures were compared after 12 days selection in medium favorable only to mutant cells.

RESULTS: Concentrations of 100 ug/ml trifluralin and greater were lethal in both the non-activated and activated tests, as was also 50 ug/ml in +S-9 cultures. Dose-related test compound cytotoxicity (relative survival compared to 100% for the DMSO control cultures) ranged from 18% at the HDT, 20 ug/ml, to 103% at the LDT, 0.5 ug/ml, in non-activated cultures; and from 3% to 104% in comparably treated +S-9 cultures.

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Slight variations in mutation frequencies were noted in all trifluralin cultures, but not appreciably different from DMSO controls and bore no relationship to dose (ratios of 0.8 to 1.0 compared to controls in non-activated test cultures; 0.8 to 1.9 x controls under activation). A 2.3-fold increase over control was found in one 15 ug/ml S-9 culture, at a relative survival value of 5%. By contrast, both mutagens induced clearly increased mutation frequencies of 10 to 20 times controls, accompanied by moderate cytotoxicity.

CONCLUSIONS: The author conclude, that trifluralin was not mutagenic in the L5178Y-TK foreward mutation assay up to cytotoxic concentrations (5-20% relative survival), with or without metabolic activation.

TB EVALUATION: Acceptable

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