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

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CASWELL FILE

MEMORANDUM

TO: Robert Taylor, PM#25
Registration Division (TS-767)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

RRB 9/14/83

SUBJECT: EPA Reg. No. 100-568. Terbuthylazine: submitted data demonstrating previously unknown adverse effects.

Conclusion:

We agree with the conclusion of Ciba-Geigy Study No. 820677 (see review below), reporting that adverse effects appear to a significant degree at low dose, 500 mg/kg/day (28-day dermal exposure). The following effects are reported or tabulated for low dose: symptoms of toxicity, depressions of body weight and food consumption (both sexes, and appearing from initial treatment to termination), increased brain, liver, and adrenal weights in males, decreased gonad and spleen weights in males, decreased heart and kidney weights (both sexes), and very marked decrease in thymus weights in both sexes. Mesenteric and axillary lymph nodes exhibited increased hyperplasia at low dose.

Prior to granting any further tolerances or registrations for terbuthylazine, Toxicology Branch requires that the registrant submit data to adequately characterize the lymph node hyperplasia and other effects seen in this 28-day rabbit dermal study (Ciba-Geigy No. 820677).

The registrant should be reminded that the reduction factor for some of the copied tabular data is entirely to great: some data are practically unreadable.

Reviews:

28-Day Repeated-Dose Dermal Toxicity Study in Rabbits. GU Project No. 820677 (Ciba-Geigy, Ltd.), January 1983 (Annex II), and related interim reports and other new statements (Annexes III-V). Accession No. 250673. Tox. Chem. No. 125B.

New Zealand White rabbits (2-3 kg, 12-14 weeks) were housed individually under specified controlled ambient conditions. Five males and five females were randomly assigned to each dose group: 0, 500, 1000, and 2000 mg/kg/day for 28-day exposure. An additional group of 6 males and 4 females, treated at the top dose for 28 days, was further observed during a recovery period of 14 days.

The test material was identified as TK 12669/1, Batch No. EN 16727, a solid of 99.8% purity.

Before treatment, and weekly thereafter, the flanks of the rabbits were shaved for application of gauze patches soaked [sic] with adequate quantities of test material, pulverized and soaked with distilled water. The patches, covered with impermeable material, were fastened to the body with adhesive tape, and then were removed after 6 hours. This procedure was performed once a day on a five-day-per-week basis for 28 days.

The diet was pelleted NAFAG No. 814 Tox, assayed and provided ad libitum along with tap water of drinking water quality. Mortality and signs were observed daily, body weight was measured weekly, and food consumption was measured twice weekly. Hematology and blood chemistry determinations were performed on all animals at end of treatment, using determination methods with specified references. The summary (but not the body of the report) states that all animals, at termination of appropriate observation, were sacrificed for pathological examination. All animals killed in extremis or found dead were subjected to macroscopic examination, with tissues preserved where possible. The following organs were weighed for all animals sacrificed: brain, heart, liver, spleen, kidneys, adrenals, thymus and gonads. The report states that histopathological examination was performed on 41 tissues from specimens preserved in 10% neutral formalin. The number of animals sampled for each tissue is not stated.

Statistical analysis included the non-parametric method of Lepage, and the trend test of Jonckheere.

Results:

In all treatment groups the animals showed sedation, curved body position, ataxia, and tremors during the entire application period. In the recovery group, animals were free of symptoms only in the last week of recovery. One male in the high dose group died. Body weights were significantly depressed from control values in all groups and in both sexes, with visible dose-relation. Food consumption was depressed in both sexes of all dose groups during the entire application peirod. Initial depression of consumption was particularly marked.

Hemoglobin and hematocrit values were significantly depressed at high dose in both sexes and with some dose-relation. Prothrombin time was depressed in males and slightly depressed in females. Glucose in males showed a significant increasing trend with dose; and BUN showed a significantly decreasing trend in both sexes.

From tabulation of organ weights and O/B ratios we infer that the following weight changes (relative to controls) may indicate significant organ-specific effects: brain weight increases in males at low and high dose; heart weight decrease in both sexes at all doses, and dose-related in males; increased liver weight in males at low and mid dose; decreased kidney weights in both sexes at all doses; increased adrenal weights in males at all doses; very marked decreases in thymus weights at all doses in both sexes; dose-related decrease in gonad weight in males; and decreased spleen weight in males at all doses, and in females at the mid and high dose. The report notes that following the two-week recovery period the weights of heart and testes in males and of thymus and spleen in females had reversed, but that the extent of the reversal could not be compared to controls, which were not carried through recovery.

Skin application sites did not differ from remote sites or from controls.

Microscopical examination revealed a dose-related atrophy of lymphatic tissue (axillary lymph nodes) at mid and high dose, with hyperplasia at low dose. In the mesenteric lymph nodes hyperplasia also was increased at all doses, including "recovery period" animals. Splenic congestion and atrophy were somewhat increased in all treated groups. Recovery animals showed somewhat increased nephritis and renal tubular calcification.

Classification: Minimum Data.

Additional Comments:

The above study was submitted with three communications (Annexes III-V, described below), and also by a resubmission of IBT Study No. 601-06531 (Annex I), all in Accession No. 250673.

1. A copy of a one-page Telex (Annex III, Huntingdon Research Centre) partially supports a statement of the registrant that during a pilot teratogenicity study in rabbits (preliminary to GU Test No. 821314) treatment was discontinued after three days of attempted feeding of terbuthylazine at 25, 50, and 100 mg/kg/day. No food was eaten and there was severe weight loss at all dosages. Symptoms of lethargy and jerky movement appeared in the mid-dose group, and hunched posture was observed at top dose.

In an additional study, 13-day feeding of 5 and 12.5 mg/kg/day produced severe weight loss. The letter states that no side-effects were seen at 2 mg/kg/day.

2. A communication (Annex IV) from Huntingdon Research Centre describes provisional data for a rabbit teratology study (apparently No. 821314) using TK 12 669/1. Treatment was at 0.5, 1.5, and 4.5 mg/kg/day. To compensate for anticipated lower pregnancy rate at top dose, a few extra animals were mated subsequent to initial mating. The letter states the absence of clinical signs due to treatment. Food consumption of all treated groups was slightly higher than controls. Mean body weight gain of pregnant dams is graphed as generally superior to controls in a dose-related manner. There were no obvious treatment-related macroscopic changes in the dams at sacrifice. The letter states that litter parameters (mean number of implantations, fetal loss, litter size, mean litter weight and mean fetal weight) did not reveal obvious treatment-related effects. Mean fetal loss was stated as slightly higher than control values at 4.5 mg/kg/day, and consisted mainly of isolated litters with high individual losses. In the course of continuing skeletal examination, macroscopic examination reveals two obvious malformations - one each at 1.5 and 4.5 mg/kg/day. Tabulation of pregnancy rate shows a deficit at high dose.

3. Annex V consists of an interim statement from Huntingdon Research Centre reporting the histological results for some thymus tissue samples from the on-going rabbit teratogenicity Study No. 821314. The letter tabulates the thymus regression as follows (the note suggests the data will not appear in the final report):

	State of regression of thymus			
	Within normal limits	Minimal	Moderate	Marked
Control	0	1	2	1
0.5 mg/kg/day	2	0	0	0
1.5 mg/kg/day	0	0	1	3
4.5 mg/kg/day	2	2	1	3

The low number of tissues examined, particularly at low dose, reduces the significance of these data on thymic regression.

None of the reported adverse effects of this submission (Accession No. 250673), including effects noted by preliminary data, occur at dosages as low as the low dose (0.43 mg/kg/day) of the Carcinogenicity and Chronic Toxicity Study, Rat (Ciba-Geigy No. 791229, One-Year Status Report), in which effects at low dose included (in one or both sexes) elevated reticulocytes and normoblasts, depressed lymphocytes, increased BUN, increased cholesterol, and elevated adrenal 0/B ratios.

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