11-16-82

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

MEMORANDUM

002291

TO: Dick Mountfort (23)
Registration Division (TS-767)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Review of Rat Teratology Study of Bolero (Thiobencarb), Reg. Nos.: 239-2449/239-2450, Acc. No. 248485, CASWELL#207DA

Registrant: Chevron Chemical Co.
Ortho Agricultural Chemicals Division
940 Hemsley Street
Richmond, CA 94804

Recommendation:

It is recommended that this study be classified as Core-Guidelines. The NOEL for maternal and fetotoxicity is 25 mg/kg. No teratogenic potential is indicated at 150 mg/kg (HDT).

Review of Data:

Rat Teratology Study. Performed at Science Applications, Inc., La Jolla, California, Report No. 581007, July 13, 1982 and submitted by Chevron Chemical Company.

NOTE: This study was originally evaluated in my review of December 14, 1982. At that time, a complete Final Report was not available. The Final Report has recently been submitted.

One hundred Sprague-Dawley derived female rats were mated with male rats for a 14 day period or until pregnancy occurred as detected by a vaginal plug and/or sperm in the vaginal fluid. The day that an animal exhibited a positive response for mating was considered as day 0 of gestation.

Animals were dosed on days 6-19 of gestation. Twenty-five females per dose level were administered 0, 5, 25 or 150 mg/kg via oral intubation. Tween 80 (carboxymethyl cellulose sodium salt) and dionized water was used as a vehicle. Control animals received only the vehicle.

Body weights were taken on days 0, 6-19 and prior to cesarian section. Food consumption was measured on days 3, 6, 10, 14, 17 and 20. Mortality and observations were recorded twice daily.

On day 20 of gestation, animals were killed by $CO_2$ asphyxiation. Animals were examined for gross morphological abnormalities. Abnormal tissues were preserved for possible histological examination. The uterus and ovaries were removed, weighed and examined for number of corpora lutea, number of live and dead fetuses, number of late and early resorptions and the condition of the uterus and placenta were examined.

Fetuses were removed, weighed, sexed and examined externally for abnormalities. Approximately one-half of the fetuses were decapitated and the heads were fixed in Bouin's solution for at least one week. The heads were then sectioned and examined for soft tissue abnormalities. Each fetus was also examined viscerally with care taken not to disturb skeletal structure. Following visceral examination, all fetuses were stained with Alizarin Red S and examined for skeletal abnormalities.

Results:

Maternal toxicity was evident only at 150 mg/kg and was indicated by decreased mean weight gain (73.5 grams compared to 98.1 grams in the control). No clinical observations of toxicity were evident in any group.

No apparent effect on resorptions/litter, implantations/litter or number of live pups/litter was observed. The mean weight of live fetuses was decreased in the high dose group (3.3 g compared to 3.8 g in controls). Fetotoxicity was suggested only in 150 mg/kg dose group based on visceral and external examination of fetuses and this dose level also evidenced maternal toxicity. An increased number of runts were observed in that group (10 runts/20 litters compared to 1/17, 1/23 and 3/23 in the 0, 5 and 25 mg/kg groups, respectively) and an increased incidence of hydroureter was also observed in the 150 mg/kg dose group (5 occurrences/20 litters compared to 1/23, 2/23 and 3/17 in the 0, 5 and 25 mg/kg groups. However it is noted that only 3 litters were affected at the high dose (hydroureter and/or hydronephrosis).

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TABLE I

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Results of Fetal Visceral and External Examination Findings*

| | 0 mg/kg | 5 mg/kg | 25 mg/kg | 150 mg/kg |
|---|---|---|---|---|
| Hydronephrosis | 1/17 (1) | 1/23 (0) | 0/23 (0) | 2/20** (2) |
| Hydroureter | 1/17 (1) | 2/23 (2) | 3/23 (3) | 5/20 (3) |
| Runt | 1/17 (1) | 1/23 (1) | 3/23 (2) | 15/20 (7) |

*Number of pups with observation/number of litters examined. Number in parenthesis is number of litters affected.

**Both pups with hydronephrosis also had hydroureter and are included in both categories in this table.

Additional Comments:

The historical data submitted by the laboratory performing the study indicates that the apparently increased incidences of hydroureter and hydronephrosis in the high dose group are comparable with the historical incidence at that facility (2.1 averag. percentage per litter of hydroureter both historically and in the high dose of this study). Runting is increased at the high dose level, in both the number of pups and the number of litters affected, and is clearly higher than historical data (0.2 average percentage per litter historically compared to 4.7 mean litter percent in high dose group). However, because runts are classified as such on the basis of lower body weights in this study, it is not unexpected that an increased number of runts would be observed at a dose level which is associated with a lower mean pup weight (3.3 grams vs. 3.7 grams in the historical group. It thus appears that the runting should not be considered a teratogenic effect in this study but rather a fetotoxic response associated with lower body weights in the high dose group.

Core Classification: Core-Guidelines

NOELs for maternal and fetotoxicity are 25 mg/kg. No teratogenic effect is indicated at 150 mg/kg (HDT).

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