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

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MAY 18 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of a Teratology Study With Thiobencarb in rabbits
EPA # 239-2450 Caswell # 207 DA
EPA Accession # 265667 Tox. Proj. # 70-0163

TO: Mr. Richard Mountfort
Product Manager # 23
Registration Division (TS-767C)

FROM: Quang Q. Bui, Ph.D. Quang Bui 5/15/87
Acting Head, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Theodore M. Farber, Ph.D. 5/18/87
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant Chevron Chemical Corporation
Richmond, CA 94804

Recommendation

Administration of Technical Thiobencarb (Bolero) to pregnant rabbits during the period of major organogenesis (days 6-18) up to and including a dosage level of 200 mg/kg did not exhibit evidence of developmental toxicity.

It is recommended that the teratology study in rabbits (Imamichi Institute, 9/1/86, Japan, Report # 158-8) be classified as Core Minimum Data with a developmental NOEL established at 200 mg/kg (HDT) and a maternal NOEL at 100 mg/kg.

The registrant has fulfilled the regulatory requirements for 2 teratology studies in 2 species (rat and rabbit).

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DATA EVALUATION RECORD

Study Type: Developmental Toxicity
Chemical: Thiobencarb, Benthiocarb, Bolero
Test Material: Technical 96% a.i., pale yellow liquid

Study Identification:

"Teratology Study of Thiobencarb in the Rabbit-Pilot Study"

Testing Facility: Imamichi Institute for Animal Reproduction, Japan
Report No.: 158 A
Report Date: 9/1/86
Study Author: Kiyonori Tauchi et al.,

EPA Accession No.: 265667

Study Reviewed by: Quang Q. Bui, Ph.D.
Toxicologist, Section V
Toxicology Branch/HED (TS-769C)

RECOMMENDATION

It is recommended that this study be classified as Core Supplementary Data (dose-range finding study).

Under the conditions of this study, evidence of maternal toxicity was observed at the two highest doses tested, 250 and 560 mg/kg/day. At the 250 mg/kg dosage level, one dam aborted and was sacrificed. However, at the 560 mg/kg dosage level, four out of five dams tested were sacrificed in extremis due to deteriation of health (sedation, hypothermia, and ataxia) and the remaining dam aborted. Statistically significant decreases in body weight gains and food consumption were noted at these two dose levels.

At laparotomy, a slight decrease in fetal body weight was noted at the 250 mg/kg but no frank teratogenic effects were observed in any of the tested fetuses.

Based upon these findings, selection of 20, 100, and 200 mg/kg for the primary teratology study was justified.

I. MATERIALS AND METHODS

1. Test Material: Technical Thiobencarb, 96% a.i., pale yellow liquid. The test material was dissolved in an aqueous solution of 0.5% carboxymethylcellulose containing 0.1% Tween 80. The test solution was given by gavage at 10 ml/kg b.w.

2. Dose Levels: 0, 10, 50, 100, 250, and 560 mg/kg given to 5 dams each from days 6-18 of gestation. The control group was treated with the vehicle alone.

3. Animals: New Zealand white rabbits (Ichikaways, Japan) Average female body weights = 2.4 - 3.2 kg Copulated female animals were supplied by the breeder on day 0 of gestation.

4. Housing: Animals were individually housed under climate controlled environment (T°= 22 - 26°C; Humidity= 45-65%; Light= 14 hours/day).

5. Diet: Food and water were provided ad libitum. Drinking water and food were analyzed for contaminants twice a year.

6. Examinations: All dams were examined daily for overt signs of toxicity and mortality. Maternal body weights were recorded on days 0, 6, 9, 12, 15, 18, 23, and 28 of gestation with food consumption measured daily. All surviving dams were sacrificed on day 28 of gestation and a gross necropsy observation was conducted. Several organs were removed and weighed. External, visceral, and skeletal examinations were performed on all pups following routine teratology procedures.

II. RESULTS

1. Maternal Toxicity

Four animals were not pregnant: one 10 mg/kg, one 100 mg/kg, and two 250 mg/kg. In the 250 mg/kg group, one female aborted and was sacrificed on day 23 of gestation. Four out of

five does in the 560 mg/kg group were sacrificed due to deteriorated health condition (ataxia, hypothermia, and sedation). The remaining high dose doe aborted.

Statistically significant decreases in body weight gains and food consumption were noted in the 250 and 560 mg/kg groups during and after the dosing period (days 6-18 of gestation).

At laparotomy, no changes in corpora lutea, implantation, resorption, little size, and dead fetus were found among the groups. Gross necropsy did not reveal any evidence of a compound-related effect.

The brain, liver, kidney, spleen, heart, and adrenals were removed and weighed. No apparent dose- and treatment-related effects were noted. The liver of the 250 mg/kg group weighed slightly more than control (139 g vs 116 g, respectively), but a statistical significance was not attained, probably due to the small sample size.

2. Developmental Toxicity

Fetuses collected from mothers treated with Thiobencarb weighted slightly less than controls. Respective fetal body weights of 44.7, 41.7 , 38.6, 41.0, and 32.7 grams were found in the 0, 10, 50, 100, and 250 mg/kg groups. External, visceral, and skeletal observations were conducted on all fetuses and evidence of a treatment-related effect was not demonstrated. However, it should be emphasized that the small sample size used in a dose-range study precluded accurate assessment of developmental toxicity.

## III. DISCUSSION AND CONCLUSION

Under the conditions of this study, administration of 250 and 560 mg/kg Technical Thiobencarb to pregnant rabbits from days 6-18 of gestation resulted in significant maternal toxicity characterized by deteriorated health, abortion, decreased body weight gains, and decreased food consumption. The maternal LEL is established at 250 mg/kg and the NOEL at 100 mg/kg. The dose level of 250 mg/kg was also associated with decreased fetal weight. But, no evidence of a treatment related effect was noted in any of the treated fetuses with respect to external, visceral, and skeletal examination. It should be emphasized that the developmental toxicity potential of Thiobencarb cannot be ascertained in light of the nature of the study design: A dose-range finding study.

From the results of this dose-range finding study, dose levels of 0, 50, 100, and 200 mg/kg were selected for the primary study and this selection appeared appropriate.

It is recommended that this study (Imamichi #158 A) be classified as Core Supplementary Data (dose-range finding study).

DATA EVALUATION RECORD

Study Type: Developmental Toxicity
Chemical: Thiobencarb, Benthiocarb, Bolero
Test Material: Technical 96% a.i., pale yellow liquid

STUDY IDENTIFICATION

"Teratology study of Thiobencarb in the rabbit"

Testing Facility: Imamichi Institute for Animal Reproduction
Report No.: 158-B
Report Date: 9/1/86
Authors: Kiyonori Tauchi et al.,

EPA Accession No.: 255667

Study Review By: Quang Q. Bui, Ph.D.
Acting Head, Review Section V
Toxicology Branch/HED (TS-769C)

RECOMMENDATION

Under the conditions of this study, the maternal NOEL is established at 100 mg/kg. Significant increases in both absolute and relative liver weights were noted at the 200 mg/kg. Although these effects were not considered as toxicologic effects but rather as adaptive responses, they still were evidence of a treatment-related effect.

Developmental toxicity was not manisfested in any of the treated groups and there is no suggestive evidence to indicate that Technical Thiobenearb is a developmental toxicant in rabbits up to and including a 200 mg/kg dosage level.

It is recommended that this study be classified as Core Minimum Data.

Materials and Methods

A copy of the procedure used is appended. However, the following comments and highlights were noted:

1. A quality assurance statement signed off by the Director of the testing facility (T. Amegatsu, 9/1/86) was appended with the final report along with a certificate of compliance with FIFRA GLP standards signed off by Chevron Company representatives (C.L. Tellone and R.A. Zimmerman, 9/23/86).

2. Mating of animals was performed by the breeder and copulated female animals were supplied on day 0 of gestation to the testing facility.

3. All animals were housed under climate - controlled environment with food and water ad libitum. Food and water were analyzed for contaminants and the results were appended with the final report.

4. The test material was suspended in an aqueous solution of 0.5% CMC sodium. Tween 80 was added in a concentration of 0.1% of the suspension. Fresh solutions were prepared daily.

5. Animals were gavaged from days 6-18 of gestation. The dose was calculated based on day 6 body weight data.

6. Visceral abnomalities in all viable fetuses were examined by the method of Stuckhardt (1984).

Results

A. Concentration Analysis

The test solution was analyzed by gas chromatography and the following results were obtained.

| Dose level (mg/kg) | Nominal Conc. (mg/ml) | Actual Conc. (mg/ml) |
|---|---|---|
| 0 | 0 | 0 |
| 20 | 2 | 1.64 (82%) |
| 100 | 10 | 10.4 (104%) |
| 200 | 20 | 20.4 (102%) |

The data indicated that the actual concentrations were within acceptable limits.

B. Maternal Toxicity

1. Clinical Observations

One control animal aborted on day 24 of gestation and one 20 mg/kg doe aborted on day 22 of gestation. Diarrhea was the only clinical sign reported affecting 3 animals each in the 20, 100, and 200 mg/kg groups

2. Body Weight

No biologically or statistically significant differences were noted among the treated and control groups.

3. Food Consumption

No significant differences in food consumption were found in the treated groups.

4. Cesarean Section Data

| | Control | 20 mg/kg | 100 mg/kg | 200 mg/kg |
|---|---|---|---|---|
| No. mated females assigned | 16 | 16 | 16 | 16 |
| No. nonpregnant | 1 | 1 | 2 | 3 |
| Pregnancy Rate (%) | 94 | 94 | 88 | 81 |
| No. aborted | 1 | 1 | 0 | 0 |
| No. sacrificed | 14 | 14 | 14 | 13 |
| $\bar{X}$ Corpora lutea | 9.3 | 8.0 | 9.0 | 8.8 |
| $\bar{X}$ Implantation | 8.6 | 7.4 | 8.1 | 7.8 |
| Preimplantation loss (%) | 7.5 | 7.5 | 10.0 | 11.4 |
| $\bar{X}$ Live fetuses | 8.1 | 7.1 | 7.9 | 7.5 |
| Post implantation loss (%) | 5.8 | 4.1 | 2.5 | 3.0 |
| No. dams with complete resorptions | 0 | 0 | 0 | 0 |

No significant differences were found between the control and treated groups relative to corpora lutea, implantations, resorptions, pre and post implantation loss, and litter size.

The number of dams in each group at C-section was adequate for statistical purposes.

5. Necropsy Data

No apparent compound - related effects were noted.

6. Organ Weights

Organ weight data are photocopied from Table 8 of the final report. Significant increases in both absolute and relative liver weights were found at the 200 mg/kg dosage level. A significant increase in absolute heart weight was noted in high dose females. However, the biological significance of this finding is unclear.

THIOBENDICARB TOX REVIEW

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C. Developmental Toxicity

1. Cesarean Section Data

| | Control | 20 mg/kg | 100 mg/kg | 200 mg/kg |
|---|---|---|---|---|
| No. of dams | 14 | 14 | 14 | 13 |
| No. of live fetuses | 114 | 100 | 111 | 98 |
| Sex Ratio (M/F) | 0.84 | 1.13 | 0.66 | 1.18 |
| Fetal weight (g) | | | | |
| male | 37.7 ± 4.2 | 39.2 ± 4.2 | 38.0 ± 4.7 | 41.1 ± 6.0 |
| female | 40.5 ± 5.6 | 40.8 ± 3.3 | 39.2 ± 5.8 | 41.2 ± 50 |

No alterations in fetal weights were found. The fetal sex ratio in the 20 and 200 mg/kg groups apparently favored male fetuses but its biological significance is highly unlikely.

2. Gross Observations

One fetus in the control group was described with gastroschisis.

3. Visceral Observations

No visceral abnormalities were observed in either control or treated groups.

4. Skeletal Observations

Data on skeletal abnormalities are photocopied from Table 4 of the final report and appended with this DER.

Fused sternebrae was only observed in the treated groups but at a very low incidence affecting 1(1), 2(2), and 2(2) fetuses (litters) in the 20, 100, and 200mg/kg groups, respectively. No evidence of a compound-related effect was found with respect to other skeletal abnormalities.

DISCUSSION

1. Maternity toxicity

Data from the dose - range finding study indicated systemic toxicity (abortion, decreased weight gains and food consumption) at the 250 mg/kg dosage level. Data from this dose-range finding study, hence, support the selection of 200 mg/kg as the highest dose tested in the main study.

Administration of Technical Bolero up to and including a dosage level 200 mg/kg to pregnant rabbits during the period of major organogenesis (days 6-18) did not result in noticeable adverse effects on body weight, food consumption, clinical signs, or reproduction. Significant increases in both absolute and

relative liver weight were associated with high dose dams and may reflect an adaptive response rather than a toxicologic effect. Nevertheless, these alterations in liver weights should be considered as treatment - related

Under the conditions of this study, the maternal NOEL is established at 100 mg/kg and the LEL at 200 mg/kg.

2. Developmental Toxicity

No manifestations of developmental toxicity were observed in fetuses collected from treated mothers. Fusion of the sternbrae was found only in the treated groups but at a very low incidence. No compound-related evidence of a developmental delay in rabbits was found.

Under the conditions of this study, Technical Bolero was not a developmental toxicant in rabbits up to and including a dosage level of 200 mg/kg.

Developmental toxicity NOEL = 200 mg/kg (HDT)

3. Classification: Core Minimum Data

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