12-2-87

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

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DEC 2 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Thiodicarb: Two range-finging studies, in pregnant rabbits, submitted to upgrade a previous teratogenicity study in rabbits.

TO: Edwards/Kumar, PM-12
Registration Division (TS-767C)

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EPA ID No.: 6F 3417
Project No.: 7-1103
Caswell No.: 900AA
Registrant: Union Carbide Agricultural Projects Company, Inc.

Action Requested

The registrant has submitted 2 range-finding studies in rabbits for evaluation so that the Core-classification of a previously submitted teratogenicity study in rabbits may be upgraded.

Background

A teratogenicity study in rabbits with thiodicarb (Project No. WIL-95002, Performed by Wil Research Laboratories, Inc., Ashland, OH, for Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC; dated May 16, 1986) was evaluated by Dynamac Corp. (report dated May 22, 1987). It was concluded that this study provided some evidence for establishing a NOEL for maternal toxicity at 20 mg/kg/day based on minimal (but statistically significant) reduction in bodyweight gain and food intake reported at 40 mg/kg/day during the first week of treatment. However, data from range-finding studies were requested to support the LOEL for maternal toxicity.

The study was classified Core-Supplementary but it was indicated that it could be upgraded following the submission and evaluation of range-finding studies.

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Conclusion

The high-dose of thiodicarb (40mg/kg/day) in the subject teratogenicity study induced maternal toxicity in a range-finding study which was evident from mean bodyweight loss during the treatment period (days 6-19 of gestation). Therefore, the Core-classification for the teratogenicity study should be upgraded to Minimum.

Range-finding studies

Test material

Thiodicarb (48-216 A, B, C) was described as a white powder; active ingredient= 93% and inert ingredient =7%. The material was suspended in 0.5% aqueous methylcellulose at concentrations of 12.5, 25, 62.5, 125 and 250 mg/ml for dosages of 25, 50, 125, 250 and 500 mg/kg/day, respectively, in the first study (WIL-95001) and at concentrations of 1, 5, 10, 20 and 40 mg/ml for respective dosages of 1, 5, 10, 20 and 40 mg/kg/day in the second study (WIL-95001A). Dosage volumes of vehicle were 2 and 1 ml/kg in the first and second studies, respectively. Test suspensions were prepared weekly. The investigator analyzed representative samples for homogeneity and stability. Controls were administered the appropriate volume of vehicle.

Test animals

New Zealand white virgin female rabbits that were described as sexually mature (age and weight range not provided) were acclimated for a minimum of 8 days. Eight animals were assigned to each treatment or control group in each study.

Methods (a detailed description of experimental methodology is provided on appended pages 1-7)

The experimental design was comparable between studies with the exception of the dosage levels of thiodicarb administered, as previously indicated. The females in these studies were artificially inseminated. The appropriate dosage of thiodicarb suspension was administered orally (via gavage) on a daily basis from gestation day 6 through 19. The second study was performed because the investigator concluded that the dosage levels administered in the first study were "excessive" for a teratology study.

Throughout gestation all animals were observed twice daily for toxicity and body weights were recorded on days 0, 6, 9, 19, 24 and 29 of gestation. There was no indication that food and water consumption were measured. Gross necropsies were performed on animals that died or were sacrificed during the study. All surviving animals were sacrificed on gestation day 29 and the uterus and ovaries from each animal were examined. Recorded observations included the number of corpora lutea, the number and location of viable and non-viable fetuses, early and late resorptions and the total number of implantation sites. Maternal tissues were preserved in 10% neutral buffered formalin for histopathological examination only if deemed necessary by gross findings.

Results

First study

Maternal mortalities

All females in the 500 mg/kg group died on the first two days of dosing (gestation days 6 and 7) and all females in the 250 mg/kg group died between gestation days 8 and 12. Three females in the 125 mg/kg group and 1 female in the 50 mg/kg group were found dead on gestation days 14, 17, 20 and 15, respectively. The investigator indicated that one female in the 50 mg/kg group was sacrificed on gestation day 14 due to an apparent dislocated spinal column. The cause(s) of the apparent compound-induced deaths were not obvious from the gross necropsy data.

Fetal toxicity

The only evidence of fetal toxicity was an increase in mean early resorptions in the 50 and 125 mg/kg groups; females in the higher dosage groups did not live long enough for meaningful uterine examinations.

Early fetal resorptions
No. observed/No. dams (Mean, S.D.)

Dosage (mg/kg/day)—	0	25	50	125
	2/7(0.3± 0.5)	6/6(1.0± 1.3)	9/4(2.3±2.2)	7/3(2.3±2.5)

Maternal bodyweight loss

Females in the 50 and 125 mg/kg groups lost bodyweight during the treatment period, as shown below, while the females in the control and 25 mg/kg groups gained bodyweight.

Maternal bodyweight changes during gestation

Dosage group (mg/kg/day)——	0	25	50	125	250*	500*
Gestation interval(days)						
6-9	+7	-97	-166	-149	-397	——
12-19	+87	+121	-68	-269	——	——
6-19	+163	+72	-142	-393	——	——
0-29	+371	+184	+35	+377	——	——

*Blank spaces are shown because the animals had died previous to the designated intervals.

Second study

Maternal mortalities

Only 2 females died during the second study. The investigator indicated that these animals, which were in the 1 mg/kg group, apparently died from bacterial infections.

Fetal toxicity

Fetal toxicity was not evident in the second study. The mean number of viable fetuses, implantation sites, corpora lutea and post-implantation losses were comparable between the treated and vehicle control groups.

Maternal bodyweight loss

Mean maternal weight loss was observed in the 40 mg/kg group during the gestation intervals shown below as well as during the ovreall treatment period. The dams in this group gained weight following treatment (gestation days 19-29) resulting in comparable mean weight gain for females in the vehicle and 40 mg/kg groups during the entire gestation period.

Maternal bodyweight changes during gestation

Dosage group—— (mg/kg/day)	0	1	5	10	20	40
Gestation interval (days)						
6-9	+1	-46	+38	-10	+2	-63
9-12	-17	+33	+33	-13	+83	-49
6-19	+61	+74	+85	+6	+89	-63
0-29	+204	+110	+358	+80	-278*	+213

*Weight loss occurred in every animal in this group during the post-treatment period (gestation days 19-29). The mean weight loss among dams that did not deliver on gestation day 29 (6/8) was 501 ± 135g. The investigator did not explain this phenomenon, however, procedural error is probable.

Decreased excretory function

The investigator noted that treated dams decreased defecation and urination compared to controls in both studies; the incidence of this observation was treatment-related and, in the second study, dose-related. The investigator did not explain whether "decrease" meant frequency or quantity; no quantitative data were provided. There was no obvious correlation between this observation and the noted bodyweight changes. It is difficult to determine the possible significance of this apparently subjective observation, especially in the absence of food and water consumption data.

Conclusion

The investigator concluded that the 50 mg/kg/day level of thiodicarb administered in the first range-finding study was "excessive" for a teratology study because: 1) 1/8 dams died during the study, 2) maternal bodyweight loss occurred during treatment and 3) there was a slight increase in the mean number of early resorptions. Although this conclusion is debatable, maternal toxicity was adequately demonstrated in the second range-finding study at the 40 mg/kg/day dosage level at which maternal bodyweight loss was induced during the treatment period (gestation days 6-19). The NOEL for maternal toxicity, considering both studies, was 25 mg/kg/day. Therefore, the Core-classification for the subject teratogenicity study should be upgraded from Supplementary to Minimum.

Thiodicarb tox review

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Pages 6 through 12 are not included.

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