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DATA EVALUATION RECORD

BAYTAN

Teratogenicity Study in Rats

STUDY IDENTIFICATION: Renhof, M. Study for embryotoxic effects on rats after oral administration. (Unpublished study No. 86664 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Federal Republic of Germany, and submitted by Mobay Chemical Corp., Kansas City, MO; dated May 17, 1984.) Accession No. 073247.

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APPROVED BY:

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Date: 7/1/86

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1. CHEMICAL: Baytan; KWG 0519; triadimenol; beta-(4-chlorophenoxy)-alpha-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol.

2. TEST MATERIAL: KWG 0519 consisted of 95.2% of triadimenol; no other information was reported.

3. STUDY/ACTION TYPE: Teratogenicity study in rats.

4. STUDY IDENTIFICATION: Renhof, M. Study for embryotoxic effects on rats after oral administration. (Unpublished study No. 86664 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Federal Republic of Germany, and submitted by Mobay Chemical Corp., Kansas City, MO; dated May 17, 1984.) Accession No. 073~~14~~4-7.

5. REVIEWED BY:

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7. CONCLUSIONS:

A. The NOEL and LOEL for maternal toxicity in rats were 10 and 30 mg/kg/day of KWG 0519, respectively, based on significant decreases in body weight gains at 30 mg/kg/day. The NOEL and LOEL for embryo/fetal toxicity and teratogenic effects could not be assessed.

B. Because of deficiencies in the conduct and reporting of this study, such as the omission of individual data for fetal skeletal and visceral examinations (see item 14), we were unable to assess the teratogenic potential of KWG 0519. Therefore, this study is classified Core Invalid.

8. RECOMMENDATIONS: In order to upgrade this study, the sponsor must describe the methods of maternal and fetal sacrifice and submit individual data including fetal body weights, number of resorptions and dead fetuses, and visceral and skeletal findings.

Items 9 and 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: KWG 0519, batch No. 289/290, consisting of 95.2% active ingredient (triadimenol), was prepared as an aqueous emulsion in 0.5% Cremophor EL. Dosages of 0, 10, and 30 mg/kg/day were administered orally (method of administration was not specified) to mated female rats from gestational days (GD) 6 through 15 at a constant volume of 10 mL/kg of body weight.

2. Animals and Test System: Sexually mature female BAY:FB 30 rats (Bayer AG), weighing between 187 and 247 g, were mated to males of the same strain on a 2:1 basis and randomly assigned to three groups. Daily vaginal smears were performed to confirm a positive mating, and the day on which sperm was detected was designated as GD 0. Mated females were observed daily for mortality and pharmacological symptoms. Body weights were apparently measured on GD 0, 6, 15, and 20 but the author did not specify when the measurements were conducted. On GD 20, pregnancies were terminated by caesarean section, and the maternal organs were examined for abnormalities. The uteri were examined to determine the number of

[1] Only items appropriate to this DER have been included.

implantations, viable and dead fetuses, and resorptions. Ovaries were apparently not examined. An external examination of the fetuses was conducted and abnormalities and sex were recorded. Individual fetal and litter body weights and placental weights were measured. Approximately one-third of the fetuses were examined for visceral abnormalities using a modification of Wilson's technique (the modification was not reported). The remaining fetuses were eviscerated and the skeletons were cleared in a dilute KOH solution and stained with Alizarin red S for examination of skeletal abnormalities.

B. Protocol: A protocol was not provided.

12. REPORTED RESULTS:

A. Test Material Analysis: No analyses of the dose formulations for homogeneity, concentration, or stability were reported.

B. Maternal Effects: One animal in the control group died during the study (day of gestation was not reported). Examination at necropsy revealed "patchy" lungs, which indicated a possible lung infection. No other mortalities occurred during the study. Clinical signs noted during the study included soft stool/diarrhea, hypothermia, and bloody vagina. They were considered random occurrences and not attributed to test material administration. Maternal body weight gains during dose administration and throughout the entire gestational period were significantly reduced ($p < 0.05$) in the 30-mg/kg dose group compared to controls (Table 1). Body weight gains for the 10-mg/kg dose group were comparable to controls. No compound-related findings were noted at necropsy. The pregnancy rates for both dose groups were higher than that of the controls (Table 2).

C. Embryonic/Fetal Effects: The author reported no differences in the number of live fetuses and resorptions and fetal body weight between control and dose groups. Placental weights were significantly higher ($p < 0.05$) in the 30-mg/kg dose group when compared to controls. However, the author stated that increases in placental weights generally occurred after the administration of azoles. A summary of the incidences of developmental variations and malformations noted is presented in Table 3. "Humped ribs" were noted in two control fetuses (from separate litters) and one 30-mg/kg fetus. A single fetus from a high-dose litter (30 mg/kg) had multiple malformations including "exentery (disemboweled)," cleft sternum, fusion of rib and vertebral arch, asymmetric vertebrae, and curved spinal column. No malformations were reported in the 10-mg/kg group. The author considered these malformations as random occurrences and not compound related. Incidences of minor skeletal variations were comparable between control and test groups.

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TABLE 1. Effects of KWG 0519 on Maternal Body Weight Gains in Rats

Dosage Level (mg/kg/day)	Mean Body Weight Gain (g±S.D.) at GD Interval: 6-15	0-20
0	82.1±13.6	198.1±23.1
10	81.0±13.2	195.9±29.3
30	70.4±11.7*	181.2±20.8*

*Significantly different from control value ($p < 0.05$).

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TABLE 2. Effects of KWG 0519 on Reproductive and Fetal Parameters in Rats

Parameter	Dosage Level (mg/kg/day) 0	10	30
No. females mated	25	25	25
No. females pregnant	21[a]	24	23
Pregnancy rate (%)	84.0	96.0	92.0
No. implantations[b]	13.1 ±1.5	12.7 ±2.5	12.1 ±1.7
No. viable fetuses[b]	12.6 ±1.7	11.4 ±3.6	11.4* ±1.4
Viability index	0.96	0.89	0.94
Fetal body weight (g)[b]	4.33 ±0.21	4.43 ±0.50	4.40 ±0.23
Placental weight (g)[b]	0.65 ±0.06	0.69 ±0.07	0.72* ±0.07
Sex ratio[c]	1.14	1.04	1.57[d]

[a]Includes the animal that died during the study.

[b]Mean±SD.

[c]Male fetuses/female fetuses.

[d]One litter consisted of 11 male and 1 female fetuses.

*Significantly different from control value ($p < 0.05$).

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TABLE 3. Summary of Effects of KWG 0519 on Incidence of Developmental Variations and Malformations in Fetal Rats

	Litter Incidence at Dosage Level (mg/kg/day)		
	0	10	30
No. litters examined	20	23[a]	23
Minor skeletal variations (%)	18 (90.0)	21 (91.3)	22 (95.7)
Malformations (%)	2 (10.0)	0 (0)	2 (8.7)

[a]One litter was totally resorbed.

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13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The author concluded that KWG 0519 was toxic to pregnant rats at a dose level of 30 mg/kg but not at 10 mg/kg. No embryonic/fetal toxicity or teratogenic effects were noted even at the highest dose tested.

B. No quality assurance statement was present in the study report.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Because of the following deficiencies in the conduct and reporting of this study, we were unable to assess the teratogenic potential of KWG 0519. We therefore classified the study Core Invalid.

1. Corpora lutea counts were not reported. Therefore, we could not assess whether normal ovulation had occurred nor calculate preimplantation losses.

2. The numbers of resorptions and dead fetuses were not specified. Instead, the author reported the number of fetal "losses" for each litter, but did not specify what these losses included. Therefore, we were unable to calculate postimplantation losses or assess the embryonic/fetolethal toxicity of KWG 0519.

3. Individual fetal body weights and data from visceral and skeletal examinations were not reported. Therefore, we could not verify mean body weight values or the numbers of skeletal variants and malformations reported in the summary tables.

4. The number of fetuses in each litter with minor skeletal variations was reported. However, the types of variations observed were not reported. Although some degree of skeletal variation is normal, increases in certain types may be indicative of a compound-related teratogenic effect; without data on the types of variations noted, the teratogenic potential cannot be assessed.

5. Because no external or visceral variations or malformations were reported, we question the thoroughness of the fetal examinations.

6. The method of fetal sacrifice was not specified; therefore, we were unable to assess the acceptability of the method of sacrifice for use in a teratogenicity study.

7. The method used (if any) to confirm pregnancy status of uteri with no visible implantations was not reported; therefore, we could not assess the accuracy of the reported pregnancy rates.

8. There was a discrepancy between the text and Table 4 of the report. In the text, the author stated that there were no significant differences in number of viable fetuses between control and test groups. However, in the summary table (Table 4) this parameter was significantly lower ($p < 0.05$) at the 30-mg/kg dose level when compared to control. We were unable to perform statistical analysis because the individual litter data did not clearly separate viable and nonviable fetuses.

9. No analyses on the stability, homogeneity, or concentration of the test material in the dose formulations were reported. Therefore, we were unable to assess whether the animals received the correct doses.

10. The age of the females was not specified; the author stated only that they were sexually mature. Selection of animals that are too young or old can affect fertility.

11. The author did not specify the criteria for the selection of fetuses for skeletal and visceral examinations.

12. Only two dose levels were tested.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Methods, CBI pp. 4-6.

APPENDIX A

Methods

Baytan

Page _____ is not included in this copy.

Pages __11__ through __13__ are not included in this copy.

The material not included contains the following type of information:

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_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

__X__ FIFRA registration data.

_____ The document is a duplicate of page(s) _____

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