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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Paraquat Dichloride: Teratogenicity Study in the Mouse. Report No.
CTL/P/364; 6/12/78, EPA Accession No. 244499.

Caswell No. 634

FROM: Krystyna K. Locke
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for Edwin Budd 5/21/81

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THRU: Christine F. Chaisson, Acting Branch Chief
Toxicology Branch/HED (TS-769) *for WB*

Registrant: Chevron Chemical Company
Richmond, California

Conclusions:

1. Paraquat was not teratogenic at 10 mg paraquat ion/kg body weight (highest level tested).
2. Classification of study: Core-Minimum.

SUMMARY

1. Paraquat was not teratogenic at all levels tested (1, 5 and 10 mg paraquat ion/kg body weight).
2. There was a tendency for group mean fetal weight to decrease with increasing dose, but the differences were small (3-6%) and statistically insignificant.
3. The number of late resorptions increased with dose, but these changes were small (0.6-2.3%) and statistically insignificant.
4. The incidence of external and soft tissue abnormalities was low and did not appear to be related to treatment with paraquat.
5. There were occasional statistical differences in ossification of individual bones, but these were dose-unrelated.
6. There was a reduction in maternal body weight gain at the 5 mg/kg (14.2%) and 10 mg/kg (10.8%) level which was attributed to paraquat treatment. Only the reduction of 14.2% was statistically significant ($p < 0.05$).

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7. Gross necropsy and histopathology of maternal tissues revealed no abnormalities related to treatment with paraquat.

EVALUATION

This study was started on 5/26/77. Dose levels were determined in a preliminary study. The test material was 100% paraquat dichloride. Positive control was not used.

Experimental Procedures:

Young adult mice (SPF colony, Alderley Park, Cheshire, England) were mated and then were given daily 0 (Group 1), 1 (Group 2), 5 (Group 3) or 10 (Group 4) mg of paraquat ion/kg body weight, from days 6 through 15 of pregnancy. The mice were killed on day 18 of pregnancy. The test material (0.1 ml/10 g body weight) was given by gavage in 0.5% aqueous solution of Tween 80. The concentration of paraquat in each dosing solution was checked analytically just before use. Control animals received Tween 80 alone.

This study was started with 120 mated mice, 30 per each test level. Because several mice in each group either were not pregnant, died or littered (and were excluded from the experiment), insufficient litters were available for teratological examination. An additional 42 female mice were, therefore, mated 4-5 weeks after the first matings and were allocated to the four test groups as follows: 6 each to Groups 1 and 2, 20 to Group 3, and 10 to Group 4.

Parameters Tested:

1. Maternal: body weight, clinical observations, resorptions, viable fetuses and number of implantations. All of the mice were examined grossly. Histopathology was done on the following tissues: lungs and kidney from at least 8 mice/dosage; heart, lungs, kidney, spleen, liver, ovary and uterus from all sick mice; and the same seven tissues plus placenta, if fetal abnormalities were seen.
2. Fetal: fetal and litter weight, ratio of males to females, examination for gross abnormalities and skeletal and soft tissue changes.

Statistical Evaluation of Data:

Mean fetal weight per litter was used in the calculation of the group mean. Total litter weight, maternal weight, mean fetal weight, number of viable fetuses, number of resorptions, and number of viable fetuses as a proportion of total implants were evaluated by analysis of variance. All above analyses were carried out taking into account the two sets of

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matings. In addition, the proportion of litters with any resorptions were compared by χ^2 test. If there were indications that skeletal and/or soft tissue abnormalities were related to the treatment of the animals with paraquat, the results were analyzed by the 2 X 2 Contingency Tables of Finney et al.*

*"Tables for Testing Significance in 2 X 2 Contingency Table" (1963). D. J. Finney, R. Latscha, B. N. Bennett, and P. Hsu. Cambridge University Press.

Results:

1. Food and Water Consumption

Visual observation did not reveal any obvious differences between groups.

2. Maternal Body Weights

Both mean and individual body weights are reported during days 0, 3, 6, 9, 12, 15 and 18 of pregnancy. These weights are reported for 20, 22, 28 and 23 pregnant mice from Groups 1, 2, 3 and 4, respectively. Mice which littered, were not pregnant or died, were excluded.

There was a reduction in body weight gain at the 5 mg/kg (14.2%) and 10 mg/kg (10.8%) level which was attributed to paraquat treatment. However, only the reduction of 14.2% was statistically significant ($p < 0.05$).

3. Maternal Clinical Observations

No adverse reaction to the administration of paraquat was seen in any group. Two animals (Groups 1 and 3) died and one (Group 3) was ill as a result of intubation accidents (lung dosed or perforated esophagus). The ill animal (# 79), killed on day 18 of pregnancy, was hunched, subdued and had piloerection and some respiratory distress. Observation at post mortem revealed 5 early and 2 late resorptions.

4. Maternal Pathology

Individual pathology reports are presented for 11, 10, 15 and 11 animals from Groups 1, 2, 3 and 4, respectively. Gross necropsy revealed no abnormalities in any group, with the exception of one animal. In that animal (# 35; Group 2), the left kidney was completely hollow and full of clear liquid.

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Histopathology revealed no abnormalities related to treatment with paraquat. Animal #79 (Group 3), which suffered from perforated esophagus, had a large abscess in the lymph node adjacent to the esophagus, severe epicarditis, widespread vacuolation in the liver and an infected and hemorrhagic placenta. Four other animals from Group 3 showed varying degrees of fatty changes in their livers. No tissue abnormalities were observed in Group 4.

5. Pregnancy Data

Pregnancy data are tabulated below.

Group	Paraquat ion mg/kg b. wt.	No. of Mice	Not Pregnant or Dead %	Pregnant %	Littered %
1	0	36*	25	75	26
2	1	36	28	72	15
3	5	50*	26	74	24
4	10	40	27	73	21

* One animal died as a result of intubation accident.

It can be seen from these data that the frequency of pregnancy and the incidence of littering were similar in all groups.

6. Litter Data

All of the litters, that is, 20, 22, 28, and 23 from Groups 1, 2, 3 and 4, respectively, were examined. The following parameters tested were unaffected by treatment with paraquat: number of implantations (13-14.3/litter), early resorptions (9-13%), viable fetuses (11-12/litter), litter weight (14.5-16.1 g) and sex ratio (M/F = 1.02-1.12). There was a tendency for group mean fetal weight to decrease with increasing dose but the differences were small (3, 4.4 and 6% for Groups 2, 3 and 4, respectively) and statistically insignificant. The number of late resorptions also increased with dose but these changes, too, were small (0.6, 1.4 and 2.3% for Groups 2, 3, and 4, respectively).

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7. Runts

Data pertaining to runts are summarized below.

	Group 1 Control	Group 2 1 mg/kg	Group 3 5 mg/kg	Group 4 10 mg/kg
Number of runts present	13	7	28	17
<u>Litters Affected:</u>				
Number	5	6	9	5
Percent	25	27	32	22
Litters examined	20	22	28	23

There was one litter with 14 runts and one litter with 5 runts in Group 3. Group 4 had one litter with 12 runts. Two litters with multiple runts (4 and 5 per litter) were also seen in the Control group. Although Group 3 had a higher percentage of litters with runts than did Group 1, the difference was only 7% and was not dose-related.

8. Fetal External Abnormalities

The number of fetuses examined was 236, 272, 312 and 272 from Groups 1, 2, 3 and 4, respectively. There were no abnormalities in Group 1. In Group 2, 3 fetuses had malformed hind legs. The following abnormalities were observed in Group 3: umbilical hernia in 8 fetuses (5 in one litter); no genital opening in 2 fetuses; head deformity in one fetus; and vestigial tail in another fetus. An umbilical hernia in one fetus was the only abnormality seen in Group 4. Because 5 fetuses with umbilical hernia came from one litter in Group 3 and there was only one occurrence of hernia in Group 4, no dose-related trends were apparent.

9. Fetal Skeletal Examination

The number of fetuses examined was 120, 130, 156 and 137 from Groups 1, 2, 3 and 4, respectively. There was occasional statistical differences in ossification of individual bones, but these were dose-unrelated. These differences are detailed below.

- a. In Group 4, 36 fetuses (26.3%) had partially ossified sternebrae ($p < 0.05$).
- b. Ossification of forelimb and hindlimb digits was evaluated on a grading scale ranging from 1 (good) to 7 (poor). As is shown below, many fetuses in Groups 2 and 3 were assigned to Grades 2-5.

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Group	Number of Fetuses	Percent	Grade	P Value	Digits
2	36	27.7	5	< 0.05	H
3	36	23.1	4	< 0.05	H
3	60	38.5	2	< 0.01	F
3	28	17.9	4	< 0.05	F
3	19	12.2	5	< 0.05	F

H = hindlimb; F = forelimb.

The extent of ossification of digits in Group 4 was the same as in Group 1 (control).

10. Fetal Soft Tissue Examination

The number of fetuses examined was 116, 135, 155 and 139 from Group 1, 2, 3 and 4, respectively. The incidence of abnormalities was low and was not affected by treatment with paraquat. Three fetuses in each Group 1 and 4 had slight-to-moderate hydronephrosis and 6 fetuses in Group 3 had hydronephrosis. The other abnormalities were as follows: one hydrocephalus in Group 2; one slight dilation of brain lateral ventricles in Groups 1 and 3; one lobed kidney in Group 3; three displaced kidneys, one in Group 3 and two in Group 4; and one instance of displaced testis in Group 4.

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