3.13.81 RB-1061
TXR-830

Supplementary
(incomplete autopsy reports)

NOEL: 1.0 mg paraquat ion / kg body wt. 000368

LEL: 5 mg paraquat ion / kg body wt.

Paraquat Dichloride: Teratogenicity Study in the Rat.

Report No. CTL/P/365 ; date of issue: 6/5/78

Received by EPA RD: 1/15/79
EPA Acc. No. 236763

(Study was started on 5/31/77)

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Notes were taken from the microfiche ; received the microfiche here from Program Manager (Mr. Taylor) on 3/13/81

Also checked the hard-cover copy which SPRD had.

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* From Pathology Section; no title.

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Paraquat Dichloride: Teratogenicity study in the rat.
Report # CTL/P/365 ; received by EPA RD 1/15/79

by NCE Hodge, Shawn Palmer, TM Weight & June Wilson*
EPA Acc.# 236763 Date of issue: 6/5/78

Summary: groups of at least 20 pregnant rats were dosed orally by gavage with levels of 0, 1, 5 or 10 mg paraquat ion/kg b.w. each day from days 6 to 15 inclusive.

Maternal body wt was measured at intervals during the study and on day 21 the animals were killed and their uteri were examined for resorptions. The fetuses were removed, weighed, sexed, and observed for gross abnormalities, then preserved prior to examination for either soft tissue or skeletal changes. Maternal lung & kidney (the target organs of paraquat toxicity) were submitted from at least 11 surviving animals/group for histological examin.

There were clinical signs of maternal toxicity at both 5 and 10 mg/kg. At the 10 mg/kg level, there was histological evidence that the death of several animals was due to paraquat.

Slight fetotoxicity was seen at 5 and 10 mg/kg as shown by slightly reduced fetal wt and slightly retarded ossification; these effects were probably associated with the maternal toxicity. There was no effect on embryonic or fetal survival and no increase in fetal abnormalities.

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Mr ratio of cation : salt = 1 : 1.3.

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It is concluded, therefore, that paraquat is not teratogenic when administered orally to the rat and, although it is without effect on embryonic or fetal development at 1 mg/kg, it does produce slight fetotoxicity at 5 mg/kg and above." BEST DOCUMENT AVAILABLE

Test material : 100% pure paraquet (so identified by ICI the supplier)
Solvent used : 0.5% aq. solution of Tween 80 (Polysorbate 80 BCP); used nulliparous females (never had offsprings). 29 or 30 rats / group. Dosed : from days 6-15 inclusive of pregnancy.

Rats were weighed on days: 0, 3, 6, 8, 12, 16, 21. Food & H2O intake were observed but not measured.

At autopsy, maternal tissues from all animals were examined, macroscopically.
Histology : lung + kidney from at least 11 rats / group.
From side animals ~~were~~: heart, lung, kidney, adrenals, spleen, liver, ovary & uterus. If fetal abnormalities were seen, placenta was also examined.

During autopsy, the intact uterus was examined for the number of live fetuses & resorptions. Corpora lutea were counted. Then fetuses were removed. (See p. 2a)

(p. 2a)

Statistics: 2×2 Contingency Tables of Finney et al. if there were indications of adverse effects compared with controls. Applies to incidences of skeletal variations & soft tissue abnormalities.

* Stated on p. 4 of this report that the purpose of this study was "to assess the teratogenic potential of paraquat in the rat following oral admin." Study started on 5/31/72 (which was day 6 of pregnancy). Dose levels were determined by a preliminary study (Appendix 1).

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Determined: Fetal sex, fetal wt, external abnormalities; Alternate fetuses from each litter were eviscerated & the viscera were examined macroscopically for abnormalities. The eviscerated fetuses were fixed in 70% Etoh & stained with Alizarin Red for subsequent skeletal exam. During this exam., ossified bones were examined both for abnormalities & for degree of ossification. The remaining fetuses were preserved & decalcified in Bouin's fixative & were sectioned in order to examine the internal structure of organs.

DL Finney, R Latscha, BN Bennett & P Hsu. Tables for Testing Significance in 2 x 2 Contingency Tables. Cambridge Univ. Press, 1963.

	No		No of wts
Animal numbers	1-30	(Control; 0.5% Tween 80)	30
	31-59	1 mg/kg	29
	61-89	5 "	29
	91-120	10 "	30

* These changes are associated ± oral par. poisoning.

Individual clinical observ. are given.

RESULTS

Maternal clinical findings:

At 5 & 10 mg/kg: piloerection, wgt. loss, hunched appearance and, in some cases, respiratory distress. Loss of wgt ($P < 0.001$); both groups.

At 10 mg/kg (moribund rats or those that died during the study): red & patchy lungs, alveolar edema, polymorph infiltration — in lungs. Kidney: degenerative changes in the proximal tubules.* 6 rats studied

At 5 mg/kg: 2 rats became moribund & were killed: no evidence of par. poisoning in lungs & Kidney. One rat had extensive degenerative changes in the lumbar cord. (These 2 rats were apparently injured during dosing).

Surviving rats (mothers):

lungs & kidney examined from 0, 5, 10 mg/kg levels. 1.0 mg/kg was not examined. No evidence of par. toxicity in all rats examined (survivors, that is).

Litter Data

lower fetal wgt at 5 & 10 mg (signific. at the 5% level); tendency for lower mean litter weights in par. groups (not statistically significant).

No. of fetuses examined: 165, 140, 147, 115 for groups 0, 1, 5, 10.

p. 3a

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Results (fetal)

Although there was a suggestion that dosing with paraquat affected embryonic & fetal survival in utero, differences between test & control groups were statistically insignificant.

Fetal external abnormalities : No gross abnormal.

Fetal skeletal exam. Slight retardation in ossification at 5 mg & 10 mg/kg

Fetal soft tissue exam.
High incidence of hydronephrosis (pelvic dilatation of kidneys), but this was within normal limits for the strain of rats used (overall incidence of 18% in controls within the last 6 years in their labs.) Dan. had no effect.

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RESULTS

1. Table 3A. Body wgt. of pregnant rats + SD on days specified earlier (0, 3, 6, 8, 12, 16, 21) & wgt gain.

2. Table 4D. Proportions of litters with one or more resorptions. (p. 20)

level (mg/kg)		
0	12/27	0.44 (or 44%)
1	10/23	0.43
5	15/24	0.62
10	11/18	0.61

3. Appendix I (Range finding study)
Levels used: 5, 10, 20, 40 mg per. ion/kg
"The maternal toxicity produced in a teratology study should be such that it will not adversely interfere with development of the embryo & or fetus."

4. Appendix 4. Individual clinical observations
gives group, rat #, day of pregnancy & description.

5. Appendix 5. Individual maternal body wgts

6. Individual litter data (Appendix 6)
listed: F number, no. of implantations, no. of resorptions (early, late), no of viable fetuses, mean fetal wgt. & total litter wgt, for controls & exp. groups.

7. Appendix 7. Individual fetal wgt.

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Checked also the hard-cover copy. Animal # or dose level are not given on individual reports.

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Appendix 10. Individual Pathology Data pp. 75-

pp. 77-120 contain the following:

① Autopsy and histology reports for 11 rats, 10 of which were killed on 21st day of pregnancy (termin. of experiment). It is not stated when the 11th rat was killed. ID numbers and dose level are not given. (It appears to be a control group). Kidneys & lungs were normal. (pp. 77-87 inclusive)

② The above-mentioned 11 pages are followed by "Group 2: macroscopic findings (lung paraquat ion / kg)"; p. 88. Data for 13 rats are summarized on this page. Rat #: 31, 32, 36, 38, 40, 42, 43, 44, 48, 50, 51, 54, 55.

a) 9 rats (-) had "dark" or red patches on their lungs.
b) # 44 had excess blood in uterus (right horn).
c) # 54 had red and mottled kidneys, and had deposits in urinary bladder.
d) # 48 & 50 had blood-filled thorax, because they were "misdosed".

③ Above is followed by pp. 89-120 inclusive (32 pages) & 32 rats, presumably. of autopsy & histology reports, all signed by June Wilson (from Pathology Section; title not given). Each page contains the following: Comments: killed day --; autopsy & histology findings; and cause of illness or death. What was killed, identification # and dosage are not stated.

a) 18 animals, killed on day 21, had normal lungs and kidneys.
b) 5 animals, killed on day 21, had nephrocalcinosis (kidneys) and perivascular polymorphic infiltration (lungs).
c) 1 animal, killed on day 21, had pale & mottled kidneys and distended large intestine, caecum & colon.
d) 2 rats died after day 18, due to "dosing accident". One rat (assuming that these were rats & from this experiment)

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had paralysis in hind legs. The other rat had clear fluid in thorax, pale lungs and liver, uterus filled with blood, severe epicarditis & liver necrosis. It was stated that there was no evidence of paraquat toxicity. Cause of death: hydrothorax & shock after accidental perforation of esophagus.

e) 2 rats died on day 17, due to paraquat poisoning: pulmon. edema and congestion, dark red patches on lungs, uterus filled with blood & tubular degeneration (kidney).

f) 1 rat was killed on day 15, due to "paraquat poisoning with misdosing". (It was suggested that there was a possible misdosing into the thorax by perforation of the esophagus). Observed blood in cervix, pulmon. edema, kidney degeneration, epicarditis, myocarditis, 2 dead fetuses in placenta.

g) 1 rat was killed on day 13, due to paraquat poisoning: pulmon. edema & polymorph. infiltration, widespread prox. tubular degeneration, focal myocarditis. Other tissues not examined.

h) 1 rat killed on day 11, due to par. poisoning. Symptoms as above.

i) 1 rat died "5 min. before it was autopsied", due to par. poisoning.

3 F died as a result of intubation accidents: #17 (control) & #93 & 101 (10 mg/kg level).