

: EPA Acc. No. 236764

000367

Dominant Lethal Study
in Mice of Paraquat

401551

Onveresk Research International (IRI)

IRI Report No. 145

Author: D.B. McGregor

BEST AVAILABLE COPY

NOEL: 4 mg paraquat ion / kg body wt. (highest level tested)

Con - Minimum

1 of 5
1

000367

0

SUMMARY

Paraquat was tested for dominant lethal mutagenic activity in male CD-1 mice.

The oral LD 21 days after initiation of dosing for 5 consecutive days was 6.5 mg/kg bw/day (paraquat ion).

" No mutagenic effects could be detected if the compound was administered orally to mice up to a dose of 4.0 mg/kg for 5 days. There was no increase in the % of early deaths or number of early deaths/frequency. Neither was there evidence of preimplantation losses or reduction in fertility of the treated males.

Mutagenic effects were obtained with ethylmethanesulphonate ~~and~~ or cyclophosphamide

(2)

000367

MATERIALS AND METHODS

Test material: a formulation of paraquat containing 28.3% paraquat ion. Paraquat was administered orally in 0.5% aq. solution of Tween 80. Positive controls were given in H₂O.

Animals: CD-1 mice (Charles River) were used. Only males were dosed with paraquat.

Dosing

To determine dosage of paraquat which would assure survival, the following exp. was done: groups of 6 males were given 5 daily doses of paraquat and their survival was recorded for 3 wks.

Paraquat ion/day (mg/kg):	0.5	1.0	2.0	4.0	8.0
Survival at 3 wks:	6	6	6	5	5

One group of 30 and five groups of 15 male mice of proven fertility were treated immediately before test mating began as follows:

Group 1	30 mice	got 0.5% Tween 80 (Control)
Group 2	15 "	" 0.04 mg paraquat ion/kg
Group 3	15 "	" 0.40 "
Group 4	15 "	" 4.00 "
Group 5	15 "	" 100 mg ethylmethane sulphonate/kg b5 (orally)
Group 6	15 "	" 200 mg cyclophosphamide/kg b5 (ip)

Groups 1-5 received their dosages orally for 5 consecutive days. The ip injection (Group 6) was given on the day prior to the 1-st test mating.

3

(3)

* not yet treated with paraquat

000367

Mating (Fertility testing)

175 males* were caged with 350 females, 1M + 2F per cage. After 7 days the females were transferred to other cages. The females were killed 12 days after first introducing them to the males and examined for pregnancies. 105 males which fertilized both females were used for dosing (as shown on p. 2).

Experimental mating

1 paraquat-treated male + 2 untreated females were caged for 7 days. Then, the 105 males were transferred to fresh cages and mated with the second batch of untreated females. This process was repeated until male mice had been mated at weekly intervals for 8 weeks. The males were then killed and not examined further. No attempt was made to establish that mating had occurred. Instead, it was assumed that it did during the 2 or 3 days after introducing females to males. Females were killed 13 days after the assumed day of fertilization, that is 15 or 16 days after caging M+F.

Uteri of the killed mice were examined for live implantations, early deaths and late deaths. The ovaries of nonpregnant mice were examined for corpora lutea graviditatis. Observed abnormalities were recorded.

Results were evaluated by 2 statistical methods: 2x2 chi-square test & a week by week hierarchical analysis of variance.

(4)

000367

RESULTS

Early deaths are considered to be important in the assessment of the mutagenic potential of test substances.

<u>Exp. group</u>	1	2	3	4	5	6		
<u>Pregnancy frequency (%)</u>	93	92	90	92	86	85		

<u>No of pregnancies with one or more early deaths</u>	197	100	100	101	105	122		
--------------------------------------------------------	-----	-----	-----	-----	-----	-----	--	--

<u>Without early deaths</u>	250	121	115	121	93	79		
-----------------------------	-----	-----	-----	-----	----	----	--	--

<u>% of total implants recorded as early deaths *</u>	5.7	5.5	5.7	6.1	12.1	18.6		
-------------------------------------------------------	-----	-----	-----	-----	------	------	--	--

<u>Total implants per F (all wk; mean)</u>	11.70	12.02	11.70	11.77	10.71	10.28		
--------------------------------------------	-------	-------	-------	-------	-------	-------	--	--

Data recorded: total implants, live implants, early deaths, late deaths /week / mouse / group and the # of male mouse involved _____ for a total of 8 wks.

* Group 1 results are based on 60 female mice. Groups 2-6 are each based on the pregnant females out of a possible 20.

5