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DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - rat
OPPTS 870.1100 [§81-1]

DP BARCODE: D217134
P.C. CODE: 061601

SUBMISSION CODE: S490083
TOX. CHEM. NO.: 634

TEST MATERIAL (PURITY): Paraquat dichloride (33.0% w/w)

CITATION: Duerden, L. (1994) Paraquat dichloride technical concentrate: acute oral toxicity to the rat. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No. CTL/P/4424, Study No. AR5737, September 30, 1994. MRID 43685001. Unpublished.

SPONSOR: Zeneca, Inc. Agricultural Products, Wilmington, Delaware

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 43685001), groups of fasted, Alpk:APfSD SPF Wistar-derived young adult rats (5/sex) were given a single oral dose of paraquat dichloride (33.0% a.i.) in deionized water at doses of 100, 250, 400 or 600 mg/kg (males only at top dose) and observed for up to 15 days.

Oral LD_{50} Males = 344 mg/kg (246-457 95% C.I.)
Females = 283 mg/kg (182-469 95% C.I.)

Paraquat is classified as TOXICITY CATEGORY II based on the LD_{50} in both sexes.

Clinical signs began on either days 3 or 4. Surviving animals recovered by day 6 in the lower doses and day 11 in the higher doses. Signs included decreased activity, chromodacryorrhea, dehydration, piloerection, sides pinched in, stains around nose and mouth, upward curvature of the spine, reduced splay reflex, hypothermia and breathing irregularities. Gross necropsy revealed mottling and dark areas in the lung.

This acute oral study is classified as acceptable. This study satisfies the guideline requirement for an acute oral study (81-1) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: paraquat dichloride
Description: brown/black liquid
Lot/Batch #: YF6219; batch reference F42; CTL reference # Y00061/160
Purity: 33.0 % a.i.
CAS #: 1910-42-5

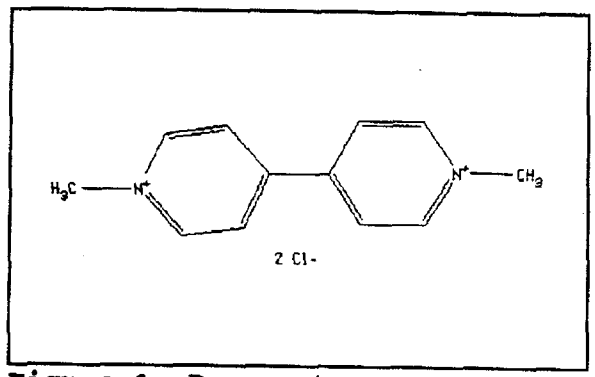

Figure 1 Paraquat

Verification of concentration/homogeneity: not stated in report.

2. Vehicle: deionized water

3. Test animals: Species: rat
Strain: SPF Wistar-derived Alpk:APfSD albino
Age and/or weight at dosing: 244-286g (♂); 167-202g (♀)
Source: Barriered Animal Breeding Unit, Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK
Acclimation period: six days
Diet: Porton Combined Diet ad libitum
Water: tap ad libitum

Housing: suspended stainless steel cages; 5/cage with sexes separate.
Environmental conditions
Temperature: 21 ± 2 °C
Humidity: 55 ± 15%
Air changes: 25-30/hour
Photoperiod: 12 hours light, 12 hours darkness

B. STUDY DESIGN and METHODS:

1. In life dates - not stated; approximately as follows: start: March 1994 end: May 1994

2. Animal assignment and treatment: Animals were assigned to the test groups noted in table 1. Following an overnight fast, rats were given a single dose of paraquat by gavage in a volume of 10 ml/kg. They were then observed for clinical signs of toxicity and mortality once within 2 hours of dosing, between 4 and 7 hours after dosing and then daily (once or twice depending upon significance of signs) up to day 15. They were weighed on the day before dosing (day -1), the day of dosing (day 1) and on a selected schedule of days depending upon the dose administered. Animals in extremis and survivors were sacrificed by inhalation of halothane vapor followed by exsanguination and were subjected to a macroscopic post mortem examination.

TABLE 1. Doses and Mortality/Animals Treated

Dose (mg/kg)	Males	Females	Combined
100	0/5	0/5	0/10
250	1/5	2/5	3/10
400	3/5	4/5	7/10
600	5/5	-	5/5

3. Statistics: The oral LD_{50} was calculated by logistic regression using nominal dose values. Confidence limits were calculated using a likelihood ratio interval.

II. **RESULTS AND DISCUSSION:**

A. Mortality is given in table 1.

The calculated acute oral LD_{50}'s are as follows:
males: 344 mg/kg (246-457 95% confidence limits)
females: 283 mg/kg (182-469 95% confidence limits)

B. Clinical observations: No signs of toxicity were observed of 100 mg/kg. At 250 mg/kg, signs of toxicity were observed just prior to death (days 4 and 7). These included decreased activity, chromodacryorrhea, dehydration, piloerection, sides pinched in, stains around nose and mouth, upward curvature of the spine,

reduced splay reflex, hypothermia and breathing irregularities. The report stated that "signs of transient, slight toxicity were observed in the surviving animals on day 4 with complete regression by day 6." At 400 mg/kg, death was observed on days 4 and 5. Signs of toxicity were similar to those dosed with 250 mg/kg. The signs of toxicity regressed by day 11. At 600 mg/kg, all animals were either found dead or killed in extremis on days 3 and 4. Clinical signs were observed that were similar to those observed at 250 mg/kg. In the higher dose levels, clinical signs started on days 3 and 4.

C. Body Weight: All surviving animals had exceeded their initial bodyweight by day 8 and the majority continued to gain weight for the remainder of the study.

D. Necropsy: Findings that are consistent with paraquat toxicity were observed as well as findings that are often seen in dead or moribund animals. Mottling and dark area in the lungs were observed which is considered to be related to treatment. The following table summarizes the findings in the lung.

Post Mortem Findings in the Lung							
Lung	Males				Females		
Dose Level (mg/kg)	100	250	400	600	100	250	400
# With findings but not submitted	0	1	3	5	0	2	4
Mottled	0	0	0	0	0	1	0
Dark	0	1	0	4	0	1	4
Dark areas	0	0	3	1	0	0	0

E. Deficiencies: There are no deficiencies in the study. The study is acceptable for regulatory purposes.