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[Dichlormid]

Acute Oral Study (§81-1)

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DATA EVALUATION RECORD

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

DP BARCODE: D248305
P.C. CODE: N/A
SUBMISSION CODE: S546651
TOX. CHEM. NO.: N/A

TEST MATERIAL (PURITY): Dichlormid (97.2%)

SYNONYMS: R25788; N, N-diallyl dichloroacetamide; 2,2-dichloro-N,N-di-2-propenylacetamide; N,N-diallyl-2,2-dichloroacetamide

CITATION: Robinson, P.(1990) Dichlormid: Acute Oral Toxicity to the Rat. ICI Central Toxicology Laboratory, Cheshire, UK. Report no. CTL/P/2197. November 16, 1990. MRID 44606401

SPONSOR: Zeneca Ag Products

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 44606401), groups of fasted, young adult Wistar-derived albino rats/sex (5/sex) were given a single oral dose of dichlormid (97.2 % a.i.) in corn oil at doses of 500, 1,000, 2,000, 3,000, or 4,000 mg/kg and observed for 15 days.

Oral LD_{50} Males = 2,816 mg/kg (95% C.I. 2,143, 3,664 mg/kg)
Females = 2,146 mg/kg (95% C.I. 1,478, 2,910 mg/kg)

Dichlormid is classified as **TOXICITY CATEGORY III** based on the LD_{50} in both **sexes**.

No compound-related mortality occurred at 500 or 1,000 mg/kg. However, one female rat dosed at 500 mg/kg was killed *in extremis* on Day 5, but this was not thought to be compound related. Compound-related mortality occurred in 19/30 animals tested at ≥2,000 mg/kg within 5 days of administration. Clinical signs of toxicity seen in all dose groups included piloerection, upward curvature of the spine, decreased breathing rate, decreased activity, bizarre behavior and excessive grooming(500 and 1,000 mg/kg only), chromodacryorrhea, lachrymation, and salivation. Most animals dosed at 500 mg/kg and 1,000 mg/kg recovered by day 5. Animals from the 2,000, 3,000 or 4,000 mg/kg dose groups also exhibited tip toe gait, dehydration, reduced stability, and breathing abnormalities. All surviving animals in the ≥2,000 mg/kg dose groups recovered in 9 or 10 days after dosing. No

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treatment-related effects on body weight were observed in surviving animals. Gross necropsy of decedent animals revealed abnormal livers in 3 animals at 2,000 mg/kg, mottled liver and dark red intestines in one female at 3,000 mg/kg, and pale livers in 2 females at 4,000 mg/kg. Necropsy of animals sacrificed on day 15 revealed no abnormalities.

This acute oral study is classified **ACCEPTABLE (§81-1)**. This study does satisfy 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: Dichlormid
   Description: Amber liquid
   Lot/Batch #: CTL Reference #Y06015/002/007
   Purity: 97.2% a.i.
   CAS #: N/A
   Verification of concentration/homogeneity as necessary

2. Vehicle: Corn Oil

3. Test animals: Species: Rat
   Strain: Alpk:APfSD, albino
   Age and weight at dosing: 7.5 weeks old, 213-304 g (males); 9 weeks old, 160-268 g (females)
   Source: Animal Breeding Unit, ICI Pharmaceuticals, Cheshire, UK
   Acclimation period: 6 days (minimum)
   Diet: Porton Combined Diet, Special Diet Services Ltd., ad libitum
   Water: Automatic system, ad libitum
   Housing: 5 rats/sex/cage
   Environmental conditions:
   Temperature: 15-24°C
   Humidity: 50±10%
   Air changes: 20-30 ACH
   Photoperiod: 12-hr light/12-hr dark

B. STUDY DESIGN and METHODS:

1. In life dates - Approximately July 20-August 3, 1988 (based on QA inspection/audit dates). Specific dates

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were not reported.

2. Animal assignment and treatment - Animals were assigned to the test groups noted in Table 1. Following an overnight fast (16-24 hours), rats were given a single dose of dichlormid by gavage then observed between 30 and 90 minutes after dosing, between 4 and 6 hours after dosing, and once daily, up to 15 days. The animals were weighed on the day before dosing (Day -1), the day of dosing (Day 1), and on Days 3, 5, or 6, 8 and 15. Survivors were sacrificed and a necropsy was performed.

TABLE 1. Doses, mortality/animals treated

Dose (mg/kg)	males	Females	Combined
500	0/5	1/5*	1/10
1,000	0/5	0/5	0/10
2,000	1/5	3/5	4/10
3,000	2/5	3/5	5/10
4,000	5/5	5/5	10/10

*One female rat dosed at 500 mg/kg was killed *in extremis* on Day 5, but this was not thought to be compound related.

3. Statistics - The oral LD_{50} was calculated using logistic regression. Confidence limits were calculated using a likelihood ratio interval.

II. RESULTS AND DISCUSSION:

A. Mortality is given in table 1. There was no compound-related mortality at 500 or 1,000 mg/kg. However, one female rat dosed at 500 mg/kg was killed *in extremis* on Day 5. Necropsy findings for this animal included enlarged bladder and large mass above it which hemorrhaged. This finding was not thought to be compound related. Compound-related mortality occurred in 19/30 animals tested at ≥2,000 mg/kg within 5 days of administration. Females were more sensitive to the test material.

Oral LD_{50} (C.I.) for males = 2,816 mg/kg (95% confidence limits (2,143, 3,664 mg/kg))
females = 2,146 mg/kg (95% confidence limits (1,478, 2,910 mg/kg))

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B. Clinical observations - Clinical signs of toxicity seen in all dose groups included piloerection, upward curvature of the spine, decreased breathing rate, decreased activity, bizarre behavior and excessive grooming(500 and 1,000 mg/kg only), chromodacryorrhea, lachrymation, and salivation. Most animals dosed at 500 mg/kg and 1,000 mg/kg recovered by day 5. Animals from the 2,000, 3,000 or 4,000 mg/kg dose groups also exhibited tip toe gait, dehydration, reduced stability, and breathing abnormalities. All surviving animals in the ≥2,000 mg/kg dose groups recovered in 9 or 10 days after dosing.

C. Body Weight - No treatment-related effects on body weight were observed in surviving animals, which exhibited overall (day 1-day 15) increases of 30% for males and 31% for females.

D. Necropsy - Gross necropsy of decedent animals revealed abnormal livers in 3 animals (1 male [pale liver], 2 females [no description reported]) at 2,000 mg/kg, mottled liver and dark red intestines in one female at 3,000 mg/kg, and pale livers in 2 females at 4,000 mg/kg.

E. Deficiencies - There were no deficiencies that affected the validity of the study results.

SignOff Date:
DP Barcode:
HED DOC Number:
Toxicology Branch:

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