CASWELL FILE

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Screen of an Ametryn Chronic Feeding Study in Rats.

EPA No. 80801-04
Record No. 253683, 253808

Project No. 0-0056
Tox. Chem. No. 431

TO: Thomas Luminello, PM #50
Registration Division (H7505C)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section 1, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

John Whalan 11-9-89

THROUGH: Roger L. Gardner, Acting Section Head
Section 1, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

R.L.G. 11-24-89

Ametryn was recently selected to be a pilot chemical in the FIFRA 88 review process. A Chronic Feeding/Oncogenicity Study in Rats (Ciba Geigy, Project No. 842119, August 24, 1987) was screened for acceptability for review at that time. The study was found to be unacceptable by HED Acceptance Criteria.

The report did not mention the purity of the test article. There were three dose groups. The dose level for the high-dose group was reduced twice (from 5000 ppm to 4000 ppm to 2000 ppm) because of severe weight changes. This matter will require further scrutiny. Survival to termination (2 years) was low in all groups, but especially in the controls (43%). Creatinine was not measured. This parameter is not strictly required, and BUN was measured in its place. This study received Quality Assurance review.

Because of these inadequacies, the Registrant should be required to initiate a new study unless these issues can be resolved.

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REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Ametryn

CAS #: 834-12-8
Caswell #: 431

Carcinogenicity: No data available

Systemic Toxicity: See below.

Preparation Date: 12/03/86

Endpoint	Experimental Doses	UF	MF	RfD
Roulet et al. (1961)	8.6 mg/kg/day* NOEL	1000	—	0.009 mg/kg/day
Rat Subchronic Oral Bioassay	86 mg/kg/day* LEL			
liver toxicity				

*10 mg/kg/day adjusted because chemical was fed 6 of 7 days

Endpoint and Experimental Doses:

Roulet et al.
Toxicology of Ametryn
Ciba-Giegy; 1961

The chosen effect level is a rat subchronic oral NOEL by water gavage; the LEL is associated with fatty degeneration of the liver. The chosen CBI study appears to have been well conducted with 12 males and 12 female rats in each of the two dose groups.

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Uncertainty Factors (UFs):

An uncertainty factor of 1000 was used to account for the inter- and intraspecies differences, and to account for the subchronic duration of the critical study.

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Modifying Factors (MFs):

None

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Additional Comments:

Although the rat teratology study had a NOEL of 5 mg/kg/day it was not used to establish the RfD for the following reasons. (1) The exposure in the teratology study was by gavage, thus exaggerating exposure, (2) the NOEL of the rat study used to establish the RfD is not significantly different from the NOEL in the teratology study and (3) the effects noted at the 50 mg/kg/day in the teratology study are minimal and of marginal biological significance.

Data Considered for Establishing the RfD

1) 90-Day Feeding - Rat (NOEL = 8.6 mg/kg; LEL = 86 mg/kg (liver toxicity; doses are adjusted since feeding regium; CBI)

2) 4-Week Feeding (Range Finding) - Rat (NOEL = 100 mg/kg; LEL = 250 mg/kg; decrease in body weight and bloody nasal secretion; CBI)

3) 90-Day Feeding - Dog (Systemic NOEL = 25 mg/kg; IBT study)

4) Reproduction - Rabbit (NOEL = 10 mg/kg; LEL = 100 mg/kg; body weight loss; CBI)

5) Teratology - Rat (Maternal and Fetotoxic NOEL = 5 mg/kg; Maternal and Fetotoxic LEL = 50 mg/kg; reduction in food consumption and body weight, hypoactivity, elevated forepaw metacarpals not-ossified, and increase in salivation and ptosis; CBI)

6) Teratology - Rabbit (Maternal NOEL = 10 mg/kg; Fetotoxic NOEL = 60 mg/kg [HDT]; Maternal LEL = 60 mg/kg; weight loss (gestational days 7-10); CBI)

Data Gap(s)

1) Chronic Dog Feeding Study
2) Chronic Rat Feeding Study
3) Rat Reproduction Study - Note: CIBA Geigy is currently conducting a rat reproduction study (see attached document 7/22/85)

Other Data Considered

Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

The critical study is of fair quality and is given a medium confidence rating. The confidence in the RfD is low due to the fact that the data base on chronic toxicity is incomplete and therefore, the most sensitive toxicological endpoint can not be determined.

Documentation of RfD and Review:

Registration Files

Agency RfD Review:

First Review: 12/16/87
Second Review: 2/18/87
Verification Date: 2/18/87

U.S. EPA Contact:

Primary: Reto Engler FTS 557-7491

Secondary: George Ghali FTS 557-7490

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