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

AUG 0 2 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

Subject: I.D. No. 080801-000100: Ametryn
New Chemical Screen and Data Review: Ametryn Technical
PC Code 080801
Tox. Chem. No. 431
HED Project No. 2-0182
Submission No. S405107
DP Barcode No. 174062

From: Myron S. Ottley, Ph. D. 7/23/92
Section IV
Toxicology Branch I
Health Effects Division (H7509C)

To: ~~Julie Fairfax PM21~~ Tom Luminello
~~Registration Division (H7505C)~~ SRRD

Thru: Marion P. Copley, D.V.M., D.A.B.T. 7/24/92
Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C) KB 7/29/92

CONCLUSIONS

The Mouse Onco study (MRID #403499-04) of Ametryn Technical passes the pre-review toxicology screen, as evaluated by the registration Acceptance Criteria. In addition, it has been classified as Core Minimum following detailed review (DER attached). It satisfies the guideline [83-2(b)] requirements for a rodent oncogenicity study.

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ACTION REQUESTED

Toxicology Branch I has been requested to review data submitted by Ciba Geigy to determine whether they meet the criteria for the pre-review toxicity scre n. TB1 had rejected the Mouse Onco study since no toxicity was demonstrated at any dose level. The Submitter then provided data on the 28-day range finding study (Study # 483-126, MRID #920020-41) that provided the basis for dose level selection in the Onco study. TB1 was requested to review these data.

TB1 also conducted a detailed review of the mouse Onco study (DER attached).

RESULTS and DISCUSSION

TB1 has reviewed the 28-day range finding study and concluded that, based on the results of that study, the dose levels used in the Onco study are justified. The conclusions reached after review of the Onco study are as follows:

NOEL		2000 ppm (300 mg/kg/d)
LOEL	>	2000 ppm

Classification: **Core Minimum.** Although dose levels were not high enough to demonstrate toxicity such as body weight loss, it is expected that, based on results from the range-finding study, 2000 ppm is near the maximally tolerated dose.

This study satisfies the guideline requirements (83-2) for Mouse Oncogenicity on Ametryn Technical and is acceptable for regulatory purposes.

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Reviewed by: Myron S. Ottley, Ph.D. M.S. Ottley 7/21/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 7/24/92

DATA EVALUATION REPORT

STUDY TYPE: **Chronic Onco -- Mouse** 83-2(b)

TOX. CHEM. No: 431
PC No.: 080801
MRID No.: 403499-04
92020-22C
92020-21I
TEST MATERIAL: **Ametryn**

SYNONYMS: Evik®, Gesapax®

STUDY NUMBER: 483-128

SPONSOR: Ciba Geigy Corporation

TESTING FACILITY: Hazleton Laboratories, America, VA 22180

TITLE OF REPORT: FINAL REPORT. 102-Week Oncogenicity Study In Mice. Project No 483-128

AUTHOR: George Burdock

REPORT ISSUED: March 20, 1981

CONCLUSION:

NOEL 2000 ppm (300 mg/kg/d)
LOEL > 2000 ppm

Classification: **Core Minimum**. Although dose levels were not high enough to demonstrate toxicity such as body weight loss, it is expected that, based on results from the range-finding study, 2000 ppm is near the maximally tolerated dose.

This study satisfies the guideline requirements (83-2) for Mouse Oncogenicity on Ametryn Technical and is acceptable for regulatory purposes.

A. MATERIALS:

1. **Test compound:** Ametryn Technical. Description: white powder w/ small lumps. Batch No.: FL-761356. Purity: 98.9% (see MRID #920020-22C). Stability: not provided (Compound in food mixture stored at room temperature).

2. **Test animals:** Species: Mouse, Strain: HAM/ICE Swiss, Charles River CD®-1. Age: Weanling. Weight: 12 - 35 gm (male), 11 - 27 gm (female). Source: Charles River Breeding Labs., Wilmington, MA.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned to the following test groups:

TABLE 1. STUDY DESIGN

Test Group	Dose in Diet		No. of Animals	
	ppm	mg/kg/d**	Males	Females
Control	0	0	60	60
Low-Dose	10	1.5	60	60
Mid-dose	1000	150	60	60
High-Dose	2000	300	60	60

** Estimated 1 ppm = 0.15 mg/kg/d

2. Dose Selection

In a 28-day range-finding study (Study #483-126, MRID #920020-41) mice of the same strain (5/sex/group) were fed ametryn technical at dietary dose levels of 0, 30, 100, 300, 600, 1,000, 3,000, 10,000, and 30,000 ppm. All 30,000 ppm animals died by the end of week 3. At 10,000 ppm 1 male and 2 females also died. At 3,000 ppm clinical signs (hunched posture, labored breathing and thin appearance) were observed in one of five females. At 3,000 and 1,000 ppm decreased mean body weight gain was observed in males and females (cf. Table 2).

TABLE 2. RESULTS OF 28-DAY RANGE-FINDING STUDY

Dose Level (ppm)	Body Weight Gain		Clinical Signs		Death	
	Male *	Female *	Male	Female	Male	Female
1,000	-12%	-17%				
3,000	-24%	-46%		1		
10,000			5	5	1	2
30,000			5	4	5	5

* N = 5

The NOEL was 600 ppm, with minimal effects occurring at 1,000, and marked effects occurring at 3,000 ppm. Based on these findings, the authors selected 2,000 ppm as the high dose for the full study. This dose level is 67% of the level (3,000 ppm) where marked decreases in body weight were observed in both sexes, and seems justified.

3. **Diet preparation**

Diets were prepared weekly during the 102-week study. First, the required amount of ametryn for the specific dose level (w/w) was premixed with a small amount of basal diet in a Waring blender. This premix was then added to basal diet and thoroughly mixed in a twin-shell Patterson-Kelley blender fitted with an intensifier bar. Mixing time was one min/kg of diet. Prepared diets storage information not provided. Samples of treated food were frozen and sent to sponsor for analysis of stability and concentration.

Analysis results showed a that Ametryn at concentrations of 10 ppm and 300 ppm is stable in the rodent chow for up to 2 weeks when stored at room temperature. Results of concentration analyses of prepared diets sampled at 0, 13, 26, and approx. four-wk intervals thereafter, indicated average ppm concentrations of 10.9, 1007.8 and 2008.6 for the low-, mid- and high-dose groups, respectively. Homogeneity of the diet mixes was not determined.

4. **Food and Water**

Animals received treated food and water ad libitum.

5. Statistics

The mean body weight values at Weeks 0 and 102 of the control groups were compared to those of the treated groups by a multiple pairwise comparison procedure. Survival through Week 100 was analyzed by a life table technique. All analyses were evaluated at the 5.0% probability level. No statistical analysis of food consumption data was performed due to apparent food wastage.

6. Quality Assurance

A quality assurance statement was signed by Charles Breckenridge.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality.

No treatment-related signs of toxicity were observed at any dose level, compared with controls. Signs of fighting among males (swellings, alopecia primarily on the back, lower midlines, and/or ano-genital area) were more evident among treated groups than controls. Survival (see table 2) was not affected by treatment.

TABLE 2. NUMBER OF ANIMALS THAT DIED OR WERE SACRIFICED MORIBUND THROUGH WEEK 100.

Group ⇒	Controls	10 ppm	1000 ppm	2000 ppm
Males	40	46	30	38
Females	31	37	30	35

2. Body weight

Individual body weights were recorded monthly.

Group mean body weights and body weight gains were not statistically different from controls in any of the treatment groups.

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body

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weight gain data.

Food consumption was not statistically significantly effected by treatment.

4. **Ophthalmological examination**

Ophthalmological examinations were not performed.

5. **Blood**

Blood samples were not collected for analysis.

6. **Urinalysis**

Urine was not collected from animals.

7. **Sacrifice and Pathology**

All animals that died during the study, along with the high-dose and control groups that were sacrificed on schedule, were subject to gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		**Cardiovasc./Hemat.**		**Neurologic**	
	Tongue	X	Aorta	X	Brain
X	Salivary glands	X	Heart	X	Periph. nerve
X	Esophagus		Bone marrow	X	Spinal cord (3 levels)*#
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes (optic n.)
X	Jejunum		Thymus*	**Glandular**	
X	Ileum	**Urogenital**		X	Adrenal gland
X	Cecum	X	Kidneys		Lacrimal gland
X	Colon	X	Urin. bladder		Mammary gland
	Rectum	X	Testes	X	Parathyroids
X	Liver	X	Epididymides	X	Thyroids
X	Gall bladder	X	Prostate	**Other**	
X	Pancreas	X	Seminal vesicle	X	Bone
Respiratory		X	Ovaries		Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lung			X	All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

a. Organ weight No data on absolute or relative organ weights were reported.

b. Gross pathology No treatment-related findings were made.

c. **Microscopic pathology** All animals from the controls and high dose groups were examined histologically; selected animals from the low-dose and mid-dose groups were also examined, based on observations made during gross necropsy.

1) **Non-neoplastic** The incidence and nature of lesions observed in treatment groups were not statistically different from controls.

2) **Neoplastic** The incidence and nature of lesions observed in treatment groups were not statistically different from controls.

D. **DISCUSSION:**

No treatment-related tumors, either neoplastic or non-neoplastic, were observed during this study. Other toxic manifestations, such as body weight loss, decreased food consumption, and clinical signs, were also absent at all dose levels tested. Organ weights were not reported.

Adequate Dose Levels

Because of the lack of overt toxicity at the high dose level, questions arise concerning the adequacy of this study to serve as a basis for a regulatory decision on the oncogenic potential of ametryn technical. The range-finding study (see Table 2) demonstrated marginal decreases female body weight gain at 1,000 ppm, and marked decreases in body weight gain in both sexes at 3,000 ppm. This suggests that 2,000 ppm is near or at the maximally tolerated dose level, and is an appropriate high-dose level selection for the 102-week study.

Homogeneity of Test Mixtures

The homogeneity of the Ametryn food mixtures was not determined. However, the authors state (in MRID # 920020-22C) that other Ametryn technical studies demonstrated homogeneity of mixture. These studies were not specified. They also state that none of the stability or concentration assays gave any indications that the Ametryn food mixtures were not homogeneous.

Since Ametryn is a powder, it is expected to blend with fairly easily with rodent diet meal. The Ametryn food mixtures were prepared in a two-stage process (see page 3) of grinding, blending and admixing Ametryn powder with food meal, that should yield a homogeneous mixture. Therefore this deficiency (missing data on homogeneity) is not regarded as significant in this case.

NOEL

This study established a NOEL of 2000 ppm for chronic toxicity in the mouse.

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