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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: I.D. No.: 080805. Prometryn. Evaluation of Toxicity Data Submitted and Identification of Outstanding Toxicology Data Requirements

Tox. Chem. No.	097
PC Code No.	80805
DP Barcode Nos.	D168675, D164420, D168672, D164686, D165344
Submission Nos.	S402460, S396143, S402456, S396591, S397722

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To: Carol Peterson/Walter Waldrop (PM71)
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Through: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 1/24/94
Section Head
Section IV, Toxicology Branch I
Health Effects Division (7509C) KB 1/25/94

I. CONCLUSIONS

The seven studies listed below were evaluated by TB1 for acceptability for regulatory purposes (DERs attached). It is expected that the RfD committee's input will be required before final levels are set.

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STUDY		CONCLUSION (Core Classification)
82-2	21-Day Dermal Study -- Rabbit	Supplementary -- Upgradeable
83-1	Chronic Oncogenicity Study -- Rat	Guideline
N/A	28-Day Feeding Study -- Mouse	None -- Not applicable
83-2	Oncogenicity Study -- Mouse	Supplementary -- Not Upgradeable
83-3	Developmental Toxicity -- Rat	Supplementary -- Upgradeable
83-4	Two-Generation Reproduction Study -- Rat	Minimum
85-1	General Metabolism Study -- Rat	Minimum

II. ACTION REQUESTED

Review the above-listed data to determine the toxicity of prometryn and determine the acceptability of the studies for regulatory purposes (reregistration).

III. RESULTS/DISCUSSION

A prior HED memo entitled "Prometryn, Toxicology Chapter of the Reregistration Standard (J. Whalen 12/12/86, attached) lists the generic data requirements for Prometryn Technical, and delineates the following data gaps due to invalid or supplementary studies:

81-3 Acute Inhalation—Rat
81-4 Eye Irritation—Rabbit
81-6 Dermal Sensitization—Guinea Pig

82-1 90-day Feeding—Rodent
82-2 21-Day Dermal

83-1 Chronic Toxicity—Rodent
83-2 Oncogenicity—Mouse
83-2 Oncogenicity—Rat
83-3 Developmental Toxicity—Rat
83-4 Reproduction

84-2 Battery of Mutagenicity Tests

85-1 Metabolism Studies

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Below is a summary of data submitted and reviewed to satisfy these data gaps:

A. **21-Day Dermal—Rabbit** (82-2)
MRID No. 405737-02; Study No. HLA 483-260

Prometryn Technical was exposed to five male and five female New Zealand White rabbits per dose group at 0, 10, 100, or 1000 mg/kg/d, 5 days/wk for three weeks and observed for signs of toxicity

SYSTEMIC
NOEL > 1000 mg/kg/d for males & females
LOEL not established

DERMAL
NOEL > 1000 mg/kg/d for males & females
LOEL not established

CORE CLASSIFICATION: Supplementary upgradeable. Data incompletely reported.

B. **Chronic/Oncogenicity Study—Rat** (83-5, or 83-1 & 83-2)
MRID No. 419012-01; Study No. MIN 872225

Prometryn Technical was fed to groups of 80 male and 80 female Sprague-Dawley rats at dietary levels of 0, 10, 100, 750, or 1500 ppm for 104 weeks and observed for signs of toxicity including oncogenicity.

NOEL 750 ppm (29.45 mg/kg in males; 37.25 mg/kg in females)
LOEL 1500 ppm (60.88 mg/kg in males: 80.62 mg/kg in females) based on decreased body weight gain in both sexes, and renal lesions (mineralized concretions) in males.

No oncogenicity was observed.

CORE CLASSIFICATION: Guideline

C. **28-Day Range-Finding Study in Mouse**
MRID No. 404575-15; Study No. 483-127

Prometryn Technical was fed to groups of five male and five female Charles River CD mice at dietary levels of 0, 30, 100, 300, 600, 1000, 3000, 10,000 or 30,000 ppm for 28 days and observed for signs of toxicity.

NOEL 3000 mg/kg/d for males & females

LOEL 10,000 ppm based on decreased body weight. All high-dose animals died.

CORE CLASSIFICATION: Not Applicable, since this is a pilot study.

D. Oncogenicity Study in Mouse (83-2)
MRID 404662-01; Study No. 438-128

Prometryn Technical was fed to groups of 60 male and 60 female Charles River CD mice at dietary levels of 0, 10, 1,000, or 3,000 ppm for 102 weeks and observed for signs of toxicity including oncogenicity.

NOEL 1,000 ppm (100 mg/kg) for females
LOEL 3,000 ppm (300 mg/kg) for females based on decreased body weight gain.

No oncogenicity was observed.

CORE CLASSIFICATION: Supplementary -- Not Upgradeable. Several deficiencies were noted, including inadequate demonstration of toxicity in males.

E. Developmental Toxicity Study in Rat (83-3)
MRID No. 4045745-17; Study No. MIN 862228

Prometryn Technical was administered by gavage groups of 26 pregnant Sprague-Dawley rats at levels of 0, 10, 50 or 250 mg/kg/day during gestational days 6 to 15.

MATERNAL
NOEL 50 mg/kg/day
LOEL 250 mg/kg/day, based on salivation and decreases in body weight and food consumption.

DEVELOPMENTAL
NOEL 50 mg/kg/day
LOEL 250 mg/kg/day, based on decreased fetal body weight and increased incomplete ossification of sternebrae & metacarpals.

CORE CLASSIFICATION: Supplementary -- Upgradeable. Data incompletely reported.

F. Two-Generation Reproductive Toxicity Study in Rat (83-4)
MRID No. 414451-01; Study No. MIN 872222

Prometryn Technical was administered in the diet to groups of 30 male and 30 female Sprague-Dawley rats at levels of 0, 10, 750 or 1500 ppm.

PARENTAL SYSTEMIC TOXICITY
NOEL 10 ppm (0.6 mg/kg/d in males, 0.7 mg/kg/d in females)
LOEL 750 ppm (47.8 mg/kg/d in males, 53.6 mg/kg/d in females), based on decreased food consumption, body weight & body weight gain.

REPRODUCTIVE
NOEL 10 ppm (0.65 mg/kg/d)
LOEL 750 ppm (≈50 mg/kg/d), based on decreased pup weight.

CORE CLASSIFICATION: Minimum

G. **General Metabolism Studies** (85-1)
MRID No. 412559-01; Study Nos. M22-104-7A, M22-104-8A, M22-104-9A, M22-104-10A

Prometryn is distributed in blood > spleen > lungs (the three highest tissues measured). Distribution is not dosage-dependant. It is extensively metabolized with <2% of recovered ^{14}C radioactivity representing the parent compound. Twenty-eight metabolites were identified in the urine, and 28 in the feces. Ten metabolites were identified in both urine and feces. Prometryn is excreted predominantly in the urine and feces, with slightly higher concentrations in the urine. The 7-day recovery of ^{14}C radioactivity averaged 95% for all dosing groups.

CORE CLASSIFICATION: Minimum

IV. OTHER TOXICOLOGICAL CONSIDERATIONS

The following data gaps still remain for this chemical. The list on that appears on page two is shorter now, as seen below:

81-3 Acute Inhalation—Rat
81-4 Eye Irritation—Rabbit
81-6 Dermal Sensitization—Guinea Pig

82-2 21-Day Dermal

83-2 Oncogenicity—Mouse
83-3 Developmental Toxicity—Rat

84-2 Battery of Mutagenicity Tests

However, the available data may be adequate to determine an RfD, which will be discussed in the HED RfD Committee.

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MEMORANDUM

SUBJECT: Prometryn, Toxicology Chapter of the Registration Standard

Tox. Chem. No. 97

TO: Robert J. Taylor
Product Manager #25
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

12-12-86

THRU: Robert P. Zendzian PhD
Registration Standard Coordinator
Toxicology Branch
and
William Burnam, Deputy Chief
Toxicology Branch

Attached is an amended Harrison Table A to the Toxicology Chapter of the Prometryn Registration Standard. This amendment was necessary in order to better define Toxicology Branch requirements regarding rat subchronic studies.

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F. TOXICOLOGY SUMMARY TABLES

Table A
Generic Data Requirements for Prometryn

Data Requirement	Composition[1]	Use Patterns[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No, or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3]
§158.135 Toxicology					
ACUTE TESTING:					
81-1 Acute Oral - Rat	TGAI	A	Yes	60646, 60314	No
81-2 Acute Dermal	TGAI	A	Yes	60647, 60315	No
81-3 Acute Inhalation - Rat	TGAI	A	No	—	Yes
81-4 Eye Irritation - Rabbit	TGAI	A	No	—	Yes
81-5 Dermal Irritation - Rabbit	TGAI	A	Yes	60649, 60316	No
81-6 Dermal Sensitization - Guinea Pig	TGAI	A	No	—	Yes
81-7 Acute Delayed Neurotoxicity - Hen	TGAI	A	—	—	No[4]
SUBCHRONIC TESTING:					
82-1 90-Day Feeding -					
Rodent	TGAI	A	No	—	Yes[5]
Nonrodent	TGAI	A	No	—	No[6]

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§158.135 Toxicology (cont.)					
82-2 21-Day Dermal	TGAI	A	No	—	Yes[7]
82-3 90-Day Dermal	TCAI	A	No	—	No[8]
82-4 90-Day Inhalation	TGAI	A	No	—	No[8]
82-5 90-Day Neurotoxicity	TGAI	A	—	—	No[4]
CHRONIC TESTING:					
83-1 Chronic Toxicity -					
Rodent	TGAI	A	No	42794	Yes[9]
Nonrodent	TGAI	A	Yes	42794	No
83-2 Oncogenicity -					
Rat	TGAI	A	No	—	Yes[10]
Mouse	TGAI	A	No	—	Yes[10]
83-3 Teratogenicity -					
Rat	TGAI	A	No	—	Yes[11]
Rabbit	TGAI	A	Yes	157995	No

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Generic Data Requirements for Prometryn

Data Requirement	Composition[1]	Use Patterns[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3]
§158.135 Toxicology (cont.)					
83-4 Reproduction	TGAI	A	No	24472	Yes[12]
MUTAGENICITY TESTING:					
84-2 Gene Mutation	PAI	A	No	—	Yes[13]
84-2 Chromosome Aberration	PAI	A	No	—	Yes[13]
84-2 Other Mechanism of Mutagenicity	PAI	A	No	—	Yes[13]
SPECIAL TESTING:					
85-1 General Metabolism	PAIRA	A	No	—	Yes[14]

1 Composition: TGAI = Technical Grade of the Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radio-labelled; Choice = Choice of several test substances determined on a case-by-case basis.

2 The Use Patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aq[illegible], Food Crop; D = Aquatic Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forest H = Domestic, Outdoor; I = Indoor; IP = Industrial Preservative.

3 Unless otherwise specified, data must be submitted no later than six months after publication o

4 This study is not required since the test article is not an organophosphate.

5 Subchronic feeding data need not be submitted since chronic studies in the rat are required. However, the Registrant should be aware that subchronic studies are useful and often necessary in determining the maximum tolerated dose (MTD) used for oncogenicity studies in rodents (mice and rats).

6 A subchronic nonrodent feeding study is not required since an acceptable chronic dog feeding study was submitted.

7 Data must be submitted no later than 7 months after the publication of this standard.

8 Additional data are not required because of the nature of the exposure pattern.

9 Data must be submitted no later than 42 months after the publication of this standard.

10 Data must be submitted no later than 42 months after the publication of this standard.

11 Data must be submitted no later than 12 months after the public[illegible] of this standard.

12 Data must be submitted no later than 20 months after the publication of this standard.

13 Data must be submitted no later than 10 months after the publication of this standard.

14 Data must be submitted no later than 14 months after the publication of this standard.