SECTION HEAD

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Terbutryn - 21-Day Dermal Toxicity Study in Rats and Acute Inhalation Study in Rats; Submitted by Ciba Geigy Corporation July 6, 1987 in Response to the Terbutyrn Registration Standard.
EPA ID No.: Tox. Project No.:
Tox Chem. No. 125D

To: Robert Taylor/James Yowell
Product Manager No. 25
Registration Division (TS-767C)

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 12/11/87
Head, Section VI
Toxicology Branch/HED (TS-769C)

Thru: Theodore M. Farber, Ph.D., Chief
Toxicology Branch/HED (TS-769C)

Action Requested: Review acute inhalation study in rats and 21-day dermal toxicity study in rabbits for adequacy in response to the terbutryn registration standard.

Conclusions: The DER's for these two studies are attached. The conclusions reached by Toxicology Branch on the studies is as follows:

1. 21-Day Dermal Toxicity Study in Rabbits

   Systemic NOEL > 1000 mg/kg/day (HDT)
   No dermal irritation was seen at any dosage level tested.
   Core Classification: Minimum

2. Acute Inhalation Study in Rats

   The LC_{50} was reported to be >2.2 mg/l; however, this study is unacceptable for the reasons outlined in the attached DER.

   Core Classification: Supplementary

000001

Reviewed by: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 12/7/87
Section VI, Tox. Branch (TS-769C)
Secondary Reviewer:

DATA EVALUATION REPORT

Study Type: 21-day dermal - rabbit (82-2) Tox. Chem. No: 125D

Accession Number: MRID No: 40255805

Test Material: Terbutryn

Synonyms: FL 87004

Study Number: 87040

Sponsor: Ciba-Geigy Corporation

Testing Facility: Agricultural Division
Ciba-Geigy Corporation
Greensboro, NC

Title of Report: 21-Day Dermal Toxicity Study in Rabbits

Author(s): DM Schiavo, JR Hazelette and JD Green

Report Issued: June 30, 1987

Conclusion:

Systemic NOEL > 1000 mg/kg/day (HDT)

No dermal irritation was seen at any dosage level tested.

Classification: Core-minimum

Special Review Criteria(40CFR154.7): There are no special review triggers as a result of this study.

A. Materials:

1. Test compound: Technical terbutryn. Description: white powder, purity not given.
2. Test animals: Species: rabbit; Strain: New Zealand; Age: 12-14 weeks; Weight: 2.14-2.58 kg for males and 2.00-2.97 kg for females; Source: H.A.R.E., Inc., Hewitt, New Jersey; Rabbits were acclimated for three weeks prior to initiation of dosing.

B. Study Design:

1. Animal Assignment:

Animals were randomly assigned into groups via the Beckman TOXSYS®

computer system. Five rabbits/sex were assigned to each of the following groups: 0, 10, 100 and 1000 mg/kg/day. Rabbits were treated for a minimum of 22 days.

2. Preparation of Animals for Treatment:

The flank and back of each rabbit were shaved as needed during the study. The test compound was applied to the test site daily for 22 days. The area treated comprised 5-10% of the total body surface. A gauze dressing was placed over the treated site and secured with nonirritating adhesive tape. The treatment period was six hours, after which time the bandage was removed, the skin was washed with tap water and dried with a paper towel.

3. Animals received food (Purina Certified Rabbit Chow® #5325) and water ad libitum throughout the study.

4. Statistics: The statistical methods for evaluating the data are attached in Appendix 1 taken from the report.

5. A signed quality assurance statement was present.

C. Methods and Results:

1. Observations:

Animals were examined twice daily for signs of toxicity at predosing and two to four hours postdosing.

No deaths occurred during the study. No signs of toxicity or dermal irritation were noted.

2. Body Weight:

Body weights were recorded on test day -8, just prior to dosing on test day 1, weekly thereafter, and prior to necropsy.

No statistically significant changes in body weight or body weight gain were noted between the control and treated groups.

3. Food Consumption:

Food consumption was measured predose from days -8 to 1 and weekly thereafter.

No treatment related effects were noted on food consumption.

4. Physical/Auditory and Ophthalmoscopic Examinations:

These examinations were done predose day -10 and on test day 17. No treatment-related effects were noted.

5. Dermal Observations:

The skin was checked for signs of erythema, edema and other dermal

changes on predose day 1, prior to dosing and approximatley 30 minutes after the end of each dosing period (after washing) and prior to sacrifice.

No signs of dermal irritation were noted for any group.

6. Blood was collected on predose days -15, -14 and -10 (called day -14), and on test days 20, 21 and 23 (called day 19) from all animals. The CHECKED (X) parameters were examined.

a. Hematology:

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB conc. (MCHC)
X	Leucocyte count (WBC)*		Mean corpusc. volume (MCV)
X	Erythrocyte count (RBC)*		Reticulocyte count
X	Platelet count*		RBC morphology
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* required for subchronic and chronic studies.

Results - Although the Materials and Methods Section states that hemotology was done on the days listed above, summary hematology values were reported as days -14 and 19 only. There was a statistically significant decrease in hematocrit in the females of the high dose group on day 19. The mean value (hematocrit) for this group was within the historical control range according to the report. No other effects of treatment were seen in the measured hematologic paramenters.

b. Clinical Chemistry

X		X	
	Electrolytes:	X	Albumin*
X	Calcium *	X	Blood creatinine*
X	Chloride*	X	Blood urea nitrogen*
	Magnesium*		Cholesterol*
X	Phosphorous*		Globulins
X	Potassium*	X	Glucose*
X	Sodium*	X	Total bilirubin
		X	Total serum Protein (TP)*
	Enzymes:		Triglycerides
X	Alkaline phosphatase (ALK)		Serum protein electrophoreses
	Cholinesterase (ChE)#		
	Creatinine phosphokinase*		
	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies
# Should be required for OP

Results - Summary values were reported as days -14 and 19. There was a statistically significant increase in albumin and total protein in the male rabbits at the high dose. The values at the high dose were within the historical controls according to the report albiet at the high end. There was also a statistically significant increase in calcium levels in males at the 100 and 1000 mg/kg dose levels. This change was not seen in females and the values in males were within the historical controls according to the report. A statistically significant increase in phosphorus levels was noted for males of the high dose group; however, in comparison in females phosphorus levels were statistically significantly decreased at the same dosage level.

Table 1.
Selected Hematology and Clinical Chemistry Values

Males:	Total Protein		Albumin		Phosphorus		Females:	HCT	
Day:	-14	19	-14	19	-14	19		-14	19
Dose (mg/kg/day)									
0	5.16	5.44	4.66	4.60	8.16	7.48		40	40
10	5.04	5.86	4.44	4.48	8.42	8.18		41	39
100	5.56	5.50	4.86	4.64	8.06	8.20		38	40
1000	5.32	5.98	4.70	4.86	8.48	8.50		40	38

7. Sacrifice and Pathology:

All animals were sacrificed on day 23 or 24. All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collectd for histological examination. Microscopic examinations were conducted on the liver, kidney, organs showing gross lesions or changes in size, and treated and untreated skin for each animal. The (XX) organs, in addition, were weighed in all groups.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta*	X	Brain*
X	Salivary glands*	X	Heart*	X	Periph. nerve*+
X	Esopnagus*	X	Bone marrow*	X	Spinal cord(3 levels)*#
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen	X	Eyes (optic n.)*#
X	Jejunum*	Urogenital		Glandular	
X	Ileum*	XX	Kidneys*+	X	Adrenal gland*
X	Cecum*	X	Urinary bladder*		Lacrimal gland#
X	Colon*	XX	Testes*+	X	Mammary gland*#
X	Rectum*	X	Epididymides	X	Parathyroids*++
XX	Liver*+	X	Prostate	X	Thyroids*++
X	Gall bladder*		Seminal vesicle	Other	
X	Pancreas*	XX	Ovaries*+	X	Bone*#
Respiratory		X	Uterus*	X	Skeletal muscle*#
X	Trachea*	X	Vagina	X	Skin*#

X	Lung*		X	All gross lesions and masses*
	Nose		X	Application site
	Pharynx		X	Area next to test site
	Larynx			

* Required for subchronic and chronic studies
\# In subchrnic studies, examined only if indicated by signs of toxicity or target organ involvement
\+ Organ weight required in subchronic and chronic studies
++Organ weight required for non-rodent studies

a. Organ Weights:
No treatment-related effects were noted on organ weights.

b. Gross Pathology:

There were no treatment-related tissue alterations noted at necropsy.

c. Microscopic Pathology:

No treatment-related changes were found.

D. Discussion:

This was a well conducted 21-day dermal study in the rabbit. No treatment-related effects were seen on clinical signs, mortality, or organ weights. No dermal irritation was seen that could be attributed to treatment at any dosage level tested. The highest dose tested was at the limit dose of one gram per kilogram of body weight.

At the 19 day time point, a statistically significant increase in albumin and total protein was seen in the males at the highest dose tested. The increase in both of these mean values was < 10% when compared to the control value at this time point. In addition, the albumin value for the high dose group was within the range of the pretest values for all groups (Table 1). These changes in the HDT were within the historical range as reported and are not considered to be biologically significant nor treatment-related.

Other statistically significant changes seen at the high dose that could be treatment-related were increased calcium levels in males (however, calcium levels were decreased in females), increased phosphorus levels in males (however, the pretest and 19 day values were the same, i.e. 8.48 and 8.50, respectively) and decreased hematocrit in females (however, this values was within the range of the pretest values for all groups). All of these values were within the historical control range. This reviewer does not feel that these changes are treatmentrelated for the reasons discussed above.

The systemic NOEL for this study is > 1000 mg/kg/day.

Core Classification: Core-Minimum

Appendix 1

Terbutryn toxicology review

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Pages 8 through 10 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 10/6/87
Section VI, Tox. Branch (TS-769C)
Secondary reviewer:

DATA EVALUATION REPORT

Study Type: Acute Inhalation - rat (81-3) Tox. Chem. No.: 125D

Accession Number: MRID No.: 40255804

Test Material: Terbutryn Technical

Synonyms: Igran

Study Number: 87023

Sponsor: Ciba-Geigy Corporation

Testing Facility: Research Department
Pharmaceuticals Division
Ciba-Geigy Corporation

Title of Report: Acute Inhalation Toxicity Study in Rats.

Author(s): ER Lasinski, JC Kapeghian and JD Green

Report Issued: June 1, 1987

Conclusions: The authors reported that the LC_{50} for terbutryn is > 2.2 mg/l over a four hour exposure period; however, this study is unacceptable primarily because the mean particle size was too large (for the rat the size should be in the range of 1 um), the test agent was not adequately characterized and the methodology was not completely described.

Core Grade: Supplementary

Special Review Criteria (40CFR154.7): There are no special review triggers as a result of this study.

A. Materials:

1. Test compound: Technical terbutryn. Description: powder

2. Test animals: Species: rat; Strain: Sprague-Dawley; Age: 8-10 weeks; Weight: Males 228-267g, Females 184-219g; Source: Taconic Inc., Germantown, New York; Rats were acclimated for one week prior to start of the study.

B. Study Design:

Two groups were used, a control group and a group exposed to the test substance. Five rats/sex were assigned randomly to each group. The animals were housed individually in suspended wire-bottom cages.

Treated animals were exposed to 2.2mg of Terbutryn Technical/liter of room air. Untreated animals were exposed to room air only under the same experimental conditions as the treated animals. The animals were exposed to the test substance for a period of four hours. They were observed for 14 days post treatment.

A description of the equipment as well as its operation and methodology used in this study are attached and can be found in Appendix 1. This was copied directly from the report.

A signed quality assurance statement was present.

C. Results:

All animals survived the study. The following clinical signs of toxicity were observed in the animals exposed to terbutryn: chromorhinorrhea/rhinorrhea, test material covering fur, red stains around facial area; perineal staining (males only) and chromodacryorrhea (females only). These changes were listed in Table 7.2 of the report. By day 6 after exposure all of the animals appeared normal.

No treatment related lesions were noted in the treated animals upon necropsy. All animals gained weight during the study. Lung weights were unaffected by treatement.

The mean gravimetric concentration over the four hour exposure period was 2.2 mg/l. The nominal concentration was 6.9 mg/l. The mass median diameter was 5.5 um and the geometric standard deviation was 1.8 um. The percent of mass for particles of $\leq$ 9 um was reported to be 81%.

D. Discussion:

The authors concluded that the LC_{50} for technical terbutryn was >2.2 mg/l over a four hour exposure period.

Dr. Stan Gross of Tox. Branch was asked to review this study as well. His recommendations on this study are attached. He feels that this study is unacceptable for the following reasons:

1. Only one concentration was used which was below the limit test level.

2. The test agent was not characterized adequately.

3. The chambers used were not described in sufficient detail.

4. Since the generation system used is not routinely used for inhalation studies, the company should provide a description of the equipment with copies of the literature describing their use.

5. The particle sizes averaged a MMAD of 5.5 um which is too large for rodent studies. Particle sizes in the range of 1 um should be used for rats to ensure respirability of a sufficient amount of the particles.

6. The flow rates to the chamber were reported as 60.00 lpm for 8 determinations

without any variation which is normally seen in chamber flow rates. An explanation should be provided explaining why this would occur.

This reviewer agrees with Dr. Gross's assessment and that this study is unacceptable.

Core Grade: Supplementary

CONSULTATION 12/11/87 006536

Subject: Terbutryn Acute Inhalation Study
EPA 100-540; Caswell # 125D

TO: Judy Hauswirth, TB

FROM: Stan Gross, TB

cc: Albin Kocialski, TB

Study: Terbutryn Technical. Acute Inhalation Toxicity Study in Rats. By Lasinski, E.R., et al. Ciba-Geigy Corporation Study No. 87023, June 1, 1987.

Recommendations:

This study should be rejected for the following reasons:

1) Only one concentration was used which was below the limit test level.

2) The test agent was not characterized adequately -- the percent composition was not given, lot no.; source, etc.

3) The chambers used were not described in sufficient detail--type of chamber, design for agent distribution, the sizes: 22 cubic inch or 200-liter?; etc.

4) Since the generation system used (the Trost Air Mill and revolving disc driven by the Sage motor) is not routinely used for inhalation studies, the company should provide a description of the equipment with copies of the literature describing their use.

5) The particle sizes averaged a MMAD of 5.5 um is too large for rodent studies which should be in the range of 1 um.

6) The flow rates to the chamber were reported as 60.00 lpm for 8 determinations without any variation which is normally seen in chamber flow rates. The company should explain how this could occur.

Appendix 1

Terbutryn toxicology review

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