8-12-86
CASWELL FILE
125B

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

005339

AUG 12 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: 28-day Study in Rats

To: John Lee
Registration Division TS 767C

From: Marcia van Gemert, Ph.D. M van Gemert 8.6.86
Head, Section III, Toxicology Branch

Thru: Theodore Farber, Ph.D. Theodore M. Farber 8/8/86
Chief, Toxicology Branch/HED

Compound: Terbuthylazine

Tox Chem No: 125B

Registrant: Ciba Geigy

Action: Review submitted study

Conclusions: There was a dose-dependent decrease in terminal body weights in both males and females with no no-effect level seen in males. Female absolute liver weight and liver/brain weight ratios were significantly decreased at all doses tested. ($p>0.05$) Male absolute kidney weights were significantly decreased at all doses tested. ($p>0.05$) Male absolute thymus/body weight ratios were decreased at all doses tested with statistical significance seen in groups 2,4, and 5. ($p>0.05$)

No no-effect level was found in this study because of toxicity seen at all doses tested.

NOEL $<$ 25 ppm (LDT)

~~NOEL = none~~

Core Classification: ~~Supplementary~~

1/19

005339

Reviewed by: Marcia van Gemert, Ph.D. M. van Gemert 8.6.86
Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore Farber, Ph.D.
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: 28-day study in rats Tox Chem. No: 125B

Accession No. 263626 MRID No: ?

Test Chemical: Terbuthylazine

Synonyms: Belclene 329

Study Number: 830289

Sponsor: Ciba Geigy

Testing Facility: Ciba Geigy Ltd. Basle Switzerland

Title of Report: 28 days Toxicity Study in Rats

Author: Dr. Phil W. Basler

Report Issued: June 28, 1984

Conclusions: Significant dose-related effects were seen at the lowest dose tested in body weights, food consumption and organ weight parameters.

NOEL < 25 ppm(LDT)

~~NOEL = none~~

Classification: ~~Supplementary~~ Acceptable MM 6/8/12/86; no NOEL

A. Materials:

1. Test Compound: Terbuthylazine, Description, white crystalline powder, Batch #, EN 16727, Purity 99.8%, contaminants: not given

2. Test Animals: Species: rat, Strain: RAI (spf), Age: 4 weeks, Weight: males:89-91 gms. females, 76-80 gms. Source:Animals Production Ciba Geigy Ltd. 4332 Stein, Switzerland

B. Study Design:

1. Animal Assignment: Animals were assigned randomly to the following test groups:

005339

Test Group	Dose in Diet(ppm)	28-day study Male	female
1. Control	0	10	10
2. Low (LDT)	25	10	10
3. Mid-1 (MDT)	75	10	10
4. Mid-2 (MDT)	250	10	10
5. High (HDT)	750	10	10

2. Diet Preparation: Diet was prepared once and stored at room temperature. Samples of treated food were analyzed for stability and concentration at initiation of the study.

Results: Mean concentration of active compound was 87.2 to 104.4% of added amount. Analytical results indicated that test compound was administered at doses of 2.4, 7.7, 26.6, and 68.7 mg/kg body weight in males and 2.3, 8.1, 27.9, 63.4, mg/kg body weight for females. Weekly dosage levels are on appended page 1.

3. Animals received pelleted certified standard diet Nafag Tox No890 and water ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data: Univariate analysis was carried out for each time point and parameter.

5. Quality assurance was not certified by a GLP compliance group.

C. Methods and Results:

1. Observations: Animals were inspected daily for signs of toxicity and mortality.

Results: No clinical signs of toxicity were observed. No deaths occurred on study. One male (group 1) died after blood withdrawal on day 29 of the study.

2. Body Weight: Animals were weighed weekly (mid-week) for 4 weeks.

Results: There was a dose-dependent decrease in body weight in males and females which reached statistical significance at all dose groups in week 5 for males, and in dose groups 4 and 5 for females in week 5. Graphs of body weight gains are on appended pages 2 and 3, and tables of mean body weights for each week are appended on page 4.

3. Food Consumption and Compound Intake: Consumption was determined weekly and mean diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results: Food consumption in all treated males was depressed

In a dose-related manner (P> 0.01) for all groups. Mean food consumption data are on appended page 5.

Water consumption was depressed in a dose-dependent manner. Statistical analysis of food conversion was not done. Mean water consumption data are on appended page 6.

4. Ophthalmalogical Examinations: They were performed on day 4 at the beginning and towards the end (day 25) of treatment on high dose and control animals.

Results: No evidence of a treatment-related effect was evident.

5. Clinical Pathology: Blood was collected before treatment and at the end of the experiment for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

A. Hematology-

X		X	
X	Hematocrit (CHT)	X	Total plasma protein
X	Hemoglobin (HGB)	X	Leukocyte Differential count
X	Leukocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)		Mean corpuscular HGB conc. (MCHC)
X	Platelet count	X	Mean corpuscular volume (MCV)
		X	Prothrombin time

Results: In females, there was a significant ($p > 0.05$) increase in erythrocyte count and prothrombin time in group 5. Mean corpuscular volume and mean corpuscular hemoglobin were depressed significantly ($p > 0.05$) at the highest dose. See appended pages 7 and 8 for tabulated data from the text.

b. Clinical Chemistry:

X	Electrolytes:	X	Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorous	X	Cholesterol
X	Potassium	X	Globulins
X	Sodium	X	Glucose
	Enzymes	X	Total Bilirubin
X	Alkaline phosphatase	X	Total Protein
	Cholinesterase		Triglycerides
	Creatinine phosphokinase		
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (SGPT)		
X	Serum aspartate aminotransferase (SGOT)		
X	Gamma glutamyl transpeptidase		

1. Alanine aminotransferase was significantly increased ($p > 0.05$) in both male and female groups 4 and 5.
2. Aspartyl aminotransferase was also elevated significantly ($p > 0.05$) elevated in groups 4 and 5 females.
3. Serum potassium was elevated significantly ($p > 0.05$) in group 2,4,and 5 females.
4. Total serum protein and albumin were depressed in groups 4 and 5 females. Globulins were also depressed but showed significance only in group 5.
5. In males, group 5 showed a significant ($p > 0.05$) decrease in calcium and glucose.
6. Chloride in males increased slightly ($p > 0.05$) in group 5
7. Inorganic phosphorous in males dropped significantly in groups 3,4 and 5.

Clinical tables are appended on pages 7 and 8.

6. Urinalysis: No urinalysis was performed in this study.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED(X) tissues were collected for histological examination. The (XX) organ in addition were weighed.

X	Digestive system
	Tongue
X	salivary glands
X	Esophagus
X	Stomach
X	Duodenum
X	Jejunum
X	Ileum
X	Cecum
X	Colon
X	Rectum
XX	Liver
	Gall Bladder
X	Pancreas
	Respiratory
X	Trachea
X	Lung

X	Cardiovascular/Hemat.
X	Aorta
X	Heart
X	Bone marrow
X	Lymph nodes
X	Spleen
XX	Thymus
	Urogenital
XX	Kidneys
X	Urinary bladder
XX	Testes
X	Epididymides
X	Prostate
X	Seminal vesicle
XX	Ovaries
X	Uterus

X	Neurologic
XX	Brain
X	periph. nerve
X	spinal cord(3 levels)
X	Pituitary
X	Eyes
	Glandular
XX	Adrenals
X	Lacrimal gland
X	Mammary gland
X	Parathyroids
X	Thyroids
	other
X	Bone
X	Skeletal muscle
X	Skin
X	All Gross Lesions

Results: Organ Weight:

Brain: Males: There was an apparent decrease in grain weight which was significantly ($p > 0.05$) decreased in groups 3 and 5. Brain/body weight ratios were increased in groups 3,4 and 5 primarily due to the drop in body weight, which was significant ($p > 0.05$) in males at all dose levels tested.

Females: There was also an increase in brain/body weight ratios in groups 4 and 5 ($p>0.05$) primarily due to a significant drop in body weights in groups 4 and 5.

Liver: Males: There was a significant increase in absolute organ weights and organ / brain weight ratios only in group 4, whereas both groups 4 and 5 showed statistically significant ($p>0.05$) increase in liver/body weight ratios.

Females: Absolute liver weights as well as liver/brain weight ratios were significantly decreased ($p>0.05$) at all doses tested. Liver/body weight ratios were significantly decreased ($p>0.05$) in groups 2 and 4.

Kidney: Males: Absolute kidney weights were significantly decreased ($p>0.05$) at all dose levels tested. However, only groups 4 and 5 showed significantly decreased ($p>0.05$) kidney/brain weight ratios.

Females: Absolute kidney weights and kidney/brain weights were significantly decreased ($p>0.05$) in group 5. Group 4 kidney/body weights were the only group showing statistical significance.

Adrenals: Males: Absolute adrenal weights were significantly decreased in groups 4 and 5 with adrenal/body weight ratios significantly increased in group 5.

Females: Absolute adrenal weights and adrenal/brain weights were significantly decreased also in groups 4 and 5 with adrenal/body weight ratios having significantly increased only in group 5.

Thymus: Males: Absolute thymus weights were decreased at all doses with statistical significance ($p>0.05$) seen in groups 4 and 5. Thymus/body weight ratios were decreased at all doses tested with statistical significance ($p> 0.05$) seen in groups 2,4 and 5.

Females: Absolute thymus weights and thymus/brain weights were significantly ($p>0.05$) in group 5 only.

Gonads: Males: Groups 4 and 5 absolute testes weights and testes/brain weight ratios were significantly increased ($p>0.05$). Groups 3,4 and 5 gonad/brain weights were increased significantly ($p>0.05$) in groups 3,4 and 5.

Females: Group 5 absolute ovarian weights and ovary/brain weight ratios were significantly increased ($p>0.05$). In groups 2 and 4, ovary/body weight ratios were only increased significantly ($p>0.05$).

A summary of organ weight parameters can be seen on the appended pages 9 through 12.

b. Gross and Histopathology: The text reported a slight but significant dose-related decrease in mean body weight after exanguination in all treated group 4 and 5 males and females. No other macroscopic or microscopic treatment-related signs were evident.

D. Discussion: There was a dose-dependent decrease in terminal body weights in both males and females with no no-effect level seen in males seen. Female absolute liver weight and liver/brain weight ratios were significantly decreased at all doses tested. Male absolute kidney weights were significantly decreased at all doses tested. Male absolute thymus/body weight ratios were decreased at all doses tested with statistical significance seen in groups 2,4 and 5.
No no-effect level was found in this study because of toxicity seen at all doses tested.

NOEL ~~LEL~~ = 25 ppm (LDT)

Core Classification: ~~Supplementary~~ Minimum

TERBUTHYLAZINE TOX R 005339

Page _____ is not included in this copy.

Pages 8 through 19 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 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.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

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.
