8-18-86
CASWELL FILE
125B

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

005354

AUG 18 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: 28-day Dermal Toxicity Study in Rabbits

To: John Lee, pm 31
Registration Division, TS 767C

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch/HED
M. van Gemert 8.11.86

Thru: Theodore Farber, Ph.D.
Chief, Toxicology Branch, HED
Theodore M. Farber 8/12/86

Compound: Terbuthylazine

Tox Chem No.: 125B

Registrant: Ciba Geigy

Action: Review Submitted Study

Conclusions:

There was a dose-dependent decrease in body weights and food consumption which was significant ($p>0.05$) at all doses tested. Alkaline phosphatase was significantly ($p>0.05$) decreased at all doses tested. No NOEL was found for several organ weight parameters of the spleen, thymus and testes, with other organ weights showing trend-related decreases to the lowest dose tested. Histopathological results included dose-related lesions evident at all doses tested in skin, spleen, thymus and testes.

LEL = 1 ml/kg (LDT)

NOEL = none

Core Classification: ~~Supplementa~~ry

1/39

Reviewed by: Marcia van Gemert, Ph.D. M. van Gemert 8.11.86 005354
Section III, Tox Branch (TS-769C)
Secondary Reviewer: Theodore Farber, Ph.D.
Chief, Toxicology Branch, HED

DATA EVALUATION REPORT

Study Type: 28-day dermal study

Tox.Chem No.: 125B

Accession No. 263453

MRID NO: ?

Test Material: Terbuthylazine

Synonyms: Belclene 329, Gardoprim 500 FW

Study number: 8206300

Sponsor: Ciba Geigy

Testing Facility: Ciba Geigy Ltd. Basle Switzerland

Title of Report: 28-day Repeated Dose Dermal Toxicity Study in Rabbits

Authors: G. Seifert

Report Issued: May, 1983

Conclusions: All test animals showed decreased body weight, food consumption, decreased alkaline phosphatase. Various hematological and clinical chemistry parameters showed dose-related changes, along with various organ weight parameters, and histological changes.

LEL = 1 ml/kg (LDT)

NOEL = none found MRID 8.11.86

Classification: ~~Supplementary~~ Minimum, no no-effect level found for numerous parameters

A. MATERIALS:

1. Test compound: Gardoprim 500 FW, Description- dispersion in water, batch- # 0P103006, Purity- 50%, contaminants- not given.

2. Test animals: Species- rabbits, Strain- New Zealand White, Age: 12-14 weeks, Weight: male + female 2-3 kg, Source: Kleintierfarm
Madoerin At Ch 4414
Fuellinsdorf

B. STUDY DESIGN:

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

Test Group	Dose in Ml/kg	Main Study male	female	Duration of Dosing (days)
1. Cont.	0	5	5	28
2. Low (LDT)	1	5	5	28
3. Mid (MDT)	2	5	5	28
4. High (HDT)	4	5	5	28
5 High (recovery)	4	5	5	28 + recovery

2. Route of Application: Before treatment and weekly for the duration of the experiment, flanks of animals were shaved, gauze patches soaked with appropriate doses of test substance were applied and covered for 6 hours duration, 5 days per week exposure.

3. Diet: Standard Nafag No. 814 tox diet was given ad libitum, plus tap water was available ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data: Univariate analysis was conducted on each time point and parameter. Trend test was applied considering all groups.

5. Quality Assurance: Certified with 5 inspections and 5 reports.

C. METHODS AND MATERIALS:

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

Results: Toxicity: According to the text of the study, all treated animals showed signs of sedation with curved body position, ataxia, tremors and dyspnoea.

Mortality: At the 4 ml/kg dose, 6/10 males died and 9/10 females died. At the 2 ml/kg dose, only 1 female died.

2. Body Weights: They were weighed weekly .

Results: Body weight increases were significantly depressed in both males and females of all dose groups tested. See appended pages for text graphs and tables.

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

Results: There was a depression in food consumption at all dose levels tested. Food conversion was depressed in all male and female dose groups. No statistical analyses were performed on these values. Graphs and tables of food conversion from the text are appended in the back.

4. Ophthalmalogical examinations were not performed.

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

Hematology:

X	
X	Hematocrit
X	Hemoglobin
X	Leukocyte cound
X	Erythrocyte count

X	
	Total plasma protein
X	Leukocyte differential cound
	Mean corpuscular HGB
	Mean corpuscular HGB conc.
X	Prothrombin time

Results:

Males: There was a significant drop ($p>0.05$) at the high dose in monocytes and a dose-related increase in thrombocytes with statistical significance at the 2 ml/kg dose. However, only 3 animals were tested at the high dose, so no meaningful data can be derived from so few samples.

Females: There was a dose-related decrease in leukocytes with statistical significant in the 2 ml/kg dose. Only 1 animal survived in the 4 ml/kg dose, so again, no meaningful data can be derived from this group.

b. Clinical Chemistry:

X	Electrolytes:
X	Calcium
X	Chloride
	Magnesium
X	Phosphorous
X	Potassium
X	Sodium
	Enzymes
X	Alkaline phosphatase
	Cholinesterase
	Creatinine phosphokinsase
	Lactic acid dehydrogenase
X	Serum alanine aminotransferase (SGPT)
X	Serum aspartate aminotransferase (SGOT)
X	Gamma glutamyl transpeptidase

X	Other:
X	Albumin
X	Blood Creatinine
X	Blood urea Nitrogen
X	Cholesterol
X	Globulins
X	Glucose
X	Total Bilirubin
X	Total Protein
	Triglycerides

Results:
Males: There was a dose-related decrease in alkaline phosphatase which was significant at all dose levels tested. Potassium levels showed a slight drop in the 2 top doses, however, only the 2 ml/kg dose showed statistical significance. There was a dose-related increase in bilirubin and cholesterol with statistical significance at the 2 ml/kg dose for cholesterol and both at the 4 ml/kg dose.

females: There was also a dose-related decrease in females in alkaline phosphatase although no statistical significance was evident probably due to the small sample size, the decrease was marked. Chloride and albumin levels rose in a dose-related manner with statistical significance at the 2 ml/kg dose, whereas inorganic phosphate dropped at the 2 ml/kg dose, although it didn't appear dose-related by the trend test.

6. Urinalysis: Not done

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 was weighed.

X	X	X
Digestive system	Cardiovascular/hemat.	Neurologic
Tongue	X Aorta	XX Brain
X Salivary glands	XX Heart	X Periph. nerve
X Esophagus	X Bone marrow w/sternum	X spinal cord 3 levels
X Stomach	X Lymph nodes	pituitary
X Duodenum	XX spleen	X eyes
X Jejunum	XX Thymus	Glandular
X Ileum	Urogenital	XX Adrenals
X Cecum	XX Kidneys	Lacrimal gland
X Colon	X Urinary bladder	X Mammary gland
X Rectum	XX Testes	X Parathyroids
XX Liver	X Epididymides	X Thyroids
X Gall Bladder	X Prostate	Other
X Pancreas	X Seminal vesicle	X Bone
Respiratory	XX Ovaries	X Skeletal muscle
X Trachea	X Uterus	X Skin,application + remote
X Lung		X All gross lesions

Results: Organ weights; Data for the 4 ml/kg males and females and recovery period are useless since so few animals survived.

Brain:
Males: there was a dose-related increase in brain/body weight which was statistically significant at the 2 ml/kg dose.
Females: Absolute brain weight was increased in an apparent dose-related fashion but was not significant. Brain/body weight was significantly increased at both 1 and 2 ml/kg doses.

Heart:
Males: Absolute heart weight and heart/brain weight ratios were decreased in an apparent dose-related manner, but did not reach statistical significance. Heart/body weight ratios showed an apparent increase in a similar manner.
Females: Results were similar to males with an apparent dose-related decrease in absolute heart and heart/brain weight ratios with only the 2 ml/kg heart/brain weight ratios showing any statistical significance.

Kidney:
Males: Kidney/body weight was increased in a dose-related manner and was statistically significant at 2 ml/kg.
Females: Kidney weights and kidney/brain weights were decreased over controls at both 1 and 2 ml/kg doses with only the 2 ml/kg kidney/brain weight ratios showing statistical significance.

Adrenals:
Males: There was a significant increase in absolute weights and adrenal/brain weight ratios at the 2 ml/kg dose with a dose-response increase in adrenal/body weight ratios significant at the 2 ml/kg dose.

Thymus:

Males: All parameters showed a dose-related significant decrease ($p < 0.05$) in thymus weight with all parameters significant at the 2 ml/kg dose. 040354

Females: All parameters also showed a significant dose-related decrease in absolute weight with all parameters significant at both the 1 and 2 ml/kg dose except 1 ml/kg thymus/body weight was not significantly different from controls.

Gonads:

Males: There was a trend toward decreased testicular weight with significant dose-response evident in gonad/brain weight ratios.

Spleen:

Males and Females: here was a slight drop in absolute spleen weight but no statistical significance was evident.

b. Gross pathology: Macroscopic changes were not remarkable for any of the treated animals. A summary of findings is appended.

c. Microscopic pathology:

Skin: All treated animals showed congestion, adema, hemorrhages, ulceraton, inflammatory cell infiltration, hyperkeratosis, acanthosis and parakeratosis. See appended pages for a summary of these microscopic changes. The "skin remote" sites also included some of these findings. However, the study authors noted that these lesions were nearly always focal, mainly slight and probably resulted from micro-traumatism.

Spleen: The authors of the study text reported that only minimal amounts of hemosiderin were present in control spleens. However, as can be noted in the summary tables appended, moderate to marked amounts of hemosiderin were found in many animals of all treated groups including the recovery group. The authors were not clear on the cause, however, they said it was associated with atrophy of the white pulp which was obviously present and reported in 5/8 males and 5/8 females at 4 ml/kg.

Thymus: Atrophy, as the study authors phrased it, sometimes slight or moderate but more commonly marked (complete absence of parenchymal tissue) was seen in 3/10 of the 1 ml/kg group and 9/10 of the 2 ml/kg group. All high dose animals were effected. This atrophy was sometimes accompanied, according to the text, by hemorrhage.

Lymph Nodes: 1. Atrophy of the lymphatic tissue in the axillary/mesenteric lymph nodes was present in the high dose group with 3/8 males and 5/9 females showing atrophy.

2. Atrophy of lymphatic tissue in the cecum was also evident in 1/5 males in the 2ml/kg dose and 5/8 males and 7/9 females in the 4 ml/kg dose.

Gastric Mucosa: One animal in the 2 ml/kg dose group showed erosion with hemorrhage and 2/8 males and 4/19 females in the 4 ml/kg dose group showed minimal fibrosis.

Testes: One male in the 1 ml/kg dose group showed tubular atrophy. A less advanced condition of reduced spermatogenesis was bilaterally present as mainly minimal but the text claimed that there were some moderate or marked cases. One other male in the 1 ml/kg dose group and all males in the 2 and 4 ml/kg dose

group showed reduced spermatogenesis.

Congestion in lungs, liver and kidneys: In the 4 ml/kg dose liver congestion, and lung consolidation was evidently a sequel to morbidity.

Liver: 3/8 males and 2/9 females of the 4 ml/kg dose group showed fatty changes in the liver. 1/8 and 2/9 also showed "recent necrosis". No explanation for these animals, # 168, 193 and 198, would be found for this term in the individual microscopic findings.

Discussion:

No no-effect level was found for various parameters such as body weights, food consumption and some clinical chemistry parameters. Dose-response relationships were seen in many organ weight parameters with significance or trend-related decreases evident at all doses tested.
Histopathologic treatment-related changes were seen at all doses tested, including thymic atrophy, tubular atrophy of the testes, and hemosiderin in the spleen. No no-effect level was evident for this study.

TERBUTHYLAZINE TOXR 005354

Page _____ is not included in this copy.

Pages 8 through 39 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.
