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

008237

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

EXPEDITE

MEMORANDUM

SUBJECT: ID. Nos. 8F03658 and 000100-TNR; Amber: 21 Day Dermal Study in Rabbits and an Amendment to the Chronic Rodent Study

Tox. Chem. No.: 861C
Project No.: 0-1946
Submission #s: S383137
S383142

FROM: Melba S. Morrow, D.V.M. M.S. Morrow 1/10/91
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Registration Division (H7505C)

THRU: Marion P. Copley, D.V.M. Marion P. Copley 1/10/91
Section Head, Review Section II
Toxicology Branch I
Health Effects Division (H7509C)

CONCLUSIONS:
Based on the results of the 21-day dermal toxicity study (study # 831257) in rabbits, the systemic NOEL and the systemic LEL for Triasulfuron (Amber) in males were 10 mg/kg and 100 mg/kg, respectively. The LEL in males was characterized by the occurence of dyspnea and ruffled fur. A NOEL could not be determined in females; the LEL in this sex was observed at 10mg/kg/day and was also characterized by dyspnea and ruffled fur.

A copy of the DER for this study is attached. The study is classified as minimum. Although a NOEL for females has not been established, an additional study is not required because the LEL is considered a borderline treatment related effect.

In addition, the supplementary information filed to bring the chronic feeding study (study # 410-1864) in rats up to an acceptable classification has been found to be satisfactory. A summary of this supplemental information is also attached and based on the information provided, it is recommended that the study be upgraded to core minimum.

ACTION REQUESTED:
A review of the 21 day dermal toxicity and a review of the supplement to the chronic feeding study in rats has been requested.

Reviewed by: Melba S. Morrow, D.V.M. MSMorrow 1/10/91
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion P. Copley 1/10/91
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

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STUDY TYPE: 21 Day Dermal - Rabbits

GUIDELINE #: 82-2

TOX. CHEM. #: 861C

MRID #: 415858-01

TEST MATERIAL: CGA 131036 (Technical 94.5%)

SYNONYMS: Triasulfuron, Amber

STUDY NUMBER: 831257

SPONSOR: Ciba - Geigy
Greensboro, N.C.

TESTING FACILITY: Ciba - Geigy, Ltd.
Basle, Switzerland

TITLE OF REPORT: 21 Days Repeated Dose Dermal Toxicity Study in Rabbits

AUTHORS: M. Schoch

REPORT ISSUED: March 17, 1986

CONCLUSIONS: Based on the clinical observations of ruffled and dyspnea it was concluded that the systemic NOEL was 10 mg/kg/day and the systemic LEL was 100 mg/kg in males. The systemic NOEL in females could not be determined from the data presented; the LEL was observed at 10 mg/kg/day.

The dermal NOEL = 1000 mg/kg/day; The dermal LEL > 1000 mg/kg/day

CLASSIFICATION: Minimum . Although a systemic NOEL was not obtained for female rabbits, it is felt that the observed LEL was a borderline treatment related effect and an additional study would not be needed. It is felt that the NOEL in female rabbits is just below the 10 mg/kg/day tested in this study.

TOX. CATEGORY: N/A

MATERIALS: Forty New Zealand White rabbits (20 males and 20 females) served as the test species. The animals weighed between 2.1 and 2.7 kg and ranged in age from 12 to 14 weeks. CGA 131036, having a purity of 94.5% was the test article.

METHODS: Animals were housed individually in metal cages and exposed to a 12 hour light/dark cycle. Food and water were provided ad libitum.

After an acclimation period of 12 days, five males and five females were assigned to each of the following four dose groups:

GROUP	DOSE (mg/kg)
1	control (0)
2	10
3	100
4	1000

Prior to treatment, the backs of the rabbits were shaved so as to expose an area equal to approximately 10% of the body surface area. The area was prepared not less than 24 hours before application of the test compound. Gauze patches containing the test material were moistened with distilled water which contained 0.5% carboxymethylcellulose and 0.1% polysorbate 80 and applied to the shaven area. Patches were covered and fastened to the body and held in place for 6 hours. After the 6 hour exposure period, the area was cleaned with luke warm water. This procedure was followed for five days a week for a 3 week period. (Total number of exposures = 15).

Control animals were treated in the same manner but received only the vehicle (distilled water, carboxymethylcellulose and polysorbate 80).

Observations were made for systemic signs of toxicity and signs of local irritation. Body weights were monitored weekly and food consumption was measured twice weekly. Mean food conversion was calculated by using the following formula:

$$\frac{\text{weekly food consumption (g)}}{\text{midweek body weight (g)}} \times \frac{1000}{7}$$

Hematology, blood chemistry and urinalysis were performed on each animal after an overnight fast. Blood samples were obtained from the orbital veins. The following parameters were examined:

Hematology
x Hematocrit (HCT)
x Hemaglobin (HGB)
x Leucocyte count (WBC)
x Erythrocyte count (RBC)
x Platelet count
x Leukocyte differential
x Mean corpuscular hemaglobin
x Mean corpuscular hemaglobin concentration
x Mean corpuscular volume
Reticulocytes

Blood clotting measurements:
Thromboplastin time
Clotting time
x Prothrombin time

Serum Chemistry

Electrolytes:
Calcium
Chlorine
Magnesium
x Phosphorous
x Potassium
x Sodium

Enzymes:
Creatinine phophokinase
x Alkaline phosphatase
x Lactic dehydrogenase
x SGPT
x SGOT
Gamma glutamyl transferase
Glutamate dehydrogenase

Other Serum Chemistry Values:
x Albumen
Blood creatinine
x BUN
Cholesterol
x Globulin
x Glucose
Total Bilirubin
Total protein
Triglycerides
Serum protein electrophoresis

At the end of the 21 day test period, animals were exsanguinated while under T-61 anesthesia. Body weights were recorded and complete autopsies were performed. Tissue samples were collected from all high dose and control animals and from those animals in groups 2 and 3 which showed gross changes at necropsy. Samples of skin were collected from all animals and were examined microscopically.

The following CHECKED (x) tissues were collected for histological examination. Weighed organs are designated by (xx)

Digestive system	Cardiovasc./Hemat.	Neurologic
Tongue	x Aorta	xx Brain
x Salivary glands	x Heart	x Periph. nerves
x Esophagus	x Bone marrow	x Spinal cord
x Stomach	x Lymph nodes	
x Duodenum	xx Spleen	
x Jejunum	xx Thymus	
x Ileum		Glandular
x Cecum		Parathyroids
x Colon	Urogenital	xx Adrenals
Rectum	xx Kidneys	xx Thyroid
	x Urinary bladder	x Pituitary
xx Liver	xx Testes	x Mammary
x Gall bladder	x Epididymides	Other
x Pancreas	x Prostate	x Bone
	x Seminal vesicle	x Skin
Respiratory	xx Ovaries	Skel. muscle
x Trachea	x Uterus	x All gross lesions
Lung	x Vagina	
Nose		
Pharynx		
Larynx		

QUALITY ASSURANCE: A statement of quality assurance and a statement of compliance with Good Laboratory Practices were both included in the submission.

RESULTS:

Clinical Observations

No deaths were reported and no signs of local irritation were observed in any of the rabbits. There were no differences in body weights between control and treated animals and there was no difference in food consumption.

Clinical observations in treated rabbits included dyspnea and ruffled fur, which the sponsor attributed to the stress from handling; signs of sedation and abnormal body positions. No clinical observations were made in the control animals.

In the high dose group, signs of sedation and abnormal body positions were observed in both sexes. (See Table I for relationship between the frequency of the occurence of clinical signs). Dyspnea and ruffled fur was observed in all males and all females in this dose group at some time during the study.

At 100 mg/kg, dyspnea was observed in 3/5 males and in 3/5 females. Ruffled fur was reported in 2/5 males and in all females in this group.

At 10 mg/kg no symptoms were observed in males and 1/5 females had dyspnea and ruffled fur. This one animal in the 10 mg/kg group exhibited dyspnea for 3 days (days 11, 12 and 13) and ruffled fur for 5 days (days 11 - 15, inclusive). In the other affected groups, the onset of dyspnea and ruffled fur was earlier and the duration of the symptoms was longer.

The observations made in female rabbits treated at 10 mg/kg, are probably indicative of a borderline treatment related effect.

Hematology/Serum Chemistry
At 1000 mg/kg/day, the percentage of segmented neutraphils was higher and the percentage of lymphocytes was lower in the differential count for both males and females. These values were within the range of normal and do not have biological significance. At this dose level a significant difference (decrease) was also observed in the alanine aminotransferase in males. This value was also within the normal biological limits.

Pathology
Liver weights in males receiving the highest dose were slightly decreased when compared to controls but this was not considered statistically or biologically significant. Female rabbits at the highest dose level had elevated mean kidney weights, but this difference was not biologically significant.

Microscopically, skin changes characterized by inflammatory cell infiltration were present in all groups at about the same frequency. This finding was probably the result of the trauma caused by preparing the application site. Therefore, the dermal NOEL is equal to the highest dose tested.

DISCUSSION: Contrary to the conclusions reported by the sponsor, it appears as if the occurence of ruffled fur and dyspnea are related to the compound and not to the stress caused by the application methods. If the latter were true, some of the control animals would have the same type of clinical signs.

Based on this, the systemic NOEL is 10 mg/kg/day for males and the systemic LEL in the same sex would be 100 mg/kg. For females, a systemic NOEL was not determined because dyspnea and ruffled fur were reported at the lowest dose tested. However, since the observed effects at the lowest dose tested appear to be borderline treatment related effects, an additional study would not be required to determine a systemic NOEL for females.

The dermal NOEL is equal to the highest dose tested (1000 mg/kg/day); the dermal LEL would be greater than 1000 mg/kg/day.

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Although the sponsor states that it was used as an anesthetic, T-61 is a euthanasia solution. Its use in the termination of the test animals will not compromise the results obtained in this study.

The study is Minimum .

TABLE I - MAXIMUM FREQUENCY of OBSERVED CLINICAL SIGNS

Clinical Signs	Dose Group (mg/kg/d)			
	control	10	100	1000
males				
Dyspnea	0/5	0/5	3/5	5/5
Ruffled Fur	0/5	0/5	2/5	5/5
Abnormal body position	0/5	0/5	0/5	2/5
Sedation	0/5	0/5	0/5	1/5
females				
Dyspnea	0/5	1/5	3/5	5/5
Ruffled Fur	0/5	1/5	5/5	5/5
Abnormal body position	0/5	0/5	0/5	1/5
Sedation	0/5	0/5	0/5	3/5

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DATA EVALUATION REPORT
Supplement (See HED Doc# 007582)

STUDY TYPE: chronic toxicity/oncogenicity - rat

GUIDELINE #: 83-5

TOX. CHEM. #: 861C

MRID #: 415858-02 (former MRID # 407283-018)

TEST MATERIAL: CGA 131036 Technical (92.5%)

SYNONYMS: Amber, Triasulfuron

STUDY NUMBERS: 410-1864

SPONSOR: Ciba Geigy Corporation
Greensboro, N.C.

TESTING FACILITY: American Biogenics Corporation
Decatur, Illinois

TITLE OF REPORT: Combined Chronic Toxicity/Oncogenicity Study in Rats

AUTHORS: Leslie D. Morrow

REPORT ISSUED: July 26, 1987

CONCLUSIONS: Triasulfuron feeding in rats did not cause a dose related increase in the incidence of neoplasms in this study.

NOEL = 1000 ppm (32.1 mg/kg)
LEL = 6000 ppm (220.8 mg/kg) based upon a decrease in mean body weight gain in both sexes at weeks 13 and 103. In males, a decrease in mean absolute heart and testes weights were also reported.

Classification: Based on the following responses provided by the sponsor, the study has been upgraded to core minimum:

1. With regard to the discrepancy in the final body weights, the sponsor states that one set of data were recorded at week 103 and the other set of data were recorded at necropsy following an overnight fast. All weights recorded prior to necropsy were not taken on the same day as were the body weights on week 103. Therefore, it is the sponsor's belief that the body weights at

week 103 provide a better basis for group comparisons.

It is agreed that the body weights for males and females at week 103 are a better measurement for comparison. This finding will have no bearing on the determination of the chronic toxicity or the oncogenicity of the compound as stated in the DER (no dose-related increase in the incidence of neoplasms; NOEL = 1000 ppm, LEL = 6000 ppm, based on a decrease in mean body weight in both sexes and a decrease in mean absolute heart and testes weights in males).

2. A summary table with survival incidence in both males and females has been provided. A copy of this table follows:

Conc.(ppm)	MALES		FEMALES	
	Incidence	percent	Incidence	Percent
0	52/90	57.8	61/89	68.5
10	45/80	56.3	44/80	55.0
100	41/80	51.3	42/80	52.5
1000	70/90	77.8	53/90	58.9

3. The purity of the technical grade material was not included in the initial summary. The sponsor states that the material was 92.5% pure and that this information was forwarded to Mr. Robert Taylor on January 15, 1990 in an Analytical Short Report.