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Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 6/3/92
Tox. Branch II, Section II (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 6/3/92
Tox. Branch II, Head Section II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal - rabbit TOX. CHEM. NO.: 463-O

MRID NO.: 421373-38

TEST MATERIAL: Fluroxypyr methylheptyl ester

SYNONYMS: 4-amino-3,5-dichloro-6-fluoro-2-pyridyloxy-, 1-methylheptyl ester

STUDY NUMBER: K-137992-003

SPONSOR: DowElanco

TESTING FACILITY: The Toxicology Research Laboratory/Health & Environmental Sciences/Dow Chemical Co.

TITLE OF REPORT: Fluroxypyr Methylheptyl Ester: Dermal Probe Study and 21-Day Dermal Toxicity Study in New Zealand White Rabbits

AUTHORS: PF Cosse, JW Crissman, and U Vedula

REPORT ISSUED: September 11, 1991

QUALITY ASSURANCE: A quality assurance statement was provided.

CONCLUSIONS: Under the conditions of the study, exposure to fluroxypyr methylheptyl ester via dermal exposure for 21 days at dose levels of 100, 300, and 1000 mg/kg failed to elicit any dermal or systemic toxicity. The NOEL can be set at 1000 mg/kg, the limit dose.

Classification: Core Minimum. This study satisfies the guideline requirement (82-2) for a 21-day dermal toxicity study.

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A. MATERIALS:

1. Test Compound: Fluroxypyr MHE; Description: white crystalline solid; Batch #: none per se, identified as AGR 248743; Purity: HPLC-98.5%, differential scanning calorimetry-99.1%.

2. Test Animals: Species: rabbit; Strain: New Zealand white; Age: ≈ 5 months old; Weight: males ≈3800 g (day 1), females ≈3850 g (day 2); Source: Hare Marland, Hewitt, NJ.

3. Statistics: Statistical evaluation of the data is described on pages 17-19 of the study report (copy of pages appended).

B. STUDY DESIGN

1. Methodology: **Probe Study:** One male rabbit received a dermal application of 1000 mg (limit dose) fluroxypyr MHE/kg body weight/day, six hours/day for 4 days. The rabbit was weighed prior to the first application (this weight used to determine dose) and at study termination. Following each daily exposure, a careful evaluation was made of the skin at the application site (using the same dermal irritation scoring system described below in the design of the 21-day study), and the rabbit was observed for signs of toxicity. The rabbit was not subjected to necropsy. The purpose of this probe study was to establish acceptable dose levels for use in the 21-day dermal study.

21-Day Dermal Study: Twenty male and 20 female adult rabbits were randomly assigned (randomization based on body weight) to one of four groups [0, 100, 300, or 1000 mg/kg] of 5 rabbits/sex/group. The dose levels were chosen, based on the probe study described above. No dermal irritation or evidence of systemic toxicity was observed in the probe study. The animals were fed a basal diet of Purina Certified Chow # 5322 (Purina Mills, Inc., St. Louis, MO), which was given at a rate of 4 ounces/day to each rabbit. Water was available ad libitum. The test material was applied in powder form, as supplied by the Sponsor. The applied dose was adjusted weekly based on the most recent individual animal body weight.

For ≈ 6 hours/day for 4 days prior to study initiation, each rabbit was acclimated to an elastic jacket, which was used to hold the test material dressing in dermal contact. An area ≈10 x 15 cm (≈10% of the body surface area) on the back of each rabbit was clipped free of fur prior to study initiation and as necessary during the study. The test material was held in dermal contact by a dressing consisting of absorbent gauze and non-absorbent cotton. Approximately 6 hours after application of the test material, the jacket and dressing were removed and the test site wiped with a water-dampened disposable towel to remove any residual test material. Each rabbit received a

total of 15 applications during a 23-day period (weekends/ holidays excluded).

2. Clinical Observations: The rabbits were given a careful clinical examination [thorough evaluation of the skin, fur, mucus membranes, respiration, circulatory system function, autonomic and central nervous system function (e.g., tremors, convulsions) and behavior pattern] prior to study initiation and at weekly intervals during the study. Daily cageside examinations for signs of toxicity, mortality/moribundity, availability of food/water were also made. Individual body weights were recorded ≈ weekly. Food consumption was not measured since rabbits tend to consume their entire daily ration.

Evaluation of dermal application site - Subjective evaluations of the condition of the dermal test site were made when the jacket and dressing were removed from each rabbit on the last day of the dosing week and on the afternoon prior to necropsy. The scoring system used was a modification of the acute dermal irritation scoring system recommended by OECD (1981, Part 404, see below). Additionally, necrosis, scabs, and/or scars were noted, if present, but these were not graded.

Erythema and Eschar	Grade
Within Normal Limits	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema to slight eschar formation	4

Edema	
Within Normal Limits	0
Very slight erythema (barely perceptible)	1
Well-defined (edges raised)	2
Moderate (raised ≈ 1 millimeter)	3
Severe (raised more than 1 millimeter)	4

Scaling and Fissuring	
Within Normal Limits	0
Slight scaling	1
Moderate - severe scaling	2
Slight fissuring	3
Moderate - severe fissuring	4

RESULTS

Survival and Clinical Observations

Probe Study - There were no adverse effects noted in the rabbit tested at 1000 mg/kg.

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Main Study - All animals survived until study termination. There were no treatment-related clinical findings seen during the study suggestive of systemic toxicity. The observations at the dermal test site (see table below) were attributed to trauma associated with wrapping/handling procedures, rather than to any test material effect.

Dermal Test Site Scoring

Finding/Group/	Day 2/3				Day 9/10				Day 16/17				Day 22			
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H
MALES																
Erythema																
(within normal limits)	5	5	5	5	5	4	5	4	5	4	5	3	5	4	4	4
(very slight)	0	0	0	0	0	1	0	1	0	1	0	2	0	1	1	1
Edema																
(within normal limits)	5	5	5	5	5	4	5	4	4	3	3	4	5	5	4	5
(very slight)	0	0	0	0	0	1	0	1	1	2	2	1	0	0	1	0
FEMALES																
Erythema																
(within normal limits)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4
(very slight)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Edema																
(within normal limits)	5	5	5	5	5	5	5	4	5	5	5	5	5	5	5	5
(very slight)	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
scaling/fissuring																
(within normal limits)	5	5	5	5	5	5	5	5	5	5	5	4	5	5	5	5
(slight scaling)	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0

Body Weight

Body weight was comparable among the groups throughout the study for both sexes. The males groups all lost weight during the study, as did the control females. The low- and high-dose females gained weight, while the mid-dose females showed no weight gain over the time-frame reported.

Mean Body-Weight Change (g)

Interval/Group	0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
MALES 1-21	-51	-67	-37	-40
FEMALES 2-21	-13	43	0	16

3. Blood Analyses

Hematology: Blood samples were obtained from all survivors one day prior to necropsy. It was not stated whether food was withheld prior sacrifice and sample collection (from the ear vein). The CHECKED (X) parameters were examined.

X		X	
X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)

X	Leukocyte count (WBC)		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)		Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements (Thromboplastin time) (Activated partial thromboplastin time)	X	Red cell/leuko/plat morphology
	Nucleated erythrocytes normoblasts		

RESULTS

There were no significant treatment-related effects observed on any of the measured parameters in either sex.

Clinical Chemistry: Blood samples were obtained as stated above. The CHECKED (X) parameters were examined.

X	Electrolytes:	X	Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorous		Cholesterol
X	Potassium	X	Globulins
X	Sodium	X	Glucose
	Iron		Phospholipids
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum Protein (TP)
	Cholinesterase (ChE)		Triglycerides
	Creatine kinase (CK)		Lipids, total
	Lactate dehydrogenase (LAD)		Triiodothyronine, total T3
X	Serum alanine aminotransferase		
X	Serum aspartate aminotransferase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase (GLDH)		
	Ornithine carbamyltransferase (OCT)		
	Serum protein electrophoresis*		
	Thyroxine, total T4		

RESULTS

There were no treatment-related effects on any of the parameters measured.

4. Urinalysis: Urine samples were not collected.

5. Gross Pathology: All animals were subjected to a full macroscopic examination at sacrifice ≈ 24 hours after the final application (no information on whether animals were fasted overnight was provided). The necropsy included examination of the eyes by visual inspection of the cornea, lens, and other internal components via placement of a

moistened glass slide on the corneal surface under fluorescent light illumination. Special attention was given to the skin at the application site. The following organs were weighed: kidneys, liver, and testes (♂♂ only).

RESULTS

The only statistically significant effect noted on organ weight was an increase in kidney weight in both sexes at the high-dose level. The authors stated that, since there were no histological lesions indicative of kidney toxicity or alteration in clinical chemistry parameters, the increase in kidney weight is not considered toxicologically significant. TB II points out that the kidney appears to be a target organ for Fluroxypyr, and kidney lesions have been observed in subchronic and chronic feeding studies with Fluroxypyr. There were no other significant differences noted in organ weights, and the incidence of gross lesions was comparable among the groups of both sexes.

6. Histopathology: The following organs/tissues (CHECKED (X)) were preserved from all animals at terminal sacrifice. A complete histopathological evaluation of untreated and treated skin, liver, kidneys, and any gross lesions was performed on all animals.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta	X	Brain♣
X	Salivary glands	X	Heart	X	Periph. nerve
X	Esophagus	X	Bone marrow	X	Spinal cord□
X	Stomach	X	Lymph nodes♦	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes
X	Jejunum	X	Thymus	Glandular	
X	Ileum	Urogenital		X	Adrenal gland
X	Cecum	X	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	X	Testes	X	Parathyroids
X	Liver	X	Epididymides	X	Thyroids
X	Gall bladder	X	Prostate	Other	
X	Pancreas		Seminal vesicle	X	Bone♥
Respiratory		X	Ovaries/oviduct	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lung	X	Vagina	X	All gross lesions
X	Nasal tissues		Coagulating gl.	X	Oral tissue
	Pharynx	X	Appendix	X	Sacculus rotundus
X	Larynx	X	Cervix		

♥including joint; ♦ mediastinal & mesenteric/and tissues; ♣ cerebrum, brainstem, cerebellum corpus, & cervix; □cervical, thoracic, & lumbar

RESULTS

No evidence of systemic toxicity was observed at the histological evaluation of the kidney and liver, and the lesions at the dermal test site are considered a result of mechanical irritation due to the procedures used. Lesions observed in the kidneys and at the dermal test site are listed below.

Incidence of Kidney/Skin Lesions♦

Lesion/Group	0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
MALES				
Kidneys				
(normal)	1	1	2	1
(inflammation-slight)	1	0	0	0
mineralization*				
(very slight)	1	0	1	0
(slight)	1	1	0	4
(moderate)	0	0	1	0
tubular degeneration/ regeneration				
(very slight)	4	4	3	1
(slight)	0	0	0	2
(moderate)	0	0	0	0
Skin				
(normal)	1	1	1	0
hyperplasia♦				
(very slight)	4	4	4	5
(slight)	0	0	0	0
inflammation				
(focal)	2	1	0	1
(multifocal)	1	0	2	0
FEMALES				
Kidneys				
(normal)	1	0	2	0
(inflammation-slight)	0	0	0	0
mineralization*				
(very slight)	2	2	1	2
(slight)	1	2	0	2
(moderate)	0	0	1	0
tubular degeneration/ regeneration				
(very slight)	2	2	1	3
(slight)	2	2	1	2
(moderate)	0	0	1	0
Skin				
(normal)	0	0	0	0
hyperplasia♦				
(very slight)	5	4	4	4
(slight)	0	0	0	1
inflammation				
(focal)	0	0	1	1
(multifocal)	2	3	4	2

♦ n=5 for each group; * tubule, multifocal; ♦ epithelial, diffuse

DISCUSSION

There were no clinical signs, differences in body weight or clinical pathology, and no gross or histopathological lesions that could be attributed to exposure to the test material. No dermal or systemic toxicity was observed at dose levels up to

1000 mg/kg, the limit dose.

CONCLUSION

Under the conditions of the study, exposure to fluroxypyr methylheptyl ester via dermal exposure for 21 days at dose levels of 100, 300, and 1000 mg/kg failed to elicit any dermal or systemic toxicity. The NOEL can be set at 1000 mg/kg, the limit dose. This study is classified Core Minimum, and it satisfies the guideline requirement (82-2) for a repeated dose dermal toxicity study.

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