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TR-6357

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

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JUL 20 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of the 21-day dermal toxicity study on Fenoxyprop-ethyl

To: Richard Mountfort, PM-23
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D. M. van Gemert 7/10/87
Head, Section III
Toxicology Branch, HED

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

American Hoechst was given a conditional registration for the chemical Fenoxyprop-ethyl. The firm was directed to submit an acceptable 21-day dermal toxicity study within one year from the date of registration (Feb. 26, 1987). American Hoechst has submitted this 21-day dermal study, and the DER is enclosed.

No treatment-related effects were seen in mortality, toxicity, body weight, food consumption, ophthalmology, urinalysis, or hematology. There was a compound-related increase in glucose levels in group 4 males and group 3 and 4 females. Chloride levels were elevated in group 3 and 4 males but not in females. The lipid and cholesterol lowering effects seen at higher doses were not evident in this study. There was a statistically significant decrease in absolute and relative liver weights at all doses tested in both males and females. This is contrary to the findings seen at higher doses where liver weights are actually increased.

the NOEL for this study is < 5 mg/kg, based on decreased liver weights

Core classification = minimum but no NOEL was established for this study, and it will have to be repeated.

This study will not satisfy the requirements for an acceptable 21-day dermal toxicity study.

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Reviewed by: Marcia van Gemert, Ph.D. M. van Gemert 7/14/87
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Theodore M. Farber, Ph.D.
Chief, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: 21-day dermal study

TOX. CHEM. NO.: 431C

ACCESSION NUMBER: 402308-00-01

MRID NO.:

TEST MATERIAL: Fenoxyprop-ethyl

SYNONYMS: HOE 033171

STUDY NUMBER(S): 082642

SPONSOR: American Hoechst

TESTING FACILITY: Research and Consulting Co. Switzerland

TITLE OF REPORT: Subacute (21-day) repeated dose dermal toxicity study in rats

AUTHOR(S): L. Ullman, et al

REPORT ISSUED: May 12, 1987

CONCLUSIONS: Dermal doses administered to Wistar outbred rats for 21 days, 6 hours/day, 5 days/week were 0, 5, 10, and 20 mg/kg. No treatment-related mortality, toxicity, body weight or food consumption changes, ophthalmological, urinalysis or hematological changes were evident. There was a compound-related increase in glucose levels in group 4 males and group 3 and 4 females. Chloride levels were elevated in group 3 and 4 males but not in females. The lipid and cholesterol lowering effects seen at higher doses were not evident in this study. There was a statisticaly significant decrease in absolute and relative liver weights at all doses tested in both males and females. This is contrary to the findings seen at higher doses where liver weights are actually increased. NOEL < 5 mg/kg, based on decreased liver weights

Classification: core-minimum

Special Review Criteria (40 CFR 154.7)

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A. MATERIALS:

1. Test compound: [illegible] technical grade
Description: not given
Batch # HOE 033171 OH 296 0001
Purity 96.5%.

Test article was stated to be soluble in diluted form at least 2 hours and was stored at -21°C in the dark.
Vehicle was sesame oil.
Test article was prepared freshly daily prior to application.

2. Test animals: Specific pathogen free rat.
Strain: Wistar KFM-1Han, Outbred albino rat
Age: 7-8 weeks
Weight: males: 200-231 gms, females: 173-214 gms
Source: Kleintierfarm Madoerin Switzerland

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet mg/kg	Main Study 21 days male	female
1 Cont.	0	10	10
2 Low (LDT)	5	10	10
3 Mid (MDT)	10	10	10
4 High(HDT)	20	10	10

2. Treatment: 21 dermal applications were administered to the shaved skin of the back, (10% of total body surface) and covered with an occlusive bandage for 6 hours/day, 5 days/week for a total of 21 applications. Test article was washed off with water after termination of each daily treatment.

3. Animals received food (pelleted standard Kliba 343 diet) and water ad libitum.

4. Statistics - The procedures utilized are on appended page 2.

5. Quality assurance statement was signed and dated May 26, 1987

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C. METHODS AND RESULTS: 006357

1. Observations

Animals were inspected daily for signs of toxicity and mortality. Local irritation was recorded according to Draize test. The assessment of erythema and eschar formation are on appended page 1.

Mortality (survival): Two high dose females died one test, one spontaneously and the second from a blood sampling accident.
Toxicity: No treatment-related signs of toxicity were evident.

2. Body weight

Animals were weighed once during acclimation period and weekly thereafter.
Results: No treatment-related changes in body weight were seen.

3. Food consumption and compound intake

Consumption was determined once during acclimation and weekly thereafter.

Results: No treatment-related changes in food consumption were evident.

4. Ophthalmological examinations
Performed on all animals at 4 weeks of treatment using a Heine Microflex 2 Ophthalmoscope.

Results: No treatment-related changes were evident.

5. Blood was collected before treatment and after 4 weeks for hematology and clinical analysis The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*	X	Reticulocyte count
X	Blood Clotting Measurements	X	Nucleated erythrocytes-normoblasts
X	(Thromboplastin time)	X	Red cell morphology
X	(partial thromboplstin time)		

* Required for subchronic and chronic studies

Results: no treatment-related changes in hematological parameters were evident.

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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*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total and direct Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#	X	Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
X	Lactic acid dehydrogenase	X	Total lipids
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

There was a compound-related increase in glucose levels in group 4 males and group 3 and 4 females.
Chloride levels in groups 3 and 4 males were elevated but no effect was noted in females.
The lipid and cholesterol-lowering effects seen in previous studies at and above 20 mg/kg were not evident in this study.

6. Urinalysis°

Urine was collected from fasted animals after 4 weeks. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

Results: No treatment-related effects were seen in urinalysis.

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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 and fixed in 4% phosphate buffered neutral formaldehyde. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
| |	Tongue	| |	.Aorta*	XX	.Brain*†
| |	.Salivary glands*	XX	.Heart*	| |	Periph. nerve*#
| |	.Esophagus*	| |	.Bone marrow*	X	Spinal cord (cervical)
| |	.Stomach*	| |	.Lymph nodes*	| |	.Pituitary*
| |	.Duodenum*	XX	.Spleen*	| |	Eyes (optic n.)*#
| |	.Jejunum*	| |	.Thymus*		Glandular
| |	.Ileum*		Urogenital	XX	.Adrenals*
| |	.Cecum*	XX	.Kidneys*†	| |	Lacrimal gland#
| |	.Colon*	| |	.Urinary bladder*	| |	Mammary gland*#
| |	.Rectum*	XX	.Testes*†	| |	.Parathyroids*††
XX	.Liver*†	| |	Epididymides	| |	.Thyroids*††
| |	Gall bladder*#	| |	Prostate		Other
| |	.Pancreas*	| |	Seminal vesicle	| |	Bone*#
	Respiratory	XX	Ovaries*†	| |	Skeletal muscle*#
| |	.Trachea*	| |	.Uterus*	X	Skin*# [1]
X	.Lung*			X	All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies
[1] Treated and untreated skin was preserved.

A. Organ Weight: A statistically significant decrease in liver weights was seen at all three dose levels tested in both males and females in absolute, organ/body and organ/brain weights. Data are presented in table I below. No other treatment-related changes in organ weights were evident.

B. Macroscopic pathology: No treatment-related changes were evident in macroscopic pathology.

C. Microscopic pathology: No treatment-related effects were reported.

TABLE I
LIVER WEIGHTS

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N = 10

	Group 1	Group 2	Group 3	Group 4
Males				
Absolute wts.	10.12± 0.65	7.97±0.47**	8.01± 0.62**	8.01±0.74**
Liver/body wts.	3.71±0.21	3.01± 0.16**	3.01± 0.25**	3.02± 0.20**
Liver/brain wts.	528.59±35.42	413.7±23.08**	406.5±28.73**	412.79±34.58**
Females				
Absolute wts	7.37±0.79	6.28± 0.54**	6.31±0.57**	5.65±0.50**
Liver/body wts.	3.66± 0.28	3.31±0.21*	3.34± 0.30*	3.11± 0.23**
Liver/brain wts.	398.98± 36.76	334.33±29.33**	342.43±0.64**	306.77±31.93**

Discussion:
No treatment-related effects were seen in mortality, toxicity, body weight or food consumption, opthalmology, urinalysis or hematology. There was a compound-related increase in glucose levels in group 4 males and group 3 and 4 females. Chloride levels were elevated in group 3 and 4 males but not in females. The lipid and cholesterol lowering effects seen at higher doses were not evident in this study. There was a statistically significant decrease in absolute and relative liver weights at all doses tested in both males and females. This is contrary to the findings seen at higher doses where liver weights are actually increased.

NOEL < 5 mg/kg, based on decreased liver weights,
Core classification: minimum

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Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 8 through 13 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.