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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **Fenoxaprop-ethyl:** Carcinogenicity study in mice

FROM: Yung G. Yang, Ph.D. Yung G. Yang 3/7/97
Toxicology Branch II, Section II
Health Effects Division (7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 3/14/97
Section Head, Section II
Toxicology Branch II, HED (7509C)
and
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Branch Chief
Toxicology Branch II, HED (7509C)

TO: Steven Robbins
RCAB, HED (7509C)

DP Barcode: D232425/D231679 **Case:** 031424
Submission: S514959 **ID No.:** 045639-00188
Chemical: Fenoxaprop-p-ethyl **PC No.:** 129092
Registrant: AgrEvo USA Company

ACTION REQUESTED: Review a carcinogenicity study in mice for fenoxaprop-ethyl.

RESPONSE: The carcinogenicity study in mice (MRID# 44157402) has been reviewed and is acceptable. A data evaluation record (DER) is attached and the executive summary is as follows.

EXECUTIVE SUMMARY: In a carcinogenicity toxicity study in mice (MRID 44157402), Fenoxaprop-ethyl (96.8% a.i.) was administered to NMRI mice (50/sex/group) via the diet at dose levels of 0, 40, 115, or 320 ppm (0, 5.7, 16.6, or 44.6 mg/kg/day for males and 0, 6.8, 19.4, or 53.7 mg/kg/day for females, respectively) for 105 weeks. Clinical observations indicated an increased incidence of swollen abdomen in both sexes at 115 and 320 ppm from week 55 onward. No other significant findings were noted on mortality and clinical observations. Absolute liver weight was increased at 320 ppm (males only) while relative liver weight was increased at 115 and 320 ppm (males only). Microscopic pathology showed that alterations occurred in the liver including hypertrophy, single cell necrosis, pigmentation in macrophages and lipofuscin deposit at 115 ppm (males only) and 320 ppm (both sexes). **The NOEL for**

chronic toxicity is 40 ppm (5.7 mg/kg/day for males or 6.8 mg/kg/day for females), and the LOEL is 115 ppm (16.6 mg/kg/day for males and 19.4 mg/kg/day for females) based on histopathological findings in the liver. At the doses tested, there was a treatment related increase in tumor incidence of hepatocellular adenoma and carcinoma when compared to controls. A significant increase in liver tumors, mainly adenomas, was observed in males at 320 ppm (30%) compared to the control (2%). In addition, microscopic pathology indicated that hepatocellular hypertrophy was observed in the majority of all treated animals (both sexes). Dosing was considered adequate based on clinical signs (swollen abdomen), increased liver weight, and histopathology data at the high dose. This study is **Acceptable** and satisfies the guideline requirement for a carcinogenicity study in mice (§83-2(b)).

NOTE: Previously, a mouse carcinogenicity study with fenoxaprop-ethyl was submitted to the Agency in which no tumor was observed. However, the study was reclassified as supplemental because it did not meet the MTD. Since a significant increase in liver tumors was observed in this new study, **TB II recommends that this new mouse carcinogenicity study to be submitted to the RfD Peer Review Committee for evaluation of its carcinogenic potential.**

EPA Reviewer: Yung G. Yang, Ph.D. Yung G. Yang, Date 3/7/97
Review Section II, Toxicology Branch II (7509C)
EPA Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel Date 3/14/97
Review Section II, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity Study - Mice
OPPTS 870.3200 [§83-2 (b)]
DP BARCODE: D232425/D231679 SUBMISSION CODE: S514959
P.C. CODE: 129092 TOX. CHEM. NO.: 431C
CASE: 031424

TEST MATERIAL (PURITY): Technical Fenoxaprop-ethyl (96.8% a.i.)
SYNONYMS: ethyl-2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propanoate

CITATION: Troschau, G. (1996) Fenoxaprop-ethyl-Substance Technical (Code: Hoe 033171 00 ZD96 0005) Carcinogenicity Study in Mice. Hoechst AG, Frankfurt, Germany. Report Nos. 96.0880 & A57500, October 10, 1996. MRID 44157402. Unpublished.

SPONSOR: AgrEvo USA Company, Wilmington, DE

EXECUTIVE SUMMARY:

In a carcinogenicity toxicity study in mice (MRID 44157402), Fenoxaprop-ethyl (96.8% a.i.) was administered to NMRI mice (50/sex/group) via the diet at dose levels of 0, 40, 115, or 320 ppm (0, 5.7, 16.6, or 44.6 mg/kg/day for males and 0, 6.8, 19.4, or 53.7 mg/kg/day for females, respectively) for 105 weeks. Clinical observations indicated an increased incidence of swollen abdomen in both sexes at 115 and 320 ppm from week 55 onward. No other significant findings were noted on mortality and clinical observations. Absolute liver weight was increased at 320 ppm (males only) while relative liver weight was increased at 115 and 320 ppm (males only). Microscopic pathology showed that alterations occurred in the liver including hypertrophy, single cell necrosis, pigmentation in macrophages and lipofuscin deposit at 115 ppm (males only) and 320 ppm (both sexes). **The NOEL for chronic toxicity is 40 ppm (5.7 mg/kg/day for males or 6.8 mg/kg/day for females), and the LOEL is 115 ppm (16.6 mg/kg/day for males and 19.4 mg/kg/day for females) based on histopathological findings in the liver.** At the doses tested, there was a treatment related increase in tumor incidence of hepatocellular adenoma and carcinoma when compared to controls. **A significant increase in liver tumors, mainly adenomas, was observed in males at 320 ppm (30%) compared to the control (2%).** In addition, microscopic pathology indicated that hepatocellular hypertrophy was observed in the majority of all treated animals (both sexes). Dosing was considered adequate based on clinical signs (swollen abdomen), increased liver weight, and histopathology data at the high dose. This study is **Acceptable**

and satisfies the guideline requirement for a carcinogenicity study in mice (§83-2(b)).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Fenoxaprop-ethyl, technical grade
   Description: Colorless or gray gross powder
   Lot/Batch #: 4663
   Purity: 96.8% a.i.
   Stability of compound: Greater than 24 months at -10 °C
   CAS #: 71283-80-2

2. Vehicle: diet

3. Test animals: Species: Mouse
   Strain: Hoe:NMRIf(SPF71)
   Age and weight at study initiation: 5-6 weeks;
   Male: 22.1 g, Female: 20.8 g
   Source: Hoechst AG, Kastengrund
   Housing: Individually
   Diet: Altromin 1321 powder diet, ad libitum
   Water: Tap water in plastic bottle, ad libitum
   Environmental conditions: Temperature: 21 ± 2 °C
   Humidity: 65 ± 20%
   Air changes: No information provided
   Photoperiod: 12-hr light/ 12-hr dark
   Acclimation period: 1 week

B. STUDY DESIGN:

1 In life dates - start: 8/9/1993 end: 8/16/1995

2. Animal assignment - Animals were assigned randomly to test groups as described in Table 1.

Table 1. Study Design

Test Group	Conc.in Diet (ppm)	Dose (mg/kg/day)		Number of animals	
		Male	Female	Male	Female
Control	0	0	0	50	50
Low (LDT)	40	5.7	6.8	50	50
Mid (MDT)	115	16.6	19.4	50	50
High (HDT)	320	44.6	53.7	50	50

3. Dose Selection: The dose selection was based on a 90-day range-finding study in mice which was concurred by TB II (Memorandum, KC Swentzel to J Miller, June 4, 1993). In this range-finding study, the test material was mixed with diets at levels of 0, 320, 640, or 1280 ppm. The following effects were reported at 320 ppm and above: "clinical signs of intoxication (swollen abdomen, flank drawn in, straddling hind limbs and bristling coat); slight effects on hematology/clinical chemistry (anemia as shown by reticulocytosis, and increased MCV); liver function (increased alkaline phosphatase and albumin and decreased bilirubin); organ weight changes (liver [M, +80%; F, +50%], kidneys and adrenals (males only); histopathology (centrilobular hepatocellular hypertrophy, increased incidence of single cell necrosis (M, 16/20; F, 6/20; grade 2); peroxisome proliferation, vacuolation of tubular cells (females only at 320 ppm), increased extramedullary erythropoiesis (males) and increased marker enzymes (catalase, malic enzyme, LDH, GPDH)". An examination of the histopathology data revealed that most of the single cell necrosis was grade 1 in severity at this dietary level but increased at the higher levels. Additional effects as well as increased severity of the effects noted at 320 ppm were reported at 640 and 1280 ppm.

4. Diet preparation and analysis

Diets were prepared at 4-week intervals by mixing appropriate amounts of test substance with the standard pulverized diet Altromin®-1321 and were stored at ambient temperature. Homogeneity and stability were tested at 4-week intervals. During the study, samples of treated food were analyzed for stability and concentration.

Results - Homogeneity Analysis: 81% - 115%

Stability Analysis: Stable for 24 months at -10 °C.

Concentration Analysis: 83% - 105% of nominal.

The analytical data indicated that the mixing procedure was adequate and the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics - All parameters were tested with a one-way analysis of variance with sequentially multiple comparisons ($p<0.05$). For tumor analysis, a one-side exact Fisher Test and the trend test analysis for neoplastic and non-neoplastic lesions with respect to dose rates are integrated into a PathData system.

C. METHODS:

1. Observations:

Animals were inspected twice daily (except weekends and holidays) for signs of toxicity and mortality. The animals were examined monthly for neurological disturbance, impairment of dental growth and changes in the eye and the oral mucosa.

2. Body weight

Animals were weighed once weekly.

3. Food consumption and compound intake

Food consumption was measured weekly at the same time as the body weights. The amount of fenoxaprop-ethyl consumed was calculated per day from the food consumption and body weight.

4. Ophthalmoscopic examination

Eyes were not examined (* Not required for carcinogenicity study in mice based on Subdivision F Guidelines).

5. Blood was collected from the retrobulbar venous plexus of non-fasted animals for hematology analysis from all surviving animals at the 12, 18, and 24 month intervals.

a. Hematology

x	Hematocrit (HCT)	x	Leukocyte differential count*
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpusc. HGB conc. (MCHC)
x	Erythrocyte count (RBC)	x	Mean corpusc. volume (MCV)
x	Platelet count	x	Reticulocyte count
	Blood clotting measurements	x	Heinz bodies
	(Thromboplastin time)	x	Methemoglobin
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (only on Cont. and HDT unless effects are observed; based on Subdivision F Guidelines.

b. Clinical Chemistry*

No clinical chemistry analyses were performed (* Not required for carcinogenicity study in mice based on Subdivision F Guidelines).

6. Urinalysis*

No urinalyses were performed (* Not required for carcinogenicity study in mice based on Subdivision F Guidelines).

7. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph.nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*		
x	Duodenum*	xx	Spleen*	x	Pituitary*
x	Jejunum*	x	Thymus*	x	Eyes (optic n.)*
x	Ileum*				
x	Cecum*		UROGENITAL		
x	Colon*	xx	Kidneys*+		GLANDULAR
x	Rectum*	x	Urinary bladder*	xx	Adrenal gland*
xx	Liver*+	xx	Testes*+		Lacrimal gland
x	Gall bladder*	x	Epididymides	x	Mammary gland*
x	Pancreas*	x	Prostate	x	Parathyroids*++
		x	Seminal vesicle	x	Thyroids*++
	RESPIRATORY	xx	Ovaries*+		
x	Trachea*	x	Uterus*		
xx	Lung*				OTHER
x	Nose			x	Bone*
	Pharynx			x	Skeletal muscle*
	Larynx			x	Skin*
					All gross lesions and masses*

* Required for carcinogenicity studies based on Subdivision F Guidelines.
+ Organ weight required in chronic studies.
++ Organ weight required for non-rodent studies.

II. **RESULTS**

A. Observations

1. Toxicity - An increased incidence of swollen (inflated) abdomen was noted in both sexes treated at 115 and 320 ppm from week 55 onwards. No other significant clinical observations were reported.

2. Mortality - Mortality was not affected by treatment with the test article in any treated group.

B. Body weight - There were no significant treatment-related effects on body weights and body weight gains.

C. Food consumption and compound intake

1. Food consumption - Food consumption was comparable in all dose groups as compared with the control.

2. Compound intake

Table 2. Daily intake of Fenoxaprop-ethyl

Treatment group	Dose (mg/kg/day)	
	Males	Females
Control	0	0
40 ppm	5.7	6.8
115 ppm	16.6	19.4
320 ppm	44.6	53.7

The data were extracted from page 24 of the report.

3. Food efficiency - Not provided.

D. Ophthalmoscopic examination - Eye examinations were not performed.

E. Blood work:

1. Hematology - There were no significant treatment-related effects on hematology parameters.

2. Clinical Chemistry - No clinical chemistry analyses were performed.

F. Urinalysis - No urinalyses were performed.

G. Sacrifice and Pathology:

1. Organ weight - Absolute liver weight was increased at 320 ppm (in males only) while relative liver weight was increased in 115 and 320 ppm males (Table 3). Females showed the same tendency as males but was less pronounced. Absolute kidney weights were increased in both sexes at the high-dose group and relative kidney weights were increased in high-dose males.

Table 3. Absolute Organ Weights and Organ to Body Weight Ratios

Test	Males / Dose (mg/kg)				Females / Dose (mg/kg)			
	0	40	115	320	0	40	115	320
Body wt (g)	37.8	38.4	37.5	38.9	32.8	33.2	34.9	35.9
Liver wt (g)	1.87	1.94	2.06	2.34*	1.78	1.76	1.90	2.13
ratio (%)	4.92	5.03	5.47*	6.01*	5.36	5.28	5.45	5.99
Kidney wt (g)	0.58	0.61	0.58	0.64*	0.43	0.44	0.46	0.50*
ratio (%)	1.54	1.58	1.56	1.66*	1.31	1.33	1.33	1.42

Data were extracted from pages 229-236 of the report.
* Significantly different from control ($p < 0.05$).

2. Gross pathology - A brown or olive discoloration occurred in the liver of animals (both sexes) from the 320 ppm group. The adrenal glands in some male animals were enlarged.

3. Microscopic pathology - Compound related alterations only occurred in the liver.

a) Non-neoplastic- In the 320 ppm group, hepatocellular hypertrophy was present with a slight grade in nearly all females (40/50) and with a moderate grade in nearly all males (46/50) (Table 4). Increased numbers of degenerative liver lesions, such as pigment in macrophages (both sexes), hepatocellular lipofuscin deposit (both sexes), and single cell necrosis (males only) were observed. In addition, basophilic and eosinophilic foci were detected in the liver of three (6%) males and one (2%) female (basophilic foci only).

In the 115 ppm group, hepatocellular hypertrophy with a slight grade was observed in females (6/50) and males (35/50). Increased numbers of degenerative liver lesions were observed in males only. In addition, two (4%) males showed basophilic foci.

In the 40 ppm group, hepatocellular hypertrophy with a slight grade was observed in males (5/49) and females (5/50)

Table 4. Non-neoplastic Microscopic Findings

Non-neoplastic liver findings	Males/Dose (ppm)				Females/Dose (ppm)			
	0	40	115	320	0	40	115	320
# animals exmained	50	49	50	50	49	50	49	50
Hypertrophy-diffuse	-	4	31**	46**	-	5*	4	39**
-centrilobular	-	1	4	-	-	-	2	1
Single cell necrosis	12	13	24*	22*	7	15	11*	12
Pigment in macrophages	2	9	21**	45**	14	25*	15	36**
Lipofuscin deposit	-	-	11**	22**	-	-	-	12**
Foci-basophilic	-	-	2(1)	3(2)	-	-	-	1
Foci-eosinophilic	-	-	-	3(1)	-	-	-	-

Data extracted from pages 26, 262, 263 of the report.
* Statistically significant; * p ≤0.05; ** p ≤0.01
() Number of animals without liver tumors.

b) Neoplastic- In the 320 ppm group, hepatocellular tumors, mainly adenomas, occurred in 30% of males (15/50) and 2% of females (1/50) (Table 5). The first neoplasm was detected after a period of approximately 15.5 months. An increased incidence of adrenal gland adenoma was observed in males only (42.9% compared to 22% in the control).

In the 115 ppm group, a slight increase in hepatocellular tumors was observed in males (6%) only.

In the 40 ppm group, the incidence of hepatocellular tumors (2%) was comparable to the control.

Historical control data indicated that the ranges for the hepatocellular adenoma was 0.3-3.0% for males or 0-4.0% for females. The ranges for hepatocellular carcinoma was 0-2.0% for males and 0-1.0% for females. For adrenal gland, there was only one study with 50 males available in which 32% of males showed positive adrenal gland neoplastic finding.

Table 5. Neoplastic findings

Neoplastic finding	Males/Dose (ppm)				Females/Dose (ppm)			
	0	40	115	320	0	40	115	320
# animals exam	50	49	50	50	49	50	49	50
Liver								
# hepatocellular adenoma	1	1	2	12*	-	-	-	-
% hepatocellular adenoma	2.0	2.0	4.0	24	-	-	-	-
# hepatocellular carcinoma	-	-	1	4	-	-	-	1
% hepatocellular carcinoma	-	-	2.0	8.0	-	-	-	2.0
# animals with tumors	1	1	3	15*	-	-	-	1
% animals with tumors	2.0	2.0	6.0	30	-	-	-	2.0
Adrenal Gland								
# subcapsular adenoma, type B	11	11	15	21*	-	-	-	-
% subcapsular adenoma, type B	22	22.5	30	42.9	-	-	-	-
Historical control								
Liver								
Hepatocellular adenoma: Males: 1.2% (0-3.0%); Females: 0.2% (0-4.0%)								
Hepatocellular carcinoma: Males: 0.8% (0-2.0%); Females: 0.2% (0-1.0%)								
Adrenal gland[a]								
Subcapsular adenoma, type B: 32% (one study in males only)								

Data extracted from page 27 of the report.
* Statistically significant. * p ≤0.05; ** p ≤0.01.
[a] Only one study with 50 males is available with the new WHO nomenclature.

III. DISCUSSION

A. In a carcinogenicity study, Fenoxaprop-ethyl (96.8% a.i.) was fed to NMRI mice (50/sex/group) in the daily diet for 105 weeks. No treatment-related mortality was observed. Clinical examinations revealed an increased incidence of swollen abdomen in males and females at 115 and 320 ppm from week 55 onward. Body weight and food consumption was not affected by the treatment. Hematology parameters did not reveal any significant changes. Absolute and relative liver weights in the males were dose-dependently increased. Females showed nearly the same tendency as the males, but was less pronounced and statistically not significant. Kidney weights were slightly increased in both sexes of the highest dose group. The author indicated that although no histological correlate was observed, this change was considered to be test article related.

At necropsy, dose-related macroscopic findings were detected in the liver of both sexes at 115 and 320 ppm and in the adrenal gland of males from the 320 ppm group. A brown or olive discoloration occurred in the liver of both sexes at

320 ppm. The adrenal glands in some males at 320 ppm were enlarged.

Compound-related microscopic findings only occurred in the liver. Hepatocellular tumors, predominantly adenomas, were observed in the 320 ppm group (30% males and 2% females) and 115 ppm group (6% males only). In addition, basophilic and eosinophilic foci were detected in the 320 ppm and 115 ppm groups. Hepatocellular hypertrophy known to be caused by the test compound and based on proliferation of peroxisome was present in animals at 320 ppm (both sexes) and 115 ppm (males only). Increased numbers of degenerative liver lesions, such as pigment in macrophage and hepatocellular lipofuscin and cell necrosis, were observed in animals at 320 ppm (both sexes) and 115 ppm (males). These findings were considered to be the consequence of chronic metabolic disorder of the liver due to the life-span treatment with the test compound. In the 40 ppm group, no compound-related tumors or foci were detected. Slight hepatocellular hypertrophy was observed in 5/50 males and 5/50 females. This reviewer concurs with the author's comment that the findings is considered as the result of the pharmacodynamic property of the test article, not as a toxic effect.

Under conditions of the study, the NOEL for chronic toxicity is 40 ppm (5.7 mg/kg/day for males or 6.8 mg/kg/day for females), and the LOEL is 115 ppm (16.6 mg/kg/day for males and 19.4 mg/kg/day for females) based on histopathological findings in the liver. At the doses tested, there was a treatment related increase in tumor incidence of hepatocellular adenoma and carcinoma when compared to controls.

The author of the report also addressed the relevance to human risk: "Fenoxaprop-ethyl is known be a peroxisome proliferating compound in the liver of mice as shown by short-term toxicity studies including special electron microscopic examinations and measurements of enzyme clusters associated with peroxisome. Published data indicate that hepatocarcinogenesis induced by peroxisomal proliferating compounds is of minimal relevance to humans since human and primates do not respond with peroxisome proliferation when exposed to this type of compound."

B. Study deficiencies - No significant deficiencies were noted.

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Pages 13 through 43 are not included in this copy.

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