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DATA EVALUATION RECORD

ETOFENPROX (MTI-500)

Study Type: §82-1a; 90-Day Oral Toxicity Study in Rats

Work Assignment No. 3-02-126C (MRID 40449703)

Prepared for

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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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Registration Action Branch 3 (7509C)
TXR: 0050128

DATA EVALUATION RECORD (DER)

This DER is an upgrade to previously written executive summary and DER (TXR no. 006852 and 014167)

STUDY TYPE: Subchronic Oral Toxicity in rats (feeding); OPPTS 870.3100 (rodent), §82-1

DP BARCODE: D239026 SUBMISSION CODE: S530012
P.C. CODE: 128965

TEST MATERIAL (PURITY): Ethofenprox, MTI-500 (96.3 %)

SYNONYMS: 2-(4-ethoxyphenyl)-2-methylpropyl-3-phenoxybenzylether

CITATION: Owen, P., et. al. (1986). Assessment of the toxicity of MTI-500 in rats during dietary administration for 13 weeks. Huntingdon Research Center Ltd., Huntingdon, Cambridgeshire, England. MTC 56/821067/2 April 2, 1986. MRID no. 40449703. Unpublished.

SPONSOR: Mitsui Toatsu Chemicals, Inc. 2-5 Kasumigaseki 3-chome, Chiyoda-Ku, Tokyo, Japan.

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID 40449703), MTI-500 (96% a.i.) was administered to 20 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 50, 300, 1800, and 10800 ppm (3.3, 20, 120, and 734 mg/kg/day males; 3.8, 23, 142, and 820 mg/kg/day females) for 13 weeks. Five animals were housed/cage. No treatment related effects were observed in mortality, food consumption, ophthalmology, and urinalysis.

One control male died during the study as a result from human error in blood withdrawal. Animals showed significant decrease in body weight gains ((-16% M and -10% F) at 10800 ppm. At 10800 ppm, animals also showed significant decline in water consumption at weeks 4, 10, 11, and 12.

Increases and/or decreases in RBCs, MCHC, MCH, and MCV were ambiguous and could not be related to treatment. At weeks 6 and 12, an increase in platelets was observed in females of the 10800 ppm group. At week 6, platelet count and leukocytes were statistically increased in males of the 10800 ppm. At week 13 activated partial prothrombin time was statistically increased in males of the 10800 group relative to control while at week 14, the prothrombin time, thromboplastin time, and activated partial prothrombin time were statistically increased in males of the 10800 ppm group. At week 12, males showed decreased Na+, K+, and glucose levels at 10800 ppm, whereas, females showed decreased glucose levels at 300, 1800, and 10800 ppm.

Liver weights were increased in males (30%) at 10800 ppm and in females at 1800 and 10800 ppm (9% and 35%, respectively). Enlarged livers were noted in 2/20 and 4/20 males of the 1800 and 10800 ppm groups, respectively, and in 4/20 females of the 10800 group (0/20 in male and female controls). Centrilobular liver cell enlargement was observed in 1/20 and 9/20 females of the 1800 and 10800 ppm groups (0/20 control). Indicative of liver effects, cholesterol at week 6 and 12 was statistically increased in males of the 10800 ppm group. GPT, GOT, and LDH were statistical increased in the 1800 and 10800 ppm groups at week 6. Cholesterol was statistically increased at10800 ppm in females at week 12.

Thyroid weights were increased in the males at 1800 and 10800 ppm (23% and 32, respectively) and in females at 10800 ppm (14%, not s.s.). The incidence of thyroids with microfollicles was increased in both sexes at 1800 (19/20 M, 2/20 F) and.10800 ppm (18/20 M, 9/20 F ; control: 10/19 M, 0/20 F). At week 6 and 12, T4 was statistically decreased in males at 1800 and 10800 ppm. A significant increase in T3 was observed in females at week 6 in the 10800 ppm group, while T3 was increased (not s.s.) in the 1800 and 10800 ppm groups at week 12. It is also of interest that in the 2-year rat study (MRID - 40449707) thyroid follicular adenomas and carcinomas were more prevalent in males than in females. Thus there appears to be a higher frequency in thyroid follicle changes in males that in females even in this 13- week study.

Adrenal gland weights were increased at 10800 ppm (18% and 16%, respectively) in both sexes. In gross necropsy, 2/20 males of the 10800 ppm group exhibited congestion of the lung (0/19 control). Enlarged spleen was noted in males of the 10800 ppm group (2/20) compared to control (0/19 for control).

The LOAEL is 1800 ppm (120 mg/kg/day males, 142 mg/kg/day females), based on decreased body weight gain, increased weights of the liver and thyroid, and histopathological changes in the liver and thyroid, changes in hematology and clinical chemistry. The NOAEL is 300 ppm (20 mg/kg/day males, 23 mg/kg/day females).

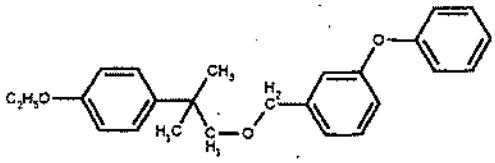
This subchronic toxicity study is classified **acceptable-guideline** and does satisfy the guideline requirement for a subchronic oral study (82-1) in rat.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Etofenprox technical (MTI-500)
   Description: Brown crystalline solid
   Lot/Batch #: ST-101
   Purity (w/w): 96% a.i.
   Stability of compound: The compound was stable in the diet for up to 18 days at room temperature.
   CAS #: 80844-07-1
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
   Strain: CD (Sprague Dawley)
   Age and weight at the start of dosing: Approximately 40 days old; group mean body weights ranged 192-194 g, males; 148-149 g, females
   Source: Charles River Laboratories, Portage, MI, USA
   Housing: In cages; 5 rats per cage.
   Diet: Spratt's Laboratory Animal Diet No. 2, *ad libitum*, except during overnight fasting prior to urinalysis and clinical chemistry.
   Water: Tap water, *ad libitum*
   Environmental conditions:
   Temperature: Approximately 22°C
   Humidity: Approximately 50%
   Air changes: Not provided
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: 12 days

B. STUDY DESIGN

1. In life dates - start: 06/29/82 end: approximately 09/29/82

2. Animal assignment - The rats were randomly assigned (stratified by weight) to the test groups shown in Table 1. An additional 10 rats/sex were sacrificed prior to treatment, necropsied, and examined macroscopically for health check purposes.

Table 1. Study design [a]

Test Group	Nominal Dose (ppm)	Achieved Dose (mg/kg/day) M/F	Assigned animals	
			Males	Females
Control	0	0/0	20	20
Low	50	3.3/3.8	20	20
Mid	300	20/23	20	20
Mid-High	1800	120/142	20	20
High	10,800	734/820	20	20

a Data obtained from the study report, pages 31 and 56.

3. Dose selection rationale - None provided.

4. Treatment preparation, dosing, and analysis - Each week, a pre-mix was made by melting the solid test material at a temperature of ≤40°C, suspending the required mass of this liquid test material in corn oil, and mixing the suspension with ground diet to achieve 2% (w/w) corn oil suspension/diet premix. Dietary concentrations were then prepared by serial dilution of this premix with additional diet. Prior to the study, homogeneity (top, middle, bottom) was determined for a 20 and a 20,000 ppm diet preparation, and stability was analyzed for a 20 and a 20,000 ppm diet preparation stored for up to 18 days at room temperature. Concentration analyses were performed on all test diets from Week 1 and Week 13 of the study. Each sample was analyzed in duplicate.

Results -

Homogeneity analysis (range as % of nominal): 96.5-106.0%

Stability analysis (range as mean % of day 0): 100.5-104.5%

Concentration analysis (range as mean % of nominal): 95.8-113.2%

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

5. Statistics - Food consumption, body weight, and water consumption data were analyzed by one-way analysis of variance (ANOVA) followed by pair-wise comparisons of treatment groups with controls by Student's t-test. Hematology, clinical chemistry,

and urinalysis data were analyzed by Bartlett's test for homogeneity of variances, followed by one-way ANOVA and Student's t-test and Williams' test if variances were homogeneous, or by Kruskal-Wallis and the non-parametric equivalent of the Student's t-test and Williams' test if variances were heterogeneous. Log and square-root transformations were applied in an attempt to achieve homogeneous group variances. Organ weight data were analyzed by analysis of covariance, using the terminal body weight as a covariate, followed by Williams' test for dose-related response.

C. METHODS

1. Observations - The rats were monitored for mortality and moribundity twice daily. More detailed observations of clinical condition or behavior were recorded daily for the first four weeks and weekly thereafter during the study.

2. Body weight and body weight gains - Each animal was weighed prior to treatment, weekly throughout the study, and at necropsy. Statistical analyses were performed on cumulative (Weeks 0-13) body weight gains.

3. Food consumption/efficiency - Food consumption (g/animal/week) was calculated for each animal using weekly food consumption per cage and the number of rats surviving in each cage for the majority of days in that week. Group mean food conversion ratio was calculated for selected intervals as food consumption (g)/body weight gain (g). Compound intake values (mg/kg/day) were calculated for each week using the food consumption and body weight data and the nominal dose.

4. Water consumption - Water consumption was measured for each cage for 7 consecutive days during Week 11 and for cages in the control and high-dose groups for 24-hour periods during Weeks 4 and 10.

5. Ophthalmoscopic examination - The eyes of each animal in the control and high-dose groups were examined by indirect ophthalmoscopy prior to dosing and during Weeks 5 and 13.

6. Blood - Blood was collected from the orbital sinus of animals under light ether anesthesia during the pre-treatment period (health check group), during Weeks 6 and 12 (10 rats/sex/group), and during Weeks 13 and 14 (10 males from the control and high-dose groups for hematology only). Animals were fasted overnight prior to blood sampling, except during Week 13 for determination of prothrombin time and activated partial thromboplastin time. The following checked (X) hematology and clinical blood chemistry 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 corpusc. HGB conc. (MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
X	(Thromboplastin time)		
X	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Potassium	X	Total Cholesterol
X	Sodium	X	Globulins
X	Phosphorus	X	Glucose
	ENZYMES		Direct bilirubin
X	Alkaline phosphatase (AP)	X	Total bilirubin
	Serum Cholinesterase (ChE)	X	Total serum protein (TP)
	Erythrocyte Cholinesterase		Triglycerides
	Creatine phosphokinase (CPK)	X	Tri-Iodothyronine (T_3)
X	Lactic acid dehydrogenase (LDH)	X	Thryoxine (T_4)
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

7. Urinalysis - Urine was collected overnight from 10 rats/sex/group during Weeks 6 and 12. Animals were deprived of food and water during the collection period. The following checked (X) parameters were examined:

	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific Gravity		Bilirubin
X	pH		Blood
X	Sediment		Nitrite
X	Protein	X	Urobilinogen
		X	Bile pigments
		X	Hemoglobin

8. Sacrifice and Pathology - At study termination, all surviving animals were sacrificed by CO_2 asphyxiation and were subjected to a detailed necropsy. The following checked (X) tissues were collected from all animals, preserved in 10% buffered formalin (except for the eyes which were preserved in Davidson's fixative), and examined histologically. The (XX) organs were weighed from all animals surviving to treatment and, at the discretion of the pathologist, from any animals that died during the study.

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

II. RESULTS

A. Observations

1. Mortality - There were no treatment-related mortalities. One control male died following blood sampling during Week 13. Post-mortem examination detected the

odor of ether in the thoracic cavity and the presence of frothy blood in the external jugular vein, the posterior vena cava, and the right auricle.

2. Clinical signs - No treatment-related clinical signs were observed. One 10,800 ppm male exhibited red discharge from the penis during Week 1; however, because this finding did not persist throughout dosing, it was deemed unrelated to treatment. Other clinical observations included hair loss, cutaneous ulceration, staining of the fur, missing, discolored, or malocclucded teeth, swollen or discolored tail, hypersensitivity, and an apparent increase in salivation; however, the Sponsor stated that these findings were not dose-related and are commonly seen in rats of this age and strain.

B. Body weight and body weight gains - Overall (Weeks 0 to 13) body weight gains (Table 2) were decreased in the 10,800 ppm males (↓16%; $p<0.001$) and females (↓10%; $p<0.05$) compared to controls.

Table 2. Mean (± SD) overall (week 0 to 13) body weight gains (g) for rats fed etofenprox for up to 13 weeks.[a]

Dose (ppm)				
0	50	300	1800	10,800
Males				
323 ± 44.4	320 ± 40.8	307 ± 38.9	323 ± 35.6	272*** ± 40.4 (↓16)
Females				
138 ± 18.7	132 ± 28.7	139 ± 23.0	127 ± 14.0	124* ± 16.1 (↓10)

a Data obtained from the study report, page 30; n=19-20
*, *** Significantly different from controls at $p<0.05$ or 0.001, respectively; percent difference from control is in parentheses.

C. Food consumption, food efficiency, and compound intake:

1. Food consumption - There were no treatment-related effects on food consumption. Minor decreases in food consumption were observed at 10,800 ppm in the males (↓2-10%; statistics not provided) during Weeks 3-13 and in the females (↓6-8%; statistics not provided) during Weeks 9-13. Overall (Weeks 0-13) food consumption was decreased ($p<0.05$) in the 50 and 10,800 ppm females (↓5% each treated). However, these decreases were minor and/or not dose-related.

2. Compound consumption - The mean achieved dosages are presented in Table 1.

3. Food efficiency - Minor increases in food conversion ratio were observed in the 1800

ppm females and in the 10,800 ppm animals (Table 3).

Table 3. Group mean food conversion ratio at selected intervals in rats fed etofenprox for up to 13 weeks.[a]

Study Week	Dose (ppm)				
	0	50	300	1800	10,800
Males					
1-4	3.9	4.0	4.1	4.0	4.3
5-8	8.6	8.4	9.6	7.8	9.5
9-12	19.4	25.0	18.7	22.5	34.3
1-13	7.2	7.3	7.5	7.3	8.3
Females					
1-4	6.9	6.6	6.5	6.9	6.7
5-8	13.9	14.4	14.9	18.2	14.4
9-12	33.1	31.5	32.2	26.6	66.4
1-13	11.9	12.0	11.8	12.9	12.7

a Data was obtained from the study report, page 31; n=19-20.

D. Water consumption - Water consumption (Table 4) was decreased ($p<0.05$, 0.01, or 0.001) at 10,800 ppm in the males (↓11%) and females (17%) at Week 4, in the males (↓18%) and females (↓7%) at Week 10, and in the males (↓11%) and females (↓11%) at Weeks 11-12.

Table 4. Mean (± SD) water consumption in rats fed etofenprox for up to 13 weeks.[a]

Study Week	Dose (ppm)				
	0	50	300	1800	10,800
Males					
4	37 ± 3.5	NP	NP	NP	33*** ± 2.6 (↓11)
10	38 ± 6.4	NP	NP	NP	31*** ± 3.3 (↓18)
11-12	36 ± 5.2	37 ± 3.8	35 ± 4.0	34 ± 3.2	32** ± 5.2 (↓11)
Females					
4	29 ± 3.6	NP	NP	NP	27** ± 2.0 (↓7)
10	27 ± 3.0	NP	NP	NP	25* ± 4.3 (↓7)
11-12	27 ± 4.1	28 ± 2.7	28 ± 3.6	27 ± 3.4	24** ± 2.5 (↓11)

a Data were obtained from the study report, Table 4, pages 43-45; n=4 cages; numbers listed parenthetically represent the percent difference from controls.
NP Data not provided.
*,**,*** Significantly different from controls $p<0.05$, 0.01, or 0.001, respectively.

E. Ophthalmoscopic examination - There were no treatment-related observations. Unilateral and/or bilateral hyaloid remnants were present in the controls and 10,800 ppm groups prior to treatment and in a single control male at Week 13; however, these findings were not dose-related.

F. Blood analyses

1. Hematology - Table 5a and 5b provide changes in hematology. Etofenprox induced numerous significant increases and/or decreases in various hematological parameters. Many of these changes were ambiguous, the differences were minor and/or not dose-related, hence were not considered treatment-related. However, significant changes in platelet counts, leukocytes, activated partial thromboplastin time, prothrombin time, and thromboplastin time at 10800 ppm were clearly considered treatment-related. The following differences ($p<0.05$, 0.01, or 0.001) were observed in the 10,800 ppm males (Table 5a): (i) increased platelets at Week 6 (↑16%); (ii) increased activated partial thromboplastin time (APTT) at Week 13 (↑36%) and 14 (↑71%); (iii) increased prothrombin time (↑18%) and thromboplastin time (↑31%) at Week 14; (iv) increased lymphocytes (↑31%) at Week 6; and (v) decreased neutrophils (↓52%) and monocytes (↓95%) at Week 6.

Table 5a. Selected hematology values (mean ± SD) for male rats fed etofenprox for up to 13 weeks.[a]

Hematological Parameter	Study Week	Dose (ppm)			
		0	300	1800	10,800
Platelets (10^3/mm^3)	6	746 ± 141.0	827 ± 68.6	788 ± 10.8	869** ± 50.7 (↑16)
Activated partial thromboplatin time (sec)	13	18.7 ± 1.75	NA	NA	25.5*** ± 1.26 (↑36)
	14	20.7 ± 3.14	NA	NA	35.3*** ± 9.36 (↑71)
Prothrombin time (sec)	14	11.4 ± 0.28	NA	NA	13.4*** ± 1.41 (↑18)
Thromboplastin time (sec)	14	25.8 ± 1.62	NA	NA	33.9*** ± 6.12 (↑31)
Lymphocytes (10^3/mm^3)	6	10.14 ± 2.64	8.83 ± 2.28	9.98 ± 3.09	13.27* ± 3.24 (↑31)
Neutrophils (10^3/mm^3)	6	3.23 ± 0.89	3.26 ± 1.11	2.58 ± 1.57	1.56** ± 0.56 (↓52)
Monocytes (10^3/mm^3)	6	1.72 ± 0.58	1.89 ± 0.56	1.37 ± 1.17	0.08** ± 0.09 (↓95)

a Data were obtained from the study report, Table 5, pages 46-51; n=10; numbers listed parenthetically represent the percent difference from controls; results from the 50 ppm group (not reproduced here) were either not sampled or were similar to controls.

NA Data not available.

*,**,*** Significantly different from controls $p<0.05$, 0.01, or 0.001, respectively.

The following changes in blood parameters ($p<0.05$ or 0.01) were observed in the females (Table 5b): (i) decreased hematocrit at 10,800 ppm at Weeks 6 (↓7%) and 12 (↓4%); (ii) decreased mean corpuscular hemoglobin (MCH) at Week 6 at 300 ppm (↓3%), 1800 ppm (↓3%), and 10,800 ppm (↓4%) and at Week 12 at 1800 ppm (↓5%) and 10,800 ppm (↓7%); (iii) decreased mean corpuscular volume (MCV) at Week 6 at 1800 ppm (↓6%) and 10,800 ppm (↓7%) and at Week 12 at 1800 ppm (↓7%) and 10,800 ppm (↓11%); (iv) increased erythrocytes at Week 6 at 1800 ppm (↑8%) and 10,800 ppm (↑3%) and at Week 12 at 1800 ppm (↑6%) and 10,800 ppm (↑6%); (v) increased mean corpuscular hemoglobin concentration (MCHC) at Week 6 at 1800 ppm (↓3%) and 10,800 ppm (↓4%) and at Week 12 at 10,800 ppm (↓4%); and (vi) increased platelets at 10,800 ppm at Weeks 6 (↑11%) and 12 (↑17%).

Table 5b. Selected hematology values (mean ± SD) for female rats fed etofenprox for up to 13 weeks.[a]

Hematological Parameter	Study Week	Dose (ppm)			
		0	300	1800	10,800
Hematocrit (%)	6	45 ± 1.8	46 ± 1.9	46 ± 2.0	42** ± 1.5 (↓7)
	12	50 ± 1.2	51 ± 2.0	50 ± 1.9	48** ± 2.1 (↓4)
Mean corpuscular hemoglobin (pg)	6	24.9 ± 0.92	24.2* ± 0.41 (↓3)	24.2* ± 0.62 (↓3)	24.0** ± 0.89 (↓4)
	12	24.1 ± 0.91	23.5 ± 0.50	22.8** ± 0.61 (↓5)	22.3** ± 0.80 (↓7)
Mean corpuscular volume (tL)	6	72 ± 3.2	71 ± 1.2	68** ± 2.3 (↓6)	67** ± 2.1 (↓7)
	12	74 ± 2.6	72 ± 1.8	69** ± 1.7 (↓7)	66** ± 2.1 (↓11)
Erythrocytes (10^6/mm^3)	6	6.2 ± 0.25	6.4 ± 0.24	6.7* ± 0.29 (↑8)	6.4* ± 0.30 (↑3)
	12	6.8 ± 0.33	7.0 ± 0.37	7.2* ± 0.31 (↑6)	7.2* ± 0.41 (↑6)
Mean corpuscular hemoglobin concentration (%)	6	34.4 ± 0.61	33.9 ± 0.51	35.5** ± 0.98 (↑3)	35.9** ± 0.62 (↑4)
	12	32.5 ± 0.54	32.5 ± 0.56	33.0 ± 0.66	33.7** ± 0.58 (↑4)
Platelets (10^3/mm^3)	6	780 ± 63.9	821 ± 52.8	805 ± 76.2	867** ± 182.3 (↑11)
	12	728 ± 75.1	735 ± 82.9	717 ± 97.2	855** ± 64.3 (↑17)

a Data were obtained from the study report, Table 5, pages 46-51; n=10; numbers listed parenthetically represent the percent difference from controls; results from the 50 ppm group (not reproduced here) were similar to controls.

*,** Significantly different from controls $p<0.05$ or 0.01, respectively.

2. Clinical chemistry - Significant changes in cholesterol, glucose, sodium, potassium, GPT, GOT, LDH, and thyroxins were considered treatment-related, however, several other clinical chemistry parameters attained significance ($p<0.05$ or 0.01) but were deemed unrelated to treatment because the differences were minor and/or not dose-related and ambiguous. The following changes ($p<0.05$ or 0.01) were observed (Table 6): (i) increased glutamic-pyruvic transaminase in the 1800 (↑30%) and 10,800 (↑56%) ppm males at Week 6; (ii) increased glutamic-oxaloacetic transaminase in the 1800 (↑32%) and 10,800 (↑50%) ppm males at Week 6; (iii) increased lactic dehydrogenase in the 1800 (↑42%) and 10,800 (↑180%) ppm males at Week 6; (iv) increased cholesterol at 1800 ppm in the males at Week 12 (↑19%) and at 10,800 ppm in the males at Week 6 (↑22%) and in the males (↑41%) and females (↑49%) at Week 12; (v) increased tri-iodothyronine (T3) in the 1800 (↑2; not significant) and 10,800 (↑28%; not significant) ppm females at Week 6, in the 1800 (↑8%; not significant) and 10,800 (↑6%; not significant) ppm females at Week 12, and in all treated males (↑11-20%; not significant) at Week 12; (vi) decreased thyroxine (T4) in the 1800 (↓9%; not

significant) and 10,800 (↓21%) ppm males at Week 6 and in the 1800 (↓17%) and 10,800 (↓25%) ppm males at Week 12; (vii) decreased glucose at Week 12 in the 300 ppm males (↓12%) and females (↓15%), in the 1800 ppm males (↓11%) and females (↓15%), and in the 10,800 ppm males (↓17%) and females (↓24%); (viii) increased protein in the 10,800 ppm males (↑4%) at week 6; (ix) decreased potassium in the 1800 and 10,800 ppm males at week 12 (↓10% each); and (x) decreased sodium (↓1%) in the 10,800 ppm males at Week 12.

Table 6. Selected clinical chemistry values (mean ± SD) for rats fed etofenprox for up to 13 weeks.[a]

Parameter	Study Wk.	0 ppm	300 ppm	1800 ppm	10,800 ppm
Males					
Glutamic-pyruvic transaminase (mU/mL)	6	27 ± 6.2	29 ± 5.3	35* ± 8.9 (↑30)	42** ± 12.9 (↑56)
Glutamic oxaloacetic transaminase (mU/mL)	6	56 ± 11.4	66 ± 9.6	74** ± 10.3 (↑32)	84** ± 20.8 (↑50)
Total lactate dehydrogenase (mU/mL)	6	598 ± 514.5	872 ± 569.2	1036 ± 549.5 (↑42)	1675** ± 1025.6 (↑180)
Cholesterol (mg/dL)	6	49 ± 6.6	51 ± 3.0	51 ± 5.2	60** ± 4.7 (↑22)
	12	37 ± 5.3	41 ± 4.3	44* ± 4.1 (↑19)	52** ± 3.8 (↑41)
Tri-iodothyronine (T3) (ng/dL)	12	46 ± 6.2	55 ± 8.3 (↑20)	51 ± 5.8 (↑11)	51 ± 6.6 (↑11)
Thyroxine (T4) (µg/dL)	6	7.2 ± 1.29	7.8 ± 0.67	6.3 ± 1.05 (↓9)	5.7** ± 0.51 (↓21)
	12	5.2 ± 0.68	4.9 ± 0.77	4.3* ± 0.83 (↓17)	3.9** ± 0.66 (↓25)
Glucose (mg/dL)	12	133 ± 19.9	117* ± 15.7 (↓12)	118* ± 14.1 (↓11)	111** ± IL (↓17)
Protein (g/dL)	6	6.8±0.12	6.7±0.24	6.7±0.14	7.1**±0.30 (↑4)
Sodium (mEq/L)	12	149 ± 1.9	147 ± 1.6	150 ± 2.5	147* ± 1.3 (↓1)
Potassium (mEq/L)	12	3.9 ± 0.26	3.6 ± 0.43	3.5* ± 0.26 (↓10)	3.5* ± 0.22 (↓10)
Females					
Cholesterol (mg/dL)	12	39 ± 9.1	44 ± 0.9	42 ± 11.3	58** ± 10.9 (↑49)
Tri-iodothyronine (T3) (ng/dL)	6	47 ± IL	47 ± 0.5	48 ± 13.0 (↑2)	60 ± 12.4 (↑28)
	12	53 ± 6.4	54 ± 6.9	57 ± 6.1 (↑8)	56 ± 8.9 (↑6)
Glucose (mg/dL)	12	131 ± 18.7	111* ± 17.0 (↓15)	112* ± 13.0 (↓15)	100** ± 15.2 (↓24)

a Data were obtained from the study report, Table 6, pages 52-55; n=10; numbers listed parenthetically represent the percent difference from controls; results from the 50 ppm group (not reproduced here) were similar to controls.

*,** Significantly different from controls $p<0.05$ or 0.01, respectively.

IL Data illegible

G. Urinalysis - There were no treatment-related findings in any urinalysis parameter. At Week 6 in the males, urine volume was increased ($p<0.05$) at 1800 (↑81%) and 10,800 (↑39%) ppm; specific gravity was decreased ($p<0.05$) in all treated groups (↓≤1%); and protein was increased ($p<0.05$) at 1800 (↑74%) and 10,800 (↑45%) ppm. In the females, pH was decreased (↓2%; $p<0.05$) at 10,800 ppm at Week 12. However, these differences were minor, not dose-related, and/or did not persist throughout treatment.

H. Sacrifice and Pathology:

1. Organ weight - Significant treatment-related increases in liver, thyroid and adrenal weights were observed at 10800 ppm. The following increases ($p<0.05$ or 0.01) were observed in adjusted (for body weight) organ weights (Table 7): (i) liver in the 10,800 ppm males (↑30%) and in the 1800 (↑9%) and 10,800 (↑35%) ppm females; (ii) thyroid in the 1800 ppm males (↑23%) and 10,800 ppm males (↑32%) and females (↑14%; not significant); and (iii) adrenals in the 10,800 ppm males (↑18%) and females (↑16%). Additionally in the males, adjusted heart weights were increased at 1800 (↑8%; $p<0.05$) and 10,800 (↑12%; $p<0.01$) ppm, and absolute thymus weights were decreased at 10,800 (↓23%; $p<0.01$) ppm. All other organ weights were comparable to controls.

Table 7. Selected adjusted (for body weight) organ weights in rats fed etofenprox for up to 13 weeks.[a]

Organ	Dose (ppm)			
	0	300	1800	10,800
Males				
Liver (g)	22.2 ± 2.79	23.0 ± 3.15	23.4 ± 3.69	28.6** ± 2.81 (↑30)
Thyroid (mg)	22 ± 4.2	24 ± 5.5	27* ± 8.2 (↑23)	29** ± 7.4 (↑32)
Adrenals (mg)	57 ± 8.2	60 ± 9.3	57 ± 12.0	67** ± 9.1 (↑18)
Heart (g)	1.46 ± 0.14	1.52 ± 0.12	1.58* ± 0.16 (↑8)	1.64** ± 0.19 (↑12)
Thymus[b] (g)	0.422 ± 0.115	0.398 ± 0.089	0.385 ± 0.097	0.326** ± 0.071 (↓23)
Females				
Liver (g)	11.9 ± 1.75	12.2 ± 1.64	13.0** ± 1.32 (↑9)	16.1** ± 2.36 (↑35)
Thryoid (mg)	21 ± 4.7	20 ± 4.8	22 ± 5.7	24 ± 5.5 (↑14)
Adrenals (mg)	76 ± 13.2	73 ± 9.9	82 ± 13.9	88** ± 10.7 (↑16)

a Data were obtained from the study report, Tables 9 & 10, pages 62-66; n=19-20; standard deviations are from unadjusted data; results from the 50 ppm group (not reproduced here) were similar to controls.

b. Absolute values (not adjusted) were used in analyses of thymus weights and are reported in this table.

*, ** Significantly different from controls at $p<0.05$ or 0.01, respectively.

2. Gross pathology - Several macroscopic changes (Table 8) were observed (data presented as number of affected animals vs 0 controls, unless otherwise noted). Liver enlargement was observed in the 1800 ppm males (2/20) and in the 10,800 ppm males (4/20) and females (4/20). Lung congestion was observed in the 10,800 ppm males (2/20). Spleen enlargement was observed in the 10,800 ppm males (2/20) and in the other treated males (1/20 each treated vs 0/19 controls). Scab formation was observed on the skin of the 1800 ppm (1/20 treated vs 0 controls) and 10,800 ppm (3/20 treated) males. Other macroscopic findings, such as malocclusion of the teeth and pustules on the tail, were either not dose-related or were stated by the Sponsor to occur commonly in this age and strain of rat.

Table 8. Selected macroscopic findings (# of affected animals/ # of animals examined) in rats fed etofenprox for up to 13 weeks.[a]

Observation	Dose (ppm)				
	0	50	300	1800	10,800
Males					
Liver- enlarged	0/19	0/20	0/20	2/20	4/20
Spleen- enlarged	0/19	1/20	1/20	1/20	2/20
Lung- congestion	0/19	0/20	0/20	0/20	2/20
Skin- scab formation	0/19	0/20	0/20	1/20	3/20
Females					
Liver- enlarged	0/20	0/20	0/20	0/20	4/20

a Data obtained from the study report, Table 8, pages 60-61.

3. Microscopic pathology - Treatment-related histopathological changes in the liver and thyroid are presented in Table 9. Centrilobular liver cell enlargement was observed in the females at 1800 ppm (1/20 treated vs 0/20 controls) and at 10,800 ppm (9/20 treated vs 0/20 controls). Minimal to moderate numbers of thyroid microfollicles were observed in the 1800 ppm males (19/20 treated vs 10/19 controls) and females (2/20 treated vs 0/20 controls) and in the 10,800 ppm males (18/20 treated vs 10/19 controls) and females (9/20 treated vs 0/20 controls). Hyperplasia of the spleen was observed in the 10,800 ppm males (2/20 treated vs 0/19 controls) and in the other treated males (1/20 each treated vs 0/19 controls).

Several other microscopic changes were observed, but were deemed unrelated to treatment because they were incidental, not dose-related, and/or considered to be spontaneous in origin. For example, foci of mineralization was observed in the lungs of the 10,800 ppm males (2/20 treated vs 0/19 controls); hydronephrosis was observed in

the 1800 ppm males (1/20 treated vs 1/19 controls); and slight enlargement of the adrenals was observed in the 10,800 ppm females (2/20 treated vs 1/20 controls).

Table 9. Selected microscopic findings (# of animals affected/ # of animals examined) in rats fed etofenprox for up to 13 weeks.[a]

Observation	Dose (ppm)				
	0	50	300	1800	10,800
Males					
Liver- centrilobular liver cell enlargement	0/19	0/20	0/20	0/20	0/20
Thyroid- microfollicles (minimal to moderate)	10/19	11/20	5/20	19/20	18/20
Spleen- hyperplasia	0/19	1/20	1/20	1/20	2/20
Females					
Liver- centrilobular liver cell enlargement	0/20	0/20	0/20	1/20	9/20
Thyroid- microfollicles (minimal to moderate)	0/20	0/20	0/20	2/20	9/20

a Data obtained from the study report, pages 35 & 37.

III. DISCUSSION

A. Investigator's conclusions - It was concluded that oral administration of etofenprox for 13 weeks reduced body weight gains in the 10,800 ppm animals and food efficiency in the 1800 ppm females and in the 10,800 ppm animals. Changes in the liver and thyroid were also induced in these animals. In the liver, adjusted weights were increased in the 1800 ppm females and in the 10,800 ppm animals. Macroscopically, liver enlargement was observed in the 1800 ppm males and in the 10,800 ppm animals. Microscopically, centrilobular hepatocyte enlargement was observed in the 10,800 ppm females. In the thyroid, adjusted weights were increased in the 1800 ppm males and in the 10,800 ppm animals, and an increased incidence of animals with thyroid microfollicles was observed in the 1800 and 10,800 ppm animals. It was concluded that the LOAEL was 1800 ppm and the NOAEL was 300 ppm.

B. Reviewer's discussion/conclusions - In this subchronic oral study, etofenprox was administered in the diet to 20 rats/sex/group at doses of 0, 50, 300, 1800, or 10,800 ppm (equivalent to 0, 3.3/3.8, 20/23, 120/142, and 734/820 mg/kg/day for males/females) for 13 weeks. The analytical data indicated that the mixing procedure was adequate and the variation between nominal and actual dosage to the study animals was acceptable.

There were no treatment-related mortalities. One control male died during Week 13 due to error during blood sampling. No treatment-related differences were observed in clinical

signs, food consumption, ophthalmology, or urinalysis.

The liver and thyroid were target organs of etofenprox toxicity. Liver weights were increased ($p<0.05$ or 0.01) in the 1800 ppm females (↑9%) and 10,800 ppm animals (↑30-35%) compared to controls. Macroscopically, liver enlargement was observed in the 1800 ppm males (2/20 vs 0/19 controls) and in the 10,800 ppm males (4/20 vs 0/20 controls) and females (4/20 vs 0/20 controls). Centrilobular liver cell enlargement was observed in the females at 1800 ppm (1/20 treated vs 0/20 controls) and at 10,800 ppm (9/20 treated vs 0/20 controls). Cholesterol was increased ($p<0.05$ or 0.01) in the 1800 ppm males (↑19%) and in the 10,800 ppm animals (↑22-49%). GPT (↑30-56%) and GOT (↑32-50%) were increased ($p<0.05$ or 0.01) in the 1800 and 10,800 ppm males, respectively. LDH was increased ($p<0.01$) in the 10,800 ppm males (↑180%).

Thyroid weights were increased ($p<0.05$ or 0.01) in the 1800 ppm males (↑23%) and 10,800 ppm animals (↑14-32%) compared to controls. The incidence of thyroids with microfollicles was increased in both sexes of the 1800 (19/20 M, 2/20 F) and 10,800 (18/20 M, 9/20 F) ppm groups (vs 10/19 M, 0/20 F in the controls). T3 was increased in the 10,800 ppm females (↑28%) and in all treated males (↑11-20%; not significant), while T4 was decreased in the 1800 (↓9%; not significant) and 10,800 (↓21%; $p<0.01$) ppm males at week 6 and in the 1800 (↓17%; $p<0.05$) and 10,800 (↓25%; $p<0.01$) ppm males at week 12.

Food consumption was essentially comparable among treated groups and controls. However, minor increases in food conversion ratios were observed in the 1800 ppm females and in the 10,800 ppm animals. Consequently, overall (weeks 0 to 13) body weight gains were decreased in the 10,800 ppm males (↓16%; $p<0.001$) and females (↓10%; $p<0.05$) compared to controls. Water consumption was also decreased (↓7-18%; $p<0.05$, 0.01, or 0.001) in the 10,800 ppm animals at Weeks 4, 10, and 11-12.

Etofenprox induced numerous significant increases and/or decreases in various hematological parameters. Many of these changes were ambiguous, the differences were minor and/or not dose-related, hence were not considered treatment-related. However, significant changes in platelet counts, leukocytes, activated partial thromboplastin time, prothrombin time, and thromboplastin time at 10800 ppm were clearly considered treatment-related. Etofenprox induced numerous hematological changes ($p<0.05$ or 0.01) in the females, including: (i) decreased hematocrit at 10,800 ppm (↓4-7%); (ii) decreased MCH at 300 ppm (↓3%), 1800 ppm (↓3-5%), and 10,800 ppm (↓4-7%); (iii) decreased MCV at 1800 ppm (↓6-7%) and 10,800 ppm (↓7-11%); (iv) increased MCHC at 1800 ppm (↑3%) and 10,800 ppm (↑4%); and (v) increased platelets at 10,800 ppm (↑11-17%). In the 10,800 ppm males, clotting indices and leukocyte numbers were altered ($p<0.05$, 0.01, or 0.001) by treatment. Increases were observed in platelets (↑16%), APTT (↑36-71%), prothrombin time (↑18%), thromboplastin time (↑31%), and lymphocytes (↑31%), while neutrophils (↓52%) and monocytes (↓95%) were decreased.

Adrenal gland weights were increased ($p<0.01$) in the 10,800 ppm animals (↑16-18%) compared to controls. Additionally in the males, heart weights were increased at 1800

(↑8%; p<0.05) and 10,800 (↑12%; p<0.01) ppm, and absolute thymus weights were decreased at 10,800 (↓23%; p<0.01) ppm. All other organ weights were comparable to controls.

Macroscopically at 10,800 ppm, lung congestion was observed in the males (2/20 treated vs 0/19 control), and spleen enlargement was observed in the males (2/20 vs 0/19 controls). Spleen enlargement was also observed in the other treated males (1/20 each treated vs 0/19 controls).

Additional clinical chemistry parameters which were affected by treatment with etofenprox include decreased glucose (p<0.05 or 0.01) in the 300 (↓12-15%), 1800 (↓11-15%), and 10,800 (17-24%) ppm animals, increased (p<0.01) protein in the 10,800 ppm males (↑4%), decreased (p<0.05) sodium (↓1%) in the 10,800 ppm males, and decreased (p<0.05) potassium (↓10% each) in the 1800 and 10,800 ppm males.

The LOAEL is 1800 ppm (120/142 mg/kg/day for males/females), based on decreased body weight gains, increased weights of the liver and thyroid, histopathological changes in the liver and thyroid, and changes in hematology and clinical chemistry. The NOAEL is 300 ppm (20/23 mg/kg/day for males/females).

The submitted study is classified as **acceptable/guideline (§82-1a)** and satisfies the requirements for a subchronic oral toxicity study in the rat.

C. Study deficiencies - The following deficiencies were noted but do not alter the conclusions of this DER:

- No dose rationale was provided.
- No summary tables were provided for clinical signs, gross pathology, or histology data.
- Individual tables for clinical observations did not include clinical signs that the Sponsor considered typical for this age and strain of rat, thereby precluding dose-related examination of this data.