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(12-16-04)

DATA EVALUATION RECORD

THIDIAZURON

Study Type: §83-5; Combined Chronic Toxicity / Carcinogenicity Study in Rats

Work Assignment No. 2-01-46 A (MRID 46345201)

Prepared for
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Disclaimer

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DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity (diet)- rats; OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 120301
DP BARCODE: D307336
TXR#: 0052174
SUBMISSION NO.: None

TEST MATERIAL (PURITY): Thidiazuron (99.5% a.i.)

SYNONYMS: AE B049537; 1-phenyl-3-(1,2,3-thiadiazol-5-yl)urea

CITATION: Steiblen, G. (2004) Chronic toxicity and carcinogenicity study of thidiazuron in the Wistar rat by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Report of Study Id.: SA 01269, July 27, 2004. MRID 46345201. Unpublished.

SPONSOR: Bayer Ag, Bayer CropScience, Alfred Nobel Str. 50, Monheim, Germany

EXECUTIVE SUMMARY - In this combined chronic toxicity/carcinogenicity study (MRID 46345201), Thidiazuron (99.5% a.i.; Batch No.: 107623-03) was administered in the diet for 2 years to 70 WI-IOPS AF Wistar rats/sex/dose at doses of 0, 200, 900, or 1800 ppm (equivalent to 0/0, 8.0/11.3, 36.4/51.4, and 75.6/105 mg/kg/day). After 12 months, 10 rats/sex/dose were sacrificed. Additionally, 15 rats/sex/dose were treated at 0 or 1800 ppm for 12 months, fed control diet for 3 months, and then sacrificed.

No treatment-related effects were observed during the ophthalmoscopic examinations or hematology.

In the 200 ppm group, there were some minor changes seen after 24 months but these observations were equivocal and not considered adverse.

At >=900 ppm, the following findings were observed: (i) increased incidence of a wasted appearance in the males during the second year; (ii) decreased body weights in males, either sporadically (900 ppm) or generally throughout the study (1800 ppm); (iii) decreased overall

(Days 1-708) body weight gains in males; (iii) decreased food consumption in females, frequently throughout the study; and (iv) increased serum urea in males at Months 6 and 12 (900 ppm) or throughout the study (1800 ppm). The following microscopic lesions were observed at 12 months: renal glomerular mineralization in both sexes; golden brown pigment in the tuboepithelial cells in the kidney in the males; and renal papillary mineralization in the females. The following lesions were observed at 24 months: (i) renal collecting duct hyperplasia in both sexes; (ii) suburothelial congestion in the females; (iii) glomerular mineralization in both sexes; (iv) bilateral pelvic dilatation in the males; (v) chronic progressive nephropathy in the females; (vi) urothelial mineralization in the females; and (vii) bilateral seminal vesicle atrophy.

At 1800 ppm, several additional findings were observed: (i) reduced motor activity, general pallor, and soiling around the anogenital region in the males during the second year; (ii) increased mortality in the males; (iii) decreased body weights and overall (Days 1-708) body weight gain in males; (iv) decreased food consumption in males; (v) increased cholesterol, triglycerides, and phosphorus in the males; (vi) increased urea and cholesterol in the females; (vii) decreased albumin/globulin and glucose in males; and (viii) increased incidence of urinary protein concentration >=3 g/L in both sexes. Grossly, an increased incidence of irregular kidney surface was observed in males at 15 months (recovery). After 24 months, an increase of small seminal vesicles in males; and irregular kidney surface and pale kidney in both sexes were observed. Increased relative to body kidney weights were observed after 24 months. Increased incidence of the following microscopic lesions were also observed: (i) chronic progressive nephropathy in both sexes at 12, 15, and 24 months; (ii) bilateral renal pelvic dilatation in the females at 12 months; (iii) diffuse germinal cell atrophy in the testes, unilateral at 12 months and bilateral at 24 months; (iv) unilateral luminal dilation in the testes at 12 months; (v) oligospermia in the epididymis, unilateral at 12 months and bilateral at 24 months; (vi) renal glomerular mineralization in both sexes at 15 months; (vii) golden brown pigment in the renal tuboepithelial cells in males at 15 and 24 months; and (viii) renal suburothelial congestion in the females at 15 months. Additionally, increased incidence of the following microscopic lesions were observed in males at 24 months: (i) renal transitional cell hyperplasia; (ii) renal glomerular hyaline deposit, (iii) arteritis in kidneys, testes, and epididymis; (iv) epithelial degenerative changes in the epididymis; (v) mixed cell infiltrate in the seminal vesicles; (vi) diffuse parathyroid hyperplasia; (vii) focal/multifocal parathyroid hyperplasia; (viii) fibrous osteodystrophy in the sternum and articular surface; and (ix) hyperosteoidosis in the articular surface.

Only 13% of the 1800 ppm males survived 24 months. The cause of death of 26/49 of these males was considered to be chronic progressive nephropathy, and at least 95% of the animals at this dose had chronic progressive nephropathy and renal glomerular mineralization. Therefore, findings in these animals may have been confounded by severe renal dysfunction. In particular, parathyroid hyperplasia, osteodystrophy, and hyperosteoidosis may have been related to renal dysfunction.

The LOAEL is 900 ppm (equivalent to 36.4/51.4 mg/kg/day in males/females), based on decreased body weight and body weight gain in the males, increased bilateral seminal vesicle atrophy, and nephrotoxicity in both sexes. The NOAEL is 200 ppm (equivalent to 8.0/11.3 mg/kg/day).

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At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased survival, body weights, body weight gains, and food consumption, increased clinical signs, differences in clinical chemistry parameters, nephrotoxicity, and male reproductive system toxicity.

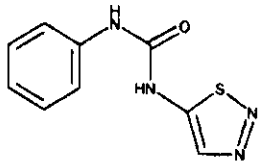
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Thidiazuron

Description:	Light yellow powder
Batch/Lot #:	107623-03
Purity (w/w):	99.5% a.i.
Stability of compound:	Stable in the diet for up to 10 weeks at room temperature or up to 9 weeks at -15°C followed by one week at room temperature
CAS #:	51707-55-2
Structure:	

2. Vehicle - Diet

3. Test animals

Species:	Rat
Strain:	WI-IOPS AF Wistar
Age and mean weight at study initiation:	Approximately 6 weeks; 186-239 g males; 142-183 g females
Source:	R. Janvier (Le Genest St Isle, France)
Housing:	In groups of 5 (same sex) in suspended, stainless steel, wire mesh cages with grid bottoms
Diet:	Ground and irradiated U.A.R. Certified Rodent Meal A04C-10 P1 (Usine d'Alimentation Rationnelle, Villemoisson-sur-Orge, France), *ad libitum* except for an overnight fasting period prior to blood sampling
Water:	Filtered and softened tap water, *ad libitum* except during urine collection
Environmental conditions	
Temperature:	20-24°C
Humidity:	40-70%
Air changes:	10-15/hour
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	14 days

B. STUDY DESIGN

1. In life dates - Start: 9/12/01 End: 9/26/03

2. Animal assignment - The animals within ±20% of the mean body weight for each sex were randomly assigned, stratified by body weight, to the test groups presented in Table 1.

Table 1. Study design. [a]

Conc. in diet (ppm)	Dose to animal (mg/kg/day; M/F)	Interim Sacrifice (12 months; rats/sex)	Recovery Sacrifice (15 months; rats/sex) [b]	Terminal Sacrifice (24 months; rats/sex)
0	0/0	10	15	60
200	8.0/11.3	10	0	60
900	36.4/51.4	10	0	60
1800	75.6/105	10	15	60

a Data were obtained from pages 22 and 37 of MRID 46345201.
b After 12 months of treatment, these animals were untreated for 3 months prior to sacrifice.

3. **Dose-selection rationale** - A dose-selection rationale was not provided.

4. **Treatment preparation, analysis, and administration** - Dietary formulations were prepared by mixing the appropriate amount of the test compound with diet every 4 weeks. Storage conditions of the dietary formulations were not provided. Stability of the test substance at 50 and 15,000 ppm in the diet was confirmed in a prior study (MRID 46121505) for up to 10 weeks at room temperature or up to 9 weeks at -15°C followed by one week at room temperature. During the study, homogeneity (3 samples each from the top, middle, and bottom levels) was evaluated once for the 200 and 900 ppm formulations and twice for the 1800 ppm formulation. Concentration analyses for each dose formulation were conducted on Weeks 4, 12, 16, 23, 27, 36, 40, 44, and 51.

Results: Homogeneity (% nominal): 91-107%, except for 1 measurement of 85%

Stability (% nominal): 93-113%

Concentration (% of nominal): 83-105%

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

5. **Statistics** - Data were subjected to the statistical procedures listed below. Group means were compared at the 5% and 1% levels of significance.

Parameter	Statistical procedure
Body weight gain, body weight, food consumption, organ weights, and hematology and clinical chemistry parameters, and urine volume and refractive index	Bartlett's test for homogeneity of variance. If homogeneous, one-way ANOVA was performed, followed by Dunnett's test (2-sided) when significant. If heterogeneous, the Kruskal-Wallis test was performed, followed by the Dunn test (2-sided) when significant. Body weight and food consumption data were log transformed when necessary to achieve homogeneity of variance. Erythrocyte, leukocyte, thrombocyte, neutrophil, lymphocyte, and reticulocyte counts were square root transformed when necessary to achieve homogeneity of variance.
Urinary pH	The Kruskal-Wallis test was performed, followed by the Dunn test (2-sided) when significant.
Mortality (terminal sacrifice group only)	Adjusted mortality rates were estimated using Kaplan-Meier estimation procedures. Cox's test was used for pairwise comparison between treated and controls groups and dose-related trends in survival.
Selected neoplastic and non-neoplastic microscopic findings	Fisher's Exact test (1-sided) and Cochran-Armitage trend test (1-sided) were performed.

C. METHODS

1. Observations

1a. Cageside observations - Except for Day 538 (experimental error), all animals were observed twice daily for morbidity and mortality (once daily on weekends or public holidays), and once daily for signs of toxicity.

1b. Clinical examinations - Detailed physical examinations, including palpation for masses, were performed weekly.

1c. Neurological evaluations - Neurological evaluations were not performed.

2. Body weight - All animals were weighed prior to treatment, weekly during the first 13 weeks of study, every 4 weeks thereafter, and at termination. Mean body weight gain/day (g) and absolute body weight gains (g) were reported for each day (after the first) that body weights were measured.

3. Food consumption and compound intake: Mean food consumption for each cage (g/day) was reported twice a week from the second to the sixth week (due to high food spillage), weekly during the next 7 weeks of treatment, and once every 4 weeks thereafter. Food efficiency was not reported. Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the nominal dose, food consumption, and body weight data.

4. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed on all animals prior to initiation of treatment and on all surviving animals at approximately 12 and 24 months.

5. Hematology and clinical chemistry - Blood was collected through the retro-orbital venous plexus. The animals were fasted overnight and anesthetized by inhalation with isofluorane prior to blood sampling. Samples were collected from all the survivors in the interim sacrifice groups and 10 animals/sex/dose of the recovery and terminal sacrifice groups on Weeks 25-26 and 51-52. Additionally, 10 animals/sex/dose from the recovery groups were sampled on Week 66 and from the terminal groups on Weeks 78-79 and 105. Blood smears were prepared but were not examined. 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
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for combined chronic/carcinogenicity studies based on Guideline 870.4300.

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	X	Globulins*
X	Sodium*	X	Glucose (fasting)*
	ENZYMES (more than 2 hepatic enzymes)*	X	Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	X	Albumin/globulin
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
	Sorbitol		
	Glutamate dehydrogenase*		

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

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6. **Urinalysis** - Overnight urine samples were collected from all the survivors in the interim sacrifice groups and 10 animals/sex/dose from the recovery and terminal sacrifice groups on Weeks 24-25 and 50-51. Additionally, 10 animals/sex/dose of the recovery groups were sampled on Week 65 and from the terminal groups on Weeks 77 and 104. Diet and water were withdrawn during the overnight (approximately 16 hours) collection period. The following CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity / osmolality*	X	Bilirubin*
X	pH*	X	Blood/ red blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

7. **Sacrifice and pathology** - Animals were sacrificed by exsanguination under deep pentobarbital anesthesia on Days 365-367 (interim sacrifice), Days 97-99 of the recovery phase (recovery sacrifice), and Days 729-745 (terminal sacrifice). Animals were diet fasted overnight prior to sacrifice. An approximately equal number of animals randomly distributed amongst all groups sacrificed each day at the chronic and recovery sacrifices. One control female from the interim sacrifice group was killed on Day 17 without necropsy, because it was found in the cage of another dose group. All other animals that died or were sacrificed *in extremis* and those sacrificed on schedule were subjected to gross pathological examination, and the following CHECKED (X) tissues were collected for histological examination. Additionally, the (XX) organs were weighed from all animals that were sacrificed on schedule.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerves)*
X	Jejunum*	XX	Thymus		GLANDULAR
X	Ileum*		UROGENITAL	XX	Adrenal glands*+
X	Cecum*	XX	Kidneys*+	X	Lacrimal gland
X	Colon*	X	Urinary bladder*	XX	Thyroid (with parathyroids)*
X	Rectum*	XX	Testes*+	X	Harderian gland
XX	Liver*+	XX	Epididymides*+		
	Gall bladder* (not rat)	XX	Prostate*		OTHER
X	Bile duct* (rat)	X	Seminal vesicle*	X	Bone (sternum)
X	Pancreas*	XX	Ovaries*+	X	Skeletal muscle
	RESPIRATORY	XX	Uterus*+ with cervix	X	Skin*
X	Trachea*	X	Mammary gland*	X	Joint (femoro-tibial)
X	Lung*++	X	Vagina	X	All gross lesions and masses*
X	Nasal cavity*				
X	Pharynx*				
X	Larynx*				

* Required for carcinogenicity studies based on Guideline 870.4200
\+ Organ weight required in carcinogenicity studies
++ Organ weight required if inhalation route

In the interim sacrifice animals, all tissues from decedents; the liver, lungs, kidneys, and gross lesions from all animals; and all tissues from the 1800 ppm group and the controls were examined microscopically. In the recovery group sacrifice, only the kidney was evaluated in the animals that survived to the scheduled sacrifice, but all tissues were evaluated in the animals that died prior to scheduled sacrifice. At the terminal sacrifice, all tissues were examined from all animals (including decedents when possible). The exorbital lacrimal gland, larynx/pharynx, and nasal cavities were not examined microscopically. Bone marrow smears were prepared, but were not examined. Representative slides and diagnoses (including all tumors and hyperplastic changes) were subjected to peer review analysis.

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II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity** - During the first year of treatment, no treatment-related clinical signs were observed. During the second year of treatment, the incidence of a wasted appearance was increased in all treatment groups; however, the increase in the 200 ppm males was slight and other clinical observations in this group were comparable to those of the controls (Table 2). Additionally, in the 1800 ppm males, increased incidences (treated vs controls) of reduced motor activity (22/59 vs 6/59), general pallor (17/59 vs 1/59), and soiling around the anogenital region (9/59 vs 2/59) were observed. The incidence of other clinical signs in the treated groups were minor or similar to controls.

Table 2. Incidence of selected clinical observations in male rats treated with Thidiazuron in the diet for up to 2 years. [a]

Parameter	Dose (ppm)			
	0	200	900	1800
Wasted appearance	4/59	7/59	11/58	29/59
Reduced motor activity	6/59	6/59	7/58	22/59
General pallor	1/59	2/59	3/58	17/59
Soiling around the anogenital region	2/59	1/59	1/58	9/59

a Data were obtained from page 68 and Table 2c (pages 77 and 78) of MRID 46345201.

2. **Mortality** - Survival was decreased ($p \leq 0.01$) in the 1800 ppm males from the terminal sacrifice group at Week 107 (18% treated vs 45% controls; Table 3). The cause of death in 26/49 males was considered to be chronic progressive nephropathy. Survival was also decreased (statistical analysis was not performed; n=70-85) in the 1800 ppm males at Week 105 (13% treated vs 32% controls). Survival exceeded guideline requirements of 50% at Week 78 in both sexes and 25% at Week 105.

Table 3. Survival (%) at selected intervals in male rats treated with Thidiazuron in the diet for up to 2 years. [a]

Parameter	Dose (ppm)			
	0	200	900	1800
Week 78, all animals (n=70-85, initially)	59	77	76	56
Week 105, all animals (n=70-85, initially)	32	26	41	13
Week 107, terminal sacrifice (n=60, initially)	45	43	47	18**

a Data were obtained from page 32 and Table 1 (pages 62 and 63) of MRID 46345201. Percent survival was calculated by reviewers.

** Significantly different from controls; $p \leq 0.01$ (statistical analysis was performed only on the terminal sacrifice group)

B. BODY WEIGHT AND BODY WEIGHT GAINS - Body weights were generally decreased ($p \leq 0.05$-0.01) throughout the study at 1800 ppm in males (↓4-17%) and females (↓4-18%; Table 4). Body weights were decreased ($p \leq 0.05$) by 4-9% on Days 148, 372, and 596-708 in the 900 ppm males. Overall (Days 1-708) body weight gains were decreased in the 900 ppm males (↓13%) and the 1800 ppm males (↓23%) and females (↓26%). Other differences ($p \leq 0.05$) in body weights and body weight gains of the treated groups relative to the controls were minor and/or transient. At the end of the recovery phase, body weights were similar to controls.

Table 4. Mean (±SD) body weights and body weight gains (g) at selected intervals in rats treated with Thidiazuron for up to 2 years. [a]

Day(s)	Dose (ppm)			
	0	200	900	1800
Males				
1	214±10	215±11	214±10	215±10
8	281±13	281±16	276±13	265±15** (↓6)
92	535±38	538±44	530±40	492±47** (↓8)
204	619±46	613±56	609±48	597±54* (↓4)
372	693±67	688±70	665±54* (↓4)	655±56** (↓5)
708	682±81	662±98	622±90* (↓9)	569±93** (↓17)
BWG: 1-92	321±36	323±42	316±38	277±44** (↓14)
BWG: 1-372	479±66	473±69	450±52* (↓6)	441±55** (↓8)
BWG: 1-708	468±83	448±97	408±90* (↓13)	360±90** (↓23)
Females				
1	164±9	164±9	164±9	163±9
8	193±11	192±13	186±12** (↓4)	178±10** (↓8)
92	293±17	289±20	282±19** (↓4)	273±22** (↓7)
267	336±24	332±25	328±28	321±26** (↓4)
372	362±35	354±33	352±42	329±31** (↓9)
680	460±81	447±67	425±79	375±50** (↓18)
708	454±78	450±66	422±81	378±56** (↓17)
BWG: 1-92	129±14	125±17	118±14** (↓9)	110±18** (↓15)
BWG: 1-372	198±31	189±30	188±37	167±28** (↓16)
BWG: 1-708	290±76	285±64	259±78	215±55** (↓26)

a Data (n=70-85 initially) were obtained from Table 3c (pages 94-101) and Table 5c (pages 124-131) of MRID 46345201. Percent difference from controls, calculated by reviewers, is included in parentheses.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

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C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption** - Food consumption was decreased ($p \leq 0.01$) generally throughout the study in the 1800 ppm males (↓4-10%) and females (↓5-15%) and was periodically decreased ($p \leq 0.05$) in the 900 ppm females (↓3-11%; Table 5). Other differences ($p \leq 0.05$) were minor and sporadic. At the end of recovery, food consumption was similar to controls.

Table 5. Mean (±SD) food consumption (g/day) in rats treated with Thidiazuron for up to 2 years. [a]

Day(s)	Dose (ppm)			
	0	200	900	1800
Males				
8	27.6±0.9	28.3±0.9	27.9±1.0	26.5±1.2** (↓4)
43	27.1±1.0	27.0±1.2	26.4±0.8	24.3±1.5** (↓10)
372	24.5±0.7	24.7±1.1	24.4±0.9	25.1±1.1
708	22.3±1.4	21.6±3.1	19.7±3.8	20.5±5.4
Females				
8	20.9±0.8	21.2±0.9	20.5±0.8	19.4±1.0** (↓7)
38	17.7±1.2	17.1±0.8	16.8±1.0* (↓5)	15.1±0.9** (↓15)
43	20.7±0.8	20.3±0.7	20.0±0.9* (↓3)	18.1±0.5** (↓13)
148	18.2±0.6	18.2±0.6	18.0±0.7	17.3±0.6** (↓5)
372	19.6±1.1	19.7±0.9	20.0±1.1	18.5±1.2** (↓6)
680	21.9±1.7	19.7±1.9*	19.4±2.2* (↓11)	19.4±1.7** (↓11)
708	20.2±2.5	20.4±2.6	20.5±2.0	18.3±2.0

a Data (mean ± SD; n=10-17 cages) were obtained from Table 6c (pages 141-148) of MRID 46345201. Numbers listed parenthetically represent the percent difference from controls (calculated by the reviewers).
* Statistically different ($p \leq 0.05$) from the controls
** Statistically different ($p \leq 0.01$) from the controls

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

D. OPHTHALMOSCOPIC EXAMINATION - No treatment-related effects were observed during the ophthalmoscopic examinations.

E. BLOOD ANALYSES

1. **Hematology** - No treatment-related adverse effects were observed on hematology. Differences ($p \leq 0.05$) were minor or incidental.

2. **Clinical chemistry** - Increases ($p \leq 0.05$) in the following clinical chemistry parameters were observed (Tables 6a and 6b): (i) serum urea in the 900 ppm males at Months 6 and 12 (↑19-24%)

and 1800 ppm males throughout treatment (↑30-179%) and 1800 ppm females at Months 6 and 12 (↑13-21%); (ii) cholesterol in the 1800 ppm males throughout treatment (↑22-83%) and the 1800 ppm females on Months 6, 12, and 24 (↑20-56%); (iii) triglycerides in the 1800 ppm males at Month 24 (↑245%); and (iv) phosphorus in the 1800 ppm males at Months 12 and 24 (↑9-27%). In the 1800 ppm males, decreases were observed in albumin/globulin at Months 18 and 24 (↓20-24%) and glucose at Month 24 (↓25%). There were no differences ($p \leq 0.05$) detected in these parameters at Month 15 in the recovery group. Creatinine was increased ($p \leq 0.01$) in the 1800 ppm males at Month 18 (↑179%); however, except for this instance, the values were similar in magnitude to control, or the variation was too large to demonstrate a statistical difference. Other differences were observed, but were minor and/or transient.

Table 6a. Mean (±SD) of selected clinical chemistry parameters in male rats treated with Thidiazuron for up to 2 years.[a]

Parameter	Dose (ppm)			
	0	200	900	1800
Urea (mmol/l)				
Month 6	4.46±0.37	4.51±0.45	5.15±0.56** (↑24)	5.78±0.62** (↑30)
Month 12	4.26±0.35	4.32±0.58	5.06±0.63** (↑19)	5.88±0.86** (↑38)
Month 15[b]	4.57±0.49	—	—	11.68±22.10
Month 18	4.58±0.45	4.92±0.54	5.37±0.80	12.76±20.42** (↑179)
Month 24	4.49±0.85	6.20±3.75	4.93±0.77	7.58±4.36** (↑69)
Cholesterol (mmol/l)				
Month 6	1.89±0.56	1.74±0.24	2.14±0.45	2.31±0.62* (↑22)
Month 12	2.52±0.61	2.31±0.36	2.64±0.65	3.54±2.72* (↑40)
Month 15[b]	2.49±0.69	—	—	3.06±1.37
Month 18	2.83±0.72	2.80±0.72	3.10±1.40	5.19±1.75** (↑83)
Month 24	2.80±0.84	3.79±1.48	3.62±0.77	4.68±1.47** (↑67)
Triglycerides (mmol/l)				
Month 6	0.83±0.40	0.62±0.24	0.86±0.26	0.83±0.26
Month 12	0.84±0.32	0.82±0.39	0.83±0.42	1.30±2.18
Month 15[b]	1.17±0.46	—	—	1.94±1.18
Month 18	1.10±0.51	1.13±0.86	1.13±0.88	2.79±2.12
Month 24	0.64±0.22	1.43±1.34	1.13±0.49	2.21±1.20** (↑245)
Phosphorus				
Month 6	1.79±0.17	1.85±0.17	1.84±0.17	1.85±0.16
Month 12	1.59±0.12	1.66±0.15	1.68±0.13	1.74±0.15** (↑9)
Month 15[b]	1.43±0.09	—	—	2.01±2.00
Month 18	1.51±0.12	1.60±0.10	1.52±0.13	1.93±1.00
Month 24	1.43±0.13	1.49±0.27	1.45±0.10	1.81±0.45** (↑27)
Albumin/Globulin				
Month 6	1.41±0.14	1.48±0.17	1.48±0.16	1.47±0.13

(table continues next page)

Parameter	Dose (ppm)			
	0	200	900	1800
Month 12	1.44±0.14	1.59±0.18* (↑10)	1.52±0.14	1.43±0.26
Month 15[b]	1.42±0.17	—	—	1.52±0.23
Month 18	1.40±0.21	1.48±0.14	1.33±0.23	1.07±0.34* (↓24)
Month 24	1.14±0.16	1.18±0.26	1.15±0.14	0.91±0.16* (↓20)
Glucose (mmol/l)				
Month 6	7.27±1.05	7.04±0.98	6.79±1.10	7.09±0.89
Month 12	6.85±1.04	6.88±1.42	6.69±1.26	6.15±0.86
Month 15[b]	7.79±0.83	—	—	7.12±0.83
Month 18	7.20±1.47	6.55±0.86	6.01±1.57	6.07±0.78
Month 24	6.08±1.23	5.33±0.92	5.33±0.69	4.53±0.72** (↓25)

a Data were obtained from Tables 9a through 9e (pages 187-217) of MRID 46345201. Numbers listed parenthetically represent the percent difference from controls (calculated by reviewers).
b Results after 12 months of treatment followed by 3 months of recovery.
* Statistically different ($p \leq 0.05$) from the controls
** Statistically different ($p \leq 0.01$) from the controls
— Not tested

Table 6b. Mean (±SD) of selected clinical chemistry parameters in female rats treated with Thidiazuron for up to 2 years.[a]

Parameter	Dose (ppm)			
	0	200	900	1800
Urea (mmol/l)				
Month 6	4.93±0.71	5.33±0.78	5.37±0.78	5.59±0.69** (↑13)
Month 12	4.64±0.75	4.95±0.51	5.53±1.88	5.62±0.85** (↑21)
Month 15[b]	5.40±0.89	—	—	5.19±0.82
Month 18	4.63±1.01	5.60±0.85	5.77±1.43	5.78±0.78
Month 24	4.53±1.38	4.90±1.44	5.62±1.10	5.70±1.02
Cholesterol (mmol/l)				
Month 6	1.92±0.42	1.97±0.30	2.28±0.41** (↑19)	2.30±0.44** (↑20)
Month 12	2.09±0.42	2.17±0.32	2.37±0.56	2.53±0.53** (↑21)
Month 15[b]	1.89±0.44	—	—	1.82±0.35
Month 18	2.38±0.55	2.08±0.43	2.40±0.50	2.53±0.49
Month 24	2.25±0.36	2.08±0.33	2.61±0.47	3.50±1.36** (↑56)

a Data were obtained from Tables 9a through 9e (pages 187-217) of MRID 46345201. Numbers listed parenthetically represent the percent difference from controls (calculated by reviewers).
b Results after 12 months of treatment followed by 3 months of recovery.
* Statistically different ($p \leq 0.05$) from the controls
** Statistically different ($p \leq 0.01$) from the controls
— Not tested

F. URINALYSIS - The incidence of urinary protein concentration ≥3 g/L was increased in the 1800 ppm males (66-90% treated vs 31-50% controls) and females (14-78% treated vs 0-10% controls) throughout the study, except in males at Month 6. Urinary volume was increased in the 1800 ppm males at Month 24 (14.2 mL treated vs 9.2 mL controls); but may have been a secondary effect following the extreme renal dysfunction found in this group. All other differences ($p \leq 0.05$) were transient.

G. SACRIFICE AND PATHOLOGY

1. Organ weights - Terminal (24 months) body weights were decreased ($p \leq 0.01$) in the 1800 ppm males (↓21%) and females (↓17%; Table 7). Relative to body kidney weights were increased ($p \leq 0.01$) in the 1800 ppm males (0.926% treated vs 0.608% controls) and females (0.876% treated vs 0.727% controls). Only minor increases ($p \leq 0.01$) to relative to body liver weights were observed in the 1800 ppm males (2.74% treated vs 2.04% controls) and ≥900 ppm females (2.63-2.87% treated vs 2.43% controls).

Changes observed in recovery group (15 months) were considered incidental because they were not observed at the terminal sacrifice. Other differences ($p \leq 0.05$), including all differences observed at the interim sacrifice at 12 months, were not related to dose, were not corroborated pathologically, or were considered incidental because absolute weights of the organs were comparable to controls and these organs do not scale with body weight (discounting differences such as relative to body brain weight).

Table 7. Mean (±SD) organ weights in rats treated with Thidiazuron in the diet for up to 2 years.[a]

Weights	Dose (ppm)			
	0	200	900	1800
Males				
Terminal body (g)	637.4±82.4	622.4±95.2	585.3±74.4	505.4±52.0** (↓21)
Kidney Absolute (g)	3.82±0.43	3.88±0.59	4.12±1.78	4.63±1.06
Relative to body (%)	0.608±0.096	0.634±0.122	0.707±0.289	0.926±0.241**
Relative to brain (%)	162±21	164±24	175±81	196±48
Females				
Terminal body (g)	425.3±77.9	412.8±61.0	388.7±78.2	353.5±56.6** (↓17)
Kidney Absolute (g)	3.02±0.38	2.86±0.39	3.02±0.60	3.04±0.51
Relative to body (%)	0.727±0.125	0.703±0.110	0.797±0.187	0.876±0.175**
Relative to brain (%)	141±19	133±20	139±26	143±25

a Data were obtained from Table 13c (pages 287-288 and 291-292) of MRID 46345201. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

2. Gross pathology - At 1800 ppm at the terminal (24 months) sacrifice, the incidences of the following gross lesions were increased (treated vs controls; Table 9): (i) obviously small seminal vesicles (4/11 vs 2/27); (ii) irregular kidney surface in males (5/11 vs 2/27) and females (10/49 vs 3/39); and (iii) pale kidney in males (7/11 vs 5/27) and females (17/49 vs 10/39).

In the 1800 ppm males of the recovery group (15 months), an increase of irregular kidney surface was observed (3/15 vs 0/15). The incidence of other gross lesions in the interim (12 months) and recovery groups were similar to the controls or incidental.

Table 9. Incidence of selected gross lesions in rats treated with Thidiazuron in the diet for up to 2 years. [a]

Gross lesion	Dose (ppm)			
	0	200	900	1800
Males				
Kidney				
Irregular surface	2/27 (7)	6/26 (23)	8/28 (29)	5/11 (45)
Pale	5/27 (19)	11/26 (42)	5/28 (17)	7/11 (63)
Seminal vesicles Obviously small	2/27 (7)	1/26 (4)	3/28 (11)	4/11 (36)
Females				
Kidney Irregular surface	3/39 (8)	1/43 (2)	2/35 (6)	10/49 (20)
Pale	10/39 (26)	8/43 (17)	4/35 (11)	17/49 (35)

a Data were obtained from Tables 14e and 14f (pages 304-318) of MRID 46345201.
( ): % affected

3. Microscopic pathology

a. Non-neoplastic -

INTERIM SACRIFICE

At the interim sacrifice (12 months; Table 10a), the incidences (treated vs controls, severity) of the following renal lesions were increased: (i) glomerular mineralization in the ≥900 ppm males (10/10 - 9/9 each, minimal to slight) vs controls (0/10) and the ≥900 ppm females (10/10 - 9/9 each, minimal to slight) vs controls (3/9, minimal); (ii) chronic progressive nephropathy in the 1800 ppm males (5/9, minimal to moderate) vs controls (3/10, minimal to moderate) and 1800 ppm females (8/10, minimal) vs controls (0/9); (iii) golden brown pigment in the tuboepithelial cells in ≥900 ppm males (3/10-4/9, minimal) vs controls (1/10, minimal); (iv) papillary mineralization in the ≥200 ppm females (4/10-5/10, minimal) vs controls (2/9, minimal); and (v) bilateral pelvic dilatation in the 1800 ppm females (4/10, minimal to moderate) vs controls (1/9, minimal). Additionally, at 1800 ppm the following lesions were observed: diffuse, unilateral germinal cell atrophy in the testes (2/9, severe) vs controls (0/10); unilateral luminal dilation in the testes (2/9, minimal to slight) vs controls (0/10); and unilateral oligospermia in the epididymis (3/9, severe to marked) vs controls (1/10, moderate). Although the increase in germinal cell atrophy in the testes and oligospermia in the epididymis were unilateral at the

interim sacrifice, these findings were bilateral at the terminal sacrifice. Luminal dilation in the testes was not increased at the terminal sacrifice. The incidence of other lesions were similar to controls.

RECOVERY SACRIFICE

At the recovery sacrifice (15 months; Table 10b), the incidences of the following renal lesions were increased at 1800 ppm: (i) glomerular mineralization in the males (15/15, minimal to slight) vs controls (3/15) and females (15/15, minimal to slight) vs controls (2/15, minimal); (ii) chronic progressive nephropathy in the males (3/15, minimal to severe) vs controls (9/15, minimal) and females (4/15, minimal) vs controls (0/15); (iii) golden brown pigment in the tuboepithelial cells in males (7/15, minimal) vs controls (2/15, minimal); and (iv) suburothelial congestion in the females (9/15, minimal to slight) vs controls (2/15, minimal). These kidney lesions in males increased in incidence and/or severity in the 3 month recovery period. In the female kidney, glomerular mineralization incidence and severity was similar to the interim sacrifice, chronic progressive nephropathy decreased, and suburothelial congestion increased. The incidence of other lesions were similar to controls.

TERMINAL SACRIFICE

At the terminal sacrifice (24 months; Table 10c), increased incidence of the following lesions were observed at 200 ppm: (i) renal collecting duct hyperplasia in the males (17/60, minimal to slight vs 5/60, minimal to slight); (ii) renal suburothelial congestion in the females (21/60, minimal to marked vs 11/60, minimal to slight); and (iii) bilateral seminal vesicle atrophy (9/60, minimal to marked vs 3/60, slight to moderate).

Also at the terminal sacrifice, increased incidence of renal lesions were observed as follows: (i) collecting duct hyperplasia in the ≥900 ppm males (16/60-39/60, minimal to moderate vs 5/60, minimal to slight) and females (22/60-32/60, minimal to slight vs 13/60, minimal to slight); (ii) suburothelial congestion in the ≥900 ppm females (20/60-24/60; minimal to slight vs 11/60, minimal to slight); (iii) glomerular mineralization in the ≥900 ppm males (54/60-60/60, minimal to moderate vs 9/60, minimal) and females (54/60-60/60, minimal to moderate vs 17/60, minimal); (iv) bilateral pelvic dilatation in the ≥900 ppm males (11/60-12/60, minimal to moderate vs 5/60, minimal to slight); (v) chronic progressive nephropathy in the 1800 ppm males (57/60, minimal to marked vs 41/60 minimal to marked) and the ≥900 ppm females (40/60-50/60, minimal to marked vs 36/60, minimal to moderate); (vi) urothelial mineralization in the ≥900 ppm females (43/60-45/60, minimal to moderate vs 37/60, minimal to moderate); (vii) transitional cell hyperplasia in the 1800 ppm males (11/60, minimal to moderate vs 0/60); (viii) tubuloepithelial golden brown pigment in the 1800 ppm males (30/60, minimal to moderate vs 7/60, minimal to slight); (ix) glomerular hyaline deposit in the 1800 ppm males (36/60, minimal to moderate vs 2/60, minimal), and (x) arteritis in the 1800 ppm males (14/60, minimal to moderate vs 0/60).

Additionally at the terminal sacrifice, the male reproductive system was affected. Increased incidence of lesions were observed as follows at 1800 ppm: (i) bilateral germinal cell atrophy in

the testes (21/60, minimal to marked vs 3/60, moderate to severe); (ii) arteritis in the testes (26/60, minimal to moderate vs 7/60, minimal to moderate); (iii) bilateral oligospermia in the epididymis (29/60, minimal to marked vs 9/60, moderate to marked); (iv) epithelial degenerative changes in the epididymis (35/60, minimal to moderate vs 12/60, minimal to moderate); (v) arteritis in the epididymis (13/60, minimal to slight vs 1/60 , slight); (vi) bilateral atrophy of the seminal vesicles (20/60, minimal to moderate vs 3/60, slight to moderate); and (vii) mixed cell infiltrate in the seminal vesicles (5/60, minimal to marked vs 0/60). Bilateral seminal vesicle atrophy was also increased at 900 ppm (9/60, minimal to marked vs 3/60, slight to moderate).

At the terminal sacrifice, other microscopic findings were also observed in the 1800 ppm males, and the incidence was increased as follows: (i) diffuse parathyroid hyperplasia (12/55, minimal to moderate vs 0/56); (ii) focal/multifocal parathyroid hyperplasia (7/60, minimal to marked vs 0/60); (iii) fibrous osteodystrophy in the sternum (10/60, minimal to slight vs 0/60) and articular surface (12/60, minimal to slight vs 0/60); and (iv) hyperosteoidosis in the articular surface (8/60 , minimal to slight vs 0/60). Accumulation of brown pigment in Kupffer cells (11/60, minimal to slight vs 1/60, minimal) was considered to be incidental, and mineralization of the stomach (12/60, slight to moderate vs 0/60) was considered unrelated to the test substance toxicity.

Table 10a. Selected non-neoplastic histological findings in rats treated with Thidiazuron for 1 year. [a]

Non-neoplastic lesion		Dose (ppm)			
		0	200	900	1800
Males					
Kidney Glomerular mineralization, focal/multifocal	Total minimal slight	0/10	1/10 1/10	1/10 1/10	1/9 2/9 8/9
Chronic progressive nephropathy, focal/multifocal	Total minimal slight moderate	3/10 2/10 1/10	3/10 3/10	2/10 2/10	5/9 3/9 1/9 1/9
Golden brown pigment, tubuloepithelial, focal/multifocal	Total minimal	1/10 1/10	2/10 2/10	3/10 3/10	4/9 4/9
Testes Atrophy, germinal cell, unilateral, diffuse	Total severe	0/10	0/10	1/10 1/10	2/9 2/9
Dilation, luminal, unilateral	Total minimal slight	0/10	1/10 1/10	1/10 1/10	2/9 1/9 1/9
Epididymis Oligospermia, unilateral	Total moderate severe marked	1/10 1/10		1/10 1/10	3/9 2/9 1/9
Females					

(table continues next page)

Non-neoplastic lesion		Dose (ppm)			
		0	200	900	1800
Kidney Glomerular mineralization, focal/multifocal	Total minimal slight	3/9 3/9	1/10 1/10	9/10 9/10	10/10 5/10 5/10
Chronic progressive nephropathy, focal/multifocal	Total minimal	0/9 0/9	4/10 4/10	1/10 1/10	8/10 8/10
Papillary mineralization, focal/multifocal	Total minimal	2/9 2/9	4/10 4/10	5/10 5/10	5/10 5/10
Pelvic dilatation, bilateral	Total minimal slight moderate	1/9 1/9	0/10	0/10	4/10 1/10 2/10 1/10

a Data were obtained from Table 15a-15b (pages 321-350) and Appendix L1 (pages 1057-1188) of MRID 46345201.

Table 10b. Selected non-neoplastic histological findings in rats treated with Thidiazuron for 1 year followed by a 3 month recovery period. [a]

Non-neoplastic lesion		Dose (ppm)		
		0		1800
Males				
Kidney Glomerular mineralization, focal/multifocal	Total minimal slight	3/15 3/15		15/15 1/15 14/15
Chronic progressive nephropathy, focal/multifocal	Total minimal slight moderate severe	9/15 9/15		13/15 9/15 2/15 1/15 1/15
Golden brown pigment, tubuloepithelial, focal/multifocal	Total minimal	2/15 2/15		7/15 7/15
Females				
Kidney Glomerular mineralization, focal/multifocal	Total minimal slight	2/15 2/15		15/15 8/15 7/15
Chronic progressive nephropathy, focal/multifocal	Total minimal	0/15 0/15		4/15 4/15
Congestion, suburothelial, focal/multifocal	Total minimal slight	2/15 2/15		9/15 7/15 2/15

a Data were obtained from Table 15c-15d (pages 355 and 371) and Appendix L2 (pages 1189-1252) of MRID 46345201.

(table continues next page)

Table 10c. Selected non-neoplastic histological findings in rats treated with Thidiazuron for 2 years. [a]

Non-neoplastic lesion		Dose (ppm) 0	200	900	1800
Males					
Kidney Collecting ducts hyperplasia	Total	5/60	17/60	16/60	39/60
	minimal	4/60	15/60	15/60	20/60
	slight	1/60	2/60	1/60	12/60
	moderate				7/60
Transitional cell hyperplasia, diffuse	Total	0/60	3/60	0/60	11/60
	minimal		2/60		2/60
	slight		1/60		7/60
	moderate				2/60
Chronic progressive nephropathy, focal/multifocal	Total	41/60	42/60	45/60	57/60
	minimal	23/60	29/60	22/60	11/60
	slight	12/60	4/60	11/60	5/60
	moderate	4/60	6/60	8/60	12/60
	severe		1/60		22/60
	marked	2/60	2/60	4/60	7/60
Golden brown pigment, tubuloepithelial, focal/multifocal	Total	7/60	13/60	9/60	30/60
	minimal	6/60	11/60	8/60	23/60
	slight	1/60	2/60	1/60	6/60
	moderate				1/60
Glomerular hyaline deposit	Total	2/60	2/60	2/60	36/60 (48/60)[b]
	minimal	2/60		2/60	12/60
	slight				13/60
	moderate				11/60
Arteritis, focal/multifocal	Total	0/60	1/60	0/60	14/60
	minimal		1/60		10/60
	slight				3/60
	moderate				1/60
Glomerular mineralization, focal/multifocal	Total	9/60	14/60	54/60	60/60
	minimal	9/60	14/60	49/60	19/60
	slight			5/60	40/60
	moderate				1/60
Pelvic dilatation, bilateral	Total	5/60	9/60	11/60	12/60
	minimal	3/60	2/60	3/60	1/60
	slight	2/60	4/60	3/60	6/60
	moderate		3/60	5/60	5/60

(table continues next page)

Non-neoplastic lesion		Dose (ppm) 0	200	900	1800
Testes Atrophy, germinal cell, bilateral, focal/multifocal	Total	3/60	5/60	1/60	21/60
	minimal		1/60		12/60
	slight				3/60
	moderate	1/60	1/60		5/60
	severe	2/60	1/60		
	marked		2/60	1/60	1/60
Arteritis	Total	7/60	9/60	6/60	26/60
	minimal	2/60	4/60	1/60	13/60
	slight	3/60	3/60	4/60	4/60
	moderate	2/60	1/60	1/60	7/60
	severe		1/60		
	marked				2/60
Epididymis Oligospermia, bilateral	Total	9/60	9/60	3/60	29/60
	minimal				9/60
	slight		2/60		4/60
	moderate	2/60	2/60		6/60
	severe	5/60	3/60	1/60	3/60
	marked	2/60	2/60	2/60	7/60
Epithelial degenerative changes	Total	13/60	23/60	12/60	35/60
	minimal	4/60	4/60	1/60	13/60
	slight	6/60	10/60	10/60	18/60
	moderate	3/60	9/60	1/60	4/60
Arteritis	Total	1/60	1/60	1/60	13/60
	minimal			1/60	7/60
	slight	1/60	1/60		6/60
Seminal vesicles Atrophy, bilateral, diffuse	Total	3/60	9/60	9/60	20/60
	minimal		4/60	1/60	9/60
	slight	1/60	1/60	4/60	8/60
	moderate	2/60	2/60	2/60	3/60
	marked		2/60	2/60	
Mixed cell infiltrate	Total	0/60	2/60	2/60	5/60
	minimal				1/60
	slight		1/60	1/60	
	moderate		1/60	1/60	3/60
	marked				1/60
Parathyroid Hyperplasia, diffuse	Total	0/56	2/56	0/56	12/55
	minimal		1/56		4/55
	slight				3/55
	moderate				5/55
	marked		1/56		

(table continues next page)

Non-neoplastic lesion		Dose (ppm) 0	200	900	1800
Hyperplasia, focal/multifocal	Total	0/60	3/60	3/60	7/60
	minimal				5/60
	slight		2/60	2/60	1/60
	moderate		1/60	1/60	1/60
	marked				
Bone, sternum Fibrous osteodystrophy	Total	0/60	1/60	0/60	10/60
	minimal				5/60
	slight				5/60
	moderate				
Articular surface Fibrous osteodystrophy	Total	0/60	1/60	0/60	12/60
	minimal				5/60
	slight				7/60
	moderate				
Hyperosteoidosis	Total	0/60	0/60	0/60	8/60
	minimal				7/60
	slight				1/60
Females					
Kidney Collecting ducts hyperplasia	Total	13/60	11/60	22/60	32/60
	minimal	10/60	9/60	20/60	21/60
	slight	3/60	2/60	2/60	11/60
Chronic progressive nephropathy, focal/multifocal	Total	36/60	39/60	42/60	50/60 (43/60)[b]
	minimal	23/60	22/60	23/60	14/60
	slight	9/60	15/60	13/60	19/60
	moderate	3/60	1/60	6/60	10/60
	severe		1/60		3/60
	marked	1/60			4/60
Glomerular mineralization, focal/multifocal	Total	17/60	13/60	54/60	60/60
	minimal	17/60	13/60	52/60	35/60
	slight			2/60	24/60
	moderate				1/60
Urothelial, mineralization, focal to multifocal	Total	37/60	32/60	43/60	45/60
	minimal	22/60	14/60	19/60	21/60
	slight	14/60	17/60	24/60	23/60
	moderate	1/60	1/60		1/60
Congestion, suburothelial, focal/multifocal	Total	11/60	21/60	20/60	24/60
	minimal	9/60	14/60	4/60	15/60
	slight	2/60	6/60	16/60	9/60
	marked		1/60		

a Data were obtained from Table 15e (pages 373-386) and Appendix L3 (pages 1255-2735) of MRID 45710212.
b Tabulation of the individual data by the reviewers resulted in a total that differed from that reported by the Sponsor (included in parentheses) in the summary table.

b. Neoplastic - Neoplasia data from pages 429-450 of MRID 46345201 are included in the Appendix of this DER. No treatment-related effect was observed on the incidence of neoplasia.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS - The LOAEL was 900 ppm based on a wasted appearance in the males, decreased body weights and body weight gains in both sexes, and increased renal glomerular mineralization in both sexes. The NOAEL was 200 ppm. There was no evidence of tumorigenic potential.

B. REVIEWER COMMENTS - No treatment-related effects were observed during the ophthalmoscopic examinations or hematology.

At 200 ppm after 24 months, some minor changes were seen but these observations were equivocal and not considered adverse.

At ≥900 ppm, the following findings were observed: (i) increased incidence of a wasted appearance in the males during the second year; (ii) decreased body weights in males, either sporadically (900 ppm) or generally throughout the study (1800 ppm); (iii) decreased overall (Days 1-708) body weight gain in males; (iii) decreased food consumption in females, frequently throughout the study; and (iv) increased serum urea in males at Months 6 and 12 (900 ppm) or throughout the study (1800 ppm). The following microscopic lesions were observed at 12 months: renal glomerular mineralization in both sexes; golden brown pigment in the tuboepithelial cells in the kidney in the males; and renal papillary mineralization in the females. The following lesions were observed at 24 months: (i) renal collecting duct hyperplasia in both sexes; (ii) suburothelial congestion in the females; (iii) glomerular mineralization in both sexes; (iv) bilateral pelvic dilatation in the males; (v) chronic progressive nephropathy in the females; (vi) urothelial mineralization in the females; and (vii) bilateral seminal vesicle atrophy.

At 1800 ppm, several additional findings were observed: (i) reduced motor activity, general pallor, and soiling around the anogenital region in the males during the second year; (ii) increased mortality in the males; (iii) decreased body weights and overall (Days 1-708) body weight gain in males; (iv) decreased food consumption in males; (v) increased serum cholesterol, triglycerides, and phosphorous in the males; (vi) increased serum urea and cholesterol in the females; (vii) decreased albumin/globulin and glucose in males; and (viii) increased incidence of urinary protein concentration ≥3 g/L in both sexes. Grossly, an increased incidence of irregular kidney surface was observed in males at 15 months (recovery). After 24 months, an increase of small seminal vesicles in males; and irregular kidney surface and pale kidney in both sexes were observed. Increased relative to body kidney weights were observed after 24 months. Increased incidence of the following additional microscopic lesions were observed: (i) chronic progressive nephropathy in both sexes at 12, 15, and 24 months; (ii) bilateral renal pelvic dilatation in the females at 12 months; (iii) diffuse germinal cell atrophy in the testes, unilateral at 12 months and bilateral at 24 months; (iv) unilateral luminal dilation in the testes at 12 months; (v) oligospermia in the epididymis, unilateral at 12 months and bilateral at 24 months; (vi) renal glomerular mineralization in both sexes at 15 months; (vii) golden brown pigment in the renal tuboepithelial cells in males at 15 and 24 months; and (viii) renal suburothelial congestion in the females at 15 months. Additionally, increased incidence of the following microscopic lesions were observed in males at 24 months: (i) renal transitional cell hyperplasia; (ii) renal glomerular hyaline deposit,

(iii) arteritis in kidneys, testes, and epididymis; (iv) epithelial degenerative changes in the epididymis; (v) mixed cell infiltrate in the seminal vesicles; (vi) diffuse parathyroid hyperplasia; (vii) focal/multifocal parathyroid hyperplasia; (viii) fibrous osteodystrophy in the sternum and articular surface; and (ix) hyperosteoidosis in the articular surface.

Only 13% of the 1800 ppm males survived 24 months. The cause of death of 26/49 of these males was considered to be chronic progressive nephropathy, and at least 95% of the animals at this dose had chronic progressive nephropathy and renal glomerular mineralization. Therefore, findings in these animals may have been confounded by severe renal dysfunction. In particular, parathyroid hyperplasia, osteodystrophy, and hyperosteoidosis may have been related to renal dysfunction.

The LOAEL is 900 ppm (equivalent to 36.4/51.4 mg/kg/day in males/females), based on decreased body weight and body weight gain in the males, increased bilateral seminal vesicle atrophy, and nephrotoxicity in both sexes. The NOAEL is 200 ppm (equivalent to 8.0/11.3 mg/kg/day).

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased survival, body weight, body weight gain, and food consumption, increased clinical signs, differences in clinical chemistry parameters, nephrotoxicity, and male reproductive system toxicity.

C. <u>STUDY DEFICIENCIES</u> - Summary severity data for histological lesions were not provided.

DATA FOR ENTRY INTO ISIS

Chronic/Carcinogenicity Study - rodents (870.4300)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
120301	46345201	chronic/onco	rat	2 years	oral	diet	1-105	0/0, 8.0/11.3, 36.4/51.4, 75.6/105	8.0	36.4	BW, BWG, Clinical Signs, FC, Clinical Chemistry, Kidney, Testes, Epididymis, Seminal Vesicle	

APPENDIX

RID-0672-05

DER for MRID No. 46345201

Page____ is not included in this copy.

Pages 28 through 49 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
