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DATA EVALUATION RECORD

THIDIAZURON

Study Type: §83-2b; Carcinogenicity Study in Mice

Work Assignment No. 2-01-46 B (MRID 46346001)

Prepared for
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U.S. Environmental Protection Agency
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DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity study in mice [feeding] OPPTS 870.4200b [§83-2b]; OECD 451.

PC CODE: 120301 **DP BARCODE:** 307336
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: Wason, S. (2004) Carcinogenicity study of thidiazuron in the C57BL/6 mouse by dietary administration. Bayer CropScience, Sophia Antipolis, France. Laboratory Report No.: SA01333, July 23, 2004. MRID 46346001. Unpublished.

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

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 46346001), Thidiazuron (99.5% a.i.; Batch # 107623-03) was administered in the diet to C57BL/6 mice (60/sex/dose) at doses of 0, 200, 650, or 2000 ppm (0/0, 26.5/33.4, 86.7/107.8, and 279.9/329.7 mg/kg/day in males/females) for up to 18 months. Ten mice/sex/dose were sacrificed at 52 weeks.

No treatment-related effect was observed on mortality or hematology.

At 2000 ppm, tremors were observed in both sexes. In the females, increased incidences of wasted appearance, prolapsed rectum, and soiled anogenital region were observed. Body weights were decreased in both sexes throughout the study. Body weight gain was decreased at 2000 ppm in both sexes at Days 1-92, 92-540, and 1-540. In both sexes, food consumption generally was decreased throughout treatment, and overall (Weeks 1-80) group mean food consumption was also decreased.

At 2000 ppm at the interim sacrifice (n=10), increased incidence of slight renal cortical basophilic tubules was observed in the females.

At 2000 ppm at the terminal sacrifice, the epididymis and kidney were identified as target organs. The incidence of grossly enlarged epididymis was increased. The incidences of the following microscopic lesions in the epididymis were increased: (i) dilated tubules; (ii) interstitial mononuclear cell infiltrate; (iii) unilateral and bilateral oligospermia; and (iv) spermatic granuloma. Relative to body kidney weight was increased in the females, as was the incidence of gross renal pelvic dilatation. The incidences of the following microscopic renal lesions were increased: (i) cortical basophilic tubules in the females; (ii) proteinaceous casts in the males; (iii) interstitial mononuclear cell infiltrate in the males; and (iv) bilateral pelvic dilatation in the males and females. Additionally, there was a decrease in renal corticoepithelial vacuolation in the males.

At 650 ppm, marginal effects were observed. At the terminal sacrifice, the incidences of the following lesions in the epididymis were slightly increased: (i) dilated tubules; (ii) interstitial mononuclear cell infiltrate; and (iii) bilateral oligospermia. Additionally, there was a decrease in renal corticoepithelial vacuolation in the males. In females, minor decreases in body weight gain at Days 92-540 and at Days 1-540 and. overall group mean food consumption was observed. The incidence of renal cortical basophilic tubules was increased in the females. The above effects found in 650 ppm animals became more severe and numerous at 2000 ppm indicating that the syndrome of toxicity may have begun at 650 ppm..

Hepatotoxicity was equivocally indicated as follows. At the interim sacrifice (n=10), slight to minimal centrilobular hypertrophy was observed in the 2000 ppm males. Relative to body liver weights were increased in the 2000 ppm males and the >=650 ppm females at the interim sacrifice. The incidences (and usually severity) of the following hepatic lesions were increased at the terminal sacrifice: oval cell proliferation in the >=650 ppm males and 2000 ppm females; centrilobular hepatocellular hypertrophy and focus(i) of altered hepatocytes (basophilic cells) in the 2000 ppm males. There was no indication that hepatic function was impaired nor that carcinogenesis resulted from these observed effects.

The LOAEL is 650 ppm (equivalent to 86.7/107.8 mg/kg/day in males/females) based on decreased body weight gain, and food consumption; and increased nephrotoxicity in females; and increased epididymis toxicity in males. The NOAEL is 200 ppm (equivalent to 26.5/33.4 mg/kg/day in males/females).

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on systemic toxicity and toxicity in the kidney and epididymis.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

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

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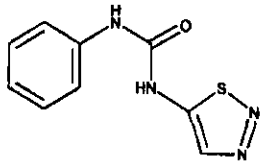
I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Thidiazuron

Description:	Light yellow powder
Batch #:	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:	Mouse
Strain:	C57BL/6
Age and mean weight at Week 1:	Approximately 6 weeks; 16.5-21.5 g males; 12.8-18.5 g females
Source:	Iffa Credo (Saint Germain-sur-l'Arbresle, France)
Housing:	Individually in suspended, stainless steel wire mesh cages
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*
Environmental conditions	
Temperature:	20-24°C
Humidity:	40-70%
Air changes:	10-15/hour
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	13 days

B. STUDY DESIGN

1. In life dates: Start: 10/23/01 End: 5/14/03

2. Animal assignment/dose levels: Animals within ±20% of the mean body weight for each sex were randomly assigned, stratified by weight, to the test groups shown in Table 1.

Table 1. Study design[a]

Nominal dose (ppm)	Actual Intake (mg/kg/day)	Terminal Sacrifice 78 Weeks (#/sex)	Interim Sacrifice 52 Weeks (#/sex)
0	0/0	50	10
200	26.50/33.37	50	10
650	86.66/107.79	50	10
2000	279.9/329.7	50	10

a Data obtained from pages 20 and 116 of MRID 46346001.

3. **Dose-selection rationale:** It was stated that the doses chosen for the current study were based on the results of 90-day subchronic oral toxicity study in mice (MRID 46121505). In this subchronic toxicity study, Thidiazuron was administered to 10 C57BL/6 mice/sex/dose in the diet at doses of 0, 500, 1000, 2000, or 4000 ppm for up to 90 days. All mice in the 4000 ppm group died or were sacrificed moribund on Days 6-9. At 2000 ppm, body weights were decreased generally throughout treatment in both sexes, as was overall (Days 1-90) body weight gains, and weekly food consumption was decreased throughout treatment in the females. The LOAEL was 1000 ppm (equivalent to 170.9/202.6 mg/kg/day in males/females) based on decreased cholesterol in the males and increased incidences of centrilobular hepatocellular hypertrophy in the males and diffuse acinar hypertrophy in the salivary glands in the females. The NOAEL was 500 ppm (equivalent to 85.2/99.8 mg/kg/day in M/F).

Based upon the results of this 90-day subchronic study, the doses summarized in Table 1 were selected for the current carcinogenicity study.

4. **Dose preparation and analysis:** Dietary formulations were prepared by mixing the appropriate amount of the test compound with diet every 6 weeks for the first 12 months of the study and every 8 weeks thereafter. Dietary formulations were kept at room temperature. 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. Homogeneity in each dose formulation (2 samples each from the top, middle, and bottom levels) was evaluated prior to animal treatment. Concentration analyses for each dose formulation were conducted prior to animal treatment, and on Weeks 1, 2, 14, 26, 38/39, and 52.

Results: **Homogeneity (% nominal):** 85-92%

Stability (% nominal): 93-113%

Concentration (% of nominal): 86-96%

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

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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 parameters	Bartlett's test for homogeneity of variance was performed. 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, and lymphocyte counts were square root transformed when necessary to achieve homogeneity of variance.
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: Animals were observed twice daily for morbidity and mortality (once daily on weekends or public holidays), and once daily for signs of toxicity. Detailed physical examinations, including palpation for masses, were performed weekly.

2. Body weight and body weight gain: 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) was reported for each day (after the first) that body weights were measured.

3. Food consumption and compound intake: Mean food consumption (g/animal/day) was reported weekly for the first 13 weeks and every 4 weeks thereafter. Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight data.

4. Ophthalmoscopic examination: Ophthalmoscopic examinations were not performed and are not required by the Guidelines (OPPTS 870.4200b/OECD 451).

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 terminal sacrifice groups on Weeks 52 or 53 and on 20 animals/sex/dose of the terminal sacrifice groups on Weeks 79 or 80. Blood smears were prepared but were not examined. The CHECKED (X) parameters were examined.

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a. Hematology

X	Hematocrit (HCT)	X	Leukocyte differential count*
X	Hemoglobin (HGB)	X	Mean corpuscular hemoglobin (MCH)
X	Leukocyte count (WBC)	X	Mean corpuscular hemoglobin concentration (MCHC)
X	Erythrocyte count (RBC)	X	Mean corpuscular volume (MCV)
X	Platelet (thrombocyte) count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (Control and HDT unless effects are observed) based on Guideline 870.4200 & OECD 451.

b. Clinical chemistry: Clinical chemistry evaluations were not performed and are not required by the Guidelines (OPPTS 870.4200b/OECD 451).

6. Urinalysis: Urinalysis was not performed and is not required by the Guidelines (OPPTS 870.4200b/OECD 451).

7. Sacrifice and pathology: Animals were sacrificed by exsanguination under deep pentobarbital anesthesia on Days 365-367 (interim sacrifice) and Days 547-569 (terminal sacrifice). Animals were fasted overnight prior to sacrifice. An approximately equal number of animals randomly distributed amongst all groups were sampled each day. All 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*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerves)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*		UROGENITAL	XX	Adrenal glands*+
X	Cecum*	XX	Kidneys*+	X	Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Parathyroids*
X	Rectum*	XX	Testes*+	X	Thyroid*
XX	Liver*+	XX	Epididymides*+	X	Harderian gland
X	Gall bladder* (not rat)	X	Prostate*		OTHER
	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

At the interim sacrifice, the following tissue samples were examined: all tissues from the decedents; the liver, submaxillary salivary gland, and all gross lesions from all animals; and the kidney in the 2000 ppm group and the controls. Samples from all animals in the terminal sacrifice groups (including decedents when possible) were examined. The exorbital lacrimal gland, larynx/pharynx, and nasal cavities were not examined microscopically.

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II. RESULTS

A. OBSERVATIONS

1. Clinical signs of toxicity: Tremors were observed in the 2000 ppm males (2/60) and females (1/60) vs (0/60 controls, each; Table 2). In the 2000 ppm females, increased incidences (# affected/60) of wasted appearance (12 treated vs 5 controls), prolapsed rectum (10 treated vs 0 controls), and soiled anogenital region (4 treated vs 0 controls) were also observed. The incidences of other clinical signs in the treated groups were similar to controls.

Table 2. Incidence (# affected/60) of selected clinical signs in mice treated with Thidiazuron in the diet for up to 18 months.[a]

Sign	Dose (ppm)			
	0	200	650	2000
Males				
Tremors	0	0	0	2
Females				
Tremors	0	0	0	1
Wasted appearance	5	4	3	12
Prolapsed rectum	0	1	2	10
Soiled anogenital region	0	0	0	4

a Data were obtained from pages 86-89 of MRID 46346001.

2. Mortality: No treatment-related effect was observed on mortality. After 53 weeks, the mortality rate was 15% in the 2000 ppm females (n=60) vs 5% in controls. Pathology did not corroborate a treatment-related effect, and increased mortality was not observed at study termination. Survival exceeded the guideline requirements of 50% at Week 65 and 25% at Week 78.

B. BODY WEIGHT: Body weights were decreased ($p \leq 0.01$) in the 2000 ppm males (↓5-13%) and females (↓6-17%) throughout the study (Table 3). Body weights were also slightly decreased in the 650 ppm males at days 344 (↓ 4%; $p \leq 0.01$). A similar effect was observed in the reported mean body weight gains/day. Body weight gain was decreased at 2000 ppm in both sexes at Days 1-92 (↓22-32%), 92-540 (↓30-48%), and 1-540 (↓25-41%) and in the 650 ppm females at Days 92-540 (↓23%) and 1-540 (↓13%). Other differences ($p \leq 0.05$) in body weights and body weight gains were sporadic and/or minor.

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Table 3. Mean (±SD) body weights and body weight gains (g) at selected intervals in mice treated with Thidiazuron in the diet for up to 18 months. [a]

Day(s)	Dose (ppm)			
	0	200	650	2000
Males				
1	19.4±1.0	19.3±1.0	19.2±1.0	19.3±0.9
43	24.4±1.1	24.4±1.2	24.2±1.1	23.2±1.1** (↓5)
92	26.8±1.3	26.6±1.2	26.4±1.3	25.1±1.0** (↓6)
344	31.6±2.0	31.4±1.9	30.4±2.1** (↓4)	27.6±1.3** (↓13)
540	31.5±2.1	31.9±2.2	31.0±2.4	28.4±1.7** (↓10)
	Body weight gains			
1-92	7.4	7.3	7.2	5.8 (↓22)
92-540	4.7	5.3	4.6	3.3 (↓30)
1-540	12.1	12.6	11.8	9.1 (↓25)
Females				
1	15.8±0.9	16.0±0.7	16.1±0.8	16.0±0.8
92	21.7±1.3	21.8±1.0	21.9±1.0	20.0±1.2** (↓8)
148	22.9±1.3	23.3±1.2	23.3±1.2	21.5±1.1** (↓6)
344	26.0±2.2	26.3±2.4	25.8±2.3	22.2±1.2** (↓15)
540	28.3±2.9	28.1±2.7	27.0±2.4	23.4±1.6** (↓17)
	Body weight gains			
1-92	5.9	5.8	5.8	4.0 (↓32)
92-540	6.6	6.3 (↓5)	5.1 (↓23)	3.4 (↓48)
1-540	12.5	12.1 (↓3)	10.9 (↓13)	7.4 (↓41)

a Data were obtained from pages 91-97 of MRID 46346001. Percent differences from controls (included in parentheses) and body weight gains were calculated by the reviewers.

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

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption: Food consumption was generally decreased ($p \leq 0.01$) throughout treatment in the 2000 ppm males (↓3-11%) and females (↓5-24%) and was sporadically decreased ($p \leq 0.05$) in the 650 ppm females (↓5-20%; Table 4). Overall (Weeks 1-80) group mean food consumption was decreased (statistical analysis not reported) in the 2000 ppm males (↓7%) and females (↓16%), and 650 ppm females (↓5%). The Sponsor stated that food consumption was unusually low on Day 456 in the females, and suspected that this effect was not due to treatment; however, a definitive explanation or the results of a statistical test to determine an outlying data value was not provided.

Table 4. Mean food consumption (g/animal/day) at selected intervals in mice treated with Thidiazuron in the diet for up to 18 months.[a]

Time	Dose (ppm)			
	0	200	650	2000
Males				
Day 8	3.6±0.4	3.6±0.3	3.5±0.3	3.2±0.3** (↓11)
Day 43	3.8±0.4	3.8±0.3	3.9±0.3	3.7±0.3** (↓3)
Day 92	3.7±0.3	3.8±0.3	3.7±0.3	3.6±0.2
Day 344	4.1±0.4	4.0±0.3	3.9±0.3** (↓5)	3.8±0.6** (↓7)
Day 540	4.1±0.5	4.2±0.4	4.1±0.4	4.0±0.5
Weeks 1-13	3.8	3.8	3.8	3.6 (↓5)
Weeks 1-52	3.9	3.9	3.8	3.7 (↓5)
Weeks 1-80	4.0	3.9	3.9	3.7 (↓7)
Females				
Day 8	3.3±0.4	3.4±0.3	3.3±0.4	3.1±0.3** (↓6)
Day 22	3.8±0.4	3.8±0.4	3.6±0.3* (↓5)	3.3±0.3** (↓13)
Day 43	4.0±0.4	4.0±0.4	4.0±0.3	3.8±0.3** (↓5)
Day 92	4.0±0.6	4.0±0.6	3.8±0.4	3.5±0.3** (↓13)
Day 344	4.3±0.6	4.3±0.5	4.2±0.5	3.6±0.8** (↓16)
Day 428	4.6±0.5	4.1±0.4** (↓11)	4.1±0.3** (↓11)	3.5±0.3** (↓24)
Day 456	4.5±0.4	4.4±0.5	3.6±0.3** (↓20)	3.7±0.6** (↓18)
Day 540	4.7±0.4	4.6±0.6	4.6±0.5	3.6±0.8** (↓23)
Weeks 1-13	3.9	3.9	3.8 (↓3)	3.5 (↓10)
Weeks 1-52	4.1	4.1	4.0 (↓2)	3.6 (↓12)
Weeks 1-80	4.3	4.2	4.1 (↓5)	3.6 (↓16)

a Data were obtained from pages 30 and 105-110 of MRID 46346001. Percent differences from controls (calculated by the reviewers) are included in parentheses.
* Significantly different from controls at $p \leq 0.05$
** Significantly different from controls at $p \leq 0.01$

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

D. BLOOD ANALYSES: No treatment-related effect was observed on hematology. In both sexes, minor increases (↑5-8%; $p \leq 0.05$) in erythrocytes (not statistically significant at Month 18 in the 2000 ppm females), hemoglobin concentration, and hematocrit were observed at Month 12 at 2000 ppm and at Month 18 at ≥650 ppm. Other differences ($p \leq 0.05$) were also minor.

E. SACRIFICE AND PATHOLOGY

1. Organ weights: Terminal (Month 18) body weights were decreased ($p \leq 0.01$) in the 2000 ppm males (↓11%) and females (↓21%; Table 5). Relative to body **liver** weights were increased ($p \leq 0.05$-0.01) in the 2000 ppm males (4.58% treated vs 4.17% controls) and the ≥650 ppm

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females (5.07-5.10% treated vs 4.84% controls). Absolute kidney weights were decreased in all treated males but the decreases in the 200 and 650 ppm groups were slightly less than 10% relative to the controls. Relative to body **kidney** weight was increased ($p \leq 0.01$) in the 2000 ppm females (1.63% treated vs 1.48% controls). There was a slight decrease ($p \leq 0.05$) in absolute weight observed in the testes in the ≥650 ppm males (↓11-17%); however, pathology did not corroborate toxicity. Other differences ($p \leq 0.05$) at the terminal sacrifice and all differences at the interim sacrifice were considered incidental for the following reasons: (i) absolute weights of these organs were comparable to controls and these organs do not scale with body weight (discounting differences such as relative to body epididymis weight); (ii) relative weights of these organs were comparable to controls and these organs scale with body weight (discounting differences such as absolute kidney and liver weights in males); (iii) minor (discounting differences such as absolute brain weight in females); (iv) unrelated to dose (discounting differences such as absolute adrenal gland weight in females); or (v) not corroborated by pathological evidence (discounting differences such as relative to body heart weight in males).

Table 5. Mean (±SD) organ weights in mice treated with Thidiazuron in the diet for up to 18 months.[a]

Weights	Dose (ppm)			
	0	200	650	2000
Males				
Terminal body (g)	28.1±1.7	28.2±2.3	27.4±2.3	24.9±1.2** (↓11)
Epididymis Absolute (g)	0.10±0.01	0.10±0.01	0.10±0.02	0.12±0.04
Relative to body (%)	0.35±0.04	0.35±0.04	0.37±0.06	0.48±0.15**
Relative to brain (%)	21.72±2.52	21.69±2.56	22.31±3.65	25.85±8.21
Kidney Absolute (g)	0.44±0.03	0.41±0.03* (↓7)	0.40±0.04** (↓9)	0.38±0.09** (↓14)
Relative to body (%)	1.56±0.10	1.46±0.10**	1.47±0.15**	1.56±0.41*
Relative to brain (%)	96.46±6.99	91.28±5.02*	88.82±6.81**	84.73±18.37**
Liver Absolute (g)	1.2±0.1	1.2±0.1	1.2±0.2	1.1±0.1
Relative to body (%)	4.17±0.36	4.20±0.43	4.35±0.48	4.58±0.32**
Relative to brain (%)	258.02±25.05	262.05±28.59	264.50±40.46	251.39±23.62
Testes Absolute (g)	0.18±0.02	0.17±0.02	0.16±0.02	0.15±0.03
Females				
Terminal body (g)	25.6±2.7	25.3±2.9	24.1±2.4	20.2±1.3** (↓21)
Kidney Absolute (g)	0.38±0.03	0.38±0.04	0.37±0.09* (↓3)	0.33±0.03** (↓13)
Relative to body (%)	1.48±0.13	1.53±0.21	1.54±0.39	1.63±0.14**
Relative to brain (%)	80.39±6.05	81.06±8.91	78.61±20.25**	74.38±6.66**
Liver Absolute (g)	1.2±0.2	1.2±0.2	1.2±0.1	1.0±0.1** (↓17)
Relative to body (%)	4.84±0.33	4.79±0.45	5.07±0.39*	5.10±0.48*

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Relative to brain (%)	264.08±28.56	256.60±36.60	259.33±26.64	233.41±23.90**

a Data were obtained from pages 133-138 of MRID 46346001 Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from controls; p≤0.05
** Significantly different from controls; p≤0.01

2. Gross pathology: At 2000 ppm at the terminal (18 month) sacrifice, the incidences of enlarged epididymis was increased (14% treated vs 2% controls), as was renal pelvic dilatation in the females (38% treated vs 0% controls; Table 6). The incidences of other gross lesions at both the interim (12 month) and terminal sacrifices were similar to controls or transient without corroborating evidence of toxicity.

Table 6. Incidence (%) of selected gross lesions in mice treated with Thidiazuron in the diet for up to 18 months.[a]

Gross lesion	Dose (ppm)			
	0	200	650	2000
Males				
Epididymis Enlarged	2	0	2	14
Females				
Kidney Pelvic dilatation	0	6	2	38

a Data (n=50) were obtained from pages 143, 145, 147 and 150 of MRID 46346001.

3. Microscopic pathology

a. Non-neoplastic: Treatment-related non-neoplastic lesions are detailed in Tables 7a and 7b. At the interim sacrifice (n=10), slight renal cortical basophilic tubules was observed in the 2000 ppm females (7 treated vs 1 control), and slight to minimal centrilobular hypertrophy was observed in the 2000 ppm males (10 treated vs 0 controls).

At the terminal sacrifice, the incidences (% treated, severity vs % controls, severity) of the following lesions in the epididymis were increased: (i) dilated tubules at ≥650 ppm (14-22%, minimal to moderate) vs controls (0%); (ii) interstitial mononuclear cell infiltrate at ≥650 ppm (10-28%, minimal to moderate) vs (6%, minimal); (iii) bilateral oligospermia at ≥650 ppm (10-16%, slight to marked) vs controls (0%); (iv) spermatic granuloma at 2000 ppm (12%, slight to moderate) vs controls (2%, minimal); and (v) unilateral oligospermia at 2000 ppm (22%, slight to marked) vs controls (4%, minimal).

The incidences of the following renal lesions were increased: (i) cortical basophilic tubules in the ≥200 ppm females (59-82%, minimal to moderate) vs (40%, minimal to slight); (ii) proteinaceous casts in the 2000 ppm males (66%, minimal to slight) vs controls (31%, minimal); (iii) interstitial mononuclear cell infiltrate in the 2000 ppm males (40%, minimal to slight) vs controls (22%, minimal); and (iv) bilateral pelvic dilatation in the 2000 ppm males (50%,

minimal to marked, $p \leq 0.01$) vs controls (0%) and 2000 ppm females (76%, minimal to marked, $p \leq 0.01$) vs controls (4%, minimal). Additionally, there was a decrease in renal corticoepithelial vacuolation in the ≥650 ppm males (0-12%, minimal to slight) vs controls (88%, minimal to moderate).

Equivocal hepatotoxicity was indicated. The incidences (% treated, severity vs % controls, severity) of the following hepatic lesions were increased at the terminal sacrifice: (i) oval cell proliferation in the ≥650 ppm males (32-38%, minimal to slight) vs controls (18%, minimal) and 2000 ppm females (47%, minimal) vs controls (28%, minimal to slight); (ii) centrilobular hepatocellular hypertrophy in the 2000 ppm males (34%, minimal to slight) vs controls (2%, minimal); and (iii) focus(i) of altered hepatocytes (basophilic cells) in the 2000 ppm males (6%, minimal or marked) vs controls (0%).

The incidences of the following adrenal lesions were increased at the terminal sacrifice in the 2000 ppm males: subcapsular; cortical hypertrophy/ degeneration; and cortical atrophy. These effects were considered to be due to stress, a secondary effect of treatment.

Amyloid deposition was observed in the kidney, thyroid, parathyroid, heart, jejunum, and testes; however, this effect was related to dose and corroborated (equivocally) by other clinical or pathological evidence of toxicity only in the liver. Furthermore, the Sponsor stated that amyloid deposition was considered to have occurred as a systemic consequence of renal changes.

Table 7a. Incidence (%) of selected non-neoplastic microscopic lesions in mice treated with Thidiazuron in the diet for up to 12 months.[a]

Microscopic lesion			Dose (ppm)			
			0	200	650	2000
Males						
Liver	Centrilobular hepatocellular hypertrophy	Slight	0	0	0	10
		Minimal	0	0	0	90
		Total	0	0	0	100
Females						
Kidney	Cortical basophilic tubules, focal/multifocal	Slight	10	0	0	70
		Minimal	0	0	10	0
		Total	10	0	10	70

a Data (n=10) were obtained from pages 153, 154, 167, and 474-567 of MRID 46346001.

(table continues next page)

Table 7b. Incidence (%) of selected non-neoplastic microscopic lesions in mice treated with Thidiazuron in the diet for up to 18 months.[a]

Microscopic lesion			Dose (ppm)			
			0	200	650	2000
Males						
Epididymis	Dilated tubules, unilateral/bilateral	Minimal	0		2	2
		Slight		4	6	16
		Moderate			6	4
		Total	0	4	14	22
	Mononuclear cell infiltrate, interstitial	Minimal	6	2	2	6
		Slight		2	6	20
		Moderate			2	2
		Total	6	4	10	28
	Oligospermia, bilateral	Slight	0			6
		Moderate		2	4	6
		Marked			6	4
		Total	0	2	10	16
	Spermatic granuloma, focal/multifocal	Minimal	2	2	2	
		Slight				10
		Moderate		2		2
		Total	2	4	2	12
	Oligospermia, unilateral	Minimal	4	2		
		Slight			2	4
		Moderate			2	12
		Marked				6
		Total	4	2	4	22
Kidney	Proteinaceous cast(s), multifocal	Minimal	31	32	12	44
		Slight		2	4	22
		Moderate			4	
		Total	31	34	20	66
	Mononuclear cell infiltrate, interstitial, focal/multifocal	Minimal	22	18	18	30
		Slight		4	10	10
		Moderate		2		
		Total	22	24	28	40
	Pelvic dilatation, bilateral	Minimal	0	2	2	24
		Slight				22
		Moderate			2	2
		Marked				2
		Total	0	2	4	50**
	Corticoepithelial vacuolation, multifocal/diffuse	Minimal	29	58	10	0
		Slight	53	20	2	
		Moderate	6	2		
		Total	88	80	12**	0**

(table continues next page)

Microscopic lesion			Dose (ppm) 0	200	650	2000
Liver	Centrilobular hepatocellular hypertrophy	Minimal	2	0	2	30
		Slight				4
		Total	2	0	2	34
	Oval cell proliferation, multifocal/diffuse	Minimal	18	10	32	36
		Slight		2		2
		Total	18	12	32	38
	Focus(i) of altered hepatocytes, basophilic cells	Minimal	0	0		4
		Moderate			2	
		Marked				2
		Total	0	0	2	6
	Amyloid deposition, perivascular, focal/multifocal	Minimal	4	2	4	12
		Slight	2		4	8
		Moderate			2	6
		Total	6	2	10	26
Females						
Kidney	Basophilic tubules, cortical, focal/multifocal	Minimal	36	41	44	12
		Slight	4	16	30	64
		Moderate		2	2	6
		Total	40	59	76	82
	Pelvic dilatation, bilateral	Minimal	4		2	2
		Slight		2		34
		Moderate		4		6
		Marked			2	4
		Total	4	6	4	76**
Liver	Oval cell proliferation, multifocal/diffuse	Minimal	26	16	34	47
		Slight	2	2		
		Total	28	18	34	47

a Data (n=49-50) were obtained from pages 207-218 and 571-1529 of MRID 46346001.

b. **Neoplastic**: Neoplasia data from pages 223-232 of MRID 46346001 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 2000 ppm, based on increased incidences of clinical signs of toxicity, decreased body weight, body weight gain, and food consumption, increased erythrocytes, hemoglobin concentration, and hematocrit levels, and increased incidence of microscopic renal lesions in both sexes; increased epididymis weight and incidence of microscopic lesions in the epididymis in males, and increased kidney weight in females. The NOAEL was 650 ppm. There was no evidence of tumorigenic potential.

B. REVIEWER COMMENTS:

No treatment-related effect was observed on mortality or hematology.

At 2000 ppm, tremors were observed in both sexes. In the females, increased incidences of wasted appearance, prolapsed rectum, and soiled anogenital region were observed. Body weights were decreased in both sexes throughout the study. Body weight gain was decreased at 2000 ppm in both sexes at Days 1-92, 92-540, and 1-540. In both sexes, food consumption generally was decreased throughout treatment, and overall (Weeks 1-80) group mean food consumption was also decreased.

At 2000 ppm at the interim sacrifice (n=10), increased incidence of slight renal cortical basophilic tubules was observed in the females.

At 2000 ppm at the terminal sacrifice, the epididymis and kidney were identified as target organs. The incidence of grossly enlarged epididymis was increased. The incidences of the following microscopic lesions in the epididymis were increased: (i) dilated tubules; (ii) interstitial mononuclear cell infiltrate; (iii) unilateral and bilateral oligospermia; and (iv) spermatic granuloma. Relative to body kidney weight was increased in the females, as was the incidence of gross renal pelvic dilatation. The incidences of the following microscopic renal lesions were increased: (i) cortical basophilic tubules in the females; (ii) proteinaceous casts in the males; (iii) interstitial mononuclear cell infiltrate in the males; and (iv) bilateral pelvic dilatation in the males and females. Additionally, there was a decrease in renal corticoepithelial vacuolation in the males.

At 650 ppm, marginal effects were observed. At the terminal sacrifice, the incidences of the following lesions in the epididymis were slightly increased: (i) dilated tubules; (ii) interstitial mononuclear cell infiltrate; and (iii) bilateral oligospermia. Additionally, there was a decrease in renal corticoepithelial vacuolation in the males. In females, minor decreases in body weight gain at Days 92-540 and at Days 1-540 and. overall group mean food consumption was observed. The incidence of renal cortical basophilic tubules was increased in the females. The above effects found in 650 ppm animals became more severe and numerous at 2000 ppm indicating that the syndrome of toxicity may have begun at 650 ppm..

Hepatotoxicity was equivocally indicated as follows. At the interim sacrifice (n=10), slight to minimal centrilobular hypertrophy was observed in the 2000 ppm males. Relative to body liver

weights were increased in the 2000 ppm males and the >=650 ppm females at the interim sacrifice. The incidences (and usually severity) of the following hepatic lesions were increased at the terminal sacrifice: oval cell proliferation in the >=650 ppm males and 2000 ppm females; centrilobular hepatocellular hypertrophy and focus(i) of altered hepatocytes (basophilic cells) in the 2000 ppm males. There was no indication that hepatic function was impaired nor that carcinogenesis resulted from these observed effects.

The LOAEL is 650 ppm (equivalent to 86.7/107.8 mg/kg/day in males/females) based on decreased body weight gain, and food consumption; and increased nephrotoxicity in females; and increased epididymis toxicity in males. The NOAEL is 200 ppm (equivalent to 26.5/33.4 mg/kg/day in males/females).

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on systemic toxicity and toxicity in the kidney and epididymis.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

C. STUDY DEFICIENCIES: Summary severity data for histological lesions were not provided.

DATA FOR ENTRY INTO ISIS

Carcinogenicity Study –mice (870.4200b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
120301	46346001	carcinogenicity	mice	18 months	oral	diet	26.5-329.7	0/0, 26.5/33.4, 86.7/107.8, 279.9/329.7 (M/F)	86.7	279.9	BW, BWG, FC, Clinical signs, Kidney, Epididymis	

APPENDIX

RID-0672-05

DER for MRID NO. 46346001

Page_____ is not included in this copy.

Pages 21 through 30 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.

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