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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

December 9, 2004

MEMORANDUM

Subject: **Thidiazuron** - Reviews of Five Toxicity Studies, Updating Executive Summaries for Four Studies and Toxicology Chapter for RED:

PC CODE: 120301
DP BARCODE: D294540, D294560, D307336, D300853
TXR#: 0052174

To: Stephanie Plummer/Susan Lewis
Reregistration Branch I
Special Review and Reregistration Division (7508C)

From: Paul Chin, Ph.D.
Reregistration Branch I
Health Effects Division (7509C)

Through: Whang Phang, Ph.D.
Senior Scientist
Reregistration Branch I
Health Effects Division (7509C)

The registrant, Aventis CropScience, submitted five studies (see below). Four of the five studies were reviewed by the contractor, Dynamac Corporation and went through the secondary review process in HED. Rat *In Vivo* Dermal Absorption study was reviewed by HED scientist. The DERs for these studies are attached to this memorandum. The following lists each study with the MRID number:

Rat *In Vivo* Dermal Absorption (MRID 46261502; barcode D294540)
28-Day Dermal Toxicity in Rats (MRID 46261501; barcode D294540)
Combined Chronic Toxicity / Carcinogenicity Study in Rats
(MRID 46345201; DP barcode)
Carcinogenicity Study in Mice (MRID 46346001; DP barcode D307336)
Multigeneration Reproduction Study in Rats (MRID 46209601; DP barcode D300853)

The brief summaries of the above studies are as follows:

Dermal absorption after a 8-hour exposure and termination at 120 hours post-application was 0.20%, 0.75%, and 1.18% for high dose, middle dose, and low dose, respectively.

There was no systemic or localized hazard noted in a 28-day dermal toxicity study in the rat tested at limit dose (1000 mg/kg).

Carcinogenicity studies in both rats and mice produced no treatment-related increase in tumor incidence.

In a 2-generation reproduction study in rats, maternal toxicity such as decreased body weight gain was seen at 108 mg/kg/day. The test chemical did not significantly affect any of the reproductive parameters. For the offspings, there was a decrease in pup body weight gain at 108 mg/kg/day.

Attached are also updated executive summaries for four studies. The executive summaries of many studies were found to be different from the current format and they were appropriately modified to reflect the current policy and guidelines of the Agency. The attached studies are listed as follows:

Chronic Toxicity [diet] - Dog (MRID 00159344)
Combined chronic toxicity/carcinogenicity [diet]- Rat (MRID 00159346)
Metabolism - Rat (MRID 42529001)
Developmental Toxicity - Rat (MRID 00077127)

In lieu of the Toxicology Chapter, the Hazard Characterization/Assessment Section will be prepared and incorporated in the HED Risk Assessment Document (RAD) for thidiazuron.

B

DATA EVALUATION RECORD

THIDIAZURON

Study Type: §82-2; 28-Day Dermal Toxicity in Rats

Work Assignment No. 1-01-39 (MRID 46261501)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer:
David McEwen, B.S.

Signature: David A. McEwen
Date: 8/30/04

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W. Allran
Date: 8/30/04

Program Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L. Menetrez
Date: 8/30/04

Quality Assurance:
Steven Brecher, Ph. D

Signature: Steven Brecher
Date: 8/30/04

Disclaimer

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

EPA Reviewer: Paul Chin, Ph.D. **Signature**: Paul Chin
Reregistration Branch 1, Health Effects Division (7509C) **Date** 9/28/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature**: Whang Phang
Reregistration Branch 1, Health Effects Division (7509C) **Date** 9/29/04
Work Assignment Manager: P.V. Shah, Ph.D. **Signature**: Shazi Dawson
Registration Action Branch 1, Health Effects Division (7509C) **Date** 12/16/04
Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: 28-Day Dermal Toxicity - Rat; OPPTS 870.3200 [§82-2]; OECD 410.

PC CODE: 120301 **DP BARCODE:** D294540
TXR #: 0052174 **SUBMISSION NO.:** Not reported

TEST MATERIAL (PURITY): Thidiazuron (>99.9% a.i.)

SYNONYMS: AE B049537; N-phenyl-N'-1,2,3-thiadiazol-5-ylurea

CITATION: Krötlinger, F. and M. Rosenbruch (2004) Thidiazuron: Subacute dermal toxicity study in rats (Four-week dermal administration). Bayer HealthCare AG, PH-PD T Experimental Toxicology, Wuppertal, Germany. Study No.: T8073134, April 5, 2004. MRID 46261501. Unpublished.

SPONSOR: Bayer CropScience AG, Regulatory Toxicology, 355, rue Dostoïevski, 06903 Sophia-Antipolis Cedex, France

EXECUTIVE SUMMARY - In a 28-day dermal toxicity study (MRID 46261501), Thidiazuron (>99.9% a.i., Batch #: 107623-03) was moistened with tap water and applied by semi-occlusive dressing to the shaved intact skin of 10 HsdCpb:WU rats/sex/dose at dose levels of 0, 100, 300, or 1000 mg/kg bw/day (limit dose), 6 hours/day for 5 days/week (males and females received 20 and 21 applications, respectively) during a 29-day period.

No compound-related effects were observed in mortality, clinical signs, dermal effects, body weight, body weight gain, food or water consumption, hematology, clinical chemistry, ophthalmology, absolute or relative organ weights, gross or histologic pathology.

The LOAEL was not observed. The NOAEL was 1000 mg/kg/day (HDT) (limit dose).

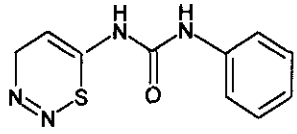
This study is classified as **acceptable/guideline** and satisfies the Guideline requirement (OPPTS 870.3200; OECD 410) for a 28-day dermal toxicity study in rats. A LOAEL was not observed; however, the compound was tested at the limit dose.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Thidiazuron

Description:	Light yellow powder
Batch #:	107623-03
Purity (w/w):	>99.9% a.i.
Stability of compound:	As the compound was applied neat, stability was not determined.
CAS #:	51707-55-2
Structure:	

2. Vehicle - The compound was moistened with tap water immediately prior to application.

3. Test animals

Species:	Rat
Strain:	HsdCpb:WU (Wistar derived)
Age and weight at Day 1:	9-10 weeks (males) and 12-13 weeks (females); 226-273 g males; 210-235 g females
Source:	Harlan Winkelmann GmbH Experimental Animal Breeders, Borchen, Germany
Housing:	Individually in Type IIIH cages
Diet:	Fixed formula standard diet Provimi Kliba® 3883.0.15 (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions	
Temperature:	22±2°C
Humidity:	55±5%
Air changes:	At least 10/hr
Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	At least 5 days

B. STUDY DESIGN

1. In-life dates- Start: 09/16/2003 End: 10/14/2003

2. Animal assignment - Animals were randomly assigned, stratified by body weight, to the test groups noted in Table 1.

Table 1. Study design [a]

Dose (mg/kg/day)	# of Animals (M/F)	Applied Dose (mg/cm² skin)	
		Males	Females
0	10/10	0	0
100	10/10	3.5-3.9	3.6-4.3
300	10/10	6.0-7.2	5.6-7.4
1000	10/10	11.0-13.0	9.7-10.9

a Data were obtained from the Study Report, pages 20 and 27.

3. **Dose selection rationale** - It was stated that the doses for the current study were based on the results of a previous acute dermal study in rats (study number not provided) and a 3-week dermal study in rabbits (study number not provided). In the acute study, the LD50 was reported to be >5000 mg/kg. In the 3-week rabbit study, dose levels of 50, 275, and 1500 mg/kg/day were applied to the intact or abraded skin for 6 hrs/day for 5 days/week. It was stated that the test material was a slight irritant, but did not cause any signs of systemic toxicity. No further information was provided.

4. **Preparation and treatment of animal skin** - Approximately 24 hours prior to the first application and twice weekly thereafter, the fur of each test animal was clipped from the back and flanks of the trunk. The appropriate amount of test material was placed on a pre-moistened (tap water) gauze patch (Cutiplast® sterile; 6 x 5 cm = 30 cm^2) and applied to the shaved skin (>10% of the total body surface). The gauze was secured using cohesive tape (Peha-Haft®), and the mobility of the rats was impaired by a rat jacket (Lomir Biomedical Inc.). The applied quantities of the test substance were based on the most recent individual body weights. The dressings were removed after 6 hours and the application areas were cleaned with soap and water. Animals in the control group were treated with tap water using the same procedure as described for the treated animals.

5. **Statistics** - The data were subjected to the following statistical methods. Significance was defined at $p \leq 0.05$. The reviewers considered the methods of analysis to be appropriate.

Parameters	Statistical Method
Hematology (atypical leucocytes, basophils, eosinophils, hepato-quick test, leucocytes, lymphocytes, monocytes, neutrophils, and reticulocytes) and clinical chemistry (A/G ratio, total bilirubin, and GGT)	Kruskal-Wallis test followed by an adjusted U test
Absolute organ weight, body weight, food consumption, water consumption, hematology (erythrocytes, hemoglobin, hematocrit, MCH, MCHC, MCV, and platelets), and clinical chemistry (albumin, creatinine, chloride, glucose, protein, and urea)	ANOVA followed by Dunnett's test
Relative (to body) organ weights	Log. ANOVA followed by Dunnett's test
Clinical chemistry (ALT, AST, ALP, cholesterol, calcium, potassium, sodium, and inorganic phosphate)	Adjusted Welsh test

C. METHODS

1. Observations

a. Cageside observations - Animals were observed at least once daily for signs of mortality and moribundity.

b. Clinical examinations - Clinical examinations (including open-field observations) were conducted once daily prior to the study and prior to dosing on Days 1, 8, 15, 22, and 29. Examinations for dermal irritation were performed using the guidelines published by the US Dept. of Agriculture and the Draize method before the study and on all dosing days. Evaluation of swelling was measured in both sexes on Days 1, 4, 8, 11, 15, 18, 22, 25, and 29, and in females only on Day 30. Skin-fold thickness was measured at two locations in the treated area using a cutimeter or skin-fold caliper, and the mean was calculated.

c. Neurological evaluations - Neurological evaluations were not performed in this study.

2. Body weight - Animals were weighed prior to treatment, weekly throughout the study, and at necropsy.

3. Food and water consumption - Individual food and water consumption were determined weekly, and were reported as mean consumption/animal/day and mean consumption/kg body weight/day.

4. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed on all animals prior to treatment and on the control and 1000 mg/kg/day groups prior to termination. The pupillary reflex was tested and the anterior regions of the eye were examined in a darkened room; the refractive elements of the eye (as well as the iris and fundus) were examined using an appropriate mydriatic agent and an indirect ophthalmoscope; and the transparent structures were examined with a Zeiss photo-slit lamp.

5. Hematology and clinical chemistry - Blood for glucose determination was collected in the morning from the tail vein of non-fasted, non-anesthetized animals. Blood for the other clinical pathology tests was collected from the retroorbital venous plexus under light CO_2 anesthesia one day prior to necropsy. 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 corpusc. HGB conc. (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*	X	Erythrocyte morphology
	(Thromboplastin time)		
X	(Clotting time 'Hepato-Quick')		
	(Prothrombin time)		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Inorganic phosphate	X	Total cholesterol*
X	Potassium* (K)		Globulins
X	Sodium* (NA)	X	Glucose*
	ENZYMES	X	Total bilirubin
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	X	A/G Ratio
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase*		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

6. Sacrifice and pathology - All animals were sacrificed via exsanguination under deep ether anesthesia, and subjected to gross pathological examination. The CHECKED (X) tissues were collected from all animals. In addition, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain*+
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 nerve)*
X	Jejunum*	XX	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	X	Thyroid*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin* (treated & untreated)
	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	X	Oviducts	X	Harderian glands
X	Lung*	XX	Uterus*+	X	Eyelids
X	Nasal cavity*	X	Mammary gland*	X	Peyer's patches
X	Pharynx*	X	Vagina	X	Zymbal's glands
X	Larynx*			X	Urethra
				X	Ureters

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
\+ Organ weights required.

The eyes, kidneys and testes were fixed in Davidson's solution. All other organs and tissues collected from all animals, as well as all gross lesions were preserved in 10% neutral buffered formalin, embedded in paraplast, sectioned, and stained with hematoxylin and eosin. Cryocuts of the liver were stained with Oil-Red-O. The tissues collected from the control and 1000 mg/kg animals were examined microscopically.

II. RESULTS

A. OBSERVATIONS

1. Clinical signs - No treatment-related clinical signs were observed in any animal in either sex.

2. Mortality - All animals survived to scheduled necropsy.

3. Dermal irritation - No treatment-related dermal effects were observed in any animal in either sex. The transient moderate skin reddening noted in two 1000 mg/kg/day females between Days 3 and 8 and slight formation of scale on Days 6-8 were considered to be as a result of mechanical irritation and not compound-related. Skin-fold thickness was similar between treated and control animals at all doses in both sexes.

B. BODY WEIGHT AND WEIGHT GAIN - No treatment-related effects on body weight or body weight gain were observed in either sex. A minor decrease ($p \leq 0.05$) in body weight was observed in the 1000 mg/kg females at Day 29 (↓6%; Table 2); however, weekly body weight gains did not vary significantly from controls during the study.

Table 2. Selected mean (±SD) body weights and body weight gains (g) in rats dermally treated with Thidiazuron for four weeks. [a]

Parameter	Days	Dose (mg/kg/day)			
		0	100	300	1000
Males					
Body Weight	1	242±10.4	243±11.5	254±8.6* (↑5)	247±9.9
	29	302±24	304±34.1	329±34.6	301±23.1
Body Weight Gain	1-8	19±6.6	21±8.6	25±10.5	17±5.3
	22-29	9±5.3	9±7.3	11±3.4	8±4.0
Females					
Body Weight	1	222±4.8	216±4.3	222±7.3	218±7.1
	8	225±7.1	223±8.0	223±10.3	218±9.9
	15	230±12.1	222±8.9	228±14.3	219±11.8
	22	235±10.3	225±10.5	234±16.7	222±14.2
	29	237±10.0	227±11.2	235±17.5	222±10.7* (↓6)
Body Weight Gain	1-8	3±3.4	7±6.3	1±6.2	0±4.6
	8-15	5±5.9	-1±3.2	5±9.6	1±5.4
	15-22	6±3.0	3±6.4	6±5.6	3±6.8
	22-29	2±4.3	3±3.9	1±3.5	1±6.5

a Data were obtained from the Study Report Annex. 9.12, pages 91-92 and 95-96, n=10. Numbers presented parenthetically represent percent difference from controls (calculated by reviewers).

* Significantly different from the control at $p \leq 0.05$

C. FOOD AND WATER CONSUMPTION - No treatment-related effects on mean food or water intake (g/animal/day) were observed at any dose in either sex.

D. OPHTHALMOSCOPIC EXAMINATION - No treatment-related ocular lesions were observed in any control or 1000 mg/kg/day animals.

E. BLOOD ANALYSES

1. Hematology - No treatment-related effects were observed in any hematological parameter in either sex. In the 100 mg/kg females, monocytes were decreased ($p \leq 0.05$) by 47% compared to controls; however, this finding was not dose-dependent.

2. Clinical chemistry - No treatment-related effects were observed in any clinical chemistry parameter in either sex. The minor differences ($p \leq 0.05$) noted in creatinine, calcium, chloride, and inorganic phosphate were not dose-dependent and/or were within the historical control ranges (historical data were provided in Table 7-13 on page 34 of the study report) for these parameters. Additionally, as there were no corroborative histopathological effects noted in the kidney, the slight decreases ($p \leq 0.05$) in creatinine noted in the 1000 mg/kg/day males (↓6%) and ≥300 mg/kg/day females (↓7-8%) were not considered to be toxicologically significant.

F. SACRIFICE AND PATHOLOGY

1. Organ weight - No compound-related effects on absolute or relative (to body) organ weights were observed at any dose in either sex. The increased absolute kidney weight (↑15%, $p \leq 0.05$) and decreased relative thymus weight (↓17, $p \leq 0.05$) noted in the 300 mg/kg males were not dose-dependent. The decreases ($p \leq 0.05$) in absolute brain (↓4%) and kidney (↓11%) weights, and increased ($p \leq 0.05$) relative adrenal weight (↑14%) noted in the 1000 mg/kg females were considered to be related to the decreased terminal body weight (↓5%, not statistically significant) in this group.

2. Gross pathology - No treatment-related gross lesions were observed in any animal in either sex.

3. Microscopic pathology - No treatment-related histopathological findings were observed in any animal in either sex. Any lesions noted occurred with similar frequency in the treated and control animals.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATOR'S CONCLUSIONS - The investigator concluded that under the conditions of this study, Thidiazuron did not induce any adverse treatment-related effects in rats dermally exposed for 6 hrs/day, 5 days/week for 4 weeks at up to 1000 mg/kg/day (limit dose).

B. REVIEWER COMMENTS - No compound-related effects were observed in mortality, clinical signs, dermal effects, body weight, body weight gain, food or water consumption, hematology, clinical chemistry, ophthalmology, absolute or relative organ weights, gross or histologic pathology.

The LOAEL was not observed. The NOAEL was 1000 mg/kg/day (HDT) (limit dose).

This study is classified as **acceptable/guideline** and satisfies the Guideline requirement (OPPTS 870.3200; OECD 410) for a 28-day dermal toxicity study in rats. A LOAEL was not observed; however, the compound was tested at the limit dose.

C. STUDY DEFICIENCIES - None

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rats (870.3200)

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	46261501	subchronic	rat	28 days	dermal	dermal	100-1000	0, 100, 300, 1000	1000	Not observed		Systemic
120301	46261501	subchronic	rat	28 days	dermal	dermal	100-1000	0, 100, 300, 1000	1000	Not observed		Dermal

C

EPA Reviewer: Robert P. Zendzian PhD
Toxicology Branch, Health Effects Division (7509C)
EPA Secondary Reviewer: Rebecca Daiss
RRB 4, Health Effects Division (7509C)

Signature: [signature]
Date 11/29/04
Signature: Becky Daiss
Date 11/29/04

TXR# 0052174

DATA EVALUATION RECORD

STUDY TYPE: Rat *In Vivo* Dermal Absorption - OPPTS 870.7600 [§85-2]; OECD none.

PC CODE: 120301 **DP BARCODE:** 294540 **SUBMISSION NO.:**

TEST MATERIAL (PURITY): Thidiazuron

SYNONYMS: none given

CITATION: Artus-Jacenko, L. (2004) Thidiazuron. *in vivo* Dermal Absorption Study in the Male Rat. Bayer Crop Science. SA 02427. 01 March 2004 MRID 46261502 Unpublished

SPONSOR: Bayer AG.

EXECUTIVE SUMMARY:

In a dermal penetration study (MRID 46261502) Thidiazuron (99.9 %a.i., batch # OR 1844 (SEL/1098), [phenyl-U-^{14}C]-thidiazuron) was administered to 5 male Sprague Dawley CD rats/dose to a 12 cm^2 area of the back in a formulation and water dilution thereof at dose levels of 5.0, 0.04 and 0.004 mg/cm^2. Exposure durations and percent of dose absorbed are presented in the table below.

Dose Level	Mean Percentage of Dose Absorbed						
	1 hour	4 hours	8 hours	24 hours	24 hours*	72 hours*	120 hours*
5.0 mg/cm^2	0.114	0.147	0.141	0.204	0.137	0.178	0.220
0.04 mg/cm^2	0.214	0.406	0.388	0.754	0.634	0.660	1.252
0.004 mg/cm^2	0.455	0.534	0.721	1.179	0.635	0.910	1.170

* washed at 8 hours

The mean total recoveries were in the range 88-88% and 99.54% dose for all groups. The amount in the stratum corneum was 0.73%, 10.68% and 8.14% at 24 hours for the high, middle and low

dose groups respectively after a 24-hours exposure and 0.41%, 3.24% and 5.37% at 120 hours following 8-hours exposure for the high, middle and low dose groups respectively. However, the results showed that the majority of the radioactive material in the stratum corneum was lost by desquamation and upward renewal of the stratum corneum with time.

This study in the rat is acceptable and satisfies the guideline requirement for a dermal penetration study (870.7600) in rats.

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

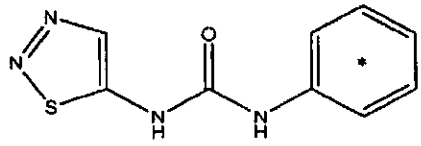
I. MATERIALS AND METHODS

A. MATERIALS:

1. Radiolabeled Material

Specific Activity:	50.87mCi/mmol (8.48MBq/mg)
Radiochemical Purity:	99.9%
Batch number:	OR 1844 (SEL/1098)
Source:	Scynexis, Fyfield business and research park, Ongar, Essex, United Kingdom.

Radiolabeling:



*: indicates the position of the uniformly radiolabelled phenyl ring.

2. Test Material Thidiazuron

Description: (e.g. technical, nature, color, stability)	
Lot/Batch #:	107623-03
Purity: (% a.i.)	99.6%
Compound Stability:	
CAS # for TGAI:	
Source:	Bayer Crop Science, PRoduktanalytik, Frankfurt, Germany

3. Formulation

Thidiazuron formulations were obtained from Bayer Crop Science, Centre de recherche, la Dargoire, Lyon (Appendix A). These formulations were identified as follows:
High dose level: 019JCZ02
Medium dose level-. 017JCZ02
Low dose level: 016JCZ02

These solutions were stored in darkness between +2 and +30'C.

4. Vehicle Solvent
tap water

5. Test animals:

Species:	Male Rat
Strain:	Sprague Dawley CD
Age/weight at study initiation:	weight range 243 - 332g
Source:	Charles River, France

B. STUDY DESIGN

1. Dose

The doses applied were: a high level formulated at the commercially available concentration (500 g/l nominal), a medium and a low dose level (4.00 g/l and 0.40 g/l corresponding to possible field use rates. The high dose level was nominally 464g Thidiazuron, equivalent to the commercially supplied concentrate. The actual mean concentration of the high dose formulation was 416.9g/l during the preliminary study and 465.6g/l for the main study. The intermediate dose level was nominally 4.00g/l, the actual mean concentration being 3.17g/l. the low dose level was nominally 0.4g/l and the actual mean concentration was 0.327g/l in the preliminary study and 0.295g/l in the main study.

2. Experimental Design

Details of treatment groups are given in the table below.
Two male rats are sacrificed at each time for the Preliminary Study and 5 male rats at each time for the Main Study.

	Groups	Number of male rats	Time of exposure (hours)	Time of sacrifice (hours)	Dose rate (mg/cm²)	Concentration (mg/kg)
Preliminary Study	A	8	8	8, 24, 72, 120	5.00	300
	B	8	8	8, 24, 72, 120	0.004	0.24
Main Study High Dose	C	5	1	1	5.00	300
	D	5	4	4	5.00	300
	E	20	8	8, 24, 72, 120	5.00	300
	F	5	24	24	5.00	300
Main Study Low Dose	G	5	1	1	0.004	0.24
	H	5	4	4	0.004	0.24
	I	20	8	8, 24, 72, 120	0.004	0.24
	J	5	24	24	0.004	0.24
Main Study Medium dose	K	5	1	1	0.04	2.40
	L	5	4	4	0.04	2.40
	M	20	8	8, 24, 72, 120	0.04	2.40
	N	5	24	24	0.04	2.40

Prior to the main experiment, a preliminary study was performed to obtain an indication of the proportion of the [phenyl-U-^{14} C]-Thidiazuron that could be absorbed, was absorbable and recovered from the skin surface following a topical application of the low dose formulation and high dose formulation. Following these preliminary results, the termination times for groups E, I, M were scheduled at 8, 24, 72 and 120 hours.

3. Method

Animal Preparation, Dose Application and Site Protection

An area of dorsal skin was shaved approximately 24 hours prior to dosing. Just prior to dosing the animals were lightly anesthetized using isoflurane and two plastic protective saddles were glued in place using cyanoacrylate glue to define two sites for application of the test substance (Total area = 12cm^2). Approximately 120ul of the dose formulations was applied to these sites, this amount of formulation corresponding to a radiochemical dosage between 777 and 978 kBq/animal for the high dose level, between 273 and 374kBq/animal for the low dose level and between 431 and 443 kBq/animal for the intermediate dose level.

When dose application was completed, the skin was semi-occluded with a perforated plastic cover (to allow ventilation) which was held in place over the plastic saddles with surgical tape. The cover was designed to prevent loss of test substance but permitted air circulation over the application site. The cover was not in direct contact with the test material on the skin.

Immediately after dose application the rats were housed individually in metabolism cages

5. Sample Collection

a. Preliminary study

After each exposure, all animals were swabbed using small pieces of natural sponge which were used to carefully clean the site of application of the non-absorbed dose.

The times of sacrifice were 8h, 24h, 72h and 120h after the beginning of application. At each time of collection two male rats were sacrifice The following samples were collected at 24h time intervals: urine, faeces and cage wash. The other samples were collected after the sacrifice: treated skin (site of application), skin surrounding the application site (1 cm wide to investigate possible leaching), -untreated clipped skin, dressing (saddle, cover and tape), stripping samples, carcass and cardiac blood.

b. Main study

The samples of the main study were the same as the preliminary study, except for the treated skin, which was divided into two sites: **a,** corresponding to treated skin following tapestripping procedure and **b,** corresponding to treated skin without tape-stripping procedure.
The swabs were used to clean the site of application at the end of application and before skin removal.

c. Sampling procedure and observations

All animals were examined at least once daily for mortality and signs of ill health and reaction to treatment throughout the study period. The observations were noted in the appropriate animal room log-book and the study raw data file.

After each end of time exposure, the cover was removed. The cover and application site were swabbed with freshly prepared 1% w/v Tween 80 in PBS (phosphate buffered saline) using small pieces of natural sponge, in order to remove and retain non-absorbed dose. The site was swabbed up to 10 times (until no more radioactivity is detected in the swabs with a Geiger monitor). The swabs were retained for analysis.

The clean covers were replaced back over the protective saddle until the end of the observation period.

Urine and faeces were collected separately into receivers surrounding with dry ice. At the end of each collection period all debris were removed from the metabolism cages and retained. At each sampling, the cages were carefully washed with distilled water. At the termination of the experiment the cages were washed with water and appropriate organic solvent. These washings were retained for measurement of radioactivity

d. Termination

At termination, rats were exsanguinated while under isoflurane anaesthesia and a blood sample was withdrawn by cardiac puncture and placed into vials containing lithium heparin. Following the sacrifice, the skin was swabbed prior to removal. Then the skin was shaved, if necessary, prior to tape-stripping the surface to remove the stratum corneum. The tapestripping was continued until a 'shiny' appearance of the viable epidermis was evident, indicating that the stratum corneum was removed.

The treated area of skin was removed and taken for analysis. Further skin samples were also taken for analysis. An area of untreated skin, clearly separate from the application site was retained for analysis.

The residual carcass was also retained for analysis.

c. List the Samples Analyzed

II. RESULTS

A. SIGNS OF TOXICITY

No signs of toxicity were reported

B. SUMMARY TABLES

Summary tables from the report are presented below under the section on **INVESTIGATORS CONCLUSIONS.**

C. TOTAL ABSORBED DOSE

The total absorbed dose was calculated as the sum of urine, feces, cage wash, cardiac blood and carcass.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS:

The extent of the dermal absorption of [phenyl-U-^{14}C]-Thidiazuron was investigated following a single topical application to male Sprague Dawley CD rats. The doses applied were: a high level formulated at the commercially available concentration (500 g/l nominal), a medium and a low dose level (4.00 g/l and 0.40 g/l corresponding to possible field use rates.

A preliminary study was conducted at two dose levels (high and low) on four groups of two rats, with an exposure time of 8 hours and sacrifice at 8, 24, 72 and 120 hours post application. The objectives of this first study were to obtain an indication of the Radiolabeled material distribution on and through skin and to determine the sacrifice time for the definitive study.

The objectives of the preliminary study were achieved and the sacrifice times for the main study were set, at 8, 24, 72 and 120 hours for the protocol corresponding to the OECD guidelines with the swabbing procedure to be performed at the end of an 8-hour exposition and repeated at termination,

A second protocol was performed, which corresponded to the US-EPA guidelines. Male rats were exposed for a period of 1 to 24 hours and were sacrificed immediately thereafter. The samples analyzed were the same as for OECD protocol, except the swabbing procedure which was carried out only at termination.

The main study consisted of three phases, following the three formulations, within which there were seven groups of five rats, corresponding to US-EPA and OECD guidelines.

The mean total recoveries were in the range 88-88% and 99.54% dose for all groups. The distribution of radioactivity observed for both protocols is presented in the following two Tables (expressed as mean percentages of the applied dose) that may be found *on* the next page.

The amount of chemical washed off or associated with the skin surface following exposure for 24 hours was 88.77%, 73.27% and 73.97% for the high, middle and low dose respectively. The amount of chemical washed off or associated with the skin surface following exposure for 8 hours was 89.82%, 83.38% and 80.29% at 120 hours for the high, middle and low dose respectively.

The amount in the stratum corneum was 0.73%, 10.68% and 8.14% at 24 hours for the high, middle and low dose groups respectively after a 24-hours exposure and 0.41%, 3.24% and 5.37% at 120 hours following 8-hours exposure for the high, middle and low dose groups respectively. However, the results showed that the majority of the radioactive material in the stratum corneum was lost by desquamation and upward renewal of the stratum corneum with time. Therefore, these radioactivity amounts were considered as non-absorbed.

The amount remaining within the skin at the treated site was 0.29%, 3.88% and 5,59% at 24 hours for high, middle and low dose after a 24-hours exposure and 0. 1 9%, 0.73% and 1.53% at 120 hours following an 8-hours exposure for high, middle and low dose respectively.

The amount in systemic compartment (excreta & tissues) corresponding to the total amount of test chemical directly absorbed was similar after a 24-hour exposure or a 8-hour exposure and termination at 120 hours post-application (0.20% and 0.22% for high dose, 0.75% and 1.25% for middle dose, 1. 1 8% and 1. 1 7% for low dose).

US-EPA protocol	High dose				Mid dose				Low dose			
Group/Exposure time	**C/1h**	**D/4h**	**E/8h**	**F/24h**	**K/1h**	**L/4h**	**M/8h**	**N/24h**	**G/1h**	**H/4h**	**I/8h**	**J/24h**
Dressing	0.515	0.820	0.492	0.834	1.785	0.687	1.278	1.053	0.802	0.753	0.620	0.898
Fur	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Dose site swabs	91.422	85.674	88.647	87.638	75.260	74.269	73.760	69.702	78.324	74.570	77.729	71.241
Surface dose**	0.242	0.163	0.193	0.302	2.133	2.592	2.388	2.516	1.123	1.429	2.506	1.832
Total non absorbed	**92.179**	**86.658**	**89.332**	**88.773**	**79.178**	**77.547**	**77.425**	**73.271**	**80.249**	**76.752**	**80.854**	**73.971**
Surrounding skin	0.815	1.691	1.014	0.949	1.601	1.324	1.261	1.308	1.027	1.340	0.896	1.102
Non-treated skin	0.113	0.159	0.142	0.121	0.262	0.422	0.490	0.268	0.257	0.222	0.263	0.220
Non treated skin surface	**0.929**	**1.850**	**1.156**	**1.069**	**1.863**	**1.746**	**1.751**	**1.576**	**1.283**	**1.562**	**1.159**	**1.322**
Treated skin**	0.401	0.305	0.467	0.296	3.185	1.867	5.024	3.876	3.692	3.960	2.009	5.590
Stratum corneum*	1.159	0.876	0.851	0.731	8.987	10.443	14.130	10.676	10.707	10.488	10.115	8.141
Dose site	**1.560**	**1.181**	**1.318**	**1.026**	**12.171**	**12.310**	**19.153**	**14.552**	**14.400**	**14.447**	**12.124**	**13.731**
Urine	N.A.	0.002	0.004	0.009	0.0004	0.003	0.014	0.106	0.003	0.040	0.151	0.364
Faeces	N.A.	N.A.	N.A.	0.002	N.A.	N.A.	N.A.	0.081	N.A.	N.A.	N.A.	0.203
Cage Wash	N.A.	0.004	N.A.	N.A.	N.A.	N.A.	0.004	0.039	0.013	0.014	0.012	0.066
Cardiac blood	0.0004	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	0.001	N.A.	N.A.	N.A.	N.A.
Carcass	0.114	0.141	0.137	0.193	0.213	0.402	0.370	0.526	0.440	0.479	0.558	0.546
Direct Absorption†	**0.114**	**0.147**	**0.141**	**0.204**	**0.214**	**0.406**	**0.388**	**0.754**	**0.455**	**0.534**	**0.721**	**1.179**

OECD protocol	High dose				Mid dose				Low dose			
	E8	**E24**	**E72**	**E120**	**M8**	**M24**	**M72**	**M120**	**I8**	**I24**	**I72**	**I120**
Dressing	0.492	0.698	1.449	1.603	1.278	1.117	0.619	3.336	0.620	2.470	0.568	1.706
Fur	N.A.	0.134	0.150	0.308	N.A.	N.A.	N.A.	N.A.	N.A	0.511	N.A	0.251
Swabs at 8 hours	88.647	88.050	85.882	87.320	73.760	76.817	68.857	74.352	77.729	81.507	68.977	73.621
Swabs at termination	N.A.	0.656	0.868	0.417	N.A.	9.611	11.383	4.790	N.A.	5.273	9.617	3.218
Surface dose**	0.193	0.082	0.170	0.168	2.388	0.835	0.854	0.905	2.506	0.906	1.534	1.493
Total non absorbed	**89.332**	**89.534**	**88.519**	**89.816**	**77.425**	**88.380**	**81.714**	**83.383**	**80.854**	**90.462**	**80.696**	**80.289**
Surrounding skin	1.014	0.755	1.511	1.076	1.261	1.006	0.763	1.519	0.896	1.362	1.154	1.824
Non-treated skin	0.142	0.095	0.113	0.092	0.490	0.261	0.144	0.391	0.263	0.343	0.122	0.428
Non treated skin surface	**1.156**	**0.850**	**1.625**	**1.167**	**1.751**	**1.267**	**0.907**	**1.910**	**1.159**	**1.705**	**1.276**	**2.252**
Treated skin*	0.467	0.154	0.188	0.186	5.024	2.142	1.018	0.727	2.009	1.324	4.073	1.534
Stratum corneum*	0.851	0.332	0.434	0.408	14.130	6.978	3.366	3.239	10.115	6.290	5.676	5.369
Dose site	**1.318**	**0.486**	**0.623**	**0.595**	**19.153**	**9.119**	**4.385**	**3.966**	**12.124**	**7.614**	**9.749**	**6.902**
Urine	0.004	0.009	0.015	0.039	0.014	0.128	0.231	0.336	0.151	0.132	0.284	0.389
Faeces	N.A.	N.A.	0.002	0.007	N.A.	0.063	0.127	0.281	N.A.	0.073	0.160	0.236
Cage Wash	N.A.	0.001	0.002	0.006	0.004	0.027	0.027	0.200	0.012	0.026	0.075	0.063
Cardiac blood	N.A.	N.A.	N.A.	0.0002	N.A.	N.A.	N.A.	0.0004	N.A.	N.A.	N.A.	N.A.
Carcass	0.137	0.124	0.159	0.167	0.370	0.416	0.274	0.435	0.558	0.403	0.391	0.482
Direct Absorption†	**0.141**	**0.134**	**0.178**	**0.220**	**0.388**	**0.634**	**0.660**	**1.252**	**0.721**	**0.635**	**0.910**	**1.170**

* Recalculated for 12 cm²

** Tape-strips 1 and 2 which represents residual surface amount

B. REVIEWER COMMENTS:

No problems or deficiencies were observed in this study

In general this reviewer agrees with the investigators' conclusions.

1) Recovery of the applied dose (mass balance) was acceptable

2) The majority of the administered dose was recovered from the application site wash .

3) 1-20 % of the applied dose was retained at the application site with the percentage increasing with decreasing dose.

4) Estimates of dermal absorption were based on the sum of urine (including cage wash and rinse) + feces + carcass + blood.

5) Absorption pattern.

Percent absorbed increases with increasing duration of exposure but decreases with dose (indicative of saturation of absorption).

Skin fate following washing. The percent of dose in the washed skin, following an 8 hour wash, decreases with time up to 112 hours after washing.

D

DATA EVALUATION RECORD

AE B049537 (THIDIAZURON)

Study Type: §83-4; Multigeneration Reproduction Study in Rats

Work Assignment No. 2-01-40; formerly 1-01-40 (MRID 46209601)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road
Building 100, Suite B
Durham, NC 27713

Primary Reviewer:
Michael E. Viana, Ph.D.

Signature: Michael E. Viana
Date: 9/24/04

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W. Allran
Date: 9/24/04

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L. Menetrez
Date: 9/24/04

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 9/24/04

Disclaimer

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

EPA Reviewer: Paul Chin **Signature:** Paul Chin
Reregistration Branch 1, Health Effects Division (7509C) **Date** 10/7/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 10/22/04
EPA Work Assignment Manager: P. V. Shah, Ph.D. **Signature:** Shaz Dawman
Registration Action Branch 1, Health Effects Division (7509C) **Date** 12/16/04
Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study - [rat] OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 120301 **DP BARCODES:** D300853
TXR#: 0052174 **SUBMISSION NO.:** None

TEST MATERIAL (PURITY): AE B049537 (Thidiazuron; 99.5% a.i.)

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

CITATION: Myers, D.. (2003) AE B049537 (Thidiazuron): study of reproductive performance in Han Wistar rats treated continuously through two successive generations by dietary administration. Huntingdon Life Sciences, Ltd., Alconbury, Huntingdon, Cambridgeshire, England. Laboratory Project ID.: AES 089/024162, July 18, 2003. MRID 46209601. Unpublished.

SPONSOR: Bayer AG, Bayer Crop Science, 40789 Alfred Nobel Street, Monheim, Germany.

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 46209601), Thidiazuron (99.5% a.i.; Batch 107623-03) was administered continuously in the diet to Han Wistar (HsdBrl Han:Wist) rats (28 animals/sex/dose) at dose levels of 0, 100, 400, or 1200 ppm (equivalent to 0/0, 8.8/9.9, 35.4/39.8, and 108.5/121.1 mg/kg/day [M/F]). The P and F_1 parents were dosed for 10 weeks before they were mated to produce the F_1 and F_2 litters. The F_1 pups were weaned on postnatal day (PND) 21, and 24 pups/sex/group (1 pup/sex/litter as nearly as possible) were randomly selected as parents of the F_2 generation.

In the parental animals, no treatment-related effects were observed on survival, clinical signs, body weight, or food consumption or efficiency.

At 1200 ppm, body weight gains were decreased in the P males (statistics not performed) during pre-mating (Weeks 0-10) by 10%, and overall (Weeks 0-17) by 10% ($p \leq 0.05$). In the P females at this dose, body weight gains were decreased ($p \leq 0.01$) during pre-mating by 16%. Body weight gains continued to be decreased ($p \leq 0.05$) by 10% throughout gestation (GD 0-20). In the

F_1 females at this dose, an increased ($p \leq 0.01$) incidence of five day irregular estrous cycles or acyclicity was observed. However, since no effects were noted on fertility or reproductive performance, this finding was considered equivocal.

No treatment-related findings were noted at 100 or 400 ppm.

The LOAEL for parental toxicity is 1200 ppm (equivalent to 108.5/121.1 mg/kg/day [M/F]), based on decreased body weight gains in both sexes. The NOAEL is 400 ppm (equivalent to 35.4/39.8 mg/kg/day [M/F]).

In the offspring, no treatment-related effects were observed on post-implantation survival, live birth, viability, or lactation indices, on the sex ratio, clinical signs, sexual maturation, organ weights, or gross pathology.

At 1200 ppm, body weight gains were decreased (↓7-10%; $p \leq 0.05$) in the F_1 pups during PND 1-21 and during PND 1-28, and in the F_2 pups during PND 1-28 in the males, and during PND 1-21 and PND 1-28 in the females.

No effects of treatment were observed at 100 or 400 ppm.

The LOAEL for offspring toxicity is 1200 ppm (equivalent to 108.5/121.1 mg/kg/day [M/F]), based on decreased body weight gains in both sexes. The NOAEL is 400 ppm (equivalent to 35.4/39.8 mg/kg/day [M/F]).

In the parental animals, no treatment-related effects were observed on sperm measures, ovarian follicles, corpora lutea, pre-coital interval, duration of gestation, or on mating, fertility, gestation, or parturition indices.

The LOAEL for reproductive performance was not observed. The NOAEL for reproductive performance is 1200 ppm (equivalent to 108.5/121.1 mg/kg/day [M/F]).

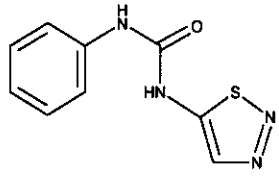
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: AE B049537 (Thidiazuron)

Description:	Yellow/brown powder
Batch #:	107623-03
Purity:	99.5% a.i.
Compound Stability:	Stable in the diet for at least 15 days at room temperature
CAS # of TGAI:	51707-55-2
Structure:	

2. Vehicle: Diet

3. Test animals

Species:	Rat
Strain:	Han Wistar (HsdBrl Han:Wist)
Age at study initiation:	Approximately 6 weeks old
Weight range on Study Day 1:	129-240 g males; 100-158 g females
Source:	Harlan (UK) Ltd., Blackthorn, Bicester, Oxfordshire, England
Housing:	Males and females during acclimation and pre-mating, males post-mating, females post-weaning, and offspring post-weaning, up to 4/sex/cage in TR18 stainless steel cages with grid floors; during mating, 1 male and 1 female in RB3 modified high density polypropylene cages with stainless steel grid floors. Individual females and their litters were housed in RB3 polypropylene cages with solid floors from gestation day 17 through lactation day 14-18, and in TR18 stainless steel cages with grid floors from lactation day 14 to weaning.
Diet:	UAR VFR1 Certified powdered diet (Usine D'Alimentation Rationnelle, France), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature** 19-23°C **Humidity** 40-70% **Air changes** Not reported (air filtered and not recirculated) **Light cycle** 12 hrs light/12 hrs dark
Acclimation period:	Approximately 8 days

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Males and females from the same treatment group were paired on a one-to-one basis for up to three weeks. If no positive indication of mating was found after 14 days, the male was replaced with a proven male from the same dose group. Sibling matings were

avoided. Each morning following pairing, females were examined for the presence of vaginal plugs and vaginal smears were examined for the presence of sperm (positive mating) and estrous cycle stage. The day on which positive mating was observed was designated as gestation day (GD) 0. Mated females were removed from the mating cage and housed individually. If mating was inconclusive, vaginal smears were continued for up to five days to confirm positive mating.

2. Study schedule: Rats were exposed to the test substance continuously in the diet throughout the study. The P animals were dosed for 10 weeks prior to mating; thus, the P animals were approximately 16 weeks old at mating. The F_1 pups were weaned on postnatal day (PND) 21, and 24 pups/sex/group (1 pup/sex/litter, as nearly as possible) were randomly selected from as many different litters as were available to be parents of the F_2 generation. When necessary, additional animals were selected on a random basis, with a maximum of two pups of one sex and one pup of the opposite sex per litter. The F_1 parents had access to the same diet as the P parents throughout lactation; however, dosing of the F_1 generation was considered to formally start at Week 4. F_1 parents were then dosed for 10 weeks before they were mated; therefore, the F_1 parents were approximately 14 weeks old when mated. The F_1 pups not selected to be parents of the F_2 generation were killed.

3. Animal assignment: On receipt, rats were identified by litters and caged at a maximum of 4 litter mates/sex/cage. Prior to treatment, all animals were weighed and the four litters/sex with the greatest within-litter variation of body weights were discarded. One rat from each cage was then assigned to the test groups shown in Table 1. No test group contained more than one male or female from the same litter.

TABLE 1. Animal assignment[a]

Test Group	Dose[b] (ppm)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	28	28	24	24
Low	100	28	28	24	24
Mid	400	28	28	24	24
High	1200	28	28	24	24

a Data were obtained from page 20 of the study report.
b Exposure to the test substance was continuous throughout the study.

4. Dose-selection rationale: It was stated that the dose levels summarized in Table 1 were chosen in collaboration with the Sponsor, based on the results of a previous reproductive toxicity study conducted by the performing laboratory (Report No. AES081/022079, not provided). In this study, rats treated with 2000 ppm demonstrated decreased growth rates and reduced relative (to body) reproductive organ weights. Therefore, a dose of 1200 ppm was selected and was expected to cause decreased growth rates in the parental animals. No other information was provided.

5. Dosage preparation and analysis: It was stated that test diets were prepared at various intervals during the study up to 2 weeks in advance of the last day of feeding. A premix was prepared by combining approximately equal quantities of diet and test substance. Final dietary formulations were prepared by direct dilution of the premix with appropriate amounts of feed. It was also stated that in a previous reproductive toxicity study (Report No. AES081/022079), homogeneity and stability were verified in 50 and 3000 ppm dietary formulations, and the test substance was found to be stable in the diet for up to 15 days at room temperature. However, these data were unavailable for review. In the present study, concentration analyses were performed on samples of each dose level prepared for use on Weeks 1, 11, 18, 28, and 38.

Results

Concentration (range of % nominal)

100 ppm = 92.5-103.0%
400 ppm = 92.7-100.8%
1200 ppm = 96.7-100.8%

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

6. Dosage administration: All doses were administered continuously in the diet throughout the study.

C. OBSERVATIONS

1. Parental animals: All animals were observed at least twice daily for mortality, morbidity, and clinical signs of toxicity. Detailed physical examinations were performed weekly. The time elapsing between initial pairing and positive signs of mating (pre-coital interval) was recorded. Beginning on GD 20, females were inspected three times daily for evidence of onset, progress, and completion of parturition. Body weights were measured prior to study initiation, at the beginning of treatment, and then weekly until termination for the P males. P females were weighed weekly until mating was detected; on GD 0, 6, 13, and 20; and on lactation days (LD) 1, 4, 7, 14, 21, and 28. F_1 males were weighed at the formal start of the generation, twice weekly for the first three weeks, and then weekly thereafter. F_1 females were weighed on the same schedule as the F_1 males until mating was detected, and then were weighed on the same schedule as the P females. Food consumption (g/rat/week) was recorded weekly for males and females until mating. Food consumption for females after mating was recorded on an individual basis on GD 0-5, 6-12, and 13-19, and on LD 1-3, 4-6, and 7-13. Estrous cycle staging (determined by examining daily vaginal smears) was determined for all P and F_1 females from 22 days prior to pairing until evidence of positive mating was observed, and on Days 25-28 following parturition. The duration and regularity of cycle stages were evaluated, based on vaginal cytology. Sperm enumeration, motility, and morphology were evaluated in all males at termination.

2. Litter observations: The following litter parameters (X) were observed (Table 2).

TABLE 2. F_1/F_2 litter observations[a]

Observation	Postnatal Day							
	Day 1	Day 4[b]	Day 4[c]	Day 7	Day 14	Day 21	Day 25	Day 28
Number of live pups	X	X	X	X	X	X	X	X
Number of dead pups	X	X	X	X	X	X	X	X
Pup weight	X	X	X	X	X	X	X	X
External alterations	X							
Clinical signs	X	X	X	X	X	X	X	X
Sex of each pup (M/F)	X	X	X	X	X	X	X	X

a Data were obtained from page 23-24 and 84 of the study report.
b Before standardization (culling)
c After standardization (culling)

On PND 4, litters of 9 or more pups were standardized by random selection to a maximum of 8 pups/litter (4 pups/sex/litter, as nearly as possible). On PND 1, anogenital distance was measured and recorded for all F_1 control pups (not presented in this study report) and for all F_2 pups. Balano-preputial separation was evaluated in the males daily beginning on PND 32; vaginal patency was evaluated in the females daily beginning on PND 28. Body weights were recorded when criterion was reached.

3. Postmortem observations

1) Parental animals: All adults, including those killed for humane reasons, were killed by CO_2 asphyxiation and were subjected to a complete macroscopic examination. The number of implantation sites per uterus was recorded. Males were killed once the majority of litters had weaned. Females were killed on Day 28 after parturition. Estrous cycle stages were determined in all adult females at termination. The following tissues were collected for histological examination (X) and fixed in 10% neutral buffered formalin (except for the testes and epididymides, which was fixed in Bouin's fixative). Additionally, the (XX) tissues were weighed.

XX	Adrenals	XX	Pituitary	XX	Thyroids[b]
XX	Brain	XX	Prostate (ventral lobe)	XX	Parathyroids[b]
XX	Epididymides	XX	Seminal vesicle[a]	XX	Uterus[c]
XX	Kidney	XX	Coagulating gland[a]	XX	Cervix[c]
XX	Liver	XX	Spleen	XX	Oviduct[c]
X	Mammary gland	XX	Testes	X	Vagina
XX	Ovaries	XX	Thymus	X	Gross lesions and masses

a Seminal vesicles were weighed with coagulating glands
b Thyroid and parathyroids were weighed together
c Uterus was weighed with cervix and oviducts

Microscopic examination was performed on the epididymides, ovaries, pituitary gland, prostate (ventral lobe), seminal vesicles, coagulating gland, testes, uterus, cervix, oviducts, and vagina from the control and 1200 ppm groups killed at scheduled termination, and in all animals killed or dying prematurely. Abnormalities were examined in all animals. Ovaries of the females in all treatment groups were qualitatively examined for the presence of primordial follicles, growing follicles, and corpora lutea. Additionally, quantitative evaluation of ovarian follicles was performed on the ovaries of all control and 1200 ppm F_1 females and any F_1 females that failed to mate or conceive, or suffered a total litter loss.

2) Offspring: F_1 pups not selected to become parents of the F_2 generation, and all F_2 pups were killed on PND 30 by CO_2 asphyxiation. Culled pups and any pups killed *in extremis* prior to PND 14 were killed by an intraperitoneal injection of pentobarbitone sodium. A complete macroscopic examination was performed on all dead pups whenever possible; culled pups were discarded without necropsy. Unselected F_1 pups and all F_2 pups were examined macroscopically, and for one/pup/sex/litter, the brain, epididymides, ovaries, prostate (ventral lobe), seminal vesicles, coagulating gland, spleen, testes, uterus, cervix, oviduct, and vagina were weighed. Microscopic examinations were not performed.

D. DATA ANALYSIS

1. Statistical analyses: For data from the parental animals, homogeneity of variance was assessed using Bartlett's test. Whenever this was statistically significant (level not given), a Behrens-Fisher test was used to perform pairwise comparisons; otherwise, a Dunnett's test was used.

For body weights and body weight gains during gestation and lactation, pup body weights and body weight gains, food consumption during pre-mating, gestation and lactation, age of vaginal opening, seminology data, and pup organ weights, the following sequence of statistical tests was used:

- If Bartlett's test for variance homogeneity was not significant at the 1% level, then parametric analysis was applied. If the F1 test for monotonicity of dose-response was not significant at the 1% level, Williams' test for a monotonic trend was applied. If the F1 test was significant, suggesting that the dose-response was not monotone, Dunnett's test was

performed instead.

- If Bartlett's test was significant at the 1% level, then logarithmic and square-root transformations were tried. If Bartlett's test was still significant, then non-parametric tests were applied. If the H1 test for monotonicity of dose-response was not significant at the 1% level, Shirley's test for a monotonic trend was applied.

The estrous cycle data for F1 females were analyzed using an exact one-tailed Linear-by-linear test, with step down, using scores appropriate to the severity of the observation (assuming a 4-day cycle to be normal).

Significant differences between control and treated groups were expressed at $p \leq 0.05$ and $p \leq 0.01$.

2. Indices

Reproductive indices: The following reproductive/viability indices were calculated by the performing laboratory from breeding and parturition records of animals in the study:

Mating (%) = # animals mated/# animals paired x 100

Conception rate (%) = # animals pregnant or siring a pregnancy/# animals mated x 100

Fertility index (%) = # animals pregnant or siring a pregnancy/# animals paired x 100

Gestation index (%) = # live litters born/# females pregnant x 100

Offspring viability indices: The following viability indices were calculated by the performing laboratory from lactation records of litters in the study:

Post-implantation survival index (%) = total # offspring born/total # uterine implantation sites x 100

Live birth (%) = total # live offspring on PND 1/total # offspring born x 100

Viability (%) = # live offspring on PND 4 (pre-culling)/# live offspring on PND 1 x 100

Lactation (%) = # live offspring on day of examination/# of live offspring on PND 4 (post culling) x 100

3. Historical control data: Historical control data were not provided.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: There were no unscheduled deaths in the P or F_1 females. One 400 ppm P male (#1057) was killed *in extremis* during Week 4, after presenting with thin build, piloerection, hunched posture, and slow respiration. One F_1 control male (#2018) was killed for humane reasons during Week 12 of the F_1 generation, after presenting with an ulceration on the palate, maloccluded teeth, and brown staining around the right eye. Both of these deaths were considered incidental, as dose-dependency was not observed. No treatment-related clinical signs of toxicity were observed in either generation.

2. Body weight and food consumption: Body weight and food consumption data are presented in Tables 3a, b, c, and d. In the 1200 ppm P males, body weight gains were decreased (statistics not performed; calculated by reviewers) during pre-mating (Weeks 0-10) by 10%, and overall (Weeks 0-17) by 10% ($p \leq 0.05$). In the 1200 ppm P females, body weight gains were decreased ($p \leq 0.01$) during pre-mating by 16%. Body weight gains continued to be decreased ($p \leq 0.05$) by 10% throughout gestation (GD 0-20). Body weights and body weight gains were unaffected by treatment in the P females during lactation. No effects of treatment were noted on body weights or body weight gains in the F_1 females during pre-mating, gestation, or lactation.

There was no treatment-related effect on food consumption in the P or F_1 generation. Food consumption was decreased ($p \leq 0.05$) in the 1200 ppm P females during LD 7-13 (↓9%), but this minor finding was considered incidental. No treatment-related effect was observed on food efficiency in either generation.

TABLE 3a. Selected mean (±SD) body weights, body weight gains, and cumulative food consumption (g) - P and F_1 generation males[a]

Observation/study day		Dose Group (ppm)			
		0	100	400	1200
P Generation (n=27-28)					
Body weight	Week 0	170±19.8	174±23.7	176±25.1	174±21.8
Body weight	Week 5	311±36.7	323.±39.7	319±38.7	298±26.5
Body weight	Week 10	381±47.8	395±47.0	391±43.7	363±33.0
Body weight	Week 17	429±49.3	436±49.9	439±49.2	408±33.6 (↓5)
Body weight gain	Week 0-10[b]	211	221	215	189 (↓10)
Body weight gain	Week 0-17	260±44.1	263±36.0	263±33.7	234±25.3* (↓10)
Food consumption	Week 1-10	1558	1610	1617	1541
F_1 Generation (n=23-24)					
Body weight	Week 0	80±9.7	80±8.6	79±9.0	72±8.7 (↓10)
Body weight	Week 5	293±28.2	289±23.2	294±19.8	272±16.4
Body weight	Week 10	385±35.1	385±32.8	392±30.6	365±25.6
Body weight	Week 19	453±43.7	444±37.4	457±41.6	421±29.2 (↓7)
Body weight gain	Week 0-10[b]	305	305	313	293
Body weight gain	Week 0-19[b]	373	364	378	349
Food consumption	Week 1-14	1643	1630	1652	1586

a Data were obtained from pages 60-64, 71, 110-115 and 122 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

b Calculated by reviewers from data presented in this table

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

TABLE 3b. Selected mean (±SD) body weights, body weight gains, and cumulative food consumption (g) - P and F_1 generation pre-mating females[a]

Observation/study day		Dose Group (ppm)			
		0	100	400	1200
P Generation (n=28)					
Body weight	Week 0	132±14.4	131±11.6	131±16.4	131±13.8
Body weight	Week 10	236±19.2	235±23.3	235±22.0	219±16.7
Body weight gain	Week 0-10	104±11.7	104±18.3	104±10.8	87±10.3** (↓16)
Food consumption	Week 1-10	1197	1206	1212	1142
F_1 Generation (n=24)					
Body weight	Week 0	73±9.6	74±8.6	73±7.7	68±9.1
Body weight	Week 10	238±19.7	236±21.1	239±24.1	226±14.2
Body weight gain	Week 0-10	164±14.6	163±19.6	166±24.8	158±13.9
Food consumption	Week 1-10	1311	1270	1281	1244

a Data were obtained from pages 65-68, 72, 116-119, and 123 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

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

TABLE 3c. Mean (±SD) body weights, body weight gains (g), and food consumption (g/rat/day) - P and F_1 generation females during gestation[a]

Observation/gestation day		Dose Group (ppm)			
		0	100	400	1200
P Generation (n=26-28)					
Body weight	GD 0	236±20	236±23	233±22	217±18
Body weight	GD 6	257±21	255±25	254±24	235±19
Body weight	GD 13	282±22	281±26	280±26	256±22
Body weight	GD 20	342±24	343±33	342±35	313±27
Body weight gain	GD 0-20	106±12	107±17	109±20	95±15* (↓10)
Food consumption	GD 0-5	22±2	24±3	24±5	21±2
Food consumption	GD 6-12	26±2	26±3	28±4	25±3
Food consumption	GD 13-19	26±2	26±3	28±3	25±6
F_1 Generation (n=22-24)					
Body weight	GD 0	236±17	235±21	238±24	225±13
Body weight	GD 6	252±17	250±23	253±24	240±15
Body weight	GD 13	274±17	271±25	277±26	260±16
Body weight	GD 20	331±21	333±32	335±31	316±24
Body weight gain	GD 0-20	95±17	98±19	97±15	91±17
Food consumption	GD 0-5	23±3	23±3	22±2	21±3
Food consumption	GD 6-12	26±3	25±3	25±2	24±3
Food consumption	GD 13-19	26±3	27±3	26±4	27±3

a Data were obtained from pages 69-70, 73, 120-121, and 124 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

* Significantly different from controls; p≤0.05

TABLE 3d. Mean (±SD) body weights, body weight gains (g), and food consumption (g/rat/day) - P and F_1 generation females during lactation[a]

Observation/lactation day		Dose Group (ppm)			
		0	100	400	1200
P Generation (n=26-28)					
Body weight	LD 1	267±22	264±28	264±27	242±20
Body weight	LD 4	276±21	269±27	269±26	250±20
Body weight	LD 7	281±23	277±29	274±25	254±18
Body weight	LD 14	298±23	293±26	289±25	266±20
Body weight	LD 21	295±20	292±23	291±25	272±20
Body weight gain	LD 1-21	28±11	28±10	27±11	30±12
Food consumption	LD 1-3	39±9	39±9	39±7	36±7
Food consumption	LD 4-6	45±8	46±11	46±8	41±7
Food consumption	LD 7-13	57±6	57±7	57±7	52±8* (↓9)
F_1 Generation (n=22-24)					
Body weight	LD 1	261±21	260±25	264±29	251±17
Body weight	LD 4	272±21	270±23	272±26	261±16
Body weight	LD 7	277±21	272±23	278±26	266±18
Body weight	LD 14	295±18	291±26	297±24	278±18
Body weight	LD 21	293±19	291±21	292±19	281±21
Body weight gain	LD 1-21	32±11	31±9	28±18	30±10
Food consumption	LD 1-3	35±6	34±8	34±8	35±11
Food consumption	LD 4-6	41±11	37±9	40±6	37±8
Food consumption	LD 7-13	50±10	53±7	52±7	49±13

a Data were obtained from pages 69-70, 73, 120-121, and 124 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

* Significantly different from controls; p≤0.05

3. **Test substance intake:** The mean achieved doses of the P and F_1 generations during pre-mating, based on food consumption, body weight, and nominal dietary concentration, are presented in Table 4. These values are considered to be representative of the test substance intake for the entire study.

TABLE 4. Mean test substance intake during premating (mg/kg body weight/day)[a]

Generation	Males			Females		
	100 ppm	400 ppm	1200 ppm	100 ppm	400 ppm	1200 ppm
P	7.7	31.2	94.3	9.0	36.1	108.3
F_1	9.9	39.5	122.6	10.8	43.4	133.9
Study mean[b]	8.8	35.4	108.5	9.9	39.8	121.1

a Data were obtained from pages 75 and 126 in the study report.

b Study mean was calculated by the reviewers as the average of the test substance intake for the P and F_1 generations.

4. Reproductive function

a. Estrous cycle length and periodicity: In the 1200 ppm F_1 females, an increased ($p \leq 0.01$) incidence of five day irregular estrous cycles (13% treated vs 4% controls) or acyclicity (8% treated vs 0% controls) was observed. No effects of treatment were observed on estrous cycle length or periodicity in the P females.

b. Sperm measures: No treatment-related effects were noted on sperm enumeration, motility, or morphology in the P or F_1 males. In the 1200 ppm P males, the sperm count per gram of tissue in the cauda epididymides was increased (↑14%; $p \leq 0.05$); however, the sperm count per gram of tissue in the testis and the total sperm count in the epididymis (not corrected per weight) were comparable to controls. Therefore, this finding was considered incidental.

c. Ovarian follicle and corpora lutea count: No effects of treatment were observed on the number of growing or primordial follicles, or on the number of corpora lutea in the F_1 females.

5. Reproductive performance: There were no effects of treatment on the precoital or gestation intervals or on mating, fertility, gestation, or parturition indices (Table 5).

TABLE 5. Reproductive performance[a]

Observation	Dose Group (ppm)			
	0	100	400	1200
P Generation				
Number males mated	28	28	27	28
Number females mated	28	28	28	28
Male percentage mating (%)	100	100	100	100
Female percentage mating (%)	100	100	100	100
Male conception rate (%)	100	93	93	100
Female conception rate (%)	100	93	93	100
Male fertility index (%)	100	93	93	100
Female fertility index (%)	100	93	93	100
Precoital interval (mean±SD days)[b]	2.7±1.1	2.9±2.6	2.4±1.1	3.1±2.0
Gestation index (%)	100	100	100	100
Duration of gestation (mean±SD days)[b]	22.7±0.4	22.7±0.4	22.6±0.4	22.8±0.3
Females with stillborn pups[b]	3	5	4	3
F_1 Generation				
Number males mated	24	24	24	24
Number females mated	24	24	24	24
Male percentage mating (%)	100	100	100	100
Female percentage mating (%)	100	100	100	100
Male conception rate (%)	92	96	100	100
Female conception rate (%)	92	96	100	100
Male fertility index (%)	92	96	100	100
Female fertility index (%)	92	96	100	100
Precoital interval (mean±SD days)[b]	2.7±1.7	3.0±1.0	2.4±1.3	2.8±2.5
Gestation index (%)	100	100	96	100
Duration of gestation (mean±SD days)[b]	22.7±0.4	22.8±0.5	22.8±0.4	22.8±0.4
Females with stillborn pups[b]	1	1	2	2

a Data were obtained from pages 59, 78-80, 109, 130-132, 220-223, and 586-589 of the study report.
b Calculated by reviewers

6. Parental postmortem results

a) Organ weights: No treatment-related differences on organ weights were observed. Numerous increases ($p \leq 0.05$) in relative (to body) organ weights were observed in the 1200 ppm males of both generations; however, absolute weights were comparable to controls. Similarly, several decreases ($p \leq 0.05$) in absolute organ weights were noted in the 1200 ppm P and F_1 females; however, relative weights were comparable to controls. Thus, these changes were

considered to be reflective of decreased terminal body weight. Also, no corroborating micropathology findings were observed.

b) Pathology

1) Macroscopic examination: No treatment-related macroscopic findings were observed.

2) Microscopic examination: No treatment-related microscopic findings were observed.

B. OFFSPRING

1. Viability and clinical signs: Litter data for the F_1 and F_2 pups are presented in Table 6. There were no effects of treatment on the post-implantation survival, live birth, viability, or lactation indices or on the sex ratio in either generation. No clinical signs of toxicity were observed in either generation.

TABLE 6. Litter parameters for F_1 and F_2 generations[a]

Observation		Dose Group (ppm)			
		0	100	400	1200
F_1 Generation					
Mean (±SD) implantation sites		12.6±2.5	12.5±3.2	13.1±2.7	12.4±2.3
Number born live[b]		323	301	301	306
Number born dead[b]		5	7	6	3
Mean sex ratio (% live ♂) on Day 1		50.4±16.7	51.3±16.7	49.6±14.4	52.3±16.4
# Deaths Days 1-4[b]		4	1	8	12
# Deaths Days 5-21[b]		4	5	2	4
Mean (±SD) litter size	Day 1	11.5±2.6	11.6±2.9	11.6±2.6	10.9±2.9
	Day 4[c]	11.4±2.5	11.5±2.8	11.3±2.4	10.5±3.2
	Day 4[d]	7.8±0.7	7.7±1.0	7.9±0.4	7.5±1.4
	Day 7	7.7±0.9	7.6±1.0	7.8±0.5	7.5±1.4
	Day 14	7.6±1.1	7.5±1.1	7.8±0.5	7.4±1.4
	Day 21	7.6±1.1	7.5±1.1	7.8±0.5	7.4±1.5
Post-implantation survival (%)		92.5	95.4	90.3	89.0
Live birth index (%)		98.0	97.5	98.0	99.2
Viability (Days 0-4) index (%)		99.0	99.7	97.9	96.9
Lactation (Days 4-21) index (%)		96.9	97.6	99.0	97.5
F_2 Generation					
Mean (±SD) implantation sites		11.0±3.0	11.9±4.0	11.1±2.9	10.6±2.0
Number born live[b]		226	262	241	235
Number born dead[b]		1	1	2	2
Mean sex ratio (% live ♂) on Day 1		50.2±19.3	51.1±19.0	51.7±13.6	55.3±16.4
# Deaths Days 1-4[b]		0	2	1	4
# Deaths Days 5-21[b]		0	3	2	2
Mean (±SD) litter size	Day 1	10.3±3.4	11.9±3.2	10.5±2.9	9.8±2.3
	Day 4[c]	10.3±3.4	11.8±3.2	10.4±2.8	9.6±2.2
	Day 4[d]	7.3±1.8	7.5±1.5	7.6±1.3	7.7±1.3
	Day 7	7.3±1.8	7.4±1.5	7.6±1.3	7.6±1.3
	Day 14	7.3±1.8	7.4±1.5	7.5±1.3	7.6±1.3
	Day 21	7.3±1.8	7.4±1.5	7.5±1.3	7.6±1.3
Post-implantation survival (%)		93.7	96.4	94.3	92.5
Live birth index (%)		99.1	95.3	99.3	99.2
Viability (Days 1-4) index (%)		100	99.3	99.7	98.5
Lactation (Days 4-21) index (%)		100	98.3	98.9	99.0

a Data were obtained from pages 81-83, 133-135, 220-223, and 586-589 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.
b Calculated by reviewers
c Before standardization (culling)
d After standardization (culling)

2. **Body weight:** Mean pup body weight data are presented in Tables 7a and b. In the 1200 ppm

F_1 pups, body weight gains were decreased ($p \leq 0.05$-0.01) during PND 1-21 (↓7%), and during PND 1-28 (↓8-10%). In the 1200 ppm F_2 pups, body weight gains were decreased ($p \leq 0.05$-0.01) during PND 1-28 in the males (↓7%), and during PND 1-21 in both sexes (↓7%) and PND 1-28 (↓10%) in the females. No effects of treatment were observed on body weight or body weight gain at 100 or 400 ppm. Litter weights were not provided.

TABLE 7a. Mean (±SD) male pup weights (g)[a]

PND	Dose Group (ppm)			
	0	100	400	1200
F_1 Pups				
1	6.3±0.5	6.4±0.6	6.4±0.5	6.4±0.5
4[b]	9.0±1.3	8.9±1.6	9.3±1.2	9.3±1.2
4[c]	9.1±1.3	8.9±1.6	9.4±1.2	9.3±1.1
7	14.3±2.2	13.9±2.6	14.3±2.0	14.2±1.9
14	30.2±3.8	30.1±4.3	30.0±3.2	28.6±2.9
21	47.8±5.5	47.0±5.7	47.2±4.3	45.0±3.9
28	80.7±8.0	78.0±8.3	78.3±7.4	73.7±5.9
Gain (Days 1-21)	41.5±5.4	40.5±5.5	40.8±4.0	38.6±3.5* (↓7)
Gain (Days 1-28)	74.4±7.8	71.5±7.9	71.9±7.1	67.3±5.5** (↓10)
F_2 Pups				
1	6.5±0.7	6.6±0.6	6.5±0.5	6.5±0.7
4[b]	9.4±1.3	9.1±1.4	9.6±1.2	9.5±1.4
4[c]	9.3±1.3	9.2±1.3	9.7±1.2	9.6±1.3
7	15.1±1.8	14.8±2.3	14.8±2.3	14.9±2.0
14	30.4±3.8	30.4±4.9	30.5±4.5	30.0±3.6
21	47.8±6.1	47.9±7.0	47.7±5.8	46.5±5.2
28	83.9±8.1	82.7±10.4	81.4±7.3	78.1±8.3
Gain (Days 1-21)	41.3±5.9	41.4±6.9	41.2±5.7	40.0±4.7
Gain (Days 1-28)	77.4±7.9	76.1±10.3	75.0±7.2	71.6±7.8* (↓7)

a Data were obtained from pages 84-85 and 136-137 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.
b Before standardization (culling)
c After standardization (culling)
* Significantly different from controls; $p \leq 0.05$
** Significantly different from controls; $p \leq 0.01$

TABLE 7b. Mean (±SD) female pup weights (g)[a]

PND	Dose Group (ppm)			
	0	100	400	1200
F_1 Pups				
1	6.0±0.4	6.2±0.6	6.1±0.4	6.0±0.4
4[b]	8.8±1.2	8.6±1.5	9.0±1.2	8.9±1.2
4[c]	8.9±1.2	8.7±1.5	9.1±1.2	9.0±1.2
7	13.8±2.2	13.7±2.5	14.0±2.1	13.8±2.0
14	30.0±3.4	29.4±3.9	29.4±3.2	27.9±3.4
21	46.6±4.9	45.4±5.2	45.4±4.2	43.8±4.0
28	75.2±7.3	73.6±7.3	73.2±6.9	69.7±5.8
Gain (Days 1-21)	40.6±4.8	39.2±5.0	39.3±4.0	37.7±3.8* (↓7)
Gain (Days 1-28)	69.2±7.2	67.4±7.0	67.1±6.6	63.6±5.6** (↓8)
F_2 Pups				
1	6.2±0.7	6.3±0.6	6.2±0.6	6.2±0.5
4[b]	9.2±1.3	9.0±1.3	9.3±1.2	9.3±1.1
4[c]	9.2±1.3	9.0±1.2	9.3±1.2	9.3±1.1
7	15.1±1.5	14.6±1.9	14.5±2.1	14.3±1.9
14	30.6±2.3	30.4±2.8	30.1±4.0	29.3±3.2
21	47.8±3.2	47.4±3.7	46.6±5.3	44.9±4.1
28	80.2±4.5	78.2±5.9	76.9±7.1	73.0±6.4
Gain (Days 1-21)	41.6±2.9	41.1±3.4	40.4±5.1	38.7±3.8* (↓7)
Gain (Days 1-28)	74.0±4.1	72.0±5.6	70.7±6.8	66.8±6.0** (↓10)

a Data were obtained from pages 86-87 and 138-139 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.
b Before standardization (culling)
c After standardization (culling)
* Significantly different from controls; $p \leq 0.05$
** Significantly different from controls; $p \leq 0.01$

3. <u>Sexual maturation (F_1)</u>: No effects of treatment were observed on age or body weight at preputial separation. Vaginal opening was significantly ($p \leq 0.01$) delayed in the 1200 ppm females (37.3 days vs 34.3 days for controls; Table 8). Body weights of these animals were similar to controls at attainment of criterion. These animals did demonstrate significantly reduced body weight gains earlier in development; therefore, this finding was considered to be due to a slower rate of physical development. There were no treatment-related effects on vaginal opening in the 100 or 400 ppm females.

TABLE 8. Vaginal opening (days) in F_1 female rats[a]

Parameter	Dose group (ppm)			
	0	100	400	1200
Vaginal opening	34.3±1.9	35.2±2.8	34.0±2.1	37.3±2.8** (19)
Body weight at attainment	106±12	107±14	103±13	110±12

a Data were obtained from page 128 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

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

4. Ano-genital distance (F_2): No effects of treatment were observed on PND 1 ano-genital distance in the F_2 pups.

5. Offspring postmortem results

a) Organ weights: No treatment-related differences in organ weights were observed.

b) Pathology

1) Macroscopic examination: There were no treatment-related gross pathological findings in the F_1 or F_2 pups.

2) Microscopic examination: Microscopic examinations were not performed.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Dietary administration of AE B049537 at concentrations of 100, 400, or 1200 ppm was generally well tolerated by the parental animals and their subsequent progeny. It was concluded that a dietary concentration of AE B049537 of 1200 ppm was the LOAEL for parental and offspring toxicity, based on decreased body weight gains and food consumption, delayed offspring development and vaginal opening in females, and estrus acyclicity. The LOAEL for fertility and reproductive performance was not observed.

B. REVIEWER COMMENTS

1. PARENTAL ANIMALS: In the parental animals, no treatment-related effects were observed on survival, clinical signs, body weight, or food consumption or efficiency.

At 1200 ppm, body weight gains were decreased in the P males (statistics not performed) during pre-mating (Weeks 0-10) by 10%, and overall (Weeks 0-17) by 10% ($p \leq 0.05$). In the P females at this dose, body weight gains were decreased ($p \leq 0.01$) during pre-mating by 16%. Body weight gains continued to be decreased ($p \leq 0.05$) by 10% throughout gestation (GD 0-20). In the F_1 females at this dose, an increased ($p \leq 0.01$) incidence of five day irregular estrous cycles or acyclicity was observed. However, since no effects were noted on fertility or reproductive performance, this finding was considered equivocal.

No treatment-related findings were noted at 100 or 400 ppm.

The LOAEL for parental toxicity is 1200 ppm (equivalent to 108.5/121.1 mg/kg bw/day [M/F]), based on decreased body weight gains in both sexes. The NOAEL is 400 ppm (equivalent to 35.4/39.8 mg/kg bw/day [M/F]).

2. OFFSPRING: In the offspring, no treatment-related effects were observed on post-implantation survival, live birth, viability, or lactation indices, on the sex ratio, clinical signs, sexual maturation, organ weights, or gross pathology.

At 1200 ppm, body weight gains were decreased (↓7-10%; $p \leq 0.05$) in the F_1 pups (both sexes) during PND 1-21 and during PND 1-28, and in the F_2 pups during PND 1-28 in the males, and during PND 1-21 and PND 1-28 in the females.

No effects of treatment were observed at 100 or 400 ppm.

The LOAEL for offspring toxicity is 1200 ppm (equivalent to 108.5/121.1 mg/kg bw/day [M/F]), based on decreased body weight gains in both sexes. The NOAEL is 400 ppm (equivalent to 35.4/39.8 mg/kg bw/day [M/F]).

In the parental animals, no treatment-related effects were observed on sperm measures, ovarian follicles, corpora lutea, pre-coital interval, duration of gestation, or on mating, fertility, gestation, or parturition indices.

The LOAEL for reproductive performance was not observed. The NOAEL for reproductive performance is 1200 ppm (equivalent to 108.5/121.1 mg/kg bw/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

C. STUDY DEFICIENCIES: The following minor deficiency was noted, but does not alter the conclusions of this DER:

- Although it was stated that homogeneity and stability of the test substance in the diet were confirmed in a previous study, these data were not available for review.

DATA FOR ENTRY INTO ISIS

Reproductive Study - rats (870.3800)

PC code	MRID	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg	Doses tested mg/kg	NOAEL mg/kg	LOAEL mg/kg	Endpoints(s)	Comments
120301	46209601	reproductive	rats	2 generation	oral	diet	8.8-121.1	0/0, 8.8/9.9, 35.4/39.8, 108.5/121.1	35.4	108.5	BWG	Parental
120301	46209601	reproductive	rats	2 generation	oral	diet	8.8-121.1	0/0, 8.8/9.9, 35.4/39.8, 108.5/121.1	35.4	108.5	BWG	Offspring
120301	46209601	reproductive	rats	2 generation	oral	diet	8.8-121.1	0/0, 8.8/9.9, 35.4/39.8, 108.5/121.1	108.5	Not observed		Reproductive

E

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
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Rd, Bldg. 100, Ste. B
Durham, NC 27713

Primary Reviewer:
Ronnie J. Bever Jr., Ph.D.

Signature: Ronnie J. Bever Jr.
Date: 10/13/04

Secondary Reviewer:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 10/13/04

Program Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 10/13/04

Quality Assurance:
Steven Brecher, Ph.D.

Signature:
Date: 10/13/04

Disclaimer

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

EPA Reviewer: Paul Chin **Signature:** Paul Chin
Reregistration Branch 1, Health Effects Division (7509C) **Date** 11/23/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 11/23/04
Work Assignment Manager: P.V. Shah, Ph.D. **Signature:** Shah Deliman
Registration Action Branch 1, Health Effects Division (7509C) **Date** 12/16/04

Template version 11/01

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).

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.

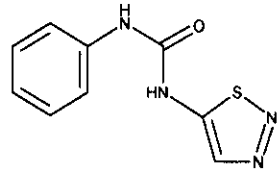
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

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.

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.

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; $p \leq 0.01$

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

CHRONIC TOXICITY AND CARCINOGENICITY STUDY OF THIDIAZURON
IN THE WISTAR RAT BY DIETARY ADMINISTRATION

TABLE 16 - INCIDENCE SUMMARY TABLE OF NEOPLASTIC CHANGES

Tab. 16a 12-month chronic and 24-month carcinogenicity phases combined - including unscheduled and scheduled sacrifice

Tab. 16b 24-month carcinogenicity phase - including unscheduled and scheduled sacrifice

Group	Diet concentration of Thidiazuron (ppm)
1	0
2	200
3	900
4	1 800

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Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males				-- Animals Affected -- Females			
	Group dosage level:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
	No. in group:	70	70	70	70	70	70	70	70
LIVER	Number examined:	70	70	70	70	69	70	70	70
M-Hepatocellular carcinoma		0	1	0	0	0	0	1	0
M-Lymphoma, malignant		1	0	1	0	1	0	0	1
M-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hepatocellular adenoma		3	0	3	0	0	0	0	2
KIDNEY(S)	Number examined:	70	70	70	70	69	70	70	70
M-Transitional cell carcinoma		0	0	0	0	0	0	1	0
M-Squamous cell carcinoma		1	0	0	0	0	0	0	0
M-Nephroblastoma		1	0	0	0	0	0	0	0
M-Mesenchymal tumor		0	0	0	1	0	0	0	0
M-Lymphoma, malignant		1	0	1	0	0	0	0	0
M-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Lipoma		1	0	1	1	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
URINARY BLADDER	Number examined:	69	60	61	69	67	59	59	67
M-Lymphoma, malignant		1	0	0	0	0	0	0	0
M-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Transitional cell papilloma		0	0	0	1	0	0	0	0
LUNG(S)	Number examined:	69	70	70	70	69	70	70	69
M-Lymphoma, malignant		1	0	1	0	0	0	0	1
M-Schwannoma, malignant		0	0	0	1	0	0	0	0
M-Squamous cell carcinoma		1	0	0	0	0	0	0	0
M-Pheochromocytoma, malignant		0	0	0	0	1	1	0	0
M-Thymoma, malignant		0	0	0	0	0	0	1	0
M-Histiocytic sarcoma		0	0	1	0	0	0	0	0
M-Osteosarcoma		0	0	0	1	0	0	0	0
M-Sarcoma, not otherwise specified		0	1	0	0	0	0	0	0
B-Bronchiolo-alveolar adenoma		1	0	1	1	0	0	1	1
B-Bronchial papilloma		0	0	0	1	0	0	0	0
THYROID GLAND(S)	Number examined:	68	60	60	67	69	60	60	69
M-Follicular cell carcinoma		0	0	0	0	0	0	0	1
M-C cell carcinoma		0	0	1	0	1	0	0	0
M-Schwannoma, malignant		0	1	0	0	0	0	0	0
B-C cell adenoma		3	4	3	3	4	3	5	0
B-Follicular cell adenoma		0	0	1	0	0	0	1	1
B-Ganglioneuroma		0	1	0	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
	No. in group:	70	70	70	70	70	70	70	70
PARATHYROID(S) ..... Number examined:		66	56	56	62	68	57	54	62
ADRENAL GLAND(S) ..... Number examined:		70	60	61	70	69	60	60	70
M-Pheochromocytoma, malignant		1	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Pheochromocytoma, benign		2	5	0	0	0	1	0	0
B-Adenoma, zona fasciculata		0	0	0	0	2	0	1	0
PITUITARY GLAND ..... Number examined:		70	60	61	70	68	62	60	70
M-Adenocarcinoma		0	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
B-Adenoma, pars distalis		19	18	15	8	29	30	28	21
HEART ..... Number examined:		70	60	60	70	69	60	60	69
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Pheochromocytoma, malignant		0	0	0	0	1	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Schwannoma, benign		0	1	2	1	0	0	0	0
AORTA ..... Number examined:		70	60	60	70	69	59	59	69
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
TRACHEA ..... Number examined:		69	60	60	70	69	60	60	69
ESOPHAGUS ..... Number examined:		69	60	60	70	69	60	60	69
M-Lymphoma, malignant		0	0	0	0	0	0	0	1
SPLEEN ..... Number examined:		70	65	63	70	69	61	62	70
M-Sarcoma, not otherwise specified		0	0	0	0	1	0	0	0
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
THYMUS ..... Number examined:		68	65	62	66	67	67	63	69
M-Thymoma, malignant		0	0	0	0	0	0	1	0
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
B-Thymoma, benign		3	0	3	1	2	4	1	3

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
	No. in group:	70	70	70	70	70	70	70	70
SUBMAXILLARY GL ..... Number examined:		70	59	61	68	69	60	60	68
SUBMAXILLARY LN ..... Number examined:		70	60	60	68	69	60	60	68
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Squamous cell carcinoma		0	0	1	0	0	0	0	0
STOMACH ..... Number examined:		70	60	60	70	69	61	61	70
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
CECUM ..... Number examined:		70	59	60	68	69	60	60	68
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
RECTUM ..... Number examined:		70	60	59	69	69	60	60	70
MESENTERIC LN ..... Number examined:		70	60	60	68	69	60	60	70
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hemangioma		0	0	1	2	0	0	0	0
PANCREAS ..... Number examined:		69	59	60	70	69	60	60	69
M-Islet cell carcinoma		0	0	0	0	1	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Islet cell adenoma		4	1	5	2	0	1	0	0
B-Acinar cell adenoma		1	1	1	4	0	0	0	1
B-Acinar-islet cell adenoma		1	1	1	0	0	1	0	0
DUODENUM ..... Number examined:		70	54	58	66	66	60	59	69
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
JEJUNUM ..... Number examined:		70	54	57	67	67	58	58	69
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
ILEUM ..... Number examined:		69	56	57	66	66	57	58	67
M-Adenocarcinoma		0	0	0	0	0	0	0	1
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Leiomyoma		0	0	0	0	0	1	0	0
B-Fibroma		0	0	0	0	1	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Controls from group(s): 1	Animal sex:	-- Animals Affected --							
Dosing Units: PPM	Group dosage level:	-- Males --				-- Females --			
Tissues With Diagnoses	No. in group:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
		70	70	70	70	70	70	70	70
COLON ..... Number examined:		70	59	60	68	69	59	58	69
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
SKIN ..... Number examined:		70	61	60	69	69	58	60	70
M-Squamous cell carcinoma		0	0	1	0	0	0	0	0
M-Basal cell tumor, malignant		0	1	0	0	0	0	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
B-Keratoacanthoma		0	0	0	1	0	0	0	0
B-Papilloma, benign		0	0	1	0	0	0	0	0
B-Sebaceous cell adenoma		0	1	0	0	1	0	0	0
B-Hair follicle tumour		0	0	0	1	0	0	0	0
MAMMARY GLAND(S) ..... Number examined:		63	57	50	63	69	59	60	69
M-Adenocarcinoma		1	0	0	0	13	7	7	5
B-Fibroadenoma with atypia		0	0	0	0	2	4	4	4
B-Fibroadenoma		2	2	0	0	23	14	22	15
B-Adenoma		0	0	0	0	0	0	0	1
SKELETAL MUSCLE ..... Number examined:		69	59	60	70	69	60	60	70
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
TONGUE ..... Number examined:		69	60	60	69	69	60	60	70
SCIATIC NERVE ..... Number examined:		69	59	60	70	69	60	60	70
M-Schwannoma, malignant		0	0	1	0	0	0	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
EYE(S) ..... Number examined:		70	62	60	68	69	59	61	70
N-Schwannoma, malignant		0	0	1	0	0	0	0	0
N-Squamous cell carcinoma		0	1	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
OPTIC NERVE(S) ..... Number examined:		70	60	60	68	68	58	59	70
M-Schwannoma, malignant		0	0	1	0	0	0	0	0
HARDERIAN GLAND ..... Number examined:		70	60	60	68	69	60	60	70
N-Schwannoma, malignant		0	0	1	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	70	70	70	70	70	70	70	70
BRAIN ..... Number examined:		70	60	60	70	69	60	60	70
M-Astrocytoma, malignant		2	1	0	0	0	1	0	0
M-Oligodendroglioma, malignant		1	0	0	0	0	0	0	0
M-Mixed glioma, malignant		1	0	0	0	0	0	0	0
M-Anaplastic glioma, malignant		0	0	0	1	0	0	0	0
M-Reticulosis, malignant		0	0	0	0	0	0	1	0
N-Squamous cell carcinoma		0	0	0	1	0	0	0	0
N-Adenocarcinoma		0	0	0	0	1	1	0	0
N-Lymphoma, malignant		0	0	1	0	0	0	0	0
B-Granular cell tumor		1	0	0	0	1	0	0	0
B-Pinealoma, benign		1	0	0	0	0	0	0	0
B-Schwannoma, benign		0	0	0	0	0	1	0	0
BONE, STERNUM ..... Number examined:		70	60	60	68	69	60	60	70
N-Lymphoma, malignant		0	0	0	0	0	0	0	1
B.MARROW,STERNUM ..... Number examined:		70	60	60	69	69	60	60	70
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Thymoma, malignant		0	0	0	0	0	0	1	0
SPINAL CORD ..... Number examined:		70	59	60	70	69	59	60	70
M-Schwannoma, malignant		1	0	0	0	0	0	0	0
N-Reticulosis, malignant		0	0	0	0	0	0	1	0
ARTICULAR SURF. ..... Number examined:		68	60	60	70	69	60	59	70
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
TESTIS[ES] ..... Number examined:		70	61	62	70				
N-Histiocytic sarcoma		0	0	1	0				
EPIDIDYMIS(IDES) ..... Number examined:		70	60	61	70				
M-Mesothelioma, malignant		1	0	0	0				
N-Lymphoma, malignant		1	0	0	0				
N-Schwannoma, malignant		0	0	0	1				
N-Squamous cell carcinoma		1	0	0	0				
N-Histiocytic sarcoma		0	0	1	0				
B-Mesothelioma, benign		0	0	1	0				

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
Dosing units: PPM	Group dosage level:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
Tissues With Diagnoses	No. in group:	70	70	70	70	70	70	70	70
SEMINAL VESICLES ..... Number examined:		70	60	60	69				
N-Lymphoma, malignant		1	0	0	0				
N-Schwannoma, malignant		0	0	0	1				
PROSTATE ..... Number examined:		70	62	60	69				
N-Lymphoma, malignant		1	0	0	0				
N-Schwannoma, malignant		0	0	1	0				
B-Adenoma		1	0	0	1				
OVARY(IES) ..... Number examined:						69	61	62	70
M-Tubulostromal adenocarcinoma						0	1	0	1
M-Granulosa cell tumour, malignant						0	1	0	2
B-Tubulostromal adenoma						2	2	0	3
B-Mixed sex cord stromal adenoma						0	0	0	1
B-Sertoli cell tumor, benign						0	1	0	0
B-Cystadenoma						0	0	0	1
UTERUS ..... Number examined:						69	64	66	70
M-Endometrial adenocarcinoma						0	0	1	3
M-Squamous cell carcinoma						0	0	1	0
M-Schwannoma, malignant						1	0	1	0
M-Leiomyosarcoma						0	1	0	0
N-Lymphoma, malignant						1	0	0	0
B-Endometrial adenoma						0	0	1	0
B-Endometrial stromal polyp						9	10	9	11
B-Leiomyoma						2	0	0	0
VAGINA ..... Number examined:						67	60	60	70
M-Schwannoma, malignant						0	1	2	0
N-Lymphoma, malignant						1	0	0	0
B-Leiomyoma						0	1	0	0
B-Stromal polyp						0	0	1	0
URETER(S) ..... Number examined:		0	0	0	1	0	0	0	0
ORAL CAVITY ..... Number examined:		1	0	0	0	0	1	0	0
EXORBITAL GL ..... Number examined:		22	28	21	17	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
	Group dosage level:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
	No. in group:	70	70	70	70	70	70	70	70
NASAL CAVITY ..... Number examined:		1	1	0	0	0	2	0	0
M-Squamous cell carcinoma		0	1	0	0	0	0	0	0
SUBCUTIS ..... Number examined:		10	15	12	6	5	3	4	2
M-Schwannoma, malignant		0	1	3	0	0	0	1	0
M-Squamous cell carcinoma		0	0	0	1	0	0	0	0
M-Hemangiosarcoma		1	1	0	0	0	0	1	0
M-Fibrosarcoma		1	3	3	2	2	1	1	1
M-Osteosarcoma		0	0	2	0	0	0	0	0
M-Sarcoma, not otherwise specified		0	2	0	0	0	1	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Lipoma		2	2	0	0	2	0	0	0
B-Fibroma		7	6	5	2	0	1	1	1
B-Schwannoma, benign		0	1	0	0	1	0	0	0
Fact. rel. death ..... Number examined:		33	34	32	50	22	17	25	11
BONE ..... Number examined:		2	0	2	0	0	0	0	0
M-Osteosarcoma		0	0	2	0	0	0	0	0
MESENTERY ..... Number examined:		2	1	0	8	1	0	0	1
M-Lymphoma, malignant		1	0	0	0	0	0	0	0
M-Schwannoma, malignant		0	0	0	1	0	0	0	0
M-Mesenchymal tumor		0	0	0	1	0	0	0	0
TAIL ..... Number examined:		1	1	0	2	0	0	0	0
Hemolympho syst. ..... Number examined:		1	0	2	0	1	0	0	1
M-Lymphoma, malignant		1	0	1	0	1	0	0	1
M-Histiocytic sarcoma		0	0	1	0	0	0	0	0
ABDOMINAL CAVITY ..... Number examined:		1	0	3	2	0	0	0	0
M-Osteosarcoma		0	0	0	1	0	0	0	0
M-Schwannoma, malignant		0	0	3	1	0	0	0	0
M-Fibrosarcoma		1	0	0	0	0	0	0	0
LYMPH NODE(S) ..... Number examined:		1	1	4	1	0	0	1	2
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
Dosing units: PPM	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
Tissues With Diagnoses	No. in group:	70	70	70	70	70	70	70	70
BRONCHIAL LN	Number examined:	1	0	0	0	0	0	0	0
N-Squamous cell carcinoma		1	0	0	0	0	0	0	0
RENAL LN	Number examined:	1	0	0	0	0	0	0	0
HINDLEG(S)	Number examined:	0	0	0	0	2	1	0	0
SALIVARY GLAND	Number examined:	0	0	0	0	1	0	0	0
M-Adenocarcinoma		0	0	0	0	1	0	0	0
CLITORAL GLAND	Number examined:	0	0	0	0	0	0	0	1
B-Adenoma		0	0	0	0	0	0	0	1

All Neoplastic Diagnoses; Phases: P2; Death types: All scheduled plus U1, U2, U3, U6, U7, U8
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
LIVER ..... Number examined:		60	60	60	60	60	60	60	60
M-Hepatocellular carcinoma		0	1	0	0	0	0	1	0
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hepatocellular adenoma		2	0	3	0	0	0	0	2
KIDNEY(S) ..... Number examined:		60	60	60	60	60	60	60	60
M-Transitional cell carcinoma		0	0	0	0	0	0	1	0
M-Squamous cell carcinoma		1	0	0	0	0	0	0	0
M-Nephroblastoma		1	0	0	0	0	0	0	0
M-Mesenchymal tumor		0	0	0	1	0	0	0	0
N-Lymphoma, malignant		1	0	1	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Lipoma		1	0	1	1	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
URINARY BLADDER ..... Number examined:		59	60	60	59	59	59	59	57
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Transitional cell papilloma		0	0	0	1	0	0	0	0
LUNG(S) ..... Number examined:		59	60	60	60	60	60	60	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
N-Squamous cell carcinoma		1	0	0	0	0	0	0	0
N-Pheochromocytoma, malignant		0	0	0	0	1	1	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
N-Osteosarcoma		0	0	0	1	0	0	0	0
N-Sarcoma, not otherwise specified		0	1	0	0	0	0	0	0
B-Bronchiolo-alveolar adenoma		1	0	1	1	0	0	1	1
B-Bronchial papilloma		0	0	0	1	0	0	0	0
THYROID GLAND(S) ..... Number examined:		58	60	60	57	60	60	60	59
M-Follicular cell carcinoma		0	0	0	0	0	0	0	1
M-C cell carcinoma		0	0	1	0	1	0	0	0
N-Schwannoma, malignant		0	1	0	0	0	0	0	0
B-C cell adenoma		3	4	3	3	4	3	5	0
B-Follicular cell adenoma		0	0	1	0	0	0	1	1
B-Ganglioneuroma		0	1	0	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	Animals Affected -- Males --				Animals Affected -- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
PARATHYROID(S) ..... Number examined:		56	56	56	55	59	57	54	53
ADRENAL GLAND(S) ..... Number examined:		60	60	60	60	60	60	60	60
M-Pheochromocytoma, malignant		1	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Pheochromocytoma, benign		3	5	0	0	0	1	0	0
B-Adenoma, zona fasciculata		0	0	0	0	2	0	1	0
PITUITARY GLAND ..... Number examined:		60	60	60	60	59	60	59	60
M-Adenocarcinoma		0	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
B-Adenoma, pars distalis		19	18	15	8	29	29	27	20
HEART ..... Number examined:		60	60	60	60	60	60	60	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Pheochromocytoma, malignant		0	0	0	0	1	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Schwannoma, benign		0	1	2	1	0	0	0	0
AORTA ..... Number examined:		60	60	60	60	60	59	59	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
TRACHEA ..... Number examined:		59	60	60	60	60	60	60	59
ESOPHAGUS ..... Number examined:		59	60	60	60	60	60	60	59
N-Lymphoma, malignant		0	0	0	0	0	0	0	1
SPLEEN ..... Number examined:		60	60	60	60	60	60	60	60
M-Sarcoma, not otherwise specified		0	0	0	0	1	0	0	0
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
THYMUS ..... Number examined:		58	57	57	56	58	59	58	59
M-Thymoma, malignant		0	0	0	0	0	0	1	0
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
B-Thymoma, benign		3	0	3	1	2	4	1	3

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
SUBMAXILLARY GL ..... Number examined:		60	59	60	58	60	60	60	58
SUBMAXILLARY LN ..... Number examined:		60	59	60	58	60	60	60	58
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Squamous cell carcinoma		0	0	1	0	0	0	0	0
STOMACH ..... Number examined:		60	60	60	60	60	60	60	60
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
CECUM ..... Number examined:		60	59	60	58	60	60	60	58
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
RECTUM ..... Number examined:		60	60	59	59	60	60	60	60
MESENTERIC LN ..... Number examined:		60	60	60	58	60	60	60	60
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hemangioma		0	0	1	2	0	0	0	0
PANCREAS ..... Number examined:		59	59	60	60	60	60	60	59
M-Islet cell carcinoma		0	0	0	0	1	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Islet cell adenoma		4	1	5	2	0	1	0	0
B-Acinar cell adenoma		1	1	1	4	0	0	0	1
B-Acinar-islet cell adenoma		1	1	1	0	0	1	0	0
DUODENUM ..... Number examined:		60	54	58	56	57	60	59	59
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
JEJUNUM ..... Number examined:		60	54	57	57	58	58	58	59
N-Lymphoma, malignant		1	0	0	0	0	0	0	0

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.0	900.0	1800.	0.0	200.0	900.0	1800.
	No. in group:	60	60	60	60	60	60	60	60
LIVER ..... Number examined:		60	60	60	60	60	60	60	60
M-Hepatocellular carcinoma		0	1	0	0	0	0	1	0
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hepatocellular adenoma		2	0	3	0	0	0	0	2
KIDNEY(S) ..... Number examined:		60	60	60	60	60	60	60	60
M-Transitional cell carcinoma		0	0	0	0	0	0	1	0
M-Squamous cell carcinoma		1	0	0	0	0	0	0	0
M-Nephroblastoma		1	0	0	0	0	0	0	0
M-Mesenchymal tumor		0	0	0	1	0	0	0	0
N-Lymphoma, malignant		1	0	1	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Lipoma		1	0	1	1	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
URINARY BLADDER ..... Number examined:		59	60	60	59	59	59	59	57
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Transitional cell papilloma		0	0	0	1	0	0	0	0
LUNG(S) ..... Number examined:		59	60	60	60	60	60	60	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
N-Squamous cell carcinoma		1	0	0	0	0	0	0	0
N-Pheochromocytoma, malignant		0	0	0	0	1	1	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
N-Osteosarcoma		0	0	0	1	0	0	0	0
N-Sarcoma, not otherwise specified		0	1	0	0	0	0	0	0
B-Bronchiolo-alveolar adenoma		1	0	1	1	0	0	1	1
B-Bronchial papilloma		0	0	0	1	0	0	0	0
THYROID GLAND(S) ..... Number examined:		58	60	60	57	60	60	60	59
M-Follicular cell carcinoma		0	0	0	0	0	0	0	1
M-C cell carcinoma		0	0	1	0	1	0	0	0
N-Schwannoma, malignant		0	1	0	0	0	0	0	0
B-C cell adenoma		3	4	3	3	4	3	5	0
B-Follicular cell adenoma		0	0	1	0	0	0	1	1
B-Ganglioneuroma		0	1	0	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
Dosing units: PPM	Group dosage level:	0.	200.	900.	1800.	0.	200.	900.	1800.
Tissues With Diagnoses	No. in group:	60	60	60	60	60	60	60	60
PARATHYROID(S)	Number examined:	56	56	56	55	59	57	54	53
ADRENAL GLAND(S)	Number examined:	60	60	60	60	60	60	60	60
M-Pheochromocytoma, malignant		1	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Pheochromocytoma, benign		2	5	0	0	0	1	0	0
B-Adenoma, zona fasciculata		0	0	0	0	2	0	1	0

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
LIVER ..... Number examined:		60	60	60	60	60	60	60	60
M-Hepatocellular carcinoma		0	1	0	0	0	0	1	0
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hepatocellular adenoma		2	0	3	0	0	0	0	2
KIDNEY(S) ..... Number examined:		60	60	60	60	60	60	60	60
M-Transitional cell carcinoma		0	0	0	0	0	0	1	0
M-Squamous cell carcinoma		1	0	0	0	0	0	0	0
M-Nephroblastoma		1	0	0	0	0	0	0	0
M-Mesenchymal tumor		0	0	0	1	0	0	0	0
N-Lymphoma, malignant		1	0	1	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Lipoma		1	0	1	1	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
URINARY BLADDER ..... Number examined:		59	60	60	59	59	59	59	57
M-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Transitional cell papilloma		0	0	0	1	0	0	0	0
LUNG(S) ..... Number examined:		59	60	60	60	60	60	60	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
N-Squamous cell carcinoma		1	0	0	0	0	0	0	0
N-Pheochromocytoma, malignant		0	0	0	0	1	1	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
N-Osteosarcoma		0	0	0	1	0	0	0	0
N-Sarcoma, not otherwise specified		0	1	0	0	0	0	0	0
B-Bronchiolo-alveolar adenoma		1	0	1	1	0	0	1	1
B-Bronchial papilloma		0	0	0	1	0	0	0	0
THYROID GLAND(S) ..... Number examined:		58	60	60	57	60	60	60	59
M-Follicular cell carcinoma		0	0	0	0	0	0	0	1
M-C cell carcinoma		0	0	1	0	1	0	0	0
N-Schwannoma, malignant		0	1	0	0	0	0	0	0
B-C cell adenoma		3	4	3	3	4	3	5	0
B-Follicular cell adenoma		0	0	1	0	0	0	1	1
B-Ganglioneuroma		0	1	0	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Rat/Wistar

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SA 01269
P.T.S.4.2.2

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
PARATHYROID(S) ..... Number examined:		56	56	56	55	59	57	54	53
ADRENAL GLAND(S) ..... Number examined:		60	60	60	60	60	60	60	60
M-Pheochromocytoma, malignant		1	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Pheochromocytoma, benign		2	5	0	0	0	1	0	0
B-Adenoma, zona fasciculata		0	0	0	0	2	0	1	0
PITUITARY GLAND ..... Number examined:		60	60	60	60	59	60	59	60
M-Adenocarcinoma		0	0	0	0	1	1	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
B-Adenoma, pars distalis		19	18	15	8	29	29	27	20
HEART ..... Number examined:		60	60	60	60	60	60	60	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
N-Pheochromocytoma, malignant		0	0	0	0	1	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Schwannoma, benign		0	1	2	1	0	0	0	0
AORTA ..... Number examined:		60	60	60	60	60	59	59	59
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
TRACHEA ..... Number examined:		59	60	60	60	60	60	60	59
ESOPHAGUS ..... Number examined:		59	60	60	60	60	60	60	59
N-Lymphoma, malignant		0	0	0	0	0	0	0	1
SPLEEN ..... Number examined:		60	60	60	60	60	60	60	60
M-Sarcoma, not otherwise specified		0	0	0	0	1	0	0	0
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hemangioma		1	0	0	0	0	0	0	0
THYMUS ..... Number examined:		58	57	57	56	58	59	58	59
M-Thymoma, malignant		0	0	0	0	0	0	1	0
N-Lymphoma, malignant		1	0	1	0	0	0	0	1
B-Thymoma, benign		3	0	3	1	2	4	1	3

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled F6, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

Bayer CropScience
Center of Toxicology
Sophia-Antipolis
Rat/Wistar

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
SUBMAXILLARY GL ..... Number examined:		60	59	60	58	60	60	60	58
SUBMAXILLARY LN ..... Number examined:		60	59	60	58	60	60	60	58
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Squamous cell carcinoma		0	0	1	0	0	0	0	0
STOMACH ..... Number examined:		60	60	60	60	60	60	60	60
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
CECUM ..... Number examined:		60	59	60	58	60	60	60	58
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
RECTUM ..... Number examined:		60	60	59	59	60	60	60	60
MESENTERIC LN ..... Number examined:		60	60	60	58	60	60	60	60
N-Lymphoma, malignant		1	0	1	0	1	0	0	1
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Hemangioma		0	0	1	2	0	0	0	0
PANCREAS ..... Number examined:		59	59	60	60	60	60	60	59
M-Islet cell carcinoma		0	0	0	0	1	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
B-Islet cell adenoma		4	1	5	2	0	1	0	0
B-Acinar cell adenoma		1	1	1	4	0	0	0	1
B-Acinar-islet cell adenoma		1	1	1	0	0	1	0	0
DUODENUM ..... Number examined:		60	54	58	56	57	60	59	59
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
JEJUNUM ..... Number examined:		60	54	57	57	58	58	58	59
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
ILEUM ..... Number examined:		59	56	57	56	57	57	58	57
M-Adenocarcinoma		0	0	0	0	0	0	0	1
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
B-Leiomyoma		0	0	0	0	0	1	0	0
B-Fibroma		0	0	0	0	1	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled F8, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

Bayer CropScience
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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Animals Affected -- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
COLON ..... Number examined:		60	59	60	58	60	59	58	59
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
SKIN ..... Number examined:		60	60	60	59	60	58	60	60
M-Squamous cell carcinoma		0	0	1	0	0	0	0	0
M-Basal cell tumor, malignant		0	1	0	0	0	0	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
B-Keratoacanthoma		0	0	0	1	0	0	0	0
B-Papilloma, benign		0	0	1	0	0	0	0	0
B-Sebaceous cell adenoma		0	1	0	0	1	0	0	0
B-Hair follicle tumour		0	0	0	1	0	0	0	0
MAMMARY GLAND(S) ..... Number examined:		54	56	50	53	60	57	60	60
M-Adenocarcinoma		1	0	0	0	13	6	7	5
B-Fibroadenoma with atypia		0	0	0	0	2	4	4	4
B-Fibroadenoma		2	2	0	0	23	13	22	15
B-Adenoma		0	0	0	0	0	0	0	2
SKELETAL MUSCLE ..... Number examined:		59	59	60	60	60	60	60	60
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
TONGUE ..... Number examined:		59	60	60	59	60	60	60	60
SCIATIC NERVE ..... Number examined:		59	59	60	60	60	60	60	60
M-Schwannoma, malignant		0	0	1	0	0	0	0	0
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
EYE(S) ..... Number examined:		60	60	60	58	60	59	60	60
N-Schwannoma, malignant		0	0	1	0	0	0	0	0
N-Squamous cell carcinoma		0	1	0	0	0	0	0	0
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
OPTIC NERVE(S) ..... Number examined:		60	60	60	58	59	58	59	60
M-Schwannoma, malignant		0	0	1	0	0	0	0	0
HARDERIAN GLAND ..... Number examined:		60	60	60	58	60	60	60	60
N-Schwannoma, malignant		0	0	1	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
BRAIN ..... Number examined:		60	60	60	60	60	60	60	60
M-Astrocytoma, malignant		2	1	0	0	0	1	0	0
M-Oligodendroglioma, malignant		1	0	0	0	0	0	0	0
M-Mixed glioma, malignant		1	0	0	0	0	0	0	0
M-Anaplastic glioma, malignant		0	0	0	1	0	0	0	0
M-Reticulosis, malignant		0	0	0	0	0	0	1	0
M-Squamous cell carcinoma		0	0	0	1	0	0	0	0
M-Adenocarcinoma		0	0	0	0	1	1	0	0
M-Lymphoma, malignant		0	0	1	0	0	0	0	0
B-Granular cell tumor		1	0	0	0	1	0	0	0
B-Pinealoma, benign		1	0	0	0	0	0	0	0
B-Schwannoma, benign		0	0	0	0	0	1	0	0
BONE, STERNUM ..... Number examined:		60	60	60	58	60	60	60	60
M-Lymphoma, malignant		0	0	0	0	0	0	0	1
B.MARROW,STERNUM ..... Number examined:		60	60	60	59	60	60	60	60
M-Lymphoma, malignant		1	0	1	0	0	0	0	1
M-Thymoma, malignant		0	0	0	0	0	0	1	0
SPINAL CORD ..... Number examined:		60	59	60	60	60	59	60	60
M-Schwannoma, malignant		1	0	0	0	0	0	0	0
M-Reticulosis, malignant		0	0	0	0	0	0	1	0
ARTICULAR SURF. ..... Number examined:		58	60	60	60	60	60	59	60
M-Lymphoma, malignant		1	0	0	0	0	0	0	0
TESTIS(ES) ..... Number examined:		60	60	60	60				
M-Histiocytic sarcoma		0	0	1	0				
EPIDIDYMIS(IDES) ..... Number examined:		60	60	60	60				
M-Mesothelioma, malignant		1	0	0	0				
M-Lymphoma, malignant		1	0	0	0				
M-Schwannoma, malignant		0	0	0	1				
M-Squamous cell carcinoma		1	0	0	0				
M-Histiocytic sarcoma		0	0	1	0				
B-Mesothelioma, benign		0	0	1	0				

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled PS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
Dosing units: PPM	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
Tissues With Diagnoses	No. in group:	60	60	60	60	60	60	60	60
SEMINAL VESICLES ..... Number examined:		60	60	60	59				
N-Lymphoma, malignant		1	0	0	0				
N-Schwannoma, malignant		0	0	0	1				
PROSTATE ..... Number examined:		60	60	60	59				
N-Lymphoma, malignant		1	0	0	0				
N-Schwannoma, malignant		0	0	1	0				
B-Adenoma		1	0	0	1				
OVARY(IES) ..... Number examined:						60	60	60	60
M-Tubulostromal adenocarcinoma						0	1	0	1
M-Granulosa cell tumour, malignant						0	1	0	2
B-Tubulostromal adenoma						2	2	0	3
B-Mixed sex cord stromal adenoma						0	0	0	1
B-Sertoli cell tumor, benign						0	1	0	0
B-Cystadenoma						0	0	0	1
UTERUS ..... Number examined:						60	60	60	60
M-Endometrial adenocarcinoma						0	0	1	3
M-Squamous cell carcinoma						0	0	1	0
M-Schwannoma, malignant						1	0	1	0
M-Leiomyosarcoma						0	1	0	0
N-Lymphoma, malignant						1	0	0	0
B-Endometrial adenoma						0	0	1	0
B-Endometrial stromal polyp						9	9	8	10
B-Leiomyoma						2	0	0	0
VAGINA ..... Number examined:						59	60	60	60
M-Schwannoma, malignant						0	1	2	0
N-Lymphoma, malignant						1	0	0	0
B-Leiomyoma						0	1	0	0
B-Stromal polyp						0	0	1	0
URETER(S) ..... Number examined:		0	0	0	0	0	0	0	0
ORAL CAVITY ..... Number examined:		0	0	0	0	0	0	0	0
EXORBITAL GL ..... Number examined:		20	27	19	15	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
	No. in group:	60	60	60	60	60	60	60	60
NASAL CAVITY ..... Number examined:		0	1	0	0	0	1	0	0
M-Squamous cell carcinoma		0	1	0	0	0	0	0	0
SUBCUTIS ..... Number examined:		10	15	12	6	4	3	4	2
M-Schwannoma, malignant		0	1	3	0	0	0	1	0
M-Squamous cell carcinoma		0	0	0	1	0	0	0	0
M-Hemangiosarcoma		1	1	0	0	0	0	1	0
M-Fibrosarcoma		1	3	3	2	2	1	1	1
M-Osteosarcoma		0	0	2	0	0	0	0	0
M-Sarcoma, not otherwise specified		0	2	0	0	0	1	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0
B-Lipoma		2	2	0	0	1	0	0	0
B-Fibroma		7	6	5	2	0	1	1	1
B-Schwannoma, benign		0	1	0	0	1	0	0	0
Fact. rel. death ..... Number examined:		33	34	32	49	21	17	25	11
BONE ..... Number examined:		2	0	2	0	0	0	0	0
M-Osteosarcoma		0	0	2	0	0	0	0	0
MESENTERY ..... Number examined:		2	1	0	8	1	0	0	1
N-Lymphoma, malignant		1	0	0	0	0	0	0	0
N-Schwannoma, malignant		0	0	0	1	0	0	0	0
N-Mesenchymal tumor		0	0	0	1	0	0	0	0
TAIL ..... Number examined:		1	1	0	2	0	0	0	0
Hemolympho syst. ..... Number examined:		1	0	2	0	1	0	0	1
M-Lymphoma, malignant		1	0	1	0	1	0	0	1
M-Histiocytic sarcoma		0	0	1	0	0	0	0	0
ABDOMINAL CAVITY ..... Number examined:		1	0	3	2	0	0	0	0
M-Osteosarcoma		0	0	0	1	0	0	0	0
M-Schwannoma, malignant		0	0	3	1	0	0	0	0
M-Fibrosarcoma		1	0	0	0	0	0	0	0
LYMPH NODE(S) ..... Number examined:		1	1	4	1	0	0	1	2
N-Histiocytic sarcoma		0	0	1	0	0	0	0	0
N-Thymoma, malignant		0	0	0	0	0	0	1	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled F8, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

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Rat/Wistar

Incidence summary of microscopic observations lesion
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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM

Tissues With Diagnoses		Animal sex:	-- Animals Affected -- Males --				-- Females --			
		Group dosage level:	0.0	200.	900.	1800.	0.0	200.	900.	1800.
		No. in group:	60	60	60	60	60	60	60	60
BRONCHIAL LN	Number examined:		1	0	0	0	0	0	0	0
N-Squamous cell carcinoma			1	0	0	0	0	0	0	0
RENAL LN	Number examined:		1	0	0	0	0	0	0	0
HINDLEG(S)	Number examined:		0	0	0	0	2	1	0	0
SALIVARY GLAND	Number examined:		0	0	0	0	1	0	0	0
M-Adenocarcinoma			0	0	0	0	1	0	0	0
CLITORAL GLAND	Number examined:		0	0	0	0	0	0	0	1
B-Adenoma			0	0	0	0	0	0	0	1

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3, U6
Date of death range: 30-Aug-01 To 26-Sep-03

F

DATA EVALUATION RECORD

THIDIAZURON

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

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

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Rd, Bldg. 100, Ste. B
Durham, NC 27713

Primary Reviewer:
Ronnie J. Bever Jr., Ph.D.

Signature: Ronnie J. Bever Jr.
Date: 10/5/04

Secondary Reviewer:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 10/5/04

Program Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 10/5/04

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 10/5/04

Disclaimer

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

EPA Reviewer: Paul Chin **Signature:** Paul Chin
Reregistration Branch 1, Health Effects Division (7509C) **Date** 10/26/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 10/27/04
Work Assignment Manager: P.V. Shah, Ph.D. **Signature:** Shah
Registration Action Branch 1, Health Effects Division (7509C) **Date** 12/16/04
Template version 11/01

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.

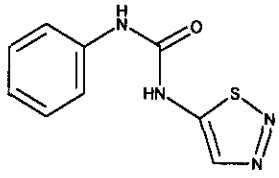
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

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

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.

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.

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.

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.

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

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*

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

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Center of Toxicology
Sophia-Antipolis
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Incidence summary of microscopic observations lesion
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Chronic/Diet Admix

Controls from group(s) : 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
Dosing units: PPM	Group dosage level:	0	200	650	2000	0	200	650	2000
Tissues With Diagnoses	No. in group:	60	60	60	60	60	60	60	60
LIVER ..... Number examined:		60	60	60	60	60	59	60	59
M-Hepatocellular carcinoma		1	0	0	0	0	1	0	0
N-Lymphoma		1	2	0	0	2	1	0	1
N-Histiocytic sarcoma		0	0	0	0	0	1	0	1
B-Hepatocellular adenoma		0	2	1	1	1	1	0	0
GALLBLADDER ..... Number examined:		46	43	47	44	47	48	50	48
N-Lymphoma		0	0	0	0	0	1	0	0
KIDNEY(S) ..... Number examined:		59	51	51	60	60	50	51	60
N-Lymphoma		1	0	0	0	1	0	1	1
URINARY BLADDER ..... Number examined:		50	49	51	48	47	49	49	49
N-Lymphoma		1	0	0	0	0	1	0	0
LUNG(S) ..... Number examined:		50	51	51	50	51	51	50	51
M-Adenocarcinoma		0	0	2	0	0	0	0	0
N-Lymphoma		1	0	0	0	1	1	1	1
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
B-Adenoma, bronchiolo-alveolar		1	0	0	0	0	2	1	1
THYROID GLAND(S) ..... Number examined:		50	50	50	48	50	50	49	50
M-Follicular cell carcinoma		0	0	0	0	1	0	0	0
N-Lymphoma		0	0	0	0	0	0	0	0
B-Follicular cell adenoma		0	1	0	0	5	3	2	0
PARATHYROID(S) ..... Number examined:		36	38	45	33	40	42	36	43
ESOPHAGUS ..... Number examined:		48	51	51	49	50	50	50	50
TRACHEA ..... Number examined:		50	50	51	50	50	50	49	51
ADRENAL GLAND(S) ..... Number examined:		50	50	50	50	50	50	50	50
M-Pheochromocytoma		0	0	0	0	0	0	1	0
N-Lymphoma		0	0	0	0	0	1	0	0
B-Pheochromocytoma		0	0	0	1	1	1	0	0
PITUITARY GLAND ..... Number examined:		47	46	48	45	50	50	48	46
N-Lymphoma		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	1	0	0	0	0	0	0
B-Adenoma, pars distalis		0	0	1	0	23	16	18	4
B-Adenoma, pars intermedia		0	0	0	0	0	1	1	0

All Neoplastic Diagnoses; Phases: All, Death types: All, Date of death range: 10-Oct-01 To 14-May-03

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Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected --							
		-- Males --				-- Females --			
	Group dosage level:	0	200	650	2000	0	200	650	2000
	No. in group:	60	60	60	60	60	60	60	60
HEART ..... Number examined:		50	51	51	50	50	51	50	51
N-Lymphoma		0	0	0	0	0	1	0	0
AORTA ..... Number examined:		49	50	48	50	50	48	49	47
SPLEEN ..... Number examined:		51	52	53	50	50	51	51	51
N-Lymphoma		1	0	0	0	1	2	1	2
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
THYMUS ..... Number examined:		46	49	48	46	46	47	50	47
N-Lymphoma		1	0	0	0	0	1	0	0
SUBMAXILLARY GL ..... Number examined:		60	60	60	60	59	59	60	60
N-Lymphoma		0	0	0	0	0	0	1	0
SUBMAXILLARY LN ..... Number examined:		47	44	49	47	49	45	46	48
N-Lymphoma		1	0	0	0	4	2	2	0
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
STOMACH ..... Number examined:		49	50	51	52	50	50	51	50
N-Lymphoma		1	0	0	0	1	2	0	0
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
B-Papilloma		0	0	0	0	0	1	0	0
CECUM ..... Number examined:		48	43	49	46	50	49	50	48
B-Leiomyoma		0	0	0	0	0	0	0	1
RECTUM ..... Number examined:		49	47	51	48	49	50	50	49
MESENTERIC LN ..... Number examined:		48	48	49	42	48	49	50	44
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
N-Lymphoma		1	4	1	0	4	4	3	1
PANCREAS ..... Number examined:		50	51	51	50	51	50	50	49
N-Lymphoma		1	0	0	0	0	3	1	0
DUODENUM ..... Number examined:		47	43	49	46	49	49	50	48
N-Adenocarcinoma		1	0	0	0	0	0	0	0
N-Lymphoma		0	0	0	0	0	1	0	0
B-Adenoma		0	0	0	0	0	0	1	0

All Neoplastic Diagnoses; Phases: All, Death types: All; Date of death range: 10-Oct-01 To 14-May-03

Bayer CropScience
Center of Toxicology
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Chronic/Diet Admix

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
Dosing units: PPM	Group dosage level:	0	200	650	2000	0	200	650	2000
Tissues With Diagnoses	No. in group:	60	60	60	60	60	60	60	60
JEJUNUM ..... Number examined:		47	43	50	45	49	49	50	48
N-Lymphoma		0	0	0	0	0	1	0	0
ILEUM ..... Number examined:		48	43	49	44	49	48	50	48
COLON ..... Number examined:		48	44	48	47	49	49	50	49
SKIN ..... Number examined:		50	51	50	50	50	50	50	49
M-Malignant basal cell tumor		0	0	0	0	0	0	1	0
MAMMARY GLAND(S) ..... Number examined:		4	1	1	1	47	50	49	45
SKELETAL MUSCLE ..... Number examined:		50	50	51	50	50	51	50	51
N-Lymphoma		1	0	0	0	0	1	0	0
N-Fibrosarcoma		0	0	1	0	0	0	0	0
TONGUE ..... Number examined:		50	51	51	50	50	51	50	51
SCIATIC NERVE ..... Number examined:		49	50	50	48	49	50	50	48
EYE(S) ..... Number examined:		50	52	52	50	51	52	50	51
N-Lymphoma		0	0	0	0	0	1	0	0
OPTIC NERVE(S) ..... Number examined:		48	46	45	44	46	45	48	43
HARDERIAN GLAND ..... Number examined:		50	51	51	50	50	50	50	51
B-Adenoma		0	4	1	2	1	0	0	1
BRAIN ..... Number examined:		50	51	51	50	50	51	50	50
N-Lymphoma		0	0	0	0	0	0	0	1
SPINAL CORD ..... Number examined:		49	51	51	49	50	50	49	49
N-Lymphoma		0	0	0	0	0	0	0	1
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
BONE, STERNUM ..... Number examined:		50	51	51	50	50	51	50	51
B.MARROW,STERNUM ..... Number examined:		50	51	51	50	50	50	50	50
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
N-Lymphoma		0	1	0	0	1	1	0	0

All Neoplastic Diagnoses; Phases: All; Death types: All; Date of death range: 10-Oct-01 To 14-May-03

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Chronic/Diet Admix

Controls from group(s) 1 / Dosing units: PPM / Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level.	0	200	650	2000	0	200	650	2000
	No. in group:	60	60	60	60	60	60	60	60
ARTICULAR SURF ..... Number examined:		49	51	50	50	49	47	50	50
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
N-Lymphoma		0	1	0	0	0	0	0	0
TESTIS(ES) ..... Number examined:		50	51	51	50				
EPIDIDYMIS(IDES) ..... Number examined:		50	51	51	50				
PROSTATE ..... Number examined:		48	49	51	48				
SEMINAL VESICLES ..... Number examined:		50	51	52	50				
OVARY(IES) ..... Number examined:						55	54	55	54
N-Lymphoma						0	1	1	0
N-Histiocytic sarcoma						0	1	0	0
B-Cystadenoma						0	0	0	1
UTERUS ..... Number examined:						58	59	58	59
M-Choriocarcinoma						1	0	0	0
N-Histiocytic sarcoma						0	0	0	2
VAGINA ..... Number examined:						49	50	50	50
N-Histiocytic sarcoma						0	0	0	1
B-Squamous cell papilloma						0	0	0	1
NASAL CAVITY ..... Number examined:		0	0	0	0	0	0	0	0
EAR(S) ..... Number examined:		1	0	0	0	0	0	0	0
TAIL ..... Number examined:		1	0	0	0	0	0	0	0
LYMPH NODE(S) ..... Number examined:		2	1	1	2	3	3	2	0
N-Lymphoma		1	1	0	0	2	1	1	0
LUMBAR LN ..... Number examined:		0	0	1	0	1	1	1	0
N-Lymphoma		0	0	0	0	1	1	1	0
BRONCHIAL LN ..... Number examined:		0	1	1	0	1	0	1	0
N-Lymphoma		0	0	0	0	0	0	1	0

All Neoplastic Diagnoses; Phases: All; Death types: All; Date of death range: 10-Oct-01 To 14-May-03

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

		-- Animals Affected --							
	Animal sex:	-- Males --				-- Females --			
	Group dosage level:	0	200	650	2000	0	200	650	2000
	No. in group:	60	60	60	60	60	60	60	60
DEATH FACTOR ..... Number examined:		11	12	9	8	5	8	4	12
SUBCUTIS ..... Number examined:		1	5	4	0	1	0	2	0
M-Fibrosarcoma		0	1	1	0	1	0	2	0
URETER(S) ..... Number examined:		0	0	1	1	0	0	0	1
HEMATOPOIET SYS ..... Number examined:		2	5	2	0	9	7	5	4
M-Lymphoma		2	4	1	0	8	6	5	2
M-Histiocytic sarcoma		0	1	0	0	0	1	0	2
BONE ..... Number examined:		1	0	1	0	0	0	0	0
AXILLARY LN ..... Number examined:		0	0	0	0	1	0	0	0
INTESTINES ..... Number examined:		0	0	0	1	0	0	0	0
EXORBITAL GL ..... Number examined:		1	5	6	2	13	7	12	4
PREPUTIAL GLAND ..... Number examined:		2	7	5	1	0	0	0	0
OVIDUCT(S) ..... Number examined:		0	0	0	0	0	0	3	0
BULBOURETHRAL GL ..... Number examined:		1	0	0	0	0	0	0	0

All Neoplastic Diagnoses; Phases: All; Death types: All; Date of death range: 10-Oct-01 To 14-May-03

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Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males				-- Females			
	Group dosage level:	0	200	650	2000	0	200	650	2000
	No. in group:	50	50	50	50	50	50	50	50
LIVER ..... Number examined:		50	50	50	50	50	49	50	49
M-Hepatocellular carcinoma		1	0	0	0	0	1	0	0
N-Lymphoma		1	2	0	0	2	1	0	1
N-Histiocytic sarcoma		0	0	0	0	0	1	0	1
B-Hepatocellular adenoma		0	2	1	1	1	1	0	0
GALLBLADDER ..... Number examined:		46	43	46	44	47	47	50	47
N-Lymphoma		0	0	0	0	0	1	0	0
KIDNEY(S) ..... Number examined:		49	50	50	50	50	49	50	50
N-Lymphoma		1	0	0	0	1	0	1	1
URINARY BLADDER ..... Number examined:		50	48	50	48	47	48	49	48
N-Lymphoma		1	0	0	0	0	1	0	0
LUNG(S) ..... Number examined:		50	50	50	50	50	50	50	50
M-Adenocarcinoma		0	0	2	0	0	0	0	0
N-Lymphoma		1	0	0	0	1	1	1	1
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
B-Adenoma, bronchiolo-alveolar		1	0	0	0	0	2	1	1
THYROID GLAND(S) ..... Number examined:		50	49	49	48	50	49	49	49
M-Follicular cell carcinoma		0	0	0	0	1	0	0	0
N-Lymphoma		0	0	0	0	0	0	0	0
B-Follicular cell adenoma		0	1	0	0	5	3	2	0
PARATHYROID(S) ..... Number examined:		36	37	44	33	40	42	36	43
ESOPHAGUS ..... Number examined:		48	50	50	49	50	49	50	49
TRACHEA ..... Number examined:		50	49	50	50	50	49	49	50
ADRENAL GLAND(S) ..... Number examined:		50	49	49	50	50	49	50	49
M-Pheochromocytoma		0	0	0	0	0	0	1	0
N-Lymphoma		0	0	0	0	0	1	0	0
B-Pheochromocytoma		0	0	0	1	1	1	0	0
PITUITARY GLAND ..... Number examined:		47	45	47	45	49	48	48	45
N-Lymphoma		1	0	0	0	0	0	0	0
N-Histiocytic sarcoma		0	1	0	0	0	0	0	0
B-Adenoma, pars distalis		0	0	1	0	23	16	18	4
B-Adenoma, pars intermedia		0	0	0	0	0	1	1	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3
Date of death range: 10-Oct-01 To 14-May-03

Bayer CropScience
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Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

		-- Animals Affected --							
	Animal sex:	-- Males --				-- Females --			
	Group dosage level.	0	200	650	2000	0	200	650	2000
	No. in group:	50	50	50	50	50	50	50	50
HEART ..... Number examined:		50	50	50	50	50	50	50	50
N-Lymphoma		0	0	0	0	0	1	0	0
AORTA ..... Number examined:		49	49	47	50	50	47	49	46
SPLEEN ..... Number examined:		50	50	50	50	49	49	50	49
N-Lymphoma		1	0	0	0	1	2	1	2
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
THYMUS ..... Number examined:		46	48	46	46	46	46	50	46
N-Lymphoma		1	0	0	0	0	1	0	0
SUBMAXILLARY GL ..... Number examined:		50	50	50	50	50	49	50	50
N-Lymphoma		0	0	0	0	0	0	1	0
SUBMAXILLARY LN ..... Number examined:		47	44	48	47	48	44	46	47
N-Lymphoma		1	0	0	0	4	2	2	0
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
STOMACH ..... Number examined:		49	49	50	49	50	49	50	49
N-Lymphoma		1	0	0	0	1	2	0	0
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
B-Papilloma		0	0	0	0	0	1	0	0
CECUM ..... Number examined:		48	43	48	46	50	48	50	47
B-Leiomyoma		0	0	0	0	0	0	0	1
RECTUM ..... Number examined:		49	46	50	48	49	49	50	48
MESENTERIC LN ..... Number examined:		48	47	48	42	47	48	50	43
N-Histiocytic sarcoma		0	0	0	0	0	1	0	0
N-Lymphoma		1	4	1	0	4	4	3	1
PANCREAS ..... Number examined:		50	50	50	50	50	49	50	48
N-Lymphoma		1	0	0	0	0	3	1	0
DUODENUM ..... Number examined:		47	43	48	46	49	48	50	47
M-Adenocarcinoma		1	0	0	0	0	0	0	0
N-Lymphoma		0	0	0	0	0	1	0	0
B-Adenoma		0	0	0	0	0	0	1	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled PS, U1, U2, U3
Date of death range: 10-Oct-01 To 14-May-03

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Center of Toxicology
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SA 01333
P.T.S.4.2.2

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Chronic/Diet Admix

Controls from group(s): 1
Dosing units: PPM
Tissues With Diagnoses

	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Group dosage level:	0	200	650	2000	0	200	650	2000
	No. in group:	50	50	50	50	50	50	50	50
JEJUNUM ..... Number examined:		47	43	49	45	49	48	50	47
N-Lymphoma		0	0	0	0	0	1	0	0
ILEUM ..... Number examined:		48	43	48	44	49	47	50	47
COLON ..... Number examined:		48	44	47	47	49	48	50	48
SKIN ..... Number examined:		50	50	49	50	50	49	50	48
M-Malignant basal cell tumor		0	0	0	0	0	0	1	0
MAMMARY GLAND(S) ..... Number examined:		4	0	1	1	47	49	49	44
SKELETAL MUSCLE ..... Number examined:		50	49	50	50	50	50	50	50
N-Lymphoma		1	0	0	0	0	1	0	0
N-Fibrosarcoma		0	0	1	0	0	0	0	0
TONGUE ..... Number examined:		50	50	50	50	50	50	50	50
SCIATIC NERVE ..... Number examined:		49	49	49	48	49	49	50	47
EYE(S) ..... Number examined:		50	50	50	50	50	49	50	50
N-Lymphoma		0	0	0	0	0	1	0	0
OPTIC NERVE(S) ..... Number examined:		48	46	44	44	45	44	48	42
HARDERIAN GLAND ..... Number examined:		50	50	50	50	50	49	50	50
B-Adenoma		0	4	1	2	1	0	0	1
BRAIN ..... Number examined:		50	50	50	50	50	50	50	49
N-Lymphoma		0	0	0	0	0	0	0	1
SPINAL CORD ..... Number examined:		49	50	50	49	50	49	49	48
N-Lymphoma		0	0	0	0	0	0	0	1
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
BONE, STERNUM ..... Number examined:		50	50	50	50	50	50	50	50
B.MARROW,STERNUM ..... Number examined:		50	50	50	50	50	49	50	49
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
N-Lymphoma		0	1	0	0	1	1	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3
Date of death range: 10-Oct-01 To 14-May-03

Bayer CropScience
Center of Toxicology
Sophia-Antipolis
Mouse/C57 Bl

Incidence summary of microscopic observations lesion
SA 01333
P.T.S.4.2.2

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Chronic/Diet Admix

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
Dosing units: PPM	Group dosage level:	0	200	650	2000	0	200	650	2000
Tissues With Diagnoses	No. in group:	50	50	50	50	50	50	50	50
ARTICULAR SURF	Number examined:	49	50	49	50	49	46	50	49
N-Histiocytic sarcoma		0	1	0	0	0	1	0	0
N-Lymphoma		0	1	0	0	0	0	0	0
TESTIS(ES)	Number examined:	50	50	50	50				
EPIDIDYMIS(IDES)	Number examined:	50	50	50	50				
PROSTATE	Number examined:	48	49	50	48				
SEMINAL VESICLES	Number examined:	50	50	50	50				
OVARY(IES)	Number examined:					49	49	50	47
N-Lymphoma						0	1	1	0
N-Histiocytic sarcoma						0	1	0	0
B-Cystadenoma						0	0	0	1
UTERUS	Number examined:					50	49	49	49
M-Choriocarcinoma						1	0	0	0
N-Histiocytic sarcoma						0	0	0	2
VAGINA	Number examined:					49	49	50	49
N-Histiocytic sarcoma						0	0	0	1
B-Squamous cell papilloma						0	0	0	1
NASAL CAVITY	Number examined:	0	0	0	0	0	0	0	0
EAR(S)	Number examined:	0	0	0	0	0	0	0	0
TAIL	Number examined:	0	0	0	0	0	0	0	0
LYMPH NODE(S)	Number examined:	1	1	1	2	3	3	2	0
N-Lymphoma		1	1	0	0	2	1	1	0
LUMBAR LN	Number examined:	0	0	1	0	1	1	1	0
N-Lymphoma		0	0	0	0	1	1	1	0
BRONCHIAL LN	Number examined:	0	1	1	0	0	0	1	0
N-Lymphoma		0	0	0	0	0	0	1	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3
Date of death range: 10-Oct-01 To 14-May-03

Bayer CropScience
Center of Toxicology
Sophia-Antipolis
Mouse/C57 B1

Incidence summary of microscopic observations lesion
SA 01333
P.T.S.4.2.2

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Chronic/Diet Admix

Controls from group(s) 1		-- Animals Affected --							
Dosing units: PPM	Animal sex:	-- Males --				-- Females --			
Tissues With Diagnoses	Group dosage level:	0	200	650	2000	0	200	650	2000
	No. in group:	50	50	50	50	50	50	50	50
DEATH FACTOR	Number examined:	11	11	8	8	5	7	4	11
SUBCUTIS	Number examined:	1	4	4	0	1	0	2	0
M-Fibrosarcoma		0	1	1	0	1	0	2	0
URETER(S)	Number examined:	0	0	0	1	0	0	0	1
HEMATOPOIET SYS	Number examined:	2	5	2	0	9	7	5	4
M-Lymphoma		2	4	1	0	8	6	5	2
M-Histiocytic sarcoma		0	1	0	0	0	1	0	2
BONE	Number examined:	1	0	1	0	0	0	0	0
AXILLARY LN	Number examined:	0	0	0	0	1	0	0	0
INTESTINES	Number examined:	0	0	0	1	0	0	0	0
EXORBITAL GL	Number examined:	1	5	6	2	13	7	12	4
PREPUTIAL GLAND	Number examined:	2	7	5	1	0	0	0	0
OVIDUCT(S)	Number examined:	0	0	0	0	0	0	3	0
BULBOURETHRAL GL	Number examined:	1	0	0	0	0	0	0	0

All Neoplastic Diagnoses; Phases: P2; Death types: Scheduled and unscheduled FS, U1, U2, U3
Date of death range: 10-Oct-01 To 14-May-03

G

Supplement to TXR No. 002308-DER for MRID No. 00077127. Developmental Toxicity Study in Rats. This supplement provides a revised Executive Summary to upgrade the original DER.

EPA Reviewer: P. Chin, Ph.D. **Signature:** Paul Chin
Reregistration Branch 1, Health Effects Division (7509C) **Date** 12/18/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 12/19/04

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity Study in Rats OPPTS 870.3700a [§83-3a]

PC CODE: 120301 **DP BARCODE:**D294560

TXR No.: 0052174

TEST MATERIAL (PURITY): Thidiazuron (99.4% a.i.)

SYNONYMS: SN 49537; N-phenyl-N'-(1, 2, 3-thiadiazol-5-yl) urea

CITATION:

MRID No. 00077127
Reprotox GmbH (1981) Thidiazuron (SN 49 537): Teratology Study in the Rat: Reprotox Order No. 536/A. Rev. final rept. (Unpublished study received May 29, 1981 under 2139-122; submitted by Nor-Am Agricultural Products, Inc., Naperville, Ill.; CDL: 070129-C)

SPONSOR: Nor-Am Agricultural Products

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID No. 00077127), 25 presumed pregnant Wistar Han 78 strain rats per group were administered thidiazuron (purity: 99.4%; batch/lot No.: 271006B) by oral gavage in Myrj 53 solution at doses of 0, 25, 50, 100 or 300 mg/kg/day on gestation days (GD) 6-15, inclusive.

On GD 19, dams were sacrificed and examined grossly. The ovaries and uteri were excised and the number of corpora lutea, live young, resorptions, fetal weights and the incidence of external fetal abnormalities were recorded. Approximately 2/3 of the litters were examined for skeletal abnormalities and the 1/3 were examined for visceral abnormalities. Uteri were examined for evidence of implantation. Dams were observed daily and weighed on days 0, 6, 15 and 19 of pregnancy.

Maternal Toxicity

No dams died during the course of the study. No clinical observations of toxicity were noted. A slight decreased mean body weight gain (87% of controls) was observed in the females of the 300 mg/kg/day group. The absolute maternal weight decrease was marginal (6%) but the weight loss persisted even after termination of treatment (day 15) (Table 1). Although maternal toxicity was only marginal at 300 mg/kg/day, the previous study (MRID No. 00077126) also showed significant decreased mean body weight gain (90% of controls) at 250 mg/kg/day and a frank maternal toxicity (mortality and reduced body weights) at 900 mg/kg/day. Therefore, the two studies taken together, the maternal LOAEL in this study was considered to be 300 mg/kg/day based on slightly reduced body weight gains.

The maternal LOAEL was 300 mg/kg/day based on reduced body weight gains. The maternal NOAEL was 100 mg/kg/day.

Developmental Toxicity

There were no differences between the control group and the all treated groups for number of litter size, rate of implantation, and pre- and post-implantation losses. Mean fetal weights and mean litter body weights were significantly decreased in the 300 mg/kg/day group (Table 1). There were no treatment-related external, visceral, or skeletal malformations.

The developmental LOAEL was 300 mg/kg/day based on decreased fetal body weights. The developmental NOAEL was 100 mg/kg/day.

This study is classified **acceptable/guideline (OPPTS 870.3700b)** and satisfies the requirements for a developmental study in the rat.

TABLE 1: Selected mean maternal body weights, litter weights, and fetal weights (g)

GD	0	15 mg/kg/day	40 mg/kg/day	120 mg/kg/day
Absolute Body Weights (g)				
0	218	224	214	212
6	250	250	247	243
15	290	286	282	275
19	326	322	313	306 (94%) [a]
Litter weights (g)				
	18.6	19.7	18.1	16.7 (90%) [a]
Fetal weights (g)				
	2.23	2.29	2.24	2.08* (93%) [a]

[a] **Number in parentheses is per cent of control; calculated by reviewer.**

H

Supplement to TXR No. 006330 and 007950-DER for MRID No. 00159344. Chronic toxicity in dog. This supplement provides a revised Executive Summary to upgrade the original DER.

EPA Reviewer: P. Chin, Ph.D. **Signature:** Paul Chi
Reregistration Branch 1, Health Effects Division (7509C) **Date** 10/26/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 11/16/04

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Chronic toxicity [feeding] - dog;[OPPTS 870.4100b (§83-1b)] OECD 452.

PC CODE: 120301 **DP BARCODE:**D294560
TXR No.: 0052174

TEST MATERIAL (PURITY): Thidiazuron (98.8% a.i.)

SYNONYMS: SN 49537; N-phenyl-N'-(1, 2, 3-thiadiazol-5-yl) urea

CITATION:

MRID 00159344
Schuppler, J. and Khater, A. R. (1985) SN 49 537: Systemic Tolerance Study in Dogs following Daily Administration via the Feed over a Period of One Year: Report No. PF 55/84: Study No. TX 83.003. October 17, 1985.

SPONSOR: Schering AG

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID No. 159344), thidiazuron (purity: 98.8% a.i.; Batch No: 7/9.82) was administered to 4 beagle dogs/sex/dose in the diet at levels of 0, 100, 300, or 1000 ppm for 1 year. Corresponding daily intakes of test material for the one-year study were 0, 3.93, 11.8, or 38.3 mg/kg/day for males and 0, 4.01, 11.1, or 36 mg/kg/day for females.

No spontaneous deaths occurred during the study. One high-dose male (No. 4744) and female (No. 4731) exhibited compound related signs of toxicity (apathy, high heart frequency, severe anemia, and inspiratory dyspnea). The male dog was sacrificed moribund in study week 7. The female dog was fed control diet for a reversibility study after week 38.

Thidiazuron caused no significant change in group mean body weights and food consumption except for the two high-dose animals (Nos. 4744 and 4731) described above.

In the low-dose group, no compound-related clinical signs of toxicity were observed.

In the mid-dose group, one male dog showed symptoms of anemia. Also, in two males (Nos. 4702 and 4728), there were a decreased hematocrit (64-66% of controls at week 27), decreased hemoglobin (56% of controls at week 27), decreased red cell count (43-57% of controls at weeks 27 and 39), and increased reticulocyte count (280-1480% of controls at weeks 27 and 39).

Significant ($p<0.05$ or 0.01) compound-related changes in clinical chemistry parameters (alkaline phosphatase and albumin/globulin ratio) were observed in the mid-dose animals, however, the observed changes were not considered biologically significant because there were no clear dose-related trends.

The changes in organ weights were statistically insignificant because of the small number of animals used in the test. In mid-dose males, increases in absolute and relative weights for liver (19% and 24% of controls, respectively), spleen (22% and 27% of controls, respectively), and lymph nodes (48% and 49% of controls, respectively) were observed. In females, absolute and relative spleen weights (21% and 22% of controls, respectively) were increased . Histologically, there was an increased incidence of marked hemosiderosis in Kupffer cells in liver (2/5) and spleen (1/5) and an increase in Kupffer cells in liver (3/5) of males.

In the high-dose group, four animals (two of each sex) showed symptoms of anemia. Also, in the females, there were a decreased hematocrit (at weeks 12 and 29), decreased hemoglobin (week 12) and increased reticulocyte count (week 12). Significant ($p<0.05$ or 0.01) compound-related changes in clinical chemistry parameters (alkaline phosphatase, total serum protein and albumin/globulin ratio) were observed in the high-dose animals, however, the observed changes were not considered biologically significant because there were no clear dose-related trends.

The changes in organ weights were statistically insignificant because of the small number of animals used in the test. In high-dose males, absolute and relative weights for liver (14 % and 19% of controls, respectively), spleen (123 and 107% of controls, respectively), and lymph nodes (116% and117% of controls, respectively) were increased . In females, absolute and relative weights for liver (29% and 12% of controls, respectively), spleen (167% and 132% of controls, respectively) and lymph node (54% and 31% of controls, respectively) were increased compared to controls.

Histologically, there was an increased incidence of pigment deposition in liver, kidney, and spleen and an increase in Kupffer cells in liver of high-dose males and females. The two high-dose females with severe anemia had increased Kupffer cells, hemosiderin in the spleen, increased splenic hematopoiesis, and iron-negative pigment in the tubular epithelium of the kidney. Localized infiltration of lymphocytes in the mucosa of the gallbladder was found in all high-dose animals (2/5 control males; 1/5 control females). In addition, following lesions were found in females:

early or progressive involution in the thymus (high-dose, 4/5; control, 1/5),
interfollicular cell increase in the thyroid (high-dose; 3/5 ;control, 0/5), and
follicular hyperplasia in the lymph nodes (high-dose, 2/5; control, 1/5).

The LOAEL was 300 ppm (11.1 mg/kg/day) based on increased incidence of anemia, changes in hematological parameters and marked hemosiderosis in liver and spleen. The NOAEL was 100 ppm (3.93 mg/kg/day).

This chronic study in the dog is classified as **acceptable/guideline** and satisfies the guideline requirement for a chronic oral study in the dog [OPPTS 870.4100b]. The additional data has been requested relative to the additional study undertaken to clarify the etiology of the observed hemolytic anemia (see TXR 007950).

I

Supplement to TXR No. 006330-DER for MRID No. 00159346. Combined chronic toxicity/carcinogenicity in rat. This supplement provides a revised Executive Summary to upgrade the original DER.

EPA Reviewer: P. Chin, Ph.D. **Signature:** Paul Chin
Reregistration Branch 1, Health Effects Division (7509C) **Date** 10/26/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 10/28/04

Template version 11/01

DATA EVALUATION RECORD

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

PC CODE: 120301 **DP BARCODE:**D294560
TXR No.: 0052174

TEST MATERIAL (PURITY): Thidiazuron (>98.7% a.i.)

SYNONYMS: SN 49537; N-phenyl-N'-(1, 2, 3-thiadiazol-5-yl) urea

CITATION:

MRID 00159346
Sachsse, K. (1986) 104-Week Chronic Toxicity and Oncogenicity Study with Thidiazuron Technical in the Rat: RCC Project No. 011924. April, 15, 1986.

SPONSOR: Schering AG

EXECUTIVE SUMMARY:

In a combined chronic/carcinogenicity study (MRID No. 159346), thidiazuron (purity: >98.7% a.i.: Batch No: 7/9.82) was administered to Wistar KFM-Han rats (70/sex/dose) in the diet at levels of 0, 70, 200, or 600 ppm for 2 years. Corresponding daily intakes of test material for the two-year study were 0, 3.7, 10.6, or 31.7 mg/kg/day for males and 0, 4.6, 13, or 40.1 mg/kg/day for females.

There were no signs of toxicity or dose-related effects on mortality, body weight gains, clinical chemistry, hematology or urinalysis parameters, and absolute or relative organ weights at all doses.

In the 600 ppm dose males, slight but statistically significant reductions in mean body weights (94-95% of controls, $p<0.05$) or food consumption (96% of controls, $p<0.05$) were sporadically noted throughout the test period when compared to controls. No changes in body weight or food

consumption were noted for females at any dose level.

The type, incidence, and severity of non-neoplastic lesions was considered to be similar between control and treated groups. Slight (not statistically significant) increases in incidences of myofibrosis, lymphoid cell infiltration in the kidneys, and lymphoid hyperplasia in the thymus were noted in the 600 ppm dose animals when compared to controls.

There was no treatment-related increase in tumor incidence in any treated groups when compared to controls. Slight increases in incidence of neoplastic lesions were mainly observed in the 600 ppm (high) dose males, however, these increases were not considered to be biologically significant because they did not occur in a dose-related manner. The lesions include C-cell adenoma (5/70 in high-dose vs 2/70 in controls), follicular carcinoma (3/70 in high-dose vs 0/70 in controls) of the thyroid gland, and malignant lymphoma (7/70 in high-dose vs 4/70 in controls).

Dosing in this study was considered inadequate to allow accurate interpretation of the oncogenic response because systemic toxicity (decreased body weight and food consumption) was observed in males. Systemic toxicity for females was not observed.

The LOAEL/NOAEL for systemic toxicity was not established. The treatment did not produce any consistent effect. The systemic toxicity (decreased body weights and food consumption) observed at 600 ppm (31.7 mg/kg/day in males) were sporadic and minimal. It is questionable that the effects in the highest dose should be considered as adverse.

This study is classified as Acceptable/Guideline and satisfies the Subdivision F guideline requirements for a chronic toxicity study (83-1) in rats. However, carcinogenicity testing part (83-2) in rats is classified as unacceptable/guideline and further testing for oncogenicity is required because the dose levels for this study were not appropriately chosen to allow accurate interpretation of the oncogenic response.

It should be noted that a new combined chronic toxicity/carcinogenicity study in rat was conducted recently (MRID No. 46345201) and 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. The doses employed in this study were 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). 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). Under the conditions of this study, there was not a treatment-related increase in tumor incidence when compared to controls.

Supplement to TXR No. 010318-DER for MRID No. 42529001: Metabolism study in rats. This supplement provides a revised Executive Summary to upgrade the original DER.

EPA Reviewer: P. Chin, Ph.D. **Signature:** Paul Chi
Reregistration Branch 1, Health Effects Division (7509C) **Date** 10/26/04
EPA Secondary Reviewer: Whang Phang, Ph.D. **Signature:** Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) **Date** 10/27/04

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat [OPPTS 870.7485 (§85-1)] OECD 417.

PC CODE: 120301 **DP BARCODE:**D294560
TXR No.: 0052174

TEST MATERIAL (PURITY): ^{14}C-labeled Thidiazuron [>97.0% a.i., (^{14}C-aniline) thidiazuron or (^{14}C-thiadizaole) thidiazuron]

SYNONYMS: SN 49537; N-phenyl-N'-(1, 2, 3-thiadiazol-5-yl) urea

CITATION:

MRID 42529001
Hawkins, D.; Mayo, B.; McEwen, A.; et al. (1992) M13 Thidiazuron: The Metabolism of ^{14}C-Thidiazuron in Rats: Lab Project Number: HRC/SMS/254/920450. Oct. 13, 1992.

SPONSOR: Schering AG

EXECUTIVE SUMMARY:

In a metabolism study (MRID 42529001), groups of male and female Sprague-Dawley CD rats were dosed with ^{14}C-thidiazuron [(^{14}C-aniline) thidiazuron or (^{14}C-thiadizaole) thidiazuron (purity: >97% a.i.; batch No: 1695-3 and 1695-4)] at a single oral gavage dose (10 or 1000 mg/kg) or 14-day repeated oral doses of thidiazuron at 10 mg/kg followed by a single oral dose of ^{14}C-thidiazuron at 10 mg/kg. An intravenous dose group was not included in this study.

The results of the pilot study showed that less than 2% of administered radioactivity was eliminated as $^{14}CO_2$ from administration of either (^{14}C-aniline) thidiazuron or (^{14}C-thiadizaole) thidiazuron. In addition, the study showed no significant differences in the percentages eliminated through urine or feces from administration of the two radiolabeled forms.

Absorption of thidiazuron was rapid but incomplete at both doses, and appeared decreased at the high dose relative to the low dose. Elimination of thidiazuron was relatively rapid at the single low oral dose level. The major route of elimination was shown to be via urine. The single low,

single high, and multiple low oral dose studies indicate that the total radioactivity recovered within 5 days after dosing in the urine and feces were 91-104% of administered dose. At the low dose, the radioactivity recovered in the urine and feces was 60-66% and 29-31% of the dose over a 5-day period, respectively. At the repeated low oral dose, the radioactivity recovered in the urine and feces was 73-75% and 26-28% of the dose over a 5-day period, respectively. At the high dose, the radioactivity recovered in the urine and feces was 41-47% and 56-60% of the dose over a 5-day period, respectively. Administration of a single high dose resulted in a decreased percentage of thidiazuron derived radioactivity eliminated in urine (approximately 20%), with concomitant rise in fecal elimination. This alteration is likely due to reduced absorption of test material at the high dose.

Terminal tissue distribution data showed that highest concentrations of thidiazuron derived radioactivity at sacrifice were found in the liver, kidneys, thyroid, whole blood and adrenals at both low and high doses. Repeated oral dosing did not significantly affect distribution of thidiazuron derived radioactivity.

Identification of urinary and fecal metabolites by TLC and HPLC indicated the presence of one oxidative metabolite in urine (4-hydroxy thidiazuron, metabolite J) and the presence of sulfate and glucuronide conjugates of 4-hydroxy thidiazuron (metabolites A/B, D, and F). However, insufficient evidence was presented to justify the presence of more than one sulfate and one glucuronide conjugate of 4-hydroxy thidiazuron in urine. This deficiency does not render the study inadequate, as the other possible oxidative metabolite(s) as candidates for conjugation represent a minor percentage of metabolized thidiazuron.

In urine, the significant metabolites found at low dose were metabolite F (males, 36-38% of dose; females, 14-21%), metabolite J (males, 11%; females, 18-19%), metabolite A/B (males, 4%; females, 3-6%), and metabolite D (males, 5-8%; females, 7-9%). Significant urinary metabolites in rats from the repeated low dose group were metabolites F (24-41%), metabolite J (12-25%), metabolite A/B (3-4%), and metabolite D (7-9%). Percentages of each of metabolites F and J rose slightly in both sexes of rats from repeated low dose administration, indicating a possible mild induction of metabolism. At high dose, the percentage of metabolite F in males and females (2% of dose) was smaller than that of metabolite J (7-11%).

In feces, the major metabolites identified were 4-hydroxy thidiazuron (14-16%) at the low and repeated low dose, and unmetabolized thidiazuron (37-44%) at the high dose.

This study is classified as Acceptable/Guideline and satisfied the guideline data requirement for a metabolism study (85-1) in rats.

13544

R105961

Chemical:	**Thidiazuron**
PC Code:	**120301**
HED File Code	**13000 Tox Reviews**
Memo Date:	**12/09/2004**
File ID:	**TX0052174**
Accession Number:	**412-05-0094**

HED Records Reference Center
04/12/2005