DATA EVALUATION RECORD

NOA 446510 (MANDIPROPAMIDE)

OPPTS 870.4300 [§83-5]; Combined Chronic Toxicity/Carcinogenicity Study in Rats

Work Assignment No. 4-1-121 J, formerly 3-1-121 J (MRID 46800234)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity, dietary study in rats; OPPTS 870.4300 [§ 83-5]; OECD 453.

PC CODE: 036602 **DP BARCODE:** D328539
TXR#: 0054273

TEST MATERIAL (PURITY): NOA 446510 (Mandipropamide; 96.5% a.i.)

SYNONYMS: 4-chloro-*N*-[2-[3-methoxy-4-(2-propynyloxy)phenyl]ethyl]-α-(2-propynyloxy)benzeneacetamide

CITATION: Pinto, P.J. (2005) NOA446510: Two year chronic toxicity and carcinogenicity study in rats. Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Project ID.: Report No.: CTL/PR1274 REG, Syngenta No.: T004616-02, November 9, 2005. MRID 46800234. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, P.O. Box 18300, Greensboro, NC

EXECUTIVE SUMMARY - In a combined chronic toxicity/carcinogenicity study (MRID 46800234), NOA 446510 (Mandipropamide; 96.5% a.i.; Batch No. SEZ2BP007) was administered in the diet to Alpk:AP$_f$SD rats (52/sex/dose) at doses of 0, 50, 250, or 1000 ppm (equivalent to 0, 3.0/3.5, 15.2/17.6, and 61.3/69.7 mg/kg bw/day in males/females) for up to 2 years. Additionally, 12 rats/sex/dose were treated similarly and terminated after 1 year.

No treatment-related effects were observed on mortality, clinical signs, neurological evaluation, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, or organ weights. No treatment-related pathological findings were noted at 12 months.

In the 1000 ppm males, decreased ($p<=0.05$) body weights were generally observed during Weeks 2-15 and 67-103 (decr 1-6%). A similar effect was observed on cumulative body weight gain (decr 3-7%; $p<=0.05$). Overall (Weeks 1-105) body weight gain was decreased by 6% (not statistically significant). Food utilization was decreased during Weeks 1-4, 5-8, 9-13, and 1-13 by 5-7% ($p<=0.01$; except not statistically significant at Weeks 9-13).

In the kidney of the 1000 ppm males, an increased incidence of a roughened surface was observed (13/64 treated vs 5/64 controls). Severity of chronic progressive nephropathy was increased, with an increased incidence of moderate to marked severity of 53% treated vs 38% controls. Associated increases in the incidences of minimal to marked renal osteodystrophia fibrosa (19% treated vs 8% controls) and minimal to marked parathyroid hyperplasia (28% treated vs 17% controls) were also noted.

The LOAEL is 1000 ppm (equivalent to 61.3/69.7 mg/kg/day in males/females), based on decreased body weight gain and food utilization and increased nephrotoxicity in the males. The NOAEL is 250 ppm (equivalent to 15.2/17.6 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 decreased body weight gain and food utilization and increased nephrotoxicity in the males.

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 Compliance, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: NOA 446510

Description: Slightly beige solid

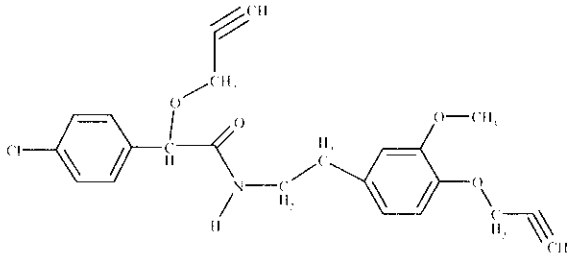
Batch No.: SEZ2BP007

Purity (w/w): 96.5% a.i.

Stability of compound: Stable in the diet for up to 44 or 48 days at room temperature in the 100 and 10,000 ppm formulations, respectively

CAS #: 374726-62-2

Structure:



2. Vehicle: Diet

3. Test animals

Species:	Rat
Strain:	Alpk:AP$_f$SD (Wistar-derived)
Age and mean weight at Week 1:	Approximately 5 weeks old; 112-194 g males; 109-163 g females
Source:	AstraZeneca Biological Services Section (Cheshire, UK)
Housing:	Housed in groups of four by common sex and dose in "multiple rat racks"
Diet:	CT1 diet (Special Diets Services Ltd., Essex, UK), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions	
Temperature:	22±3°C
Humidity:	30-70%
Air changes:	≥15 air changes/hour
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	Approximately 2 weeks

B. STUDY DESIGN

1. In life dates: Start: 01/14/03 End: Approximately 01/14/05

2. Animal assignment/dose levels: The animals were randomly assigned to the test groups shown in Table 1, using a procedure to ensure that each litter was equally represented in all dose groups.

TABLE 1. Study design [a]

Nominal concentration in diet (ppm)	Dose to animal (mg/kg/day; M/F) [b]	Interim Sacrifice (52 Weeks, # rats/sex)	Terminal Sacrifice (104 Weeks; # rats/sex)
0	0/0	12	52
50	3.0/3.5	12	52
250	15.2/17.6	12	52
1000	61.3/69.7	12	52

a Data were obtained from pages 21, 48, and 50 of MRID 46800234.
b Overall group mean for 104 weeks.

3. **Dose-selection rationale:** In a subchronic oral toxicity study (MRID 46800216), NOA 446510 was administered in the diet to rats (10/sex/dose) at dose levels of 0, 100, 500, 3000, or 5000 ppm for 90 days. Slightly decreased body weights and cumulative body weight gains were observed in the males. Decreases of 11-28% in body weight gain were noted in the ≥3000 ppm males during Weeks 1-7, 7-14, and overall (1-14). Decreased food utilization was noted in the ≥3000 ppm males during Weeks 1-4, 5-8, 9-13, and 1-13 (↓9-29%), but not in the 5000 ppm males during Weeks 5-8. Indications of slight hepatotoxicity were observed. Plasma gamma-glutamyl transferase was increased in the ≥3000 ppm males. Absolute and adjusted for body weight liver weights were increased in both sexes at ≥3000 ppm. Minimal to slight eosinophilia in the liver was noted in the 5000 ppm males (8/10) and the ≥3000 ppm females (10/10 each treated) vs 0/10 in the controls and other dose groups. The LOAEL was 3000 ppm (equivalent to 260 mg/kg/day in both sexes).

   In a range-finding study (MRID 46800214), NOA 446510 was administered in the diet to rats (5/sex/dose) at dose levels of 0, 1000, 3000, 10,000 or 16,000 ppm for 28 days. The 10,000 and 16,000 ppm groups were terminated on Days 2-4 due to bodyweight loss. At 1000 and 3000 ppm, decreased food consumption was noted in both sexes, and decreased body weights and body weight gains were observed in males.

4. **Dose preparation and analysis:** Dietary formulations were prepared by first making a premix with the appropriate amount of test substance with milled diet. The premixes were then diluted with diet to the desired concentration. It was not stated how frequently the dietary formulations were prepared. Concentrations at each dietary level were measured in samples taken prior to the start of the study and at approximately 2-month intervals throughout the study. Homogeneity of the test compound in the 50 and 1000 ppm formulations was tested prior to the start of the study. Stability of the compound in the diet at room temperature was determined at 100 and 10,000 ppm in a separate study (CTL study no. WK0441) and at 50 ppm in this study. Stability was measured for up to 42 (50 ppm), 48 (100 ppm), or 44 (10,000 ppm) days.

Results

Homogeneity analysis (% CV): 1.2-3.2%

Stability analysis (% of initial concentration): 97.3-103.5%

Concentration analysis (% of nominal concentration): 92.8-108.2%

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:** All data were evaluated using the MIXED procedure in SAS. Least-squares means for each group were calculated, and each group was compared to the control using a 2-sided Student's t-test, based on the error mean square in the analysis. All statistical tests were 2-sided. Significance was indicated at 5 and 1% probability.

PARAMETER	ANALYSIS CONDUCTED
Body weight	Analysis of covariance (ANCOVA) on initial (Week 1) body weight
Food consumption, food utilization, motor activity measurements, time to tail-flick, landing foot splay, grip strengths, hematology, clinical chemistry, urinalysis	Analysis of variance (ANOVA)
Organ weights	ANOVA and ANCOVA on final body weight
Mortality	Kaplan-Meier survival estimates; logrank test (Peto and Pike)
Tumor incidence	Fisher's Exact Test; Cochran-Armitage Test; time to tumor tested by prevalence, death rate, and combined analyses (Peto, *et al*)

If the assumptions for parametric testing were met, these analyses were considered appropriate.

C. METHODS:

1. Observations:

1a. Cageside observations: Animals were inspected twice daily for signs of toxicity and mortality.

1b. Clinical examinations: Clinical examinations were conducted weekly.

1c. Neurological evaluations: A functional observational battery (FOB) and locomotor activity tests were performed on all interim kill animals during Week 50, as detailed below. Additionally, subchronic (MRID 46800240) and acute (MRIDs 46800242 and 46800241) neurotoxicity studies were concurrently submitted.

(i) **Functional observational battery (FOB):** One observer, who was blind with respect to the animal's treatment, evaluated all animals. The presence and/or absence of all listed observations was recorded, and the degree of condition noted (slight, moderate, or extreme) where appropriate. Environmental conditions, the specific equipment used for the evaluations, and duration of observation in the open field were not reported. The CHECKED (X) parameters were examined.

	HOME CAGE OBSERVATIONS		HANDLING OBSERVATIONS		OPEN FIELD OBSERVATIONS
	Posture	X	Respiratory abnormalities	X	Mobility
	Gait	X	Lacrimation / chromodacryorrhea		Rearing
	Convulsions	X	Salivation	X	Arousal/ general activity level
	Tremors	X	Piloerection	X	Convulsions
	Abnormal Movements	X	Fur appearance	X	Tremors
	Palpebral closure	X	Ptsosis	X	Abnormal movements
	Arousal upon opening cage	X	Miosis / mydriasis	X	Urination / defecation
X	Vocalization	X	Stains around nose or mouth	X	Grooming
X	Bizarre behavior	X	Skin color	X	Gait abnormalities / posture
	SENSORY OBSERVATIONS	X	Eye prominence		Gait score
X	Startle response	X	Approach response	X	Bizarre / stereotypic behavior
X	Pain response	X	Response to touch		Backing
X	Pupil response	X	Dehydration		Time to first step
X	Righting reflex	X	Abdominal tone	X	Vocalization
X	Corneal tactile reflex	X	Urination/defecation	X	Time to tail flick
X	Splay reflex	X	Vocalization		
X	Visual placing response	X	Tremor		
X	Palpebral membrane reflex	X	Convulsion		
X	Pinna reflex	X	Thin appearance		**NEUROMUSCULAR OBSERVATIONS**
					Hindlimb extensor strength
			PHYSIOLOGICAL OBSERVATIONS	X	Forelimb grip strength
			Body weight	X	Hindlimb grip strength
		X	Body temperature	X	Hindlimb foot splay
			OTHER OBSERVATIONS		

(ii) **Locomotor activity:** Locomotor activity was monitored by an automated activity recording apparatus (source not provided) for 10 scans of 5 minute duration. Treatment groups were counterbalanced across test times and across devices. Motor activity was assessed in a separate room to minimize disturbances (environmental conditions were not provided).

2. **Body weight and body weight gain:** All animals were weighed prior to treatment, on Day 1, every subsequent week for Weeks 2-15, every 2 weeks until termination, and at necropsy. Mean cumulative body weight gain was calculated each time the animals were weighed beginning at Week 2.

3. **Food consumption and compound intake:** Food consumption was calculated as a mean value (g food/rat/day) for each cage. Mean food consumption was determined weekly during the first 14 weeks, Week 16, and every fourth week thereafter. Compound intake (mg/kg bw/day) values were calculated from the nominal doses, food consumption, and body weight data. Food utilization (per cage) was calculated as the bodyweight gained by the rats in the cage per 100 g of food eaten.

4. **Ophthalmoscopic examination**: All animals scheduled for the terminal sacrifice were subjected to ophthalmoscopic examinations during acclimation (with the exception of 4 control females by mistake) and on all surviving control and 1000 ppm animals during Weeks 51 and Weeks 100 or 101.

5. **Hematology and clinical chemistry**: Blood was collected via the tail vein. For interim (week 53) and terminal (week 105) sacrifice rats, blood was obtained by cardiac puncture. Samples were taken during Weeks 14, 27, 53, and 79 from a pre-designated set of 13 rats/sex/dose for hematology and a different set of 13 rats/sex/dose for clinical chemistry. Animals that died prior to sampling were replaced when necessary to maintain a minimum of 10 rats/sex/group. Animals were not fasted. 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 concentration (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*	X	Blood cell morphology
X	(Activated partial 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*		Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase (ALP)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
X	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	X	Albumin/globulin ratio
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
	Sorbitol dehydrogenase*		
	Glutamate dehydrogenase*		

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

6. **Urinalysis:** Samples were taken during Weeks 13, 26, 52, 78, and 104 from a pre-designated set of 13 rats/sex/dose (same rats sampled for hematology assays). Animals that died prior to sampling were replaced when necessary to maintain a minimum of 10 rats/sex/group. Samples were collected over a period of 16-18 hours during which the rats were housed individually in metabolism cages and denied access to food. The 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), abnormal urine samples only		Nitrate
X	Protein*		Urobilinogen

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

7. **Sacrifice and pathology**: With the exception of animals found dead, all rats were killed by over exposure to halothane Ph. Eur. vapor followed by exsanguination by cardiac puncture. All decedents and animals sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Collected tissues from all animals were fixed in the "appropriate" fixative (data not provided), routinely processed, stained with hematoxylin and eosin, and examined by light microscopy. The (XX) organs were also weighed; paired organs were weighed together.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta *	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 (retina, optic nerve)*
X	Jejunum*	XX	Thymus		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
X	Rectum*	X	Urinary bladder*	X	Thyroids*
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 vesicle*	X	Skin*
	RESPIRATORY	XX	Ovaries*+	X	Knee joint
X	Trachea*	XX	Uterus*+ (with cervix)	X	All gross lesions and masses*
X	Lung*++	X	Mammary gland* (females only)	X	Harderian gland
X	Nose*	X	Oviduct		
X	Pharynx*	X	Vagina		
X	Larynx*				

* Required for combined chronic/carcinogenicity studies based on Guideline 870.4300.
+Organ weight required in combined chronic/carcinogenicity studies.
++Organ weight required if inhalation route.

II. RESULTS

A. OBSERVATIONS

1. **Mortality:** No treatment-related effect was observed on mortality. The guideline requirements of 50% survival at Week 78 and 25% survival at Week 104 were met.

2. **Clinical signs of toxicity:** No treatment-related clinical signs were observed.

3. **Neurological evaluations:** No treatment-related effects were noted in the FOB or during motor activity evaluations. Differences ($p \leq 0.05$) observed during motor activity were unrelated to dose.

B. BODY WEIGHT: Selected body weights and body weight gains are presented in Table 2. Slightly decreased body weights and body weight gains were observed in the 1000 ppm males. These were not considered to be of biological significance because: the differences between the means were ≤ one half of one standard deviation; there was not an apparent decrease in body weights or gains as the study progressed; no difference in group mean food consumption was observed; and there were no statistically significant differences in group mean actual body weights or weight gains throughout almost the entire duration of the study ($p \leq 0.05$ at interval weeks 1-13 for weight gains; ↓3%). There were no group mean differences in body weights or body weight gains for any treated groups compared with control values.

TABLE 2. Mean (±SD) body weights and cumulative body weight gains (g) at selected intervals in rats treated with NOA 446510 in the diet for up to 2 years.[a]

Week	Dose (ppm)			
	0	50	250	1000
Males (n=21-64)				
1	147.3±15.4	147.5±16.0	146.8±16.4	146.7±16.8
2	201.9±18.3	202.6±18.7	202.7±21.6	199.3±22.6
13	494.7±38.3	494.8±43.9	491.0±42.6	482.9±55.3
53	654.5±51.4	655.8±61.8	654.6±58.3	644.0±61.1
103	575.4±51.3	570.7±58.5	567.2±62.2	546.4±55.6
105	567.9±45.4	555.5±58.4	553.5±71.2	545.8±37.3
Adjusted weights				
2	201.6	202.0	203.1	199.9* (↓1)
53	654.1	654.1	655.6	644.7
103	586.0	572.6	568.5	552.9* (↓6)
105	572.9	561.5	556.4	548.9
BWG (1-13)	347.5±33.7	347.3±39.7	344.2±35.6	336.2±46.6* (↓3)
BWG (13-53)	159.8	161.0	163.6	161.1
BWG (53-105)	-86.6	-100.3	-101.1	-98.2
BWG (1-105)	423.4±43.0	412.6±56.7	411.7±68.4	399.6±41.5 (↓6)
Females (n=23-64)				
1	133.7±12.3	135.0±12.2	135.4±13.5	134.3±11.3
13	268.9±23.7	270.8±22.4	270.8±20.3	270.6±19.2
53	340.1±40.7	344.3±39.9	346.8±34.6	340.7±42.4
105	390.3±40.8	399.6±53.1	401.7±50.3	393.0±56.2
Adjusted weights				
13	270.1	270.7	269.6	271.0
53	342.2	344.3	344.9	341.4
105	390.3	401.1	400.6	389.0
BWG (1-105)	257.4±41.8	264.2±48.7	268.6±46.0	259.7±52.2

a Data were obtained from Tables 9-10 on pages 83-114 of MRID 46800234. Percent difference from controls, calculated by reviewers, is included in parentheses. Body weight gains (Weeks 13-53 and 53-105) were also calculated by the reviewers from the cited data. Analysis of covariance (ANCOVA) on initial (Week 1) bodyweight was performed by the Sponsor to determine significant differences.

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

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption:** No treatment-related effect was observed on food consumption.

2. **Compound consumption (time-weighted average):** Compound intake is reported in Table 1.

3. **Food utilization:** Food utilization was decreased in the 1000 ppm males during Weeks 1-4, 5-8, 9-13, and 1-13 by 5-7% ($p \leq 0.01$; except not statistically significant [NS] at Weeks 9-13). Food utilization in females was unaffected by treatment.

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related finding was noted during ophthalmoscopic examination.

E. BLOOD ANALYSES

1. **Hematology:** No treatment-related effect was observed during hematology. All differences ($p \leq 0.05$), such as mean cell volume and mean cell hemoglobin, were minor, transient, and/or unrelated to dose.

2. **Clinical Chemistry:** No treatment-related effect was noted during clinical chemistry. Decreases ($p \leq 0.05$) in alkaline phosphatase were observed, but were not associated with a toxic effect. All other differences ($p \leq 0.05$), such as increased gamma glutamyl transferase and serum albumin, were minor, transient, and/or unrelated to dose.

F. URINALYSIS: No treatment-related effect was observed during urinalysis.

G. SACRIFICE AND PATHOLOGY

1. **Organ weights:** No treatment-related effect was noted on organ weights

2. **Gross pathology:** The Sponsor stated that no treatment-related findings were observed in the interim kill animals (Week 53; tabulated interim kill data not presented). An increased incidence (# affected/64 [combined interim and terminal kills]) of kidneys with a roughened surface was observed in the 1000 ppm males (13) compared to controls (5), 50 ppm (4) and 250 ppm (8) males. Increased incidences of other lesions were considered minor and/or unrelated to dose.

3. **Microscopic pathology**

   a. **Non-neoplastic:** No treatment-related effect was observed on microscopic pathology at the interim kill. Selected non-neoplastic lesions are detailed in Table 3. After 2 years at 1000 ppm, incidences (% treated vs % controls) of the following lesions were increased: (i) minimal to marked renal osteodystrophia fibrosa in males (19% vs 8%); (ii) minimal to slight pancreas acinar hyperplasia in males (31% vs 19%); (iii) minimal to marked parathyroid hyperplasia in males (28% vs 17%); and (iv) minimal to marked renal intratubular microlithiasis in females (97% vs 84%). Additionally, severity of chronic progressive nephropathy was increased in the 250 and 1000 ppm males, with an increased incidence of moderate to marked severity of 47-53% treated vs 38% controls. The incidences of other lesions were similar to controls.

TABLE 3. Incidence (# affected/# examined [%]) of microscopic lesions in selected organs of rats treated with NOA 446510 in the diet for up to 2 years.[a]

Parameter		Dose (ppm)			
		0	50	250	1000
Males					
Bone-femur and stifle joint	Renal osteodystrophia fibrosa	5/62 (8)	5/63 (8)	6/64 (9)	12/63 (19)
	Minimal	0	2	3	1
	Slight	5	1	1	4
	Moderate	0	1	1	5
	Marked	0	1	1	2
Kidney	Chronic progressive nephropathy	61/64 (95)	61/64 (95)	63/64 (98)	64/64 (100)
	Minimal	21	17	18	21
	Slight	16	18	15	9
	Moderate	9	9	12	10
	Marked	15	17	18	24
Pancreas	Acinar cell hyperplasia	12/64 (19)	15/64 (23)	12/64 (19)	20/64 (31)
	Minimal	2	6	3	5
	Slight	10	9	9	15
Parathyroid gland	Hyperplasia	10/58 (17)	9/61 (15)	6/60 (10)	15/53 (28)
	Minimal	1	0	1	0
	Slight	8	5	3	11
	Moderate	0	4	2	3
	Marked	1	0	0	1
Females					
Kidney	Intratubular microlithiasis	54/64 (84)	47/64 (73)	55/64 (86)	62/64 (97)
	Minimal	44	41	45	35
	Slight	10	4	9	26
	Moderate	0	2	0	1
	Marked	0	0	1	0

a Data were obtained from Table 28 on pages 356-395 of MRID 46800234.

b. **Neoplastic**: Summary data for incidences of neoplastic lesions were reported in the Study Report on pages 396-415 and 451-454 and are included as an Appendix to this DER. No increases in neoplastic lesions were observed in any treated group.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATOR'S CONCLUSIONS: The LOAEL was 1000 ppm, based on decreased body weight gain and food efficiency, and effects in the kidney, red blood cells, and liver. The test substance was not carcinogenic in the rat.

B. REVIEWER COMMENTS: No treatment-related effects were observed on mortality, clinical signs, neurological evaluations, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, or organ weights. No treatment-related pathological findings were noted at 12 months.

In the 1000 ppm males, decreased ($p \leq 0.05$) body weights were generally observed during Weeks 2-15 and 67-103 (↓1-6%). A similar effect was observed on cumulative body weight gain (↓3-7%; $p \leq 0.05$). Overall (Weeks 1-105) body weight gain was decreased by 6% (NS). Food utilization was decreased during Weeks 1-4, 5-8, 9-13, and 1-13 by 5-7% ($p \leq 0.01$; except not statistically significant [NS] at Weeks 9-13). Because of the relatively small differences between group mean body weights and body weight gains in the treated versus control groups (≤ one half of one S.D.), the observed differences are not considered to be either adverse or of biological significance. No affects on female body weights or body weight gains were noted.

In the kidney of the 1000 ppm males, an increased incidence of a roughened surface was observed (13/64 treated vs 5/64 controls). Severity of chronic progressive nephropathy was increased in the 250 and 1000 ppm males, with an increased incidence of moderate to marked severity of 47-53% treated vs 38% controls. However, this finding at 250 ppm was considered not adverse in the absence of further evidence of toxicity at this dose level. In the 1000 ppm males, associated increases in the incidences of minimal to marked renal osteodystrophia fibrosa (19% treated vs 8% controls) and minimal to marked parathyroid hyperplasia (28% treated vs 17% controls) were also noted.

An increased incidence of minimal to marked renal intratubular microlithiasis was observed in the 1000 ppm females (97% treated vs 84% controls). Only one 1000 ppm female had this lesion at a severity greater than slight. An increased incidence of minimal to slight pancreas acinar hyperplasia was noted in males (31% treated vs 19% controls). Due to the slight increases in incidence and severity, these findings were considered not adverse in the absence of corroborating evidence of toxicity.

The Sponsor stated that at 1000 ppm, there were decreases in mean cell volume (MCV) and mean cell hemoglobin (MCH) in both sexes, which indicated red blood cells as a target. MCV and MCH were decreased ($p \leq 0.05$) by only 2-5% in both sexes, and a statistically significant difference was not observed at Week 105 (except for MCH in females). The S.D. for males at 1000 ppm at the 79-week interval for hemoglobin, hematocrit and erythrocytes were 2-3 times the S.D. of other groups. These differences were considered minor, and were not considered adverse in the absence of further evidence of erythrocyte toxicity.

The Sponsor stated that the liver was confirmed as a target organ at 1000 ppm, based on increased liver weight in both sexes at 53 weeks and in females at 105 weeks, a sustained increase in gamma-glutamyl transferase (GGT) in males, and an increase in the incidence of periportal eosinophilia in the liver in both sexes at Week 53. The reviewers concluded that these changes were minimal and are not considered adverse. The adjusted liver weights were increased only 10-14% at Week 53 and were only increased by 11% (females only) at Week 105. GGT was increased by only 31-65%. Periportal eosinophilia was only of minimal severity, and only a minor increase in incidence was observed. The incidence at Week 53 was 2/12 treated males vs 0/12 controls and 5/11 treated females vs 3/11 controls. The total incidence (n=64) was 2 treated males vs 0 controls and 5 treated females vs 3 controls.

The LOAEL is 1000 ppm (equivalent to 61.3/69.7 mg/kg/day in males/females), based on decreased body weight gain and food utilization and increased nephrotoxicity in the males. The NOAEL is 250 ppm (equivalent to 15.2/17.6 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 decreased body weight gain and food efficiency and increased nephrotoxicity in the males.

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.

STUDY DEFICIENCIES: No deficiencies were noted.

ATTACHMENT

The following are pages 396 through 415 and pages 451 through 454 of the study report

TABLE 29 INTERGROUP COMPARISON OF TUMOUR BEARING ANIMALS

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
NUMBER OF TUMOUR BEARING ANIMALS.....	40	44	41	41	53	48	52	50
ANIMALS WITH MALIGNANT TUMOURS.....	21	19	19	13	29	20	26	20
BENIGN TUMOURS.....	34	32	29	34	47	44	48	41
MULTIPLE TUMOURS.....	26	16	16	17	32	23	29	21
SINGLE TUMOURS.....	14	28	25	24	21	25	23	29
MULTIPLE MALIGNANT TUMOURS	0	2	3	2	3	1	3	5
MULTIPLE BENIGN TUMOURS...	17	11	11	12	16	13	15	10
METASTATIC TUMOURS.....	12	12	13	7	21	16	17	16

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	25	27	23	31	30	21	20	23
ABDOMINAL CAVITY								
EXAMINED	0	1	2	0	4	0	0	1
Sarcoma NOS..(MALIGNANT)	0	1	0	0	0	0	0	0
ADRENAL GLAND								
EXAMINED	25	27	23	31	30	21	20	23
Benign phaeochromocytoma..(BENIGN)	3	3	1	2	0	1	0	0
Cortical adenoma..(BENIGN)	0	0	0	0	0	0	1	0
ANUS								
EXAMINED	1	0	0	0	0	0	0	0
Squamous cell carcinoma..(MALIGNANT)	1	0	0	0	0	0	0	0
BRAIN								
EXAMINED	25	27	23	31	30	21	20	23
Malignant astrocytoma..(MALIGNANT)	0	1	0	0	0	1	0	0
CAECUM								
EXAMINED	25	26	21	30	29	20	20	22
MISSING	0	1	2	1	1	1	0	1
Haemangioma..(BENIGN)	0	1	0	0	0	0	0	0
Haemangiosarcoma..(MALIGNANT)	0	0	1	0	0	0	0	0
CERVIX								
EXAMINED	-	-	-	-	27	20	18	23
MISSING	-	-	-	-	3	1	2	0
Adenocarcinoma..(MALIGNANT)	-	-	-	-	2	2	1	0
Malignant schwannoma..(MALIGNANT)	-	-	-	-	0	0	2	1
DUODENUM								
EXAMINED	25	27	23	31	29	21	20	23
MISSING	0	0	0	0	1	0	0	0

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	25	27	23	31	30	21	20	23
DUODENUM	(CONTINUED)							
Adenocarcinoma..(MALIGNANT)	0	0	0	1	0	0	0	0
Fibroma..(BENIGN)	0	0	0	0	1	0	0	0
HEART								
EXAMINED	25	27	23	31	30	21	20	23
Malignant endocardial schwannoma (MALIGNANT)	0	0	0	0	1	0	0	0
JEJUNUM								
EXAMINED	25	26	21	30	28	20	19	21
MISSING	0	1	2	1	2	1	1	2
Adenocarcinoma..(MALIGNANT)	0	0	1	0	0	0	0	0
Leiomyosarcoma..(MALIGNANT)	1	0	0	0	0	0	0	0
Fibroma..(BENIGN)	1	0	0	0	0	0	0	0
KIDNEY								
EXAMINED	25	27	23	31	30	21	20	23
Liposarcoma..(MALIGNANT)	0	1	0	0	0	0	0	0
Renal mesenchymal tumour..(MALIGNANT)	0	1	0	0	0	0	0	0
LIVER								
EXAMINED	25	27	23	31	30	21	20	23
Hepatocellular adenocarcinoma (MALIGNANT)	1	0	1	0	0	0	0	0
Hepatocellular adenoma..(BENIGN)	0	0	0	1	0	0	1	0
LYMPH NODE-MESENTERIC								
EXAMINED	24	25	20	31	30	19	20	22
MISSING	1	2	3	0	0	2	0	1
Haemangioma..(BENIGN)	1	1	0	1	0	0	0	1
LYMPH NODE-PARA-AORTIC								
EXAMINED	2	0	0	0	0	0	0	0

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	25	27	23	31	30	21	20	23
LYMPH NODE-PARA-AORTIC	(CONTINUED)							
Haemangioma..(BENIGN)	1	0	0	0	0	0	0	0
LYMPHORETICULAR SYSTEM								
EXAMINED	7	3	2	4	6	4	5	6
Lymphosarcoma..(MALIGNANT)	1	0	0	1	0	0	1	0
Large granular lymphocyte leukaemia (MALIGNANT)	6	3	2	3	4	4	4	6
Histiocytic sarcoma..(MALIGNANT)	0	0	0	0	2	0	0	0
MAMMARY GLAND								
EXAMINED	-	-	-	-	30	21	20	23
Adenocarcinoma..(MALIGNANT)	-	-	-	-	3	0	1	0
Fibroadenoma..(BENIGN)	-	-	-	-	1	0	1	0
MESENTERY/OMENTUM								
EXAMINED	0	0	2	0	1	1	0	1
MISSING	0	0	0	1	0	0	0	0
Malignant schwannoma..(MALIGNANT)	0	0	0	0	0	0	0	1
ORAL CAVITY								
EXAMINED	1	2	1	1	0	1	0	2
Squamous cell carcinoma..(MALIGNANT)	0	1	0	1	0	0	0	2
PANCREAS								
EXAMINED	25	27	23	31	29	21	19	23
MISSING	0	0	0	0	1	0	1	0
Acinar cell adenocarcinoma (MALIGNANT)	0	0	0	1	0	0	0	0
Islet cell adenoma..(BENIGN)	1	0	0	2	0	0	0	0
Islet cell adenocarcinoma (MALIGNANT)	1	0	0	0	0	0	0	0
PITUITARY GLAND								
EXAMINED	24	27	23	29	30	21	19	22
MISSING	1	0	0	2	0	0	1	1

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	25	27	23	31	30	21	20	23
PITUITARY GLAND	(CONTINUED)							
Adenoma pars distalis..(BENIGN).....	8	12	7	13	21	14	15	14
Adenoma pars intermedia..(BENIGN).....	1	0	2	0	0	0	1	0
Carcinoma pars diatalis..(MALIGNANT)..	0	0	0	0	0	0	0	1
Neuromyoblastoma..(MALIGNANT).....	0	0	0	0	0	0	0	1
PRIMARY TISSUE UNKNOWN								
EXAMINED.....	0	0	0	0	1	0	0	0
Adenocarcinoma..(MALIGNANT).....	0	0	0	0	1	0	0	0
SALIVARY GLAND								
EXAMINED.....	24	27	21	30	30	21	20	23
MISSING.....	1	0	2	1	0	0	0	0
Squamous cell carcinoma..(MALIGNANT)..	1	0	0	0	0	0	0	0
SEMINAL VESICLE								
EXAMINED.....	25	27	23	31	-	-	-	-
Adenocarcinoma..(MALIGNANT).....	0	0	0	1	-	-	-	-
SKIN								
EXAMINED.....	25	27	23	30	30	21	20	23
MISSING.....	0	0	0	1	0	0	0	0
Infundibular keratinising acanthoma - (Keratoacanthoma)..(BENIGN).....	0	0	0	1	0	0	0	0
Benign hair follicle - tumour(pilomatrixoma/t-epithel/t-foll - ic/t-lemm)..(BENIGN).....	5	1	3	4	1	0	0	0
Squamous cell papilloma..(BENIGN).....	0	0	0	0	1	0	0	0
SKULL								
EXAMINED.....	0	0	0	0	0	1	0	0
Chondroma..(BENIGN).....	0	0	0	0	0	1	0	0
STOMACH								
EXAMINED.....	25	27	23	31	30	21	20	23

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	25	27	23	31	30	21	20	23
STOMACH	(CONTINUED)							
Malignant schwannoma..(MALIGNANT)	0	0	1	0	0	0	0	0
SUBCUTANEOUS TISSUE								
EXAMINED	6	2	5	3	6	2	4	2
Lipoma..(BENIGN)	0	0	0	0	0	0	1	0
Malignant Schwannoma..(MALIGNANT)	1	0	2	2	1	0	0	0
Sarcoma NOS..(MALIGNANT)	1	0	0	0	0	0	0	0
TESTIS								
EXAMINED	25	27	23	31	-	-	-	-
Benign Leydig cell tumour..(BENIGN)	3	1	2	0	-	-	-	-
Malignant mesothelioma..(MALIGNANT)	0	0	1	0	-	-	-	-
THYMUS								
EXAMINED	24	24	20	28	30	21	20	23
MISSING	1	3	3	3	0	0	0	0
Benign thymoma..(BENIGN)	0	0	0	1	0	0	0	0
THYROID GLAND								
EXAMINED	24	27	23	30	30	21	20	23
MISSING	1	0	0	1	0	0	0	0
Follicular cell adenoma..(BENIGN)	0	0	0	0	1	0	1	0
Follicular cell carcinoma (MALIGNANT)	0	0	0	1	0	0	0	0
C-cell adenoma..(BENIGN)	0	1	2	1	1	1	1	0
C-cell carcinoma..(MALIGNANT)	0	0	1	0	0	0	0	0
UTERUS								
EXAMINED	-	-	-	-	30	21	20	23
Stromal cell polyp..(BENIGN)	-	-	-	-	3	1	1	0
Adenocarcinoma..(MALIGNANT)	-	-	-	-	5	2	4	3

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	25	27	23	31	30	21	20	23
UTERUS	(CONTINUED)							
Adenoma..(BENIGN).....	-	-	-	-	0	1	1	1
Malignant schwannoma..(MALIGNANT).....	-	-	-	-	1	0	0	1

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERIM	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	12	12	12	12	11	12	12	11
EPIDIDYMIS								
EXAMINED	12	12	12	12	-	-	-	-
Malignant mesothelioma..(MALIGNANT)	0	0	1	0	-	-	-	-
LYMPH NODE-MESENTERIC								
EXAMINED	12	12	12	12	10	12	12	11
MISSING	0	0	0	0	1	0	0	0
Haemangioma..(BENIGN)	0	1	0	0	0	1	0	0
MAMMARY GLAND								
EXAMINED	-	-	-	-	11	12	12	9
MISSING	-	-	-	-	0	0	0	2
Fibroadenoma..(BENIGN)	-	-	-	-	0	0	1	0
PITUITARY GLAND								
EXAMINED	12	12	12	12	11	12	12	11
Adenoma pars distalis..(BENIGN)	0	0	0	0	1	1	4	3
THYROID GLAND								
EXAMINED	12	12	12	12	11	12	12	11
C-cell adenoma..(BENIGN)	0	1	0	0	0	0	0	0

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	27	25	29	21	23	31	32	30
ABDOMINAL CAVITY								
EXAMINED	0	0	0	0	0	0	0	1
Lipoma..(BENIGN)	0	0	0	0	0	0	0	1
ADRENAL GLAND								
EXAMINED	27	25	29	21	23	31	32	30
Benign phaeochromocytoma..(BENIGN)	5	0	5	0	0	1	0	0
Cortical adenoma..(BENIGN)	1	0	0	0	0	0	0	1
Malignant phaeochromocytoma (MALIGNANT)	1	0	0	0	0	1	0	0
BRAIN								
EXAMINED	27	25	29	21	23	31	32	30
Malignant astrocytoma..(MALIGNANT)	0	0	0	0	1	1	0	0
Benign meningioma..(BENIGN)	0	0	0	0	0	1	1	0
CERVIX								
EXAMINED	-	-	-	-	23	31	32	30
Fibroma..(BENIGN)	-	-	-	-	1	0	0	0
HEART								
EXAMINED	27	25	29	21	23	31	32	30
Benign endocardial schwannoma (BENIGN)	0	0	0	1	0	0	0	0
JEJUNUM								
EXAMINED	27	25	29	21	23	31	32	30
Leiomyoma..(BENIGN)	0	0	0	0	0	1	0	0
LIMB								
EXAMINED	2	1	1	1	0	0	0	0
Infundibular keratinising acanthoma (keratoacanthoma)..(BENIGN)	1	0	0	0	0	0	0	0
LIVER								
EXAMINED	27	25	29	21	23	31	32	30

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	27	25	29	21	23	31	32	30
LIVER (CONTINUED)								
Hepatocellular adenoma..(BENIGN).....	0	0	0	1	0	0	0	0
LUNG								
EXAMINED.....	27	25	29	21	23	31	32	30
Adenoma..(BENIGN).....	0	1	0	0	0	0	0	0
LYMPH NODE-AXILLARY								
EXAMINED.....	0	0	0	1	0	0	0	0
Haemangioma..(BENIGN).....	0	0	0	1	0	0	0	0
LYMPH NODE-MESENTERIC								
EXAMINED.....	27	25	29	21	23	31	32	30
Haemangioma..(BENIGN).....	1	2	1	1	2	1	1	2
LYMPHORETICULAR SYSTEM								
EXAMINED.....	4	9	7	2	7	9	9	5
Lymphosarcoma..(MALIGNANT).....	0	1	1	0	0	0	0	0
Large granular lymphocyte leukaemia (MALIGNANT).....	4	8	6	2	7	9	9	5
MAMMARY GLAND								
EXAMINED.....	-	-	-	-	23	30	32	30
MISSING.....	-	-	-	-	0	1	0	0
Adenocarcinoma..(MALIGNANT).....	-	-	-	-	1	0	1	1
Adenoma..(BENIGN).....	-	-	-	-	0	0	2	0
Cystadenoma..(BENIGN).....	-	-	-	-	0	1	0	0
Fibroadenoma..(BENIGN).....	-	-	-	-	2	1	1	1
Fibroma..(BENIGN).....	-	-	-	-	0	1	0	0
ORAL CAVITY								
EXAMINED.....	2	0	1	1	0	0	1	0

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	27	25	29	21	23	31	32	30
ORAL CAVITY (CONTINUED)								
Squamous cell carcinoma..(MALIGNANT)..	1	0	0	1	0	0	0	0
OVARY								
EXAMINED	-	-	-	-	23	31	32	30
Benign granulosa/theca cell tumour (BENIGN)	-	-	-	-	0	1	0	0
PANCREAS								
EXAMINED	27	25	29	21	23	31	32	30
Acinar cell adenoma..(BENIGN)	0	0	1	0	0	0	0	0
Acinar cell adenocarcinoma (MALIGNANT)	0	0	0	1	0	0	1	0
Islet cell adenoma..(BENIGN)	1	0	0	0	0	1	0	0
PARATHYROID GLAND								
EXAMINED	25	24	26	15	21	25	27	26
MISSING	2	1	3	6	2	6	5	4
Adenoma..(BENIGN)	1	0	0	0	0	0	1	0
PITUITARY GLAND								
EXAMINED	27	25	29	21	23	29	32	30
MISSING	0	0	0	0	0	2	0	0
Adenoma pars distalis..(BENIGN)	9	9	7	8	20	23	27	20
Adenoma pars intermedia..(BENIGN)	0	1	0	0	1	0	0	1
SALIVARY GLAND								
EXAMINED	27	25	29	21	23	31	32	30
Adenoma..(BENIGN)	0	0	1	0	0	0	0	0
SEMINAL VESICLE								
EXAMINED	27	25	28	21	-	-	-	-
MISSING	0	0	1	0	-	-	-	-

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	27	25	29	21	23	31	32	30
SEMINAL VESICLE	(CONTINUED)							
Adenocarcinoma..(MALIGNANT).....	0	0	1	0	-	-	-	-
SKIN								
EXAMINED.....	27	25	29	21	23	31	32	30
Infundibular keratinising acanthoma - (Keratoacanthoma)..(BENIGN).....	1	0	0	0	0	0	0	0
Benign hair follicle - tumour(pilomatrixoma/t-epithel/t-foll - ic/t-lemm)..(BENIGN).....	2	0	2	3	0	0	0	1
Sebaceous adenoma..(BENIGN).....	0	0	1	0	0	0	0	0
SUBCUTANEOUS TISSUE								
EXAMINED.....	3	2	4	4	2	2	4	3
Fibroma..(BENIGN).....	0	2	1	1	0	0	0	0
Haemangioma..(BENIGN).....	0	0	1	0	0	0	0	0
Lipoma..(BENIGN).....	2	0	1	0	0	0	0	0
Sarcoma NOS..(MALIGNANT).....	0	0	1	0	0	0	0	0
TAIL								
EXAMINED.....	8	13	11	10	0	0	0	0
MISSING.....	1	0	0	0	0	0	0	0
Infundibular keratinising - acanthoma(Keratoacanthoma)..(BENIGN)..	0	0	0	1	0	0	0	0
Squamous cell papilloma..(BENIGN).....	0	0	0	1	0	0	0	0
TESTIS								
EXAMINED.....	27	25	29	21	-	-	-	-
Benign Leydig cell tumour..(BENIGN)...	3	6	4	4	-	-	-	-
Malignant mesothelioma..(MALIGNANT)...	1	3	1	0	-	-	-	-
THYMUS								
EXAMINED.....	26	25	29	21	23	31	32	30
MISSING.....	1	0	0	0	0	0	0	0

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TABLE 30 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	27	25	29	21	23	31	32	30
THYMUS	(CONTINUED)							
Benign thymoma..(BENIGN).....	0	0	2	0	1	0	0	0
Malignant thymoma..(MALIGNANT).....	0	1	1	0	0	0	2	0
THYROID GLAND								
EXAMINED.....	27	25	28	21	23	31	32	30
MISSING.....	0	0	1	0	0	0	0	0
Follicular cell adenoma..(BENIGN).....	0	0	0	1	0	0	0	0
C-cell adenoma..(BENIGN).....	4	1	3	1	3	4	3	5
C-cell carcinoma..(MALIGNANT).....	0	0	0	0	0	0	0	1
UTERUS								
EXAMINED.....	-	-	-	-	23	31	32	30
Stromal cell polyp..(BENIGN).....	-	-	-	-	4	3	0	1
Adenocarcinoma..(MALIGNANT).....	-	-	-	-	3	1	3	1
Squamous cell carcinoma..(MALIGNANT)..	-	-	-	-	0	0	0	1

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
ABDOMINAL CAVITY								
EXAMINED	0	1	2	0	4	0	0	2
Lipoma..(BENIGN)	0	0	0	0	0	0	0	1
Sarcoma NOS..(MALIGNANT)	0	1	0	0	0	0	0	0
ADRENAL GLAND								
EXAMINED	64	64	64	64	64	64	64	64
Benign phaeochromocytoma..(BENIGN)	8	3	6	2	0	2	0	0
Cortical adenoma..(BENIGN)	1	0	0	0	0	0	1	1
Malignant phaeochromocytoma (MALIGNANT)	1	0	0	0	0	1	0	0
ANUS								
EXAMINED	1	0	0	0	0	0	0	0
Squamous cell carcinoma..(MALIGNANT)	1	0	0	0	0	0	0	0
BRAIN								
EXAMINED	64	64	64	64	64	64	64	64
Malignant astrocytoma..(MALIGNANT)	0	1	0	0	1	2	0	0
Benign meningioma..(BENIGN)	0	0	0	0	0	1	1	0
CAECUM								
EXAMINED	64	63	62	63	63	63	64	63
MISSING	0	1	2	1	1	1	0	1
Haemangioma..(BENIGN)	0	1	0	0	0	0	0	0
Haemangiosarcoma..(MALIGNANT)	0	0	1	0	0	0	0	0
CERVIX								
EXAMINED	-	-	-	-	61	63	62	64
MISSING	-	-	-	-	3	1	2	0
Adenocarcinoma..(MALIGNANT)	-	-	-	-	2	2	1	0
Malignant schwannoma..(MALIGNANT)	-	-	-	-	0	0	2	1

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
CERVIX	(CONTINUED)							
Fibroma..(BENIGN)	-	-	-	-	1	0	0	0
DUODENUM								
EXAMINED	64	64	64	64	63	64	64	64
MISSING	0	0	0	0	1	0	0	0
Adenocarcinoma..(MALIGNANT)	0	0	0	1	0	0	0	0
Fibroma..(BENIGN)	0	0	0	0	1	0	0	0
EPIDIDYMIS								
EXAMINED	64	64	64	64	-	-	-	-
Malignant mesothelioma..(MALIGNANT)	0	0	1	0	-	-	-	-
HEART								
EXAMINED	64	64	64	64	64	64	64	64
Benign endocardial schwannoma (BENIGN)	0	0	0	1	0	0	0	0
Malignant endocardial schwannoma (MALIGNANT)	0	0	0	0	1	0	0	0
JEJUNUM								
EXAMINED	64	63	62	63	62	63	63	62
MISSING	0	1	2	1	2	1	1	2
Adenocarcinoma..(MALIGNANT)	0	0	1	0	0	0	0	0
Leiomyoma..(BENIGN)	0	0	0	0	0	1	0	0
Leiomyosarcoma..(MALIGNANT)	1	0	0	0	0	0	0	0
Fibroma..(BENIGN)	1	0	0	0	0	0	0	0
KIDNEY								
EXAMINED	64	64	64	64	64	64	64	64
Liposarcoma..(MALIGNANT)	0	1	0	0	0	0	0	0
Renal mesenchymal tumour..(MALIGNANT)	0	1	0	0	0	0	0	0
LIMB								
EXAMINED	4	1	2	3	0	0	0	1

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
LIMB (CONTINUED)								
Infundibular keratinising acanthoma (keratoacanthoma)..(BENIGN)	1	0	0	0	0	0	0	0
LIVER								
EXAMINED	64	64	64	64	64	64	64	64
Hepatocellular adenocarcinoma (MALIGNANT)	1	0	1	0	0	0	0	0
Hepatocellular adenoma..(BENIGN)	0	0	0	2	0	0	1	0
LUNG								
EXAMINED	64	64	64	64	64	64	64	64
Adenoma..(BENIGN)	0	1	0	0	0	0	0	0
LYMPH NODE-AXILLARY								
EXAMINED	1	0	0	1	0	0	1	0
Haemangioma..(BENIGN)	0	0	0	1	0	0	0	0
LYMPH NODE-MESENTERIC								
EXAMINED	63	62	61	64	63	62	64	63
MISSING	1	2	3	0	1	2	0	1
Haemangioma..(BENIGN)	2	4	1	2	2	2	1	3
LYMPH NODE-PARA-AORTIC								
EXAMINED	2	0	0	0	0	0	0	0
Haemangioma..(BENIGN)	1	0	0	0	0	0	0	0
LYMPHORETICULAR SYSTEM								
EXAMINED	11	12	9	6	13	13	14	11
Lymphosarcoma..(MALIGNANT)	1	1	1	1	0	0	1	0
Large granular lymphocyte leukaemia (MALIGNANT)	10	11	8	5	11	13	13	11

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
LYMPHORETICULAR SYSTEM	(CONTINUED)							
Histiocytic sarcoma..(MALIGNANT).....	0	0	0	0	2	0	0	0
MAMMARY GLAND								
EXAMINED.....	-	-	-	-	64	63	64	62
MISSING.....	-	-	-	-	0	1	0	2
Adenocarcinoma..(MALIGNANT).....	-	-	-	-	4	0	2	1
Adenoma..(BENIGN).....	-	-	-	-	0	0	2	0
Cystadenoma..(BENIGN).....	-	-	-	-	0	1	0	0
Fibroadenoma..(BENIGN).....	-	-	-	-	3	1	3	1
Fibroma..(BENIGN).....	-	-	-	-	0	1	0	0
MESENTERY/OMENTUM								
EXAMINED.....	1	0	3	1	1	1	1	1
MISSING.....	0	0	0	1	0	0	0	0
Malignant schwannoma..(MALIGNANT).....	0	0	0	0	0	0	0	1
ORAL CAVITY								
EXAMINED.....	3	2	2	3	0	1	1	2
Squamous cell carcinoma..(MALIGNANT)..	1	1	0	2	0	0	0	2
OVARY								
EXAMINED.....	-	-	-	-	64	64	64	63
MISSING.....	-	-	-	-	0	0	0	1
Benign granulosa/theca cell tumour (BENIGN).....	-	-	-	-	0	1	0	0
PANCREAS								
EXAMINED.....	64	64	64	64	63	64	63	64
MISSING.....	0	0	0	0	1	0	1	0
Acinar cell adenoma..(BENIGN).....	0	0	1	0	0	0	0	0
Acinar cell adenocarcinoma (MALIGNANT).....	0	0	0	2	0	0	1	0

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
PANCREAS	(CONTINUED)							
Islet cell adenoma..(BENIGN).....	2	0	0	2	0	1	0	0
Islet cell adenocarcinoma (MALIGNANT).....	1	0	0	0	0	0	0	0
PARATHYROID GLAND								
EXAMINED.....	58	61	60	53	56	55	57	58
MISSING.....	6	3	4	11	8	9	7	6
Adenoma..(BENIGN).....	1	0	0	0	0	0	1	0
PITUITARY GLAND								
EXAMINED.....	63	64	64	62	64	62	63	63
MISSING.....	1	0	0	2	0	2	1	1
Adenoma pars distalis..(BENIGN).....	17	21	14	21	42	38	46	37
Adenoma pars intermedia..(BENIGN).....	1	1	2	0	1	0	1	1
Carcinoma pars diatalis..(MALIGNANT)..	0	0	0	0	0	0	0	1
Neuromyoblastoma..(MALIGNANT).....	0	0	0	0	0	0	0	1
PRIMARY TISSUE UNKNOWN								
EXAMINED.....	0	0	0	0	1	0	0	0
Adenocarcinoma..(MALIGNANT).....	0	0	0	0	1	0	0	0
SALIVARY GLAND								
EXAMINED.....	63	64	62	63	64	64	64	64
MISSING.....	1	0	2	1	0	0	0	0
Adenoma..(BENIGN).....	0	0	1	0	0	0	0	0
Squamous cell carcinoma..(MALIGNANT)..	1	0	0	0	0	0	0	0
SEMINAL VESICLE								
EXAMINED.....	64	64	63	64	-	-	-	-
MISSING.....	0	0	1	0	-	-	-	-
Adenocarcinoma..(MALIGNANT).....	0	0	1	1	-	-	-	-
SKIN								
EXAMINED.....	64	64	64	63	64	64	64	64
MISSING.....	0	0	0	1	0	0	0	0

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES 0 ppm	MALES 50 ppm	MALES 250 ppm	MALES 1000 ppm	FEMALES 0 ppm	FEMALES 50 ppm	FEMALES 250 ppm	FEMALES 1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
SKIN (CONTINUED)								
Infundibular keratinising acanthoma - (Keratoacanthoma)..(BENIGN)	1	0	0	1	0	0	0	0
Benign hair follicle - tumour(pilomatrixoma/t-epithel/t-foll - ic/t-lemm)..(BENIGN)	7	1	5	7	1	0	0	1
Sebaceous adenoma..(BENIGN)	0	0	1	0	0	0	0	0
Squamous cell papilloma..(BENIGN)	0	0	0	0	1	0	0	0
SKULL								
EXAMINED	0	0	0	0	0	1	0	0
Chondroma..(BENIGN)	0	0	0	0	0	1	0	0
STOMACH								
EXAMINED	64	64	64	64	64	64	64	64
Malignant schwannoma..(MALIGNANT)	0	0	1	0	0	0	0	0
SUBCUTANEOUS TISSUE								
EXAMINED	9	5	9	7	8	4	9	5
Fibroma..(BENIGN)	0	2	1	1	0	0	0	0
Haemangioma..(BENIGN)	0	0	1	0	0	0	0	0
Lipoma..(BENIGN)	2	0	1	0	0	0	1	0
Malignant Schwannoma..(MALIGNANT)	1	0	2	2	1	0	0	0
Sarcoma NOS..(MALIGNANT)	1	0	1	0	0	0	0	0
TAIL								
EXAMINED	17	27	22	17	0	1	1	2
MISSING	1	0	0	0	0	0	0	0
Infundibular keratinising - acanthoma(Keratoacanthoma)..(BENIGN)	0	0	0	1	0	0	0	0
Squamous cell papilloma..(BENIGN)	0	0	0	1	0	0	0	0
TESTIS								
EXAMINED	64	64	64	64	-	-	-	-

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TABLE 31 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS, NEOPLASTIC (TOTAL)

	MALES				FEMALES			
	0 ppm	50 ppm	250 ppm	1000 ppm	0 ppm	50 ppm	250 ppm	1000 ppm
ANIMALS ON STUDY	64	64	64	64	64	64	64	64
ANIMALS COMPLETED	64	64	64	64	64	64	64	64
TESTIS	(CONTINUED)							
Benign Leydig cell tumour..(BENIGN)...	6	7	6	4	-	-	-	-
Malignant mesothelioma..(MALIGNANT)...	1	3	2	0	-	-	-	-
THYMUS								
EXAMINED.....	62	61	61	61	64	64	63	64
MISSING.....	2	3	3	3	0	0	1	0
Benign thymoma..(BENIGN).....	0	0	2	1	1	0	0	0
Malignant thymoma..(MALIGNANT).....	0	1	1	0	0	0	2	0
THYROID GLAND								
EXAMINED.....	63	64	63	63	64	64	64	64
MISSING.....	1	0	1	1	0	0	0	0
Follicular cell adenoma..(BENIGN).....	0	0	0	1	1	0	1	0
Follicular cell carcinoma (MALIGNANT).....	0	0	0	1	0	0	0	0
C-cell adenoma..(BENIGN).....	4	3	5	2	4	5	4	5
C-cell carcinoma..(MALIGNANT).....	0	0	1	0	0	0	0	1
UTERUS								
EXAMINED.....	-	-	-	-	64	64	64	64
Stromal cell polyp..(BENIGN).....	-	-	-	-	7	4	1	1
Adenocarcinoma..(MALIGNANT).....	-	-	-	-	8	3	7	4
Adenoma..(BENIGN).....	-	-	-	-	0	1	1	1
Squamous cell carcinoma..(MALIGNANT)..	-	-	-	-	0	0	0	1
Malignant schwannoma..(MALIGNANT).....	-	-	-	-	1	0	0	1

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APPENDIX 9 ADDITIONAL DATA

INTERGROUP COMPARISON OF OVERALL TUMOUR INCIDENCE

		Dietary concentration of NOA 446510 (ppm)			
		0(Control)	50	250	1000
Single Tumours					
Males					
Overall (Main+Interim)					
		13/64 (20.3%)	28/64** (43.8%)	25/64* (39.1%)	24/64 (37.5%)
	- Trend	p=0.090			
Overall (Main study)					
		13/52 (25.0%)	26/52* (50.0%)	24/52* (46.2%)	24/52* (46.2%)
	- Trend	p=0.060			
Interim					
		0/12 (0.0%)	2/12 (16.7%)	1/12 (8.3%)	0/12 (0.0%)
	- Trend	p=1.000			
Intercurrent					
		10/25 (40.0%)	14/27 (51.9%)	10/23 (43.5%)	15/31 (48.4%)
	- Trend	p=0.734			
Terminal					
		3/27 (11.1%)	12/25** (48.0%)	14/29** (48.3%)	9/21* (42.9%)
	- Trend	p=0.020*			

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APPENDIX 9 ADDITIONAL DATA

INTERGROUP COMPARISON OF OVERALL TUMOUR INCIDENCE

		Dietary concentration of NOA 446510 (ppm)			
		0(Control)	50	250	1000
Single Tumours					
Females					
Overall (Main+Interim)					
		21/64 (32.8%)	25/64 (39.1%)	23/64 (35.9%)	29/64 (45.3%)
	- Trend	p=0.228			
Overall (Main study)					
		19/52 (36.5%)	23/52 (44.2%)	20/52 (38.5%)	25/52 (48.1%)
	- Trend	p=0.380			
Interim					
		1/11 (9.1%)	2/12 (16.7%)	3/12 (25.0%)	3/11 (27.3%)
	- Trend	p=0.315			
Intercurrent					
		14/30 (46.7%)	11/21 (52.4%)	8/20 (40.0%)	16/23 (69.6%)
	- Trend	p=0.219			
Terminal					
		6/23 (26.1%)	12/31 (38.7%)	12/32 (37.5%)	10/30 (33.3%)
	- Trend	p=0.718			

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APPENDIX 9 ADDITIONAL DATA

INTERGROUP COMPARISON OF OVERALL TUMOUR INCIDENCE

		Dietary concentration of NOA 446510 (ppm)			
		0(Control)	50	250	1000
Multiple Tumours					
Males					
Overall (Main+Interim)					
		26/64 (40.6%)	16/64 (25.0%)	16/64 (25.0%)	17/64 (26.6%)
	- Trend	p=0.111			
Overall (Main study)					
		26/52 (50.0%)	16/52 (30.8%)	16/52 (30.8%)	17/52 (32.7%)
	- Trend	p=0.094			
Interim					
		0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)
	- Trend	p=1.000			
Intercurrent					
		11/25 (44.0%)	7/27 (25.9%)	7/23 (30.4%)	9/31 (29.0%)
	- Trend	p=0.365			
Terminal					
		15/27 (55.6%)	9/25 (36.0%)	9/29 (31.0%)	8/21 (38.1%)
	- Trend	p=0.167			

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APPENDIX 9 ADDITIONAL DATA

INTERGROUP COMPARISON OF OVERALL TUMOUR INCIDENCE

		Dietary concentration of NOA 446510 (ppm)			
		0(Control)	50	250	1000
Multiple Tumours					
Females					
Overall (Main+Interim)					
		32/64 (50.0%)	23/64 (35.9%)	29/64 (45.3%)	21/64 (32.8%)
	- Trend	p=0.140			
Overall (Main study)					
		32/52 (61.5%)	23/52 (44.2%)	28/52 (53.8%)	21/52* (40.4%)
	- Trend	p=0.095			
Interim					
		0/11 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	0/11 (0.0%)
	- Trend	p=1.000			
Intercurrent					
		16/30 (53.3%)	8/21 (38.1%)	11/20 (55.0%)	7/23 (30.4%)
	- Trend	p=0.217			
Terminal					
		16/23 (69.6%)	15/31 (48.4%)	17/32 (53.1%)	14/30 (46.7%)
	- Trend	p=0.196			

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