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DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding Study-rat

MRID NO.: 146394

TOX. CHEM. No.: 320

TESTING FACILITY: The Institute of Environmental Toxicology,
Japan

CITATION: Mitsumori, K. (1984) 2,4-DP Acid (2-(2,4-dichloro-phenoxy)propanoic Acid): 24-Month Oral Chronic Dietary Study in rats: Final Rept. Unpublished study prepared by the Environmental Toxicology Institute. 1069 p.

CONCLUSION: Groups of SPF Fischer 344 rats were orally administered 2,4-DP acid at dietary concentrations of 0; 100; 300; 1,000; and 3,000 ppm for 104 weeks. The following changes were observed in treated animals:

- 1). In 3,000 ppm groups, both treated males and females showed decreases in body weight and food efficiency; evidence of anemia as indicated by changes in the hematology parameters; increases in the levels of alkaline phosphatase, SGPT, and albumin; decrease in urine specific gravity and protein; increases in lipofuscin deposition in kidney proximal tubular cells; and increases in the incidence of diffused hepatocellular swelling. Increased incidence of lipofuscin deposition in hepatic cells was also observed in males.
- 2). In 1,000 ppm groups, both treated males and females showed decreases in urine specific gravity/protein and increases in the incidence of lipofuscin deposition in the proximal tubular cells of the kidneys. Increases in the levels of alkaline phosphatase and SGPT were observed in male rats at week 104.
- 3). In 300 ppm groups, treated males showed a decrease in urine specific gravity/protein.

Based upon these data, the LOEL for the toxicity of 2,4-DP acid is 300 ppm; NOEL, 100 ppm. This study is classified as minimum.

A. MATERIALS:

1. Test compound: Technical 2,4-DP acid (white crystalline solid, 95% purity, lot No. 9/22/80 and 10/31/80). This compound is reported to be stable at room temperature.
2. Test animals: 4-week old SPF Fischer 344 rats were obtained from Charles River Japan, Inc.. Males weighed 60-75 gm; females, 50-65 gm.

- B. STUDY DESIGN: A preliminary 4-week-range finding study was carried out with dietary concentrations of 0; 100; 300; 1,000; 3,000; or 5,000 ppm 2,4-DP acid. At doses of 3,000 ppm or higher, a significant decrease in body weight gain was observed in both males and females. At doses of 1,000 ppm or higher, male rats showed a significant increase in liver weight whereas in females this increase was observed at doses of 3,000 ppm or higher. Based upon these findings, the following treatment groups were selected:

Test Group (ppm)	Total No. of rats per dose group		No. of rats/Interim sac. at 26, 50, & 78 wks	
	male	female	male	female
0	80	80	8	8
100	80	80	8	8
300	80	80	8	8
1,000	80	80	8	8
3,000	80	80	8	8

2. Diet preparation

Diet was prepared twice/week; the stability of the test compound in the diet was determined. Although the report stated that the test compound in the diet was stable for at least 7 days, there was no evidence in the report to show that the analyzed chemical was chemically the same as the test compound.

3. Animals received food and water ad libitum.
4. Statistics - The following procedures were utilized in analyzing the numerical data:
 - Student's-t-test
 - Fisher's exact test
 - Mann-Whitney U test for analysis of urinalysis data.
5. Quality assurance statement was not included in the report.

C. METHODS AND RESULTS:

1. Observations

Animals were observed daily for signs of toxicity and mortality. Clinical signs of toxicity were not observed in 2,4-DP acid treated animals. The survival rates of treated and control animals were similar (Figures 1 and 2).

2. Body weight

Animals were weighed weekly during the first 26 weeks and biweekly thereafter. Consistent weight loss through out the period of the study was reported in 3,000 ppm males and females (Figures 3 & 4). Animals in other treatment groups showed sporadic body weight changes, but these changes were not biologically significant.

3. Food consumption and compound intake

Food consumption was measured twice weekly, and mean daily food intake of each animal was calculated.

There were periodic reductions in food intake in various treatment groups, but these decreases did not persist for any length of time.

The compound intake in each treatment group was calculated from food consumption and body weight data (Table 1).

TABLE 1*
Average Compound Intake of 2,4-DP Treated Rats

<u>Dose (ppm)</u>	<u>Males</u>	<u>(mg//kg/day)</u>	<u>Females</u>
100	3.64		4.42
300	11.01		13.10
1,000	36.50		45.70
3,000	116.10		147.00

* Data taken from the submission (MRID No.: 146394

Fig. 1 Survival curve in male rats

(Data taken from the submission, MRI No. 146394)

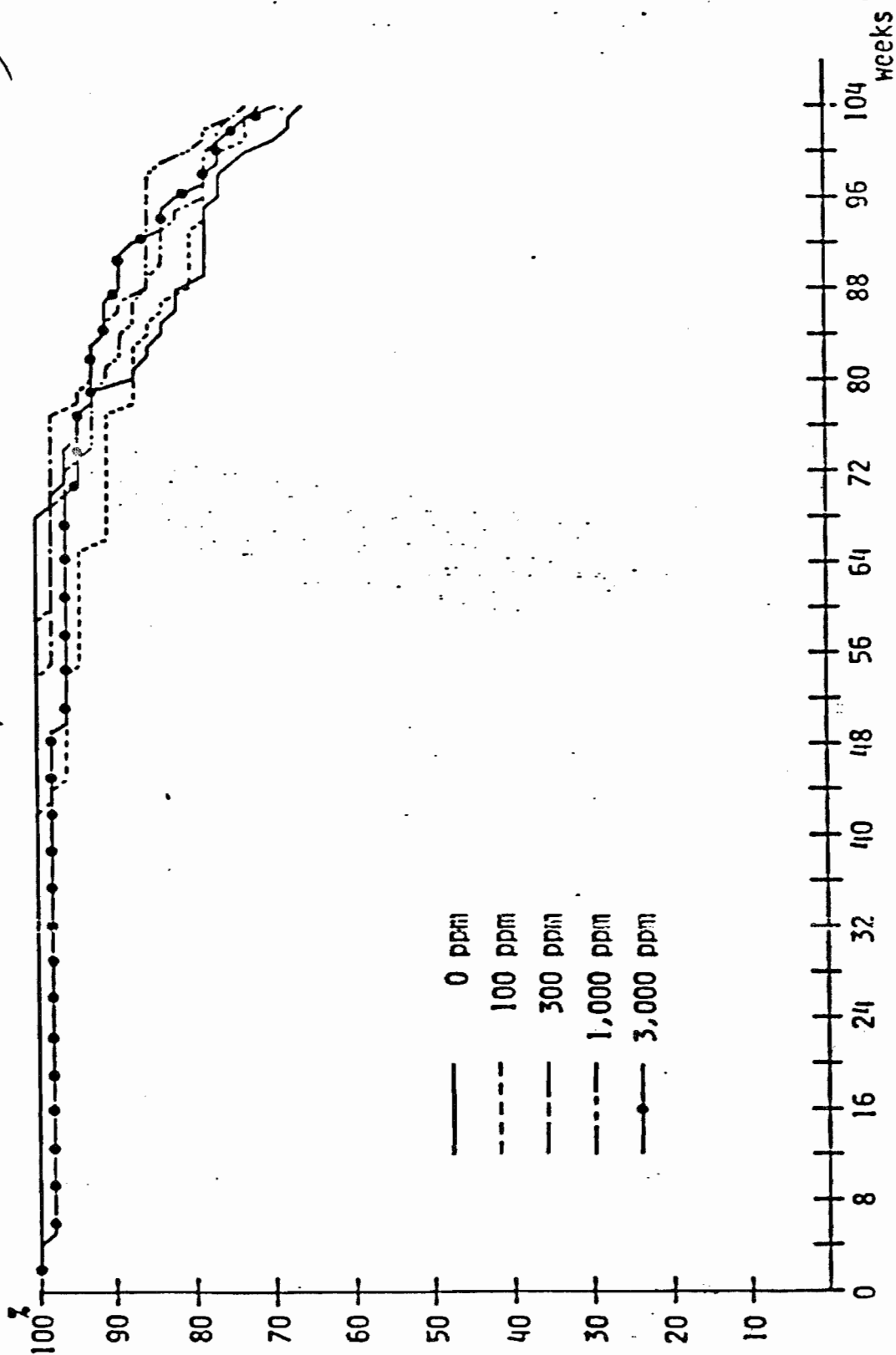
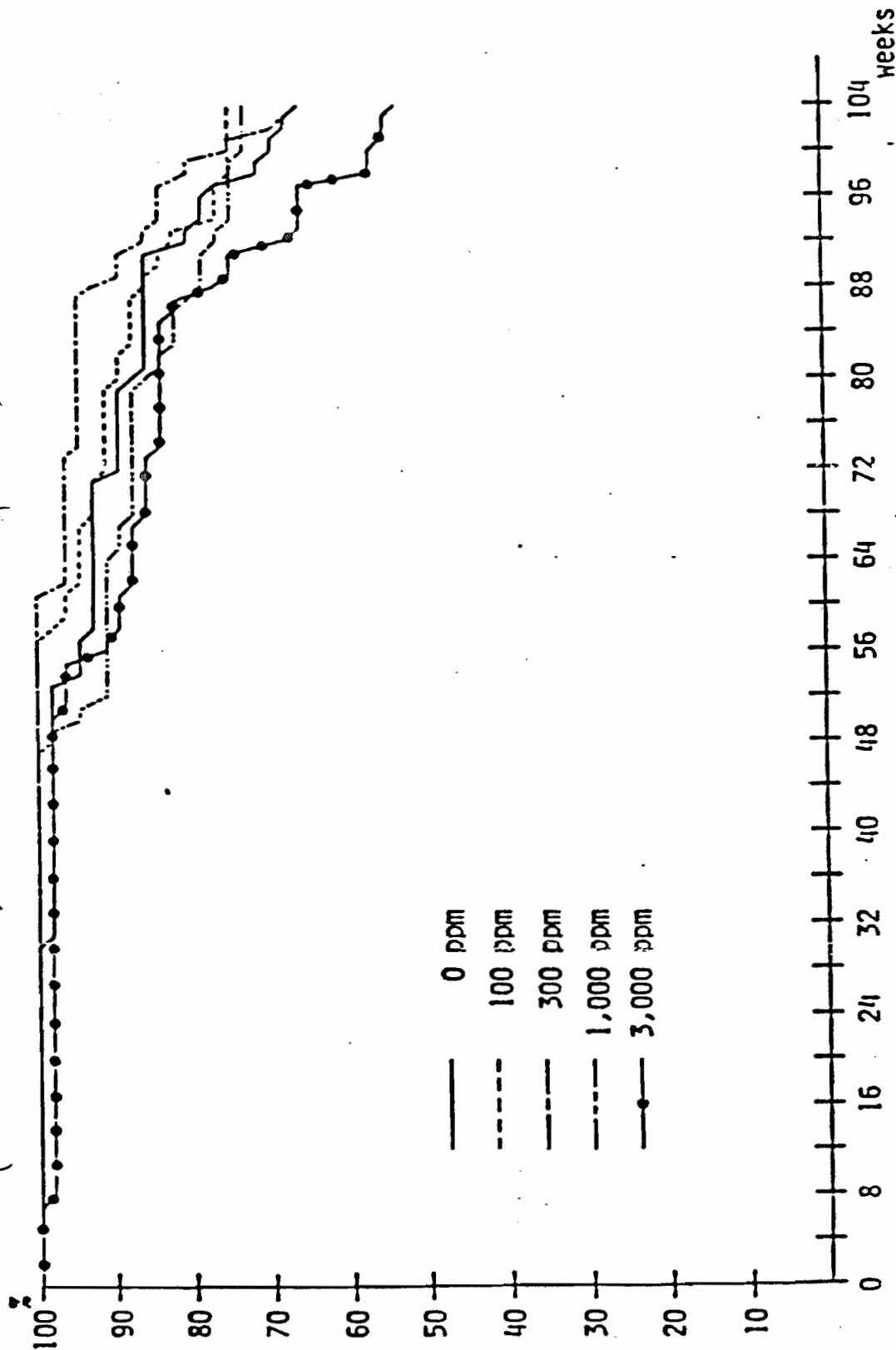


Fig. 2 Survival curve in female rats

(Data taken from the submission, MED No. 146394)



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Fig. 3 Body weight change in male rats

(Data taken from the submission, ^{MRED No.} 146394)

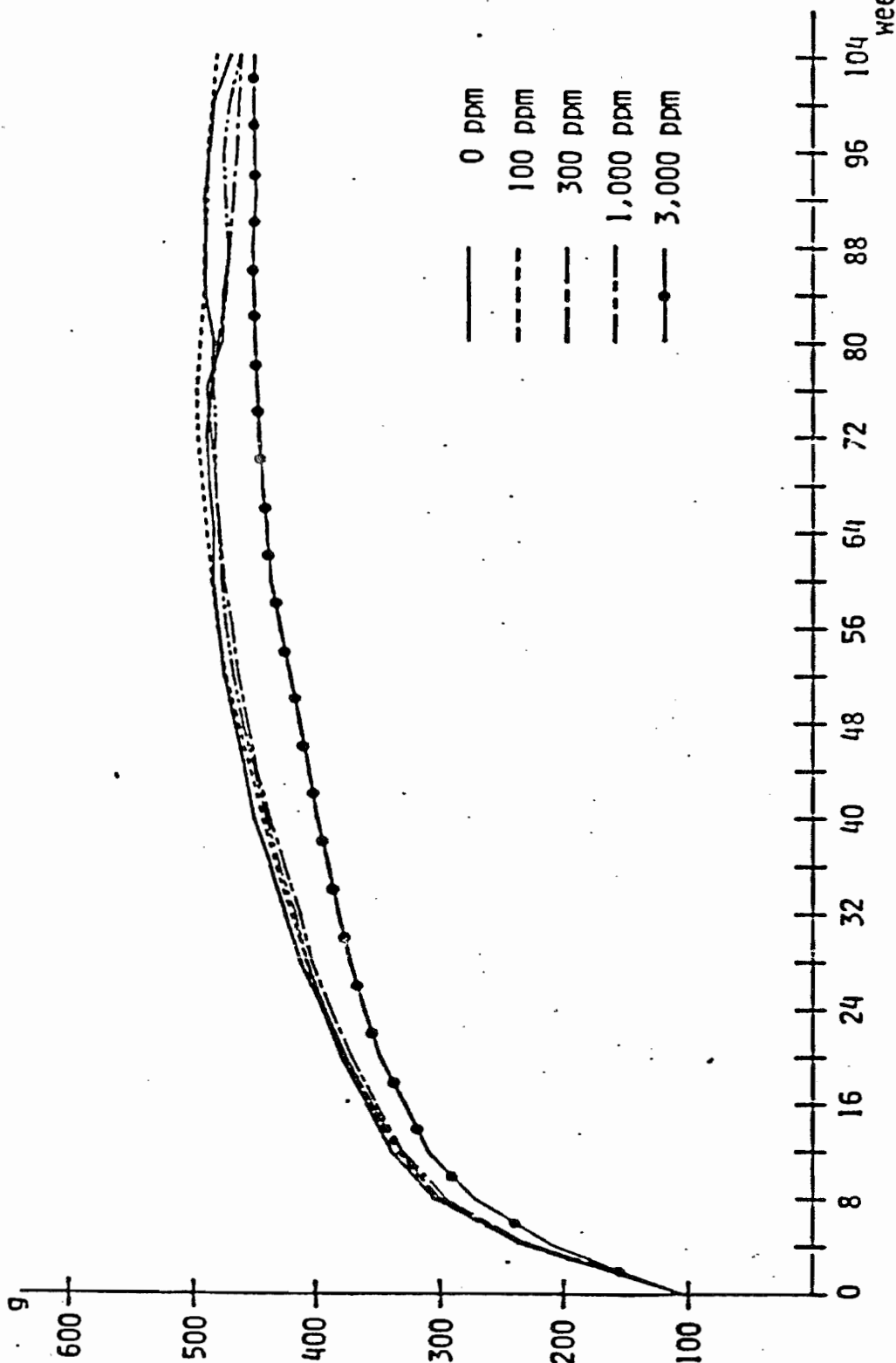
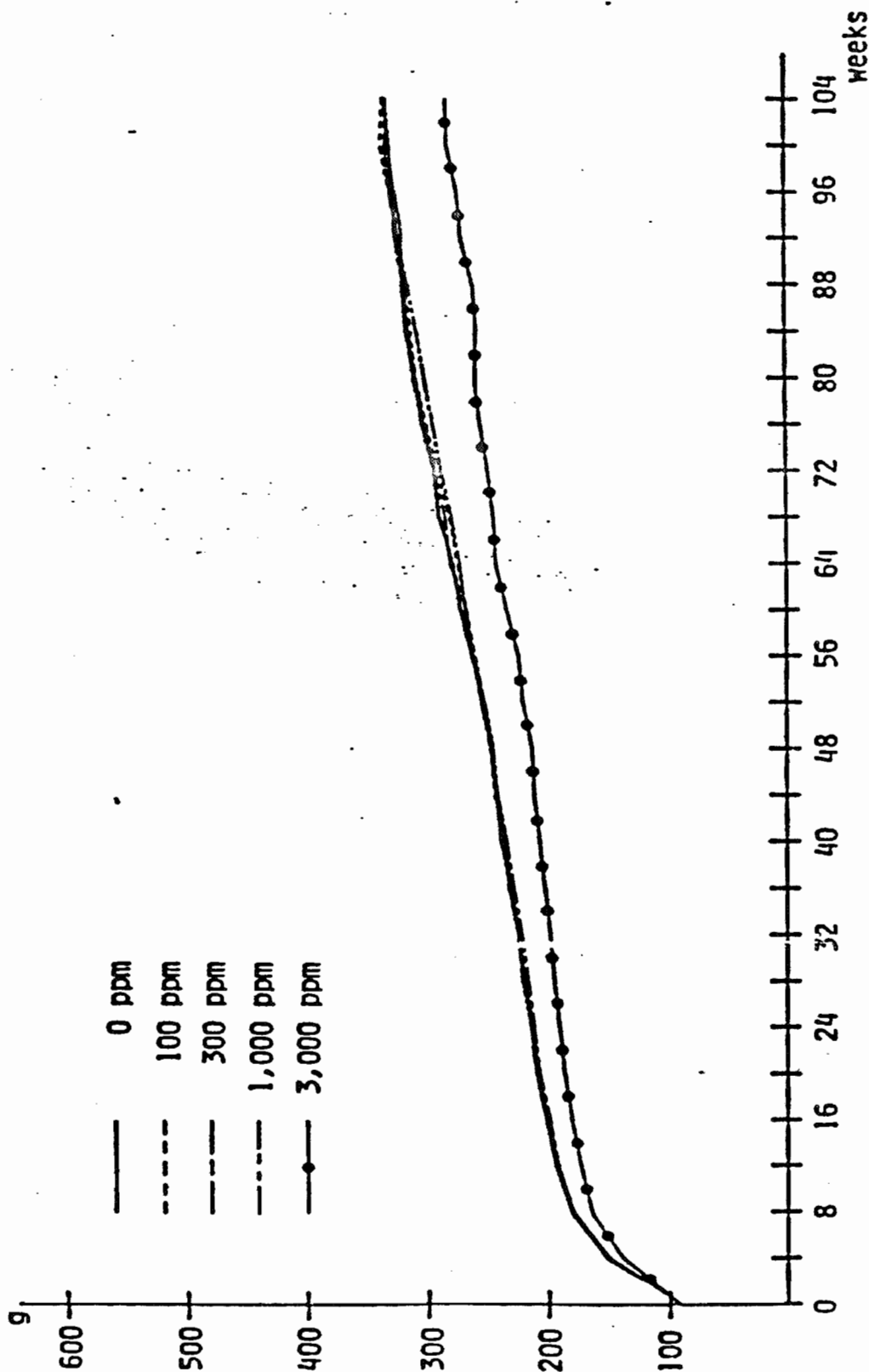


Fig. 4 Body weight change in female rats

(Data taken from the submission, ^{MEP No.} 146394)



Decreased food efficiency was seen in 3,000 ppm females; the cumulative mean value was 16% lower than that of the controls. Other treatment groups did not show any consistent changes in food efficiency relative to the controls.

4. Ophthalmological examinations: No ophthalmological examinations were carried out.
5. Blood was collected from 8 animals/sex/dose at 26, 52, & 78 weeks of treatment. At the termination of the study blood samples were collected from 10 animals/sex/dose for hematology and clinical analyses.

a. Hematology: The CHECKED (X) parameters were examined.

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
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies.

The 3,000 ppm 2,4-DP treated male and female rats developed anemia as evidenced by consistently significant decrease in hematocrit, hemoglobin, and erythrocyte counts at different examination times (Table 2).

There were also sporadic changes in platelet counts, mean corpuscular volume, and mean corpuscular hemoglobin in the 3,000 ppm rats. Other changes in hematological parameters were also observed in 1,000; 300; and 100 ppm animals, but these changes were not consistent. Thus biologically meaningful interpretation could not be made from these inconsistent changes.

TABLE 2†: Means of the Hemotological Parameters for
3,000 ppm 2,4-DP Acid Treated Rats

Dose (ppm)	HT (%)	Hb (g/dl)	RBC (mill/cmm)	MCV (fl)	MCH (pg)
<u>Males</u>					
26 weeks of treatment					
0	41.9+0.9	15.0+0.4	8.67+0.20	48.2+0.4	17.4+0.3
3,000	39.1+1.7**	14.1+0.5**	7.94+0.35***	49.1+0.4***	17.8+0.3*
52 weeks of treatment					
0	42.5+0.7	15.4+0.3	8.97+0.21	47.3+0.4	17.2+0.3
3,000	39.8+1.0***	14.5+0.3***	8.19+0.25***	48.5+0.6***	17.7+0.3
78 weeks of treatment					
0	41.1+3.6	15.9+1.1	8.46+0.74	48.4+1.0	18.8+0.5
3,000	37.1+1.1*	14.2+0.5**	7.56+0.36*	49.0+1.7	18.9+0.8
104 weeks of treatment (termination)					
0	43.7+8.3	16.4+3.1	9.18+1.55	47.3+2.9	17.8+1.1
3,000	38.6+7.9	14.4+2.9	8.36+1.50	45.8+3.5	17.2+1.2
.....					
<u>Females</u>					
26 weeks of treatment					
0	40.3+1.5	14.7+0.5	7.75+0.31	52.0+0.2	19.0+0.3
3,000	38.7+1.3*	14.1+0.5*	7.37+0.28*	52.4+0.4	19.1+0.3
52 weeks of treatment					
0	40.6+0.7	14.8+0.2	7.75+0.21	51.9+0.7	19.1+0.4
3,000	35.1+1.5***	13.3+0.3***	6.68+0.25***	52.4+0.6	19.9+0.4
78 weeks of treatment					
0	39.9+1.0	14.8+0.3	7.64+0.26	52.1+0.9	19.3+0.4
3,000	37.3+2.0**	13.5+0.9**	7.11+0.52*	52.4+1.4	19.0+0.4
104 weeks of treatment (termination)					
0	39.6+4.0	15.0+1.6	7.35+1.12	54.4+4.7	20.7+1.6
3,000	36.0+2.2*	13.7+0.8*	6.70+0.40	53.7+1.5	20.6+0.7

†: Data extracted from the submission (MRID No. 146394).

*: p = 0.05

**: p = 0.01

***: p = 0.001

b. Clinical Chemistry

Electrolytes:		Other:	
x	Calcium*	x	Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorous*	x	Cholesterol*
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
Enzymes		x	Total Bilirubin*
x	Alkaline phosphatase	x	Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*		Serum protein electrophoresis
x	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
x	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies

Should be required for OP

° Not required for subchronic studies

Male Rats:

Male rats which received doses of 1,000 and 3,000 ppm 2,4-DP acid developed significant and consistent increases in the levels of alkaline phosphatase, albumin, and SGPT. Changes in other clinical parameters were also found in males of other doses, but these changes were sporadic. A decrease in cholesterol level was observed in 3,000 ppm males (Table 3a). In 3,000 ppm males, SGOT levels were significantly increased towards the end of the study.

Female Rats:

In female rats, increases in alkaline phosphatase, serum glutamate-pyruvate transaminase, and albumin were observed at 3,000 ppm. These increases were statistically significant at the 26 week of the examination time. Cholesterol levels of 3,000 ppm females were significantly and consistently decreased throughout the period of the study. Similar to that in male rats, other sporadically changes in clinical chemistry parameters were also observed (Table 3b).

TABLE 3a†: Mean Clinical Chemistry Values in 2,4-DP Acid Treated Male Rats

Dose (ppm)	ALP (U/L)	SGPT (U/L)	ALB (g/dl)	BUN (mg/dl)	T-Chol (mg/dl)
<u>Males</u>					
26 weeks of treatment					
0	451 _± 28	43 _± 07	3.32 _± 0.06	21.9 _± 1.1	64.6 _± 6
1,000	491 _± 73	50 _± 06	3.30 _± 0.06	22.1 _± 1.6	64.5 _± 5
3,000	633 _± 26***	45 _± 16	3.66 _± 0.13***	22.3 _± 1.1	39.4 _± 4***
52 weeks of treatment					
0	390 _± 31	57 _± 09	3.18 _± 0.08	22.2 _± 0.7	94 _± 10
1,000	436 _± 40*	68 _± 33	3.29 _± 0.06*	21.9 _± 0.7	90 _± 04
3,000	736 _± 115***	100 _± 47	3.65 _± 0.10***	23.3 _± 0.3*	51 _± 14***
78 weeks of treatment					
0	355 _± 37	33 _± 06	2.97 _± 0.11	20.4 _± 0.9	92 _± 22
1,000	376 _± 68	42 _± 17	3.07 _± 0.12	19.8 _± 1.5	99 _± 17
3,000	652 _± 69***	94 _± 28***	3.46 _± 0.08***	22.5 _± 0.8***	77 _± 09
104 weeks of treatment (termination)					
0	343 _± 63	22 _± 04	2.72 _± 0.20	19.5 _± 2.2	109 _± 24
1,000	436 _± 34*	30 _± 06**	2.80 _± 0.21	20.1 _± 2.3	118 _± 24
3,000	641 _± 158***	49 _± 29*	3.15 _± 0.13***	19.3 _± 1.6	98 _± 29

†: Data extracted from the submission (MRID No. 146394).

*: p = 0.05

**: p = 0.01

***: p = 0.001

ALP: alkaline phosphatase;

ALB: albumin

T-Chol: total cholesterol

SGPT: serum glutamate pyruvate trans-aminase

BUN: blood urea nitrogen

TABLE 3b†: Mean Clinical Chemistry Values in 2,4-DP Acid Treated Female Rats

Dose (ppm)	ALP (U/L)	SGPT (U/L)	ALB (g/dl)	BUN (mg/dl)	T-Chol (mg/dl)
<u>Males</u>					
26 weeks of treatment					
0	341+31	36+8	3.66+0.13	21.4+1.2	95+7
1,000	402+38**	38+7	3.70+0.05	22.2+1.2	91+6
3,000	447+42***	67+8**	3.96+0.26*	23.5+2.1*	67+5***
52 weeks of treatment					
0	329+13	46+9	3.50+0.18	21.9+0.6	107+9
1,000	337+46	38+6	3.89+0.15	23.9+3.7	105+11
3,000	365+46	35+9*	3.91+0.13	23.2+2.0	77+8***
78 weeks of treatment					
0	364+49	37+7	3.31+0.22	20.6+1.8	105+17
1,000	346+50	38+10	3.47+0.24	21.2+1.0	104+12
3,000	364+54	32+6	3.63+0.17**	22.0+1.3	74+11***
104 weeks of treatment (termination)					
0	379+90	44+16	3.34+0.22	19.5+1.2	117+21
1,000	324+67	31+09	3.39+0.37	20.0+1.8	109+25
3,000	429+55	39+17	3.61+0.26*	20.7+1.7	70+13***

†: Data extracted from the submission (MRID No. 146394).

*: p = 0.05

**: p = 0.01

***: p = 0.001

ALP: alkaline phosphatase;

ALB: albumin

T-Chol: total cholesterol

SGPT: serum glutamate pyruvate trans-aminase;

BUN: blood urea nitrogen;

6. Urinalysis[°]

Urine was collected from 8 rats/sex/dose at weeks 26, 52, and 78 weeks of treatment. The CHECKED (X) parameters were examined.

	Appearance*	x	Glucose*
	Volume*	x	Ketones*
x	Specific gravity*		Bilirubin*
x	pH	x	Blood*
	Sediment (microscopic)*		Nitrate
x	Protein*	x	Urobilinogen

* Required for chronic studies

° Not required for subchronic studies

There were statistically significant and consistent decreases in specific gravity and protein in the urine of 3,000 ppm males and female rats. From week 78 to the end of the study, these decreases were also seen in males which received doses as low as 300 ppm; in females, as low as 1,000 ppm. In addition, the decrease in urine specific gravity in males was dose related at week 78 (Table 4). The weekly water consumption data did not show significant and consistent changes at doses of 100 and 300 ppm relative to the controls for both males and females; however, at doses of 1,000 and 3,000 ppm, water consumption was significantly increased.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

Digestive system	Cardiovasc./Hemat.	Neurologic
Tongue	x .Aorta*	xx.Brain*†
.Salivary glands*	xx.Heart*	x Periph. nerve*#
x .Esophagus*	.Bone marrow*	x Spinal cord (3 levels)*#
x .Stomach*	x .Lymph nodes*	xx.Pituitary*
x .Duodenum*	xx.Spleen*	x Eyes (optic n.)*#
x .Jejunum*	xx.Thymus*	Glandular
x .Ileum*	Urogenital	xx.Adrenals*
x .Cecum*	xx.Kidneys*†	Lacrimal gland#
x .Colon*	x .Urinary bladder*	x Mammary gland*#
.Rectum*	x .Testes*†	.Parathyroids*††
xx.Liver*†	x Epididymides	xx.Thyroids*††
Gall bladder*#	x Prostate	Other
x .Pancreas*	x Seminal vesicle	x Bone*#
Respiratory	xx Ovaries*†	xx Skeletal muscle*#
x .Trachea*	x .Uterus*	x Skin*#
x .Lung*		All gross lesions
x Pharynx°		

* Required for subchronic and chronic studies

° Required for chronic inhalation

TABLE 4

Summary of Urine Specific Gravity in 2,4-DP Treated
Male Rats at Various Examination Times†

Dose (ppm)	Urine Specific Gravity			
	26 wk	52 wk	78 wk	104 wk
0	1.074 _± 0.011	1.075 _± 0.006	1.077 _± 0.005	1.061 _± 0.013
100	1.078 _± 0.010	1.069 _± 0.017	1.064 _± 0.010*	1.058 _± 0.011
300	1.077 _± 0.009	1.079 _± 0.006	1.066 _± 0.008*	1.048 _± 0.013**
1,000	1.070 _± 0.008	1.081 _± 0.008	1.061 _± 0.009*	1.050 _± 0.013**
3,000	1.057 _± 0.009*	1.045 _± 0.004**	1.044 _± 0.011**	1.047 _± 0.010**

* : p = 0.01

** : p = 0.001

† Data abstracted from the submission (MRID No. 146394)

- # In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
- † Organ weights required in subchronic and chronic studies
- †† Organ weight required for non-rodent studies

a. Organ Weight:

Male rats:

There was a consistent and non-statistically significant increase in mean liver weight and statistically significant increase in mean heart weight in 3,000 ppm males relative to that of the controls. The mean kidney weights of 1,000 and 3,000 ppm males were also increased throughout the study. The mean muscle weight of 3,000 ppm males was sporadically decreased (Table 5a).

The mean liver to body weight ratios were increased in 3,000 ppm males at 26 and 52 weeks of the study, and those of kidney to body weight ratios were also consistently increased in 1,000 and 3,000 ppm males (Table 6a).

Increases in the ratios of organ to brain weight were observed. Consistent and statistically significant increases in heart to brain weight ratios were found in 3,000 ppm males throughout the study. At doses of 300 and 1,000 ppm, increases in kidney weight to brain weight ratios were found at terminal sacrifice, and these increases were statistically significant (Table 7a)

Females rats:

The mean liver weight of 3,000 ppm females was consistently increased, and mean heart weight was decreased in 3,000 ppm animals throughout the study. Mean muscle weight was sporadically increased (Table 5b).

The organ to body weight ratios of brain, liver, kidney and muscle were consistently increased in 3,000 ppm females. At the terminal sacrifice, the ratios of heart and muscle weights to body weights were significantly increased (Table 6b).

Few consistent changes in the ratios of organ to brain weight were observed except the heart to brain weight ratio which was consistently decreased in 3,000 ppm females throughout the study (Table 7b).

b. Gross Pathology

Male rats:

Increased incidences of dark liver and kidneys were seen in 1,000 and 3,000 ppm animals, and at 3,000 ppm these increases were statistically significant (Table 8a).

Female rats:

The number of animals with dark kidneys were significantly increased in 1,000 and 3,000 ppm females. In addition, a significant increase in the incidence of hair loss was also found in 3,000 ppm females relative to the controls (Table 9).

c. Microscopic pathology

Non-neoplastic Changes:

Several histopathological changes were observed in the experimental animals, but the following changes in the treated animals were significantly different from the controls (Tables 8 & 9).

- 1). Increased incidence of diffuse hepatocellular swelling in 3,000 ppm males and females.
- 2). Increased incidence of brown pigment deposition in proximal tubular cells in 1,000 and 3,000 ppm males and females.
- 3). Increased incidence of pigment deposition in hepatic cells, of kidney mineralization, and of prostatitis in 3,000 ppm male rats.
- 4). Increased incidence of retinal atrophy/degeneration in 3,000 ppm females.

It should be noted that brown pigment deposition in liver and kidneys was found to be due to lipofuscin deposition.

Neoplastic Changes:

Slight and non-statistically significant increase in the incidence of liver neoplastic nodules was observed in 3,000 ppm males (control: 2/80; 3,000 ppm: 6/80); but increased tumor incidence was not found in any organ in either treated males or females.

DISCUSSION:

Based upon the reported data, dietary feeding of 2,4-DP acid to SPF Fischer 344 rats produces a decrease in body weight which was associated with a decrease of food efficiency in 3,000 ppm males and females. The decrease in body weight in animals, which received doses of 3,000 ppm or higher was also seen in a preliminary 4-week range-finding study.

Both 3,000 ppm males and females developed anemia as indicated

by consistent decreases in hematocrit, hemoglobin, and erythrocytes. At doses of 1,000 and 3,000 ppm, consistent increases in the levels of alkaline phosphatase, albumin, and SGPT were observed in males and females. In histopathology, increased incidence of diffuse hepatocellular swelling in both sexes of 3,000 ppm rats and of lipofuscin deposition in hepatic cells in 3,000 ppm males was seen. Changes seen in clinical chemistry parameters correlated with the histopathology findings to clearly show that liver was a target organ for the toxic effects of 2,4-DP acid.

Increased incidence of lipofuscin deposition in proximal tubular cells of the kidney in 1,000 or 3,000 ppm males and females and decreases in urine specific gravity demonstrated that the test compound was toxic to the kidneys. Although the incidence of lipofuscin deposition in proximal tubular cells was observed in 1,000 and 3,000 ppm males and females, the decrease in urine specific gravity in males was observed in doses as low as 300 ppm. It should also be noted that the water consumption of 300 ppm males was not increased relative to the controls.

In 3,000 ppm females, there was a consistent increase in the ratios of kidney to body weight, but the absolute kidney weight was not significantly increased. Similar patterns seem to be present for liver as well. Therefore, the increase in the ratios of organ to body weight could be due to the substantial reduction in body weights.

Therefore, the data indicated that the LOEL for the toxicity of 2,4-DP acid was 300 ppm; NOEL, 100 ppm.

This study has been previously reviewed (Tox. Doc. No. 004654), but the previous DER contains insufficient amount of data and details. In addition, this reviewer does not agree with the classification (Core Guideline) given to this study by the previous reviewer. Although the report presents adequate amount of data to show the toxicology of 2,4-DP acid, the data on urine volume, certain clinical chemistry parameters, and ophthalmology examinations are not reported and are required. The data of urine volume would have been helpful in assessing the significance of the changes in urine specific gravity in treated male rats. Therefore this study is reclassified as minimum.

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Table 5a-1

Organ weight - Group mean values in male rats
Interim kill after 26 weeks of treatment

(DATA TAKEN FROM THE Submission;
MRID No. 146394)

Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
						(Mean ± SD)
0	8	407±19	2,006± 83	9.9±0.9	19.9±2.1	996±45
100	8	405±22	2,058± 77	10.1±0.6	21.3±2.7	1,020±57
300	8	402±19	1,976±105	9.6±0.7	20.6±2.4	1,017±66
1,000	8	402±27	2,023±112	10.0±0.8	21.2±3.4	1,043±98
3,000	8	370±14**	2,095±134	9.7±1.1	20.0±2.3	908±49*

Thymus (mg)	Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Testes (mg)	Muscle (mg)
149±17	12.23±0.68	2,579±187	653±35	38.2±3.4	3,129±154	2,428±216
130±28	12.67±1.09	2,804±149	659±23	40.1±3.3	3,136±158	2,371±184
151±19	12.64±1.10	2,815±178	669±29	40.5±5.1	3,080±119	2,367±133
155±30	12.94±1.09	3,099±223**	672±44	39.1±4.3	3,047±214	2,316±101
149±34	13.26±1.66	2,723±139	591±24**	39.6±3.5	3,062± 66	2,172±128

Organ weight - Group mean values in male rats
Interim kill after 52 weeks of treatment

Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
						(Mean ± SD)
0	8	479±29	2,057±34	11.1±1.3	21.8±1.6	1,115±39
100	8	480±29	2,063±15	10.3±0.9	20.6±2.4	1,107±46
300	8	462±29	2,025±47	10.4±1.3	20.5±3.5	1,086±91
1,000	8	471±31	2,086±42	11.0±1.0	22.3±2.6	1,086±45
3,000	8	422±28**	2,034±42	10.7±2.2	20.2±1.7	1,026±56*

Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Testes (mg)	Muscle (mg)
14.14±1.11	2,855±190	693± 41	41.7±2.2	3,203±162	2,360±140
13.78±0.68	2,786±110	779±237	41.1±2.1	3,000±388	2,382±169
13.01±1.54	2,958±222	649± 46	41.4±3.5	3,154±162	2,388±180
13.83±1.09	3,131±281	706± 45	42.8±5.2	3,221±117	2,349±101
14.86±1.07	3,040±246	634± 52	42.5±3.0	3,042±171	2,184±225

*, ** ; significantly different from the control at 5 and 1% level of probability, respectively

Table Sa-2 Organ weight - Group mean values in male rats (DATA TAKEN FROM THE SUBMISSION, MRED NO. 146394)
Interim kill after 78 weeks of treatment

(Mean±SD)						
Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
0	8	491±34	2,088±84	13.3±1.7	25.0±3.4	1,160±40
100	8	503±33	2,092±56	13.1±1.9	26.4±5.5	1,229±133
300	8	495±43	2,064±94	12.9±2.1	24.6±2.5	1,141±91
1,000	8	486±35	2,079±75	13.0±1.8	24.2±2.7	1,102±67
3,000	8	453±30	2,086±35	12.2±1.5	24.5±7.7	1,077±86

Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Testes (mg)	Muscle (mg)
15.78±1.34	3,057±168	854±83	51.9±3.8	4,484±1,110	2,211±146
15.26±1.62	3,108±283	860±172	58.1±9.7	4,260±1,183	2,245±237
14.92±1.72	3,247±82	782±63	51.1±4.0	3,405±461	2,125±148
14.63±1.85	3,289±240	842±96	51.7±5.6	4,143±897	2,129±109
14.97±1.30	3,304±240	978±299	50.9±4.2	3,478±1,181	2,178±65

Organ weight - Group mean values in male rats
Terminal kill after 104 weeks of treatment

(Mean±SD)						
Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
0	37	473±58	2,123±48	16.5±3.0(33)	51.3±141.4(136)	1,198±118
100	40	486±39	2,145±69	15.4±2.1(32)	29.4±5.8	1,222±132
300	41	464±43	2,106±81	16.3±2.2(34)	29.1±9.4	1,215±123
1,000	41	465±37	2,125±70	15.9±1.9(38)	28.6±5.2	1,205±175
3,000	39	455±40	2,136±56	14.8±2.6(38)	32.1±18.6	1,091±79

Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Testes (mg)	Muscle (mg)
15.19±1.94	3,179±236	1,416±626	109.7±268.2	5,857±1,714	1,829±207
16.05±2.25	3,312±319	1,267±190	70.6±18.6	5,770±1,827	1,895±162
15.37±1.58	3,304±276	1,587±1,088(40)	73.8±30.5	5,237±1,390	1,885±120
15.42±2.07	3,469±270	1,821±1,137	71.0±18.7(40)	6,003±1,964(40)	1,887±147
14.43±1.66	3,520±268	1,173±340	87.5±132.5	5,413±2,070(37)	1,934±137

() : available number of animals for the parameter

*, ** : significantly different from the control at 5 and 0.1% level of probability, respectively

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Table 5b-1

Organ weight - Group mean values in female rats (DATA TAKEN FROM THE SUBMISSION, MRID No. 146394)
Interim kill after 26 weeks of treatment

(Mean ± SD)						
Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
0	8	217±13	1,825±63	14.1±2.0	13.5±2.6	640±31
100	8	217±11	1,852±44	14.5±2.0	13.6±2.0	637±27
300	8	216±9	1,850±25	13.7±0.9	12.0±1.5	619±39
1,000	8	220±10	1,860±43	12.6±2.1	13.3±1.1	620±30
3,000	8	196±10**	1,852±36	14.3±1.6	14.2±1.3	566±28***

Thymus (mg)	Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Ovaries (mg)	Muscle (mg)
123±18	6.70±0.50	1,543±127	454±37	51.6±4.8	60.2±6.2	1,355±55
132±24	6.82±0.44	1,541±85	435±20	50.0±4.1	57.2±10.9	1,298±62
126±19	6.70±0.51	1,549±89	433±35	49.7±3.5	53.4±5.1	1,320±47
120±24	6.77±0.40	1,565±59	444±27	51.2±4.5	61.5±8.2	1,271±74
123±12	7.08±0.66	1,480±103	411±30	49.6±4.6	57.0±6.1	1,251±36

Organ weight - Group mean values in female rats
Interim kill after 52 weeks of treatment

(Mean ± SD)						
Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
0	8	255±25	1,891±41	14.5±1.3	15.3±3.0	728±49
100	8	254±16	1,891±55	14.6±2.7	15.1±2.2	695±17
300	8	256±11	1,890±56	15.2±2.1	15.4±2.0	704±38
1,000	8	255±18	1,882±46	15.7±2.2	17.1±1.9	716±39
3,000	8	221±20**	1,881±58	15.3±2.8	15.6±2.3	652±61

Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Ovaries (mg)	Muscle (mg)
7.68±0.60	1,790±145	460±31	55.5±5.9	59.5±7.7	1,353±90
7.76±0.48	1,793±61	448±21	54.5±2.9	63.9±12.6	1,388±39
8.00±0.40	1,828±86	472±42	58.4±3.9	62.5±5.1	1,380±36
7.98±0.84	1,862±141	462±35	60.9±6.6	65.1±9.0	1,318±70
8.24±0.74	1,701±172	481±65	55.5±6.6	55.8±9.7	1,310±92

*, ** ; significantly different from the control at 5 and 1% level of probability, respectively

Table 2

Organ weight - Group mean values in female rats
Interim kill after 78 weeks of treatment

(DATA TAKEN FROM THE SUBMISSION,
MIED NO. 146394)

(Mean±SD)						
Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
0	8	311±20	1,885±43	15.7±2.0	20.4±3.2	808±51
100	8	301±30	1,898±60	13.0±2.6	17.6±3.4	795±53
300	8	309±32	1,902±20	13.5±1.5	19.5±4.4	773±42
1,000	8	301±35	1,911±24	14.7±2.1	17.2±2.9	769±59
3,000	8	262±35**	1,930±49	15.2±2.9	19.2±2.1	744±58

Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Ovaries (mg)	Muscle (mg)
9.16±0.97	1,988±178	477± 64	64.4±6.4	73.6±10.9	1,336±100
8.13±1.34	1,961±131	503± 53	58.5±7.5	65.0±12.8	1,341±154
8.84±0.34	2,018±132	488± 25	60.3±5.1	60.8± 7.3	1,388± 93
8.83±0.69	2,047±135	508± 63	63.3±5.9	64.4± 7.7	1,299± 72
9.80±0.81	1,912±236	683±573	61.4±4.7	75.9±17.2	1,313±115

Organ weight - Group mean values in female rats
Terminal kill after 104 weeks of treatment

(Mean±SD)						
Dose (ppm)	No. of animals examined	Body weight (g)	Brain (mg)	Pituitary (mg)	Thyroids (mg)	Heart (mg)
0	37	332±37	1,979±60	15.8±3.7(28)	39.9±103.4	879±53
100	42	336±34	1,923±52	15.3±2.8(27)	22.6± 4.0	891±82
300	37	331±36	1,898±62	14.6±2.8(20)	29.0± 21.5	870±59
1,000	41	332±25	1,927±39	16.6±4.7(26)	23.5± 4.4	869±58
3,000	30	280±38***	1,928±45	15.4±2.8(17)	22.9± 4.4	805±63***

Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Ovaries (mg)	Muscle (mg)
9.71±1.03	2,170±159	1,112±1,060	64.5± 5.9	66.0± 12.2	1,314±104
9.79±1.05	2,203±172	817± 829(41)	71.1±19.9	74.1± 15.9(41)	1,315±107
10.33±3.09	2,256±174	1,331±2,059	66.9± 9.5	68.0± 16.7	1,287±109
9.81±1.30	2,292±180*	662± 271	77.3±62.6	208.6±872.0(40)	1,336± 89
9.80±1.57	2,156±145	562± 170	67.0± 8.0	126.5±313.7	1,247±122

() ; available number of animals for the parameter

*, **, *** ; significantly different from the control at 5, 1, and 0.1% level of probability, respectively

(Data taken from submission; MRIID No. 146394)

Table 6a-1

Organ / body weight^a ratio - Group mean values in male rats

Interim kill after 26 weeks of treatment

Dose (p.p.m)	No. of animals examined	Brain	Pituitary	Thyroids ₄	Heart	Thymus
0	8	0.49±0.04	0.0024±0.0003	0.0049±0.0006	0.25±0.01	0.037±0.003
100	8	0.51±0.02	0.0035±0.0002	0.0052±0.0006	0.25±0.01	0.032±0.007
300	8	0.49±0.04	0.0024±0.0001	0.0051±0.0004	0.25±0.02	0.038±0.005
1,000	8	0.51±0.03	0.0025±0.0002	0.0053±0.0008	0.26±0.02	0.039±0.007
3,000	8	0.57±0.04 ^{***}	0.0026±0.0002	0.0054±0.0007	0.25±0.01	0.040±0.009

Liver	Kidneys	Spleen	Adrenals	Testes	Muscle
3.00±0.13	0.63±0.04	0.16±0.01	0.009±0.001	0.77±0.03	0.60±0.03
3.13±0.24	0.69±0.02 ^{**}	0.16±0.01	0.010±0.001	0.77±0.02	0.59±0.03
3.14±0.15	0.70±0.03 ^{**}	0.17±0.01	0.010±0.001	0.77±0.03	0.59±0.02
3.21±0.15 ^{***}	0.77±0.04 ^{***}	0.17±0.01	0.010±0.001	0.76±0.06	0.58±0.02
3.58±0.35 ^{***}	0.74±0.03 ^{***}	0.16±0.01	0.011±0.001 ^{***}	0.83±0.04 ^{***}	0.59±0.03

^a (organ weight/body weight) × 100

*, **, *** ; significantly different from the control at 5, 1, and 0.1% level of probability, respectively

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(Data taken from Submission; M.R.D. No. 146394)

Table 6a-2

Organ / body weight^a ratio - Group mean values in male rats

Interim kill after 52 weeks of treatment

Dose (ppm)	No. of animals examined	(Mean ± SD)				
		Brain	Pituitary	Thyroids	Heart	
0	8	0.43 ± 0.02	0.0023 ± 0.0003	0.0046 ± 0.0003	0.23 ± 0.01	
100	8	0.43 ± 0.03	0.0022 ± 0.0002	0.0043 ± 0.0005	0.23 ± 0.01	
300	8	0.44 ± 0.03	0.0022 ± 0.0003	0.0044 ± 0.0006	0.23 ± 0.01	
1,000	8	0.45 ± 0.04	0.0024 ± 0.0002	0.0048 ± 0.0006	0.23 ± 0.01	
3,000	8	0.49 ± 0.01 ^{***}	0.0024 ± 0.0005	0.0048 ± 0.0006	0.24 ± 0.01	

Liver	Kidneys	Spleen	Adrenals	Testes	Muscle	
2.95 ± 0.13	0.60 ± 0.04	0.15 ± 0.01	0.009 ± 0.001	0.67 ± 0.04	0.49 ± 0.02	
2.87 ± 0.08	0.58 ± 0.04	0.16 ± 0.02	0.009 ± 0.001	0.63 ± 0.08	0.50 ± 0.02	
2.78 ± 0.19	0.64 ± 0.03	0.14 ± 0.01	0.009 ± 0.001	0.68 ± 0.05	0.51 ± 0.03	
2.94 ± 0.18	0.67 ± 0.05	0.15 ± 0.02	0.009 ± 0.001	0.69 ± 0.04	0.50 ± 0.02	
3.53 ± 0.24 ^{***}	0.72 ± 0.06 ^{***}	0.15 ± 0.01	0.010 ± 0.001	0.72 ± 0.06 [†]	0.52 ± 0.04	

^a : (organ weight/body weight) × 100

*, **, *** : significantly different from the control at 5, 1, and 0.1% level of probability, respectively

Table 6-3

(Data taken from submission; MRID No. 146394)

Organ / body weight^a ratio - Group mean values in male rats

Interim kill after 78 weeks of treatment

		(Mean:SD)				
Dose (ppm)	No. of animals examined	Brain	Pituitary	Thyroids	Heart	
0	8	0.43±0.03	0.0027±0.0003	0.0051±0.0006	0.24±0.01	
100	8	0.42±0.03	0.0026±0.0003	0.0052±0.0008	0.25±0.02	
300	8	0.42±0.02	0.0026±0.0005	0.0050±0.0005	0.23±0.01	
1,000	8	0.43±0.03	0.0027±0.0004	0.0050±0.0009	0.23±0.01	
3,000	8	0.46±0.03 [*]	0.0027±0.0004	0.0054±0.0006	0.24±0.01	

Liver	Kidneys	Spleen	Adrenals	Testes	Muscle
3.22±0.16	0.63±0.04	0.18±0.02	0.011±0.001	0.93±0.26	0.45±0.05
3.03±0.18	0.62±0.04	0.17±0.02	0.012±0.002	0.85±0.24	0.45±0.04
3.01±0.25	0.66±0.05	0.16±0.01 [*]	0.011±0.001	0.69±0.10 [*]	0.43±0.03
3.02±0.28	0.68±0.03 [*]	0.17±0.03	0.011±0.001	0.86±0.22	0.44±0.03
3.31±0.28	0.73±0.05 ^{***}	0.21±0.06	0.011±0.001	0.76±0.26	0.48±0.03

a : (organ weight/body weight) × 100

*, **, *** : significantly different from the control at 5 and 0.1% level of probability, respectively

Table 6a-4

(Data taken from submission; MRED No. 14694)

Organ / body weight^a ratio - Group mean values in male rats

Terminal kill after 104 weeks of treatment

Dose (ppm)	No. of animals examined	(Mean:SD)				
		Brain	Pituitary	Thyroids	Heart	
0	37	0.46±0.06	0.0035±0.0008(33)	0.0115±0.0331(36)	0.25±0.03	
100	40	0.44±0.03	0.0032±0.0005(32)	0.0061±0.0011	0.25±0.03	
300	41	0.46±0.04	0.0035±0.0006(34)	0.0063±0.0021	0.26±0.04	
1,000	41	0.46±0.04	0.0034±0.0004(38)	0.0062±0.0010	0.26±0.04	
3,000	39	0.47±0.04	0.0033±0.0006(38)	0.0070±0.0035	0.24±0.02	

Liver	Kidneys	Spleen	Adrenals	Testes	Muscle	
3.24±0.42	0.68±0.10	0.30±0.13	0.024±0.060	1.25±0.37	0.39±0.04	
3.31±0.45	0.68±0.06	0.26±0.05	0.015±0.004	1.39±0.39	0.39±0.04	
3.32±0.32	0.72±0.08	0.35±0.24(40)	0.016±0.008	1.14±0.31	0.41±0.03	
3.27±0.32	0.75±0.08***	0.39±0.47	0.015±0.004(40)	1.29±0.39(40)	0.41±0.03	
3.18±0.34	0.78±0.08***	0.26±0.10	0.019±0.027	1.19±0.45(37)	0.43±0.03***	

a : (organ weight/body weight) × 100

() : available number of animals for the parameter

*, ***, significantly different from the control at 5 and 0.1% level of probability, respectively

Table 66-1

Organ / body weight^a ratio - Group mean values in female rats
Interim kill after 26 weeks of treatment

(Data taken from submission)

Dose (ppm)	No. of animals examined	Brain	Pituitary	Thyroids	Heart	Thymus
0	8	0.84±0.04	0.0065±0.0009	0.0062±0.0013	0.30±0.01	0.057±0.010
100	8	0.85±0.05	0.0067±0.0008	0.0063±0.0009	0.29±0.01	0.060±0.010
300	8	0.86±0.04	0.0064±0.0006	0.0056±0.0006	0.29±0.01	0.059±0.007
1,000	8	0.85±0.03	0.0057±0.0010	0.0061±0.0005	0.28±0.01	0.055±0.011
3,000	8	0.95±0.04***	0.0073±0.0007	0.0073±0.0009	0.29±0.01	0.063±0.005

Liver	Kidneys	Spleen	Adrenals	Ovaries	Muscle
3.09±0.16	0.71±0.04	0.21±0.02	0.024±0.002	0.028±0.003	0.63±0.02
3.14±0.15	0.71±0.02	0.20±0.01	0.023±0.001	0.026±0.005	0.60±0.04
3.11±0.21	0.72±0.03	0.20±0.01	0.023±0.001	0.025±0.003	0.61±0.02
3.08±0.15	0.71±0.05	0.20±0.01	0.023±0.002	0.028±0.003	0.58±0.04*
3.63±0.32*	0.76±0.04	0.21±0.01	0.025±0.002	0.029±0.003	0.64±0.02

^a (organ weight/body weight) × 100

*, **, *** : significantly different from the control at 5, 1, and 0.1% level of probability, respectively

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Table 66b-2

Organ / body weight^a ratio - Group mean values in female rats
Interim kill after 52 weeks of treatment

Dose (ppm)	No. of animals examined	(Mean±SD)			
		Brain	Pituitary	Thyroids	Heart
0	8	0.75±0.08	0.0057±0.0007	0.0060±0.0010	0.79±0.01
100	8	0.75±0.06	0.0058±0.0009	0.0060±0.0009	0.77±0.01
300	8	0.75±0.03	0.0059±0.0007	0.0060±0.0008	0.78±0.01
1,000	8	0.74±0.06	0.0062±0.0008	0.0067±0.0008	0.78±0.02
3,000	8	0.85±0.06 ^{***}	0.0070±0.0015	0.0071±0.0009	0.70±0.01

Liver	Kidneys	Spleen	Adrenals	Ovaries	Muscle
3.02±0.15	0.70±0.05	0.18±0.01	0.022±0.002	0.023±0.001	0.53±0.04
3.08±0.33	0.71±0.07	0.18±0.02	0.022±0.002	0.025±0.005	0.55±0.03
3.13±0.18	0.72±0.03	0.18±0.02	0.023±0.001	0.025±0.002	0.54±0.02
3.13±0.20	0.73±0.06	0.18±0.01	0.024±0.002	0.026±0.003	0.52±0.02
3.73±0.21 ^{***}	0.77±0.06 ^{***}	0.22±0.03 ^{***}	0.025±0.002 ^{***}	0.025±0.004	0.59±0.03 ^{***}

^a : (organ weight/body weight) × 100

*, **, *** : significantly different from the control at 5, 1, and 0.1% level of probability, respectively

Table 6B-3

Organ / body weight^a ratio - Group mean values in female rats
Interim kill after 78 weeks of treatment

Dose (ppm)	No. of animals examined	(Mean ± SD)			
		Brain	Pituitary	Thyroids	Heart
0	8	0.61±0.04	0.0051±0.0009	0.0066±0.0008	0.26±0.02
100	8	0.63±0.05	0.0043±0.0008	0.0059±0.0010	0.26±0.02
300	8	0.62±0.07	0.0044±0.0007	0.0063±0.0014	0.25±0.03
1,000	8	0.64±0.07	0.0050±0.0008	0.0058±0.0009	0.26±0.03
3,000	8	0.75±0.09**	0.0059±0.0011	0.0075±0.0013	0.29±0.03

Liver	Kidneys	Spleen	Adrenals	Ovaries	Muscle
2.95±0.24	0.64±0.05	0.16±0.01	0.021±0.003	0.024±0.003	0.43±0.02
2.70±0.35	0.65±0.04	0.17±0.02	0.019±0.003	0.022±0.004	0.45±0.04
2.89±0.29	0.66±0.06	0.16±0.02	0.020±0.003	0.019±0.002	0.45±0.03
2.95±0.24	0.68±0.07	0.17±0.02	0.021±0.002	0.022±0.004	0.44±0.06
3.79±0.50**	0.74±0.10	0.27±0.25	0.024±0.003	0.029±0.005	0.51±0.04**

a : (organ weight/body weight) × 100

*, ** : significantly different from the control at 5 and 1% level of probability, respectively

Table 66-4

Organ / body weight^a ratio - Group mean values in female rats
Terminal kill after 104 weeks of treatment

Dose (p/m)	No. of animals examined	Brain	Pituitary	Thyroids	(Mean±SD)	
					Heart	Muscle
0	37	0.59±0.07	0.0049±0.0013(28)	0.0138±0.0420	0.27±0.03	
100	42	0.38±0.07	0.0047±0.0009(27)	0.0063±0.0012	0.27±0.04	
300	37	0.58±0.06	0.0042±0.0007(20)	0.0087±0.0059	0.27±0.04	
1,000	41	0.58±0.04	0.0050±0.0014(26)	0.0071±0.0015	0.26±0.02	
3,000	30	0.70±0.09 ^{***}	0.0057±0.0012(17)	0.0083±0.0016	0.29±0.03 ^{**}	
Liver	Kidneys	Spleen	Adrenals	Ovaries		
					Muscle	
2.94±0.32	0.66±0.08	0.36±0.66	0.020±0.003	0.023±0.004	0.40±0.03	
2.93±0.36	0.66±0.07	0.25±0.28(41)	0.021±0.006	0.022±0.005(41)	0.39±0.04	
3.15±1.09	0.69±0.10	0.42±0.96	0.021±0.004	0.021±0.005	0.39±0.04	
2.96±0.38	0.69±0.07 ^{***}	0.20±0.09	0.024±0.020	0.066±0.282(40)	0.40±0.04	
3.52±0.57 ^{***}	0.78±0.10 ^{***}	3.20±0.08	0.025±0.005 ^{***}	0.049±0.134	0.45±0.04 ^{***}	

a : (organ weight/body weight) × 100

() : available number of animals for the parameter

*, **, *** : significantly different from the control at 5, 1, and 0.1% level of probability, respectively

(Data taken from Submission; NRID No. 146394)

Table 7a-1

Organ / brain weight ratio - Group mean values in female rats
Interim kill after 26 weeks of treatment

Dose (mg)	No. of animals examined	Heart	Liver	Kidneys	Spleen
0	0	Mean S.D.	3.67 0.19	0.84 0.05	0.25 0.02
100	0	Mean S.D.	3.68 0.23	0.83 0.04	0.24 0.01
300	0	Mean S.D.	3.63 0.31	0.84 0.06	0.23 0.02
1,000	0	Mean S.D.	3.64 0.24	0.84 0.03	0.24 0.01
3,000	0	Mean S.D.	3.82 0.30	0.80 0.05	0.22** 0.01

S.D. / standard deviation

*, **, *** / significantly different from the control at 5, 1, and 0.1% level of probability, respectively

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(Data taken from Submission, MRID No. 146394)

Organ / brain weight ratio - Group mean values in female rats
interim kill after 52 weeks of treatment

Table 7a-2

Dose (mg)	No. of animals examined	Heart	Liver	Kidneys	Spleen
0	8	mean S.D.	4.06 0.30	0.93 0.06	0.24 0.01
100	8	mean S.D.	4.10 0.26	0.93 0.03	0.24 0.01
300	8	mean S.D.	4.21 0.21	0.96 0.04	0.25 0.02
1,000	8	mean S.D.	4.24 0.43	0.99 0.07	0.25 0.02
3,000	8	mean S.D.	4.30 0.31	0.90 0.07	0.26 0.03

S.D. / standard deviation

* / significantly different from the control at 5 % level of probability

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(Data taken from submission; MRID No. 146394)

Table 7a-3

Organ / brain weight ratio - Group mean values in female rats
Interim kill after 70 weeks of treatment

Dose (pym)	No. of animals examined	Heart	Liver	Kidneys	Spleen
0	0	Mean S.D.	4.06 0.46	1.05 0.08	0.26 0.03
100	0	Mean S.D.	4.20 0.64	1.03 0.04	0.26 0.02
300	0	Mean S.D.	4.65 0.20	1.06 0.00	0.26 0.02
1,000	3	Mean S.D.	4.62 0.36	1.07 0.06	0.27 0.03
3,000	0	Mean S.D.	5.08 0.41	0.29 0.11	0.35 0.29

S.D. / standard deviation

*,** / significantly different from the control at 5 and 1 % level of probability, respectively

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(Data taken from Submission; MRID No. 146394)

Table 7a-4

Organ / brain weight ratio - Group mean values in female rats
Terminal kill after 104 weeks of treatment

Dose (ppm)	No. of animals examined	Heart	Liver	Kidneys	Spleen
0	37	Mean S.D.	5.04 0.50	1.12 0.00	0.58 0.99
100	42	Mean S.D.	5.09 0.58	1.15 0.09	0.42 0.41 (41)
300	37	Mean S.D.	5.45 1.63	1.19** 0.11	0.70 1.50
1,000	41	Mean S.D.	5.09 0.66	1.19** 0.09	0.34 0.14
3,000	30	Mean S.D.	5.00 0.02	1.12 0.07	0.29 0.10

S.D. = standard deviation

() = available number of animals for the parameter

,* = significantly different from the control at 1 and 0.1% level of probability, respectively

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Table 8-1 (Data TAKEN From the Submissions; MRED No. 143394)
Incidence of major pathological lesions in each designated period in male rats

Findings	Dose group (ppm)	Treatment period (weeks)									
		0 - 26 fd+ke	26 lk	27 - 52 fd+ke	52 lk	53 - 78 fd+ke	78 lk	79 - 104 fd+ke	104 tk	Total	
Gross findings											
Liver: Dark in color	0	0/0 ^b	0/8	0/0	0/0	0/4	0/8	0/15	0/34	0/80	
	100	0/0	0/8	0/2	0/8	0/5	0/8	0/9	0/40	0/80	
	300	0/0	0/8	0/0	0/8	0/3	0/8	0/12	0/41	0/80	
	1,000	0/0	0/8	0/0	0/8	1/4	0/8	0/11	0/41	1/80	
	3,000	0/1	0/8	0/1	5/8*	0/2	1/8	0/13	0/39	6/80*	
Kidney: Dark in color	0	0/0	0/8	0/0	0/8	0/4	0/8	1/15	0/37	1/80	
	100	0/0	0/8	0/2	0/8	0/5	0/8	2/9	0/40	2/80	
	300	0/0	0/8	0/0	0/8	0/3	0/8	2/12	0/41	2/80	
	1,000	0/0	0/8	0/0	2/8	1/4	1/8	1/11	3/41	8/80*	
	3,000	0/1	0/8	0/1	8/8***	0/2	6/8**	4/13	13/39***	31/80***	
Histological findings											
Liver: Diffuse hepatocellular swelling	0	0/0	0/8	0/0	0/8	0/4	0/8	0/15	0/37	0/80	
	100	0/0	0/8	0/2	0/8	0/5	0/8	0/9	0/40	0/80	
	300	0/0	0/8	0/0	0/8	0/3	0/8	0/12	0/41	0/80	
	1,000	0/0	0/8	0/0	0/8	0/4	0/8	0/11	0/41	0/80	
	3,000	1/1	8/8***	1/1	8/8***	1/2	7/8***	8/13***	28/39***	62/80***	

^a n, No. of rats with lesions; n, No. of rats examined; lk, interim kill; tk, terminal kill; fd, found dead; ke, killed in extremis; *p<0.05, **p<0.01, ***p<0.001 (Fisher's exact test), as compared to the controls

Table 8-2 (Data Taken From the Submission; MRID No. 146394)

Incidence of major pathological lesions in each designated period in male rats

Findings	Dose group (pym)	Treatment period (weeks)										Total
		0 - 26 fd+ke	26 lk	27 - 52 fd+ke	52 lk	53 - 78 fd+ke	78 lk	79 - 104 fd+ke	104 lk	104 tk		
Histological findings												
Liver: Increased brown pigment deposition in hepatic cells	0	0/0 ^b	0/0	0/0	0/0	0/4	0/8	0/15	0/37	0/80		
	100	0/0	0/0	0/2	0/0	0/5	0/8	0/9	0/40	0/80		
	300	0/0	0/0	0/0	0/0	0/3	0/8	0/12	0/41	0/80		
	1,000	0/0	0/0	0/0	0/0	0/4	0/8	0/11	0/41	0/80		
	3,000	0/1	0/0	1/1	6/0 ^{**}	1/2	4/8 [*]	7/13 ^{**}	7/39 ^{**}	26/80 ^{***}		
Kidney: Mineralization	0	0/0	0/0	0/0	0/0	0/4	0/8	0/15	0/37	0/80		
	100	0/0	0/0	0/2	0/0	1/5	0/8	0/9	0/40	1/80		
	300	0/0	0/0	0/0	0/0	0/3	0/8	0/12	0/41	0/80		
	1,000	0/0	0/0	0/0	0/0	1/4	0/8	0/11	0/41	1/80		
	3,000	0/1	0/0	1/1	0/0	0/2	1/8	1/13	5/39 [*]	8/80 ^{**}		
Increased brown pigment deposition in proximal tubular cells	0	0/0	0/0	0/0	0/0	0/4	0/8	2/15	1/37	3/80		
	100	0/0	0/0	0/2	0/0	0/5	0/8	2/9	0/40	2/80		
	300	0/0	0/0	0/0	0/0	0/3	0/8	1/12	1/41	2/80		
	1,000	0/0	0/0	0/0	5/0 [*]	1/4	7/8 ^{***}	6/11 [*]	34/41 ^{***}	53/80 ^{***}		
	3,000	0/1	0/0	1/1	8/0 ^{***}	2/2	8/8 ^{***}	13/13 ^{***}	39/39 ^{***}	71/80 ^{***}		
Prostate: Prostatitis	0	0/0	0/0	0/0	0/0	1/4	0/8	2/15	6/37	9/80		
	100	0/0	0/0	0/2	0/0	0/5	0/8	0/9	8/40	8/80		
	300	0/0	0/0	0/0	0/0	1/3	0/8	0/11	9/41	10/79		
	1,000	0/0	0/0	0/0	0/0	1/4	0/8	2/11	15/41 [*]	18/80 [*]		
	3,000	0/1	0/0	0/1	0/0	1/2	0/0	1/13	16/39 [*]	18/80 [*]		

^a n, No. of rats with lesions; n, No. of rats examined; lk, interim kill; tk, terminal kill; fd, found dead; ke, killed in extremis;

^b p < 0.05, *p < 0.01, **p < 0.001 (Fisher's exact test), as compared to the controls

Table 9-1 (DATA TAKEN FROM THE SUBMISSION; MRID No. 146394)
Incidence of major pathological lesions in each designated period in female rats

Findings	Dose group (ppm)	Treatment period (weeks)												Total
		0 - 26	26	27 - 52	52	53 - 78	78	79 - 104	104	104	tk	tk	tk	
Gross findings Kidney: Dark in color	0	0/0 ^b	0/0	0/1	0/0	0/5	0/8	1/13	1/37	1/37	2/80	2/80	2/80	
	100	0/0	0/0	0/0	0/0	1/5	0/8	0/9	1/42	1/42	2/80	2/80	2/80	
	300	0/0	0/0	0/0	0/0	0/3	0/8	0/16	5/37	5/37	5/80	5/80	5/80	
	1,000	0/0	0/0	0/5	2/8	0/2	0/8	1/8	17/41***	17/41***	20/80***	20/80***	20/80***	
	3,000	0/1	0/8	0/1	6/8**	0/7	0/8	6/17	21/30***	21/30***	33/80***	33/80***	33/80***	
Skin: Hair loss	0	0/0	0/0	0/1	0/8	0/5	2/8	3/13	4/37	4/37	9/80	9/80	9/80	
	100	0/0	0/0	0/0	0/8	0/5	1/8	2/9	6/42	6/42	9/80	9/80	9/80	
	300	0/0	0/0	0/0	0/8	0/3	0/8	2/16	6/37	6/37	8/80	8/80	8/80	
	1,000	0/0	0/8	0/5	0/8	0/2	1/8	0/8	7/41	7/41	8/80	8/80	8/80	
	3,000	0/1	0/8	0/1	0/8	1/7	4/8	8/17	9/30*	9/30*	22/80**	22/80**	22/80**	
Histological findings Liver: Diffuse hepatocellular swelling	0	0/0	0/0	0/1	0/8	0/5	0/8	0/13	0/37	0/37	0/80	0/80	0/80	
	100	0/0	0/8	0/0	0/8	0/5	0/8	0/9	0/42	0/42	0/80	0/80	0/80	
	300	0/0	0/0	0/0	0/0	0/3	0/8	0/16	0/37	0/37	0/80	0/80	0/80	
	1,000	0/0	0/0	0/5	0/8	0/2	0/8	0/8	0/41	0/41	0/80	0/80	0/80	
	3,000	1/1	0/0***	1/1	8/8***	5/7*	3/8	11/17***	26/30***	26/30***	63/80***	63/80***	63/80***	

^a No. of rats with lesions; ^b No. of rats examined; lk, interim kill; tk, terminal kill; fd, found dead; ke, killed in extremis;

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Fisher's exact test), as compared to the controls

Table 9-2 (DATA TAKEN FROM THE SUBMISSION; MRID NO. 146394)
Incidence of major pathological lesions in each designated period in female rats

Findings	Dose group (n/m)	Treatment period (weeks)										Total
		0 - 26 fake	26 lk	27 - 52 fake	52 lk	53 - 78 fake	78 lk	79 - 104 fake	104 lk			
Histological findings												
Kidney: Increased brown pigment deposition in proximal tubular cells	0	0/0 ^b	0/0	0/1	0/0	0/5	0/0	7/13	1/37	R/RQ		
	100	0/0	0/0	0/0	0/0	1/5	0/0	0/9*	0/42	1/10*		
	300	0/0	0/0	0/0	0/0	0/3	0/0	0/16**	5/37	5/80		
	1,000	0/0	0/0	0/5	3/8	0/2	4/8*	3/8	29/41***	39/80***		
	3,000	0/1	0/0	1/1	8/0***	5/7*	8/8***	16/17*	30/30***	68/80***		
Eye: Retinal atrophy/degeneration												
	0	0/0	0/0	0/1	0/0	0/1	0/0	0/9	1/37	1/75		
	100	0/0	0/0	0/0	0/0	0/5	0/6	2/0	3/39	5/74		
	300	0/0	0/0	0/0	0/7	0/3	0/8	1/12	3/34	4/72		
	1,000	0/0	1/8	0/5	0/0	0/2	0/8	0/5	3/41	6/77		
	3,000	0/1	0/8	0/1	0/0	0/7	0/5	4/15	9/30**	13/75***		

n^a, No. of rats with lesions; n^b, No. of rats examined; lk, interim kill; tk, terminal kill; fl, found dead; ke, killed in extremis;

*p<0.05, **p<0.01, ***p<0.001 (Fisher's exact test), as compared to the controls