

られた。また、同群の雌雄全例に軽度な炎症細胞の集積が肝実質内に散見された。同様の変化は2,000ppm以下の群では認められなかった。そのほか雄で心筋炎、腎尿細管の好酸性小体あるいは雌の腎臓で石灰沈着が散見された。これらはいずれも本系統のこの時期の動物に観察される変化であり、程度・頻度ともに投与に関連した変動は認められなかった。休薬期間終了後の検査では、肝臓に肉眼的異常はいずれの群においても観察されず、病理組織学的検査では10,000ppm群の肝細胞脂肪化は著しく減少していた。同群の雄では軽度な脂肪化が残るものの、雌では数例に軽微な脂肪化が観察されるのみであった。また、肝細胞に脂肪化が残る個体ではリンパ球集積および小肉芽腫など炎症が慢性化した組織像が散見された。腎臓、脾臓、骨髄など造血器系の臓器には投与に関連した異常は認められなかった。

## E. 考察

雌雄のF344ラットにメバロン酸を混餌投与し、90日間反復投与毒性試験および4週間の回復性試験を実施した。メバロン酸投与に一般状態の変化など毒性兆候は観察されなかったが、最高用量群の10,000ppm群の雌雄において投与期間の後半に有意な体重増加抑制が散見された。摂餌量は投与期間中、対照群を含む全ての群で同様であったことから、10,000ppm群で観察された体重増加抑制はメバロン酸投与による影響であると考えられた。2,000ppm以下の投与群の体重では投与による影響は観察されなかった。

投与期間および休薬期間終了時に実施した尿検査の各検査項目は、全ての群で同様の値を示したことから、尿検査において投与に関連する異常は認められないと考えられた。

本試験の血液化学的検査および病理学検査結果より、メバロン酸の90日間混餌投与は10,000ppm群で小葉中心性肝細胞脂肪化とそれに関連した変化が認められることか明らかとなった。同群での肝臓の変化は肉眼的にも脂肪肝様に観察され、雄でより強い変化として認められた。同群の雌で認められた総コレステロール値および中性脂肪の有意な増加は、肝細胞脂肪化に関連した脂肪代謝異常の結果と考えられるが、病理学的変化がより強かった雄に同様の変化が観察されなかった原因については不明である。また、10,000ppm群の雌雄で炎症性細胞の集積が肝臓で認められたが、この原因として肝細胞脂肪化が進行し肝細胞質中の脂肪滴が大きくなり肝細胞を破壊したことによる反応性変化と考えられ、同群の雌雄で観察された軽度なALTの上昇も、肝細胞の軽度の破壊を示唆する所見であると考え

られた。回復期間終了後の検査では、肝細胞脂肪化は雌雄とも明らかに減少しており、雌では異常が全く認められない個体も存在した。また、炎症細胞の出現も減少し、より慢性化する方向を示したことから、メバロン酸投与による肝細胞脂肪化は、4週間の休薬では完全に回復しないものの、投与を中止することにより回復する可能性の高い可逆性の変化であることが明らかとなった。2,000ppm以下の投与群では投与に関連する異常は認められなかった。

血液学的検査では、10,000ppm群の雌雄で軽度ながら貧血傾向が認められたが、造血器系臓器に対応する組織学的変化は認められなかった。この軽度な貧血傾向は予備試験においても同用量を投与した動物で観察されたことから、メバロン酸投与に関連した変化であると考えられた。この貧血の原因については不明であるが、造血器系臓器に異常が観察されなかったことから、造血器系への直接障害であるとは考え難く、むしろ肝細胞障害に伴いヘム蛋白の合成異常が報告されていることから、この貧血傾向は同群で観察された肝代謝障害に関連した二次的な変化である可能性が示唆された。休薬後は、貧血を示唆する所見は認められず、貧血傾向は投与中止により回復すると考えられた。

2,000ppm以下の投与群では、上述の変化を始め投与に関連する有意な差異は対照群との間に認められなかった。

以上の結果より、メバロン酸の混餌投与による90日間反復投与により、10,000ppm群の雌雄で肝細胞脂肪化とそれに伴う炎症性変化が認められ、脂肪化による肝細胞破壊により雌雄で血清中ALTが上昇した。これらの肝臓の変化は、雄でより強く認められたが、雌では血清中の総コレステロールおよび中性脂肪値の上昇も観察された。これらの変化はいずれも4週間の休薬期間により回復傾向を示した。また、肝代謝障害に関連したと考えられる軽度な貧血傾向が10,000ppm群の雌雄で観察されたが、この傾向は休薬により回復した。2,000ppm以下の投与群ではメバロン酸投与による毒性影響はいずれの項目においても観察されなかった。

## F. 結論

F344ラットを用いたメバロン酸の90日間反復投与毒性試験による影響量は雌雄とも10,000ppm(雄 709.94mg/kg/day、雌 750.47mg/kg/day)、無影響量を雌雄とも2,000ppm(雄 149.54mg/kg/day、雌 155.46mg/kg/day)と結論し、10,000ppm群で認められた毒性影響はいずれも回復あるいは回復

傾向を示す可逆性の変化であると考えられた。

#### G. 健康危険情報

なし

#### H. 研究発表

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#### I. 知的所有権の取得状況

特許取得

なし

実用新案登録

なし

その他

なし

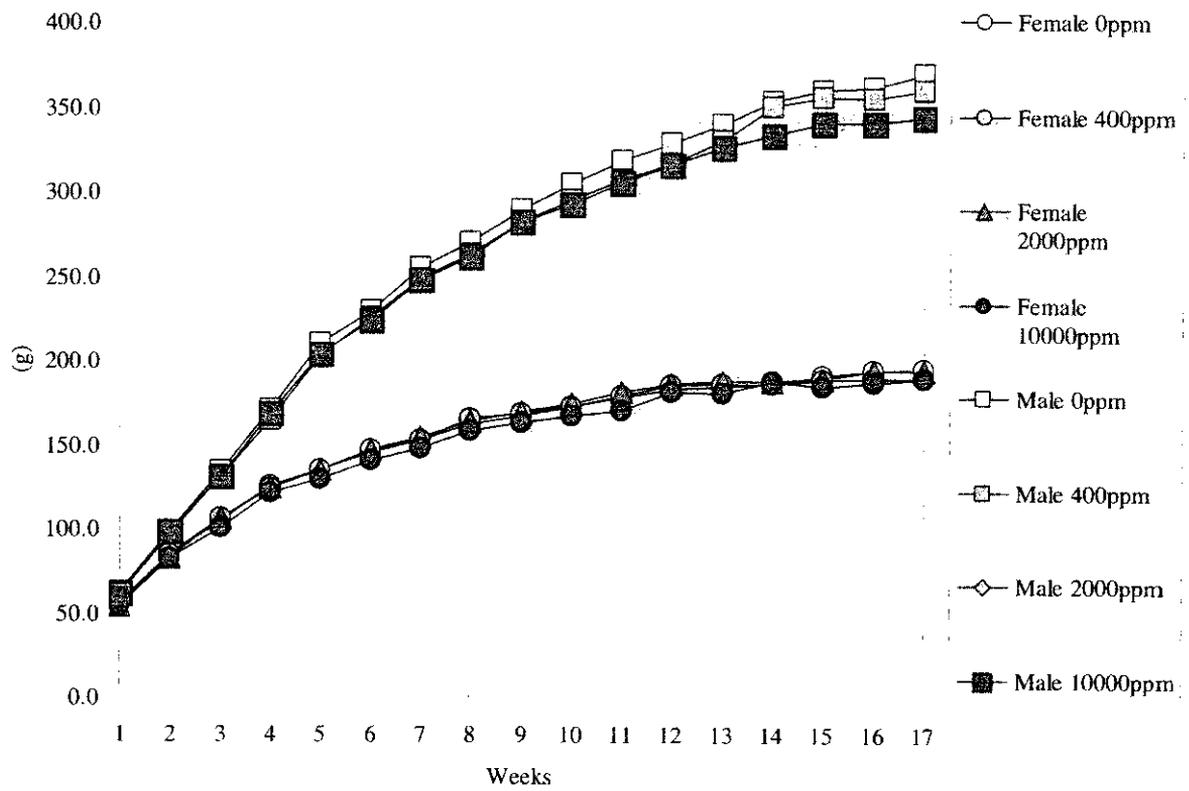


Fig 1 Growth curve

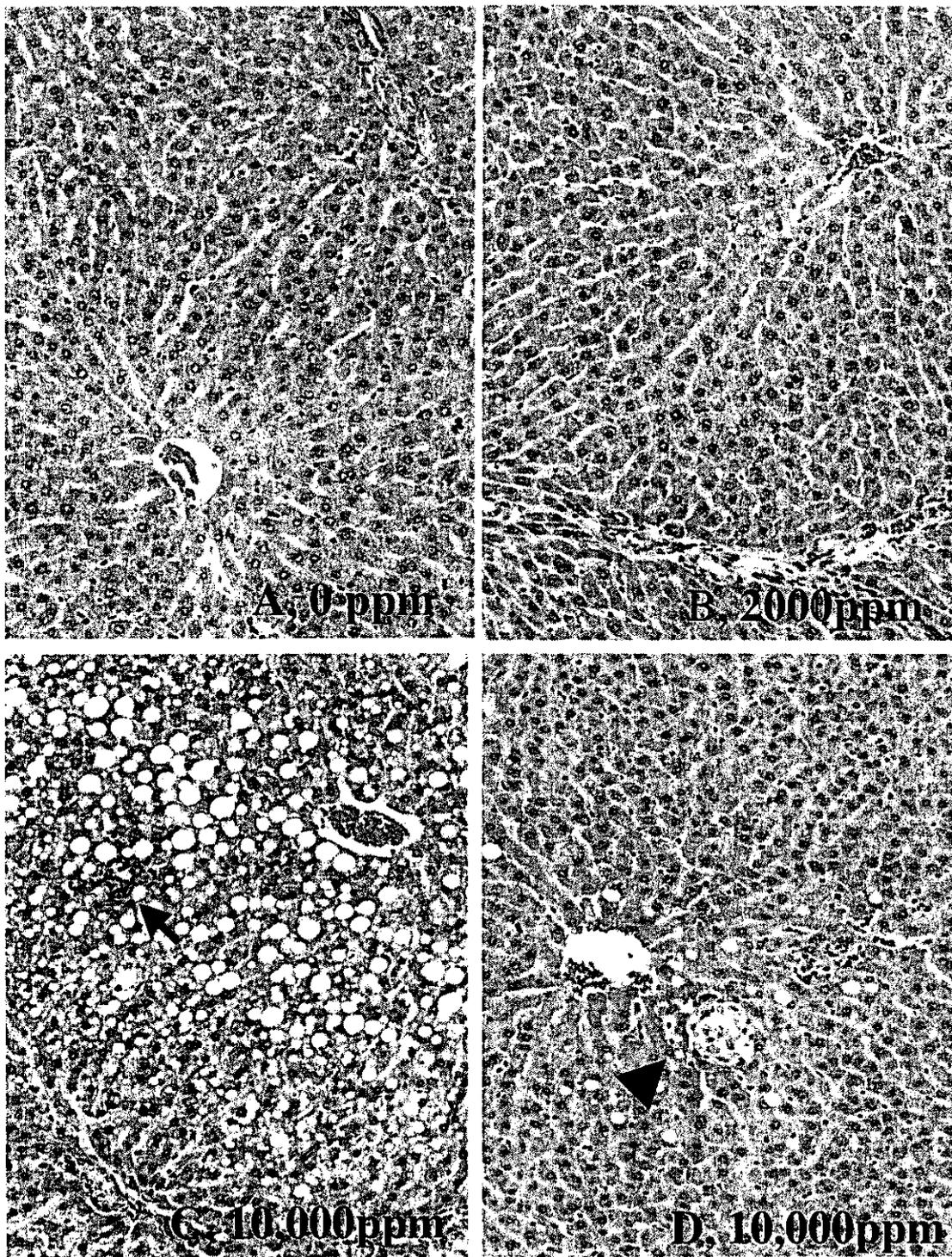


Fig.2-A Liver, males.A-C, after treatment period; D, after recovery.

A-B, No abnormalities detected. C, Moderate changes of hepatocytes in centrilobular area, and inflammatory cell aggregation (arrow). D, Fatty changes of hepatocytes, very slight, and microgranuloma surrounded by aggregation of lymphocytes (arrowhead).

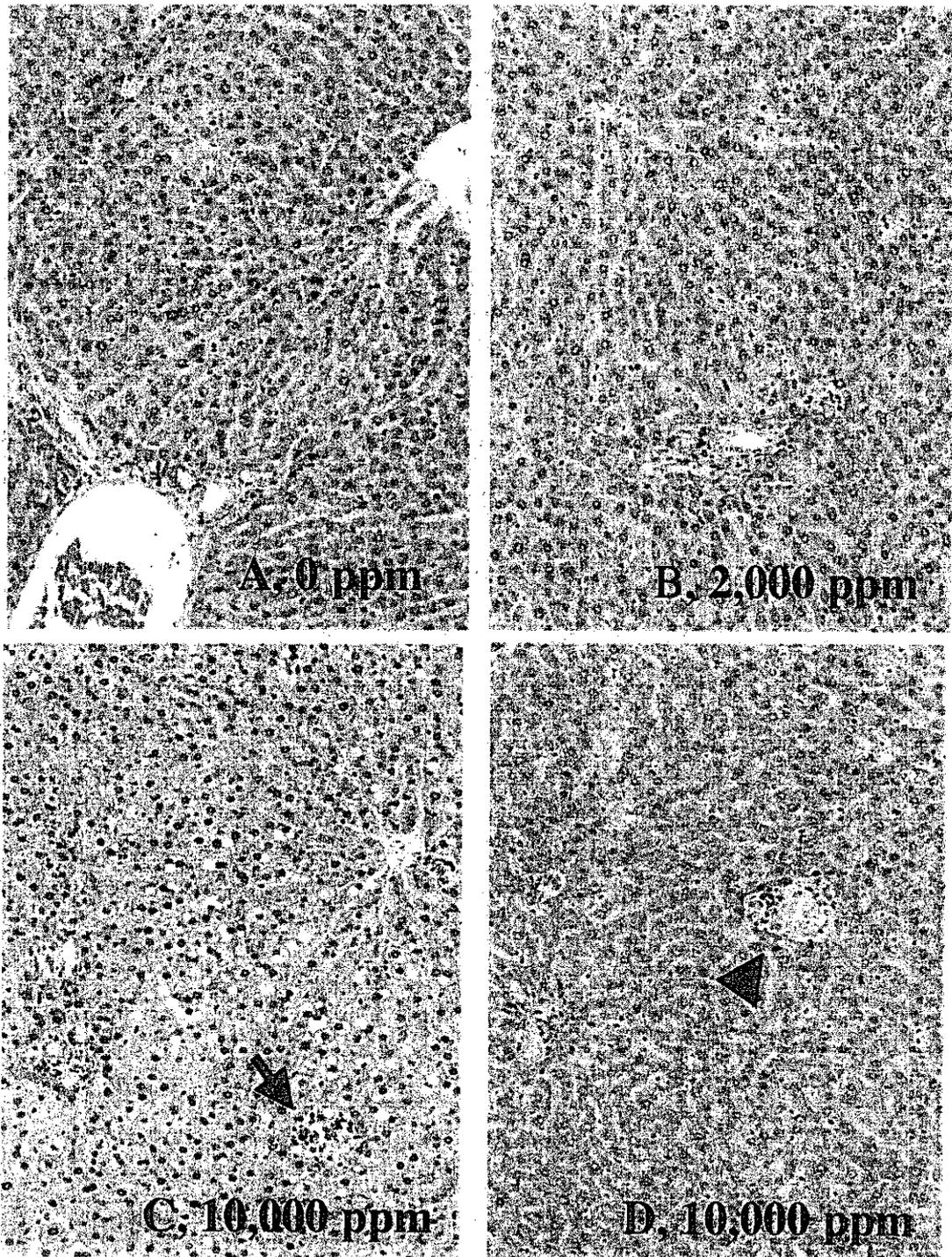


Fig.2-B Liver, females. A - C, after treatment period; D, after recovery.

A-B, No abnormalities detected. C, Slight fatty changes of hepatocytes in centrilobular area, and inflammatory cell aggregation (arrow). D, No abnormalities without microgranuloma surrounded by aggregation of lymphocytes (arrowhead).

Table 1 Summary of Food and chemical intakes

	Food intake (g/rat/day)				Chemical intake(mg/kg/day)				Total chemical intake(g/rat)	
	Male		Female		Male	Female	Male	Female		
	Treatment	Recovery	Treatment	Recovery						
0ppm	Mean	13.76	11.69	9.53	8.87	-	-	-	-	
	SD	1.41	1.05	0.74	0.84					
400ppm	Mean	13.32	11.38	9.72	9.16	29.50	31.29	0.48	0.33	
	SD	1.63	1.03	0.84	0.36	16.69	12.72			
2000ppm	Mean	13.76	11.48	9.64	8.41	149.54	155.46	2.50	1.62	
	SD	1.19	1.61	0.54	0.82	84.82	65.89			
10000ppm	Mean	13.07	11.85	9.17	8.88	709.94	750.47	11.89	7.70	
	SD	2.14	2.47	0.74	2.00	370.89	257.84			

**Table 2-A**  
**Summary of urinalysis for 90-day treatment**

		Group (ppm)			
		0	400	2,000	10,000
<b><i>Male</i></b>					
Urobilinogen	Not detected	10a/10b	10/10	10/10	10/10
Bilirubin	Not detected	10/10	10/10	10/10	10/10
Occult blood	Not detected	7/10	10/10	10/10	10/10
	Positive, very slightly	3/10	0/10	0/10	0/10
Keton body	Not detected	10/10	10/10	7/10	8/10
	Positive, very slightly	0/10	0/10	0/10	1/10
	Positive, slightly	0/10	10/10	3/10	1/10
Glucose	Not detected	9/10	9/10	10/10	10/10
	Positive, slightly	1/10	1/10	0/10	0/10
Protein	Not detected	0/10	2/10	2/10	0/10
	Positive, very slightly	10/10	4/10	5/10	10/10
	Positive, slightly	0/10	3/10	3/10	0/10
	Positive, moderately	0/10	1/10	0/10	0/10
pH	6	1/10	0/10	0/10	0/10
	7	1/10	3/10	2/10	2/10
	8	8/10	7/10	8/10	8/10
Ascorbic acid	0	10/10	0/10	10/10	10/10
<b><i>Female</i></b>					
Urobilinogen	Not detected	10/10	10/10	10/10	10/10
Bilirubin	Not detected	10/10	10/10	10/10	10/10
Occult blood	Not detected	10/10	10/10	10/10	10/10
	Positive, very slightly	0/10	0/10	0/10	0/10
Keton body	Not detected	9/10	10/10	10/10	10/10
	Positive, very slightly	0/10	0/10	0/10	0/10
	Positive, slightly	1/10	0/10	0/10	0/10
Glucose	Not detected	10/10	10/10	10/10	10/10
	Positive, slightly	0/10	0/10	0/10	0/10
Protein	Not detected	0/10	0/10	2/10	0/10
	Positive, very slightly	8/10	7/10	8/10	10/10
	Positive, slightly	2/10	2/10	0/10	0/10
	Positive, moderately	0/10	1/10	0/10	0/10
pH	6	2/10	0/10	0/10	0/10
	7	2/10	1/10	2/10	1/10
	8	6/10	9/10	8/10	9/10
Ascorbic acid	0	10/10	10/10	10/10	10/10

a / b, incidence/number of rats examined

**Table 2-B**  
**Summary of urinalysis for recovery period**

		Group (ppm)			
		0	400	2,000	10,000
<b><i>Male</i></b>					
Urobilinogen	Not detected	5a/5b	5/5	5/5	5/5
Bilirubin	Not detected	5/5	5/5	5/5	5/5
Occult blood	Not detected	5/5	4/5	4/5	3/5
Keton body	Positive, very slightly	0/5	1/5	1/5	2/5
	Not detected	5/5	5/5	5/5	5/5
	Positive, very slightly	0/5	0/5	0/5	0/5
Glucose	Positive, slightly	0/5	0/5	0/5	0/5
	Not detected	5/5	5/5	5/5	5/5
	Positive, slightly	0/5	0/5	0/5	0/5
Protein	Not detected	2/5	2/5	5/5	1/5
	Positive, very slightly	0/5	0/5	0/5	3/5
	Positive, slightly	2/5	0/5	0/5	1/5
	Positive, moderately	1/5	3/5	0/5	0/5
pH	6	0/5	0/5	2/5	0/5
	7	4/5	5/5	3/5	4/5
	8	1/5	0/5	0/5	1/5
Ascorbic acid	0	5/5	5/5	5/5	5/5
<b><i>Female</i></b>					
Urobilinogen	Not detected	5/5	5/5	5/5	5/5
Bilirubin	Not detected	5/5	5/5	5/5	5/5
Occult blood	Not detected	5/5	5/5	5/5	5/5
Keton body	Positive, very slightly	5/5	5/5	5/5	5/5
	Not detected	5/5	5/5	5/5	5/5
	Positive, very slightly	0/5	0/5	0/5	0/5
Glucose	Positive, slightly	0/5	0/5	0/5	0/5
	Not detected	5/5	5/5	5/5	5/5
	Positive, slightly	0/5	0/5	0/5	0/5
Protein	Not detected	0/5	2/5	2/5	1/5
	Positive, very slightly	3/5	3/5	3/5	3/5
	Positive, slightly	2/5	0/5	0/5	1/5
	Positive, moderately	0/5	0/5	0/5	0/5
pH	6	1/5	1/5	0/5	0/5
	7	0/5	1/5	2/5	2/5
	8	4/5	3/5	2/5	3/5
	9	0/5	0/5	1/5	0/5
Ascorbic acid	0	5/5	5/5	5/5	5/5

a / b, incidence/number of rats examined

**Table 3-A Summary of Hematology in Animals treated after 90 -day treatment**

		<b>Platelet</b> (x10 <sup>5</sup> /μL)	<b>HB</b> (g/dL)	<b>RBC</b> (x10 <sup>5</sup> /μL)	<b>WBC</b> (x10 <sup>2</sup> /μL)	<b>HT</b> (%)	<b>MCV</b> (fL)	<b>MCH</b> (pg)	<b>MCHC</b> (g/dL)
Oppm	Mean	76.79	14.59	840.86	6500.00	47.24	56.14	17.43	31.00
	SD	2.73	1.28	10.07	1132.84	0.96	0.90	1.51	2.77
400ppm	Mean	80.86	15.00	831.60	5340.00	47.28	56.80	18.00	31.80
	SD	3.99	0.14	11.26	1718.43	0.48	0.84	0.00	0.45
2,000ppm	Mean	69.67	14.73	821.50	6650.00	46.65	56.83	18.00	31.50
	SD	10.75	0.60	28.20	281.07	2.53	1.17	0.00	0.84
10,000ppm	Mean	75.08	13.76	794.00	6620.00	44.00	55.40	17.20	31.20
	SD	8.80	0.23	19.60	1023.23	1.61	0.89	0.45	1.10
<b>Female</b>									
Oppm	Mean	64.12	15.83	779.67	6450.00	47.50	60.83	20.17	33.50
	SD	9.87	0.44	19.78	1032.96	1.38	0.41	0.41	0.84
400ppm	Mean	69.03	15.78	785.38	6100.00	47.44	60.38	20.00	34.38
	SD	5.23	0.77	36.49	1359.62	2.31	0.74	0.00	3.89
2,000ppm	Mean	70.72	15.68	775.00	5583.33	46.62	60.00	20.17	33.67
	SD	8.35	0.53	17.38	1624.09	1.48	0.63	0.41	0.82
10,000ppm	Mean	59.14	14.55	751.25	6262.50	43.79	59.25	19.50	33.38
	SD	17.91	0.76	47.72	1860.06	3.18	2.05	0.53	1.30

Significantly different from control value, p\* < 0.05, p\*\* < 0.01

**Table 3-B Summary of Hematology in Animals treated after recovery period**

		Platelet	HB	RBC	WBC	HT	MCV	MCH	MCHC
		(x10 <sup>5</sup> /μL)	(g/dL)	(x10 <sup>5</sup> /μL)	(x10 <sup>2</sup> /μL)	(%)	(fL)	(pg)	(g/dL)
0ppm	Mean	73.62	15.88	895.00	6100.00	51.48	56.60	17.80	31.00
	SD	3.37	1.26	69.94	1104.54	4.16	2.19	0.45	0.00
400ppm	Mean	71.54	15.42	866.40	5560.00	50.28	58.00	17.80	31.00
	SD	4.58	0.26	14.62	439.32	1.00	0.71	0.45	0.00
2,000ppm	Mean	69.78	15.42	872.60	5620.00	50.66	58.00	17.80	30.60
	SD	3.57	0.11	6.80	1032.96	0.62	0.71	0.45	0.55
10,000ppm	Mean	70.86	14.68	876.80	5920.00	49.86	56.80	17.00	29.60
	SD	4.48	0.61	21.46	1243.78	1.73	0.84	0.00	0.55
<b>Female</b>									
		Platelet	HB	RBC	WBC	HT	MCV	MCH	MCHC
		(x10 <sup>5</sup> /μL)	(g/dL)	(x10 <sup>5</sup> /μL)	(x10 <sup>2</sup> /μL)	(%)	(fL)	(pg)	(g/dL)
0ppm	Mean	76.06	15.18	782.80	5160.00	49.12	62.80	19.20	31.00
	SD	4.89	0.52	27.86	1824.28	1.67	0.45	0.45	0.00
400ppm	Mean	67.42	15.10	774.00	4800.00	49.02	63.40	19.40	30.80
	SD	6.35	0.75	35.23	2336.66	2.27	0.55	0.55	0.45
2,000ppm	Mean	73.64	15.06	790.00	3898.00	49.60	62.80	19.20	30.40
	SD	5.98	0.35	19.53	2194.77	2.00	1.10	0.45	0.55
10,000ppm	Mean	68.00	14.64	771.40	4040.00	48.08	62.40	18.80	30.40
	SD	4.06	0.29	23.67	1570.99	1.26	0.89	0.45	0.55

Table 4-A Summary of blood biochemistry after 90-day treatment

Male

	TP (g/dL)	A/G	BIL (mg/dL)	TCHO (mg/dL)	TG (g/dL)	CRE (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/dL)	K (mEq/dL)	GGT (U/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	ALB (g/dL)
Oppm	6.89	2.10	0.00	63.56	69.78	0.30	10.20	7.44	147.11	4.90	<2	147.44	67.33	383.44	4.67
	0.24	0.12	0.00	4.56	20.50	0.02	0.38	0.96	1.27	0.58		34.58	5.00	41.53	0.10
400ppm	6.91	2.08	0.00	64.90	74.50	0.31	10.20	7.45	148.10	4.96	<2	173.10	70.30	392.20	4.67
	0.28	0.12	0.00	5.80	19.86	0.02	0.37	0.56	1.29	0.53		52.33	6.73	40.55	0.13
2,000ppm	6.71	2.06	0.00	60.70	69.00	0.32	10.14	7.30	147.00	5.16	<2	146.30	63.70	366.90	4.52
	0.24	0.05	0.00	3.65	16.22	0.05	0.32	0.67	1.15	1.17		39.12	5.95	28.93	0.16
10,000ppm	6.94	1.97	0.00	67.70	53.20	0.33	10.17	7.44	147.20	5.19	<2	205.00	103.80	382.50	4.58
	0.31	0.13	0.00	7.44	13.58	0.05	0.34	0.95	1.40	0.49		62.12	14.05	26.82	0.15

Female

	TP (g/dL)	A/G	BIL (mg/dL)	TCHO (mg/dL)	TG (g/dL)	CRE (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/dL)	K (mEq/dL)	GGT (U/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	ALB (g/dL)
Oppm	7.04	2.29	0.00	83.30	24.20	0.31	10.53	8.06	150.80	6.05	<2	172.50	60.00	254.20	4.89
	0.33	0.17	0.00	7.66	10.03	0.03	0.35	1.65	2.57	1.17		43.07	13.60	33.85	0.16
400ppm	6.90	2.30	0.00	79.50	28.80	0.31	10.41	7.37	151.30	5.12	<2	148.30	59.50	254.30	4.79
	0.45	0.23	0.00	7.18	11.00	0.03	0.44	1.16	1.64	1.17		30.74	7.47	34.24	0.22
2,000ppm	7.03	2.24	0.00	85.60	24.90	0.32	10.34	7.70	150.70	5.17	<2	148.10	55.60	241.90	4.85
	0.54	0.24	0.00	7.35	8.05	0.03	0.53	1.52	1.25	0.98		27.11	4.55	27.85	0.25
10,000ppm	7.04	1.94	0.00	110.40	49.00	0.31	10.43	8.04	150.80	5.82	3.50	206.80	93.60	249.10	4.63
	0.48	0.21	0.00	10.41	24.90	0.03	0.67	1.88	2.53	1.54	0.84	46.57	32.94	24.95	0.18

Significantly different from control value, p\*<0.05, p\*\*<0.01

Table 4-B Summary of Blood Biochemistry after recovery period

Male															
	TP	A/G	BIL	TCHO	TG	CRE	Ca	IP	Na	K	GGT	AST	ALT	ALP	ALB
	(g/dL)		(mg/dL)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(mEq/dL)	(mEq/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(g/dL)
0ppm	6.92	2.14	0.00	69.80	66.80	0.37	9.96	6.76	150.20	4.30	<2	131.80	83.20	289.60	4.70
	0.42	0.09	0.00	10.31	14.72	0.05	0.82	1.75	1.10	0.22		25.97	7.79	26.42	0.32
400ppm	6.76	2.12	0.00	66.00	58.00	0.36	9.62	5.74	122.40	4.44	<2	120.00	83.20	277.80	4.50
	0.27	0.04	0.00	4.53	11.20	0.05	0.16	0.70	60.06	0.48		13.95	13.83	35.14	0.14
2,000ppm	6.44	2.20	0.00	53.80	42.00	0.34	9.20	5.88	150.00	4.38	<2	174.60	106.20	291.40	4.50
	0.21	0.19	0.00	7.40	11.90	0.04	0.32	1.00	0.71	0.54		43.18	12.07	20.02	0.14
10,000ppm	6.86	2.00	0.00	63.40	37.20	0.35	9.62	5.96	149.60	5.08	<2	171.80	122.00	275.00	4.58
	0.15	0.19	0.00	5.32	5.07	0.05	0.22	0.47	1.52	0.30		49.76	45.80	26.30	0.11
Female															
	TP	A/G	BIL	TCHO	TG	CRE	Ca	IP	Na	K	GGT	AST	ALT	ALP	ALB
	(g/dL)		(mg/dL)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(mEq/dL)	(mEq/dL)	(U/L)	(U/L)	(U/L)	(U/L)	(g/dL)
0ppm	6.52	2.62	0.02	83.20	28.60	0.28	9.92	4.20	147.80	3.88	<2	94.80	61.00	237.80	4.72
	0.15	0.13	0.04	10.64	8.50	0.02	0.13	0.67	1.30	0.19		9.58	9.51	27.31	0.13
400ppm	6.48	2.64	0.00	84.80	52.00	0.27	9.82	4.48	148.20	3.98	<2	100.00	61.80	244.40	4.70
	0.22	0.17	0.00	7.63	28.21	0.02	0.26	0.65	2.28	0.39		23.05	16.50	43.49	0.12
2,000ppm	6.60	2.50	0.02	87.80	61.40	0.29	9.90	4.92	147.60	4.30	<2	90.40	49.20	225.60	4.70
	0.25	0.30	0.04	10.89	26.93	0.02	0.34	1.29	1.52	0.64		20.91	7.40	44.28	0.07
10,000ppm	6.70	2.48	0.00	88.20	48.60	0.28	10.12	4.68	149.00	4.20	<2	108.60	54.80	218.00	4.76
	0.10	0.28	0.00	10.43	17.90	0.02	0.28	0.61	1.73	0.93		59.06	11.32	32.83	0.22

**Table 5**  
**Summary of differential count per 100 leukocytes after 90-day treatment**

		<b>Neutrophil L.</b>	<b>Eosinophil L.</b>	<b>Lymphocytes</b>	<b>Monocytes</b>
<i>Male</i>					
<b>0ppm</b>	Mean	16.0	1.1	82.1	0.7
	SD	3.5	1.3	3.5	1.1
<b>400ppm</b>	Mean	13.25	0.38	85.50	0.88
	SD	4.56	0.52	4.96	0.83
<b>2,000ppm</b>	Mean	11.44	0.67	87.78	0.11
	SD	4.59	1.12	4.49	0.33
<b>10,000ppm</b>	Mean	10.0	0.8	89.1	0.1
	SD	6.6	1.2	7.1	0.4
<i>Female</i>					
<b>0ppm</b>	Mean	13.0	1.7	85.0	0.3
	SD	6.9	0.6	7.8	0.6
<b>400ppm</b>	Mean	13.3	0.5	86.3	0.0
	SD	8.5	0.6	8.0	0.0
<b>2,000ppm</b>	Mean	11.0	0.3	88.7	0.0
	SD	8.9	0.5	9.2	0.0
<b>10,000ppm</b>	Mean	6.4	1.3	92.1	0.3
	SD	5.5	2.0	7.6	0.5

**Table 6-A Summary of organweights after 90-day treatment Male**

Group	Final B.W. (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Spleen (mg)	Liver (g)
0ppm (n=10)	333 ± 10.4	1947 ± 131.4	302 ± 94.1	850 ± 309.7	633 ± 27.9	8.32 ± 0.67
	(	5851 ± 356.0 )a	( 813 ± 388.7 )	( 2275 ± 1213.3 )	( 1901 ± 127.7 )	( 24.99 ± 1.65 )
400ppm (n=10)	317 ± 13.9	1931 ± 116.7	265 ± 54.4	949 ± 83.1	631 ± 605.0	7.77 ± 0.62
	(	6086 ± 295.6 )	( 737 ± 317.3 )	( 2988 ± 174.3 )	( 1991 ± 80.8 )	( 24.44 ± 1.11 )
2000ppm (n=10)	328 ± 14.8	1987 ± 38.7	272 ± 64.3	972 ± 111.0	631 ± 50.4	8.39 ± 0.40
	(	6065 ± 319.8 )	( 829 ± 191.7 )	( 2962 ± 306.7 )	( 1924 ± 134.4 )	( 25.56 ± 0.73 )
10000ppm (n=10)	322 ± 13.1	1984 ± 44.5	220 ± 79.9	948 ± 69.3	658 ± 58.2	10.83 ± 0.56 **
	(	6179 ± 263.2 )	( 685 ± 256.4 )	( 2946 ± 170.1 )	( 1910 ± 457.9 )	( 33.69 ± 1.06 )**

Group	Adrenals (mg)		Kidneys (mg)		Testes (mg)		Prostate (mg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0ppm (n=10)	43 ± 6.5	( 129 ± 20.2 )	2130 ± 139	( 6397 ± 297 )	2994 ± 153.3	( 8996 ± 371.7 )	386 ± 91.7	( 1159 ± 278.1 )
400ppm (n=10)	41 ± 7.7	( 115 ± 47.7 )	1817 ± 743	( 5064 ± 2876 )	3078 ± 144.6	( 9708 ± 459.9 )	398 ± 46.8	( 1108 ± 442.2 )
2000ppm (n=10)	44 ± 9.8	( 134 ± 28.9 )	2075 ± 130	( 6332 ± 477 )	3014 ± 193.0	( 9193 ± 627.6 )	400 ± 86.0	( 1223 ± 278.3 )
10000ppm (n=10)	66 ± 47.1	( 47 ± 63.2 )	2118 ± 135	( 6591 ± 453 )	3081 ± 98.6	( 9583 ± 180.4 )	431 ± 95.2	( 1243 ± 479.4 )

( ) a, organ weight/final body weight x 1000

Significantly different from control value, \*\*:P<0.01

**Table 6-B Summary of organ weights after 90-day treatment Female**

Group	Final B.W. (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Spleen (mg)
0ppm (n=10)	177 ± 6.9	1782 ± 56 ( 10080.2 ± 477 )	201.4 ± 40.1 ( 1137.6 ± 222 )	572 ± 21.54 ( 3232.25 ± 57.36 )	394.3 ± 26.7 ( 2228.8 ± 146 )
400ppm (n=10)	179.7 ± 7.63	1783.4 ± 57.7 ( 9940.59 ± 530 )	205.4 ± 56.4 ( 1142 ± 305 )	610 ± 52.71 ( 3392.63 ± 232.4 )	403.1 ± 51.6 ( 2240.5 ± 235 )
2000ppm (n=10)	178.7 ± 5.58	1628.3 ± 568 ( 9137.21 ± 3194 )	232.5 ± 157 ( 1301.3 ± 888 )	592.9 ± 46.23 ( 3317.27 ± 230.9 )	403.9 ± 43.2 ( 2260.6 ± 239 )
10000ppm (n=10)	171.4 ± 10.5	1769.1 ± 39.5 ( 10353.2 ± 615 )	165.7 ± 65.1 ( 969.66 ± 399 )	565.9 ± 45.14 ( 3301.17 ± 153.1 )	434.4 ± 32 ( 2536.4 ± 146 )
Group	Liver (g)	Adrenals (mg)	Kidneys (mg)	Ovaries (mg)	Uterus (mg)
0ppm (n=10)	4.529 ± 0.37 ( 25.58 ± 1.77 )	47.8 ± 12.3 ( 270.134 ± 69.8 )	1282.7 ± 82.7 ( 6493.4 ± 2308 )	51.7 ± 15.25 ( 291.862 ± 82.46 )	647.8 ± 218 ( 3658.7 ± 1229 )
400ppm (n=10)	4.307 ± 0.25 ( 23.99 ± 1.51 )	52 ± 14.8 ( 289.38 ± 82.6 )	1298.1 ± 89 ( 7240.6 ± 663 )	57.9 ± 19.5 ( 320.828 ± 103.7 )	522.2 ± 167 ( 2894.9 ± 870 )
2000ppm (n=10)	4.291 ± 0.36 ( 24.02 ± 1.91 )	51.7 ± 12.9 ( 289.803 ± 73.1 )	1328.7 ± 211 ( 7439.1 ± 1200 )	57.4 ± 12.92 ( 321.919 ± 74.28 )	509.3 ± 194 ( 2847.8 ± 1077 )
10000ppm (n=10)	6.213 ± 0.45 ** ( 36.29 ± 2.36 )**	59.1 ± 13.1 ( 347.06 ± 86.7 )	1249.9 ± 66.2 ( 7303.4 ± 364 )	56.8 ± 9.319 ( 332.939 ± 60.47 )	565.6 ± 244 ( 3279.7 ± 1311 )

( ) a, organ weight/final body weight x 1000  
Significantly different from control value, \*\*:P<0.01

Table 7-A Summary of organ weights after recovery period  
Male

Group	Final B.W. (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Spleen (mg)	Liver (g)
Oppm (n=5)	288 ± 141 ( 534.7 ± 270.59 ) <sup>a</sup>	1705.5 ± 837.68 ( 534.7 ± 270.59 ) <sup>a</sup>	184.7 ± 93.87 ( 2903.7 ± 1871.48 )	997.5 ± 628.90 ( 1489.4 ± 738.30 )	513.7 ± 254.1 ( 1489.4 ± 738.3 )	6 ± 3.21 ( 19 ± 9.31 )
400ppm (n=5)	342 ± 141 ( 6036.8 ± 2497.62 )	2056.8 ± 845.48 ( 6036.8 ± 2497.62 )	180.0 ± 74.65 ( 528.1 ± 219.96 )	2932.2 ± 1214.80 ( 2932.2 ± 1214.80 )	1859.0 ± 768.2 ( 1859.0 ± 768.2 )	22 ± 9.10 ( 22 ± 9.10 )
2000ppm (n=5)	324 ± 9 ( 6124.1 ± 265.71 )	1983.6 ± 39.04 ( 6124.1 ± 265.71 )	167.8 ± 43.16 ( 517.3 ± 133.61 )	1023.2 ± 29.23 ( 3157.1 ± 92.57 )	613.6 ± 34.2 ( 1892.7 ± 92.6 )	7 ± 0.29 ( 21 ± 0.73 )
10000ppm (n=5)	271 ± 12 ( 4943.6 ± 2430.00 )	1985.2 ± 812.74 ( 4943.6 ± 2430.00 )	167.2 ± 73.62 ( 534.7 ± 270.59 )	979.8 ± 407.72 ( 2903.7 ± 1871.48 )	677.6 ± 277.8 ( 1739.3 ± 855.1 )	8 ± 3.13 ( 20 ± 9.58 )

Group	Adrenals (mg)	Kidneys (mg)	Testes (mg)	Prostate (mg)
Oppm (n=5)	34.2 ± 17.41 ( 99.0 ± 50.48 )	1827 ± 917 ( 5298 ± 2668 )	2601 ± 1284.6 ( 7534 ± 3705.6 )	412 ± 209.66 ( 201 ± 102.35 )
400ppm (n=5)	34.2 ± 17.73 ( 124.4 ± 52.08 )	1827 ± 1088 ( 5023 ± 3263 )	2601 ± 1633.8 ( 7544 ± 4872.5 )	412 ± 285.85 ( 324 ± 143.36 )
2000ppm (n=5)	41.0 ± 4.90 ( 126.4 ± 14.66 )	2132 ± 72 ( 6578 ± 214 )	3137 ± 110.8 ( 9680 ± 372.2 )	645 ± 648.00 ( 325 ± 38.57 )
10000ppm (n=5)	40.8 ± 18.67 ( 105.1 ± 58.62 )	2095 ± 951 ( 4290 ± 3338 )	2748 ± 1206.3 ( 7075 ± 3785.6 )	483 ± 205.88 ( 203 ± 104.40 )

(<sup>a</sup>) a, organ weight/final body weight x 1000

**Table 7-B Summary of organ weights after recovery period Female**

Group	Final B.W. (g)	Brain (mg)	Thymus (mg)	Heart (mg)	Spleen (mg)	Liver (g)
0ppm (n=5)	158.0 ±	1501 ±	131 ±	504 ±	343 ±	3.50 ±
	77.7 (	737.0 (	69 (	1808 ±	250 (	1.70 (
	690 ±	362.9 )	1309 )	892 ±	1808 ±	1.73 ±
						9.092 )
400ppm (n=5)	183.4 ±	1775 ±	134 ±	3248 ±	2152 ±	3.99 ±
	75.0 (	727.9 (	57 (	3248 ±	2152 ±	1.631 (
						8.885 )
2000ppm (n=5)	186.6 ±	1830 ±	148 ±	619 ±	401 ±	4.0 ±
	9.3 (	48.2 (	6 (	3321 ±	2147 ±	0.313 (
						1.141 )
10000ppm (n=5)	151.3 ±	1846 ±	135 ±	600 ±	406 ±	4.2 ±
	11.4 (	755.4 (	57 (	2658 ±	1864 (	1.752 (
						9.554 )

Group	Adrenals (mg)	Kidneys (mg)	Ovaries (mg)	Uterus (mg)
0ppm (n=5)	38.0 ±	1073 ±	41.2 ±	605.2 ±
	19.4 (	530 (	20.5 (	404.8 (
	200.3 ±	2792 )	217.1 ±	336.4 ±
				224.6 )
400ppm (n=5)	38.0 ±	1073 ±	50.0 ±	517.4 ±
	18.2 (	516 (	24.9 (	233.3 (
				127.7 )
2000ppm (n=5)	46.8 ±	1017 ±	49.6 ±	539.4 ±
	9.3 (	573 (	7.6 (	46.7 (
				23.0 )
10000ppm (n=5)	48.8 ±	1330 ±	49.8 ±	724.6 ±
	21.1 (	547 (	21.9 (	346.7 (
				186.3 )
	224.8 ±	3028 )	229.3 ±	326.5 ±
				186.3 )

( ) a, organ weight/final body weight x 1000

**Table 8-A**  
**Summary of pathological findings after 90-day treatment**

Organs/Tissues Findings		Group (ppm)			
		0	400	2,000	10,000
<b>Macroscopy</b>					
<b><u>Male</u></b>					
Number of rats examined		10	10	10	10
Liver	Fatty liver	0	0	0	10*
<b><u>Female</u></b>					
Number of rats examined		10	10	10	10
Liver	Fatty liver	0	0	0	10*
<b>Histopathology</b>					
<b><u>Male</u></b>					
Number of rats examined		10	10	10	10
Heart	Myocarditis	6	NE	NE	3
Trachya	Dilatation of gland	1	NE	NE	0
Kidney	Eosinophilic body, slight	9	7	7	8
Liver	Aggregation of lymphocytes	1	0	0	0
	Fatty change of hepatocytes, centrilobular area	0	0	0	10*
		Slight (0	0	0	0)
		Moderate (0	0	0	7)
	Severe (0	0	0	3)	
	Aggregation of inflammatory cells, slight	0	0	0	10*
Testis	Focal strophy of seminiferous tubules	1	0	0	0
Hardarian gland	Aggregation of lymphocytes	1	NE	NE	0
<b><u>Female</u></b>					
Number of rats examined		10	10	10	10
Heart	Myocarditis	2	NE	NE	0
Stomach	Aggregation of lymphocytes	1	NE	NE	0
Kidney	Calcification	1	0	1	1
Liver	Fatty change of hepatocytes, centrilobular area	0	0	0	10*
		Slight (0	0	0	4)
		Moderate (0	0	0	6)
		Severe (0	0	0	0)
	Aggregation of inflammatory cells	0	0	0	10*
Femur	Microgranuloma	1	NE	NE	0

NE, Not examined

Significantly different from control value, \*P<0.05

**Table 8-B**  
**Summary of pathological findings after recovery treatment**

Organs/Tissues Findings	Group (ppm)			
	0	400	2,000	10,000
<b>Macroscopy</b>				
<b><u>Male</u></b>				
Number of rats examined	5	5	5	5
Liver No abnormalities	5	5	5	5
<b><u>Female</u></b>				
Number of rats examined	5	5	5	5
Liver No abnormalities	5	5	5	5
<b>Histopathology</b>				
<b><u>Male</u></b>				
Number of rats examined	5	5	5	5
Liver Hepatocytes, fatty change, very slight	0	0	0	5*
Aggregation of lymphocytes, slight	1	0	1	0
Microgranuloma/aggregation of lymphocytes	0	0	0	5*
Slight	(0	0	0	3)
Moderate	(0	0	0	2)
<b><u>Female</u></b>				
Number of rats examined	5	5	5	5
Liver Hepatocytes, fatty change, very slight	0	0	0	3
Microgranuloma/aggregation of lymphocytes	0	0	0	3
Slight	(0	0	0	3)
Moderate	(0	0	0	0)

NE, Not examined

Significantly different from control value, \*P<0.05