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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: SUMITHRIN-Evaluation of a Combined Chronic/Carcinogenicity Study in F-344 Rats

Tox Chem No.:	652B
PC No.:	069005
DP No.:	D226101
Submission No.:	S505229

FROM: William B. Greear, M.P.H. William B. Greear 11/6/96
Review Section IV, Toxicology Branch I
Health Evaluation Division (H7509C)

TO: Paula Deschamp
Risk Characterization and Analysis Branch
Health Evaluation Division (7509C)

THRU: Marion P. Copley, D.V.M., Section Head Marion Copley 11/7/96
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

CC: Larry Schnaubelt, PM Team #72
Reregistration Branch
Special Review and Reregistration Division (H7508W)

I. Conclusions:

The combined chronic/carcinogenicity study on sumithrin (MRID 43927001) is classified Acceptable/Guideline and satisfies the requirement for a guideline series 83-5 combined chronic/carcinogenicity study in rats.

II. Requested Action:

The Special Review and Reregistration Division has requested that TOX I evaluate the following combined chronic/carcinogenicity study on sumithrin:

Citation: Aughton, P. (1995) Sumithrin. Combined Oncogenicity and toxicity study by dietary administration to F-344 rats for 109 weeks. Huntingdon Life Sciences, Ltd., Eye, Suffolk, England, Report No. 94/SMA012/0987, December 11, 1995. MRID 43927001. Unpublished.

III. Results/Discussion:

The results of the study (MRID 43927001) are attached in the form of a one-liner. Also attached is the DER.

CITATION	RESULTS
mithrin (94%) (83-5) ronic/Carcino ecies:Rat b. Name:Huntingdon udy :94/SMA012/0987 te: 12/11/95 ID: 43927001	In a combined chronic/carcinogenicity study (MRID 43927001), groups of 50 male and female F-344 rats were administered 0, 1000, 10,000 or 20,000 ppm of sumithrin (94% a.i., Lot # 10914) (representing 0, 51, 531 and 1116 mg/kg/day in male, and 0, 63, 653 and 1351 mg/kg/day in females) in the diet for 2 years in the onc ogenic segment of the study. Additional groups of 20 rats/sex were administered the same dosi ng regimen in the chronic segment (no histologic examination was conducted) and an additiona l 10 rats/sex/group were sacrificed at 12 months. Animals in the 20,000 ppm group and females in the 10,000 ppm group appeared thin, had a hunched posture and had yellow/urinary stai ining of the perigenital area. Treatment related deaths occurred in males in the 20,000 ppm groups from Week 64-68. Hemorrhage was the major clinical sign of toxicity observed between weeks 64-68. Body weight gain was decreased in males and females in the 10,000 and 20,000 ppm groups (60-80% of control values) during Weeks 0-64 (males) and Weeks (0-94) females. Foo i consumption was decreased at 20,000 (6-13%) and food efficiency was decreased at 10,000 and 20,000 ppm (8-20%). Posterior capsular opacity was increased in females in the 10,000 and 20,000 ppm groups. Mild anemia was apparent in animals in the 10,000 and 20,000 ppm groups based on decreases in HCT, HGB and RBCs. Fibrinogen levels were also decreased in th e 10,000 and 20,000 ppm groups. Several serum enzyme (leucine amino peptidase, alkaline p osphatase and GGT) were elevated in males and/or females in the 10,000 and 20,000 ppm groups . Triglyceride and phospholipid levels were decreased in males and/or females in the 10 ,000 and 20,000 ppm groups. Total protein was decreased at 20,000 ppm. Alpha-1 and Alpha 2 globulin were decreased in the 20,000 ppm group and Alpha-2 globulin was decreased in femal es in the 10,000 ppm group. The A/G ratio was significantly increased in the 10,000 and 2 0,000 ppm groups. A decrease in specific gravity and pH of the urine was noted in animals in the 10,000 and 20,000 ppm groups. Absolute and/or relative liver weights were increase in animals in the 10,000 and 20,000 ppm groups. At necropsy animals in the 20,000 ppm group and females in the 10,000 ppm group appeared thin. Males in the 20,000 ppm group had a greater incidence of subcapsular fluid in the testes. Hypertrophy was observed in animal s in the 10,000 (22-28%) and 20,000 (80-84%) ppm groups compared to controls (0%). Congesti on of the liver was also observed in animals in the 20,000 ppm group (14-26%) compared to c ontrols (4-6%). Hepatocellular carcinoma and hepatocellular adenoma and carcinoma combin ed were increased in males and females in the 20,000 ppm group. **The LOEL is 10,000 ppm b ased on clinical signs of toxicity, decrease in body weight gain, food efficiency, triglyce rides, phospholipids, α-2 globulin, urinary pH and specific gravity, and increases in serum en zymes, A/G ratio, posterior capsular opacity, liver weights and liver pathology. The NOE is 1000 mg/kg/day. The test material induced hepatocellular tumors in rats at doses that caused excessive toxicity.** The study is **Acceptable/Guideline** and satis fies the requirement for a guideline series 83-5 combined chronic/carcinogenicity study in r ats.

EPA Reviewer: William B. Greear, M.P.H. William B. Greear 11/6/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion P. Copley, D.V.M. Marion Copley 11/7/96
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic/Carcinogenicity Study-rats OPPTS 870.4300 (83-5)

DP BARCODE: D226101 SUBMISSION CODE: S505229

P.C. CODE: 069005 TOX. CHEM. NO. : 652B

TEST MATERIAL (PURITY): Sumithrin (94% a.i.)

SYNONYMS: D-Phenothrin, S-2539, Phenoxythrin, S-2539 Forte, 3-Phenoxybenzl, CAS #26002-80-2

CITATION: Aughton, P. (1995) Sumithrin. Combined Oncogenicity and toxicity study by dietary administration to F-344 rats for 109 weeks. Huntingdon Life Sciences, Ltd., Eye, Suffolk, England, Report No. 94/SMA012/0987, December 11, 1995. MRID 43927001. Unpublished.

SPONSOR: Sumitomo Chemical Company Limited, Osaka 554, Japan

EXECUTIVE SUMMARY: In a combined chronic/carcinogenicity study (MRID 43927001), groups of 50 male and female F-344 rats were administered 0, 1000, 10,000 or 20,000 ppm of sumithrin (94% a.i., Lot # 10914) (representing 0, 51, 531 and 1116 mg/kg/day in male, and 0, 63, 653 and 1351 mg/kg/day in females) in the diet for 2 years in the oncogenic segment of the study. Additional groups of 20 rats/sex were administered the same dosing regimen in the chronic segment (no histologic examination was conducted) and an additional 10 rats/sex/group were sacrificed at 12 months.

Animals in the 20,000 ppm group and females in the 10,000 ppm group appeared thin, had a hunched posture and had yellow/urinary staining of the perigenital area. Treatment related deaths occurred in males in the 20,000 ppm groups from Week 64-68. Hemorrhage was the major clinical sign of toxicity observed between Weeks 64-68. Body weight gain was decreased in males and females in the 10,000 and 20,000 ppm groups (60-80% of control values) during Weeks 0-64 (males) and Weeks (0-94) females. Food consumption was decreased at 20,000 (6-13%) and food efficiency was decreased at 10,000 and 20,000 ppm (8-20%). Posterior capsular opacity was increased in females in the 10,000 and 20,000 ppm groups. Mild anemia was apparent in animals in the 10,000 and 20,000 ppm groups based on decreases in HCT, HGB and

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RBCs. Fibrinogen levels were also decreased in the 10,000 and 20,000 ppm groups. Several serum enzyme (leucine amino peptidase, alkaline phosphatase and GGT) were elevated in males and/or females in the 10,000 and 20,000 ppm groups. Triglyceride and phospholipid levels were decreased in males and/or females in the 10,000 and 20,000 ppm groups. Total protein was decreased at 20,000 ppm. Alpha-1 and Alpha 2 globulin were decreased in the 20,000 ppm group and Alpha-2 globulin was decreased in females in the 10,000 ppm group. The A/G ratio was significantly increased in the 10,000 and 20,000 ppm groups. A decrease in specific gravity and pH of the urine was noted in animals in the 10,000 and 20,000 ppm groups. Absolute and/or relative liver weights were increased in animals in the 10,000 and 20,000 ppm groups. At necropsy animals in the 20,000 ppm group and females in the 10,000 ppm group appeared thin. Males in the 20,000 ppm group had a greater incidence of subcapsular fluid in the testes. Hypertrophy was observed in animals in the 10,000 (22-28%) and 20,000 (80-84%) ppm groups compared to controls (0%). Congestion of the liver was also observed in animals in the 20,000 ppm group (14-26%) compared to controls (4-6%). Hepatocellular carcinoma and hepatocellular adenoma and carcinoma combined were increased in males and females in the 20,000 ppm group. **The LOEL is 10,000 ppm based on clinical signs of toxicity, decrease in body weight gain, food efficiency, triglycerides, phospholipids, α-2 globulin, urinary pH and specific gravity, and increases in serum enzymes, A/G ratio, posterior capsular opacity, liver weights and liver pathology. The NOEL is 1000 mg/kg/day. The test material induced hepatocellular tumors in rats at doses that caused excessive toxicity.**

The study is classified **Acceptable/guideline** and **satisfies** the requirement for a guideline series 83-5 combined chronic/carcinogenicity study in rats.

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

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Sumithrin
   Description: clear pale yellow liquid
   Lot/Batch #: 10914
   Purity: 94% a.i.
   Stability of compound: stable after 2 years of storage at laboratory
   CAS #: 26002-80-2
   Structure:

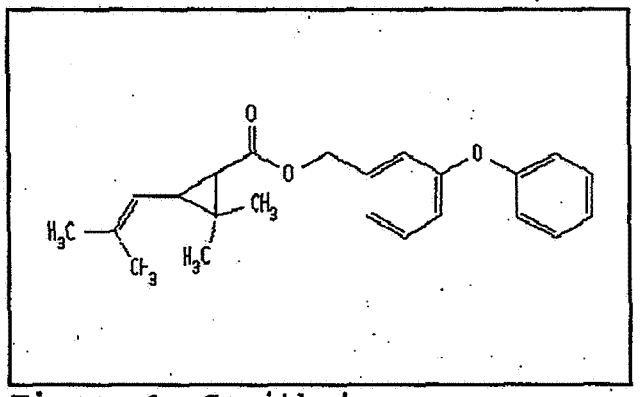

Figure 1 Sumithrin

2. Vehicle and/or Positive Control: laboratory diet

3. Test Animals: Species: rat
   Strain: F-344
   Age and weight at study initiation: 36-43 days
   Source: Charles River Limited, Kingston, NY
   Housing: individually in Type RB3 polypropylene cages with stainless steel mesh lid and floor.
   Diet: Laboratory Animal Diet No. 2 (Special Diets Services Ltd., Essex, England) ad libitum
   Water: public water supply Lowestaft, England ad libitum
   Environmental conditions:
   Humidity: 55± 15%
   Air changes: 15/hour
   Photoperiod: 12-hour/light:12-hour/dark
   Acclimation period: 8 days

B. STUDY DESIGN:

1. In life dates: start: June 11, 1992
   end: June 22, 1994

2. Animal Assignment: Animals were assigned using a set of computer-generated random numbers to the test groups in Table 1.

Table 1. Study Designs

Test Group	Conc. in Diet (ppm)	Dose to Animals (mg/kg/day)	Main Study 24 Months		Interim Sacrifice 12 Months	
			Male	Female	Male	Female
Control	0	0	50(0)[1] 20(T)[2]	50(0) 20(T)	10	10
Low (LDT)	1000	51(M) 63(F)	50(0) 20(T)	50(0) 20(T)	10	10
Mid (MDT)	10,000	531(M) 653(F)	50(0) 20(T)	50(0) 20(T)	10	10
High (HDT)	20,000	1116(M) 1351(F)	50(0) 20(T)	50(0) 20(T)	10	10

1. Oncogenicity Phase
2. Toxicity Phase

An additional 10 animals/sex were provided for baseline clinical pathology investigations. They were discarded without necropsy following sampling.

3. Dose Selection: not addressed by author

4. Diet Preparation and Analysis

Diet was prepared weekly by mixing appropriate amounts of the test material in the form of a premix (manually made) with Laboratory Animal Diet No. 2 and was packaged in sealed polyethylene bags. Homogeneity was determined initially using a trial preparation. The distribution of the test material in the diet was assessed for all 3 test concentrations by analyzing samples taken from 6 positions in the mix. Stability was demonstrated in a 13 week toxicity study conducted at the laboratory (Pharmaco LSR Report No. 71/SMA008/0942). During the study samples of treated food were analyzed at Weeks 1, 13, 26, 39, 52, 65, 78, 91 and 104 of treatment for concentration.

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Results: Homogeneity Analysis: the mean concentration of the test material in the diets ranged from 94.1 - 98.3% for all 3 diets with coefficient of variation of 1.60 - 4.70%. Stability: the mean concentration of diets containing 300 and 20,000 ppm over a 14 day period was 25 (83.7%) and 18850 ppm (94.3%), respectively when stored at 21°C. Concentration Analysis: Over a 104 week period, dietary concentration of 1000, 10,000 and 20,000 ppm groups ranged from 90.2 - 104%, 91.5 - 99.0% and 91.0 - 104% of nominal concentration.

5. Animals received fresh diets at least weekly.

6. Statistics: Mortality was analyzed by Cox's proportional hazards model and Tarone's portions of the Chi-square statistics into linear trend on dose and deviation from linearity. Student's 't'-test was used to analyzed hematology, blood chemistry and urinalysis data. Pairwise Mann-Whitney U-tests were used when the variance of one or more groups was 0. Bartlett's test was used to test for homogeneity of variance for organ weights and body weight changes. A two-tailed Fisher's Exact test was used to analyze the distribution of macroscopic and microscopic (non-neoplastic) tissues. A one-tested test was used to analyze neoplastic lesions.

C. METHODS:

1. Observations:

All animals were inspected twice daily for signs of toxicity and mortality. A more detailed examination, including palpation was performed weekly.

2. Body Weight:

All animals were weighed weekly for the first 14 weeks of treatment and once every 2 weeks thereafter.

3. Food Consumption, Water consumption and Compound Intake:

Food consumption for each animal was determined weekly and mean daily diet consumption was calculated as of food/animal/day. Weekly food conversion efficiencies were calculated for the

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first 14 weeks of treatment and reported as %. Compound intake (mg/kg/day) was calculated as time-weighted averages from the consumption and body weight gain data. Water consumption (ml/animal/day) were recorded for the first 13 weeks of treatment and approximately once monthly thereafter for 10 animals/sex in the toxicity phase.

4. Ophthalmoscopic Examination:

Before treatment started the eyes of all animals were examined. In addition, the eyes of animals in the 0 and 20,000 ppm groups of the oncogenicity phase were examined at Weeks 27, 53, 78 and 103 of treatment. At Week 103, female oncogenicity phase rats in the 1000 and 10,000 ppm groups were examined for ocular signs of toxicity.

5. Blood was collected during the acclimation period on Week 1 of treatment from 10 animals/sex in the pretreatment clinical pathology group. In Weeks 26, 52, 78 and 103/105 (males were bled in Weeks 103 and females in Week 105), blood samples were obtained from 10 fasted animals/sex/group in the toxicity phase. At Week 103/105, the number of animals/sex/group used in the toxicity phase was supplemented with animals from the oncogenicity phase to maintain the sampling size of 10 animals/sex/groups. Blood samples were obtained from the retro-orbital sinus with animals under slight halothane/nitrous oxide anesthesia. The CHECKED (x) parameters were examined.

a. Hematology:

x		x	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB(MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc. (MCH)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*	x	Fibrinogen conc.
x	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Required for chronic studies based on Subdivision F Guidelines.

b. Clinical Chemistry*:

X	ELECTROLYTES	X	OTHER
x	Calcium*		Albumin*
x	Chloride*	x	Blood Creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorous*	x	Total cholesterol
x	Potassium*		Globulins
	Sodium*	x	Glucose*
		x	Total bilirubin
X	ENZYMES	x	Direct bilirubin
		x	Total serum proteins (TP)*
x	Alkaline phosphatase (ALK)	x	Triglycerides
	Cholinesterase (ChE)	x	Serum protein electrophoresis
x	Lactic acid dehydrogenase		
x	(LDH)		
	Serum alanine amino-		
x	transferase (also SGPT)*		
	Serum aspartate amino-		
x	transferase (also SGOT)*		
x	Gamma glutamyl transferase		
x	Glutamate dehydrogenase		
	Leucine amino-peptidase (LAP)		
	Creatine phosphokinase		

* Required for chronic studies based on Subdivision F Guidelines.

6. Urinalyses*:

Urine was collected from 10 animals/sex in the pretreatment clinical pathology group prior to treatment. In Weeks 25, 50, 76 and 102 overnight urine samples were obtained from 10 animals/sex/group in the toxicity phase. At Week 102, several oncogenicity phase control males were used to supplement the available toxicity phase control males. The CHECKED (x) parameters were examined.

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

* Required for chronic studies based on Subdivision F Guidelines.

7. Sacrifice and Pathology:

All animals that died and those sacrificed were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed. Histological examination of the tissues was conducted on the group of animals sacrificed at 12 months and on animals in the oncogenicity segment.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	x	Aorta+	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone Marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph modes*		
x	Duodenum*	xx	Spleen*	xx	Pituitary*
x	Jejunum*	x	Thymus*		Eyes (optic nerve)*
x	Ileum*		**UROGENITAL**		**GLANDULAR**
x	Cecum*				
x	Colon*		Kidney*+		Adrenal gland*
x	Rectum	xx	Urinary bladder*	xx	Lacrimal gland
x	Liver+*	x	Testes*+		Mammary gland+
	Gall bladder+	xx	Epididymides	x	Parathyroid*++
x	Pancreas*	xx	Prostate	xx	Thyroids*++
	RESPIRATORY	xx	Seminal vesicle	xx	**OTHER**
			Ovaries+*		
	Trachea*	xx	Uterus*		Bone*
x	Lung*	xx	Clitoral gland		Skeletal muscle*
xx	Nose	x	Propertied gland	x	Skin*
	Pharynx	x	Vagina	x	All gross lesions and masses*
	Larynx	x		x	Handerian gland
				x	

* Required for chronic studies based on Subdivision F Guidelines
\+ Organ weight required in chronic studies.
++ Organ weight required for non-rodent studies.

II. RESULTS

A. OBSERVATIONS:

1. Toxicity: Thin build and hunched posture were observed in both sexes receiving 20,000 ppm and in females receiving 10,000 ppm. In addition, there was an increased incidence of yellow/urinary staining of the perigenital area in both sexes receiving 20,000 ppm and in females receiving 10,000 ppm. After approximately 64 weeks there was a 4 week period in which signs of general pallor, pale eyes, piloerection, under activity and reduced body temperature were seen in several animals receiving 20,000 ppm, especially males.

2. Mortality: Data are provided in Table 2 below.

TABLE 2. Mortality and Percent Survivals (%)

Test Group	Mortality (Number Dead/Number Started Male	Female
0	54/20(23)	26/70(63)
1000	55/70(21)	25/70(64)
10,000	25/70(64)	26/70(63)
20,000	28/70(60)	17/70(76)

1. Data extracted from Table 1, p. 44, study # 94/SMA012/0987(MRID 43927001)

It should be noted that survival for a background group of 320 control animals/sex ranged from 34-80% in males and 64-92% in females. There were 13 deaths in males receiving 20,000 ppm from Weeks 64 to 68 that appeared to be treatment related. Macroscopic examination revealed a number of changes indicative of internal hemorrhage: pale livers, brains and pituitaries, internal organs appeared dark, and dark contents of the GI tract, fluid in the thorax and clotted blood in the abdomen. Several animals had reduced erythrocyte parameters and high reticulocyte counts. For several of the animals hemorrhage was reported as the predominant histopathology.

B. BODY WEIGHT:

During the active growth phase (males: Week 0-64; females: Week 0-94), body weight gains of animals receiving 10,000 and 20,000 ppm were significantly lower than the controls (88% and 80% of control values

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for males and 86% and 60% for females, respectively). See Table 3.

Table 3. Body Weight Gain (g) and Percent of Controls (%)[1]

Test Group (ppm)	Body Weight Gain in Grams Week 0-13	0-26	0-52	0-78	0-104[2]
Males					
0	205	262	320	324	260
1000	207	265	325	327	292
10,000	179(87)	229(87)	281(88)	290(90)	252(97)
20,000	162(79)	206(79)	256(80)	262(81)	211(82)*
Females					
0	96	119	154	196	202
1000	94(98)	116(97)	157(98)	194(99)	208
10,000	80(83)	102(84)	129(84)	163(83)	181(90)*
20,000	69(72)	85(71)	105(68)	122(62)	124(61)*

1. Data extracted from Table 4A pp. 108-113, study #94/SMA012/0987 (MRID 43927001)
2. Statistics only done on Weeks 0-104

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

C. FOOD CONSUMPTION, WATER CONSUMPTION AND COMPOUND INTAKE:

1. Food Consumption: The total food consumption of females and males receiving 20,000 ppm was 13% and 6% lower than controls, respectively. The total food consumption of animals receiving 10,000 ppm was 4% less than controls (see Table 4).

Table 4. Food Consumption (g/Animal/Day)[1]

Test Group (ppm)	Food Consumption and Percent of Controls (%) Week					
	1	13	26	52	78	104
Males						
0	113	123	126	137	137	136
1000	113	125	126	137	138	136
10,000	111(98)	116(94)	120(95)	130(95)	130(95)	133(93)
20,000	110(97)	114(93)	118(94)	127(93)	127(93)	124(91)
Females						
0	93	97	92	99	106	107
1000	96	97	92	99	108	111
10,000	90(97)	89(92)	88(96)	97(98)	102(96)	104(97)
20,000	89(96)	83(86)	81(88)	87(88)	90(85)	97(91)

1. Data extracted from Table 5, pp. 116-126, study #94/SMA012/0987(MRID 43927001)

2. Compound Consumption: Compound intake was 51, 531 and 1116 mg/kg/day in males in the 1000, 10,000 and 20,000 ppm groups, respectively. Compound intake was 63, 653 and 1351 mg/kg/day in females in the 1000 10,000 and 20,000 ppm groups respectively (see Table 1).

3. Food Efficiency: Food efficiency was decreased 8% and 17% in males in the 10,000 and 20,000 ppm groups, respectively, when compared to the controls over a 14 week period. Food efficiency was decreased 10% and 20% in females in the 10,000 and 20,000 ppm groups, respectively, when compared to the controls over the first 14 week treatment period.

4. Water Consumption: Total water consumption was decreased 3-4, 10-11 and 18-22% in males and females in the 1000, 10,000 and 20,000 ppm groups, respectively, when compared to controls (see Table 5).

Table 5. Water Consumption in ml/rat/day and Percent of Controls (%)[1]

Test Group (ppm)	Water Consumption and Percent of Controls (%) Week				
	1-13	17-50	54-78	82-102	1-102
Males					
0	254	189	196	246	885
1000	279(110)	197(109)	182(93)	193(96)	851(96)
10,000	248(98)	191(101)	174(89)	177(89)	790(89)
20,000	226(89)	178(94)	156(80)	132(78)	692(78)
Females					
0	228	183	176	169	755
1000	228(100)	179(98)	167(95)	159(95)	733(97)
10,000	201(88)	165(90)	162(92)	149(89)	677(90)
20,000	202(89)	147(80)	135(77)	135(80)	619(82)

1. Data extracted from Table 8, pp. 132-135, study #94/SMA012/0987 (MRID 439277001).

D. OPHTHALMOSCOPIC EXAMINATION:

In Week 103/104 there was an increase in the incidence of posterior corpuscular opacity observed in females in the 10,000 and 20,000 ppm groups. The percent incidence was 5, 29, 53 and 64% in the 0, 1000, 10,000 and 20,000 ppm groups, respectively. The incidence in 142 background controls ranged from 0-6%.

E. BLOOD WORK:

1. Hematology: The hematocrit and hemoglobin were significantly decreased in females in the 10,000 and 20,000 ppm groups at Weeks 26, 52 and 78. The hematocrit was also decreased in females in the 1000 ppm group at Week 52 and in females in the 20,000 ppm group at Week 104. RBCs were significantly decreased in females in the 20,000 ppm group at Weeks 26 and 52 and in females in the 10,000 ppm group at Week 52. RBCs were also lower than controls (not statistically significant) in females receiving 10,000 ppm at Week 26, in females receiving 1000 ppm at Week 52 and in all treated females at Week 78. The MCV was significantly decreased in females in the 10,000 and 20,000 ppm groups at Weeks 26 and 52 and in males and females receiving 10,000 and 20,000 ppm at Week 78 and in males and females receiving 20,000 ppm at Week 104. The MCH was significantly decreased in females receiving 10,000 at 20,000

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ppm at Week 26, in males receiving 10,000 at 20,000 ppm and females receiving 20,000 ppm at Week 78 and in males and females receiving 20,000 ppm at Week 104. Platelet counts were increased in Week 78 for females receiving 10,000 or 20,000 ppm and in Week 104 for females receiving 20,000 ppm. Significantly decreased prothrombin times were noted in males receiving 20,000 ppm at Weeks 26 and 52, although these animals had significantly long times in Week 78 and females receiving 20,000 ppm had significantly long times at Week 52. Males in the 20,000 ppm group had significantly long activated partial thromboplastin times at Weeks 52 and 78. Fibrinogen levels were significantly lower in animals receiving 10,000 or 20,000 ppm at all occasions (except Week 104 for males receiving 10,000 ppm) and in females receiving 1000 ppm at Week 78. High leukocyte counts (primarily lymphocytes) were observed in females receiving 10,000 or 20,000 ppm at Week 26 and in females receiving 20,000 ppm at Week 78. Other intergroup differences occurred only at 1000 or 10,000 ppm and were not considered to be treatment related (see Table 6). Males in the 20,000 ppm group that were decedents especially those animals exhibiting signs of internal bleeding showed abnormally decreased erythrocyte parameters and increased reticulocyte counts.

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Table 6. Select Hematological Parameters[a]

Parameter	Dose Level (ppm)							
	0		1000		10,000		20,000	
	M	F	M	F	M	F	M	F
26 Weeks								
HCT(%)	47	47	48*	46	47	45**	46	44***
HGB(g%)	16.1	16.3	16.7**	16.2	16.3	15.9**	16.0	15.3***
RBC(10^6/mm^3)	9.88	9.27	10.18**	9.18	9.91	9.12	9.81	8.97**
MCV(cμ)	48	50	48	51	48	50*	47	49**
MCH(pg)	16	18	16	18	16	17	16	17
Fibrinogen (mg%)	208	166	203	169	183***	155*	173***	141***
52 Weeks								
HCT(%)	47	49	48*	47*	48	46**	47	44**
HGB(g%)	15.8	16.4	16.0	16.1	16.0	15.5***	15.7	15.1***
RBC (10^6/mm^3)	9.68	9.45	9.92**	9.25	9.87*	9.14**	9.75	9.01***
MCV(cμ)	48	52	48	51	48	50***	48	49***
MCH(pg)	16	17	16	17	16	17	16	17
Fibrinogen (mg%)	227	162	230	164	209*	149**	183***	139***
78 Weeks								
HCT(%)	44	46	44	45	45	44*	45	42***
HGB(g%)	15.3	16.4	15.3	15.9	15.6	15.7*	15.4	14.9***
RBC(10^6/mm^3)	8.61	9.11	8.75	8.84	9.15	8.92	9.14	8.81
MCV(cμ)	51	51	51	51	49*	50**	49**	48***
MCH(pg)	18	18	17	18	17**	18	17***	17***
Fibrinogen (mg%)	247	228	224	198***	204**	171***	175***	159***

Table 6. Select Hematological Parameters[a]

Parameter	Dose Level (ppm)							
	0		1000		10,000		20,000	
	M	F	M	F	M	F	M	F
102 Weeks								
HCT(%)	36	41	38	43	39	41	39	39*
HGB(g%)	12.6	14.4	12.9	14.7	13.6	14.5	13.6	13.8
RBC(10^6/mm)	6.95	7.76	6.91	7.92	7.79	7.91	7.90	7.75
MCV(cμ)	52	53	58	54	50	52	50*	50**
MCH(pg)	18	19	19	19	18	18	17*	18**
Fibrinogen (mg%)	359		329		327		217***	

* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.
*** Significantly different from controls at $p<0.001$.
a Data extracted from Tables 10A (pp. 144-145), 10B (pp. 146-147), 10C (pp. 148-149), 10D (pp. 150-151), Study #94/SMA012/0987, MRID 43927001.

2. Clinical Chemistry: Leucine amino peptidase (LAP) as significantly increased for females receiving 20,000 at all occasions, and for females receiving 0,000 ppm at Weeks 52, 78 and 104 and for females receiving 1000 ppm at Week 78. LAP was also significantly increased in all treated males at Week 104. Alkaline phosphatase was significantly increased in female receiving 20,000 ppm at all occasions, in males receiving 20,000 ppm at Weeks 78 and 104, in females receiving 10,000 ppm at Weeks 26 and 78 and in males receiving 10,000 ppm at Week 104. SGOT was decreased in males receiving 10,000 or 20,000 ppm at Weeks 26 and 52 and in females receiving 10,000 and 20,000 ppm at Weeks 52 and 78. SGOT was also decreased in females receiving 10,000 ppm at Week 26. SGPT was decreased in males receiving 20,000 ppm and females receiving 10,000 ppm at Week 26 and in females receiving 10,000 or 20,000 ppm and in males receiving 10,000 ppm at Week 52. CPK was significantly decreased in males receiving 10,000 or 20,000 ppm and in females receiving 10,000 ppm a Week 26, in all treated females at Week 52, and in males and females receiving 10,000 or 20,000 ppm at Week 78. Females receiving 20,000 had low (not significant) CPK at Weeks 26 and 104. LDH was decreased in males and females receiving 10,000 or 20,000 ppm at Week 26, in all treated females at Weeks 52 and 78 and in males receiving 10,000 or 20,000 ppm at Week 78. CPK was also decreased in males receiving 10,000 ppm at Week 104. GGT was significantly increased in females receiving 20,000 ppm on all occasions and in females receiving 10,000 ppm at Week 26. BUN was significantly increased in males receiving 10,000 or 20,000 ppm and in females receiving 20,000 ppm at Week 52 and in females receiving 10,000 or 20,000 ppm at Week 78. Glucose was decreased in males receiving 20,000 ppm at Week 26 and for males receiving 10,000 or 20,000 ppm at Week 52. However, at Week 104 males in the 20,000 ppm group had high glucose levels. Males receiving 10,000 or 20,000 ppm had low triglyceride levels at Weeks 26, 52 and 78 and in females receiving 10,000 or 20,000 ppm at all occasions. Females receiving 1000 ppm also had low triglyceride levels at Week 78 and 104. Phospholipid levels were significantly decreased on all occasions in animals receiving 20,000 ppm and in females receiving 10,000 ppm at Weeks 26, 52 and 78 and in females receiving 1000 ppm at Weeks 78. Cholesterol was decreased in all animals receiving 20,000 ppm and in females receiving 10,000 ppm on all occasions. Cholesterol was also decreased in males receiving 10,000 ppm at Week 104 and in

females receiving 10,000 ppm at Week 78. Males receiving 10,000 ppm had a nonsignificant decrease in cholesterol at Weeks 52 and 78. A/G ratios were significantly increased in animals receiving 10,000 or 20,000 ppm on all occasions except for Week 52 for males receiving 10,000 ppm on Week 78. Females in the 1000 ppm group had increased A/G ratio at Weeks 26. The altered A/G ratio was attributed to increased albumin concentration on all occasions for females receiving 10,000 or 20,000 ppm at Weeks 26, 52 an 78 in females receiving 1000 ppm, at Weeks 26, 52 and 78 in males receiving 20,000 ppm and at Week 78 in males receiving 10,000 ppm. Males receiving 10,000 or 20,000 ppm had a nonsignificant increase in albumin at Week 104. Alpha-1 and alpha-2 globulin were decreased in animals receiving 20,000 ppm on all occasions except for alpha-2 in males at Week 52. Alpha-1 levels were low in animals receiving 10,000 ppm at Weeks 26 and 104 an in females receiving 1000 ppm at Week 26. Alpha-2 levels were decreased in males receiving 10,000 ppm at Weeks 26 and 78, in females receiving 10,000 ppm at Weeks 26, 52 and 78 and in females receiving 1000 ppm at Week 78. Beta globulins were low in animals receiving 20,000 ppm and in females receiving 10,000 ppm at Weeks 26 and 52. Total protein was decreased in females receiving 20,000 ppm at Weeks 26, 52 and 78, in males receiving 20,000 ppm at Weeks 78 and 104 and in males receiving 10,000 ppm at Week 104. Males in the 10,000 and 20,000 ppm groups had increased potassium at Weeks 26 and 78. Potassium was also increased in females receiving 20,000 ppm at Weeks 26, 78 and 104 and in females receiving 10,000 ppm at Week 78. Calcium was decreased in animals receiving 20,000 ppm and in males receiving 10,000 ppm at Week 104 and in males receiving 20,000 ppm at Week 52. Phosphorus levels were increased in males receiving 20,000 ppm at Week 26. Chloride was decreased in males receiving 10,000 or 20,000 ppm at Week 26 but were high in females receiving 20,000 ppm at Week 104 (see Table 6). Other intergroup differences were inconsistent temporally and between the sexes or occurred only at 1000 or 10,000 ppm and were not considered to be treatment related (see Table 7).

Table 7. Select Clinical Chemistry Parameters[a]

Parameter	Dose Level (ppm)							
	0		1000		10,000		20,000	
	M	F	M	F	M	F	M	F
26 Weeks								
Leucine amino peptidase (iul)	29	27	29	27	28	28	29	31***
Alkaline phosphatase (iul)	70	57	64*	52	64*	68*	68	100***
Gamma-glutamyl transferase (iul)	0	0	0	0	0	1**	0	4***
Albumin (g%)	3.0	3.6	3.5	3.9**	3.7	4.3***	3.8**	4.1***
α-1 Globulin (g%)	1.3	1.2	1.3	1.1*	1.2*	0.9***	1.1***	1.0***
α-2 Globulin (g%)	0.5	0.5	0.6	0.5	0.5*	0.4***	0.4**	0.4***
β-Globulin (g%)	1.7	1.6	1.7	1.6	1.5	1.4***	1.5*	1.3***
A/G Ratio	1.0	1.0	1.0	1.1**	1.1*	1.5***	1.3**	1.4***
Triglycerides(mg%)	149	60	186*	52	95**	33***	51***	31***
Total Proteins (g%)	7.1	7.2	7.2	7.3	7.0	7.2	7.0	7.0*
Phospholipids (g%)	129	202	186*	203	95**	178***	51***	156***
Cholesterol (mg%)	71	122	76	122	69	101***	58***	86***
52 Weeks								
Leucine amino peptidase (iul)	30	24	29	24	30	26**	30	29***
Alkaline Phosphatase (iul)	85	53	82	49	77	59	86	86***
Gamma-glutamyl transferase (iul)	0	0	1	0	0	0	0	3***
Albumin (g%)	3.1	4.1	3.2	4.4*	3.3	4.5***	3.5***	4.6***
α-1 Globulin (g%)	1.3	1.2	1.3	1.2	1.3	1.1	1.1***	0.9***
α-2 Globulin (g%)	0.4	0.6	0.5	0.5	0.5	0.4***	0.4	0.4***
β-Globulin (g%)	1.6	1.7	1.7	1.7	1.5	1.5***	1.3***	1.4***
A/G Ratio	0.9	1.1	0.9	1.2	1.0	1.4***	1.2***	1.6***

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Table 7. Select Clinical Chemistry Parameters[a]

Parameter	Dose Level (ppm)							
	0		1000		10,000		20,000	
	M	F	M	F	M	F	M	F
Triglycerides (mg%)	195	90	183	85	104***	47***	58***	42***
Total Protein (g%)	6.7	7.7	6.8*	8.0*	6.8	7.8	6.5	7.5**
Phospholipids (mg%)	177	263	189	274	157	229**	124***	190***
Cholesterol (mg/%)	113	152	120	157	95	128***	69***	111***
78 Weeks								
Leucine amino peptidase (iul)	26	19	27	21**	27	22***	28	25***
Alkaline phosphatase (iul)	68	48	64	57	75	65***	89***	100***
Gamma-glutamyl transferase (iul)	1	0	0	1	0	1	0	3***
Albumin (g%)	2.6	3.2	2.5	3.5*	2.9*	3.6*	2.7*	3.8***
-1 Globulin (g%)	2.0	1.5	2.1	1.6	1.8	1.4	1.6*	0.9***
β-Globulin (g%)	1.7	1.5	1.7	1.6	1.6	1.6	1.5	1.4
A/G Ratio	0.6	0.9	0.6	0.9	0.7*	1.0	0.8**	1.3***
Triglycerides (mg%)	342	258	384	188*	220*	57***	148***	51***
Total Proteins (g%)	6.9	7.0	7.0	7.5***	6.9	7.2	6.6***	6.7*
Phospholipids	01	339	338	284*	257	238***	189**	206***
Cholesterol (mg%)	220	215	252	176*	178	148***	122***	128***
102/104 Weeks								
Leucine amino Peptidase (iul)	27	23	29*	24	30*	29**	31**	32***
Alkaline phosphatase (iul)	40	34	47	49	65**	57	93***	114***
Gamma-glutamyl transferase (iul)	0	0	1	1	1	2	1	5***
Albumin (g%)	2.0	2.4	2.0	2.6	2.3	3.1**	2.3	3.4***
α-1 Globulin (g%)	2.3	2.0	2.3	1.9	1.8**	1.5*	1.7***	0.8***

Table 7. Select Clinical Chemistry Parameters[a]

Parameter	Dose Level (ppm)							
	0		1000		10,000		20,000	
	M	F	M	F	M	F	M	F
α-2 Globulin (g%)	0.6	0.7	0.5	0.7	0.6	0.6	0.5*	0.5***
β-Globulin (g%)	1.7	1.5	1.7	1.7	1.6*	1.5	1.5**	1.5
A/G Ratio	0.,4	0.6	0.4	0.6	0.6*	0.8**	0.6*	1.2***
Triglycerides (mg%)	426	446	222	282*	336	154***	227	96***
Total Protein (g%)	6.8	6.8	6.7	7.0	6.3*	6.8	5.9**	6.3
Phospholipids (mg%)	458	426	397	404	356	343	299**	247***
Cholesterol (mg%)	278	284	256	250	213*	211*	162***	142***

* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.
*** Significantly different from controls at $p<0.001$.
a Data extracted from Table 13B (pp. 160-163), Table 13C (pp. 164-167), Table 13D (pp. 168-171) and Table 13E (pp. 172-175).

F. URINALYSIS:

A dosage related decrease in pH was present at Weeks 25 and 50 for animals receiving 10,000 or 20,000 ppm and at Week 77 for females receiving 10,000 or 20,000 ppm. Males in the 10,000 and/or 20,000 ppm groups showed a nonsignificant decrease in pH at Week 77. Specific gravity was increased in animals receiving 10,000 or 20,000 ppm at Weeks 25, 50 and 77 although statistical significance was not achieved in females in the 10,000 ppm group at Week 26. There was reducing substance in a number of animals in the 20,000 ppm groups at Weeks 50 and 102.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight: At Week 52, there was an increase in absolute liver weight in males in the 20,000 ppm group (21.3%) and in females in the 10,000 (24%) and 20,000 ppm (48.4%) groups. The relative weight of the liver was also increased in males in the 10,000 (19.4%) and 20,000 (45.0%) ppm groups and in females in the 10,000 (38.3%) and 20,000 ppm (83.0%) groups. A dose-response relationship was apparent (see Table 8). Other changes included significant decreases in absolute heart weight in males in the 20,000 ppm group and in females in the 10,000 and 20,000 ppm groups, in absolute lung weight in females at 20,000 ppm, in absolute and relative spleen weight in males at 10,000 and 20,000 ppm, and increases in relative brain weight in males and females in the 10,000 and 20,000 ppm groups, in relative adrenal weight in males and females in the 10,000 and 20,000 ppm groups, in relative heart weight in males at 20,000 ppm, in relative thyroid weight in females a 10,000 and 20,000 ppm, in relative testes weight in males at 10,000 an 20,000 ppm, in relative kidney weight as males and females in the 10,000 and 20,000 ppm groups and in relative epididymis weight in males at 20,000 ppm. At week 104 the toxicity part of the study, there was an increase in absolute liver weight in females at 10,000 ppm (16.7%). Relative liver weights were increased in males in the 10,000 (22%) an 20,000 ppm (45.3%) groups an in females in the 10,000 (27.4%) and 20,000 (55.0%) ppm groups (see Table 9). Other changes included significant decreases in absolute heart weight in females at 10,000 ppm and in males at 10,000 and 20,000 ppm, in absolute kidney weight in females at 20,000 ppm and increases in absolute brain weight in males at 20,000 ppm, in absolute epididymis weight in males at 20,000 ppm, in relative brain weight in females at 10,000 and 20,000 ppm, in relative adrenal weight in females

at 20,000 ppm, in relative epididymis weight in males at 10,000 ppm, in relative lung and in uterus weights in females at 20,000 ppm. In the oncogenicity portion of the study at termination, there as an increase in absolute liver weight in males in the 10,000 (29.9%) and 20,000 ppm (36.7%) groups and in females in the 10,000 (11.7%) and 20,000 (21.2%) ppm groups (see Table 10). The relative weight of the liver was also increased in males in the 10,000 (22.7%) and 20,000 ppm (45.3%) groups and in females in the 10,000 (27.4%) and 20,000 ppm (45.3%) groups and in females in the 10,000 ppm (27.4% and 20,000 ppm (55.0%). Other changes included significant deceases in absolute adrenal weight in females at 20,000 ppm, in absolute heart weight in males at 20,000 ppm and in females at 10,000 and 20,000 ppm, in absolute kidney weight in females at 20,000 ppm, in absolute lung weight in males and females a 20,000 ppm, in absolute spleen and thyroid weight in females at 20,000 ppm and in relative heart weight in females at 1000 ppm, and increases in absolute and relative brain weight in females at 10,000 and 20,000 ppm and in relative adrenal weight in females at 20,000.

Table 8. Selected Organ Weights in Rats at 52 Weeks[a]

Organ Weight/Dose Level					
Male	**Female**	**0**	**1000**	**10,000**	**20,000**
Absolute					
Liver		16.9	16.8	18.6	20.5**
Spleen		0.817	0.803	0.679**	0.605**
	Liver	9.3	9.4	11.6**	13.8**
	Heart	0.85	0.83	0.79*	0.72**
Relative					
Liver		4.07	3.97	4.86**	5.90**
Spleen		0.1976	0.1897	0.1776*	0.1744*
Brain		0.461	0.453	0.499**	0.535**
Kidney		0.811	0.792	0.860*	0.911**
Testes		0.759	0.770	0.833*	0.860*
	Liver	3.89	3.94	5.38**	7.12**
	Thyroid	0.0069	0.0074	0.0091**	0.0102**
	Brain	0.727	0.706	0.802**	0.882**

* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.
a Data extracted from Tables 15A (pp. 181-183) and 15B (184-186) Study No. 94/SMA012/0987 MRID

Table 9. Selected Organ Weights at Week 104 (Toxicity Study)[a]

Organ Weight/Dose Level					
Male	**Female**	**0**	**1000**	**10,000**	**20,000**
Absolute					
Liver		18.8	20.2	22.2	22.8
Heart		1.52	1.53	1.30*	1.27*
Relative					
Liver		5.10	4.96	6.26*	7.41**
	Liver	4.96	4.86	6.32**	7.69**
	Brain	0.609	0.597	0.670*	0.885**

* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.
a Data extracted from Tables 15C (pp. 187-189), 15D (190-192) Study No. 94/SMA012/0987. MRID 43927001.

Table 10. Selected Organ Weight at Termination (Oncogenicity Study)

Organ Weight/Dose Level					
Male	**Female**	**0**	**1000**	**10,000**	**20,000**
Absolute					
Liver		17.7	20.4	23.0**	24.2**
	Liver	13.7	14.3	15.3*	16.6**
	Brain	1.74	1.75	1.81**	1.80**
Relative					
Liver		5.08	5.31	6.60**	7.77**
	Liver	4.90	4.86	5.78**	7.79**
	Brain	0.628	0.604	0.684*	0.847**

* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.
a Data extracted from Tables 15E (pp. 193-195), 15I (196-198) Study No. 94/SMA012/0987. MRID 43927001.

2. Gross Pathology: There were no treatment related macroscopic changes at 52 weeks. There was an increased incidence of abnormally shaped kidneys in females in the 20,000 ppm groups at 104 weeks. Males in the 20,000 ppm group had a greater incidence of subscapular fluid in the testes than the controls. Females in the 20,000 ppm appeared to be thin. Males in the 10,000 and 20,000 ppm group appear thin. Males in the 20,000 ppm group had higher incidence of: epididymal masses, dark kidneys, pale pituitaries, dark and small prostate

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glands, areas of change in seminal vessels, dark testes, fluid in the abdomen, area of change in abdominal fat and musculo-skeletal areas and pale brains. Females in the 20,000 ppm group also had areas of change in the lungs. Liver masses were more prevalent in rats in the 20,000 ppm group.

3. Microscopic Pathology:

Non-neoplastic: At the 52 Week sacrifice, there were no changes.

The only treatment-related changes observed in rats in the oncogenicity phase were in the liver of rats administered 10,000 and 20,000 ppm in the diet. The incidence of panacinar hypertrophy was 28% and 89%, respectively in males in the 10,000 and 20,000 ppm group, respectively; and 84% and 80% in females in the 10,000 and 20,000 ppm groups, respectively (controls and 1000 ppm group had 0 incidence). The incidence of congestion of the liver was significantly increased in females in the 20,000 ppm group (26%) when compared to controls (see Table 12).

Table 12. Select Hepatic Lesions and Percent Incidence(%) in the Oncogenicity Segment[a]

Lesion	Dose Level (ppm)							
	0		1000		10,000		20,000	
	M	F	M	F	M	F	M	F
Number examined	50	50	50	50	50	50	50	50
Panacinar hypertrophy	0	0	0	0	14	11	42**	40**
	(0)	(0)	(0)	(0)	(28)	(22)	(84)	(80)
Congestion	2	3	1	4	4	8	7	13*
	(4)	(6)	(2)	(8)	(8)	(16)	(14)	(26)
Hepatocellular adenoma	1	2	0	0	1	1	4	3
	(2)	(4)	(0)	(0)	(2)	(2)	(8)	(6)
Hepatocellular carcinoma	0	0	0	(0)	2	1	5*	8**
	(0)	(0)	(0)	(0)	(4)	(2)	(10)	(16)
Hepatocellular combined tumors	1	(2)	0	0	3	2	9**	11**
	(2)	(4)	0	0	(6)	(4)	(19)	(22)

* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.
a Data extracted from Text Table 5 (p. 56) and text Table B (p. 59) Study No. 94/SMA012/0987 MRID 43927001.

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Neoplastic: There was a significant increase in the incidence of hepatocellular carcinomas in males in the 20,000 ppm group (10%) and females in the 20,000 ppm group (16%) when compared to controls (males 2%; females 0%). In addition the incidences of combined hepatocellular adenomas and carcinomas were significantly increased in males in the 20,000 ppm group (18%) and in females in the 20,000 ppm group (22%) when compared to controls (males 2%; females 4%), (see Table 12). The authors suggest that the tumors may be associated with the early induction of hepatic drug metabolizing enzymes suggested by the histopathological and biochemical changes noted previously. No other specific lesions were considered to be treatment related.

III. DISCUSSION

Thin build, hunched posture and yellow/urinary staining of the perigenital area were observed in animals in the 20,000 ppm group and in females in the 10,000 ppm group. Treatment related deaths occurred in males in the 20,000 ppm group from Weeks 64-68. Hemorrhage was reported as the predominant histopathology. During the growth phase of the animals, animals receiving 10,000 and 20,000 ppm had reduced weight gain (60-88%) when compared to controls. Food consumption was decreased 13% and 6%, respectively in males and females in the 20,000 ppm group. Compound consumption was 51, 531 and 1116 mg/kg/day in males in the 1000, 10,000 an 20,000 ppm groups and was 63, 653 and 1351 mg/kg/day in females in the 1000, 10,000 and 20,000 ppm groups, respectively.Food efficiency was decreased 8% and 17% in males in the 10,000 and 20,000 ppm groups and 10% and 20% in females in the 10,000 and 20,000 ppm groups, respectively, over a 14-week period. Water consumption was decreased 10-11% and 18-22% in males and females in the 10,000 ppm and 20,000 ppm groups, respectively. The incidence of posterior capsular opacity was increased in females in the 10,000 ppm group (53%) and 10,000 ppm roup (64%) when compared to controls (25%). There was indication of mild anemia in animals in the 10,000 and 20,000 ppm group. On several sampling periods the hematocrit, hemoglobin levels and RBC count were significantly reduced in these groups. Fibrinogen levels were significantly decreased in males and females in the 10,000 and 20,000 ppm groups. Males in the 20,000 ppm group showing signs of hemorrhage had abnormally decreased RBC parameters and increased reticulocyte counts. Other statistically significant changes occurred sporadically and differently across the sexes. Leucine amino peptidase was significantly increased in females in the 10,000 and 20,000 ppm groups. Alkaline phosphatase was increased in females in the 10,000 and 20,000 ppm groups and in males in the 20,000 ppm groups. GGT was increased in females in the 20,000 ppm groups on all occasions and in

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females in the 10,000 ppm groups at Week 26. Triglyceride levels were low in males and females in the 0,000 and 20,000 ppm groups Triglyceride levels were also low in female in the 1000 ppm group at Weeks 78 and 104. Phospholipid levels and cholesterol were low in animals in the 10,000 ppm group and in females in the 10,000 ppm group. A/G ratios were significantly increased in animals in the 10,0,000 and 20,000 ppm groups. Alpha-1 and Alpha-2 globulin were decreased in animals in the 20,000 ppm group. Alpha-2 globulin was also decreased in females in the 10,000 ppm group. Total protein was decreased in males and females in the 20,000 ppm group. A dosage relate decrease in specific gravity and pH of the urine was noted in animals in the 10,000 and 20,000 ppm groups. Absolute and/or relative liver weights were increased in males and females in the 10,000 and 20,000 ppm groups at Weeks 52 and 104. At gross necropsy, males and females in the 20,000 ppm group and males in the 10,000 ppm group appeared thin. Males in the 20,000 ppm group had a greater incidence of subscapular fluid in the testes. At the 52 Week sacrifice males and females in the 20,000 ppm group had a significant increase in diffuse hypertrophic hepatocytes. The incidence was also increased (not significantly) in the 10,000 ppm group. At Week 104 the incidence of panacinar hypertrophy was increased in animals in the 10,000 and 20,000 ppm groups. Congestion was also seen in the livers of females in the 20,000 ppm group and to a lesser extent in males. Hepatic hypertrophy, many of the clinical chemistry and enzyme activity changes and changes in clotting times are probably related to a disturbance in hepatic metabolism.

Hepatocellular carcinoma and hepatocellular adenoma and carcinoma combined were significantly increased in males and females in the 20,000 ppm group.

DEFICIENCIES

The study, as reported, was hard to follow. Statistical analysis of body weight and food consumption was not performed. Tissues from animals in the chronic toxicity segment of the study were not histologically examined.

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