DATA EVALUATION RECORD

10/12/2000

MESOTRIONE (ZA1296)

Study Type: §83-5, Combined Chronic/Oncogenicity Study-Rats

Work Assignment No. 2-01-52Y (MRIDs 44505035 and 44505036)

Prepared for
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Disclaimer

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MESOTRIONE (ZA1296) **Chronic/Oncogenicity (§83-5)**

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DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity
OPPTS Number: 870.4300 OPP Guideline Number: §83-5

DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Mesotrione (96.8% a.i.)

SYNONYMS: ZA1296; 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; 2-(4-mesyl-2-nitrobenzoyl)-cyclohexane-1,3-dione

CITATION: Brammer, A. (1997) ZA1296: 2 Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report No. CTL/P/5481, December 16, 1997. MRID 44505035. Unpublished.

Scott, R., (1998) Pathology Characteristics of the Alderley Park Strain (AP:Alpk$_f$SD) of Rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report No. CTL/R/1349, January 9, 1998. MRID 44505036. Unpublished.

SPONSOR: Zeneca Agricultural Products, Wilmington, DE

EXECUTIVE SUMMARY: In a combined chronic/oncogenicity study (MRID 44505035, 44505036) mesotrione (96.8% a.i.) was administered via the diet to 64 Alpk:AP$_f$SD rats/sex/group at 0, 7.5, 100, or 2500 ppm (equivalent to 0, 0.48, 6.48 or 159.89 mg/kg/day in males and 0, 0.57, 7.68, or 189.48 mg/kg/day in females) for up to 104 weeks. To assess ocular toxicity, an additional 20 rats/sex/dose were dosed at 1 or 2.5 ppm (equivalent to 0.06 and 0.16 mg/kg/day in males and 0.08 and 0.19 in females). Twelve main study rats/sex/dose were terminated after 52 weeks.

No treatment-related adverse effects were observed on mortality, food consumption, food efficiency, or hematology, clinical chemistry, and urinalysis parameters for either sex at any treatment level. All male groups were terminated when survival dropped to approximately 25% during weeks 92/93 and 97/98. Chronic progressive glomerulonephropathy was the major contributory factor involved in the intercurrent deaths. There was no evidence of a trend in male or female Kaplan-Meier survival rates. Female groups were terminated as scheduled in week 104.

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The major target organ was the eye. In the 7.5-, 100-, and 2500-ppm males and in the 100- and 2500-ppm females ocular lesions consisting of cloudy eyes, corneal lesions consisting of opacity/hazy opacity/vascularization/ghost vascularization, and/or corneal keratitis were observed. No treatment-related ocular lesions were observed in the 1- and 2.5-ppm animals or in females dosed at 7.5 ppm.

Reductions ($p<0.05$ or 0.01) in mean body weight were observed throughout the study in the 7.5-ppm males (↓2-13%) and the 100- and 2500-ppm males and females (↓1-17%). Body weight reductions ($p<0.05$ or 0.01) were also observed in the 2.5- and 1-ppm male satellite groups. Body weight decreases of over 10% in the 2.5- and 7.5-ppm males were noted only from week 75 to termination after body weights had stabilized in all groups. Since there were random fluctuations of the weights among all groups during this time period, body weight changes at 7.5 ppm and below were not considered biologically relevant. Decreases in body weight gain from weeks 1 to 47 were only biologically significant in males at 100 and 2500 ppm and, in females, at 2500 ppm. There was no dose relationship with the decrease in body weight gain in either sex among all treatment groups from week 47 to termination.

Increases ($p<0.01$) in absolute kidney weights in the 7.5-ppm and the 2500-ppm males (↑12-15%) and adjusted (for body weight) kidney weights in the 7.5-, 100-, and 2500-ppm males (↑13-22%) were observed at the interim sacrifice (week 53). These differences in kidney weights were not observed at the terminal sacrifice.

Increases ($p<0.05$ or 0.01) in absolute and adjusted liver weights in the 7.5-ppm males (↑18 and 17%, respectively), adjusted liver weights in the 100- and 2500-ppm males (↑15-18%), and adjusted liver weights in the 100- and 2500-ppm females (↑11-14%) were observed at the interim sacrifice. At the terminal sacrifice, increases ($p<0.05$ or 0.01) in absolute and adjusted liver weights in the 100- and 2500-ppm males (↑7-20%) were observed. During gross examination of the 7.5-, 100-, and 2500-ppm dose groups, pale liver was observed in the males (25-27/treated group vs. 9 controls) and females (3-10/treated group vs. 2 controls). During histopathological examination, minimal to marked hepatocyte fat vacuolation was observed in the 7.5-, 100-, and 2500-ppm males (36-39/treated group vs. 17 controls) and the 100- and 2500-ppm females (14-16/treated group vs. 8 controls).

Decreased absolute adrenal weights in the 100- and 2500-ppm males (↓21 and 22%, respectively) and decreased adjusted adrenal weights in the 7.5-, 100-, and 2500-ppm males (↓19, 25, and 29%, respectively) showed a slight dose-dependent trend, but no histopathological abnormalities were observed.

The administration of mesotrione to rats up to 2500 ppm (159.9 mg/kg/day for males, 189.5 mg/kg/day for females) in the diet did not result in an overall treatment-related increase in incidence of tumor formation.

Under the conditions of this study, dosing is considered adequate to assess the carcinogenic potential of mesotrione based on the ocular and hepatic lesions and increased liver and kidney

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weights noted at 7.5 ppm and above and body weight effects at 100 ppm and above in males and increased liver weights and ocular and hepatic lesions at 100 ppm and above in females.

The LOAEL for this combined chronic toxicity/ carcinogenicity rat feeding study is 7.5 ppm (0.48 mg/kg/day for males, 0.57 for females) based on ocular lesions, increases in kidney and liver weights, and hepatocyte fat vacuolation in males. No NOAEL was determined for kidney and liver weights or hepatocyte fat vacuolation in males. The NOAEL for ocular lesions in the special study is 2.5 ppm (0.16 mg/kg/day for males, 0.19 mg/kg/day for females).

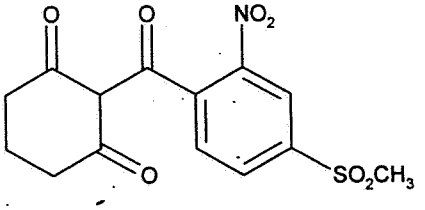
The submitted study is classified as **acceptable (§83-5)** and does satisfy the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Mesotrione (ZA1296)
   Description: Light beige solid
   Lot/Batch #: P17
   Purity (w/w): 96.8% a.i.
   Stability of compound: The test substance was stable for up to 2 years when stored at ambient temperature in the dark.
   CAS #: 104206-82-8
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
   Strain: Alpk:AP$_f$SD
   Age at start of dosing and mean weight at week 1: Approximately 34 days old; 143.3-151.6g (males), 127.0-133.0g (females)
   Source: Rodent Breeding Unit, Zeneca Pharmaceuticals, Alderley Park
   Housing: Four per cage in rat racks suitable for this strain and weight range
   Diet: CT1 (Special Diet Services, Ltd., Essex, UK), ad libitum except during urine collection
   Water: Tap water, ad libitum except during urine collection

Environmental conditions:
Temperature: 21±2°C
Humidity: 55±15%
Air changes: At least 15/hour
Photoperiod: 12 hours light/12 hours dark
Acclimation period: At least 12 days

B. STUDY DESIGN:

1. In life dates: Start: 1/95 End: 2/97

2. Animal assignment: The rats were randomly assigned to the test groups shown in Table 1.

Table 1. Study design [a]

Test Group	Dietary Concentration (ppm)	Mean Achieved Dose (mg/kg/day)[c]	Main Study		Interim Kill	
			Males	Females	Males	Females
Control	0	0	52	52	12	12
Low[b]	1	0.06/0.08	20	20	0	0
Low-mid[b]	2.5	0.16/0.19	20	20	0	0
Mid	7.5	0.48/0.57	52	52	12	12
Mid-high	100	6.48/7.68	52	52	12	12
High	2500	159.89/189.48	52	52	12	12

a Data obtained from the study report, page 19.
b Groups designated for ocular toxicity assessment only
c Achieved doses obtained from the study report, page 494

3. Dose selection rationale - It was stated that the doses chosen for the current study were based on the results of feeding studies carried out by the performing laboratory. In conjunction with this chronic/oncogenicity study, two subchronic studies were submitted. In one subchronic oral toxicity study (MRID 44505019), mesotrione was administered for 90 days to 12 Alpk:AP$_f$SD rats/sex/dose at dietary concentrations of 0, 1, 125, 1250, or 12500 ppm (equivalent to [M/F] 0/0, 0.09/0.10, 11/13, 112/126, and 1111/1213 mg/kg/day, respectively). No treatment-related findings were observed in the 1 ppm group. No deaths occurred during the study. Hematology, clinical chemistry, and urinalysis parameters and organ weights were unaffected by the test substance. In both sexes of the 125-, 1250-, and 12500-ppm groups, eye opacity/keratitis/corneal vascularization and decreased ($p \leq 0.01$ or 0.05) body weights and overall (weeks 1-14) body weight gains were observed. In addition, overall food utilization in the males was

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decreased ($p \leq 0.01$). For this study, the LOAEL was 125 ppm and the NOAEL was 1 ppm.

In a second subchronic oral toxicity study (MRID 44505020), mesotrione was administered for 90 days to 12 Alpk:AP$_f$SD rats/sex/dose at dietary concentrations of 0, 2.5, 5.0, 7.5, or 150 ppm (equivalent to [M/F] 0/0, 0.21/0.23, 0.41/0.47, 0.63/0.71, or 12.46/14.48 mg/kg/day, respectively). No treatment-related findings were observed in the 2.5- or 5.0-ppm groups. No mortalities occurred during the study. Body weights, body weight gains, food consumption and utilization, hematology, clinical chemistry, and urinalysis parameters, and organ weights were unaffected by the test substance. In the 7.5-ppm group, cloudy eyes/opacity/vascularization/keratitis were observed in the males only. At 150 ppm, cloudy eyes/opacity/ keratitis were observed in both males and females; vascularization was observed only in the males. The LOAEL for this study was 7.5 ppm for males and 150 for females. The NOAEL was 5 ppm for males and 7.5 ppm for females.

The doses selected for the current study are presented in Table 1.

4. Dose preparation, administration, and analysis - The appropriate amount of test substance was mixed with the diet to obtain a premix, and the premix was diluted with additional food to obtain the appropriate dose. Homogeneity (top, middle, bottom) was determined by analyzing samples from the 2500, 2.5, and 1 ppm dose formulations. Stability was determined at concentrations of 7000 and 1 ppm over a period of up to 16 days at room temperature and up to 40 days at -20°C. Concentration analyses were performed on all dose preparations from samples collected every two months throughout the study.

   Results:
   Homogeneity (range as mean % of nominal): 75-106%
   Stability (range as mean % of day 0):
   84.8-107.4% stored at room temperature
   87.5-114.6% stored at -20°C
   Concentration (range as mean % of nominal): 76-121%

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

5. Statistics - Body weights, food consumption, food utilization, hematology, clinical chemistry, urinalysis, and organ weight data were evaluated by analysis of variance (ANOVA) and/or covariance followed by Student's t-test. Kaplan-Meier survival estimates were calculated for each group and compared using a logrank test. Tumor incidences were compared using Fisher's Exact Test and tested for trend using the Cochran-Armitage Test. All statistical tests were two-sided.

C. METHODS:

1. Observations - Changes in clinical condition or behavior were recorded daily. Detailed clinical observations were recorded weekly.

2. Body weight - All animals were weighed weekly up to week 15, then every two weeks until study termination.

3. Food consumption and efficiency - Food consumption (g/rat/day) for each cage of rats was determined weekly for weeks 1-14 and 16 and then every fourth week until study termination. Food utilization was calculated as the body weight gained per cage/100 g food consumed.

4. Water consumption - Water consumption was not measured.

5. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed on all animals assigned to the main study group prior to dose initiation, at weeks 26, 52, and 78, and during the week prior to termination.

6. Blood analyses - Blood was collected via the tail vein from 13 animals/sex/dose at weeks 14, 27, 53, and 79. Different animals were used for the hematology and clinical chemistry blood samples. In addition, blood was collected from all surviving rats at the interim (week 53) and terminal (week 92/93 or 97/98 males and week 105 females) sacrifice. The CHECKED (X) parameters below were examined:

   a. Hematology:

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
	Corrected leukocyte count (Cor WBC)	X	Mean corpusc. volume (MCV)
X	Erythrocyte count (RBC)		Reticulocyte count
X	Platelet count		Cell morphology
X	Blood clotting measurements	X	Erythrocyte distribution width
X	(Prothrombin time)[a]		
X	(Activated partial thromboplastin time)[a]		

a Measurements made on the interim and terminal sacrifice animals only.

b. Clinical chemistry:

	ELECTROLYTES
X	Calcium
X	Chloride
	Magnesium
X	Phosphorus
X	Potassium
X	Sodium
	ENZYMES
X	Alkaline phosphatase (AP)
	Cholinesterase
X	Creatine phosphokinase (CPK)
	Lactate dehydrogenase (LDH)
X	Serum alanine aminotransferase (ALT)
X	Serum aspartate aminotransferase (AST)
X	Gamma glutamyltransferase (GGT)
	Glutamate dehydrogenase (GLDH)

	OTHER
X	Albumin
X	Blood creatinine
X	Blood urea nitrogen
X	Total cholesterol
	Globulins (calculated)
X	Glucose
X	Total bilirubin
X	Total serum protein
X	Triglycerides
	Serum protein electrophores

7. Urinalysis - Urine was collected overnight for a period of 16-18 hours during weeks 13, 26, 52, 78, and 97 (males) or 104 (females) from the same 13 animals/sex/dose chosen for blood chemistry analysis. The animals were denied access to food and water during sampling. The following CHECKED (X) parameters were examined.

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

* Assessed semi-quantitatively

8. Sacrifice and Pathology - All animals that died or were sacrificed in a moribund condition and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The following CHECKED (X) tissues were collected from animals in the 7.5-, 100-, and 2500-ppm groups. Only the eyes were collected from animals in the 1- and 2.5-ppm groups. All tissues (except for the oral and nasopharyngeal cavities) were examined microscopically. Additionally, the (XX) organs collected from animals in the 7.5-, 100-, and 2500-ppm groups were weighed.

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	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta	XX	Brain
X	Salivary glands	X	Heart	X	Periph. nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes (cervical and mesenteric)	X	Pituitary
X	Duodenum			X	Eyes
X	Jejunum	X	Spleen		
X	Ileum	X	Thymus		GLANDULAR
X	Cecum			XX	Adrenal gland
X	Colon		UROGENITAL		Lacrimal gland
X	Rectum	XX	Kidneys	X	Mammary gland
XX	Liver	X	Urinary bladder	X	Parathyroids
X	Pancreas	XX	Testes	X	Thyroids
	Gall bladder	X	Epididymides	X	Harderian gland
		X	Prostate		
	RESPIRATORY	X	Seminal vesicle		OTHER
X	Trachea	X	Ovaries	X	Bone (femur and sternum)
X	Lung	X	Uterus	X	Skeletal muscle
X	Nasopharyngeal cavity	X	Cervix	X	Skin
X	Oral cavity			X	All gross lesions and masses

II. RESULTS

A. Observations:

1. Toxicity - Selected clinical signs are presented in Table 2. In males, an increased incidence of cloudy eyes (# animals/64) was observed in the 7.5- (29), 100- (58), and 2500- (62) ppm dose groups vs the controls (2). In the females, an increased incidence of cloudy eyes (# animals/64) was also observed in the 7.5- (12), 100- (19), and 2500- (64) ppm dose groups vs the controls (5).

   An increased incidence of yellow and purple staining of the tray papers by the high-dose animals vs controls was reported. An increased incidence of urine-stained fur was also observed in the 2500-ppm females (36 treated vs 3 controls). Although these effects are considered to be treatment-related, they are not adverse. There were no increased incidences in clinical signs observed in the 1- or 2.5-ppm dose groups.

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Table 2. Incidence of cloudy eyes (# animals) observed in rats treated with mesotrione for up to 104 weeks.[a]

Males						Females					
Dose (ppm)						Dose (ppm)					
0	1	2.5	7.5	100	2500	0	1	2.5	7.5	100	2500
2	2	7	29	58	62	5	0	2	12	19	64

a Data obtained from the study report, Table 6, pages 75 and 84; n=64

2. Mortality - There were no trends in mortality. At 52 weeks, survival in all treated and control groups was 90-100%. All male groups were terminated when survival dropped to approximately 25%. The 1 and 2.5 ppm males were terminated in weeks 92/93. The control and the 7.5-, 100-, and 2500-ppm males were terminated in weeks 97/98. Chronic progressive glomerulonephropathy was the major contributory factor involved in the death of the 7.5-, 100-, and 2500-ppm male rats.

   Female groups were terminated as scheduled in week 104. At this time, survival was as follows: control-54%; 1 ppm-60%; 2.5 ppm-50%; 7.5 ppm-47%; 100 ppm-61%, and 2500 ppm-69%.

B. Body weight:

All mean body weight data were adjusted by the sponsor for initial weight. Mean body weight reductions ($p<0.05$ or 0.01) were observed at the following dose levels: (i) high-dose males (↓1-17%, weeks 2-97) and high-dose females (↓2-8%, weeks 3-103); (ii) 100-ppm males (↓1-15%, weeks 3-97) and the females (↓2-5%, weeks 4 to 75); (iii) 7.5-ppm males (↓2-13%, weeks 7-97); (iv) 2.5-ppm males (↓3-12%, weeks 49 to 91) and (v) 1-ppm males (↓4-10%, weeks 47 to 91). Body weight decreases of over 10% in the 2.5- and 7.5-ppm males were noted only from week 75 to termination after body weights had stabilized in all groups. Since there were random fluctuations of the weights among all groups during this time period, body weight changes at 7.5 ppm and below were not considered biologically relevant. Body weights of females dosed with mesotrione at 1, 2.5, or 7.5 ppm were similar to control values. Selected mean body weights are presented in Table 3a.

Dosing with mesotrione resulted in reduced overall body weight gain (calculated by the reviewers) in the 1-, 2.5-, 7.5-, 100-, and 2500-ppm males (↓15, 12, 15, 18, and 22%, respectively) (Table 3b). Overall body weight gain in the females dosed at ≥7.5 ppm was minimally decreased (↓4-8%). Decreases in body weight gain from weeks 1 to 47 were only biologically significant in males at 100 and 2500 ppm and, in females, at 2500 ppm. There was no dose relationship with the decrease in body weight gain in either sex from week 47 to termination.

Table 3a. Mean body weights [(g) adjusted for initial weight] at selected intervals in rats fed mesotrione for up to 104 weeks.[a]

Males						
Week	Dose (ppm)					
	0	1	2.5	7.5	100	2500
1	150.1	143.3	144.1	151.5	151.3	151.6
2	204.5	204.5	205.7	203.6	203.7	202.4*(↓1)
3	262.5	262.6	263.8	260.2	259.8*(↓1)	258.0**(↓2)
7	392.7	391.3	397.7	386.0*(↓2)	384.4*(↓2)	379.2**(↓3)
47	656.9	633.6*(↓4)	639.9	624.5**(↓5)	606.5**(↓8)	594.6**(↓9)
49	658.8	635.6*(↓4)	637.2*(↓3)	625.0**(↓5)	602.9**(↓8)	596.5**(↓9)
53	656.2	638.4	641.2	624.0**(↓5)	602.8**(↓8)	595.1**(↓9)
85	623.3	593.8	550.9**(↓12)	552.9**(↓11)	530.0**(↓15)	517.3**(↓17)
89	597.0	561.3	528.0**(↓12)	524.4**(↓12)	520.2**(↓13)	508.8**(↓15)
91	599.4	541.1*(↓10)	532.3*(↓11)	520.0**(↓13)	521.7**(↓13)	500.8**(↓16)
97	566.9	--	--	504.3**(↓11)	492.3**(↓13)	478.9**(↓16)
Females						
Week	Dose (ppm)					
	0	1	2.5	7.5	100	2500
1	132.3	127.0	127.3	131.8	132.3	133.0
3	187.3	186.1	189.0	187.7	186.1	183.9*(↓2)
4	207.6	208.3	209.9	206.8	202.9**(↓2)	199.6**(↓4)
41	338.6	342.9	334.2	334.8	321.9**(↓5)	311.8**(↓8)
73	407.7	413.8	396.6	394.7*(↓3)	391.6*(↓4)	375.6**(↓8)
75	407.1	409.3	397.0	397.3	391.7*(↓4)	377.4**(↓7)
103	392.2	380.4	405.6	377.1	373.8	370.3*(↓6)
105	381.3	380.6	400.8	370.3	366.6	362.8

a These data were extracted from the study report Table 9, pages 103-117. Numbers listed parenthetically represent the percent difference from controls.

* or ** Significantly different from controls $p<0.05$ or <0.01, respectively.

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Table 3b. Overall body weight gains in rats fed mesotrione for up to 104 weeks.[a]

Males						
Weeks	Dose (ppm)					
	0	1	2.5	7.5	100	2500
1-47	506.8	490.3 (↓3)	495.8 (↓2)	473 (↓7)	455.2 (↓10)	443 (↓13)
47-85	-33.6	-39.8	-89	-71.6	-76.5	-77.3
85-93	-34.6	-52.2	17.8	-	-	-
85-97	-56.4	-	-	-48.6	-37.7	-38.4
1-93	438.6	371.3 (↓15)	388.2 (↓12)	-	-	-
1-97	416.8	-	-	352.8 (↓15)	341 (↓18)	327.3 (↓22)
Females						
Weeks	Dose (ppm)					
	0	1	2.5	7.5	100	2500
1-47	220.2	226.2	221.1	218.9 (↓1)	203 (↓8)	190.9 (↓13)
1-105	249	253.6	273.5	238.5(↓4)	234.3(↓6)	229.8(↓8)

a Overall body weight gains were calculated by the reviewers from the adjusted body weight data extracted from the study report Table 9, pages 103-117. Numbers listed parenthetically represent the percent difference from controls.

- The 1 and 2.5 ppm males were sacrificed on day 93, the rest of the males were sacrificed on day 97.

C. Food consumption and efficiency:

Throughout much of the study, mean food consumption of high-dose males and females was reduced when compared to controls (Table 4a). Decreases ($p<0.05$ or 0.01) in food consumption were observed in high-dose males in weeks 40-84 (↓3-18%) and in high-dose females (↓3-10%) in weeks 1-92. There were sporadic decreases (↓3-20%, $p<0.05$ or 0.01) in food consumption in the 100-, 7.5-, and 2.5-ppm males, and in the 7.5- and 1-ppm females. Food consumption decreases of apparent biological relevance in males did not occur until the last few months of the study; however, there was no dose relationship among treatment groups. Decreases in any of the female groups were not biologically significant.

Food efficiency data are presented in Table 4b. Mean food efficiency was decreased ($p<0.01$ and 0.05) at the following dose levels: (i) high-dose males during weeks 5-8 (↓8%), weeks 9-12 (↓20%), and weeks 1-12 (↓7%); (ii) high-dose females during weeks 1-4 (↓7%), weeks 9-

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12 (↓16%), and weeks 1-12 (↓8%); (iii) 100-ppm males during weeks 5-8 (↓9%), weeks 9-12 (↓13%), and weeks 1-12 (↓6%); (iv) 100-ppm females during weeks 9-12 (↓10%) and weeks 1-12 (↓7%); (v) 7.5-ppm males during weeks 5-8 (↓8%); and (vi) 7.5-ppm females during weeks 9-12 (↓15%). Food efficiency was increased ($p<0.05$) in the 2.5-ppm males during weeks 1-4 (↑8%). Food efficiency in the low-dose males and females during weeks 9-12 was decreased at comparable levels to the 100-ppm males and females. During this time period, food efficiency appeared to be significantly affected in most treatment groups, but there was no dose relationship between the decrease and the amount of compound ingested. This effect was also temporary and not seen at other time periods and was, therefore, not considered biologically relevant at any dose.

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Table 4a. Mean food consumption (g/rat/day) at selected intervals in rats fed mesotrione for up to 104 weeks.[a]

Males						
Week	Dose (ppm)					
	0	1	2.5	7.5	100	2500
1	25.8	25.2	25.3	26.6	26.5	25.4
36	29.9	31.5*(↑5)	30.7	29.5	29.3	29.0
40	29.6	29.0	29.7	29.3	28.9	28.6*(↓3)
60	30.1	29.5	29.9	28.9*(↓4)	29.1*(↓3)	28.0**(↓7)
80	27.6	25.4	24.2*(↓12)	25.3*(↓8)	24.6**(↓11)	24.1**(↓13)
84	27.1	29.4	21.6**(↓20)	26.5	23.8*(↓12)	22.2**(↓18)
96	23.6	--	--	21.3	22.5	22.5
Females						
Week	Dose (ppm)					
	0	1	2.5	7.5	100	2500
1	20.9	20.5	20.4	20.9	20.5	19.9**(↓5)
4	22.9	22.8	22.3	22.7	22.9	22.1*(↓3)
72	24.3	25.0	24.2	22.8*(↓6)	23.5	22.7*(↓7)
76	23.6	25.5*(↑8)	23.4	23.1	23.1	23.0
88	23.5	20.6*(↓12)	23.1	22.8	22.3	21.9
92	24.0	22.6	25.0	22.9	23.0	21.7*(↓10)
104	20.8	22.5	22.4	20.2	21.1	20.8

a Numbers listed parenthetically represent the percent difference from controls. These data were extracted from the study report Table 10, pages 118-123.

* or ** Significantly different from controls $p<0.05$ or 0.01, respectively.

Table 4b. Mean food efficiency (g growth/100g food) in rats fed mesotrione for up to 104 weeks[a].

Interval (weeks)	Dietary Level (ppm)					
	0	1	2.5	7.5	100	2500
	Males					
1-4	22.91	24.27	24.74*(↑8)	22.44	22.13	22.35
5-8	10.52	10.25	10.31	9.69**(↓8)	9.57**(↓9)	9.72*(↓8)
9-12	6.10	5.35 (↓12)	5.92	5.77	5.30**(↓13)	4.88**(↓20)
1-12	12.98	12.99	13.34	12.47	12.15**(↓6)	12.14**(↓7)
	Females					
1-4	14.43	15.24	15.34	14.18	13.60	13.48*(↓7)
5-8	5.43	5.18	5.27	5.69	4.97	5.06
9-12	3.21	2.81 (↓12)	2.78 (↓13)	2.74**(↓15)	2.89*(↓10)	2.69**(↓16)
1-12	7.67	7.74	7.79	7.54	7.15**(↓7)	7.05**(↓8)

a These data were extracted from study report Table 11, page 124. n=16 except for the 1 and 2.5 ppm groups, where n=5.

* or ** Significantly different from the controls at $p<0.05$ or 0.01, respectively.

D. Ophthalmoscopic examination: An increased incidence of unilateral or bilateral corneal lesions (comprised of opacity/hazy opacity and vascularization/ghost vascularization) was observed at all intervals in the 7.5-, 100-, and 2500-ppm males and the 100- and 2500-ppm females (Table 5). At the ophthalmoscopic examination on weeks 26, 52, 78, 87/88, 95/96 (males only), and 102/103 (females only) the percentage of animals with increased corneal lesions were as follows (vs 6-21% in the controls): (i) 2500-ppm males (81-100%) and females (73-97%); (ii) 100-ppm males (77-90%) and females (10-24%); and (iii) 7.5-ppm males (25-34%). The incidence of corneal effects in females at 100 ppm was much larger than controls (14% vs. 8%, respectively) only at week 26. At all other time periods, the incidences were comparable. There were no treatment-related ophthalmological findings detected in rats of both sexes dosed with 1 or 2.5 ppm mesotrione and in female rats dosed at 7.5 ppm.

Table 5. Summary of corneal change in rats treated with mesotrione for up to 104 weeks.[a]

Week	Dose Level (ppm)	0	7.5	100	2500
Males					
26	# rats with corneal effects	3/50	15/50	40/52	42/52
	% affected	6	30	77	81
52	# rats with corneal effects	5/49	16/47	41/49	44/50
	% affected	10	34	84	88
78	# rats with corneal effects	4/37	11/35	35/39	35/37
	% affected	10	31	90	95
87/88	# rats with corneal effects	0/11	-	-	-
	% affected	0	-	-	-
95/96	# rats with corneal effects	3/22	4/16	12/15	15/15
	% affected	13	25	80	100
Females					
26	# rats with corneal effects	4/52	2/52	7/52	45/52
	% affected	8	4	14	87
52	# rats with corneal effects	6/51	1/52	5/51	49/52
	% affected	12	2	10	94
78	# rats with corneal effects	7/49	2/45	7/49	36/49
	% affected	14	4	14	73
87/88	# rats with corneal effects	0/16	-	-	-
	% affected	0	-	-	-
102/103	# rats with corneal effects	6/29	2/29	8/33	36/37
	% affected	21	7	24	97

a These data were extracted from study report Table 8, page 102.
- = Not examined

E. Blood analyses:

1. Hematology - No treatment-related differences from concurrent controls were observed in any hematological parameter. In females, platelet counts were decreased ($p<0.05$ or 0.01) relative to controls in the 2500-ppm (↓11-17%; at every interval except the interim kill), and in the 100-ppm dose group (↓11-16%; weeks 4, 27, 79, and 105). Eosinophil counts were increased ($p<0.05$) in the 2500-ppm females at weeks 53, 79, and 105 (↑34, 65, and 142%, respectively). These findings were not considered to be of toxicological significance.

   In males, platelet counts were decreased ($p<0.05$ or 0.01) in the 2500-ppm (↓10-16%) at weeks 14, 27, 52 [interim kill], and 53), and occasionally in the 100-ppm (↓13-17%), and the 7.5-ppm males (↓12-19%). Since the findings in the high-dose males were not observed at later intervals and those observed at 7.5 and 100 ppm were sporadic, these differences from controls were considered not to be treatment-related.

   Other differences ($p<0.05$ or 0.01) compared to controls observed in several hematological parameters such as mean cell hemoglobin, mean cell volume, and basophil count, were sporadic, not dose-dependent, and/or minor and were considered not to be treatment-related.

2. Blood clinical chemistry - No treatment-related differences from concurrent controls were observed in any clinical chemistry parameter. In males, plasma albumin was decreased ($p<0.05$ and 0.01) in the 100- (↓7-12%) and 2500- (↓8-9%) ppm groups at certain intervals; however, these differences were not dose-dependent. Plasma alkaline phosphatase was decreased ($p<0.05$ and 0.01) in the 2500-ppm males (↓14-21%) and females (↓17%), and the 100-ppm females (↓32%). The decreases in levels of plasma alkaline phosphatase were not considered to be treatment-related because (i) the levels in the 2500-ppm males were erratic, (ii) the differences occurred only at one interval each in the 2500- and 100-ppm females, and (iii) the decreases may be associated with a decrease in food consumption.

   Other differences ($p<0.05$ or 0.01) compared to controls observed in several clinical chemistry parameters such as plasma albumin, plasma total protein, and cholesterol, were sporadic/erratic, not dose-dependent, and/or minor and were not considered to be treatment-related.

3. Urinalysis - There was a semi-quantitative increase in the level of ketones present in the 100- and 2500-ppm males and the 2500-ppm females. It was stated that this finding was thought to be associated with the urinary excretion of phenolic acids such as 4-hydroxyphenylpyruvate (HPPA), a major metabolite of tyrosine. This finding, while treatment-related, is not considered to be adverse. Other observed differences ($p<0.05$ or

0.01) from controls, such as specific gravity, urine volume and pH, were minor and/or sporadic.

G. Sacrifice and pathology:

1. Organ weights - Differences ($p<0.05$ or 0.01) compared to controls in organ weights and organ weights adjusted for bodyweight were observed following both the interim and terminal sacrifices in male and female rats (Table 6). At the interim sacrifice (week 53) the following increases ($p<0.05$ or 0.01) in organ weights were observed: (i) absolute kidney weights in the 7.5-ppm and the 2500-ppm males (↑15 and 12%, respectively); (ii) adjusted kidney weights in the 7.5-, 100-, and 2500-ppm males (↑14, 13, and 22%, respectively); (iii) adjusted kidney weight in the 2500-ppm females (↑9%); (iv) absolute and adjusted liver weights in the 7.5-ppm males (↑18 and 17%, respectively); (v) adjusted liver weights in the 100- and 2500-ppm males (↑15 and 18%, respectively); and (vi) adjusted liver weights in the 100- and 2500-ppm females (↑11 and 14%, respectively). The differences in male and female kidney weights were not observed at the terminal sacrifice. The minimal difference in adjusted kidney weight in the 2500-ppm females is considered an incidental finding.

   At the terminal sacrifice (week 98 for the males and 105 for the females) the following differences ($p<0.05$ or 0.01) in organ weights were observed: (i) decreased absolute adrenal weights in the 100- and 2500-ppm males (↓21 and 22%, respectively); (ii) decreased adjusted adrenal weights in the 7.5-, 100-, and 2500-ppm males (↓19, 25, and 29%, respectively); and (iii) increased absolute and adjusted liver weights in the 100-ppm males (↑7 and 14%, respectively) and in the 2500-ppm males (↑12 and 20%, respectively) and adjusted liver weights in the 100-ppm females (↑11%). Increases ($p<0.05$ or 0.01) in relative testes weight in the 100-ppm males (↑29%), absolute brain weight of the 7.5-ppm females (↑4%), and relative liver weight of the 100-ppm females (↑11%) and decreased ($p<0.01$) absolute and relative brain weights in the 100- and 2500-ppm males (↓3-6%) were considered minor, incidental and/or not dose-related.

Table 6. Absolute and adjusted for bodyweight organ weights (g) of rats exposed to mesotrione for up to 104 weeks[a]

Organ	Male				Female			
	Dietary Level (ppm)							
	0	7.5	100	2500	0	7.5	100	2500
	Interim sacrifice							
Kidney								
Absolute	4.13	4.73**(↑15)	4.42	4.63**(↑12)	2.46	2.56	2.46	2.49
Adjusted	3.99	4.56**(↑14)	4.52**(↑13)	4.85**(↑22)	2.39	2.47	2.49	2.61*(↑9)
Liver								
Absolute	23.2	27.4**(↑18)	25.0	24.9	12.3	12.9	12.9	12.5
Adjusted	22.3	26.2**(↑17)	25.7**(↑15)	26.4**(↑18)	11.8	12.4	13.1**(↑11)	13.4**(↑14)
	Terminal sacrifice							
Kidney								
Absolute	5.30	5.78	5.43	5.69	3.40	3.32	3.39	3.10
Adjusted	5.68	5.67	5.22	5.52	3.31	3.28	3.39	3.08
Liver								
Absolute	22.6	23.7	24.1*(↑7)	25.2**(↑12)	16.1	16.6	17.6	17.0
Adjusted	21.7	23.8	24.7*(↑14)	26.0**(↑20)	15.9	16.6	17.6*(↑11)	17.1
Adrenal gland								
Absolute	0.101	0.087	0.080*(↓21)	0.079*(↓ 22)	0.097	0.097	0.082	0.082
Adjusted	0.106	0.086*(↓19)	0.079**(↓25)	0.075**(↓ 29)	0.094	0.095	0.083	0.081

a Data were obtained from Table 17, pages 207- 209, 211-213, and 215; n=12 or 52 for interim and terminal sacrifice, respectively.

* or ** Significantly different from the controls at $p<0.05$ or 0.01, respectively.

2. Gross pathology - During gross observations of all animals combined, including all animals that died and those sacrificed on schedule, increased incidences of eye lesions were detected (Table 7a). In the 100- and 2500-ppm males, an increased incidence (# animals/64) of opaque eyes (17 each treated vs 5 controls), corneal vascularization (9 and 14 treated, respectively, vs 3 controls), and cloudy eyes (18 and 22 treated, respectively, vs 6 controls) were observed. In the 7.5-ppm males, a minimal increase in the incidence of cloudy eyes was observed (10 treated vs 6 controls). In the 2500-ppm females, an increased incidence (# animals/64) of cloudy eyes (32 vs 2 controls) and a minimal increase in opaque eyes (17 treated vs 11 controls)were observed. There were no treatment-related macroscopic changes of the eyes in the 1- and 2.5-ppm groups of either sex, and the 7.5- and 100-ppm female groups.

Additional macroscopic findings (Table 7b) were detected as follows in the 7.5-, 100-, and 2500-ppm dose groups (# animals/64): (i) in the kidneys, roughened surface (30-33 treated vs 21 controls), cysts (23-25 treated vs 15 controls), and pale appearance (24-34 males only vs 26 controls); (ii) pale liver in the males, (25-27 vs 9 controls) and females (3-10 treated vs 2 controls); and (iii) pale adrenal glands in the males (5-12 treated vs 1 control). There were no corroborative histopathological data indicating an adverse affect on the adrenals of the males. In addition, thickened mesenteric vessels were observed in the males, however, the findings were minor and not dose-dependent and therefore not of toxicological concern.

Table 7a. Incidence of selected macroscopic findings in the eyes of rats exposed to mesotrione for up to 104 weeks.[a]

	Males						Females					
	Dietary Levels (ppm)											
Observation	0	1	2.5	7.5	100	2500	0	1	2.5	7.5	100	2500
Opacity # animals	5	0	2	6	17	17	11	6	3	10	4	17
% incidence	8	0	10	9	27	27	17	30	15	16	6	27
Corneal vascularization # animals	3	0	0	3	9	14	2	0	0	0	0	3
% incidence	5	0	0	5	14	22	3	0	0	0	0	5
Cloudy # animals	6	2	3	10	18	22	2	1	0	1	4	32
% incidence	9	10	15	16	28	34	3	5	0	2	6	50

a Data were obtained from Table 18 in study report, pages 219-270; n=64 except in the 1 and 2.5 ppm groups, where n=20

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Table 7b. Selected macroscopic findings (# of animals) in rats exposed to mesotrione for up to 104 weeks [a].

Observation	Dietary Level (ppm)			
	0	7.5	100	2500
Males				
Kidney				
Roughened surface	21	33	33	30
Cysts	15	25	25	23
Pale	26	32	24	34
Liver				
Pale	9	25	27	25
Adrenal gland				
Pale	1	5	7	12
Females				
Liver				
Pale	2	3	3	10

a Data were obtained from Table 18 of study report, pages 216-272; n=64

3. Microscopic pathology:

a) Non-neoplastic: When all animals were combined, including all animals that died and those sacrificed on schedule, an increased incidence (# animals/64) of corneal keratitis was detected in the 7.5-, 100-, and 2500-ppm males (13, 58, and 59 treated, vs 1 control) and in the 100- and 2500-ppm females (13 and 60 treated vs 3 controls) (Table 8a). There were no treatment-related eye lesions observed in the 1- and 2.5-ppm groups of either sex, and the 7.5-ppm female groups.

In the 7.5-, 100-, and 2500-ppm males an increase (# animals/64) in minimal to marked hepatocyte fat vacuolation (36, 39, 39 treated, respectively, vs 17 controls) was observed. In addition, a non-dose-dependent increase in the incidence of marked chronic progressive glomerulonephropathy (33, 34, 31 treated, respectively, vs 24 controls), and moderate/marked incidence of sciatic nerve demyelination (19, 27, and 17 treated vs 8 controls) were observed (Table 8b); the total number of incidences of each of these two findings in the 7.5-, 100-, and 2500-ppm males were similar to

controls. A slight increase, not dose-dependent, in the incidence of hepatocyte fat vacuolation was also seen in the females at 100 and 2500 ppm (16 and 14, respectively, vs. 8 controls). All other microscopic findings were similar to controls.

Table 8a. Incidence (# of animals) of keratitis of the eyes in rats treated with mesotrione for up to 104 weeks. [a]

	Males						Females					
	Dietary Levels (ppm)											
Severity	0	1	2.5	7.5	100	2500[b]	0[b]	1	2.5	7.5	100[b]	2500
Minimal	0	0	0	4	6	1	2	0	0	0	9	14
Slight	1	0	2	6	20	23	1	0	1	0	4	33
Moderate	0	0	0	3	24	28	0	0	0	0	0	12
Marked	0	0	0	0	8	7	0	0	0	0	0	1
Total	1	0	2	13	58	59	3	0	1	0	13	60

a Data were obtained from Table 20 in study report, pages 388 and 422; n=64 except where noted and in the 1 and 2.5 ppm groups where n=20.

b n=63

Table 8b. Selected non-neoplastic findings (# of animals) in male rats exposed to mesotrione for up to 98 weeks. [a]

Organ	Dietary Level (ppm)			
	0	7.5	100	2500
Liver				
Hepatocyte fat vacuolation				
minimal	6	8	9	6
slight	6	8	9	12
moderate	5	15	19	16
marked	0	5	2	5
Total	17	36	39	39
Kidney				
Glomerulonephropathy				
minimal	8	3	4	5
slight	16	18	12	17
moderate	14	9	14	10
marked	24	33	34	31
Total	62	63	64	63
Sciatic nerve				
Demyelination				
minimal	26	15	13	14
slight	29	26	20	28
moderate	8	16	23	13
marked	0	3	4	4
Total	63	60	60	59

a Data were obtained from Table 20 of study report, pages 392-413; n=64

b) Neoplastic: No treatment-related neoplastic changes were observed. Selected neoplastic lesions are presented in Table 9. There were increased incidences of uterine adenocarcinomas in the 7.5-, 100-, and 2500-ppm females (7.8, 1.6, 4.7%, respectively) vs controls (0%). Since the incidences were not dose-dependent and only the incidence in the 7.5-ppm females was outside of the historical control range (0-5.8%), this finding is considered not of toxicological concern.

There were increased incidences of benign hepatocellular adenoma in the 7.5, 100, and 2500-ppm females (3.1, 6.3, and 1.6,%, respectively) vs controls (0%). The incidence at the 100-ppm dose was beyond the historical control range of 0-3.8%. Because this finding was not dose-dependent, it is not of toxicological concern.

The incidence of benign thyroid follicular cell adenoma in the 2500-ppm females (6.3%) was outside of the historical control range (0-3.9%) while the incidences in the 7.5 and 100-ppm females (1.6%) were within the historical control range. The incidences of this finding in the 7.5-, 100-, and 2500-ppm males (1.6-4.7%) were also within the historical control range (0-11.5%). There was no increase in the incidence of thyroid follicular cell carcinoma in either sex and, therefore, there was no concern for carcinogenic potential in the thyroid gland after oral administration of the test compound.

Table 9. Incidence (# animals) of select neoplasms in rats dosed with mesotrione for up to 104 weeks.[a]

Dose (ppm)	0	7.5	100	2500	Historical Controls (%)
Males					
Thyroid gland Follicular cell adenoma	0	1	3	1	
% incidence	0	1.6	4.7	1.6	0-11.5
Thyroid gland Follicular cell adenocarcinoma	0	1	0	1	
% incidence	0	1.6	0	1.6	0-2.0
Females					
Thyroid gland Follicular cell adenoma	0	1	1	4	
% incidence	0	1.6	1.6[c]	6.3	0-3.9
Liver hepatocellular adenoma	0	2	4	1	
% incidence	0	3.1	6.3	1.6	0-3.8
Uterus Adenocarcinoma	0	5	1	3	
% incidence	0	7.8	1.6	4.7	0-5.8

a These data represent total number of tumors from intercurrent deaths and interim and terminal sacrifice. Data were obtained from Table 22, pages 462-471; n=64 except where noted.
b Historical control data were obtained from Tables 14, 15, and 17 pages 42, 43, and 45 of MRID 44505036.
c n=62

III. DISCUSSION

A. Investigators conclusions - Treatment with mesotrione for up to two years at dose levels of 7.5, 100, or 2500 ppm caused keratitis, reduced body weights, increased liver and kidney weights and an increased severity of common spontaneous lesions in the Alderley Park rat. No ocular effects were observed in the 2.5-ppm male satellite group or in the 7.5-ppm female group. Mesotrione was considered not to be carcinogenic. For females, the chronic LOAEL is 100 ppm and the NOAEL is 7.5 ppm.

B. Reviewer's discussion/conclusions - In a combined chronic/oncogenicity study (MRID 44505035), mesotrione (96.8% a.i.) was administered via the diet to 64 Alpk:AP$_f$SD rats/sex/group at 0, 7.5, 100, or 2500 ppm (equivalent to 0, 0.48, 6.48 or 159.89 mg/kg/day in males and 0, 0.57, 7.68, or 189.48 mg/kg/day in females) for up to 104 weeks. To assess ocular toxicity, an additional 20 rats/sex/dose were dosed at 1 or 2.5 ppm (equivalent to 0.06

and 0.16 mg/kg/day in males and 0.08 and 0.19 in females). Twelve main study rats/sex/dose were terminated after 52 weeks. Dietary analyses at select study intervals confirmed that nominal diet concentrations of mesotrione were achieved.

No treatment-related adverse effects were observed on mortality, food consumption, food efficiency, or hematology, clinical chemistry, and urinalysis parameters for either sex at any treatment level. All male groups were terminated when survival dropped to approximately 25% during weeks 92/93 and 97/98. Chronic progressive glomerulonephropathy was the major contributory factor involved in the intercurrent deaths. There was no evidence of a trend in male or female Kaplan-Meier survival rates. Female groups were terminated as scheduled in week 104.

The major target organ was the eye. In the 7.5-, 100-, and 2500-ppm males and in the 100- and 2500-ppm females ocular lesions consisting of cloudy eyes, corneal lesions consisting of opacity/hazy opacity/vascularization/ghost vascularization, and/or corneal keratitis were observed. No treatment-related ocular lesions were observed in the 1- and 2.5-ppm animals or in females dosed at 7.5 ppm.

Reductions ($p<0.05$ or 0.01) in mean body weight were observed throughout the study in the 7.5-ppm males (↓2-13%) and the 100- and 2500-ppm males and females (↓1-17%). Body weight reductions ($p<0.05$ or 0.01) were also observed in the 2.5- and 1-ppm male satellite groups. Body weight decreases of over 10% in the 2.5- and 7.5-ppm males were noted only from week 75 to termination after body weights had stabilized in all groups. Since there were random fluctuations of the weights among all groups during this time period, body weight changes at 7.5 ppm and below were not considered biologically relevant. Overall body weight gain was reduced in the 1-, 2.5-, 7.5-, 100-, and 2500-ppm males (approximately 12-22%). However, decreases in body weight gain from weeks 1 to 47 were only biologically significant in males at 100 and 2500 ppm and, in females, at 2500 ppm. There was no dose relationship with the decrease in body weight gain in either sex among all treatment groups from week 47 to termination.

Increases ($p<0.01$) in absolute kidney weights in the 7.5-ppm and the 2500-ppm males (↑12-15%) and adjusted (for body weight) kidney weights in the 7.5-, 100-, and 2500-ppm males (↑13-22%) were observed at the interim sacrifice (week 53). These differences in kidney weights were not observed at the terminal sacrifice. During gross examination of the kidneys of the 7.5-, 100-, and 2500-ppm males, roughened surface (30-33/treated group vs. 21 controls), cysts (23-25/treated group vs.15 controls), and pale appearance (24-34/treated group vs. 26 controls) were observed.

Increases ($p<0.05$ or 0.01) in absolute and adjusted liver weights in the 7.5-ppm males (↑18 and 17%, respectively), adjusted liver weights in the 100- and 2500-ppm males (↑15-18%), and adjusted liver weights in the 100- and 2500-ppm females (↑11-14%) were observed at the interim sacrifice. At the terminal sacrifice, increases ($p<0.05$ or 0.01) in absolute and

adjusted liver weights in the 100- and 2500-ppm males (↑7-20%) were observed. During gross examination of the 7.5-, 100-, and 2500-ppm dose groups, pale liver was observed in the males (25-27/treated group vs. 9 controls) and females (3-10/treated group vs. 2 controls). During histopathological examination, minimal to marked hepatocyte fat vacuolation was observed in the 7.5-, 100-, and 2500-ppm males (36-39/treated group vs. 17 controls) and the 100- and 2500-ppm females (14-16/treated group vs. 8 controls).

Decreased absolute adrenal weights in the 100- and 2500-ppm males (↓21 and 22%, respectively) and decreased adjusted adrenal weights in the 7.5-, 100-, and 2500-ppm males (↓19, 25, and 29%, respectively) showed a slight dose-dependent trend, but no histopathological abnormalities were observed.

The administration of mesotrione to rats up to 2500 ppm (159.9 mg/kg/day for males, 189.5 mg/kg/day for females) in the diet did not result in an overall treatment-related increase in incidence of tumor formation.

Under the conditions of this study, dosing is considered adequate to assess the carcinogenic potential of mesotrione based on the ocular and hepatic lesions and increased liver and kidney weights noted at 7.5 ppm and above and body weight effects at 100 ppm and above in males and increased liver weights and ocular and hepatic lesions at 100 ppm and above in females.

The LOAEL for this combined chronic toxicity/ carcinogenicity rat feeding study is 7.5 ppm (0.48 mg/kg/day for males, 0.57 for females) based on ocular lesions, increases in kidney and liver weights, and hepatocyte fat vacuolation in males. The NOAEL for ocular lesions is 2.5 ppm (0.16 mg/kg/day for males, 0.19 mg/kg/day for females). No NOAEL was determined for kidney and liver weights or hepatocyte fat vacuolation in males.

The submitted study is classified as **acceptable (§83-5)** and does satisfy the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats.

C. Study deficiencies - None noted.