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12/20/96

DATA EVALUATION RECORD

ISOXAFLUTOLE (RPA201772)

Study Type: §83-5; Combined Chronic\Oncogenicity Study - Rats

Work Assignment No. 2-8B (MRID 43904806)

Prepared for

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Office of Pesticide Programs
U.S. Environmental Protection Agency
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Disclaimer

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Review Section I,Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic/Carcinogenicity Study in Rats

OPPTS NUMBER: OPPTS 870.4300 OPP Guideline Number: §83-5

DP BARCODE: D224202 SUBMISSION CODE: S501233
P.C. CODE: 123000 MRID NO.: 43904806

TEST MATERIAL (PURITY): RPA201772 Technical (93-99.2% a.i.)

SYNONYMS: Isoxaflutole

CITATION: Chase, K.R., (1995) RPA201772ai: Combined Oncogenicity and Toxicity Study by Dietary Administration to CD rats for 104 weeks. Life Science Research Limited, Eye, Suffolk, England. LSR Report 95/0499, October 27, 1995. MRID 43904806. Unpublished.

SPONSOR: Rhône-Poulenc Agriculture Limited, Ongar Research Station, Fyfield Road, Ongar, Essex, England

EXECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study (MRID 43904806), RPA201772, (93-99.2% a.i.) was continuously administered to 75 Sprague-Dawley rats/sex/dose at dietary levels of 0, 0.5, 2, 20 or 500 mg/kg/day for 104 weeks. An additional 20 rats/sex/group were treated for 52 weeks, after which 10 rats/sex/group were sacrificed and the remainder were held for a maximum of eight weeks without treatment in order to assess reversibility of treatment-related changes.

Evidence of systemic toxicity observed in one or both sexes included: 1) abnormal gait, limited use of limbs at 500 mg/kg/day and eye opacity (in males) at ≥20 mg/kg/day); 2) lower body weight gains (≥36% in both sexes) and food consumption (12% in females) at 500 mg/kg/day; 3) decreased food efficiency (≥12% in both sexes) at 500 mg/kg/day during the first 14 weeks of the study; 4) elevated cholesterol levels (in both sexes) at 500 mg/kg/day throughout the 104-week study, 5) gross necropsy changes in the liver, and lungs in both sexes at 500 mg/kg/day, and eyes in males at ≥20 mg/kg/day; 6) increased absolute and relative liver weights (in both sexes) at 500 mg/kg/day; and 7)

increased incidence of periacinar hepatocytic hypertrophy, portal tract (senile) bile duct changes, focal cystic degeneration of the liver (in males at ≥20 mg/kg/day; in females at 500 mg/kg/day), thyroid hyperplasia (in males at 500 mg/kg/day)), corneal lesions (in males at ≥20 mg/kg/day), and degeneration of sciatic nerve and thigh muscles (in males at ≥20 mg/kg/day; in females at 500 mg/kg/day).

Under the conditions of this study, RPA 201772 induced benign and malignant tumors of the liver in both sexes at 500 mg/kg/day (hepatocellular adenomas in 14/75 in males and 29/74 in females vs. 2/75 and 4/74 in the control group rats and hepatocellular carcinomas (17/75 and 24/74 vs. 5/75 and 0/74 in the controls, respectively). Combined incidences of liver adenoma/carcinoma in males and females were 31/75 and 46/74, respectively, with animals bearing carcinomas in the majority. Thyroid follicular adenomas occurred with increased frequency in 500 mg/kg/day males (15/75 vs 3/74 in controls). The above tumor incidences exceeded the historical incidence of these tumors for this strain in this laboratory.

The study demonstrated that RPA 201772 is carcinogenic to rats at a dose of 500 mg/kg/day. The chemical was administered at a dose sufficient to test its carcinogenic potential. At 500 mg/kg/day, there were alterations in most of the parameters measured including clinical signs of toxicity, body weight gain, food consumption, food conversion efficiency, and clinical as well as post-mortem pathology.

The chronic LOEL is 20 mg/kg/day based on liver, thyroid, ocular, and nervous system toxicity in males and liver toxicity in females. The chronic NOEL is 2.0 mg/kg/day.

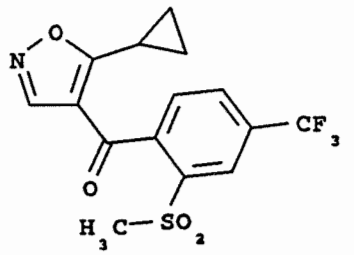
This study is classified as **acceptable** and **satisfies** the guideline requirements for a chronic toxicity study §83-1) and a carcinogenicity study (§83-2) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided. The report stated, " I have applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study meets or exceeds the criteria numbered 2" [A statistically significant ($p \leq 0.05$), incidence of any type of neoplasm in any test group (male or female animals at any dose level) compared to concurrent control animals of the same sex).

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: RPA201772
   Description: Technical; fine cream crystalline powder
   Lot/Batch #: Two batches were used, FPI 1308 during weeks 1-25 and 40 ADM 93 from week 26 to end of study
   Purity: FPI 1308-98.3% a.i.; 40 ADM 93-99.2% a.i.
   Stability of compound: Stable in diet at ambient temperature for one week
   Storage: Low temperature protected from light
   CAS #: 14112-29-0



2. Vehicle and/or positive control: Basal diet

3. Test animals: Species: Rat
   Strain: Crl:CD®(SD)BR VAF Plus™
   Age and weight at study initiation: Approx. 35-42 days; 121-176 g (males) and 108-163 g (females)
   Source: Charles River U.K. Limited, Margate, Kent, England
   Housing Stainless steel cages with lids and floors of stainless steel mesh, 5 rats of the same sex per cage
   Diet: RMI(E) SQC FG, a powdered rodent diet, ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
      Temperature: 21 °C
      Humidity: 55%
      Air changes: 15/hr
      Photoperiod: 12 hr dark/12 hr light
   Acclimation period: 14 days

B. STUDY DESIGN:

1. In life dates - Start: 1/20/93 End: 1/18/95

2. Animal assignment

   Animals were assigned to treatment groups as indicated in Table 1 using a set of computer-generated random numbers.

Table 1. Study Design

		# Animals/Sex [a]		
Test Group	Dose Levels (mg/kg/day)	Toxicity Study 52 Weeks	Reversibility Study 52 and 8 Weeks	Carcinogenicity Study 104 Weeks
Control	0	10	10	75
Low	0.5	10	10	75
Low-Mid	2	10	10	75
Mid	20	10	10	75
High	500	20	10	75

a The animals assigned to the toxicity phase of the study were dosed with RPA201772 for 52 weeks after which 10/sex/dose were sacrificed; the remaining animals were held for 8 weeks without treatment and were sacrificed after recovery phase; the animals assigned to the carcinogenicity phase of the study were dosed for 104 weeks prior to sacrifice.

3. Dose Selection: The rationale for the dose selection was based on the results of subchronic studies and a liver enzyme induction study. In these studies, treatment with RPA201772 at ≥10 mg/kg/day resulted in increased liver weight, increased pentoxyresorufin-O-dealkylase (PROD) and benzoxyresorufin-O-dealkylase (BROD) enzyme levels (260% and 233% of control, respectively), and reversible corneal eye lesions. At 400 and 1000 mg/kg/day, a reduction in bodyweight gain was detected.

   Based upon the results of these studies, the doses summarized in Table 1 above were selected for the submitted 104 week chronic/carcinogenicity study.

4. Diet Preparation and Analysis: RPA 201772 was mixed into a small amount of the ground diet in Hobart A200 mixer, and the treated feed was sieved using a Glen Creston Beater mill with a 2 mm screen. The mixture was then diluted with additional feed, and a final 500 mg/kg/day feed mix was homogenized using a Gardner 50L horizontal screw mixer. A portion of this mix was serially diluted to prepare the 0.5, 2 and 20 mg/kg/day mixes. Diets for male and female rats were prepared from different mixes. Premixes and test diets were prepared every week and stored at room temperature.

   Samples were taken from six positions in the mix; each sample was divided into two aliquots, one for homogeneity testing and the other for assessment of stability. Prior to commencement of the study, homogeneity and stability were determined on trial preparations made up to include 2.528

and 19,444 ppm diets (corresponding to the lowest and highest dose levels expected in the study). Homogeneity and stability were also determined on the low dose diet prepared for week 1. In addition, homogeneity testing at the highest and lowest dose levels was repeated in week 26 because a new batch of RPA201772 was introduced. The stability samples were pooled for each concentration and remixed; duplicate assays were performed on day 0 and after one and two weeks storage at room temperature (temperature not specified).

Concentration analyses were performed on all diets prepared for weeks 1, 2, 3, 4, 6, 8, 13, 21, 29, 37, 45, 53, 61, 69, 77, 85, 93, 101, and 104. Before week 21, diets of 100 to 4,000 ppm were extracted with acetonitrile, but this extraction procedure was found to be inadequate. A correction factor was applied to the data to overcome the reduced extraction efficiency. After week 21, the concentration samples were extracted using dichloromethane/glacial acetic acid. In addition, because RPA201772 decomposes to RPA202248, a reference standard of the decomposition product was injected with each analysis.

Results: Homogeneity Analysis: Homogeneity at pretest was acceptable (99.3%) at a test dietary level of 19,444 ppm with a relative standard deviation (RSD) of 3.1%, but for pretest and week 1 diets at 2-4 ppm, homogeneity was unacceptable (189.2 and 115.5%, respectively, and the RSDs were 33.2% and 27.9, respectively. Homogeneity for low-dose diets at 26 weeks was acceptable; at the low dose (8.47 ppm) the mean of 6 samples was 130.3% of nominal with a RSD of 4.8%; at the highest dietary level (10,273 ppm), the values were 93.8% of nominal with a RSD of 1.3%.

Stability Analysis: Analysis of stability of RPA201772 in pretest diets at a level of 19,000 ppm indicated 3% and 8% decreases in RPA201772 after 1 and 2 weeks, respectively. The week 1 diets containing RPA201772 at a level of 3 ppm were 13% and 2% higher than nominal after 1 and 2 weeks of storage, respectively, indicating stability of test material in diets.

Concentration Analysis: The dietary concentrations at target doses of 0.5 and 2 mg/kg/day were higher than nominal (Table 2); this may be partially accounted for by overloading (or in the 0.5 mg/kg/day sample by interference and non-homogeneity; sample homogeneity was acceptable after 26 weeks). The concentration values at the highest dose level may have resulted in lower analyses than actual in the first 21 weeks due to incomplete extractions of test material from the diets; the extraction procedure was modified at 21 weeks. The data in the table below were not corrected for extraction efficiency.

Table 2.
Mean concentrations as percent of nominal
for the 18 weeks of analysis

Target dose (mg/kg/day)	Mean percent of nominal ±RSD	
	Males	Females
0.5	121±16	131±18
2	108±11.6	110±12.1
20	94±3.3	95±4.6
500	92±3.3	92±3.8

a Calculated by the reviewers from data presented in study report on pages 412-419.

The analytical data indicated that the mixing procedure was adequate for the 20 and 500 mg/kg/day dose groups, somewhat more variable for the 2 mg/kg/day dose group, and poor in the 0.5 mg/kg/day dose group. This variability, however did not affect study interpretation.

Animals received fresh diet weekly. The dietary concentrations were adjusted weekly for the first 14 weeks of treatment and then every two weeks thereafter to provide the appropriate dosages on a mg/kg body weight/day basis.

6. Statistics - Cox's proportional hazards model and Tarone's partition of the Chi-square were applied to mortality data. Student's t-test using a pooled error variance was applied to appropriate hematology, blood chemistry, and urinalysis data. Bartlett's test for equality of variances was applied to organ weight and body weight gain data and, if found to be significant, was followed by a Behrens-Fisher test or Dunnett's test. Fisher's Exact Probability test, as a two-tailed test, was applied to appropriate macroscopic or microscopic (non-neoplastic) pathological findings; a one-tailed test was applied to neoplastic microscopic pathological data which indicated a dose response.

C. METHODS:

1. Observations:

Animals were inspected twice daily for signs of toxicity and mortality. Additionally, animals were examined by palpation once weekly.

2. Body weight

Animals were weighed on the day that treatment commenced, at weekly intervals for the first 14 weeks, every two weeks thereafter, and before necropsy.

3. Food and compound intake/water consumption

Food consumption was determined per cage and mean weekly diet consumption per individual animal was calculated as g food/animal/week. Weekly food conversion efficiencies were calculated for the first 14 weeks of the study. Compound intake values were calculated from the nominal dietary test material concentration, food consumption, and body weight gain data. No quantitative measurements of water consumption were made.

4. Ophthalmoscopic examination

The eyes of all the rats were examined prior to initiation of the study. After 5, 11, 23, 37, and 49 weeks of treatment, the eyes of all surviving toxicity, reversibility and 25/sex carcinogenicity phase rats were examined. All surviving reversibility animals were also examined after 6 weeks of recovery. After 75 and 101 weeks of treatment, 25/sex/dose of the surviving oncogenicity phase rats were again examined.

5. Clinical Pathology

Blood was collected for hematology and clinical analyses by "retro-orbital sinus" bleeding after 6, 24, and 50 weeks of treatment from all surviving rats in the toxicity and reversibility groups. After 7 weeks of recovery, blood samples were collected from all surviving rats in the reversibility groups. After 78 and 102 weeks of treatment, blood samples were obtained from 10 surviving rats/sex/dose rats in the carcinogenicity phase groups. Prior to bleeding, all rats were fasted overnight and anesthetized with halothane/-nitrous oxide. The following CHECKED (X) parameters were examined.

a. Hematology

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

*Required for chronic studies;"X"= examined;"-"= not examined

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	-	Albumin*
X	Chloride*	X	Blood creatinine*
-	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	-	Globulins
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)	-	Triglycerides
-	Cholinesterase (ChE)	-	Serum protein
X	Creatine phosphokinase	X	Urea
-	Lactic acid dehydrogenase (LDH)		
X	aSerun alanine amino-transferase (also SGPT)*		
X	Serum aspartate amino-transferase (also SGOT)*		
-	Gamma glutamyl transferase (GGT)		
-	Glutamate dehydrogenase		

*Required for chronic studies
"X" = examined; "-" = not examined

6. Urinalysis

Urine was collected from all surviving rats in the toxicity and reversibility groups after 6, 23, and 50 weeks of treatment. After 6 weeks of recovery, urine samples were obtained from all surviving rats in the reversibility groups. Urine samples were also collected from 10 rats/sex/dose in the oncogenicity groups after 77 and 101 weeks of treatment. The following CHECKED (X) parameters were examined.

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

*Required for chronic studies
"X" = examined; "-" = not examined

7. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examinations and the CHECKED (X) tissues were collected for histological examinations. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
-	Tongue [a]	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 nodes*		
X	Duodenum*	XX	Spleen*	XX	Pituitary*
X	Jejunum*	XX	Thymus*	X	Eyes (optic n.)*
X	Ileum*				
X	Cecum*		UROGENITAL		GLANDULAR
X	Colon*	XX	Kidneys*+		
X	Rectum*	X	Urinary bladder*	XX	Adrenal gland*
XX	Liver*+	XX	Testes*+	-	Lacrimal gland
-	Gall bladder*	X	Epididymides	X	Mammary gland*
X	Pancreas*	XX	Prostate	XX	Parathyroids*++
		X	Seminal vesicles	XX	Thyroids*++
	RESPIRATORY	XX	Ovaries*+		
X	Trachea*	XX	Uterus* (with cervix)		OTHER
XX	Lung*			X	Bone*
-	Nose	X	Vagina	X	Skeletal muscle*
-	Pharynx			X	Skin*
-	Larynx			X	All gross lesions and masses*

a Samples were not processed histologically, but were held in fixative only.
* Required for carcinogenicity studies based on Subdivision F Guidelines.
+ Organ weight required in chronic studies.
++ Organ weight required for non-rodent studies.
"X" = examined; "-" = not examined

Microscopic examinations were performed as follows: i) tissues specified above were examined for all controls and high-dose animals sacrificed at the 52 and 104 week intervals and for all animals killed or found dead during the study; ii) the liver, lungs, kidneys, and eyes for all animals dosed at 0.5, 2 or 20 mg/kg/day and sacrificed at the 52 and 104 week intervals; iii) tissues reported as abnormal after macroscopic examination were examined for all animals; iv) the adrenals from all males from the 0.5, 2 and 20 mg/kg/day groups sacrificed at the 52 week interval; v) the eyes and liver from all animals and the adrenals from all males sacrificed on completion of the reversibility phase; vi) the uterus, cervix, and vagina from all females dosed at 0.5, 2 or 20 mg/kg/day and sacrificed at the 104 week interval; vii) the left sciatic nerve and thigh muscle from all animals dosed at 20 mg/kg/day and all males dosed at 0.5 or 2 mg/kg/day and sacrificed at the 104 week interval; and viii) the thyroid from all animals dosed at 0.5, 2 or 20 mg/kg/day and sacrificed at the 104 week interval.

II. RESULTS

A. Observations

1. Toxicity - Clinical signs data are summarized in Table 3. At the interim sacrifice (week 52), male and female rats in the 500 mg/kg/day dose group had increased incidence of opaque eyes (80% and 70%, respectively). During the eight-week recovery period (following 52 weeks of treatment), the incidence of opaque eyes decreased in the males from 5/9 in the first week to 1/9 after eight weeks of recovery; in the females, 4/9 rats were affected on the first week and 0/8 were affected on the eighth week.

   In the 104 week study, an increased incidence of opaque eyes was seen in the 500 mg/kg/day group rats beginning at study week 6 (2/75 males and 9/75 females). This lesion progressed quickly, and by week 7, 20/75 males and 21/75 females were affected. By week 52 of 104 week period, 74% and 52% of the males and females, respectively were affected. These incidences increased to 83% in males and decreased to 13% in females at the end of 104 week period.

   By week 104, an increased incidence of abnormal gait and limited use of limbs was seen in the 500 mg/kg/day group rats (males: 65-68% vs 1-15% in controls; females: 12-24% vs 5-8% in controls).

   An increased incidence of thin body build was noted in the 500 mg/kg/day group rats at 52 weeks (males: 25% vs 0% in controls; females: 65% vs 5% in controls) and at 104 weeks (males: 56% vs 17% in controls; females: 76% vs 15% in controls). This observation was a reflection of low body weight gain of the high-dose animals. No change in this parameter was noted during the recovery period.

   Other signs reflecting the poor general health in both sexes of the 500 mg/kg/day group rats were brown staining of the head and tail (in males beginning in week 12) and perigenital urine staining and ungroomed coat (in females; data not shown in Table 3). These signs were first seen at study weeks 16-32 (approximately) and persisted throughout the study.

   The incidence, locations and group distributions of palpable swellings in the 500 mg/kg/day group animals were similar to the controls.

   The general conditions, behaviors, and appearances of animals in the 0.5, 2 and 20 mg/kg/day dose groups were unaffected by treatment.

Table 3. Clinical observations in rats fed RPA 201772 for up to 104 weeks[a]

Observation	Dose Groups (mg/kg/day)									
	Males					Females				
	0	0.5	2	20	500	0	0.5	2	20	500
Toxicity phase - 52 Weeks of Treatment - 20 Rats/group										
Opaque eyes[b]	0 (0%)	2 (10%)	0 (0%)	0 (0%)	16 (80%)	1 (5%)	0 (0%)	1 (5%)	1 (5%)	14 (70%)
Abnormal gait	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Limited use of limbs	1 (5%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Thin body build	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (25%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	13 (65%)
Reversibility phase- 52 Weeks of Treatment Followed by 8 Weeks of No Treatment - 9-10 Rats/group										
Opaque eyes	0 (0%)	1 (10%)	0 (0%)	1 (10%)	5 (56%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	4 (44%)
Abnormal gait	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)
Limited use of limbs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)
Thin body build	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (10%)	1 (10%)	5 (56%)
Carcinogenicity phase-Up to 104 Weeks of Treatment[c]- 75 Rats/Group										
Opaque eyes	15 (20%)	10 (13%)	17 (23%)	24 (32%)	68 (91%)	4 (5%)	4 (5%)	4 (5%)	7 (9%)	62 (83%)
Abnormal gait	1 (1%)	8 (11%)	7 (9%)	7 (9%)	49 (65%)	4 (5%)	3 (4%)	2 (3%)	1 (1%)	9 (12%)
Limited use of limbs	11 (15%)	9 (12%)	11 (15%)	10 (13%)	51 (68%)	6 (8%)	5 (7%)	4 (5%)	3 (4%)	18 (24%)
Thin body build	13 (17%)	8 (11%)	13 (17%)	14 (19%)	42 (56%)	11 (15%)	22 (29%)	8 (11%)	15 (20%)	57 (76%)

[a] Data obtained from Table 1A = Carcinogenicity (p. 84-88 and 104), 1B = Toxicity (p. 89-95); and 1C = Reversibility (p.96-99) of the study report No. 95/0499; percentages calculated by the reviewer. One female in the 0.5 mg/kg group (interim sacrifice) and one 500 mg/kg female (reversibility phase) were misdosed and excluded from mean group calculations.

[b] One or both eyes with opacity; [c] Necropsies continued until 106 weeks

2. Mortality - The 4 and 5 deaths that occurred among the animals assigned to the toxicity and recovery phases, respectively, of the study were not considered to be related to treatment. Table 4 illustrates the mortality observed among rats in the 104-week terminal phase. Through approximately week 52, mortality among the treated rats was similar to the controls. After week 52, mortality in both sexes in the 0.5 mg/kg/day dose group and females in the 2 and 20 mg/kg/day dose groups was higher than in the control groups. At week 104, mortality in the 0.5, 2 and 20 mg/kg/day dose group females and the 0.5 mg/kg/day dose group males increased but was not statistically significant. At 500 mg/kg/day, mortality for animals was significantly lower than that of controls ($p<0.05$).

   At termination (104 weeks), survival rates in controls were 55% in males and 53% in females.

B. Body weight - Selected mean body weight gain data from the 104-week terminal phase are summarized in Table 5. From the first week of the study, mean body weight gains in the 500 mg/kg/day group rats were lower than controls; weeks 0 through 104, body weight gains were decreased 36% and 49% ($p<0.01$) in males and females, respectively. These decreased body weight gains were considered to be treatment-related.

   During the six week recovery phase (following 52 weeks of treatment), the 500 mg/kg/day group male and female rats, respectively, had 104 and 59% weight gain increases over the controls ($p<0.01$ in males only). Before the recovery period, mean body weights in high-dose males and females were 22% and 18% lower than controls, respectively, and after the recovery period they were 8% and 13% lower (Data not shown in this DER).

   Body weight gains of animals in the 0.5, 2 and 20 mg/kg/day groups were unaffected by treatment.

Table 4
Cumulative Morality in Rats Treated with
RPA 201772 in the Diet[a]

Sex	Dosage Levels (mg/kg/day)									
	Males					Females				
Week Number	0	0.5	2	20	500	0	0.5	2	20	500
Toxicity Phase - 52 Weeks of Treatment- 20 Rats/group										
1-24	0	0	0	0	0	0	0	0	0	0
29-38	0	0	0	0	0	1	1[b]	0	0	0
51-52	0	0	0	0	0	3	1	0	0	0
Reversibility Phase - 52 Weeks of Treatment Followed by 8 Weeks of No Treatment - 10 Rats/Group										
33-R3[c]	1	0	0	0	1	0	0	0	0	1
R4-R8	1	0	0	0	1	0	0	0	0	2
R9	1	1	0	0	1	0	0	0	0	2
Carcinogenicity Phase - Up to 104 Weeks of Treatment - 75 Rats/group[d]										
9	0	0	0	0	1	0	0	0	0	0
32	2	1	1	1	2	1	0	2	1	0
52	2	2	2	3	2	1	2	3	4	1
72	10	12	6	7	6	7	12	15	17	5
92	27	29	19	24	15	28	37	27	37	16
104	41	47	41	37	29	40	51	50	53	27
106[e]	41†	50	41	38	29*	40	52	50	53	27

a Extracted from Tables 3A, 3B, and 3C (pages 132-138) of the study report No. 95/0499
b Culled
c WK R3 = WK 55; WK R4-R8 = WK 56-60; WK R9 = WK 61
d Includes animals killed or dying during the study
e Necropsies continued until WK 106
* $p \leq 0.05$, pairwise; † negative trend $p \leq 0.05$

B. Table 5
Body Weight Changes (g) at Selected Intervals in Rats Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

Sex	Dosage Levels (mg/kg/day)									
	Males					Females				
Body weight change (g)	0	0.5	2	200	500	0	0.5	2	20	500
Week 0-13	367	371	370	366	329**	169	167	171	170	132**
Percent change	-	+1	+1	0	-10	-	-1	+1	+1	-22
Week 13-26	129	132	131	124	103**	43	45	47	46	22**
Percent change	-	+2	+2	-4	-20	-	+5	+9	+7	-49
Week 26-52	154	163	161	144	99**	97	100	108	104	34**
Percent change	-	+6	+5	-6	-36	-	+3	+11	+7	-65
Week 52-104	71	88	89	56	-87**	124	125	133	124	24**
Percent change	-	+24	+25	-21	-	-	+1	+7	0	-81
Week 0-104	659	711	722	653	424**	415	417	431	411	211**
Percent change	-	+8	+10	-1	-36	-	0	+4	-1	-49

a Extracted from Table 4A (page 146-147) of the study report No. 95/0499; Includes data for animals from 52 Week phase
"-" = No data
** = $p<0.01$

C. Food consumption and compound intake

1. Food consumption - Food consumption data are presented in Table 6. Food consumption in the 500 mg/kg/day group females (104-week terminal phase) was decreased (4-17%) at four consecutive 6-month intervals; overall food consumption was 12% lower than controls. No adverse effects on food consumption were seen in males. Food consumption for treated animals was similar to control rats during the 6-week recovery period (following 52 weeks of dosing).

2. Compound consumption - Based on nominal dietary levels and food consumption values, compound consumption was 0.5, 2.0, 20.0 or 501.6 mg/kg/day in males and 0.5, 2.0, 20.1 or 502.1 mg/kg/day in females. Based on analytical data on the diets, compound consumption was 0.58, 2.1, 18.8 or 461.5 mg/kg/day in males and 0.69, 2.3, 19.1 or 461.8 mg/kg/day in females.

3. Food efficiency - Food conversion efficiency in the 104-week terminal phase rats, calculated through week 14, was lower in the 500 mg/kg/day group males (12%) and females (19%) compared to controls (Table 7). For rats at the lower dose levels, food conversion efficiencies were similar to those in the control groups.

D. Ophthalmoscopic examinations - Table 8 summarizes the incidence of corneal lesions during 101 weeks of the study. At 500 mg/kg/day, treatment related corneal lesions were seen in 60-80% of the males and 64-93% of the females examined at the 5, 11, 23, 37, 49, 75, and 101 weeks. Eye lesions were also seen in up to 16% of the males and 2% of the females in the 20 mg/kg/day group. The severity of the lesions in the 500 mg/kg/day group rats ranged from small focal superficial opacities to large corneal opacities with associated vascularization and with iritis in some of the animals. Although the overall incidence of corneal lesions was higher in females, the severity of the lesions was greater in the males.

No treatment-related eye lesions were seen in rats in the 0.5 or 2 mg/kg/day treatment groups.

During the 6-week recovery period (following 52 weeks of treatment) corneal lesions were noted in 7/9 males and 6/8 females at 500 mg/kg/day (Data not shown in this DER).

Table 6
Group Mean Food Consumption (g) at Selected Intervals in Rats Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

Sex	Males					Females				
Dosage (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Week 1-26	5107	5178	5189	5178	5263	4002	4007	3999	3999	3836
Percent change	-	+1	+2	+1	+3	-	0	0	0	-4
Week 27-52	5032	5064	5126	5056	5194	4025	4069	4094	4070	3645
Percent change	-	+1	+2	0	+3	-	+1	+2	+1	-9
Week 53-78	5626	5525	5587	5491	5283	4391	4389	4458	4389	3691
Percent change	-	-2	-1	-2	-6	-	0	+2	0	-16
Week 79-104	5331	5314	5300	5358	4842	4509	4315	4465	4360	3743
Percent change	-	0	-1	+1	-9	-	-4	-1	-3	-17
Weeks 1-104	21096	21081	21202	21083	20582	16927	16780	17016	16818	14915
Percent change	-	0	+1	0	-2	-	-1	+1	-1	-12

a Extracted from Table 5A (pages 161-162) of the study report No. 95/0499; includes data for animals from 52-Week phase

Table 7
Food Conversion Ratios in Rats Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

Sex	Males					Females				
Dosage (mg/kg/day)	0'	0.5	2	20	500	0	0.5	2	20	500
Week 1	28.5	26.3	27.7	25.6	24.4	17.3	17.7	17.4	18.1	15.0
Mean of Weeks 1-14 % change	13.9 -	14.0 +1	13.9 0	13.7 -1	12.3 -12	7.8 -	7.8 0	7.9 +1	7.9 +1	6.3 -19

a Extracted from Table 6 (page 164) of the study report No.95/0499.

Table 8.
Number of rats with treatment related corneal lesions (expressed as the number of animals with the reported finding in one or both eyes)

Study Week	Number Observed/Number Examined				
Dose Group (mg/kg/day)	0	0.5	2	20	500
Males					
5	0/45	0/45	0/45	0/45	28/45 (62%)
11	0/45	0/45	0/45	0/45	27/45 (60%)
23	0/45	0/45	0/45	2/45 (4%)	29/45 (64%)
37	0/44	0/45	0/45	1/45 (2%)	32/44 (73%)
49	0/44	0/45	0/45	4/45 (9%)	33/44 (75%)
75	0/25	0/25	0/25	2/25 (8%)	18/25 (72%)
101	0/25	0/25	0/25	4/25 (16%)	20/25 (80%)
Females					
5	0/45	0/45	0/45	0/45	30/45 (67%)
11	0/45	0/45	0/45	0/45	38/45 (84%)
23	0/45	0/45	0/45	0/45	42/45 (93%)
37	0/44	0/44	0/45	1/45 (2%)	39/44 (89%)
49	0/43	0/44	0/45	1/45 (2%)	39/44 (89%)
75	0/25	0/25	0/25	0/25	23/25 (92%)
101	0/25	0/25	0/25	0/25	16/25 (64%)

a These data were obtained from Tables 8A-8E, 8G, and 8H, pages 169-173 and 175-176 of the study report No. 95/0499.

E. Blood Analyses: The results of selected parameters are presented in Table 9 and 10.

1. Hematology - During 102 weeks of treatment, a few changes in platelet as well as erythrocyte counts and mean hemoglobin values were seen in the 500 mg/kg/day group rats. These differences, though occasionally statistically significant, were generally minor and not dose-related and therefore, judged not to be of toxicological concern. These changes were no longer apparent after a seven week recovery period (following 52 weeks of treatment).

2. Clinical Chemistry - Significant ($p<0.05$, 0.01 or 0.001) decreases in alkaline phosphatase (↓23-49%), alanine aminotransferase (↓14-53%), and aspartate aminotransferase (↓14-53%) activities and changes in levels of urea (↑16-31%), glucose (↓10-18%), potassium (↑6-17%), chloride (↓2-5%), and total plasma protein concentrations (↑7-18%) were seen in one or both sexes primarily in the 500 mg/kg/day dose group rats in the 104-week study. The selected findings are presented in Table 9). Cholesterol levels were increased throughout the dosing period in the 500 mg/kg/day dose group animals, from 98 mg% at 6 weeks to 213 mg% 102 weeks, representing 32-87% increases over controls ($p\leq0.05$). In the 20 mg/kg/day males cholesterol was elevated to 89 mg% at week 24 to 177 mg% at week 102 with increases of 29-54%, respectively ($p\leq0.05$, but increases were not statistically significant at 78 weeks). Levels were also increased at the 6, 50, 78, and 102 week intervals in the 20 mg/kg/day dose group females from 80-215 mg% (↑21-48%; $p<0.05$ or 0.01). The overall evidence is inconclusive with respect to the biological importance of the elevated cholesterol levels.

   The differences in electrolytes and protein levels may be correlated to possible dehydration of the rats at time of analysis.

   After seven weeks of the recovery period (following 52 weeks of dosing), cholesterol levels remained elevated (↑22-38%; $p<0.05$ or 0.001) in the 20 and 500 mg/kg/day dose group females (124 and 141 mg%, respectively vs 102 mg% in control; data not shown in this DER)).

F. Urinalysis - Statistically significant ($p\leq0.01$) differences were seen in pH (↓4-22%), output (↓40%), specific gravity (↑1-3%; see Table 10); differences in total reducing substances, ketones, and color were also observed at 50 weeks. These findings were detected primarily in the 500 mg/kg/day group. After 101 weeks of treatment, significant differences were seen only in urinary pH (↓6%) in males and specific gravity (↑2%) in females. Urine was positive for total reducing substances after 50 weeks for rats receiving 500 mg/kg/day but not at 101 weeks. Furthermore, after the 6-week recovery period, the urinary parameters in the control and treated rats were similar. Urinalysis indications of impaired renal function were not strongly corroborated by histopathological findings and there were no correlating gross pathology findings.

Table 9
Selected Clinical Chemistry Parameters in Rats
Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

	Dosage Levels (mg/kg/day)									
	Males					Females				
	0	0.5	2	20	500	0	0.5	2	20	500
After 24 Weeks of Treatment										
Urea (mg%)	32	32	34	33	32	35	35	38	32	36
Glucose (mg%)	110	124**	130***	127**	106	114	115	129**	115	93***
Total Cholesterol (mg%)	68	83**	72	88***	127***	89	88	88	90	148***
After 50 Weeks of Treatment										
Urea (mg%)	19	20	20	21	22*	26	27	26	28	32***
Glucose (mg%)	113	130**	138***	133***	122	111	122**	124***	118*	100**
Total Cholesterol (mg%)	89	103	95	112**	134***	100	107	122*	127**	181***
After 78 Weeks of Treatment										
Glucose (mg%)	113	120	121	108	99*	100	95	106	109	91
Total Cholesterol (mg%)	120	128	174**	142	158*	113	139	151*	148*	211***
After 102 Weeks of Treatment										
Glucose (mg%)	100	99	95	96	90	105	91*	108	109	86**
Total Cholesterol (mg%)	115	146	193**	177*	191**	145	131	152	215*	213*

a Extracted from Tables 10B-F (pages 193-200 and 205-212) of the study report No. 95/0499
* = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$

Table 10.
Results of urinalysis[a]

Parameters	Dose levels (mg/kg/day) Males					Females				
	0	0.5	2	20	500	0	0.5	2	20	500
At 50 weeks of treatment - 19-20 rats/sex/group										
Volume (mL)	5.5	7.5	6.5	7.5	6.5	3.5	4.0	4.5	4.0	4.0
pH	6.8	7.2**	7.2**	6.8	6.0***	6.0	5.8*	6.0	5.9	5.7**
Specific gravity	1051	1060	1050	1054	1078***	1051	1050	1047	1054	1070***
After 6 weeks of reversibility period - 10 rats/sex/group										
Volume (mL)	7.0	12.0*	8.5	9.5	6.5	7.0	8.0	8.5	5.5	5.5
pH	6.5	6.8*	6.7	6.5	6.6	6.1	5.9	6.1	6.0	6.1
Specific gravity	1048	1039	1040	1039	1048	1033	1035	1032	1042*	1038
After 101 week of treatment - 9-10 rats/sex/group										
Volume (mL)	9.0	11.0	9.5	10.5	10.0	9.5	10.5	11.0	8.0	6.5
pH	6.4	6.7	6.4	6.3	6.0**	6.2	6.0	6.0	5.8*	5.9
Specific gravity	1043	1036	1046	1037	1044	1034	1029	1034	1040	1054***

a Extracted from Tables 11C (pages 215-216), 11D (page 217), and 11F (pages 220-221) of the study report No. 95/0499
* = p<0.05; ** = p<0.01; *** = p<0.001

G. Sacrifice and Pathology:

1. Organ weights - Selected organ weights are reported in Table 11.

Interim Necropsy: At the interim sacrifice (week 52), rats in the 500 mg/kg/day dose group had increased absolute and relative liver weights (males, absolute ↑79% and relative ↑122; p<0.01 and females, absolute, ↑34% and relative ↑84%; p<0.01) and absolute and relative thyroid gland weights (males, absolute ↑74% and relative ↑115%; p<0.05 or 0.01 and females, relative ↑49%; p<0.05) compared to controls. Additionally, absolute and relative liver weights were increased in males in the 20 mg/kg/day dose group (absolute ↑25%, relative ↑37%, p<0.05 or 0.01). Relative kidney weights increased in males (43%) and females (30%) at 500 mg/kg/day. Absolute heart weights were decreased 14% in 500 mg/kg/day males (p<0.01) and relative pituitary weights increased 37% in males and 13% in females (non-significant). The body weight gains in males and females were

lower than controls (27% in males and 19% in females). Increase in relative organ weights was likely to be associated with a decrease in body weight gain at 500 mg/kg/day.

Necropsy following Recovery Period: After the 8-week recovery period (following 52 weeks of treatment), absolute and relative thyroid gland weights remained increased in the high-dose females (absolute ↑40%, relative ↑40%; $p<0.05$ or 0.01). Relative kidney weight in males at 500 mg/kg/day was 19% higher than the controls. Relative heart weights in females increased 20% over controls. At the end of recovery period, the body weight gains in males and females were lower than the controls (8% in males and 14% in females; non-significant). Increase in relative organ weights was likely to be associated with a decrease in body weight gain at 500 mg/kg/day.

Terminal Necropsy: The terminal body weights of the 500 mg/kg/day group males and females decreased (↓29% and ↓37%, respectively; $p<0.01$) as compared to the controls. At the terminal sacrifice (Week 104), rats in the 500 mg/kg/day dose group had increased absolute and relative liver weights (males, absolute ↑56% and relative ↑115%; $p<0.01$ and females absolute 24↑% and relative ↑97%; $p<0.05$ or 0.01), and relative thyroid gland weights (males, ↑56%; $p<0.01$). Additionally, males in the 20 mg/kg/day dose group had increased absolute liver weights (↑15%; $p<0.05$). Corroborative macroscopic and histopathological changes indicated treatment-related effects on the liver and thyroid gland. Absolute heart weights were decreased ($p<0.01$) by 15% in males and 23% in females; relative heart weights increased by 18% in males and 19% in females at 500 mg/kg/day. Although there were heart weight changes and increased cholesterol levels at 500 mg/kg/day, corroborating histopathological evidence of heart abnormality was lacking. Absolute kidney weight in males (16%) and relative kidney weights in both sexes increased (57 and 24%, respectively) significantly ($p\leq0.01$) at 500 mg/kg/day. However, the incidence of epithelial mineralization was decreased in females compared to control; the increased incidence of progressive senile nephropathy, although seen in all dose groups, was significantly increased only at 20 and 500 mg/kg/day dose group males that died during the treatment and those that were sacrificed at 104 weeks. Absolute pituitary weights were decreased 13% in males at 500 mg/kg/day; however, the decrease was not significant. The body weight gains in males and females were lower than the controls (29% in males and 37% in females), although the decrease was not statistically significant. Increase in relative organ weights was likely to be associated with a decrease in body weight gain at 500 mg/kg/day.

There were no effects on mean organ weights in animals in the 0.5 or 2 mg/kg/day dose groups.

Table 11
Absolute and Relative Weights of Selected Organs from Rats Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

Dosage Levels (mg/kg/day)										
	Males					Females				
Dose(mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Interim Necropsy (After 52 Weeks of Treatment)- 7-10 Rats/sex/group										
Body Weight (g)	835.3	852.5	770.0	759.8	680.3*	414.7	428.5	412.8	449.6	303.1
Liver										
A (g)	22.8	26.1	24.8	28.5*	40.8**	14.0	15.1	13.5	15.7	18.8**
R (%)	2.75	3.01	3.25	3.78**	6.11**	3.46	3.50	3.27	3.48	6.38**
Thyroids										
A (g)	0.027	0.033	0.031	0.030	0.047*	0.021	0.021	0.020	0.027	0.023
R (%)	0.0032	0.0039	0.0040	0.0040	0.0069**	0.0053	0.0048	0.0048	0.0060	0.0079*
Pituitary										
A (g)	0.014	0.012	0.014	0.012	0.012	0.014	0.026	0.017	0.017	0.014
R (%)	0.0016	0.0015	0.0018	0.0015	0.0018	0.0035	0.0059	0.0041	0.0039	0.0048
Kidney										
A (g)	4.06	4.31	3.98	4.15	4.68	2.77	2.85	2.67	2.95	2.67
R (%)	0.487	0.511	0.521	0.552	0.697**	0.693	0.667	0.650	0.666	0.900**
Heart										
A (g)	2.13	2.02	1.93	1.98	1.83**	1.35	1.42	1.39	1.43	1.13
R (%)	0.257	0.243	0.253	0.261	0.272	0.335	0.331	0.340	0.324	0.382
Testes/Uterus and cervix										
A (g)	4.28	3.76	3.94	3.92	3.72	0.83	0.87	0.88	1.02	0.73
R (%)	0.518	0.455	0.517	0.528	0.558	0.215	0.204	0.220	0.232	0.255

Table 12 continued -

Reversibility Necropsy (After 52 Weeks of Treatment and 8 Weeks of No Treatment)- 9-10 Rats/group

Sex	Male					Female				
Dose (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Bost Weight (g)	803.4	856.6	812.1	868.7	737.6	445.2	485.8	488.5	446.7	384.1
Liver										
A (g)	25.1	28.1	23.8	31.0*	24.9	14.8	16.4	15.6	15.2	14.6
R (%)	3.11	3.28	2.93	3.58	3.40	3.34	3.37	3.21	3.40	3.83
Thyroid										
A (g)	0.029	0.033	0.034	0.043	0.035	0.020	0.020	0.021	0.021	0.028**
R (%)	0.004	0.004	0.004	0.005	0.005	0.005	0.004	0.004	0.005	0.007**
Pituitary										
A (g)	0.012	0.012	0.011	0.013	0.011	0.015	0.016	0.016	0.014	0.016
R (%)	0.0014	0.0015	0.0014	0.0015	0.0015	0.0035	0.0034	0.0033	0.0033	0.0042
Kidney										
A (g)	4.38	4.79	4.51	4.85	4.78	2.73	3.17	3.01	2.84	2.73
R (g)	0.549	0.567	0.553	0.563	0.651**	0.621	0.655	0.634	0.642	0.719
Heart										
A (g)	2.05	2.00	2.00	2.14	2.07	1.35	1.50	1.46	1.38	1.39
R (g)	0.257	0.238	0.246	0.249	0.281	0.308	0.311	0.304	0.311	0.369**
Testes/Uterus and cervix										
A (g)	3.97	4.03	3.90	4.03	3.88	0.75	0.78	0.93	0.98	0.86
R (g)	0.502	0.482	0.483	0.469	0.529	0.177	0.165	0.199	0.227	0.0237

Table 12 (Continued)-

Terminal Necropsy (After 104 Weeks of Treatment)- 25-46 males/group ; 22-48 females/group

Sex	Males					Females				
Dose(mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Body Weight (g)	802.0	850.8	870.9	789.1	568.7**	548.7	551.1	564.5	543.6	347.0**
Liver										
A (g)	27.4	25.0	30.3	31.4*	42.8**	20.5	21.7	19.2	22.0	25.5**
R (%)	3.55	2.99*	3.58	4.08	7.62**	3.81	3.95	3.43*	4.11	7.51**
Thyroid[b]										
A (g)	0.051	0.055	0.046	0.063	0.055	0.046	0.031	0.042	0.034	0.029
R (%)	0.0061	0.0065	0.0053	0.0082	0.0095**	0.0095	0.0058	0.0069	0.0064	0.0085
Pituitary										
A (g)	0.015	0.015	0.017	0.015	0.013	0.019	0.017	0.016	0.015	0.019
R (%)	0.0020	0.0018	0.0019	0.0020	0.0023*	0.0039	0.0037	0.0029	0.0029	0.0058
Kidneys										
A (g)	5.47	5.06	5.84	5.77	6.37*	3.96	3.82	3.66	3.67	3.26**
R (%)	0.723	0.616	0.695	0.744	1.137**	0.767	0.728	0.661	0.697	0.952**
Heart										
A (g)	2.27	2.32	2.41	2.23	1.94**	1.80	1.77	1.75	1.64*	1.39**
R (%)	0.295	0.280	0.283	0.288	0.348**	0.345	0.333	0.315	0.310	0.409**
Testes/Uterus and cervix										
A (g)	3.72	3.59	4.01	3.89	3.42	0.85	1.00	0.78	0.84	1.10*
R (%)	0.479	0.432	0.484	0.520	0.614**	0.163	0.191	0.141	0.165	0.334**

a Extracted from Tables 12A-F (pages 222-239) of the study report no. 95/0499
A = absolute weight; R = relative weight
b Group mean calculated excluding animals with thyroid tumors.
* Significantly different from controls, p<0.05
** Significantly different from controls, p<0.01
*** Significantly different from controls, p<0.001

2. Gross pathology -

Interim Necropsy: At the interim sacrifice (Week 52; Table 12), treatment-related gross necropsy findings were observed in the livers. Swollen livers were detected in males in the at 20 mg/kg/day dose group (5/10 treated vs. 0/10 control rats; $p<0.05$) and the 500 mg/kg/day dose group males (6/10 treated; $p<0.05$). Males in this dose group also had areas of change in the liver (4/10 treated vs. 0/10 control rats) and marked liver enlargement (1/10 treated vs. 0/10 control rats; data not shown in this DER).

Necropsies following Recovery Period: The gross pathology changes in the liver detected at the interim sacrifice were not detected in rats after the eight-week recovery period.

Terminal Sacrifice and unscheduled sacrifices: At necropsy (terminal sacrifice and animals that were killed prior to terminal sacrifice; see Tables 12 and 13), female rats in the 500 mg/kg/day dose group had areas of changes in the lungs and thin body build. The later finding resulted from the lower body weights. Males had increased incidences of masses, areas of change and swelling of the livers, as well as "marked" enlargement of the thyroid glands and opaqueness of the eyes (also in the 20 mg/kg/day group males). Females had an increased incidence of the lung masses. Other findings, while occasionally statistically significant, were not considered to be biologically significant. Gross necropsy findings at terminal sacrifice in the liver, thyroid gland, eyes and lungs were confirmed by histopathological lesions (Table 14).

Table 12
Incidence of Selected Gross Pathological Findings in Rats During Treatment with RPA 201772 in the Diet for up to 104 Weeks[a]

Sex	Males					Females				
Dose(mg/kg/day	0	0.5	2	20	500	0	0.5	2	20	500
Interim Sacrifice - After 52 Weeks of Treatment[b]										
Number examined	10	10	10	10	10	7	9	10	10	10
Eyes: Opaque	0	1	0	0	1	1	0	0	0	0
Liver:										
Areas of change	0	0	0	0	4	0	0	0	0	0
Swollen	0	3	0	5*	6*	0	0	0	0	0
Masses	0	0	0	0	0	0	1	0	0	0
Lungs:										
Areas of change	0	0	0	0	1	1	1	0	1	1
Masses	0	0	0	1	0	0	0	0	0	0
Miscellaneous:										
Uterus Thickened	-	-	-	-	-	1	0	1	3	0
Thin BodyBuild	0	0	0	0	1	1	0	0	0	6
After 8 Weeks of Reversibility[b]										
Number examined	9	9	10	10	9	10	10	10	10	8
Eyes: Opaque	0	1	0	0	0	0	0	1	0	0
Liver:										
Areas of change	0	0	1	0	0	1	0	0	0	0
Swollen	0	0	0	0	1	0	0	0	0	0
Masses	0	0	0	0	0	0	1	0	0	0
Lungs:										
Areas of change	0	1	1	0	0	1	0	0	1	5*
Masses	0	1	0	0	0	0	0	0	0	0
Miscellaneous:										
Uterus Thickened	-	-	-	-	-	0	0	0	1	0
Thin BodyBuild	0	0	0	0	0	0	0	0	0	3

Table 13 (continued)

After 104 Week of Treatment[c]

Sex	Males					Females				
Dose (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Number examined	34	25	34	37	46	35	23	25	22	48
Eyes: Opaque	2	4	7	10*	14**	1	2	0	0	1
Liver:										
Areas of change	6	3	4	6	29***	11	1*	4	0**	16
Swollen	6	3	9	9	24**	8	2	7	6	13
Masses	2	1	6	3	21***	2	2	1	0	29***
Lungs:										
Areas of change	6	2	7	3	13	0	4*	3	2	14***
Masses	1	0	1	0	2	0	1	1	0	6*
Thyroid Gland:										
Masses	1	2	2	4	8	1	0	2	1	2
Enlargement	0	0	0	6*	5	0	0	0	1	0
Miscellaneous:										
Uterus Thickened	-	-	-	-	-	1	3	1	0	10*
Thin BodyBuild	2	0	0	5	14**	2	1	0	1	27***

a Extracted from Tables 13B-D (pages 252-266) of the study report no. 95/0499

b Results of the examination of the thyroids do not appear for this phase.

c Scheduled necropsies at 104 weeks

* = $p<0.05$;** = $p\leq0.01$;*** = $p\leq0.001$

Table 13
Incidence of Macroscopic Findings in Killed or Dying Rats Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

Sex	Males					Females				
Dose (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Number examined	41	50	41	38	29	40	52	50	53	27
Eyes: Opaque	2	4	5	4	12***	1	0	1	4	2
Liver:										
Areas of change	4	1	4	8	9*	5	7	4	5	4
Swollen	11	4*	17	17	12	9	10	20	17	10
Masses	6	1*	3	4	3	0	3	2	1	12***
Lungs:										
Areas of change	2	1	5	6	7*	4	6	3	4	8
Masses	2	0	1	2	3	0	1	1	1	1
Thyroid Gland:										
Dark	0	0	0	0	5**	0	0	1	1	3
Masses	1	0	2	2	4	1	0	0	0	1
Enlargement	1	0	1	1	3	0	1	0	1	0
Miscellaneous:										
Uterus Thickened	-	-	-	-	-	3	1	0	0	3
Thin body build	5	4	5	5	17***	8	16	5	6	15**

a Extracted from Tables 13A (pages 242-250) of the study report No. 95/0499; * = $p<0.05$; ** = $p<0.01$

3. Microscopic pathology

a) Non-neoplastic -

Interim Sacrifice: Ophthalmic observations (Table 14) revealed that the 500 mg/kg/day dose group males had an increased incidence of corneal lesions which were characterized by keratitis (90%; $p<0.001$), epithelial thickening (50%; $p<0.001$), superficial exfoliated epithelial cells (90%; $p<0.05$), and subepithelial fibroblastic reaction (90%; $p<0.001$). Keratitis was also observed in 30% of the females in this group. The above findings were not seen in control and lower dose groups.

Increases in the incidence of periacinar hepatocytic hypertrophy was detected in the 20 mg/kg/day males (100%; $p<0.01$) and the 500 mg/kg/day dose group rats (100%; $p<0.01$). Midzonal foamy hepatocytes were detected in 50-90% ($p\leq0.05$) of the males in the 20 and 500 mg/kg/day dose groups. Pigment laden hepatocytes were detected in the 500 mg/kg/day group males (30%) and females (60%; $p<0.05$).

Sacrifice following Recovery Period: Ocular and hepatic changes were, in general, reversible after the eight week recovery period.

Terminal Sacrifice and unscheduled sacrifices: The incidences of statistically significant ($p\leq0.05$) treatment-related non-neoplastic lesions detected in animals assigned to the carcinogenicity phase of the study (including deaths, unscheduled sacrifices and terminal sacrifice at 104 weeks) are summarized as follows (refer to macroscopic findings in Table 13):

eyes - increased incidence of keratitis in males in the 2, 20 and 500 mg/kg/day dose groups (non-dose related at the two lower doses), superficial exfoliation of epithelial cells and thickening in the 20 and 500 mg/kg/day group males, and stroma vascularization in the 500 mg/kg/day group males

liver - increased incidence of periacinar hepatocytic hypertrophy and portal tract senile changes in the bile duct in males at 20 mg/kg/day and in both sexes at 500 mg/kg/day dose levels; focal cystic degeneration in the 20 and 500 mg/kg/day group males; eosinophilic foci of hepatocellular alterations in the 500 mg/kg/day group females; and midzonal foamy hepatocytes in the 20 and 500 mg/kg/day group males and the 500 mg/kg/day group females

thyroid gland - increased incidence of cystic follicular hyperplasia in the 20 and 500 mg/kg/day group males and the 500 mg/kg/day group females

lungs - increased incidence of accumulation of alveolar macrophages in the 500 mg/kg/day group rats (males and females)

sciatic nerve - increased incidence of axonal/myelin degeneration and cholesterol cleft/granuloma in the 20 and 500 mg/kg/day group males and the 500 mg/kg/day group females

thigh muscle - increased incidence of focal degeneration and chronic inflammation in the 20 and 500 mg/kg/day group males and the 500 mg/kg/day group females

There were no treatment-related non-neoplastic lesions observed in the 0.5 mg/kg/day group rats.

b) Neoplastic - There were no treatment-related neoplastic lesions detected in the animals at the interim sacrifice or on completion of the recovery period. The incidence of selected neoplastic lesions detected in animals that were killed or died during the study and at the 104-week terminal sacrifice are presented in Table 15A and 15B.

Treatment-related neoplastic lesions were detected in the livers and thyroid glands. In the 500 mg/kg/day group rats (both sexes), there were significant increases in the incidences of hepatocellular adenomas, hepatocellular carcinomas, and combined adenomas/carcinomas (41 and 62%, respectively for males and females). In both sexes at 500 mg/kg/day, the incidence of carcinomas (23% and 32%, respectively for males and females) contributed to the overall increase in liver tumor incidence; animals with carcinomas accounted for over half of the total number of animals bearing adenomas and/or carcinomas.

Thyroid follicular cell adenomas showed a significantly increased incidence ($p<0.01$) in males at 500 mg/kg/day, but not females, although there were positive trends for both sexes ($p\leq0.05$).

There were no treatment-related neoplastic lesions detected in the 0.5, 2 or 20 mg/kg/day dose group rats.

Table 14
Incidence of Non-Neoplastic Microscopic Findings in Rats Treated with RPA 201772 in the Diet for up to 104 Weeks[a]

	Dose Levels (mg/kg/day)									
Sex	Males					Females				
Site Lesions	0	0.5	2	20	500	0	0.5	2	20	500
Toxicity Phase (52 Weeks of Treatment)[b]										
Eyes: Number examined	10	10	10	10	10	7	9	10	10	10
Keratitis	0	0	0	0	9***	0	0	0	0	3
Epithelial thickening	0	0	0	0	8***	0	0	0	0	1
Superficial Exfoliated epithelial cells	0	0	0	0	5*	0	0	0	0	1
Subepithelial fibroblastic reaction	0	0	0	0	9***	0	0	0	0	1
Liver: Number examined	10	10	10	10	10	7	9	10	10	10
Periacinar Hepatocytic hypertrophy	3	5	5	10**	10**	0	0	0	0	10***
Focal cystic degeneration	0	1	1	2	4	0	0	0	0	0
Midzonal foamy hepatocytes	0	0	0	5*	9***	0	0	0	0	2
Pigment laden hepatocytes	0	0	0	0	3	0	0	0	0	6*
Lungs: Number examined	10	10	10	10	10	7	9	10	10	10
Macrophages Accumulation	0	0	1	1	0	0	0	0	0	1
Thyroid Gland: Number examined	10	0	0	0	10	7	0	0	0	10
Cystic follicular hyperplasia	0	0	0	0	1	0	0	0	0	1
Heart: Number examined	10	0	0	0	10	7	0	0	0	10
Chronic myocarditis	6	0	0	0	2	0	0	0	0	0

Table 14 Continued-

Sex	Males					Females				
Dose (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Kidney: Number examined	10	10	10	10	10	7	9	10	10	10
Progressive (senile) nephropathy	1	4	3	4	6	3	1	2	2	4
Cortico-medullary mineralization	0	0	0	0	0	4	1	2	2	0*
Reversibility Phase (52 Weeks of Treatment + 8 Weeks of Reversibility)[b]										
Eyes: Number examined	9	9	10	10	9	10	10	10	10	8
Keratitis	0	1	1	0	4	0	0	1	0	0
Superficial exfoliated epithelial cells	0	0	0	0	1	0	0	0	0	0
Liver: Number examined	9	9	10	10	9	10	10	10	10	8
Periacinar hepatocytic hypertrophy	1	0	1	2	4	1	0	1	0	1
Focal cystic degeneration	1	1	2	2	1	0	0	0	0	0
Portal tract (senile)changes of bileducts	0	0	1	2	1	0	0	0	0	0
Midzonal foamy hepatocytes	0	0	0	1	4	0	0	0	0	0
Lungs: Number examined	0	2	1	0	0	1	0	0	1	5
Microphage accumulation	0	0	1	0	0	1	0	0	1	3

Table 14 Continued-

Carcinogenicity Phase (104 Weeks of Treatment)

Sex	Males					Females				
Dose (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Eyes: Number examined	34	25	34	37	46	35	23	25	22	48
Keratitis	4	2	8	7	31***	1	0	0	0	0
Epithelial thickening	0	1	4	5	14***	1	0	0	0	0
Superficial exfoliated epithelial cells	1	0	2	6	13**	1	0	0	0	0
Vascularization of stroma	5	4	5	7	20**	1	0	0	0	1
Liver: Number examined	34	25	34	37	46	35	23	25	22	48
Periacinar Hepatocytic hypertrophy	7	3	9	28***	46***	1	0	1	3	46***
Focal cystic degeneration	14	12	16	27**	24	2	3	0	2	4
Portal tract (senile) bile duct changes Midzonal	7	4	10	10	20	2	3	1	7*	22***
foamy hepatocytes	0	0	1	10**	7*	0	0	3	1	11**
Eosinophilic foci	14	8	17	17	21	5	1	3	6	27***
Lungs: Number examined	34	25	34	37	46	35	23	25	22	48
Macrophage Accumulation	0	2	0	0	8*	0	0	0	0	7*
Thyroid: Number examined	34	24	34	37	46	35	23	25	22	48
Cystic follicular hyperplasia	1	3	7	14***	19***	1	0	2	2	8
Heart: Number examined	34	1	1	1	46	35	0	0	0	48
Chronic myocarditis	24	1	1	1	27	21	0	0	0	14**
(% incidence)	(50)	(38)	(31)	(31)	(48)	(43)	(24)	(33)	(24)	(19***)

Table 14 Continued-

Sex	Males					Females				
Dose (mg/kg/day)	0	0.5	2	20	500	0	0.5	2	20	500
Kidney: Number examined	34	25	34	37	46	35	23	25	22	48
Progressive (senile) nephropathy	23	21	30	31	44**	24	20	17	19	27
Pelvic epithelial mineralization	1	0	1	0	0	10	12	9	5	3**
Sciatic Nerve (left): Number examined	34	25	34	37	46	35	0	0	22	48
Axonal/Myelin Degeneration	9	11	12	23**	38***	2	0	0	3	40***
Cholesterol cleft/granuloma	1	2	3	10**	26***	0	0	0	0	17***
Thigh Muscle: Number examined	34	25	34	37	46	35	0	0	22	47
Focal Degeneration/inflammation	6	4	9	21**	34***	0	0	0	1	21***

a Extracted from Tables 14G-I (pages 295-312) of the study report no. 95/0499
b No observations recorded for sciatic nerve, thigh muscle, thyroid glands, heart and kidneys; * = p<0.05; ** = p<0.01; *** = p<0.001

Table 14
Incidence of Non-neoplastic Microscopic Findings in Killed or Dying Rats During Treatment with RPA 201772 for 104 Weeks[a]

	Dose Levels (mg/kg/day)									
Sex	Males					Females				
Site Lesions	0	0.5	2	20	500	0	0.5	2	20	500
Eyes: Number examined	39	49	40	38	29	40	52	49	53	25
Keratitis	1	9*	10**	10**	16***	1	2	1	3	5*
Epithelial thickening	1	3	1	5	6*	0	0	1	0	1
Superficial exfoliated epithelial cells	0	3	3	2	4*	0	0	0	1	2
Liver: Number examined	41	50	41	38	29	40	52	50	53	26
Periacinar hepatocytic hypertrophy	1	8*	3	18***	23***	0	0	1	5	19***
Focal cystic degeneration	6	10	16*	15*	14**	0	1	1	1	2
Portal tract (senile) changes of bile ducts	5	10	7	15**	10*	2	6	5	9	12***
Midzonal foamy hepatocytes	0	0	0	3	2	0	0	0	1	1
Lungs: Number examined	41	50	41	38	29	40	52	50	53	26
Macrophage accumulation	1	1	2	0	3	1	2	1	1	3
Thyroid Gland: Number examined	40	48	40	38	29	39	50	48	52	25
Cystic follicular hyperplasia	4	3	1	6	9*	1	3	2	3	4
Heart: Number examined	41	50	41	38	29	40	52	50	53	26
Chronic myocarditis	26	37	30	30	21	22	24	33	24	5**
Kidney: Number examined	41	50	41	38	29	40	52	50	53	26
Progressive (senile) nephropathy	29	28	30	29	27*	24	27	27	28	10
Pelvic epithelial mineralization	0	2	0	0	0	17	18	18	21	0***
Sciatic nerve (left): Number examined	41	50	41	38	29	40	52	50	53	26
Axonal/Myelin degeneration	2	4	7	7	22***	0	0	1	1	10***
Cholesterol cleft/granuloma	1	2	1	2	12***	0	0	0	0	1
Thigh Muscle: Number examined	41	50	41	38	29	40	52	50	53	27
Focal degeneration/inflammation	5	10	9	11	20***	1	0	0	2	9***

a Extracted from Tables 14F (pages 280-294) of the study report no. 95/0499

* Significantly different from controls, p<0.05; ** p<0.01; *** p<0.001

Table 15A
The incidence of liver and thyroid tumors in rats fed RPA 201772 for 104 Weeks[a]

Sex	Males										Females									
Dose Levels (mg/kg/day)	0		0.5		2		20		500		0		0.5		2		20		500	
Findings	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T
Liver (examined)	41	34	50	25	41	34	38	37	29	46	40	35	52	23	50	25	53	22	26	48
Hepatocellular adenoma	0	2	0	3	0	5	2	4	0	14**	0	4	0	2	1	0	0	0	5**	24***
Hepatocellular carcinoma	3	2	1	0	1	3	2	0	3	14**	0	0	0	0	0	1	0	0	9***	15***
Thyroid (examined)	40	34	48	24	40	34	38	37	29	46	39	35	50	23	48	25	52	22	25	48
Follicular cell adenoma	2	1	0	1	4	1	1	6	3	12**	1	0	0	0	1	0	4	0	1	2
Follicular cell carcinoma	0	0	0	1	1	1	0	1	1	2	0	0	0	1	0	1	0	0	1	1

a Data were obtained Table 14A-14D on pages 267-275 and pages 336-344 of the study report no. 95/0499
** = $p \leq 0.01$; *** = $p \leq 0.001$
D = Dead or sacrificed moribund; T = Terminal sacrifice (104 weeks)

Table 15B
Overall incidence of liver and thyroid tumors in rats fed RPA 201772 (104-week Terminal Phase)a

Site/Tumor	Males					Historical controls[b]	
Dose Level (mg/kg/day)	0	0.5	2.0	20	500	Mean (%)	Range (%)
Liver							
Hepatocellular adenoma	2/75 (2.7)‡[c]	3/75 (4.0)	5/75 (6.7)	6/75 (8.0)	14**/75 (18.7)	2.51	0-10
Hepatocellular carcinoma	5/75 (6.7)‡	1/75 (1.4)	4/75 (5.3)	2/75 (2.7)	17**/75 (22.7)	2.28	0-6
Hepatocellular adenomas and/or carcinomas combined	7/75 (9.3)†	4/75 (5.3)	9/75 (12)	8/75 (10.7)	31***/75 (41.3)	Data not provided	
Thyroid							
Follicular cell adenoma	3/74 (4.1)†	1/72 (1.3)	5/74 (6.8)	7/75 (9.3)	15**/75 (20)	3.04	0-6.4
Follicular cell carcinoma	0/74	1/72	2/74	1/75	3/75	- -	- -
	Females						
Liver Hepatocellular adenoma	4/75† (5.3)	2/75 (2.7)	1/75 (1.3)	0/75 (0)	29***/74 (39.2)	1.19	0-3.6
Hepatocellular carcinoma	0/75† (0)	0/75 (0)	1/75 (1.3)	0/75 (0)	24***/74 (32.4)	0.00	0-0
Hepatocellular adenomas and/or carcinomas combined	4/75† (5.3)	2/75 (2.7)	2/75 (2.7)	0/75 (0)	46***/74 (62.2)	Data not provided	
Thyroid							
Follicular cell adenoma	1/74‡ (1.4)	0/73 (0)	1/73 (1.4)	4/74 (5.4)	3/73 (4.1)	0.72	0-2.0
Follicular cell carcinoma	0/74	1/73	1/73	0/74	2/73	- -	- -

a Data were obtained from Table 14E (pages 276-279 plus pages 336-344 of the study report no. 95/0499; includes scheduled sacrifices and unscheduled deaths.
b Historical control incidence data from 8 studies, 440 males and 420 females
c Percentage of animals with specific lesions
* = p<0.05, ** = p<0.01 ***= p<0.001 pairwise analysis
† = p<0.001, trend analysis; ‡ = p≤0.05, trend analysis

Latency period for tumor development. Table 16 summarizes the time to earliest tumor development for liver adenomas, liver carcinomas, and thyroid follicular adenomas. In males, the earliest adenoma was observed at the 52-week interim sacrifice (approximately 365 days). Otherwise, there was no indication of a treatment-related decrease in the latency period in males. In females at 500 mg/kg/day, the first liver adenoma and carcinoma appeared considerably earlier (427 and 426 days, respectively) than did these tumors in controls (728 days at the terminal sacrifice). The first thyroid tumor appeared in the 20 and 500 mg/kg/day females somewhat sooner than in controls, 576 and 623 days,respectively, versus 714 days for controls.

Table 16.
Latency periods for liver and thyroid tumor appearance in rats dosed with RPA 201772 a

Time to appearance of the first tumor of a given type (days) b					
Males (mg/kg/day)	**0**	**0.5**	**2.0**	**20**	**500**
Liver: Adenoma	728	728	728	674	365 [c]
Carcinoma	594	728	663	670	646
Thyroid follicular cell adenoma	647	728	490	701	612
Females (mg/kg/day)	**0**	**0.5**	**2.0**	**20**	**500**
Liver: Adenoma	728	728	681	728	427 [d]
Carcinoma	728	728	728	728	426
Thyroid follicular cell adenoma	714	None seen	728	576	623

a Data were obtained from Appendices 13A-13C, pages 1918- 3696 of the study report no. 95/0499
b Findings are from the 104-week Terminal Phase scheduled or unscheduled deaths, unless otherwise indicated.
c Earliest occurrence observed at the 52-week scheduled interim sacrifice.
d Earliest occurrence observed at the 61-week scheduled interim sacrifice (reversibility group).

III. DISCUSSION

A. Investigators Conclusions - The chronic LOEL is 20 mg/kg/day based on toxicity observed in the liver, eyes (corneas) and sciatic nerves of the 20 and 500 mg/kg/day animals and in the thyroid gland and lungs in the high-dose animals. The chronic NOEL is 2 mg/kg/day.

There was evidence of carcinogenic effects in rats administered 500 mg/kg/day dietary RPA201772 continuously for 104 weeks. Hepatic tumors, which were directly related to the toxicity of RPA201772 in both sexes and thyroid gland tumors, considered to be secondary to the liver changes, were produced in the males.

B. Reviewer's Discussion/Conclusions - The analytical data indicated that the mixing procedure in general was adequate at 20 and 500 mg/kg/day, somewhat more variable at 2 mg/kg/day, and poor at the lowest dose. This variability, however did not affect study interpretation.

Clinical observations consisted of an increased incidence of general opacity of the eye in 500 mg/kg/day males and females, beginning at week 6, progressing in males thereafter during treatment. Late in the study (weeks 91-104) there were increased incidences of abnormal gait, limited use of limbs, and thin body build in the 500 mg/kg/day group rats.

No treatment-related adverse effects on the survival were noted. Overall (weeks 0 through 104) body weight gains were 36-49% lower than the control rats. This decrease was associated with a decrease in food consumption in the females and decreases in food conversion efficiency in both sexes. The lower body weight gains were reflected in an increased incidence of animals with thin body build. These findings were judged to be treatment-related. During the reversibility period the 500 mg/kg/day males and females gained more weight than the controls.

Ophthalmoscopic examinations revealed treatment-related corneal lesions in the majority of the 500 mg/kg/day group rats. Eye lesions were also detected in the 20 mg/kg/day group males. The severity of these lesions was greater in males than in females and ranged from small focal superficial opacities to large corneal opacities with associated vascularization and iritis.

At terminal sacrifice, treatment-related increases were observed in the absolute and relative liver weights in the 500 mg/kg/day group rats of both sexes and in the 20 mg/kg/day group males. In addition, significant increases in relative thyroid gland weights in males at 500 mg/kg/day as well as increased incidence of eye lesions were detected in males at ≥20 mg/kg/day.

Treatment-related gross necropsy findings in the 500 mg/kg/day group males and females consisted of swollen livers (also detected in the 20 mg/kg/day group males), masses, and areas of change. Masses and/or areas of change in the lungs were observed upon necropsy of 500 mg/kg/day males and females.

Non-neoplastic liver lesions observed with significant frequencies at ≥20 mg/kg/day in males and at 500 mg/kg/day in females included periacinar hepatocytic hypertrophy, focal cystic degeneration, and midzonal foamy hepatocytes. Liver lesions were increased in severity in males. Also observed in ≥20 mg/kg/day males only, were thyroid cystic follicular hyperplasia, axonal/myelin sciatic nerve degeneration, and degeneration and inflammation of the thigh muscle. The 500 mg/kg/day males and females also had increased macrophage accumulation in the lungs.

RPA 201772 is carcinogenic to male and female rats at doses of 500 mg/kg/day. Liver adenomas, carcinomas, and combined adenomas/carcinomas exhibited significantly increased incidences in both sexes at the 500 mg/kg/day dose. The incidence of thyroid follicular cell adenoma was significantly greater than the control in males at 500 mg/kg/day. The incidences of liver and thyroid adenomas and liver carcinomas exceeded the historical incidence of these tumors. Findings in this study pertinent to the carcinogenic potential of RPA 201772 are as follows:

Liver:

The incidences of adenomas, carcinomas, and combined tumors at 500 mg/kg/day in both sexes were statistically significant.

The majority of males or females bearing adenomas and/or carcinomas at 500 mg/kg/day had the carcinoma.

The earliest observation of adenoma was at 365 and 427 days in males and females at 500 mg/kg/day, versus 728 days for controls. In 500 mg/kg/day females the earliest carcinoma was observed at 426 days versus 728 days for controls.

Absolute and relative weights, at 52 and 104 weeks, were increased significantly in both sexes at 500 mg/kg/day.

Masses, swellings and/or areas of change were observed in livers of 500 mg/kg/day males and females at 104 weeks.

Non-neoplastic lesions appeared in males at 20 mg/kg/day and 500 mg/kg/day at the 52-week interim sacrifice. At these dose levels, incidence of these lesions increased in males and appeared in females by 104 weeks.

Thyroid:

Follicular cell adenomas occurred with significantly increased frequency in 500 mg/kg/day males.

Cystic follicular hyperplasia was significantly increased in 20 mg/kg/day males and in 500 mg/kg/day males and females.

At 20 and 500 mg/kg/day, males exhibited enlarged thyroids and relative thyroid weights were significantly increased in 500 mg/kg/day males.

The reviewer agrees with the study author, that the chronic LOEL is 20 mg/kg/day based on hepatic, thyroid, and ocular toxicity in both sexes as well as degeneration of the sciatic nerve and thigh muscles in males. The chronic NOEL is 2.0 mg/kg/day.

C. Study deficiencies - Urine stains, and ungroomed coat were indicative of poor animal husbandry. However, these deficiencies do not adversely affect the outcome of the study for two reasons. First, the longevity of the Sprague-Dawley rat has been decreasing and therefore, a shortened life span was not unique to this study. Secondly, the study was long enough to have tumors develop in the treated groups.

Isoxaflutole Review

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