012255

12/20/96

DATA EVALUATION RECORD

ISOXAFLUTOLE (RPA 201772)

Study Type: §83-~~3~~; Oncogenicity study by Dietary Administration to CD-1 Mice for 78 Weeks

Work Assignment No. 2-8A (MRID 43904807)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
F. Ann Foster, Ph.D.

Signature: Ann Foster
Date: 12/18/96

Secondary Reviewer
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 12/20/96

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 12/20/96

Quality Assurance:
Michael Norvell, Ph.D., D.A.B.T.

Signature: Mike Norvell
Date:

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Sanjivani Diwan, Ph.D. Sanjivani Diwan 8/17/97
Review Section I, Toxicology Branch II (7509C)
EPA Secondary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy 3/17/97
Review Section I, Toxicology Branch II, (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity [feeding] - mice
OPPTS Number: 870.3200 OPP Guideline Number: §83-2

DP BARCODE: D224202 SUBMISSION CODE: S501233
P.C. CODE: 123000 TOX. CHEM. NO.: None
MRID NO.: 43904807

TEST MATERIAL (PURITY): RPA 201772 (≥98.7% ai)

SYNONYMS: Isoxaflutole; 5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl)isoxazole

CITATION: Chase, K.R. (1995) RPA201772ai: Oncogenicity study - by dietary administration to CD-1 mice for 78 weeks. Pharmaco LSR, Eye, Suffolk IP23 7PX, England. Pharmaco LSR Report No: 95/RHA509/0343. October 16, 1995. MRID 43904807. Unpublished.

SPONSOR: Rhone-Poulenc Agriculture Limited, Ongar Research Station, Fyfield Road, Ongar, Essex CM5 OHW, England.

EXECUTIVE SUMMARY:

In a 78-week carcinogenicity study (MRID 43904807), RPA 201772 (isoxaflutole, ≥98.7% ai) was fed (diet) to 64 or 76 mice/sex/dose at dose levels of 0, 25, 500, or 7,000 ppm daily (means of 0, 3.2, 64.4, or 977.3 mg/kg/day, respectively, for males; and 0, 4.0, 77.9, or 1161.1 mg/kg/day, respectively, for females). Interim sacrifices were made at 26 weeks (12 mice/sex at the 0 and 7,000 pm doses) and at 52 weeks (12 mice/sex at all dose levels).

RPA 201772 had no significant effect on the survival of animals. Systemic signs of toxicity in the treated groups included: 1) decreased body weight gain in both sexes at 500 ppm (males -15% and females -22%) and 7,000 ppm (males -28% and females -42%); for the 25 ppm group females the total body weight gain was also lower (-16%) compared to controls; 2) food consumption was unaffected; however, food efficiency was lower for both sexes (28% for males and 17% for females) at 7000 ppm during the first 14 weeks of the study; 3) absolute and relative/body liver weights were significantly increased in both sexes (up to >200%) at 7,000 ppm; relative liver weight was increased in males at 52

weeks (+19%) and in females at 78 weeks (+13%) at 500 ppm; 4) gross necropsy at 78-week sacrifice revealed increased occurrences of liver masses in both sexes at 7,000 ppm; 5) non-neoplastic lesions of the liver occurred at 52-week sacrifice in males at 500 ppm and in males and females at 7,000 ppm. At termination, the 500 ppm group males exhibited increased incidence of hepatocyte necrosis. At 7,000 ppm, significant increase in non-neoplastic lesions in both sexes included periacinar hepatocytic hypertrophy, necrosis, and erythrocyte-containing hepatocytes. In addition, males at the high dose had pigment-laden hepatocytes and Kupffer cells, basophilic foci, and increased ploidy; extramedullary hemopoiesis in the spleen was noted in both sexes; 6) increase incidences of hepatocellular adenoma and carcinoma were observed in both sexes at 7,000 ppm in the 52-week and 78-week studies.

Among scheduled and unscheduled deaths in the 78-week study, there were significant occurrences of hepatocellular adenomas in 27/52 males (52%) and 15/52 females (29%), and carcinomas in 17/52 males (33%) and 4/52 females (8%;non-significant). The incidences of these tumors exceeded the corresponding historical incidence with this species, in this laboratory. Combined adenoma and carcinoma incidences at 7,000 ppm were 73% for males and 35% for females. At 500 ppm, the incidences of 17% adenomas and 15% carcinomas in males and 2% adenomas in females were not statistically significant, but exceeded the means for historical controls. The 52- and 78-week studies revealed a dose-related decrease in the first occurrence of carcinomas in males; the earliest carcinomas were observed at 78, 71, 52, and 47 weeks at the 0 through 7,000 ppm doses. There were no carcinomas in females up to 78 weeks at 0, 25, or 500 ppm, although, the earliest finding at 7000 ppm was at 60 weeks.

The LOEL for this study is 500 ppm (64.4 mg/kg/day for males and 77.9 mg/kg/day for females), based on decreased body weight gains, increased liver weights, and increased incidences of histopathological liver changes. The NOEL is 25 ppm (3.2 mg/kg/day for males and 4.0 mg/kg/day for females). Although body weight was decreased marginally in females at 25 ppm, there were no corroborating findings of toxicity at this dose.

Under conditions of this study, RPA 201772 appears to induce hepatocellular adenomas and carcinomas in male and female CD-1 mice. The chemical was tested at doses sufficient to measure its carcinogenic potential.

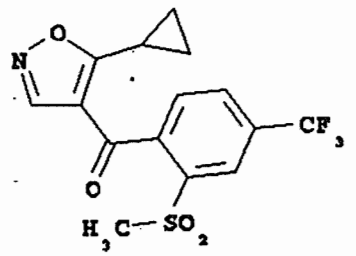
This carcinogenicity study is **Acceptable** and **satisfies** the guideline requirement (§83-2) for a carcinogenicity study in mouse.

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: RPA 201772
   Chemical Name: 5-Cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl)isoxazole; Isoxflutole
   Description: Fine yellow powder
   Lot/Batch #: 21 ADM 93
   Purity: ≥98.7% ai
   Stability of compound: RPA 201772 has been shown to be stable for "at least" 2 years at ambient temperature (99.2-99.7%; page 257 of the study report).
   CAS #: 141112-29-0
   Structure:



2. Vehicle: Basal diet

3. Test animals: Species: Mouse
   Strain: CD-1
   Age and weight at study initiation: Approximately 34-41 days of age; body weight range - male, 28.6-29.6 g; females, 22.2-22.9 g
   Source: Charles River (UK) Limited, Margate, Kent, England
   Housing: Four mice of the same sex per cage; cages consisted of a polypropylene body (13 x 29 x 12 cm) with a stainless steel mesh lid
   Diet: RM1(E) SQC FG powered rodent diet (Special Diets Services Ltd., Witham, Essex, England), ad libitum
   Water: Municipal tap water, ad libitum, via polycarbonate bottles fitted with sipper tubes
   Environmental conditions:
      Temperature: 21°C
      Humidity: 55%
      Air Changes: 15/hour
      Photoperiod: 12-Hour light/dark cycle
   Acclimation period: Approximately 13 days

B. STUDY DESIGN

1. In life dates - Start: 5/25/93 End: 12/5/94

2. Animal assignment

Mice were selected for study on the basis of pretest examinations which excluded animals with extreme body weights or ophthalmic lesions. The selected mice were assigned to the test groups in Table 1 using computer generated random numbers.

Table 1. Study design (values represent number of mice).

Test Group	Nominal Dose to Animal (ppm)	Interim 1 (26 weeks)		Interim 2 (52 weeks)		Terminal (78 weeks)	
		Male	Female	Male	Female	Male	Female
1 Control	0	12	12	12	12	52	52
2 Low	25	--	--	12	12	52	52
3 Mid	500	--	--	12	12	52	52
4 High	7,000	12	12	12	12	52	52

3. Dose selection rationale

Dose levels were selected based on 28- and 90-day dietary studies and a liver enzyme induction study. Liver weight induction and hepatocytic hypertrophy were observed at 700 ppm in the 28-day study, and at 1,000 and 2,000 ppm in the 90-day study. Liver weight increase was observed in males at 50 ppm in the 90-day study. The enzyme induction study found significant increases (11-19 fold) in pentoxyresorufin O-dealkylase (PROD) P450 and benzoxyresorufin O-debenzylase (BROD) P450 microsomal enzyme activities at and above 700 ppm. The dose response curve for enzyme induction was steep between 175 and 700 ppm, increasing 6- to 7-fold, with a plateau above 2,800 ppm.

4. Treatment preparation and dosing

Diet was prepared fresh weekly. RPA 201772 was mixed into a small amount of the ground diet, and the treated feed was sieved using an ultracentrifugal mill with a 2 mm screen. The mixture was then diluted with additional feed, and a final 7,000 ppm feed mix was homogenized using a Hobart A200 mixer. A portion of this mix was serially diluted to prepare the 25 and 500 ppm mixes. The treated

feed was stored in sealed polyethylene bags or polypropylene containers at room temperature. Unused feed was discarded at the end of each week.

Homogeneity was determined in samples collected from six positions in the 25 and 7,000 ppm mixes prepared prior to the start of the study. Because of poor recovery from the 25 ppm mix, the size of later samples was increased from 5 to 20 g; 20 g samples were used for "the rest of the study." In a previous study (Report No. 200549) the stability of RPA 201772 in diet stored at room temperature and was confirmed up to 2 weeks. In this study (Report No. 200682), the stability of the test compound in the diet was demonstrated for up to 13 weeks. The concentration of RPA 201772 in feed was confirmed by analyzing samples of the 25, 500, and 7,000 ppm treatment mixes (prepared fresh each week) at 1- to 2-month intervals through 78 weeks.

Results:

Homogeneity Analysis:
7,000 ppm, 5 g sample: 89.1-96.1% of nominal
25 ppm, 5 g sample: 57.4-94.4% of nominal
25 ppm, 20 g sample: 97.6-108.5% of nominal

Stability Analysis: RPA 201772 was shown to be stable in the diet for up to 2 weeks at ambient temperatures and up to 13 weeks in the freezer.

Concentration Analysis: 83.7-103.9% of nominal with the exception of one assay (75.5% of nominal); 85.1-103.9% at 25 ppm; 86.3-92.8% at 500 ppm and 83.7-94.5% at 7,000 ppm)

Homogeneity analysis on a 5-g sample revealed values below acceptable levels. Therefore, additional analyses were conducted on 20-g samples which indicated values within 10% of nominal.

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

5. Statistics

Mortality data were analyzed using Cox's proportional hazards model and Tarone's partition of Chi-square into linear trend on dose and deviation from linearity. Body and organ weights were analyzed using Bartlett's test of homogeneity of variances. If the variances were found to be equal, pairwise comparisons were conducted using Behrens-Fisher test. If variances proved to be unequal, the data were analyzed by the Dunnett's test. The distribution of macroscopic and microscopic (non-neoplastic) pathological abnormalities were analyzed using Fisher's two-tailed exact test, and the distribution of

neoplastic lesions was analyzed using Fisher's one-tailed test.

C. METHODS

1. Observations

Animals were observed "at least" twice daily for clinical signs, mortality, and morbidity. In addition, animals received weekly physical examinations which included palpation.

2. Body weight

Animals were weighed prior to the initial dosing, on the first day of treatment, weekly during the first 14 weeks of treatment, on alternate weeks between 14 and 78 weeks, and prior to sacrifice.

3. Food and compound intake/water consumption

Food consumption for each cage of animals was determined weekly throughout the treatment period. Food consumption was reported as g food/animal/week. Food conversion efficiency was determined for the first 14 weeks of treatment as:

weekly change in body weight ÷ weekly food consumption

The group mean test material consumption (mg/kg/day) for each sex was calculated on a weekly basis. No quantitative measurements of water consumption were made.

4. Ophthalmoscopic examination

Ophthalmoscopic examinations by indirect ophthalmoscope were conducted on all animals prior to dosing; on all surviving Interim Phase 2 animals and 12/sex of Terminal Phase animals at 11, 23, 37, and 49 week; and on all surviving animals at 75 weeks.

5. Hematology

Blood was collected from all surviving animals at 50 and 76 weeks from a tail vein without the use of anesthesia. Blood from the control and 7,000 ppm treatment groups was examined only for differential leucocyte counts by Romanowsky stain and direct visual count. Blood from the 25 and 500 ppm treatment groups was not examined.

6. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues from all animals from groups 1 and 4 were collected processed and stained with hematoxylin and eosin for histological examination. In addition, the liver, lungs, kidneys, and eyes of animals from groups 2 and 3 sacrificed upon completion of Interim phase 2 and the terminal phase as well as livers from all animals sacrificed following completion of Interim phase 1 were subjected to histopathological examination. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
-	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph.nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*T
X	Stomach*	X	Lymph nodes*		
X	Duodenum*	XX	Spleen*	X	Pituitary*
X	Jejunum*	X	Thymus*	X	Eyes (optic n.)*T
X	Ileum*				
X	Cecum*				
X	Colon*		UROGENITAL		GLANDULAR
X	Rectum*				
XX	Liver*+	XX	Kidneys*+	XX	Adrenal gland*
X	Gall bladder*	X	Urinary bladder*	-	Lacrimal glandT
X	Pancreas*	XX	Testes*+	X	Mammary glandT
		X	Epididymides	X	Parathyroids*++
		X	Prostate	X	Thyroids*++
		X	Seminal vesicle	X	Harderian glands
	RESPIRATORY	X	Ovaries*+		
		XX	Uterus*		
X	Trachea*	X	Vagina		
XX	Lung*				
-	Nose				
-	Pharynx				
-	Larynx				
					OTHER
				X	Bone*
				X	Skeletal muscle*
				X	Skin*
				X	All gross lesions and masses*

* Required for chronic toxicity studies.
+ Organ weight required in chronic studies.
++ Organ weight required for non-rodent studies.
T = Required only when toxicity or target organ.

II. RESULTS

A. Observations

1. Mortality - Among 52-week Interim phase groups, 2 males and 3 females died during weeks 47/48. Survival rates of

mice in the Terminal phase groups at selected intervals are presented in Table 2. The survival rates of the treated groups were not significantly different from controls. After 78 weeks survival rates in the 0 through 7000 ppm groups were 71, 60, 71, and 69% among males and 83, 75, 75, and 88% among females.

Table 2. Survival rate in male and female mice fed RPA 201772 for 78 weeks[a]

Week	0 ppm	25 ppm	500 ppm	7000 ppm
Males				
27	52 [b] (100%)[c]	52 (100%)	49 (94%)	52 (100%)
41	52 (100%)	50 (96%)	48 (92%)	49 (94%)
52	46 (88%)	46 (88%)	48 (92%)	48 (92%)
66	44 (85%)	39 (75%)	40 (77%)	43 (83%)
79	37 (71%)	31 (60%)	37 (71%)	36 (69%)
Females				
27	52 (100%)	52 (100%)	50 (96%)	52 (100%)
41	52 (100%)	52 (100%)	50 (96%)	52 (100%)
52	51 (98%)	51 (98%)	48 (92%)	51 (98%)
66	48 (92%)	48 (92%)	44 (85%)	48 (92%)
79	43 (83%)	39 (75%)	39 (75%)	46 (88%)

[a] Data were taken from Table 3B, p. 71-73 of the study report (No. 95/0343)
[b] Number of survivors; 52 animals/sex/group at study initiation.
[c] Values in parentheses represent % survival; percentages calculated by the reviewer

2. Clinical Signs - "Palpable swellings" were observed in all groups of the terminal phase primarily during the last 26 weeks. Table 3 summarizes the incidence of "palpable swellings" in the terminal groups. There were slight (non-significant) increases in the numbers of males affected and total numbers of swellings in the 25 and 7000 ppm dose groups. The number of animals and number of swellings were considerably higher in males than in females. No swellings were reported for the interim sacrifice groups. Other clinical signs occurred randomly and sporadically in all groups. The study report stated that the palpable swellings are commonly seen in mice of this strain, although no details were provided.

Table 3. Incidence of "palpable swellings" in male and female mice fed RPA 201772 for 78 weeks.a

Sex/dose (ppm)	Number of animals with swellings	Total number of swellings	Mean time of onset (weeks)
Male			
0	13	19	53
25	18	28	52
500	10	14	51
7000	16	23	59
Female			
0	6	7	61
25	3	3	56
500	6	9	67
7000	2	2	49

a Data were taken from Table 2, study report No. 95/0343, p. 69; 52 animals/sex/group at study initiation..

B. Body weight and weight gain

After 78 weeks of treatment, the body weights and total body weight gains of male mice in the 500 or 7,000 ppm treatment groups and female mice in the 25, 500, or 7,000 ppm treatment groups were significantly lower than the controls (Table 4). For female mice in the 25 or 500 ppm groups, this difference (16 and 22%, respectively) developed between 76 and 78 weeks, during which time the mice in the female control group gained an average 2.7 g.

Table 4. Mean body weights and body weight gains of mice during 78 weeks of treatment. a, b

Dose level (ppm)	Body weights (g)					Total body weight gains	
	0 weeks	24 weeks	50 weeks	76 weeks	78 weeks	g	% change from control
Male							
0	28.6	49.0	53.5	51.7	52.7	24.2	--
25	29.0	49.6	52.9	53.7	54.0	24.9	+3
500	29.5	48.2	51.8	49.2	50.1	20.5**	-15
7,000	29.6	43.3	46.4	47.0	46.5	17.5**	-28
Female							
0	22.2	34.3	38.4	40.6	43.3	21.2	--
25	22.4	33.9	37.3	39.8	40.3	17.9*	-16
500	22.9	34.7	37.7	40.7	39.5	16.6**	-22
7,000	22.3	32.0	33.9	35.8	34.4	12.2**	-42

a Data obtained from Table 4, pages 74-78, in the study report (No 95/0343).
b Statistical analyses were conducted only on the total body weight gain data.
* = $p<0.05$.
** = $p<0.01$.

C. Food consumption and compound intake

Food consumption was unaffected by treatment; however, food efficiency was lower in both sexes compared to controls at 7,000 ppm during the first 14 weeks of the study.

During the first 14 weeks of treatment, average weekly food conversion efficiencies for males and females in the 7,000 ppm treatment group were 72 and 83%, respectively, of the conversion efficiencies for the controls. Food conversion efficiencies for the 25 or 500 ppm treatment groups decreased ≤11% with respect to controls. Food conversion efficiencies were not determined after 14 weeks.

The actual consumption of RPA 201772 by the mice during the study is presented in Table 5.

Table 5. Actual consumption of RPA RPA 201772 by mice during 78 weeks of treatment. a

Dose Level (ppm)	Week 1 (mg/kg/day)	Week 78 (mg/kg/day)	Range Weeks 0-78 (mg/kg/day)	Mean Weeks 0-78 (mg/kg/day)
Males				
25	4.7	3.1	2.7-4.7	3.2
500	93.7	67.0	53.9-93.7	64.4
7,000	1188.4	1048.2	870.7-1257.2	977.3
Females				
25	5.0	3.6	3.3-5.3	4.0
500	99.0	69.0	65.0-104.3	77.9
7,000	1414.2	1033.2	989.9-1488.6	1161.1

a Data obtained from Table 7, pages 88-90, in the study report (No. 95/0343).

D. Ophthalmoscopic examination

No treatment-related ocular changes were observed during the study.

E. Hematology

Blood from the control and 7,000 ppm treatment groups was examined only for differential leucocyte counts by Romanowsky stain and direct visual count. No treatment-related differences in this parameter were observed. Blood from the 25 and 500 ppm treatment groups was not examined.

F. Sacrifice and Pathology

1. Organ weight - Absolute and relative liver weights of male and female mice in the 7,000 ppm treatment group were significantly higher (24-207%, $p < 0.01$) than the controls after 26, 52, and 78 weeks of treatment (Table 6). Absolute liver weights of mice of both sexes in the 500 ppm treatment group were 7-17% higher than the controls after 52 and 78 weeks of treatment; these differences were statistically significant ($p < 0.05$) only for females at 52 weeks. Relative liver weights were significantly increased in the 500 ppm males at 52 weeks (19%, $p<0.05$) and in the 500 ppm females at 78 weeks (13%, $p<0.05$).

Table 6. Absolute and relative liver weights in male and female mice after 26, 52, and 78 weeks of treatment with RPA 201772. a

Treatment interval[b]	Absolute liver weights - g [c]				Relative liver weights - % [c]			
	0 ppm	25 ppm	500 ppm	7,000 ppm	0 ppm	25 ppm	500 ppm	7,000 ppm
Males								
26 Weeks	2.14	--	--	4.47** (+109)	4.95	--	--	10.98** (+122)
52 Weeks	2.48	2.49 (+0.4)	2.90 (+17)	5.56** (+124)	4.71	5.02 (+7)	5.62* (+19)	12.19** (+159)
78 Weeks	2.71	2.83 (+4)	2.89 (+7)	7.17** (+165)	5.40	5.71 (+6)	6.24 (+16)	16.60** (+207)
Females								
26 Weeks	1.57	--	--	3.01** (+92)	4.93	--	--	10.24** (+108)
52 Weeks	1.75	1.74 (-1)	1.96* (+12)	2.93** (+67)	5.07	5.31 (+5)	5.70 (+12)	9.52* (+88)
78 Weeks	1.82	1.86 (+2)	2.07 (+14)	3.72** (+104)	4.77	5.04 (+6)	5.40* (+13)	11.21** (+135)

a Data obtained from Tables 9A through 9F, pages 93-104, in the study report (No. 95/0343); percentages calculated by the study reviewer.
b Number of animals sacrificed at 26, 52 and 78 weeks were 12/sex, 11-12/sex, and 31-37 males and 39-46 females/dose group, respectively.
c Values in parentheses are percent change from corresponding control.
- - No data
* = $p<0.05$.
** = $p<0.01$.

There were significant differences in the absolute and relative adrenal weights of females in the 7,000 ppm treatment group at 26 weeks and males in the 7,000 ppm treatment group at 52 weeks. With the exception of absolute adrenal weight in females, these differences persisted through 78 weeks. However, they were not accompanied by significant histopathological changes. No other differences were observed between mice in the treated and the control groups. The terminal body weights were significantly lower ($p\leq0.01$) for males at 500 and 7,000 ppm and for females at 7,000 ppm (49.9, 50.9, 46.5*,and 43.2 g for males and 39.0, 37.4, 38.5 and 32.7 g for females at 0, 25, 500 and 7,000 ppm, respectively).

2. Gross pathology - Male and female mice in the 7,000 ppm treatment group were found to have a higher incidence of enlarged or swollen livers, and/or liver masses, and/or "areas of change" on the liver (Table 7). Abdominal distension was also observed in males at a higher incidence ($p \leq 0.01$) at 78 weeks. Similar liver changes were observed in mice that died or were sacrificed during the study (liver masses: 11/16; $p<0.01$ in males at 7,000 ppm; data not in this DER).

"Masses" were reported in other organs. However, the incidences of these findings were low and non-dose-related, and, therefore, were not considered treatment-related.

Table 7. Gross pathological changes in the livers of male and female mice after 26, 52, and 78 weeks of treatment with RPA 201772. a

Interval: Organ abnormality	Males (dosage in ppm)				Females (Dosage in ppm)			
	0	25	500	7,000	0	25	500	7,000
26 Weeks: Liver enlargement	0/12	--	--	2/12	0/12	--	--	0/12
dark	0/12	--	--	1/12	1/12	--	--	3/12
abnormal shape	0/12	--	--	0/12	0/12	--	--	1/12
52 Weeks: Liver enlargement	0/12	0/11	0/12	1/12	0/12	0/11	0/11	0/12
areas of change	0/12	0/11	0/12	3/12	0/12	1/11	0/11	1/12
masses	1/12	0/11	1/12	6/12	0/12	0/11	0/11	0/12
swollen	0/12	0/11	0/12	2/12	0/12	0/11	0/11	2/12
78 Weeks: Liver enlargement	0/37	0/31	0/37	1/36	0/43	0/39	0/39	0/46
dark	0/37	0/31	0/37	2/36	0/43	0/39	1/39	3/46
abnormal shape	0/37	1/31	0/37	0/36	0/43	0/39	0/39	0/46
areas of change	6/37	0/31**	5/37	16/36*	0/43	0/39	1/39	1/46
masses	11/37	13/31	11/37	28/36***	0/43	1/39	0/39	15/46***
swollen	0/37	0/31	0/37	4/36	0/43	0/39	1/39	2/46
pale	4/37	1/31	0/37	1/36	1/43	4/39	2/39	0/46
Abdominal distension	1/37	1/31	0/37	9/36**	0/43	0/39	1/39	1/46

a Data obtained from Tables 10C through 10E, pages 116-127, in the study report (No. 95/0343).
-- = No data
* = $p < 0.05$.
** = $p < 0.01$.
*** = $p < 0.001$.

No other treatment-related gross postmortem differences were observed between mice in the 7,000 ppm and the control groups. No treatment-related differences were observed between mice in the 25 or 500 ppm treatment groups and the control group. All abnormalities other than those noted were typical for the species and appeared to occur randomly and sporadically in all study groups.

3. Microscopic pathology

a) Non-neoplastic - Significant increases in microscopic liver abnormalities were observed in both sexes as early as the 26-week interim sacrifice (data not shown in this DER) and were detected with increasing frequency at longer sacrifice intervals.

At the 26-week sacrifice all of the high dose males (12/12, $p<0.001$) and females (12/12, $p<0.001$) had developed periacinar hepatocytic hypertrophy. Other significant liver lesions at the 26-week sacrifice of high dose animals were hepatocyte necrosis (males 10/12, $p<0.001$; females 7/12, $p<0.01$) and pigmented Kupffer cells (males 10/12, $p<0.001$). There were also non-significant incidences in high dose males of periacinar hepatocytic fatty vacuolation (2/12) and erythrocytes in hepatocytes (3/12), compared with none in controls.

Notable non-neoplastic lesions observed in mice at the 52-week interim sacrifice are summarized in Table 8. In the 7000 ppm group there were significant increases in periacinar hepatocytic hypertrophy and periacinar hepatocytic fatty vacuolation among males and females ($p<0.001$ and $p<0.01$, respectively). In addition, the high dose males showed significant increases in other hepatocyte abnormalities. A significant increase in spleen extramedullary hemopoiesis (7/12, $p<0.01$) was observed in high dose males sacrificed at 52-weeks. Male mice in the 500 ppm group exhibited a significant increase in periacinar hepatocytic hypertrophy (7/12, $p<0.01$, versus none in controls).

Table 8. Incidences of treatment-related non-neoplastic lesions in mice fed RPA 201772 for 52 weeks. [a]

Site & Lesion	No. Observed/No. Examined			
Males				
Dose (ppm)	0	25	500	7000
Liver [Number examined]: periacinar hepatocytic hypertrophy	[12] 0	[11] 0	[12] 7**	[12] 12***
individual hepatocyte necrosis	1	0	5	7*
pigment-laden hepatocytes	0	0	0	5*
pigment-laden Kupffer cells	0	0	2	10***
periacinar hepatocytic fatty vacuolation	7	3	7	0**
increased ploidy	0	0	0	3
Lungs: lymphocytic infiltration	[12] 0	[11] 0	[12] 0	[12] 2
Spleen: extramedullary hemopoiesis	[12] 0	[3] 3	[3] 2	[12] 7**
Females				
Dose (ppm)	0	25	500	7000
Liver: periacinar hepatocytic hypertrophy	[12] 0	[11] 0	[11] 0	[12] 12***
individual hepatocyte necrosis	1	0	0	1
pigment-laden hepatocytes	0	0	0	0
pigment-laden Kupffer cells	3	2	0	2
periacinar hepatocytic fatty vacuolation	1	6*	4	10***
increased ploidy	0	0	0	0
Lungs: lymphocytic infiltration	[12] 1	[11] 0	[11] 1	[12] 4
Spleen: extramedullary hemopoiesis	[12] 6	[3] 1	[3] 1	[12] 4

a These data were extracted from the study report No 95/0343, Table 11G, p. 146-151.

* = $p<0.05$, ** = $p<0.01$; *** = $p<0.001$

Notable non-neoplastic lesions observed in mice in the 78-week terminal group are summarized in Table 9. Findings from animals sacrificed at termination and those having unscheduled deaths are presented separately, as each category was subjected to statistical analysis separately. Male and female mice in the 7,000 ppm treatment group exhibited an increased incidence

of periacinar hepatocytic hypertrophy, necrosis of individual hepatocytes and erythrocytes in hepatocytes, pigment-laden hepatocytes and Kupffer cells, compared to the controls; male mice also exhibited basophilic foci of hepatocellular alteration and increased ploidy. Male mice in the 500 ppm group exhibited necrosis of individual hepatocytes (12/37, $p<0.05$). In addition, mice in the 7,000 ppm treatment group had a higher incidence of systemic amyloidosis, involving the kidneys, small intestine, stomach, thyroid, mesenteric lymph nodes, and heart. Both sexes were significantly affected at the high dose. Amyloidosis of the thyroid occurred in 12/36 ($p<0.01$) terminal sacrifice males, 6/16 unscheduled male deaths, and 14/46 ($p<0.001$) of terminal sacrifice females at the high dose.

Table 9. Incidences of treatment-related non-neoplastic lesions in mice fed RPA 201772 for 78 weeks. a

Site & Lesion	No. Observed/No. Examined			
	Males			
Dose (ppm)	0	25	500	7000
Liver: periacinar hepatocytic hypertrophy	0/37[b] *0/15[c]*	0/31 *0/21*	2/37 *0/15*	14***/36 *4/16*
individual hepatocyte necrosis	4/37 *1/15*	5/31 *0/21*	12*/37 *1/15*	25***/36 *8*/16*
pigment-laden hepatocytes	0/37 *0/15*	0/31 *0/21*	0/37 *0/15*	6*/36 *5*/16*
erythrocyte-containing hepatocytes	0/37 *NR*	1/31 *NR*	4/37 *NR*	11***/36 *NR*
pigment-laden Kupffer cells	1/37 *1/15*	2/31 *0/21*	4/37 *1/15*	31***/36 *12***/16*
periacinar hepatocytic fatty vacuolation	17/37 *2/15*	17/31 *0/21*	14/37 *1/15*	9/36 *2/16*
basophilic foci	1/37 *0/15*	2/31 *0/21*	0/37 *0/15*	9**/36 *1/16*
clear cell foci	5/37 *NR*	0/31 *NR*	3/37 *NR*	11/36 *NR*
increased ploidy	0/37 *0/15*	0/31 *0/21*	2/37 *0/15*	10***/36 *2/16*

Site & Lesion	No. Observed/No. Examined			
Lungs:				
lymphocytic infiltration	2/37 *0/15*	4/31 *0/21*	3/37 *0/15*	2/36 *1/16*
Spleen:				
extramedullary	3/37	4/6	4/8	11*/36
hemopoiesis	*4/15*	*8/21*	*7/15*	*7/15*
Duodenum:				
amyloidosis	2/37 *3/10*	-/0 *0/14*	-/0 *0/12*	10*/36 *4/13*
Ileum:				
amyloidosis	7/37 *2/9*	-/0 *3/11*	-/0 *1/10*	15*/36 *5/11*
Jejunum:				
amyloidosis	6/37 *3/9*	-/0 *2/16*	-/0 *0/11*	13/36 *5/12*
Kidneys:				
amyloidosis	4/37 *3/15*	4/31 *3/21*	4/37 *0/15*	10/36 *4/16*
cortical cyst	11/37 *3/15*	7/31 *2/21*	1/37** *0/15*	6/36 *0/16*
Lymph nodes, mesenteric:				
sinus histiocytosis	1/37 *1/15*	1/3 *4/21*	0/1 *3/15*	3/36 *0/16*
pigment-laden macrophages	0/37 *2/15*	0/3 *2/21*	0/1 *0/15*	2/36 *0/16*
amyloidosis	5/37 *3/15*	0/3 *3/21*	0/1 *1/15*	12/36 *6/16*
Stomach:				
amyloidosis	1/37 *1/14*	0/4 *0/20*	0/7 *0/14*	3/36 *4/14*
Thyroid:				
amyloidosis	2/37 *3/15*	-/0 *2/21*	-/0 *0/15*	12**/36 *6/16*
Heart:				
chronic myocarditis	2/37 *7/15*	-/0 *3/21*	-/0 *2/15*	11**/36 *2/16*
amyloidosis	0/37 *2/15*	-/0 *0/21*	-/0 *0/15*	4/36 *2/16*

Site & Lesion	No. Observed/No. Examined			
Females				
Dose (ppm)	0	25	500	7000
Liver: periacinar hepatocytic hypertrophy	0/43 *0/9*	0/39 *0/13*	1/39 *2/13*	17***/46 *1/6*
individual hepatocyte necrosis	0/43 *1/9*	1/39 *0/13*	0/39 *0/13*	8**/46 *0/6*
pigment-laden hepatocytes	0/43 *0/9*	0/39 *0/13*	0/39 *1/13*	0/46 *0/6*
erythrocyte-containing hepatocytes	0/43 *NR*	1/39 *NR*	1/39 *NR*	9**/46 *NR*
pigment-laden Kupffer cells	7/43 *1/9*	4/39 *1/13*	2/39 *2/13*	10/46 *1/6*
periacinar hepatocytic fatty vacuolation	13/43 *0/9*	9/39 *1/13*	7/39 *1/13*	26*/46 *1/6*
basophilic foci	0/43 *0/9*	0/43 *0/13*	0/43 *0/13*	0/43 *0/6*
clear cell foci	0/43 *NR*	0/43 *NR*	0/43 *NR*	0/43 *NR*
increased ploidy	0/43 *0/9*	0/43 *0/13*	0/43 *0/13*	0/43 *0/6*
Lungs: lymphocytic infiltration	3/43 *0/9*	2/39 *1/13*	2/39 *1/13*	8/46 *1/6*
Spleen: extramedullary hemopoiesis	3/43 *6/9*	3/8 *8/13*	4/10 *5/13*	12*/46 *5/6*
Duodenum: amyloidosis	0/43 *0/9*	-/0 *0/12*	-/0 *0/10*	12***/46 *0/6*
Ileum: amyloidosis	4/43 *0/9*	-/0 *1/12*	-/0 *0/11*	17**/46 *0/6*
Jejunum: amyloidosis	1/43 *0/9*	-/0 *0/12*	-/0 *0/11*	12**/46 *0/6*

Site & Lesion	No. Observed/No. Examined			
Kidneys: amyloidosis	1/43 *1/9*	4/39 *0/13*	2/39 *1/13*	11**/46 *0/6*
cortical cyst	2/43 *1/9*	3/39 *0/13*	0/39 *0/13*	2/46 *0/6*
Lymph node, mesenteric: sinus histiocytosis	8/43 *3/9*	1/2 *1/13*	3/5 *1/13*	15/46 *1/6*
pigment-laden macrophages	1/43 *0/9*	0/2 *3/13*	0/5 *0/13*	8*/46 *0/6*
amyloidosis	0/43 *0/9*	0/2 *1/13*	0/5 *0/13*	10**/46 *0/6*
Stomach: amyloidosis	0/43 *0/9*	0/2 *0/12*	0/1 *0/12*	4/46 *0/6*
Thyroid: amyloidosis	1/43 *0/9*	-/0 *0/13*	-/0 *0/13*	14***/46 *0/6*
Heart: chronic myocarditis	0/43 *0/9*	-/0 *0/13*	0/1 *0/13*	0/46 *0/6*
amyloidosis	0/43 *0/9*	-/0 *0/13*	0/1 *0/13*	7*/46 *0/6*
Ovaries: amyloidosis	1/43 *NR*	1/26 *NR*	0/24 *NR*	3/46 *NR*

a These data were extracted from the study report No. 95/0343, Table 11E, p. 134-144 and Table 11H, p. 152-162.
b Data are from the mice sacrificed on schedule at 78 weeks
c *Data in italics are from unscheduled deaths* occurring throughout 78 week study period.
NR = Not reported; * = p<0.05, ** = p<0.01, *** = p<0.001

b) Neoplastic - There were no neoplastic lesions considered to have been test article relaed which were observed among males or females sacrificed at 26 weeks or among females in the 52-week interim group. The 7000 ppm males at the 52-week sacrifice showed an increased incidence of adenomas, 7/12 (p<0.05); in the 52-week sacrificed animals only 1/12 males in 500 ppm group developed carcinoma. For the 78-week terminal groups, Tables 10 and 11 summarize the data for unscheduled

deaths and scheduled sacrifices, respectively, and the overall incidence is presented in Table 12. The tumor incidence among unscheduled deaths (Table 10) was similar to that observed in the scheduled sacrifices. There was a significant increase in the occurrence of adenomas (7/16, $p<0.05$) in males at 7000 ppm. In animals sacrificed on schedule (Table 11), significant ($p<0.01$) increases in the incidence of adenomas and carcinomas were observed in the 7000 ppm males ($p<0.01$) and adenomas were increased significantly ($p<0.001$) in 7000 ppm females. The overall incidences of adenomas and carcinomas (Table 12) in both sexes at 7000 ppm were each considerably higher than the maxima of the historical control ranges. In males at 500 ppm, adenomas and carcinomas occurred with frequencies of 17 and 15%, higher than the corresponding mean historical control values of 15 and 6%.

Statistical analysis of neoplastic tissue data indicated significant positive treatment-related trends in the incidence of benign, malignant, and combined benign/malignant liver tumors. Pair-wise comparisons between the 7,000 ppm treatment group and the controls for benign and combined tumor incidences were statistically significant.

Table 10. Liver tumor incidence among **unscheduled deaths** in the 78-week Terminal phase mice fed RPA 201772. a

	Males				Females			
Dose level (ppm)	0	25	500	7000	0	25	500	7000
No. Examined	**15**	**21**	**15**	**16**	**9**	**13**	**13**	**6**
Hepatocellular adenoma	1 (7%)	1 (7%)	1 (7%)	7* (44%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)
Hepatocellular carcinoma	1 (7%)	3 (14%)	3 (20%)	4 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Combined adenoma and carcinoma b	2 (13%)	4 (19%)	4 (27%)	10c (63%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)

a Data obtained from the study report No. 95/0343, Table 11A, p. 128-130.
b Statistical analyses of combined tumor data were not provided; * $p<0.05$
c Some of the animals developed both adenoma and carcinoma.

Table 11. Liver tumor incidence among **scheduled sacrifices** in the 78-week Terminal phase mice fed RPA 201772. a

	Males				Females			
Dose level (ppm)	0	25	500	7000	0	25	500	7000
No. Examined	**37**	**31**	**37**	**36**	**43**	**39**	**39**	**46**
Hepatocellular adenoma	8 (22%)	9 (29%)	8 (22%)	20** (56%)	0 (0%)	1 (3%)	1 (3%)	13*** (28%)
Hepatocellular carcinoma	3 (8%)	2 (6%)	5 (14%)	13** (36%)	0 (0%)	0 (0%)	0 (0%)	3 (7%)
Combined adenoma and carcinoma b	11 (30%)	11 (35%)	10c (27%)	28c (78%)	0 (0%)	1 (3%)	1 (3%)	15c (33%)

a Data obtained from the study report No. 95/0343, Table 11D, p. 132; percentages calculated by the reviewer.
b Statistical analyses of combined tumor data were not provided for the scheduled sacrifices
c Some of the animals developed both adenoma and carcinoma.
** = $p<0.01$; *** = $p<0.001$

Table 12. Overall incidence of liver tumors in mice fed RPA 201772 (78-week terminal phase; scheduled + unscheduled sacrifices). a

No. Examined	**52 Males/Group**				**Historical controls b**	
Dose Level	0	25	500	7000	Mean	Range
Hepatocellular adenoma	9 (17%) †	10 (19%)	9 (17%)	27* (52%)	15.0%	3.8-23.1%
Hepatocellular carcinoma	4 (8%) †	5 (10%)	8 (15%)	17* (33%)	6.28%	1.9-11.5%
Adenomas and/or carcinomas combined	13 (25%) †	15 (29%)	14 (27%)	38* (73%)	Data not provided	
No. Examined	**52 Females/Group**					
Hepatocellular adenoma	0 (0%) †	1 (2%)	1 (2%)	15* (29%)	0.27%	0-2.0%
Hepatocellular carcinoma	0 (0%) ‡	0 (0%)	0 (0%)	4 (8%)	0.55%	0-2.0%
Adenomas and/or carcinomas combined	0 (0%) †	1 (2%)	1 (2%)	18* (35%)	Data not provided	

a Data obtained from the study report No. 95/0343, p. 175-181; percentages calculated by the study reviewer
b Historical control data obtained from the study report No. 95/0343; p. 182-183
* = $p<0.001$ by Pairwise Comparison
† = $p<0.001$ by Trend Test
‡ = $p<0.005$ by Trend Test

Latency period for tumor development. No liver tumors were observed in mice sacrificed at 26 weeks. Table 13 presents the earliest appearances of hepatocellular adenomas and carcinomas among all animals in the 52- and 78-week sacrifices. Adenomas appeared at approximately 1 year in controls and all dose groups of males. Carcinoma appearance, however, showed a clear trend from 78 days in controls to 47 days in the 7000 ppm dose group (the data were not analyzed statistically). In females no adenomas were observed before 77 weeks in any group. Carcinomas were not seen in any control or treated female through 500 ppm; in the 7000 ppm group the onset of carcinomas was 60 weeks. Only 1/12 500 ppm males among unscheduled deaths in the 52-week interim sacrifice developed hepatocellular carcinoma.

Table 13. Latency periods for liver tumor appearance in mice dosed with RPA 201772. a

Time to appearance of the first tumor (weeks) b				
Males (Dose in ppm)	**0**	**25**	**500**	**7000**
Adenoma	52 c	52 c	55	52 b
Carcinoma	78	71	52 c	47
Females (Dose in ppm)	**0**	**25**	**500**	**7000**
Adenoma	None seen	78	78	77
Carcinoma	None seen	None seen	None seen	60

a Data were obtained from Appendices 10B, p. 784-984, 10D, p. 1033-1129, and 10E, p. 1130-1513.
b Findings are from the 78-week Terminal Phase scheduled or in scheduled deaths, unless otherwise indicated.
c Earliest occurrence observed at the 52-week scheduled interim sacrifice.

III. DISCUSSION

A. Investigator's Conclusions

The study author concluded that the LOEL for this study was 500 ppm, based on liver toxicity and a reduction in bodyweight gain in males in this treatment group. The NOEL for this study was 25 ppm.

B. Reviewer's Discussion

We agree with the study author that the LOEL was 500 ppm and the NOEL was 25 ppm in this study.

Male and female CD-1 mice were given RPA 201772 in the diet at 0, 25, 500, and 7000 ppm. The doses were adequate to assess the carcinogenic potential of the test substance and to establish a NOEL. In the Terminal and Interim study phases, 52 mice/sex/dose were scheduled for sacrifice at 78 weeks and 12 mice/sex/dose were scheduled for sacrifice at 52 weeks. Additional interim groups of 12 mice/sex were dosed at 0 and 7000 ppm and sacrificed after 26 weeks. In the 26- and 52-week interim groups, deaths occurred among 2 males and 3 females during weeks 47/48. In the Terminal Phase there was no significant reduction in survival among the treated mice compared with controls. Survival rates were 60-71% among males and 75-88% among females. The unscheduled deaths had similar incidences of clinical and pathological abnormalities as the mice sacrificed on schedule.

The only noteworthy clinical findings were described as "palpable swellings," which appeared in all groups after approximately one year and involved primarily the limbs of males. Ventral abdominal swelling occurred more frequently (although not statistically significantly) in the high dose males than in corresponding controls. Otherwise there was no appearance of a dose relationship in the occurrence of "palpable swellings." The occurrence of the "palpable swellings" was markedly higher in males, involving 10-18/52 male mice, vs 2-6/52 female mice.

After 78 weeks of treatment, the body weights and total body weight gains of male mice in the 500 or 7,000 ppm treatment groups (15 and 28% lower, respectively) and female mice in the 25, 500, or 7,000 ppm treatment groups (16, 22, and 42% lower, respectively) were significantly lower than the controls. For female mice in the 25 or 500 ppm groups, this difference developed between 76 and 78 weeks, during which time the mice in the female control group gained an average 2.7 g.

Food consumption was unaffected by treatment. During the first 14 weeks of treatment, average weekly food conversion efficiencies for males and females in the 7,000 ppm treatment group were 72 and 83%, respectively, of the conversion efficiencies for the controls. Food conversion efficiencies for the 25 or 500 ppm treatment groups were ≥89% of the controls. Food conversion efficiencies were not

determined after 14 weeks.

No treatment-related ocular changes were observed during the study.

The liver was the target organ for RPA 201772 in both sexes exhibiting treatment-related increased weights, being visibly enlarged or swollen, and exhibiting numerous histopathological abnormalities at the high dose, including benign and malignant tumors. The non-neoplastic findings were observed as early as 26 weeks. Male mice were affected more severely than females. Liver changes in animals that were found dead or sacrificed in extremis were similar to those in animals sacrificed on schedule.

Absolute and relative liver weights of male and female mice in the 7,000 ppm treatment group were higher (males: absolute wt.= ≥109%; relative wt.= ≥122%; females: absolute wt.= ≥67%, relative wt.= ≥88%) than the controls, respectively, after 26, 52, and 78 weeks of treatment ($p<0.05$ or 0.01). Absolute liver weights of mice of both sexes in the 500 ppm treatment group were 7-17% higher than the controls after 52 and 78 weeks of treatment; these differences were statistically significant ($p<0.05$) only for females at 52 weeks. Relative liver weights were significantly increased in the 500 ppm males at 52 weeks (+19%, $p<0.05$) and in the 500 ppm females at 78 weeks (+13%, $p<0.05$).

Male and female mice in the 7,000 ppm treatment group were found to have a higher incidence of liver masses. Male mice in the 7,000 ppm treatment group were found to have a higher incidence of enlarged or swollen livers and liver "areas of change". A higher incidence of abdominal distension was also observed in males at 78 weeks. No other treatment-related gross postmortem differences were observed between mice in the 7,000 ppm and the control groups. No treatment-related differences were observed between mice in the 25 or 500 ppm treatment groups and the control group. All abnormalities other than those noted were typical of the species and appeared to occur randomly and sporadically in all study groups.

Microscopic evidence of liver toxicity was observed at the 26-week sacrifice. All of the high dose mice at 26 weeks ($p<0.001$) showed periacinar hepatocytic hypertrophy. Also significant at 26 weeks were findings of hepatocyte necrosis ($p<0.01$; $p<0.001$) and pigmented Kupffer cells ($p<0.001$). At the 52-week sacrifice several lesions were detected with significantly increased frequency, including periacinar hepatocytic hypertrophy, necrosis of individual hepatocytes, and pigment laden hepatocytes and Kupffer cells.

In the 78-week phase, male mice dosed at 500 ppm exhibited increased hepatocyte necrosis ($p<0.05$). Male and female mice in the 7,000 ppm treatment group exhibited an increased incidence of the lesions noted at earlier sacrifices consisting of pigment-laden hepatocytes and erythrocytes in hepatocytes, basophilic foci of hepatocellular alterations (males), and increased ploidy compared (males) to the controls. In addition, mice in the 7,000 ppm treatment group had a higher incidence of systemic amyloidosis involving the thyroid, kidneys, small intestine, stomach, lymph nodes, and heart. Non-neoplastic lesions occurred with similar frequencies in the unscheduled deaths and scheduled sacrifices.

Hepatocellular adenomas were found in males in the 7,000 ppm treatment group sacrificed on schedule after 52 and 78 weeks of treatment ($p<0.01$, respectively), and in females in the 7,000 ppm treatment group after 78 weeks of treatment ($p<0.001$). Hepatocellular carcinomas were found in males in the 7,000 ppm treatment group after 78 weeks of treatment ($p<0.01$). No differences in the incidence of neoplastic tissues were observed between the 25 or 500 ppm treatment groups and the control. Tumors occurred with similar frequency in mice that were found dead or killed in extremis during the study. The overall frequencies of adenomas and carcinomas in males and females at 7,000 ppm in the 78-week study were higher than the maxima of the historical control ranges. The males at 500 ppm (17%) had adenomas (higher than the 15% mean of historical controls).

The latency period for the development of hepatocellular carcinomas appeared to decrease with increased dose, although statistical analysis of the data were not presented. The earliest appearances of carcinoma in males at 0, 25, 500, and 7,000 ppm were 78, 71, 52, and 47 weeks. In females 0, 25, and 500 ppm had produced no carcinomas at 78 weeks; whereas, carcinomas were found at 60 weeks at 7,000 ppm. Statistical analysis of tumor data indicated that there were significant positive treatment-related trends in the incidence of benign, malignant, and combined benign/malignant liver tumors. The benign and combined tumor incidences were statistically significant at 7,000 ppm.

In summary, the following points are pertinent with respect to the carcinogenic potential of RPA 201772:

The 7000 ppm dosage caused significant increases in hepatocellular adenomas in males ($p<0.001$) and females ($p<0.001$).

The 7000 ppm dosage caused significant increases in hepatocellular carcinomas in males ($p<0.001$).

The incidence of hepatocellular carcinomas among 7000 ppm females exceeded the maximum of the historical control range.

At 500 ppm, the incidences of adenomas and carcinomas in males were higher than the mean of historical incidence.

The latency period for the appearance of hepatocellular carcinomas in male and female mice was decreased in a dose-response fashion.

Significant evidence of liver toxicity at 7,000 ppm was observed at the 26-, 52-, and 78-week sacrifices as well as unscheduled deaths.

The incidences of numerous non-neoplastic liver abnormalities were significantly elevated in male and female mice at 7000 ppm. The number of male mice at 500 ppm with individual hepatocyte necrosis was significantly incrased over the control number.

Under conditions of this study, RPA 201772 induced hepatocellular adenomas and carcinomas in male and female CD-1 mice.

The LOEL for this study is 500 ppm, based on decreased body weight gains, increased liver weights, and increased histopathological changes. The NOEL is 25 ppm. Although body weight was marginally decreased in females at 25 ppm, there were no corroborating findings of toxicity at this dose.

IV. STUDY DEFICIENCIES

High mortality and prevalence of "palpable masses" observed in all groups, including controls, indicates poor animal husbandry. These deficiencies do not negatively impact the outcome of the study.

Insufficient Postage

Page _____ is not included in this copy.

Pages 29 through 36 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
