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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Oxyfluorfen; Goal; 6(a)(2) data; 2-Generation Rat Reproduction study; ID # 111601-000707

Tox.Chem No.: 188AAA
MRID No.: 420149-01, -02
HED Project No.: 1-2585
Submission No.: S403949
DP Barcode No.: D169192

TO: Bruce Sidwell, Pm # 53
Reregistration Branch
Special Review and Reregistration Division (H7508W)

FROM: William Dykstra, Ph.D., Toxicologist
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Health Effects Division (H7509C)
William Dykstra 7/12/93

for THRU: Roger Gardner, Section Head, Toxicologist
Review Section 1
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Health Effects Division (H7509C)
Pamela M. Hurley 7/12/93
KB 7/20/93

ACTION REQUESTED: Rohm and Haas Company has submitted a new 2-generation rat reproduction study with oxyfluorfen to replace the existing study on file. The study has mistakenly been identified as 6(a)(2) data by the Registrant in the letter of September 4, 1991, but the MRID Number (41768700-01) cited in the letter refers to the previously reviewed rat teratology study and not the 2-generation rat reproduction study. Additionally, the Registrant has not "flagged" the 2-generation rat reproduction study as 6(a)(2) data in the study report. Toxicology Branch has been requested to review the 2-generation rat reproduction study as part of the reregistration process for oxyfluorfen.

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CONCLUSIONS: The rat reproduction study is acceptable as core-guideline data. There were no compound-related effects in reproductive performance. The NOEL for reproductive/developmental parameters is 400 ppm and the LEL is 1600 ppm (HDT) based on decreased pup body weight during lactation in both the F_1a and F_2a litters and also a decreased litter size at birth in F_1a and F_2a litters.

The parental systemic NOEL is 400 ppm. The LEL is 1600 ppm and the effects include pelvic mineralization of P_1 males, P_2 males and females, and pelvic papillary hyperplasia in P_1 and P_2 males and in P_2 females. Also at 1600 ppm, there were additional kidney effects, consisting of dilatation of collecting ductules in both P_2 sexes. Other high-dose histological findings consisted of hepatocellular hypertrophy in both sexes of P_1 and P_2 animals. Additional high-dose effects were alopecia in both sexes of P_1 and P_2 animals during growth, and decreased weight gain during growth and gestation of P_1 and P_2 parental animals.

Reviewed By: William Dykstra, Ph.D. William Dykstra 7/12/93
Toxicology Branch I - IRS (H7509C)
for Secondary Reviewer: Roger Gardner, Section Head Pamela M. Hurley 7/12/93
Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: 83-4; Two-Generation Reproduction - Rat

Tox Chem. No.: 188AAA

MRID No.: 420149-01
Vol. 1 & 2

Accession Number: N/A

Test Material: Oxyfluorfen technical; 71.4% purity; Lot 2-0956

Synonyms: Goal, Goal Technical

Study Number: Report No. 90R-007

Sponsor: Rohm & Haas Company

Testing Facility: Rohm & Haas Toxicology Department, PA

Title of Report: Two-Generation Reproduction Study in Rats

Authors: H.M. Solomon, W.R. Brown, R.E. Swenson, and T.L. Thomas

Report Issued: August 26, 1991

Conclusions:

The NOEL for reproductive/developmental parameters is 400 ppm and the LEL is 1600 ppm (HDT) based on decreased pup body weight during lactation in both the F_1a and F_2a litters and also a decreased litter size at birth in F_1a and F_2a litters.

The parental systemic NOEL is 400 ppm. The LEL is 1600 ppm and the effects include pelvic mineralization of P_1 males, P_2 males and females, and pelvic papillary hyperplasia in P_1 and P_2 males and in P_2 females. Also at 1600 ppm, there were additional kidney effects, consisting of dilatation of collecting ductules in both P_2 sexes. Other high-dose histological findings consisted of hepatocellular hypertrophy in both sexes of P_1 and P_2 animals. Additional high-dose effects were alopecia in both sexes of P_1 and

P_2 animals during growth, and decreased weight gain during growth and gestation of P_1 and P_2 parental animals.

Classification: Core-guideline

Review:

Two-Generation Reproduction Study in Rats (Rohm & Haas Toxicology Dept. Report No. 90R-007; 8/26/91).

Test Material - Oxyfluorfen; Goal® Technical Herbicide; Lot 2-0956; 71.4% purity; Reddish-Brown Solid.

Animals - Crl:CD®BR (Sprague-Dawley), 21 days old, 30 to 35 g body weight, non-litter mates were received from Charles River Breeding Labs, Inc., Raleigh, NC and were acclimated for 14 days. Tap water and Purina Rodent Chow #5002 M were provided ad libitum. Fresh diets were prepared every two weeks and fed ad libitum. Unused or uneaten diet was discarded as hazardous waste. When the first batch of diets (week 1) was prepared, samples from the top, middle, and bottom of each dietary concentration were collected and submitted for analysis of active ingredient to determine uniformity of the blend and to confirm the intended dietary concentrations. On weeks 3, 7, 11, and about every 8 weeks thereafter until termination, samples from each group were taken and analyzed for proximity to target.

Procedure - Randomized groups of 6 week old 25 male and 25 female Sprague-Dawley rats were fed diets continuously through 10 weeks of growth, during mating (one male per one female), gestation, and lactation until they were euthanized. The dietary levels were 0 (control), 100, 400, and 1600 ppm (ai).

The first parental group was P_1 and produced one generation of litters (F_1a). After weaning, selected F_1a (P_2) animals (25 males and 25 females/dose level) were fed diets from their respective groups for a 14-week growth period and throughout a mating, gestation and lactation period for the second generation of litters (the F_2a). Offspring not selected for mating were necropsied.

Adult female rats (P_1 and P_2) were cohabitated with an assigned male from the same treatment group. Females were observed daily for positive signs of mating. A female was presumed pregnant (Day 0 of gestation) if both a sperm plug was detected in her vagina or on the absorbent paper liner beneath the cage and a lavage sample was positive. Females that did not mate after seven days of cohabitation were placed with a different male from the same treatment group. If possible, a male was used that had copulated successfully during the previous seven days of mating. Females that apparently did not mate during the second seven day period were again placed with a different male from the same treatment group. Females without a confirmed copulation date were removed from the mating cages at the end of the 21-day mating period and were housed in the same manner as the presumed-pregnant females.

Adult animals were observed at least once daily for toxic signs

and were given a clinical examination on a weekly basis.

Body weight and food consumption taken on a weekly basis for the P_1 and P_2 pre-mating periods for males and females and during gestation for females. Female body weight was also recorded during lactation. F_1a and F_2a offspring were observed daily to detect dead or moribund pups. Dead offspring were necropsied. On postpartum (PP) days 0, 4, 7, 14, and 21, the offspring were individually examined and weighed. On day 4 post-partum, litters were culled randomly to 8 (4/sex) when possible. Litters with less than 8 offspring were not culled. On day 21, all maternal animals were separated from their litters and housed separately in suspended, stainless steel cages. Two male and two female offspring were randomly selected from each litter and housed by sex. When the oldest litters reached between 22 and 28 days of age, one male and one female offspring from the pairs of males and females that were saved at weaning were randomly selected to serve as parents (P_2) for the F_{2a} generation. In all, 25 F_{1a} male and female rats were selected to serve as P_2 adults. Remaining offspring were necropsied. Necropsies were performed on all P_1 and P_2 adult males and females. Reproductive organs, liver, kidney, adrenals, pituitary and any gross lesions were preserved in buffered formalin. All tissues collected were examined microscopically at 0 and 1600 ppm and gross lesions and livers and kidneys were examined microscopically from the 100 and 400 ppm groups of P_1 and P_2 rats.

Quality Assurance - A Statement of Quality Assurance was present and signed by Rita K. Brillinger of the Quality Assurance (QA) Unit but not dated. Final report of QA was August 26, 1991.

Statistics - At a $p < 0.05$ level of significance, Fisher's Exact Test was used for incidence of pregnancy, clinical signs, maternal deaths, litters with stillborn, gross necropsy, and histopathology. Dunnett's test when one-way ANOVA was significant was used for parental body weight, parental food consumption, offspring body weight, absolute and relative organ weights, and length of gestation. The Mann-Whitney U test was used for live fetuses/litter, viability index, lactation index, and sex ratio.

When more than 75 percent of the litters were unaffected for a particular parameter, then Fisher's Exact Test was used in place of the Mann-Whitney U test to detect significant differences between groups.

The following indices were calculated and statistically analyzed using the Fisher's Exact test or the Mann-Whitney U test for the P_1 and P_2 adults and for F_1a and F_2a offspring.

$$\text{Male Mating Index (\%)} = \frac{\text{Number of males that mated}}{\text{Number of males used for mating}} \times 100$$

$$\text{Female Mating Index (\%)} = \frac{\text{Number of females that mated}}{\text{Number of females used for mating}} \times 100$$

$$\text{Male Fertility Index (\%)} = \frac{\text{Number of sires}}{\text{Number of males mated}} \times 100$$

$$\text{Female Fertility Index (\%)} = \frac{\text{Number of pregnant females}}{\text{Number of females that mated}} \times 100$$

$$\text{Gestation Index (\%)} = \frac{\text{Number of females producing litters with at least one live pup}}{\text{Number of pregnant females}} \times 100$$

$$\text{Viability Index (\%)} = \left| \frac{\text{Number of pups/litter alive on Day 4 PP}}{\text{Number of pups/litter born alive}} \right| \times 100$$

$$\text{Lactation Index (\%)} = \left| \frac{\text{Number of pups/litter alive at weaning}}{\text{Number of pups/litter alive after culling (Day 4 PP)}} \right| \times 100$$

Results:

A. Analysis of Test Diets

Analysis of diets showed the goal technical was stable for 28 days at room temperature in the diet at all dose levels. Diet concentration analyses ranged between 95 to 114 percent of nominal levels for each of the three dose groups. Homogeneity analyses ranged between 109 to 114% for bottom, middle, and top analyses of the three dose levels. These results indicate that the nominal and analytical concentrations were in close agreement.

B. Mortality and Clinical Signs

1. P_1 Animals

a. Mortality - No compound-related mortalities occurred in P_1 animals. One low-dose female was sacrificed moribund during week 11 (ocular hemorrhage) and one high-dose female was sacrificed moribund at week 3 (teratoma present).

b. Clinical Signs - Although not statistically significant, the incident of alopecia was increased in high-dose males (20/4, 26/4, 28/3, and 105/9 (frequency/animals)) in the control, low-, mid-, and high-dose groups, respectively. Also, high-dose females had a higher incidence of alopecia than other groups (7/2, 5/2, 4/1, and 14/4 in control, low-, mid-, and high-dose groups, respectively.

2. P_2 Animals

a. Mortality

No compound-related deaths were seen in low, or mid-dose male or female or high-dose female rats. One high-dose male rat (90-02366) was sacrificed moribund in week 9 and had pelvic mineralization which was reported as a compound-related finding.

Other non-treatment related deaths include two high-dose males which were sacrificed at weeks 12 and 15 and an additional high-dose male was found dead at week 27. One control female died during gestation in week 15 and one high-dose female was sacrificed moribund during the second week.

b. Clinical Signs

In high-dose males, alopecia occurred more frequently than in other treated or control groups. In males (frequency/animals), alopecia occurred 28/5, 21/2, 34/4, 77/7 in control, low-, mid-, and high-dose groups, respectively. The incidences of these clinical signs in females were comparable between control and treated groups.

C. Parental Animals

1. Body weight and Food Consumption

Observation and Study Week	Dose Group Control	Low	Mid	High
	P_1 Generation Males			
Mean Body Weight (g)				
0	214	213	217	216
10	532	548	568	508
Mean Weight Gain (g)				
0 - 10	318	335	351	292
Mean Total Food Consumption (g/animal/day) 0 - 10	29.4	29.6	30.4	27.4
	P_1 Generation Females			
Mean Body Weight (g)				
0	167	163	164	164
10	304	302	301	286
Mean Weight Gain (g)				
0 - 10	137	139	137	122
Mean Total Food Consumption (g/animal/day) 0 - 10	29.4	29.6	30.4	27.5

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

In the P_1 growth phase of both sexes, body weight and body weight gain were decreased (-8.1%, males and -10.9%, females (BWG) at the high-dose in comparison to controls. The decreases were not statistically significant and are of a borderline nature, but they are considered compound-related because they were also observed in the P_2 growth phase.

Food consumption was also slightly decreased in high-dose males (-6.8%) and high-dose females (-6.7%) in comparison to controls.

Observation and Study Week	Dose Group			
	Control	Low	Mid	High
	P_2 Generation Males			
Mean Body Weight (g)				
0	91	95	86	77*
12	574	585	551	505*
Mean Weight Gain (g)				
0 - 12	483	490	465	428*
Mean Total Food Consumption (g/animal/day)				
0 - 12	29.4	29.6	30.4	27.5
	P_2 Generation Females			
Mean Body Weight (g)				
0	86	85	81	68*
12	326	326	319	300*
Mean Weight Gain (g)				
0 - 12	240	241	238	232*
Mean Total Food Consumption (g/animal/day)				
0 - 12	20.6	20.5	19.6	19.2

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

In the P2 growth phase of both sexes, body weight and body weight gain were statistically significantly decreased (-11.4%, males and -7.9%, females (BWG) in high-dose groups in comparison to controls. In high-dose males, food consumption was decreased by 6.5 percent, and in high-dose females decreased by 6.8 percent. These high-dose findings for body weight and body weight gain are considered borderline biologically significant.

Selected group mean body weights and food consumption values for pregnant or nursing dams were summarized in the report as follows:

Observation and Study Week	Dose Group			
	Control	Low	Mid	High
		P_1 Generation		
Mean Body Weight (g)				
Day 0 of gestation	294	298	301	282
Day 20 of gestation	459	461	461	424*
Day 0 of lactation	340	342	341	334
Day 21 of lactation	352	354	351	345
Mean Body Weight Gain (g)				
Days 0-20 of gestation	165	163	160	142
Day 0-21 of lactation	12	12	10	11
Mean Total Food Consumption (g/animal/day)				
Days 14-21 of gestation	25.2	25.3	26.2	25.5
Days 0-21 of lactation		Data not available		
Days 4-7 of lactation				

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

In P_1 maternal animals, body weight at day 20 was statistically significantly decreased and body weight gain was decreased (-13.9%, BWG) in high-dose dams in comparison to controls. This finding is considered compound-related. Lactation body weights and body weight gains were comparable between control and treated groups in P_1 dams. Also, food consumption during gestation (lactation was not measured) was comparable between control and treated groups.

Observation and Study Week	Dose Group			
	Control	Low	Mid	High
		P2 Generation		
Mean Body Weight (g)				
Day 0 of gestation	337	333	330	309*
Day 20 of gestation	498	485	485	441*
Day 0 of lactation	381	377	374	350*
Day 21 of lactation	375	379	376	352
Mean Body Weight Gain (g)				
Days 0-20 of gestation	161	152	155	132
Day 0-21 of lactation	-6	2	2	2
Mean Food Consumption (g/animal/day)				
Days 14-21 of gestation	27.7	25.6	26.4	26.7
Days 0-21 of lactation		Data not available		
Days 4-7 of lactation				

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

In P_2 dams during gestation, body weight at days 0 and 20 was statistically significantly decreased in high-dose dams in comparison to controls. Body weight gain was also decreased by 18% and is considered a compound-related finding. Body weight was also significantly decreased (-8.1%) at day 0 of lactation in high-dose P_2 maternal animals, but body weight gains during lactation were comparable between control and treated groups. Food consumption was comparable between control and treated groups during gestation.

2. Reproductive performance - Results for the parental animals were summarized in the report as follows:

Observation	Dose Group			
	Control	Low	Mid	High
	P_1 Generation			
Mean Precoital Interval (Days)	3.2	2.8	4.2	2.4
Males				
No. Paired	25	25	25	25
No. Mated (confirmed)	23	20	20	22
No. Impregnating at least one female (of those confirmed)	22	20	18	22
Fertility Index	96	100	90	100
Females				
No. Paired	25	25	25	24
No. Mated (confirmed)	25	24	24	24
No. Pregnant (of those confirmed)	24	24	21	24
Fertility Index	96	100	88	100
No. with signs of normal gestation and delivery	24	24	21	24
(%)	100	100	100	100
Mean duration of gestation (days)	22.5	22.2	22.3	22.5
Gestation Index	100	96	100	100
No. Surviving to Weaning of a litter	24	23	21	24
(%)	100	100	100	100

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

There were no compound-related effects in reproductive performance of P_1 male and female treated animals in comparison to controls. Values were comparable between control and treated groups for all parameters measured.

Observation	Dose Group			
	Control	Low	Mid	High
		P_2 Generation		
Mean Precoital Interval (Days)	6.4	8.7	8.6	7.2
Males				
No. Paired	25	25	25	25
No. Mated (confirmed)	14	16	13	13
No. Impregnating at least one female (of those confirmed)	12	16	13	14
Fertility Index	86	100	100	100
Females				
No. Paired	25	25	25	24
No. Mated (confirmed)	24	22	24	22
No. Pregnant (of those confirmed)	19	21	21	24
Fertility Index	79	95	96	95
No. with signs of normal gestation and delivery	18	21	23	21
(%)	95	100	100	91
Mean duration of gestation (days)	22.7	22.5	22.6	22.8
Gestation Index	95	100	100	91
No. Surviving to Weaning of a litter	18	21	23	20
(%)	100	100	100	100

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

There were no compound-related effects in reproductive performance of P_2 male and female treated animals in comparison to controls. Although the number of males mated/number paired was low, it was low in the control as well as treated groups. All values were comparable between control and treated groups for all parameters measured.

3. Offspring

Viability and clinical signs - Viability of pups during lactation was summarized in the report as follows:

Observation	Control	Low	Mid	High
	F_1a Generation			
Total no. dead pups on Day 0	7	4	0	4
Total no. viable pups on Day 0	361	351	310	321
Live Pups/litter on Day 0	15.0	15.3	14.8	13.4*
Live Pups/litter on Day 4(precull)	14.5	15.1	14.2	12.6*
Total no. viable pups on Day 4 (postcull)	204	187	179	205
Live Pups/litter on Day 4 (postcull)	8.0	8.0	8.0	7.5
Live Pups/litter on Day 7	7.9	8.0	7.9	7.5
Live Pups/litter on Day 14	7.5	7.9	7.9	7.1
Total no. viable pups on Day 21	191	184	177	196
Live Pups/litter on Day 21	7.5	7.9	7.9	7.1
Viability index	97	99	96	91
Lactation index	93	98	99	95
Sex ratio (% males)				
At birth	53	50	50	51
On Day 21	53	49	51	51

*Statistically significantly different from control, $p < 0.05$.
**Statistically significantly different from control, $p < 0.01$.

In F_1a offspring at the high-dose, there was a significant decrease in live pups/litter at Day 0 and day 4 (precull). Based on the data, it appears that there is an effect on litter size at birth in the high dose, which is carried through lactation. There were no compound-related effects in dead pups, lactation indices, or sex ratios.

Observation	Control	Low	Mid	High
	F_2a Generation			
Total no. dead pups on Day 0	8	3	10	0*
Total no. viable pups on Day 0	233	284	287	199*
Live Pups/litter on Day 0	12.9	13.5	12.5	9.9*
Live Pups/litter on Day 4(precull)	12.4	13.2	12.1	9.4*
Total no. viable pups on Day 4 (postcull)	151	177	182	154
Live Pups/litter on Day 4 (postcull)	7.6	7.8	7.4	7.2
Live Pups/litter on Day 7	7.4	7.8	7.4	7.2
Live Pups/litter on Day 14	6.9	7.7	7.0	6.8
Total no. viable pups on Day 21	115	149	155	134
Live Pups/litter on Day 21	6.8	7.4	7.0	6.7
Viability index	91	93	93	95
Lactation index	89	95	96	93
Sex ratio (% males)				
At birth	45	43	48	46
On Day 21	49	47	48	47

In F_2a offspring at the high-dose, there was a significant decrease in live pups/litter at Day 0 and live pups/litter at Day 4 (precull). There was a significant decrease in dead pups at the high-dose. There were no compound-related effects in viability or lactation indices, or sex ratios in treated groups in comparison to controls. Again, it appears that there was an effect on litter size prior to birth at the high dose.

b. Offspring Body Weight

Dose	0	100	400	1600
Means (g)				
Day 0				
F_1a	6.9	6.5	6.4*	5.7*
F_2a	7.0	6.8	7.0	6.2*
Day 4 (precull)				
F_1a	11.0	10.8	10.9	9.7*
F_2a	12.0	11.7	12.5	11.5
Day 4 (postcull)				
F_1a	11.0	10.8	10.9	9.7*
F_2a	12.0	11.7	12.5	11.5
Day 7				
F_1a	18.2	18.3	18.2	16.2*
F_2a	19.2	18.8	19.8	17.2
Day 14				
F_1a	37.7	36.8	36.3	30.5*
F_2a	40.1	38.0	39.2	34.3*
Day 21				
F_1a	59.4	57.4	55.9*	46.8*
F_2a	63.6	59.3	60.6	52.3*
Weight Gain (Day 4 postcull to Day 21) ***				
F_1a	48.4	46.6	45.0	37.1
F_2a	51.6	47.6	48.1	40.8

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*p < 0.05
**p < 0.01
*** Calculated by TB-I Reviewer (no statistical analysis)

It can be seen from pup body weight data that high-dose pups of F_1a and F_2a offspring have statistically significantly lower body weights during lactation than controls. Additionally, day 0 and day 21 body weights of F_1a pups at the mid-dose are statistically significantly decreased in comparison to controls, but were not observed to occur in the F_{2a} litters. The NOEL for pup body weight

is considered to be the mid-dose level (400 ppm).

c. Pup Necropsy Observations

In F_1a pups, there was only one fetus (1 litter) at the high-dose with a malformation (macro-phthalmia). This finding was incidental and not considered compound-related.

In F_1a pups, the following distribution of dilated renal pelvis (papilla reduced, considered to be a variation) was observed:

Dose (ppm)	0	100	400	1600
Kidney (Dilated Pelvis)				
No. Fetuses	6	9	4	8
No. Litters	5	8	4	7

The kidney necropsy findings in F_1a pups were incidental and not considered compound-related.

In F_2a pups, there was one malformed fetus (small left testicle) at the mid-dose and one malformed fetus (ovary enlarged, uterine horn shorted) at the high-dose. These findings are incidental and not considered compound-related. With respect to fetal variations in F_2a pups, the following distribution of fetal variation was observed.

Dose	0	100	400	1600
Kidney (dilated renal pelvis and dilated renal pelvis, papilla reduced)				
No. Fetuses	2	2	0	5
No. Litters	1	1	0	3

The high-dose was not statistically significantly increased and the only other high-dose finding was one fetus (one litter) with ovarian hydrocele. The fetal variations in F_2a litters were incidental and not considered compound-related.

D. Necropsy Observations - P_1 and P_2 Adult Animals

In P_2 males at the mid- and high-dose, there was an increased incidence of gritting material in the kidney pelvis, unilateral. The incidences were 0, 0, 1, 5 out of 25/dose for control, low-, mid-, and high-dose males, respectively.

Additionally at the high-dose in P_1 males and P_2 males, there were increased incidences of alopecia in comparison to controls.

E. Histopathological Findings

1. P_1 Adult Animals

Males and Females - In the kidney, there were statistically significant increased incidences of pelvic mineralization in the high-dose male group in comparison to controls. The incidences were 0/25, 1/25, 3/25, and 7/25 in control, low, mid and high-dose male groups, respectively ($p = 0.004$). Also, there was a borderline statistically significant increase in pelvic/papillary urothelium hyperplasia of the kidney in high dose males (0/25, 0/25, 3/25, and 4/25($p = 0.055$) for control, low-, mid-, and high-dose groups, respectively).

In the liver of both sexes, there were increased incidences of hepatocellular hypertrophy which occurred in males at 1/25, 1/25, 1/25 and 12/25 and in females at 1/25, 0/25, 0/25, and 14/25 in the control, low-, mid-, and high-dose groups, respectively.

2. P_2 Adult Animals

In P_2 males and females in the kidney, there were statistically significant increased incidences of pelvic mineralization at the mid- and high-dose groups. In males, the incidences were 1/25, 1/25, 5/25, and 11/25 ($p < 0.001$) and in females, the incidences were 3/25, 2/25, 8/25 ($p = 0.005$) and 13/25 ($p = 0.003$) for the control, low-, mid-, and high-dose groups, respectively. The findings at the high-dose are considered compound-related. Additionally, at the high-dose in both sexes, there were increased incidences of dilatation of collecting ducts and hyperplasia of the pelvic/papillary urothelium in the kidney.

Dose	0		100		400		1600	
	M	F	M	F	M	F	M	F
Kidney								
Hyperplasia, Urothelium	4	1	5	3	6	2	11*	8**
Dilatation of collecting ducts	0	1	0	0	0	0	11	9

* p = 0.03
** p = 0.012

In the liver of both sexes at the high-dose, there were increased incidences of hepatocellular hypertrophy. The incidences in males were 2/25, 2/25, 1/25, and 17/25 and in females, the incidences were 0/25, 0/25, 0/25 and 8/25 in the control, low-, mid-, and high-dose groups, respectively.

The liver and kidney findings are considered compound-related in both sexes. The NOEL for histological findings is 400 ppm. At the LEL of 1600 ppm, there was hyperplasia of the urothelium of the pelvis, pelvic mineralization and dilation of the collecting ducts of the kidney in both sexes. The liver effects in both sexes also occurred at 1600 ppm.

Discussion: This was a well conducted study. It is classified as Core-Guideline. The reproductive/developmental NOEL is 400 ppm and the LEL is 1600 ppm. The parental systemic NOEL is also 400 ppm and the LEL is 1600 ppm. At first glance, it appeared that there was an effect on pup viability. However, when the data were more closely examined, it became apparent that the effect occurred prior to birth, giving a reduced litter size at the high dose which was carried through the lactation period. In comparing these data with the rat developmental toxicity study, the effect was likely to be from an increase in resorptions (NOEL 18 mg/kg/day, LEL 183 mg/kg/day). A decrease in fetal weights was also observed in the rat developmental toxicity study.