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DATA EVALUATION REPORT

STUDY TYPE: 2-Generation Reproduction TOX. CHEM. NO.: 862B

ACCESSION NUMBER: 265205, 265206, 265207 MRID NO.:

TEST MATERIAL: Triazolyl alanine

SYNONYMS: triazole alanine

STUDY NUMBER(S): CTL/P/1168 (Revised); RR0255

SPONSOR: Ciba Geigy Corp., Agricultural Division (Jointly sponsored by ICI, Bayer AG, Ciba-Geigy, Rohm and Haas)

TESTING FACILITY: Imperial Chemical Industries, PLC: Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK

TITLE OF REPORT: Triazole Alanine: Two-Generation Reproduction Study in the Rat

AUTHOR(S): Milburn, Birtley, Pate, Hollis, Moreland

REPORT ISSUED: 19 August 1986

CONCLUSIONS: No observed effect level for maternal toxicity = 10000 ppm (highest dose tested).

No observed effect level for developmental toxicity = 2000 ppm; lowest observed effect level for developmental toxicity = 10000 ppm. Mean initial pup weights were lowered in F_{1B} males and females at the high dose, and in F_{2A} females at the high dose.

Classification: core-Supplementary. Summary incidence of pup abnormalities was not documented with number of litters showing abnormality or in individual pathology reports. Dose levels may not be sufficiently high to demonstrate parental toxicity. Statistical analysis of reproductive parameters was not performed. Table of males and females mated was not included. Historical control data for the observed abnormalities (eg.: blood clot on heart, imperforate vagina) were not included. Food consumption during pregnancy, lactation and weaning for parents was not reported.

Classification of the study may be upgraded following submission and evaluation of additional data.

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D. Discussion:

1. Dose selection: The rationale for dose selection was not given in the test report. The choice of doses was based on an unspecified "preliminary study". The doses were lower than previously completed studies:
   1. Teratology/rats/0, 100, 300, 1000 mg/kg bw (0, 2000, 6000, 20000 ppm): No deaths were reported prior to sacrifice. (10/13/83)
   2. Subchronic/rat/ HDT = 20000 ppm

The preliminary study should be submitted for consideration by the Agency, along with the rationale for dose selection. The report indicates the compound intake was somewhat less than 500, 2000, and 10000 ppm.

2. Animal numbers, brother-sister matings: The study used 15 males and 30 females per group. The Guidelines suggest 20 males and sufficient females to produce 20 pregnant females. Although an adequate number of pregnant females was produced, the use of only 15 males is marginally acceptable; particularly in view of the fact that a few brother-sister matings occurred due to error by the animal breeding laboratory. Male and female pups from the same litters were delivered by the lab. This resulted in 4 brother-sister matings (one per group) during the first mating (F_{1A}). Three of the litters were normal. The abnormal litter was not identified. Two brother-sister matings occurred during the second mating (F_{1B}) and both resulted in normal litters. F_1 parents were not selected from these litters. This reduced the number of litters from which to choose F_1 parents, a possible source of bias.

3. Statistical Analysis: Statistical analysis of reproductive performance data apparently was not performed. These data should be analysed using appropriate statistical methods since their interpretation is crucial to evaluation of the reproduction study.

4. Bodyweight Data: Tables of absolute bodyweights for animals throughout the study should be given. Instead, bodyweight gains and bodyweights in selected phases of the study were given. A summary table of parental mean absolute bodyweights in the premating and gestation/ lactation/weaning phases of the study should be given.

5. Mating: A table of males and females mated was apparently not given. This information is necessary to distinguish familially related effects from compound related effects.

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6. Food consumption: Food consumption after premating was not reported for F_0 or F_1 parents. There is no information on food consumption during pregnancy, lactation, or weaning. Compound intake cannot be verified for these phases of the study.

7. Incidence of pup abnormalities: Summary table of "Incidence of pup abnormalities" (Table 47, appended page 12) does not indicate number of litters showing the abnormalities and individual pathology reports (Appendix Z) do not reflect the findings of the summary table.

Page_____ is not included in this copy.

Pages 4 through 15 are not included.

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.

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_____ 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.

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Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: Triazole alanine [2-amino-3-(1,2,4-triazol-1-yl) propionic acid] . Description off-white powder; Batch # TLB 1207/018-024 (Y01210/003/005), Purity 97.8% w/w, contaminants in CBI appendix (appended pages 1-2).

2. Test animals: Species: Rat, Strain: Alpk:AP Wistar-derived, Age: 28 days, Mean weight range among groups: 73.9-74.8 g. (males), 70.5-71.5 g. (females), Source: Alderley Park Breeding Unit, Imperial Chemical Industries, PLC, Alderley Park, Macclesfield, Cheshire, UK

B. STUDY DESIGN:

1. Animal assignment

F_0 parental animals were assigned randomly by litter to the following test groups. Appended page 3 shows the allocation of rats to F_0 parental groups. F_1 parents were chosen from F_{1B} litters with 6-18 pups per litter. Thirty females and 15 males were selected from each group.

Test Group	Dose in diet (ppm)*	F_0 matings		F_1 matings	
		male	female	male	female
1 Cont.	0	15	30	15	30
2 Low (LDT)	500	15	30	15	30
3 Mid (MDT)	2000	15	30	15	30
4 High(HDT)	10000	15	30	15	30

2. Diet preparation

Diet was prepared monthly and stored at room temperature ("ambient conditions"). Samples of treated food from the 500 and 10000 ppm preparations from 21 May 1983 were analysed for stability on 27 May, 22 July, 22 August (500 ppm) and on 25 May, 27 July (10000 ppm). Homogeneity was determined from the same preparations, using 4 samples of each.

Results -

Mean concentrations ranged from 476 to 503 over the three month sampling interval and from 9114 to 9609 ppm over the two month sampling interval for stability determination. Deviations from the mean concentration ranged from -2.9 to +2.7 percent for the 500 ppm preparation, and from -4.1 to +3.1 percent for the 10000 ppm preparation.

Triazole alanine was apparently homogeneously distributed in the feed and was stable over the period tested.

3. Animals received food ("control CT1 diet" from Special Diets Services, Stepfield, Witham, Essex, UK) and water ad libitum. Content of the diet is found in appended pages 4-5.

4. Statistics - The following procedures were utilized in analyzing the numerical data: see appended pages 6-8.

5. Quality assurance was signed by J.R. Pateman on 19 August 1986. Twelve inspections or audit of reports, protocols, etc., were made from 4 May 1983 to 14 August 1986.

C. METHODS AND RESULTS:

1. Mating Schedule - Four groups each containing 15 male and 30 female rats were designated the first parental generation in the study (F_0). During the initial 12 weeks of the study, the males were housed individually and females were housed 2 (of the same group) per cage. During the mating period, each male was cohabited with 2 females of the same group. After mating the animals were individually housed. Pregnancy was initially diagnosed by a finding of sperm in vaginal smears examined daily. (Day 1 of pregnancy was the day sperm were observed in the smear.) Pregnancy was confirmed by abdominal enlargement and weight gain. Sperm-positive females which failed to become pregnant were remated as described above. The report did not specify if the same males were used in such rematings.

   Six days after weaning litter A (F_{1A}) the F_0 females were mated to different males for litter B (F_{1B}). From the F_{1B}, 30 females and 15 males were selected to become F_1 parents. F_{1B} litters were separated from the parents at 29 days post partum but litters remained housed together until day 36 post partum. F_1 parents were selected from litters with 6-18 pups.

   F_1 parents were placed on a premating feeding period for 11 weeks after which they were bred to produce F_{2A} and F_{2B} litters as described above for the previous generation.

   The mating schedule is shown in appended page 9. Reproductive performance and litter data are shown in part 5.

2. Observations: Toxicity, Mortality, and Interim Kills

   Animals were inspected daily for signs of toxicity and mortality. Detailed examinations were made at the time of weighing. Mortality and interim kills are reported below with cause of death where apparent.

   Parental Observations

   F_0 Premating (weeks 1-12)- Males showed scabs in 3/15 high dose, in 2/15 mid and low dose, v. 1/15 controls and chromodacryorrhea in 7/15 low dose v. 0/15 controls. Females showed hair loss in 6/30 at the high dose v. 1/30 controls.

   F_0 Mating/Gestation/Lactation - Observations in males were similar to controls. Two control females and one low dose female were found dead following difficult parturition. Hair loss was observed in 6/30 females at the low dose, in 10/30 at the high dose, and in 4/30 controls. One female each in the low and mid doses was

killed after finding no vaginal opening. Imperforate vagina is a congenital anomaly of the Alpk:AP strain of Alderley Park rat, according to the test report, although no documentation was given to support this statement.

F_1 Premating (weeks 1-11)- Observations in males were similar to controls. Females showed coat staining in 5/30 low dose, in 6/30 mid dose and in 3/30 controls. One low dose male was killed in extremis in week 7. This male showed a jaw abnormality (malocclusion) and was hunched and ungroomed.

F_1 Mating/Gestation/Lactation- Males showed coat staining in 4/15 at the high dose and 2/15 controls. One low dose male and 2 mid dose males were killed in extremis: At 32 weeks the low dose male appeared to have a traumatic head injury, at 29 weeks one mid dose male appeared to have been attacked by a female and at histopathology examination the adrenals and pituitary were missing, at 26 weeks another mid dose male was found with hind legs paralyzed, bladder distended, pale kidneys, and minimal hepatitis.

One high dose female was found dead at 30 weeks. Dystocia was diagnosed. Another high dose female was killed at 20 weeks to investigate failure of parturition -18 pups were found in utero and dystocia was diagnosed. One control animal was killed at 28 weeks due to difficult parturition. No underlying cause of dystocia was discovered at pathology examination. Coat staining occurred in almost half of the females at each dose including controls.

Litter Observations

F_{1A} - A few litters showed minimal signs of toxicity such as bruising, small/thin pups, pale appearance and absence of milk in stomach.

F_{1B}, F_{2A}, and F_{2B} showed similar findings with the exception of increased observations of chromodacryorrhea. There were no apparent increases in any of these findings in dose groups as compared to controls.

3. Body weight

Animals were weighed weekly through the premating periods. Males were then weighed every 4 weeks and females were weighed on days 1, 8, 15, and 22 of pregnancy. Day one of pregnancy was the day sperm were observed in the vaginal smear.

Results-

Parental mean absolute bodyweights during premating and pregnancy were similar in control and dose groups.

Parental Bodyweight Gains

F_0 Premating- Males showed no significant differences from controls. Females showed several isolated instances of bodyweights significantly different from controls but the differences showed no pattern or dose relation.

F_1 Premating- Males showed mean bodyweight gains significantly reduced compared to controls during weeks 4-11 at the low and mid doses and during weeks 4-6 at the high dose. Mean bodyweight gains of females during the F_1 premating period were similar to controls.

Selected Bodyweight Gains in F_1 Males - Premating (g)

	0	500	2000	10000 (ppm)
week 4	209.9	195.5**	196.0**	199.3*
week 5	244.0	227.5*	226.9**	232.9
week 6	272.9	252.2**	252.5**	258.3*
week 7	293.9	275.9*	273.3**	283.8
week 8	313.7	295.2*	294.5*	302.8
week 9	333.3	315.8*	313.0*	321.7
week 10	351.7	333.5*	328.9**	339.6
week 11	363.7	347.6	343.6*	354.7

* Statistically significantly different from controls at $p<0.05$.
** Statistically significantly different from controls at $p<0.01$.

All of the weight differences indicated above were at most 8% lower than control bodyweight gains and showed no dose-related trend. The weight gain differences do not therefore appear to demonstrate significant toxicity.

F_0/F_1 Gestation/Lactation/Weaning- Bodyweight gains were similar in controls and dose groups except for days 1-8 in F_0 low dose parents during the first mating (litter A). Bodyweight gain was significantly greater ($p<0.05$) than controls for this interval.

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Litter and Pup Weights

Mean absolute pup weights in dosed animals did not differ significantly from controls, as shown below.

	Mean Pup Weights (g)							
	0		500		2000		10000 ppm	
	M	F	M	F	M	F	M	F
F_{1A}								
Day 1	5.67	5.36	6.05	5.72	5.89	5.60	5.75	5.43
5	pages miss.		9.40	9.15	9.29	8.83	9.14	8.46
11	18.15	17.60	18.90	18.24	18.17	17.10	18.60	17.57
22	41.89	40.58	43.01	40.72	41.90	39.30	43.27	41.07
29	76.46	71.96	78.92	73.20	77.34	69.90	78.73	73.13
F_{1B}								
Day 1	6.40	6.03	6.30	5.83	6.25	5.83	5.91	5.57
5	9.96	9.51	9.74	9.30	10.00	9.42	9.30	8.77
11	19.78	19.17	19.36	18.73	19.56	19.06	18.80	17.87
22	45.43	43.30	44.08	42.08	44.98	42.18	43.56	41.44
29	82.33	76.15	78.92	73.47	81.66	76.24	79.00	73.15
F_{2A}								
Day 1	6.02	5.70	6.28	5.81	6.28	5.87	5.60	5.29
5	9.53	9.32	9.66	9.02	9.72	9.24	8.88	8.55
11	19.23	18.85	19.55	18.53	19.79	18.74	17.95	17.58
22	42.68	41.45	43.30	41.09	44.67	41.99	40.64	39.67
29	78.46	74.59	79.26	73.21	80.96	74.38	76.58	72.22
F_{2B}								
Day 1	6.15	5.83	6.62	6.35	6.34	5.98	5.91	5.53
5	10.73	9.99	11.37	10.88	10.82	10.23	10.21	9.65
11	22.09	21.02	22.89	21.89	21.50	20.57	19.88	19.32
22	48.79	47.06	50.67	48.25	47.63	45.24	44.33	42.95
29	87.35	81.83	90.55	83.89	85.92	78.92	81.44	76.12

Mean initial pup weights were similar in controls and dose groups, with the following exceptions.

	Selected Mean Initial Pup Weights (g)			
	0	500	2000	10000 (ppm)
F_{1A}				
Males				
Initial Weight	5.7+	6.2**	5.9	5.8
Females				
Initial Weight	5.3	5.8**	5.6	5.4
F_{1B}				
Males				
Initial Weight	6.5	6.3	6.3	6.0**
Females				
Initial Weight	6.1	5.9	5.9	5.6**
F_{2A}				
Females				
Initial Weight	5.7	5.8	5.9	5.3*
F_{2B}				
Females				
Initial Weight	5.8	6.3*	6.0	5.6

* Statistically significantly different from controls at $p<0.05$.
** Statistically significantly different from controls at $p<0.01$.
+ Mean values have been adjusted for standard deviation, as part of statistical analysis.

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Mean pup weight gains between day 1 and day 29 were similar in controls and dose groups.

Total litter weights in the F_{1A} generation were significantly lower than controls at the high dose group throughout lactation and weaning and in the mid dose group only initially. Litter weights were similar between controls and dose groups in the F_{1B} generation. In the F_{2A} generation there were significant differences between controls and mid and high dose groups through lactation and weaning and in the F_{2B} generation at the high dose through lactation and weaning, as shown below. Although the differences shown are statistically significant, total litter weight is not considered a sensitive indicator of toxicity since it can vary according to the number of pups and/or litters surviving.

Selected Mean Total Litter Weights (g)

	0	2000	10000 (ppm)
F_{1A}			
Initial	63.7	55.7 (12.5%)+	55.3 (13%)
Day 5	89.5	84.1 (6)	76.9 (14)
11	177.7	169.9 (4)	158.6 (11)
22	406.4	369.1 (9)	363.4 (11)
29	709.8	658.6 (7)	649.4 (8.5)
F_{2A}			
Initial	64.2	58.7(11.7%)	61.3 (7.8%)
Day 5	99.7	85.5 (14)	91.2 (8.5)
Day 11	202.3	172.0*(15)	182.6 (10)
Day 22	445.4	380.1*(15)	413.0 (7)
Day 29	812.5	689.7*(15)	770.3 (5)
F_{2B}			
Initial	64.2	64.9	51.8*(19%)
Day 5	105.7	107.6	88.5*(16)
Day 11	210.2	213.4	168.5**(20)
Day 22	462.7	468.8	372.4**(20)
Day 29	817.7	839.3	671.5*(18)

* Statistically significantly different from controls at $p<0.05$.
** Statistically significantly different from controls at $p<0.01$.
\+ Number in parentheses shows change from control value.

4. Food consumption and compound intake

Method: Consumption was determined for F_0 and F_1 parental animals during their respective premating periods only. Compound intake was measured from diet samples and was calculated in ppm. Efficiency was calculated from food consumption and body weight gains for weeks 1-4, 5-8, and 9-12 (F_0) or 9-11 (F_1) for the premating period.

Compound Intake

Concentration of triazole alanine in the diet was measured in ppm. The conversion to mg/kg/day appears in the following table as the average of several measurements.

Mean Intake of Triazole Alanine (ppm)

Theoretical ppm	Measured ppm	mg/kg+
0	0	0
500	477	23.85
2000	1956	97.80
10000	9586	479.30

+ Calculated from ppm as reported.

Food Consumption

F_0 Premating period- Food consumption was similar in dose groups and controls for both males and females except for males at 2000 ppm. During week 6 consumption for these males was significantly greater than controls. This apparently isolated instance does not appear to be toxicologically meaningful.

F_1 Premating period- Food consumption was similar in dose groups and controls for males and females except at 500 ppm for females where consumption was significantly lower during weeks 7,8, and 11. Total food consumption during the premating period did not appear to differ among dose groups as appears in the following table.

Total Food Consumption/Premating Period (g/rat)

	0	500	2000	10000 (ppm)
F_0 males	2430	2448	2474	2462
F_0 females	1698	1675	1690	1682
F_1 males	2366	2313	2353	2324
F_1 females	1571	1522	1564	1585

Food Utilization

Premating- Efficiency of food utilization was significantly different from controls in several intervals which did not appear to follow a pattern related to dose, as shown in the following table.

Selected Food Utilization (g food/g growth)

	0	500	2000	10000 (ppm)
F_0 parents				
Males- wk 1-4	3.56	3.61	3.60	3.69*
wk 9-12	14.49	12.57**	13.98	13.81
F_0 parents				
Females-wk 9-12	25.77	22.33**	23.65	24.26
F_1 parents				
Males- wk 1-4	3.78	3.93*	3.97*	3.91
Females-wk 9-11	25.74	27.17	39.90*	29.76

* Statistically significantly different from controls at $p<0.05$.
** Statistically significantly different from controls at $p<0.01$.

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When food utilization was calculated for the overall premating period there were no significant differences between controls and dose groups.

Food consumption during gestation/lactation/weaning was apparently not reported. (See Section D. Discussion.)

5. Reproductive Performance and Litter Data

The following table shows the summary of reproductive performance and litter data for both matings in both generations.

Summary of Reproductive Performance and Litter Data
(Adapted from Tables 13A,13B,14A,14B,25A,25B,26A,26B)

	Dose (ppm)							
	F_0 generation				F_1 generation			
	0	500	2000	10000	0	500	2000	10000
Males	15	15	15	15	15	15	15	15
Females	30	30	30	30	30	30	30	30
	First Littering							
No. females paired	29	29	29	30	30	30	30	30
No. w. positive vaginal smear	28	25	27	28	27	29	24	29
No. that littered	26	20	26	25	28	29	28	29
No. viable litters at birth	26	20	26	25	28	29	28	28
No. viable litters at day 1	26	20	26	25	28	29	28	28
No. litters stillborn	0	0	0	0	0	0	0	1
No. litters viable at weaning	24	20	24	24	27	29	28	28
No. pups born live	278	213	254	246	312	320	280	323
dead	19	2	3	2	15	3	11	8
Total pups born	297	215	257	248	327	323	291	331

Reproductive Performance (continued)

	Dose (ppm)							
	F_0 generation				F_1 generation			
	0	500	2000	10000	0	500	2000	10000
Males	15	15	15	15	15	15	15	15
Females	30	30	30	30	30	30	30	30
	Second Littering							
No. females paired	28	29	29	30	30	30	30	30
No. w. positive vaginal smear	28	29	27	24	28	28	27	26
No. that littered	27	27	27	24	27	28	27	26
No. viable litters at birth	27*	26	27	24	27	28	26	26
No. viable litters at day 1	27	26	27	24	27	28	26	26
No. litters stillborn	0	1	0	0	0	0	1	0
No. litters viable at weaning	26	25	27	23	24	27	26	24
No. pups born live	278	282	285	260	257+	255	275	221
dead	2	12	5	8	33	5	5	43
Total pups born	280	294	290	268	290	260	280	264

* Includes one litter with one viable pup but female died with remaining pups in utero.
\+ Excludes one litter not weighed on day 1.

There were decreases in the number of pups born live in the F_{1A} (12% less than controls) and in the F_{2B} (14% less than controls) generations at the high dose only. These differences were apparently due to one less viable litter at the high dose than in controls in each of these generations.

The proportion of fertile animals in the low dose group in the F_0 generation at first mating (Litter A) was 74%. This finding does not appear significant since fertility during the second mating of this group (Litter B) was 93%. Other reproductive parameters in dosed animals were similar to controls.

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6. Histopathology Examination

The examination excluded females with abnormal breeding records, which are reported separately in appended pages 10-11. Controls and high dose animals were examined. Low and mid dose animals were not examined unless gross abnormalities were found.

Histopathology: Microscopic Findings in Parents
(no. observations/no. examined)

	Males				Females			
	0	500	2000	10000	0	500	2000	10000 ppm
F_0 Parents								
Liver								
Inflammatory cell infiltration	1/15	0/0	0/0	3/15	1/30	0/4	0/2	2/30
Pituitary								
cysts	1/15	0/0	0/0	1/15	2/29	0/0	0/0	4/30
Lungs								
alveolar histiocytosis	0/0	0/0	0/0	0/0	0/1	2/3	0/0	0/0
Kidneys								
Nephrocalcinosis	0/15	0/2	0/2	1/15	29/30	3/3	3/3	30/30
Tubular dilatation	3/15	0/2	1/2	6/15	0/30	0/3	0/3	1/30
Hyaline casts	1/15	0/2	1/2	4/15	0/30	0/3	0/3	1/30
Tubular basophilia	2/15	0/2	1/2	3/15	0/30	1/3	0/3	0/30
Ovaries								
Cystic follicle(s) (follicular cysts)	-	-	-	-	5/26	0/3	0/5	3/20
F_1 Parents								
Liver								
Hepatitis	6/15	1/2	1/2	8/15	1/30	0/0	0/1	0/30
Bile duct prolif./fibrosis	4/15	1/2	1/2	5/15	0/30	0/0	0/1	0/30
Kidneys								
Nephrocalcinosis	3/15	0/3	1/4	1/15	29/30	1/1	1/1	30/30
Nephropathy	6/15	0/3	1/4	7/15	0/30	0/1	0/1	1/30
Ovaries								
Follicular cysts (cystic follicle(s))	-	-	-	-	5/25	0/2	0/2	5/28
Luteal cysts	-	-	-	-	2/25	0/2	0/2	4/28
Simple cysts	-	-	-	-	0/25	0/2	0/2	2/28

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Histopathology: Microscopic Findings in Offspring
(no. observed/no. examined)

	Males				Females				
	0	500	2000	10000	0	500	2000	10000	ppm
F_{1A} Offspring									
Kidneys									
Hydronephrosis	4/4	1/1	0/0	1/1	1/1	0/0	1/1	0/0	
F_{1B} Offspring/Full necropsy									
Kidneys									
Nephrocalcinosis	0/5	0/0	0/0	0/4	1/5	0/0	0/0	2/6	
F_{1B} Offspring/Gross necropsy									
Kidneys									
Hydronephrosis	4/4	0/0	3/4	3/3	3/3	0/0	0/0	1/1	
F_{2A} Offspring/Gross necropsy									
Kidneys									
Hydronephrosis	2/2	1/1	3/3	2/2	2/2	2/2	3/3	1/1	
F_{2B} Offspring/Full necropsy									
Kidneys									
Hyronephrosis	1/10	1/1	1/1	3/10	0/10	1/1	0/0	0/10	
Nephrocalcinosis	0/10	0/1	0/1	0/10	0/10	0/1	0/0	4/10	
F_{2B} Offspring/Gross necropsy									
Kidneys									
Hydronephrosis	0/0	1/2	2/2	1/1	2/3	0/0	0/0	0/0	

Histopathology findings were similar in controls and dose groups. A frequent finding was kidney histopathology including nephrocalcinosis and hydronephrosis. However, this observation was of similar frequency in controls and the high dose group except for offspring in the F_{2B} in which nephrocalcinosis was described in 4/10 high dose females and 0/10 controls.

The abnormal breeding records (appended pages 10-11) show similar findings between controls and dose groups. The table of significant pup abnormalities (appended page 12) summarizes abnormalities in each of the four litters produced in the study. In the high dose F_{2B} litters there were 14 pups with ureters kinked and/or dilated. Ten of the 14 pups were from one litter, and the control incidence was 3. In addition, in the high dose F_{2B} litters there were 4 pups with a blood clot on the heart. The significance of this finding and the finding of kinked and/or dilated ureters cannot be evaluated since the individual pathology reports for pups at this dose do not permit verification of the findings in the summary table (appended page 12).

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