UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 6 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Pendimethalin - Review of a Two-Generation Reproduction Study and Individual Animal Data on a Developmental Toxicity Study in Rats (#362-155; 8/17/7) - Expedited Review

TOX Chem No. 454BB
Project No. 1-0435
Submission No. 388356

FROM: William B. Greear, M.P.H. William B Greear 5/9/91
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: Terri Stowe/Lois Rossi, PM Team #74
Registration Branch
Special Review and Registration Division (H7508W)

THRU: Marion P. Copley, D.V.M., Section Head Murphy 8/28/91
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSIONS

The two-generation study, #CBG/2/90 (7/12/90), satisfies guideline requirements (Core-Minimum). The sponsor should submit the time weighted mean consumption values for the test material for each dose level and sex. After examining the individual animal data on the developmental toxicity study in rats, #362-155 (8/17/79), the study does satisfy guideline requirements (Core-Minimum). [DERs attached]

II. REQUESTED ACTION

The Special Review and Reregistration Division has requested that Toxicology Branch I review a 2-generation reproduction study and evaluate individual animal data on a previously submitted developmental toxicity study in rats to determine if the study can be upgraded from Core-Supplementary.

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Reviewed by: William B. Greear, M.P.H. William B. Greear 5/9/91
Review Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. Marion Copley 8/26/91
Review Section II, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT-SUPPLEMENT
(Original DER-DOC#000544)

Study Type: Guideline Series 83-3 Developmental Toxicity - Rat
TOX Chem No. 454BB
MRID No.: 417252-02

Accession No: 241595 (original submission) (original mrid 00025752)

Test Material: AC 92,553

Synonyms: Pendimethalin, PRCWL®

Study Number: 362-155

Sponsor: American Cyanamid Company

Testing Facility: Hazleton Laboratories America, Inc.

Title of Report: Oral Teratology Study in rats AC 92,553 Final Report

New Report: Oral Teratology in Rats - Pendimethalin, Individual animal data

Author: L. H. Mistretta and P. Miller

Report Issued: August 17, 1979

Conclusion: NOEL (developmental) > 500 mg/kg/day (HDT)
NOEL (maternal) ≥ 500 mg/kg/day (HDT)

Classification: Core-Minimum (the highest dose tested did not produce maternal toxicity but the dose level is considered to be adequate and the report is somewhat lacking in detail on skeletal observations)

Study Acceptability: The study satisfies the requirements for a Guideline Series 83-3 Developmental Toxicity Study.

Discussion

The study has been reassessed for its adequacy. The individual animal data is properly reflected in the study summary. However, several problems exist. First, the detail provided in the individual fetal skeletal evaluation is less than desireable. For example, the number of metacarpals and phalanges are grouped into one category In addition, in a study like this one would expect a greater degree of incomplete ossification of the skeletal system. However, the incidence of incomplete ossification was comparable

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among the control and treated groups. The second problem encountered is that the highest dose tested failed to produce maternal toxicity as mentioned in TB-I's memorandum dated 2/15/89, which responded to CDFA's* evaluation of the developmental toxicity study in rats and its deficiencies. (Attached) The sponsor submitted information in a letter dated 1/12/88 in response to CDFA's concerns. The individual animal data were provided. The sponsor also indicated that the highest dosage level used in the teratology study (500 mg/kg/day) was sufficient because in a chronic feeding study (#72R-746; 8/21/74) the highest dose tested of 5000 ppm (250 mg/kg/day) produced significant decrements in body weight in males and females. In addition, the oral LD_{50} in Wistar rats was 1250 mg/kg (see Exhibit 1). The chronic study has been classified a invalid. However, in a recent 2-yr chronic/carcinogenicity study (HLA# 6123-112; 4/20/87) in rats, a dose of 5000 ppm (≈ 250 mg/kg/day) produced significant decreases in body weight gain in males and females. Based on the results of the new chronic study in rats, TB-I believes that the dose levels used in the teratology study were sufficiently high to adequately assess developmental toxicity.

Based on the discussion above, the study is upgraded to Core-Minimum.

* California Department of Food and Agriculture

Exhibit 1

83-3(a) Rat Teratology

EPA informed us that this study was downgraded by the Agency after their review of a California Department of Food and Agriculture (CDFA) review, but that it is upgradable.

We wish to point out that the CDFA has recently upgraded this study to acceptable after review of the individual fetal data which we submitted to them. We are submitting these same data to EPA (Volume 4). For your convenience, following this page are copies of correspondance and reviews from CDFA pertinent to this study.

We do not agree to recondect the study, but wish to upgrade it based on the individual fetal data which we are submitting at this time.

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CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH
SUPPLEMENTAL INFORMATION OR PEER REVIEW WORKSHEET

LAURA WHA
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I. STUDY IDENTIFICATION

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Active Ingredient: pendimethalin
Formulated Product Name: AC 92,553 Prowl® Herbicide
EPA Reg #: ID #: SBDR107696E
Document #: 361-084 Record #: 064624 SB 950 #: 37
Addendum to Document #: 361-042 Addendum to Record #: 002911
Study Type: teratology-833-rat
Full Study Title: Oral Teratology Study in Rats, AC 92,553, Final Report
Company Sponsor: American Cyanamid Co.
Conducting Laboratory: Hazleton Laboratories America, Inc.
Final Report Date: 8/17/79

II. STUDY STATUS

A. Does this supplemental information or peer review lead to a new conclusion regarding the study's acceptability or changes in the status of possible adverse health effects, compared to the most recent review? Yes, study report is now acceptable.

B. STUDY STATUS: Is report complete? - Yes Is study acceptable? - Yes
- Meets EPA guidelines - Has useful data
yes- Minor variances from guidelines - Insufficient data

C. CONCLUSIONS: Does this study as reported demonstrate a possible adverse health effect?: no

D. New "one liner". Summary of the study, its status, and the conclusions, taking into account any supplemental information or peer review changes. 042 002911 "Oral Teratology Study in Rats, AC 92,553, Final Report", (Hazleton Laboratories America, Inc., Project # 362-155, 8/17/79). AC 92,553, 94.2% purity, administered by gavage to CD® rats on days 6 through 15 of gestation: 33-34 females/group at 0 (corn oil), 125, 250, and 500 mg/kg/day. Initial review (J. Wong, 3/8/85) classified report as unacceptable, but possibly upgradeable (insufficient information for assessment; lacking justification of dose levels; also lacking individual fetal data to allow independent evaluation by CDFA). The 3/8/85 review noted possible fetotoxicity (delayed ossification, slight). Report was re-reviewed by C. Aldous (9/21/87), who determined that the slight indication of "delayed ossification of extremities" did not warrant flagging as a "possible adverse effect". Report found acceptable (3/17/89) following submission of individual fetal data (record 084:064624), and considering chronic and acute toxicity data from other rat studies to justify the dosage range tested. Maternal NOEL > 500 mg/kg/day; Developmental effects NOEL = 250 mg/kg/day (slight increase in ossification delays in extremities). No adverse effects. (H. Green, C. Aldous, 3/17/89).

H. Z. Green
Associate Pesticide Review Scientist

3/31/89
Date

Charlie M Aldous 3/21/89
Staff Toxicologist

March 17, 1989
Date

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STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, Gov

DEPARTMENT OF FOOD AND AGRICULTURE

1220 N Street, Room A-400
Sacramento, California 95814

LAURA WHATLEY

APR 18 1990

April 5, 1990

008558

Laura L. Whatley, Ph.D.
American Cyanamid Company
Agricultural Research Division
P. O. Box 400
Princeton, New Jersey 08540

Dear Dr. Whatley:

The Birth Defect Prevention Act of 1984
Data Gap Status: Difference Between CDFA & EPA
Pendimethalin

The California Department of Food and Agriculture (CDFA) has been reviewing health effects data on file and data submitted pursuant to the Food and Agriculture Code, Section 13127 since 1985. Certain studies have also been reviewed by the U.S. Environmental Protection Agency (EPA) and the agency made a different determination than CDFA concerning the filling of data gaps.

Where there are differences between CDFA and EPA regarding study acceptability, CDFA has reevaluated each study and reconsidered our determination of study acceptability. The results of CDFA's reconsiderations are presented in the enclosed Medical Toxicology Response. If changes in data gap status were made, a revised Summary of Toxicology Data and new evaluation worksheets are enclosed.

If you have any questions regarding the status of data gaps for the mandatory health effects studies (SB 950) please contact me.

Sincerely,

Francisco A. Lujano

Francisco A. Lujano
Registration Specialist
Pesticide Registration Branch
(916) 322-3564

mcv/pendi.040490

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III. NATURE OF SUPPLEMENTAL INFORMATION

New data consisted of individual fetal data, including ossification data. The original report (Vol. 042, p. 19) suggested lagging ossification in extremities. The new data in 084:064624 indicated that the quantified measures were "Number of metacarpals and phalanges" in forelimbs, and "Number of metatarsals and phalanges" in hindlimbs. These data were examined in the present CDFA review, and it was apparent that almost all values for "Number of metacarpals and phalanges" in forelimbs were 10 or over for individual fetuses. Similarly, almost all values for "Number of metatarsals and phalanges" in hindlimbs were 9 or above for individual fetuses. Litters with values below the above range were counted. The numbers of litters having fetuses which fell short in at least one of the above values were 2, 3, 4, and 7 for groups control through 500 mg/kg/day, respectively. Affected dams were:

Control
75849 one fetus
75868 5 fetuses

125 mg/kg/day
75884 1 fetus
75898 1 fetus
75899 1 fetus

250 mg/kg/day
75913 4 fetuses
75924 1 fetus
75933 1 fetus
75937 1 fetus

500 mg/kg/day
75948 1 fetus
75949 1 fetus
75950 1 fetus
75952 1 fetus
75954 1 fetus
75972 4 fetuses
75976 2 fetuses

IV. DISCUSSION

The CDFA review of 9/21/87 indicated that two items were needed to upgrade this study: individual fetal data, and justification of dosage levels. The fetal data above sufficed to establish a conservative NOEL of 250 mg/kg/day, based on a slight increase in fetuses which appeared to have delayed ossification of metacarpals, metatarsals, or phalanges. These differences were small, it is equivocal whether they are treatment-related, and they clearly do not constitute indications of "possible adverse effects".

The dose justification provided in the 1/12/88 rebuttal was that there were significant body weight decrements in females in the 1974 chronic study. Indeed, over the course of a longer treatment period with comparable dosage, males and females had marked, statistically significant body weight decrements (see Vol. 9, Record 976069, Table 3). In addition, the acute oral LD50s for male and female Wistar rats were on the order of 1250 mg/kg (see tables in Vol. 009, Tab I), suggesting that the high dose in the teratology study (which used CD® rats) were probably near to the practical limit of exposure. The registrant's response allows an upgrade to acceptable status.

Reviewed by: William B. Greear, M.P.H. William B. Greear 5/7/91
Review Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Marion V. Copley, D.V.M.
Review Section II, Toxicology Branch I (H7509C)

008558

DATA EVALUATION REPORT

Study Type: Two-Generation Reproduction Study-Guideline Series 83-4
TOX Chem No. 454BB
MRID No.: 417252-03

Test Material: AC 92,533

Synonyms: Pendimethalin

Study Number: CBG/2/90

Sponsor: American Cyanamid Company
Princeton, NJ 08543-0400

Testing Facility: Toxicol Laboratories Limited
Ledburg, U. K.

Title of Report: Dietary Rat Two-Generation Reproduction Toxicity Study with AC 92,553

Author: L.F.H. Irvine, P. Boughton

Report Issued: July 12, 1990

Conclusion: NOEL (parental) = 500 ppm (≈ 25 mg/kg/day)
LEL (parental) = 2500 ppm (decreased body weight gain and food consumption in males and females ≈ 125 mg/kg/day)
NOEL (reproduction) = 500 ppm (≈ 25 mg/kg/day)
LEL (reproduction = 2500 ppm (decrease in number of pups born and pup body weight ≈ 125 mg/kg/day)

Classification: Core-Minimum

Study Acceptability: The study satisfies the requirements for a Guideline Series 83-4 Two-Generation Reproduction Study.

[The sponsor should submit the time weighted mean consumption values of the test material for each dose level and sex.]

A. Materials

1. Test compound: AC 92,553, Description: orange-brown lumpy powder, Lot # AC 5213-72A, Purity: 92.6%, Contaminants: not reported.

2. Test animals: Species: Rat, Strain: Sprague-Dawley derived OFA-SD (IOPS-CAW), Age: male 39-41 days, female 40-43 days, Weight: male 160-179g, female 140-159g, Source: Iffa Credo Ltd., Belgium.

B. Study Design:

1. Animal assignment: Animals were assigned to the following test group:

Test Group	Dietary Concentration (ppm)	Number of Animals Assigned P1 Males	P1 Females	F1 Males	F1 Females
1 - Control	0	25	25	25	25
2 - Low	540 (500)*	25	25	25	25
3 - Mid	2700 (2500)	25	25	25	25
4 - High	5400 (5000)	25	25	25	25

* Corrected for stated purity of 92.6%

The animals were housed in one room maintained at a temperature of 22 ± 4°C, relative humidity of 50 ± 20% and a 12-hour on/12-hour off light cycle using fluorescent lights. There were 16 air changes per hour. Note: The animals were individually housed except at the following times:

- when paired for mating, when one male and one female were housed together.
- during lactation, when one female and her litter were housed together,
- when weaned F1b pups were awaiting selection for the F1 generation, where litter-mates of the same sex were housed together, and
- when awaiting the last F1b litters to be weaned and all the cages to be vacated, selected F1 generation pups were temporarily housed two per cage for one week.

2. Diet preparation: Diet was prepared once weekly. Separate formulations were prepared for each dietary level. The treated food was analyzed for concentration of the test material by taking 2 samples from every test diet formulated during the study. Samples were shipped

to the American Cyanamide company weekly for the first four weeks and monthly thereafter. One week prior to the initiation of dosing, a homogeneity and a 14-day stability trial were conducted. Batches of 15 kg of the low-dose and high-dose test diets were formulated by the same methods used in the study. Three sets of 6 random samples were taken from each of low and high diet formulations. The first set was immediately frozen at -20°C. The other 2 sets were placed in separate food hoppers in the animal room. One set was frozen after being stored in the animal room for 7 days and the other set after 14 days. All samples were shipped to the American Cyanamid Company for analysis.

Results: The average concentration of test material in the 500, 2500 and 5000 ppm test diets ranged from 427-559 ppm, 2165-2586 ppm and 4148-5674 ppm, respectively. All values ranged from 85-115% of the nominal values. The average concentration of the test material in the samples taken for analysis of the homogeneity of the 500 and 5000 ppm test diets ranged from 450-494 ppm and 4360-4620 ppm, respectively. All values ranged from 90-99% of the nominal values. The average concentration of test material in the 500 ppm diets stored for 7 or 14 days averaged 455 ppm and 428 ppm, respectively. An average of 4529 ppm and 4557 ppm of the test material was found in the 5000 ppm test diet that was stored for 7 and 24 days, respectively. All values ranged from 86-91% of the nominal concentration.

3. Mating procedure: After a maturation period of 60 days P1 animals and the F1 animals when approximately 100 days old, were mated. One female was placed with 1 male in the same treatment group for a maximum of 10 days. If the female failed to mate, it was paired with another male of the same treatment group for a maximum of 10 days. On day 4 post partum, litters were randomly culled to 8 pups (4 per sex if possible). Sibling matings were avoided. In the first mating period of the F1 generation, the number of successful matings were lower than expected in all groups. Four to 6 females in each group were not pregnant. Therefore all females that failed to mate and all females that mated but were not apparently pregnant when assessed by abdominal palpation, were paired for an additional 7 days with differently randomly selected males. Mating was confirmed by vaginal smear and the day on which sperm were observed was designated as day 0 of gestation. The female was then removed on the day of mating and allowed to litter. On day 20 of gestation the females were examined at least twice per day for signs of parturition up to day 25 of gestation. The day on which parturition was observed was

designated day 0 of lactation and the duration of gestation from the day of mating to completion of parturition was calculated for each female. Pregnant P1 and F1 females were allowed to litter and rear their F1a and F1b and F2a and F2b offspring, respectively, to weaning. At weaning, the first litter of each generation was taken and necropsied. After a period of at least 1 week, the P1 and F1 generation animals were paired again for mating. After weaning the second litters of the first generation, the females were necropsied and the pups were retained until after the selection of the F1 generation was complete. Surplus pups were necropsied. After the weaning of the second litter of the second generation, the females and pups were necropsied. After the majority of F1b litters were weaned at approximate day 28 post-partum, 25 pups of each sex were randomly selected by taking 1 male and 1 female from each litter. Additional pups were taken when needed to obtain 25 animals/sex for mating by random selection from the available weaned litters.

4. Animals received food (powdered SQC rat and mouse No. 3 Breeder diet) and tap water ad libitum.

5. Statistics: Bartlett's test was conducted at the $p<0.05$ level (2-sided) for the data listed below as type 1 in order to determine if the data were normally distributed. The data were treated as normally distributed data because there were few outliers. The data were then analyzed by analysis of variance. Using the F distribution, Dunnett's test ($P<0.05$, 2-sided) was used to determine which means were significantly different from controls. The data were also analyzed by regression analysis to test for trends.

Type 1:

Weekly body weights
Body weight change (pre-mating)
Maternal body weights (pregnancy and lactation)
Maternal body weight change (pregnancy and lactation)
Weekly food consumption
Maternal food consumption (pregnancy)
Duration of gestation
Total number of pups born
Pup body weight (birth through weaning)

For Tier 2 data, a 4X2 Fisher exact test was conducted to determine if the proportion of indices differed ($p<0.05$, 2-sided) between the groups tested. Next, a 2X2 Fisher exact test was used to compare each treatment group to

the control group using $p<0.05$ (1-sided). A test for trend was not conducted because there were no obvious dose-related differences.

Type 2:

Male mating performance
Proportion of females with 1 or more estrus cycles to mate
Male fertility performance
Female mating performance
Female fertility performance
Gestation indices.

For Type 3 data, the Kruskal-Wallis test was used.

Type 3:

Live birth indices
Viability indices
Lactation indices
Cumulative survival indices
Sex ratio of pups at birth

6. Quality assurance was conducted at several intervals during the study. The QAU statement was signed by S. Trenchard-Morgan on July 12, 1990.

C. Methods and Results

Parental Data

1. Observations: All parental animals were observed twice daily for morbidity and mortality. All parental animals were given a full physical examination once per week and a brief clinical examination once daily.

Results: The number of deaths and number of animals sacrificed in extremis is provided in Table 1.

Table 1. Number of Animales Dying or Sacrificed in Extremis

Dietary Concentration (ppm)	P Generation Males	P Generation Females	F1 Generation Males	F1 Generation Females
0	0	0	0	2/25(8%)
500	0	0	0	2/25(8%)
2500	0	0	0	2/25(8%)
5000	0	0	0	1/25(4%)

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Yellow stained urine was observed in all test groups in both generations. Yellow fur staining was observed n the 5000 ppm group and occasionly in the 2500 ppm group, particularly in the first generation. The fur staining was attributed to the rats contact with the yellow colored test material.

2. Body Weight: Weekly body weights of P1 animals were recorded 1 week prior to the start of dosing. Individual male body weights were recorded weekly. Individual female body weights were recorded weekly unless they were pregnant or lactating, in which case body weights were recorded on days 0, 7, 14 and 20 of gestation and on days 0, 7, 14 and 21 of lactation. For F1 animals, weekly bodyweights were recorded after weaning and selection of pups for mating at approximately 4 weeks of age. [Refer to tables 2 and 3]

Results: (Refer to Tables 2 and 3) P1 males in the 2500 and 5000 ppm groups exhibited significantly decreased body weight gain of up to 7 and 9%, respectively, during Week - 1 to 25. P1 females in the 2500 and 5000 ppm groups had decreased body weight gains of up to 7 and 13%, respectively, during weeks 1-9 of the premating period. P1 females in the 5000 ppm group had significant decreases in body weight of up to 15% in production of the F1a and F1b litters during gestation. During lactation P1 females had significantly increased body weight gains (when compared to controls) of up to 29% in the 5000 ppm group and up to 33% in the 2500 ppm group in production of the F1a litters. Body weight gains of approximately 18% were observed in the 2500 and 5000 ppm groups during lactation for production of the F1b litters. F1 males in 5000 ppm group had significant decreases in bodyweight gain of up to 15% during weeks 5 to 30. F1 females in the 2500 and 5000 ppm groups had significant decreases of up to 8 and 21%, respectively, during weeks 4 to 25 of the premating period. During the gestation period F1 females in the 5000 ppm groups exhibited significant decreases in body weight gain of up to 15% in the production of the F2a litters and up to 20% in production of the F2b litters. F1 females in the 2500 ppm group exhibited significant decreases of up to 12% during gestation in the production of the F2b litters. During lactation body weight gain was increased by approximately 14% in females in the 2500 and 5000 ppm group in the production of the F2a and F2b litters (except for the 5000 ppm group F2b litter with a 52% increase). The increases were not statistically significant.

Table 2. Group Mean Body Weight in Grams of P1 and F1 Generation Animals and Percent (%) Decrease Compared to Controls

Dose Level (ppm)	Week											
P1 Males	**-1**	**5**		**10**		**15**		**20**		**25**	
0	211	442		526		594		613		664	
500	211	439	(0.6)	523	(0.6)	590	(0.7)	613		664	
2500	210	419**	(5.0)	488**	(7.2)	556**	(6.4)	577*	(5.9)	628*	(5.4)
5000	211	418**	(5.0)	483**	(8.2)	547**	(7.9)	573**	(6.5)	607**	(8.6)

P1 Females	-1	5		9	
0	170	279		313	
500	170	284		320	
2500	170	266*	(4.7)	292**	(6.7)
5000	170	250**	(10.4)	271**	(13.4)

F1 Males	5		10		15		20		25		30	
0	145		406		511		563		606		629	
500	154		427		537		589		634		662	
2500	141	(0.3)	404	(0.5)	503	(1.5)	556	(0.1)	593	(0.9)	622	(0.1
5000	126**	(13.1)	352**	(13.3)	433**	(15.2)	485**	(13.9)	516**	(14.9)	537**	(13.3

F1 Females	4		9		14		19		25	
0	88		247		304		358		351	
500	92		2 6		312		360		364	
2500	82	(6.8)	236	(4.5)	284*	(6.6)	329**	(8.1)	325*	(7.4)
5000	75**	(14.8)	211**	(14.6)	253**	(20.6)	308**	(14.0)	298**	(15.1)

*Statistically significant at $p < 0.05$
**Statistically significant at $p < 0.01$

Table 3. Group Mean Body Weight Gain Grams and Percent (%) Increase or Decrease Compared to Controls of Dams During Gestation and Lactation

Dose Level (ppm)	Gestation Days 0-20								Lactation Days 0-21							
Dams	P1				F1				P1				F1			
Litters	F1a		F1b		F2a		F2b		F1a		F1b		F2a		F2b	
0	153		154		123		135		8		10		18		21	
500	147	(3.9)	146	(5.2)	126		137		7 (13)		6 (40)		27 (50I)		20 (5)	
2500	148	(3.3)	143	(7.1)	120	(2.4)	119*	(11.9)	26** (325I)		17 (50I)		25 (39I)		28 (34I)	
5000	135**	(11.8)	131**	(14.5)	107	(13.0)	108**	(20.0)	23* (28.8I)		18 (70I)		27 (50I)		32 (52I)	

*Significantly different at $p < 0.05$
**Signficantly different at $p < 0.01$
I = Increase

3. Food Consumption: Food consumption was recorded weekly for males except during the mating period and for females weekly until the start of the first mating period. Food consumption was recorded for females from day 0 to 7, 7 to 14 and 14 to 20 of gestation. Food consumption for females was also recorded for 2 weeks in between the litter rest period. Food consumption was recorded for P1 animals on week-1 (prior to dosing) and for F1 animals on week 5 (5 weeks old).

Results: Food consumption was significantly decreased in P1 males and females in the 5000 ppm group (males 8%, females 14%). At 2500 ppm food consumption was significantly decreased in P1 females in the 2500 and 5000 ppm groups by approximately 10 and 15%, respectively. Food consumption was significantly deceased in F1 males and females in the 5000 ppm group by approximately 11 and 16%, respectively. (See Tables 4 and 5)

4. Compound Intake: The calculated doses of the test material consumed varied from between 23 and 68, 119 and 358 an 228 and 715 mg/kg/day for animals in the 500, 2500 and 5000 ppm groups, respectively. The investigation reported that dose levels stabilized at 25, 125 and 250 mg/kg/day for males and at 35, 175 and 350 mg/kg/day for females in the 500, 2500 and 5000 ppm groups, respectively.

Table 4. Mean Group Food Consumption (g/rat/day) and Percent Decrease Compared to Controls of P1 and F1 Generation Rats

Dose (ppm)	Mean Food Consumption (g/rat/day) Week					
P1 Males	**1**	**5**	**9**	**15**	**19**	**25**
0	29.2	30.7	29.2	31.2	30.8	30.1
500	28.9 (1.0)	31.5	28.9 (1.0)	30.7 (1.6)	30.2 (1.9)	30.1
2500	26.6** (8.9)	28.4** (7.5)	27.4* (6.2)	30.2 (3.2)	29.5 (4.2)	29.8
5000	24.0** (17.8)	28.3** (7.8)	26.6** (8.5)	29.0* (7.1)	28.7 (6.8)	27.7*
P1 Females						
0	21.2	22.2	20.8			
500	21.2	22.3	21.7			
2500	19.5** (8.0)	20.5** (7.7)	19.1* (8.2)			
5000	18.4** (13.2)	19.2** (13.5)	17.8** (14.4)			
F1 Males	**5**	**9**	**13**	**19**	**25**	**30**
0	25.7	31.7	28.9	29.7	27.6	30.8
500	25.4 (1.2)	31.3 (1.3)	31.1*	30.9	29.0	32.2
2500	24.5 (4.7)	29.5* (6.9)	30.3	29.9	28.5	30.9
5000	21.6** (16.0)	26.8** (15.5)	26.9 (6.9)	26.9 (9.4)	24.4 (8.0)	27.2
F1 Females						
0	20.7	23.0	22.0			
500	20.7	22.9 (0.4)	22.7			
2500	19.3** (6.8)	21.1 (8.3)	22.0			
5000	17.6** (15.0)	18.7** (18.7)	21.6 (1.8)			

*Significantly different at $p < 0.05$
**Signficantly different at $p < 0.01$

Table 5. Mean Group Food Consumption (g/rat/day) of Dams During Gestation

Dose (ppm)	P1 (F1a) Gestation Days						P1 (F1b) Gestation Days					
	0-7		7-14		14-20		0-7		7-14		14-20	
0	24.1		26.0		27.7		26.0		27.5		28.6	
500	23.2	(3.7)	25.1	(3.5)	26.3	(5.1)	25.4	(2.3)	26.1	(5.1)	28.4	(0
2500	22.0*	(8.7)	23.4**	(10.0)	26.4	(4.7)	23.5**	(9.6)	24.2**	(12.0)	27.2	(4
5000	20.0**	(17.0)	22.5**	(13.5)	23.9**	(13.7)	22.0**	(15.4)	22.0**	(20.0)	25.4**	(1

	F1 (F2a) Gestation Days						F1 (F2b) Gestation Days					
	0-7		7-14		14-20		0-7		7-14		14-20	
0	23.1		24.6		24.3		23.1		25.8		27.3	
500	22.8	(1.3)	25.0		25.0		23.8		26.4		28.8	
2500	20.9*	(9.5)	23.6	(4.1)	25.0		21.2	(8.2)	23.8	(7.8)	25.6	(6.2)
5000	19.3**	(16.5)	22.2*	(9.8)	21.7	(10.7)	19.7**	(14.7)	22.0**	(14.7)	24.2*	(11

*Significantly different at $p < 0.05$
**Significantly different at $p < 0.01$

5. Gross and Microscopic Pathology: P1 and F1 males were sacrificed at the start of littering of the second litters. P1 and F1 generation females were sacrificed on day 21 post partum after weaning of the second litters. females that failed to mate in the second mating period were sacrificed 26 days after the end of the second mating period. Females that failed to litter in the second mating period were sacrificed 26 days after mating. At necropsy the following tissues were taken. Tissues from males and females in the 5000 ppm group were subjected to microscopic examination:

Testes/Epididymides	Uterus
Seminal vesicles	Ovaries
Prostrate	Vagina
Pituitary	Gross Lesions

Results:

a. Gross necropsy - Yellow stained fur was noted in the 2500 and 5000 ppm groups. (This was believed to be due to physical contact with the test material in the diet.) All other findings were unremarkable.

b. Microscopic pathology - Unremarkable

6. Reproductive Toxicity: The litter size and pup sexes were recorded daily until day 21 post partum. For F1b litters observations continued until selection of the F1 generation animals was completed. Data were reported on the number of matings, number of pregnancies, total number of pups born, litter size, duration of gestation, number of pups alive, number of pups born dead, sex ratio, pup body weight at birth and during lactation. The following indices were calculated: mating index, fecundity index, mean live birth index, mean viability index, mean lactation index and mean cumulative survival index.

Results: (Refer to Tables 6 and 7) The mean number of pups born in the 5000 ppm F2a litter was significantly decreased (21%) when compared to controls. The mean number of pups born was also decreased (15%) in the 5000 ppm F2b litter. The mean number of pups born was slightly (11%) decreased in the 2500 ppm group F2b litters. Mean male pup weights were significantly decreased in the 2500 ppm and 5000 ppm groups in the F1a and F1b litters by approximately 7-11% and 10-21%, respectively, on days 7, 14 and 21 of lactation. Female pup weights in the F1a and F1b litters were significantly decreased in the 2500 ppm and 5000 ppm groups by

approximately 9-14% and 13-21%, respectively on days 7, 14 and 21 of lactation. Male and female F1b pups weights in the 5000 ppm group were also significantly (12%) decreased on day 4 of lactation. Mean body weights of F2a male and female pups in the 5000 ppm group were significantly (11-20%) decreased on days 7, 14 and 21 of lactation. Male and female F2a pups in the 2500 ppm group were also significantly (8-9%) decreased on day 21 (and for females day 14) of lactation. Male and female F2b pups in the 5000 ppm group had significant (28%) decreases in mean pup weight on day 21 (and for males (9%) day 14) of lactation.

Table 6: Reproductive Parameters of P1 Generation

Reproductive Parameters	Test Material (ppm) 0 F1a	0 F1b	500 F1a	500 F1b	2500 F1a	2500 F1b	5000 F1a	5000 F1b
No. Fertile (M)	23	20	19	16	22	23	21	23
Fertility Index (M %)	100.0	95.2	86.4	72.7*	91.7	92.0	95.5	100.0
Mating Index (%)	92.0	84.0	88.0	88.0	96.0	100.0	88.0	100.0
No. Pregnancies	24	23	20	18	23	23	23	23
Mating Index (F %)	96	100	100	96	100	100	100	100
Fecundity Index (%)	100	92	80*	75	92	92	92	100
Mean Gestation Length (Days)	22.0	22.3	22.1	22.1	22.0	22.0	22.0	22.0
Mean No. Pups	15.6	15.9	16.1	15.1	15.7	15.0	14.5	14.6
Mean Live Birth Index (%)	97.5	94.7	98.6	94.1	97.2	97.1	98.9	97.8
Mean Viability Index (%)	91.1	86.5	92.1	93.4	94.0	93.8	96.1	97.1
Mean Lacation Index (%)	98.9	99.4	93.8	92.4	97.3	98.4	98.4	99.0
Mean Cumulative Survival Index (%)	88.7	83.7	88.1	82.4	89.0	89.7	93.6	98.2
Sex Ratio (M:F)	47:53	49:51	47:53	53:47	48:52	52:48	48:52	52:48
Mean Pup BW (M) (Day 0) (g)	6.3	6.4	6.2	6.3	6.3	6.4	6.2	6.3
Mean Pup BW (M) (Day 7) (g)	16.1	16.3	16.6	16.0	15.1	15.2*	14.5*	14.5**
Mean Pup BW (M) (Day 14) (g)	34.4	35.3	34.6	33.7	31.6*	32.2**	29.0**	29.3**
Mean Pup BW (M) (Day 21) (g)	59.9	61.3	59.8	58.9	55.8*	55.2**	48.9**	48.7**
Mean Pup BW (F) (Day 0) (g)	6.0	6.1	5.9	6.1	5.9	6.0	5.9	5.8
Mean Pup BW (F) (Day 7) (g)	15.8	16.0	15.7	15.8	14.4*	13.8**	13.7*	13.7*
Mean Pup BW (F) (Day 14) (g)	34.0	33.8	33.5	33.5	30.4**	29.6**	28.2**	28.0**
Mean Pup BW (F) (Day 21) (g)	58.2	58.7	57.5	57.8	52.6**	50.4**	46.4**	46.2**

*Significantly different at $p < 0.05$
**Significantly different at $p < 0.01$

Table 7: Reproductive Parameters of F1 Generation

Reproductive Parmaters	Test Material (ppm) 0 F2a	0 F2b	500 F2a	500 F2b	2500 F2a	2500 F2b	5000 F2a	5000 F2b
No. Fertile (M)	18	21	14	18	13	21	16	23
Mating Index (M %)	76.0	91.7	60.0	76.0	70.8	95.8	76.0	95.8
Fertility Index (%)	94.7	95.5	93.3	94.7	76.5	91.3	84.2	95.8
No. Pregnancies	24	23	23	20	20	22	23	24
Mating Index (F %)	100.0	100.0	96.0	88.0	95.8	100.0	100.0	100.0
Fecundity Index (%)	96.0	95.8	95.8	90.9	87.0	91.7	92.0	95.8
Mean Gestation Length (Days)	22.0	22.1	22.1	22.2	22.1	22.1	22.3	21.9
Mean No. Pups	14.9	15.0	14.5	14.2	13.9	13.3	11.8*	12.7
Mean Live Birth Index (%)	95.8	95.5	96.0	89.7	98.2	94.4	97.3	95.0
Mean Viability Index (%)	80.9	71.2	76.5	67.1	88.5	85.3	96.5	95.7
Mean Lacation Index (%)	99.4	97.9	99.3	96.4	94.1	94.0	96.7	96.7
Mean Cumulative Survival Index (%)	78.0	68.0	74.0	61.4	83.2	77.9	90.9	87.2
Sex Ratio (M:F)	50:50	52:48	53:47	49:51	52:48	50:50	45:55	55:45
Mean Pup BW (M) (Day 0) (g)	5.9	6.0	6.0	6.1	6.1	6.3	6.1	6.2
Mean Pup BW (M) (Day 7) (g)	15.3	14.2	15.9	14.7	14.9	14.4	13.5**	13.2
Mean Pup BW (M) (Day 14) (g)	31.2	31.5	34.1	31.9	31.1	30.1	27.4**	27.7*
Mean Pup BW (M) (Day 21) (g)	57.4	55.6	59.1	56.3	52.8*	51.3	46.1**	44.6**
Mean Pup BW (F) (Day 0) (g)	5.6	5.7	5.7	5.7	5.8	5.9	5.9	5.9
Mean Pup BW (F) (Day 7) (g)	14.9	13.2	15.0	12.9	14.0	13.4	13.3*	12.6
Mean Pup BW (F) (Day 14) (g)	32.1	29.9	32.4	28.7	29.5*	29.2	27.1**	26.5
Mean Pup BW (F) (Day 21) (g)	55.2	51.5	55.7	51.4	50.1**	49.1	44.6**	42.9**

*Significantly different at $p < 0.05$
**Significantly different at $p < 0.01$

7. Clinical Signs in Pups

Results: Pups in the 5000 ppm group had yellow stained fur which was attributed to contact with the test substance in the diet.

8. Necropsy of Pups

Results: Unremarkable

D. Discussion

Treated rats exhibited yellow stained urine and/or fur which can be attributed to contact with the test material. P1 males and females in the 2500 and 5000 ppm groups had decreases in body weight gain during the pre-mating period. P1 females in the 5000 ppm group had decreases in body weight gain during gestation. Increases in body weight gain were observed during lactation in the 2500 and 5000 ppm groups. F1 males in the 5000 ppm groups exhibited decreases in body weight gain in the pre-mating period. F1 females in the 2500 and 5000 ppm group had decreases in body weight gain during the pre-mating period and during gestation but was increased during lactation. Food consumption was decreased in P1 males and females in the 2500 (females only) and 5000 ppm groups. F1 males and females in the 5000 ppm group exhibited decreases in food consumption. The number of pups born in the F2 litters in the 2500 (F2b only) and 5000 ppm groups was decreased. Male and female F1a, F1b, F2a and F2b pups in the 2500 and 5000 ppm groups had decreases in body weight.

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