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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

Date: January 14, 2004

Subject: SUBJECT: **SULFENTRAZONE** : Review of One-Generation Reproduction Toxicity Study in Rat (MRID 43869101)

PC No.: 129081
DP Barcode No.: D222213
Submission No.: S499170

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I. CONCLUSIONS

The Registration Action Branch I (RAB 1) has evaluated the one-generation reproduction toxicity study in rats (MRID 43869101) and the study is classified as **Acceptable/non-guideline.** The study results confirm the NOAELs/LOAELs for parental, reproductive and offspring toxicity established in the 2-generation reproduction study (MRID 43345408).

Note: DER attached

II. ACTION REQUESTED

FMC Corporation, Princeton, NJ., has submitted a one-generation reproduction toxicity study in rats (MRID 43869101) to clearly identify a NOAEL established in the 2-generation reproduction study (MRID 43345408). The previous study identified reproductive effects at 500 ppm and 700 ppm with equivocal effects noted at the low 200 ppm dose levels. The current study used 50 and 100 ppm dose levles in addition to previously tested 200 and 500 ppm dose levels.

III. STUDY REVIEWED

83-4 One-Generation Reproduction Toxicity Study - Rat; OPPTS 870.3800

CITATION: Barton, S.; Hastings, M. (1995) F6285 Technical: Multi-Generation Reproduction Study in Rats: Elphinstone Research Centre, Inveresk Research International, Tranent, EH33 2NE Scotland. Lab Project Number: 491210: A94-4006: P-3006, 11/22/95. MRID 43869101. Unpublished study.

EXECUTIVE SUMMARY: In a reproduction study (MRID 43869101), Sprague-Dawley rats (28/sex/dose F0; and 24/sex/dose F1) received either 0, 50, 100, 200, or 500 ppm of sulfentrazone Technical (93.5% a.i.) by dietary administration (equivalent to 3.9, 7.8, 16, and 40 mg/kg/day for F0 males; 0, 4.1, 13.4, 16, and 43 mg/kg/day for F0 females; 4.5, 9.2, 18, and 45 mg/kg/day for F1 males; 5.0, 10.1, 20, and 51 mg/kg/day for F1 females, based upon premating intake values). F0 rats received treated diet for a 12-week premating period. Mating performance, gestation, and lactation parameters were evaluated. F1 pups were selected at weaning for the second generation. The age at sexual maturation (vaginal opening or balanopreputial separation) was recorded. F1 rats were mated following a 12-week premating period; the dams were killed on gestation day 20, and uterine contents were examined. Postmortem evaluation of adult rats of both generations included evaluation of weights and histopathology of selected organs (including quantification of oocytes), and epididymal sperm count, motility, and morphology assessments. Due to the absence of second generation lactation data, this study was designated as a one-generation reproduction study.

No mortalities or clinical signs appeared associated with administration of the test material at any dose level. No effects upon mean body weights or weight gain were apparent for F0 males and females, or for F1 males. The mean body weight gain for F1 females during weeks 4-16 was decreased 11% from control values ($p \leq 0.01$). **The NOAEL for parental (systemic) toxicity is 200 ppm (20 mg/kg/day) and the LOAEL is 500 (51 mg/kg/day) based upon a decrease in F1 female body weight gain.**

There were no effects of treatment on mating performance or fertility in males or females of either generation.

Decreased survival was noted in F1 pups at 500 ppm, as evidenced by a decreased number of live pups per litter, an increased number of litters losing more than one pup, and a 2-fold increase in the overall incidence of postnatal pup mortality as compared to controls. Also at 500 ppm, F1 mean pup weights per litter were significantly decreased at postnatal days 1, 4, and 7; and F2 fetal weights were significantly decreased at gestation day 20. Vaginal opening was delayed by approximately 4 days in F1 female offspring at 500 ppm, accompanied by evidence of vaginal threads. In F1 males, significant reductions in mean epididymides, prostate and testes weights were apparent at the 500 ppm treatment level; histopathological evaluation of the reproductive organs did not identify any treatment-related findings. No effects on epididymal sperm count motility or morphology were noted at any treatment level.

In conclusion, offspring/reproductive toxicity is apparent at the high dose level based upon effects in F1 offspring. **The Offspring/Reproductive Toxicity NOAEL is at 200 ppm (16 mg/kg/day) and the Offspring/Reproductive LOAEL is at 500 ppm (40 mg/kg/day)** based upon reduced gestation day 20 fetal weights; decreased postnatal day 0, 4, and 7 pup weights; decreased pup survival; delayed vaginal patency; and reduced epididymides, prostate and testes weights.

The study is classified as **Acceptable/Non-guideline** and does not satisfy the guideline requirement for a reproduction

study (OPPTS 870.3800; §83-4). However, the study data supports the conclusions of the two-generation reproduction study in rats with sulfentrazone (MRID 43345408; FMC Study A92-3545).

EPA Reviewer: Laurence D. Chitlik, DABT
Toxicology Branch (7509C)
Secondary Reviewer: Susan Makris
Toxicology Branch (7509C)

Signature: E.A. Doyle for
Date: 5/14/03
Signature: Susan Y Makris
Date: 5/13/03

TXR#: 0051468

DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility effects Study - Rat/OPPTS 870.3800 [§83-4], OECD 416

P.C. CODE: 129081

DP BARCODE: D222213
SUBMISSION NO.: S499170

TEST MATERIAL (PURITY): Sulfentrazone (93.5%)

SYNONYMS: F6285 Technical

CITATION: Barton, S.; Hastings, M. (1995) F6285 Technical: Multi-Generation Reproduction Study in Rats: Elphinstone Research Centre, Inveresk Research International, Tranent, EH33 2NE Scotland. Lab Project Number: 491210: A94-4006: P-3006, 11/22/95. MRID 43869101. Unpublished study.

SPONSOR: FMC Corporation, Chemical R&D Centre, P.O. Box 8, Princeton, NJ 08543

EXECUTIVE SUMMARY:

In a reproduction study (MRID 43869101), Sprague-Dawley rats (28/sex/dose F0; and 24/sex/dose F1) received either 0, 50, 100, 200, or 500 ppm of sulfentrazone Technical (93.5% a.i.) by dietary administration (equivalent to 3.9, 7.8, 16, and 40 mg/kg/day for F0 males; 0, 4.1, 13.4, 16, and 43 mg/kg/day for F0 females; 4.5, 9.2, 18, and 45 mg/kg/day for F1 males; 5.0, 10.1, 20, and 51 mg/kg/day for F1 females, based upon premating intake values). F0 rats received treated diet for a 12-week premating period. Mating performance, gestation, and lactation parameters were evaluated. F1 pups were selected at weaning for the second generation. The age at sexual maturation (vaginal opening or balanopreputial separation) was recorded. F1 rats were mated following a 12-week premating period; the dams were killed on gestation day 20, and uterine contents were examined. Postmortem evaluation of adult rats of both generations included evaluation of weights and histopathology of selected organs (including quantification of oocytes), and epididymal sperm count, motility, and morphology assessments. Due to the absence of second generation lactation data, this study was designated as a one-generation reproduction study.

No mortalities or clinical signs appeared associated with administration of the test material at any dose level. No effects upon mean body weights or weight gain were apparent for F0 males and females, or for F1 males. The mean body weight gain for F1 females during weeks 4-16 was decreased 11% from control values ($p \leq 0.01$). **The NOAEL for parental (systemic) toxicity is 200 ppm (20 mg/kg/day) and the LOAEL is 500 (51 mg/kg/day) based upon a decrease in F1 female body weight gain.**

There were no effects of treatment on mating performance or fertility in males or females of either generation.

Decreased survival was noted in F1 pups at 500 ppm, as evidenced by a decreased number of live pups per litter, an increased number of litters losing more than one pup, and a 2-fold increase in the overall incidence of postnatal pup mortality as compared to controls. Also at 500 ppm, F1 mean pup weights per litter were significantly decreased at postnatal days 1, 4, and 7; and F2 fetal weights were significantly decreased at gestation day 20. Vaginal opening was delayed by approximately 4 days in F1 female offspring at 500 ppm, accompanied by evidence of vaginal threads. In F1 males, significant reductions in mean epididymides, prostate and testes weights were apparent at the 500 ppm treatment level; histopathological evaluation of the reproductive organs did not identify any treatment-related findings. No effects on epididymal sperm count motility or morphology were noted at any treatment level.

In conclusion, offspring/reproductive toxicity is apparent at the high dose level based upon effects in F1 offspring. **The Offspring/Reproductive Toxicity NOAEL is at 200 ppm (16 mg/kg/day) and the Offspring/Reproductive LOAEL is at 500 ppm (40 mg/kg/day)** based upon reduced gestation day 20 fetal weights; decreased postnatal day 0, 4, and 7 pup weights; decreased pup survival; delayed vaginal patency; and reduced epididymides, prostate and testes weights.

The study is classified as **Acceptable/Non-guideline** and does not satisfy the guideline requirement for a reproduction study (OPPTS 870.3800; §83-4). However, the study data supports the conclusions of the two-generation reproduction study in rats with sulfentrazone (MRID 43345408; FMC Study A92-3545).

COMPLIANCE: Signed and dated GLP (Authentication), Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material:

Description: F6285 Technical, described as a light tan powder.

Lot/Batch #: E8238-106, 2.55 kg received on June 17, 1994.

Purity: Reported to be 93.5% based on data presented in Appendix I, Technical Memorandum for the Test Material dated May 1995, Study Number 162AF94268, performed by FMC Corp, Agricultural Products group, Analytical Sciences, Princeton, N.J.

Stability of compound: Reported as stable for a 12 month period (at room temperature) since a change of only 0.32% was noted at the 12 month interval. Analyses were performed after 1, 2, 3, 6, and 12 month periods with results of 93.6%, 93.5%, 94%, 94.1% and 93.8%, respectively.

2. Vehicle : Technical CGA-152005 was mixed with Rat and Mouse Breeder Diet No. 3SQC (expanded ground).

3. Test animals and environmental conditions:

Species: Rat

Strain: Sprague-Dawley rats of the Charles River CD strain.

Age and weight at study initiation: The rats were reported to be 4 weeks old and weighed approximately 90 grams on arrival. Not more than 2 males or two females were derived from any one litter, siblings were apparently identified.

Source: Charles River Laboratories, UK Ltd, Margate, Kent, England.

Housing: The F0 animals were initially housed 2 per cage. Three days prior to mating, males were transferred to individual cages for mating with females. Mated females were moved to individual cages with bedding. F1 animals selected for breeding of the next generation were housed 2 per sex cage and the F0 procedure was repeated.

Environmental conditions:

Temperature: 20 ± 2 °C (targeted)

Relative humidity: 50% ± 15% (targeted)

Air changes: 15-20 air changes per hour

Photoperiod: Fluorescent lighting was provided on a 12 hour light/dark cycle.

Acclimation period: Animals were quarantined for 10 days prior to initiation of the study.

4. Diet preparation and analysis

Diet was prepared at what the investigators stated to be "appropriate intervals" but these intervals were not provided. The report stated that these diets were used within 5 weeks throughout the study. Diet was formulated by preparing a pre-mix at a concentration of 8000 ppm. This premix was stored at room temperature in the dark. Diets for groups 3-5 were formulated by adding the required premix, while group 2 diet was prepared using the group 5 diet as the premix. This was reported as being a protocol variation which the authors thought did not compromise study conduct. Diets were stored in closed containers at ambient temperature.

Concentration and homogeneity analyses were performed on each batch prior to use. The authors noted that stability was demonstrated via IRI Project No. 372238, FMC Study V94-0020. Actual analyses for concentration and homogeneity were presented in Appendix 5 for July 22, August 12, September 5, September 23, October 14-17, November 3-4, November 24, December 14-15, 1994 and January 6, January 27, February 20, and March 17, 1995. It is assumed that 3 analyses presented at each level were taken from the top, middle and bottom, but they may also be triplicate samples for each batch.

Results -

Homogeneity and concentration analyses: The report states on pg 35, "The generally low values for the coefficients of variation indicated satisfactory homogeneity." However, low mean concentrations were noted in Appendix 5 for the 50 ppm dose level on July 22, 1994 (-13% for batch B), the 100 ppm dose level on February 20, 1995 (-9.0% for batch A and -10.9% for batch B).

Homogeneity data revealed higher coefficients of Variation (%) on July 22, 1994 in the 500 ppm dose level batch B (10.6%) and on March 17, 1995 at the 300 ppm dose level batch B (9.6%).

Stability Analysis: Data presented in Table 1 of Appendix 1 suggest the technical material is stable when stored at room temperature for a 12 month period.

5. Animals received food and water ad libitum. Water was reported to be analyzed periodically for contaminants. The diet was provided with batch analyses for nutritive components and contaminants.

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Dosing began when the F0 animals were about 6 weeks of age and continued for 12 weeks prior to mating to produce the F1 litters. Treatment continued through mating, gestation and lactation and ended at termination after weaning of the litters. Selected F1 animals then received the same dose levels as their parents for the next 13 weeks when the animals were mated. Treatment of the F1 females continued through the mating and gestation periods and ended on Day 20 of gestation, at which time the F1 dams were terminated, and their F2 fetuses were removed by cesarean section. Males were sacrificed after the mating period. Since this study does not include delivery of F2 pups, and an evaluation of the second generation lactation period, it is considered to be a one-generation reproduction study.

Animals were paired on a one to one basis for mating. Females were transferred to a male cage near the end of the work day, for a total of seven nights or until mating was detected. A vaginal lavage was performed each morning. The day on which sperm were detected or when an *in situ* copulatory plug was observed was designated as Day 0 of gestation. The stage of the estrous cycle in each lavage was recorded.

After 7 nights, if no mating was observed for F0 females, they were given a 2 day rest period before the female was cohabited with a second male which had mated previously with another female. After 14 nights with the second male, if no mating was confirmed, attempts to breed this female ceased. F1 females were co-habited with males for 7 nights only. If no mating was confirmed, no further attempts at mating were made and the female was transferred and caged separately.

2. Dose selection rationale: This is a supplemental study performed to study low dose effects observed in a previous study (FMC Study A92-3545; MRID 43345408). The current study used the 200 and 500 ppm dose levels which had been tested previously. The previous study had identified reproductive effects at 500 and 700 ppm with equivocal effects noted at the low 200 ppm dose level. In order to clearly identify a NOAEL, the investigators added two lower dose levels of 50 and 100 ppm.

3. Animal assignment: Animals were assigned to test groups as presented in Table 1.

Table 1. Animal assignment.

Group Number	Treatment Level	Dietary Level (ppm)	No. of Animals Assigned			
			F0 Males	F0 Females	F1 Males	F1 Females
1	Control	0	28	28	24	24
2	Low Dose	50	28	28	24	24
3	Intermediate Dose I	100	28	28	24	24
4	Intermediate Dose II	200	28	28	24	24
5	High Dose	500	28	28	24	24

As noted above, 28 F0 males and females were mated producing a possible 28 litters. On day 21 of lactation, only 24 male and 24 female F1 pups were selected in each treatment group for mating. If possible, one male and one female were selected from each of 24 litters. If this was not possible, a third pup was taken from some litters. When more than 24 litters were available, additional pups were given "spare animal numbers." The disposition of these animals is unclear.

Within each litter, the median'th weight pup of each sex was determined on day 21 of lactation, and these animals were selected for mating of the next generation. They were earmarked and kept with the litter and dam until separation on day 24 of lactation.

4. Daily observations:

All animals were observed daily for clinical signs. In addition, animals were checked for viability twice daily.

The day on which parturition occurred was designated as day 0 of lactation. The duration of gestation was calculated. The number of live born and the number dead in each litter was recorded as soon after parturition as possible. Live pups were sexed, examined for the presence of milk in the stomach, and for the presence of external abnormalities up to day 4 of lactation. In addition, pups were counted and examined on days 7, 14, and 21 of lactation.

Any pups found dead or killed during lactation were sexed and examined. Prior to Day 14, any externally abnormal dead pup were preserved while externally abnormal pups were simply discarded without further examination. After day 14, dead pups were necropsied.

Maternal behavior was noted for inadequate construction and cleaning of the nest, pups

left scattered and cold, physical abuse of pups, or inadequate lactation or feeding.

Selected F1 pups were weaned on lactation day 24, at which time they were removed from their litter. Starting at 30 days of age, all selected F1 females were examined daily for vaginal opening; starting at 35 days of age, all F1 males were examined daily for balanopreputial separation. The day that the landmark was attained, and the body weight of each individual animal on that day, were recorded.

5. Body weights and food consumption:

For F0 animals, body weights and food consumption were recorded one week prior to treatment and determined weekly except during the cohabitation period. Males continued to be weighed weekly until termination. In addition, during gestation, body weights were determined on days 0, 7, 14, and 20, and days 1, 7, 14 and 21 of lactation. After weaning, F1 animals were weighed weekly. During gestation, F1 females were weighed on days 0, 7, 14 and 20. Food consumption was recorded for gestation days 0-7, 7-14, and 14-20. F1 offspring were weighed individually (sexes separately) and by litter on days 1, 4, 7, 14, and 21 of lactation.

During lactation, dam food consumption was determined for days 0-7, 7-14, and 14-21. Measurements were the same for F0 and F1 animals up to day 20 of gestation. Litter size was not standardized on lactation day 4.

6. Terminal sacrifice procedures:

Except for fetuses which were killed by chilling, animals were killed by carbon dioxide asphyxiation.

The gross pathology examination of F0 and F1 animals consisted of an external exam followed by internal examination of the tissues and organs of the cranial, thoracic and abdominal cavities *in situ*. Gross lesions were characterized, and representative samples of abnormal tissues were fixed in neutral buffered formalin. The reproductive tracts were examined for implantations. Carcasses were discarded. The following organs were fixed and weighed as noted:

Ovaries
Uterus, cervix and vagina
Testes: Individually weighed, then fixed in Bouins
Epididymides: Individually weighed. One cauda epididymis submitted for sperm assessment.
Seminal vesicles and coagulating glands: Weighed as a pair
Prostate gland: Weighed
Pituitary gland

F1 adult females were sacrificed on gestation day 20. The reproductive tract was dissected out and opened. The number and location of implantation sites were recorded. Each implant was classified as being live, a fetal death (death occurred after GD 16), a late embryonic death (embryonic remains visible), or an early embryonic death (only early placental remains or a decidual scar visible). Corpora lutea were counted. The total weight of live fetuses was recorded. Following killing by chilling, fetuses were retained in methylated ethyl alcohol for possible evaluation.

Necropsy of pre-weaning offspring found dead or killed on or after Day 14 of lactation consisted of an external examination followed by examination of tissues and organs of the cranial, thoracic and abdominal cavities in situ. Grossly abnormal tissues were preserved and carcasses were discarded.

Examination of offspring found dead or killed before day 14 of lactation consisted of sex determination, and examination for the presence of milk in the stomach and for any external abnormalities. If possible, abnormal pups were fixed in methylated ethyl alcohol for possible examination. Externally normal pups were discarded.

Two male and 2 female F1 weanlings (of those not selected for post weanling assessment/mating) were necropsied. This examination was the same as described above. Grossly abnormal tissues were preserved, and carcasses were discarded. The remaining pups of each litter were externally examined and then killed. Any with external abnormalities were necropsied as described above. Carcasses were then discarded.

Histopathological examination was conducted on testes and epididymides for effects on spermatogenesis. The high dose and control were processed. Representative transverse sections (4-6 μm) were cut from each testis and stained by the Periodic Acid Schiff and Hematoxylin method.

One hundred tubule cross-sections (approx. 50 from each testis) were staged according to the method of Russell et al, 1990. The following evaluations were performed:

Frequency of various stages

Evaluation of each stage for damage or absence of component cell types. The report stated that, "Suitable quantitative methods may be applied, at the discretion of the pathologist and study director."

Tubule diameter for 20 cross-sections per animal

The other available epididymis was examined for any abnormality.

Ten sections were prepared from one ovary for quantitation of the oocytes. A single

section of the other ovary was examined.

Other tissues as listed above from control and high dose animals were processed and examined.

Other (apparently abnormal tissues) were examined only after consultation with the sponsor.

Sperm evaluations for the control and high dose animals are noted below:

Sperm from the cauda epididymis were assessed for the total number of sperm, the number of motile and the number of progressively motile sperm, expressed as a percentage.

A morphological examination was performed on an eosin stained smear from the cauda epididymis. Two hundred were evaluated per animal. A copy of detailed sperm methodology was included in the report procedures.

7. Reproductive Indices:

The study investigators presented the following indices for assessment:

Fertility index	=	No. of pregnant females/siring males ÷ No. paired
Gestation index	=	No.bearing live pups ÷ No. pregnant
Birth index	=	Total no. pups born (live & dead) ÷ No. implantation scars
Live birth index	=	No. of pups live on Day 0 of lactation ÷ Total no. born
Viability index	=	No. of pups live on Day 4 of lactation ÷ No. live on Day 0
Lactation index	=	No. of pups live on Day 21 of lactation ÷ No. live on Day 4
Overall survival index	=	No. of pups live on Day 21 of lactation ÷ Total no. born (live & dead)

8. Statistical analysis:

The authors reported that, "Body weight gains of males from initiation to termination, and for F0 males also from initiation to pairing, were analyzed by analysis of variance (Snedecor and Cochran, 1980). Weight gains of females from initiation to pairing and

over Days 0-20 of gestation were analyzed by analysis of variance. Pairwise comparisons between each treatment level and control were performed using Dunnett's test. Where there was significant heterogeneity of the variances, the Kruskal-Wallis test was used instead. The litter mean pup weights during lactation, and fetal weights on Day 20 of gestation, were analyzed by the Kruskal-Wallis test. For the Kruskal-Wallis test, pairwise comparisons between each treatment level and control were performed using Dunn's procedure. Organ weight data were analyzed by analysis of variance and by analysis of covariance using the terminal body weight as the single covariate. Pairwise comparisons between each treatment level and control were performed using Dunnett's test.

9. Data Retention:

The protocol stated that "IRI was to archive for 5 years (or for such shorter period as, in the opinion of IRI, the quality of the material affords evaluation) following the date of the final report."

II. RESULTS

1. Mortality and Clinical Signs:

There were a total of five premature deaths during the course of the study, all in females. No evidence of a dose response relationship was apparent. In the first generation: 1) F0 control female #154 was sacrificed during week 17 after presenting with staining around the eyes; brown staining around the mouth, forepaws, and ventral surface; piloerection; hunched posture; thin; and pales eyes and ears. Histopathology revealed mild focal subpericardial inflammation of the heart, moderate mucosal atrophy in the ileum, mild cortical tubular vacuolation in the kidneys, mild vacuolation in the liver, white pulp depletion and increased hemosiderin in the spleen, mild focal mucosal inflammation in the stomach, severe cortical atrophy and associated karyorrhexis in the thymus, and arterial thrombosis in the uterus. 2) F0 control female #523 was sacrificed during week 15 due to the appearance of a mass on the right hindlimb. Histopathologic examination revealed plasmacytosis in the lumbar lymph nodes and hyperplasia in the red pulp of the spleen (basal cell tumor). 3) F0 50 ppm female #172 was sacrificed during week 16 after presenting with staining around the nose and forepaws, discharge from the eyes, piloerection and signs of dystocia. This female was found to have 21 live full term fetuses. 4) F0 500 ppm female #274 was sacrificed during week 19 upon evidence of pale color, piloerection, hunched posture, encrusted nose, brown staining on the nose and forepaws, and yellow perigenital staining. Necropsy and histopathology evaluation revealed lymphoma. In the second generation, there was only one death: F1 control female #507 was sacrificed due to a traumatic injury.

Clinical observation data did not identify any findings that were clearly related to treatment. The majority of clinical findings reported consisted of sporadic observations

on the condition of the fur and skin (e.g., hairloss, scruffy coat, scabbing, staining of the fur, or encrusted facial areas), noted for both sexes and generations. Agitated behavior was noted in treated animals of both generations, although without a clear dose response relationship (Table 2). The relationship of this finding to treatment is not apparent.

Table 2. Incidence of agitated behavior [a]

	Dose level (ppm)				
	0	50	100	200	500
F0 Males	0	0	0	0	3
F1 Males	0	0	0	2	1
F0 Females	0	0	1	0	0
F1 Females	0	0	2	3	1

a Data were summarized from MRID 43869101, Tables 1-4, pp. 42-45.

2. Body weight and food consumption:

Mean body weight gain data are summarized in Table 3. There was no statistically or biologically significant effect upon mean body weight or weight gain at any dose level for F0 males or females during the premating, gestation, or lactation periods. In the F1 generation, mean body weight gains were similar between control and treated males. In F1 females, the mean body weight gain for weeks 4-16 was decreased 11% from control values ($p \leq 0.01$). No significant effects on body weight gain were noted for F1 females during the gestation period.

Table 3. Mean body weight gain (g) [a]

	Dose level (ppm)				
	0	50	100	200	500
	F0 Males				
Weeks 0-12	365 ± 45	376 ± 51	358 ± 47	359 ± 53	358 ± 45 (99) [c]
	F0 Females				
Weeks 0-12	177 ± 24	178 ± 26	175 ± 29	174 ± 30	161 ± 24 (91)
Gestation days 0-20 [b]	150 ± 19	159 ± 22	152 ± 27	149 ± 25	144 ± 30 (96)
	F1 Males				
Weeks 4-16	443 ± 47	454 ± 40	440 ± 63	444 ± 50	420 ± 48 (93)
	F1 Females				
Weeks 0-12	244 ± 34	248 ± 27	230 ± 30	227 ± 35	216 ± 18 * (89)
Gestation days 0-20	156 ± 22	168 ± 34	154 ± 18	162 ± 18	149 ± 18 (96)

a Data were summarized from MRID 43869101, Tables 5-10, pp. 46-51.
b Maternal body weight gain values for the lactation period were not presented in the report.
c Percent of control value presented in parentheses.
* Statistically significant ($p \leq 0.05$) compared to control value

No statistically or biologically significant effects upon food consumption were apparent at any dose level.

3. Test substance intake:

Mean test substance intake data for the 12-week premating periods are presented in Table 4. For both generations, test substance intake during the gestation period was similar to the mean female premating intake values. Test substance intake during lactation, which was only measured for the F0 females, was substantially higher, as might be expected (data not shown). The investigators noted that the ratio between achieved dosages was essentially similar to the ratio of the dietary concentrations.

Table 4. Mean test substance intake during premating (mg/kg/day) [a]

	Dose level(ppm)			
	50	100	200	500
F0 Males	3.9	7.8	16	40
F0 Females	4.2	13.4	16	43
F1 Males	4.5	9.2	18	45
F1 Females	5.0	10.1	20	51

a Data were calculated by reviewer from MRID 43869101, Tables 17-20, pp. 58-61.

4. Reproductive performance:

Reproductive performance data for F0 and F1 matings are summarized in Table 5. There were no effects of treatment on mating performance or fertility in males or females of either generation. Although the number of dams with 23 days of gestation was increased at 500 ppm as compared to control (5 versus 1), suggesting a trend towards increased gestation duration, the mean duration of gestation was statistically similar between F0 control and treated dams.

Table 5. Reproductive performance [a]

Parameter	Dose level (ppm)				
	0	50	100	200	500
	F0 parents/ F1 pups				
No. of males paired	28	28	28	28	28
No. of siring males	20	26	23	23	25
Male fertility index (%)	71	93	82	82	89
No. of females paired	28	28	28	28	28
No. pregnant	24	27	25	27	26
Female fertility index (%)	86	96	89	96	93
Median no. of nights to positive sign of mating	3	2	2	2	2

Mean duration of gestation (days)	21.7	21.9	22.0	22.0	22.1
No. delivering at each day: 21	7	5	2	5	3
22	15	19	21	18	18
23	1	2	2	4	5
No. females with live litter	22	26	24	27	26
Gestation index (%)	96	100	96	100	100
Mean (SD) implant sites per pregnancy	17.5 ± 1.6	18.0 ± 2.3	16.7 ± 1.7	16.4 ± 3.5	16.7 ± 3.3
Mean (SD) total no. pups born	16.1 ± 1.5	15.8 ± 2.4	15.1 ± 1.9	14.9 ± 3.4	14.5 ± 3.7
	F1 parents/ F2 fetuses				
No. of males paired	22	24	24	24	24
No. of siring males	21	18	22	22	22
Male fertility index (%)	95	75	92	92	92
No. of females paired	22	24	24	24	24
No. pregnant	21	18	22	22	22
Female fertility index (%)	95	75	92	92	92
Median no. of nights to positive sign of mating	2.5	3	3	3	2

a Data were summarized from MRID 43869101, Tables 21-23, pp. 62-64.

5. Pup survival:

F1 pup survival data are summarized in Tables 6A (litter size and mortality) and 6B (survival indices). These data demonstrate an effect of treatment (decreased survival) at 500 ppm.

Decreases in the number of live pups per litter, which appeared to occur in a dose-dependant manner, were observed during the lactation period. Supporting this finding, the number of litters losing more than one pup was 1, 6, 6, 7, and 8 for the control, 50, 100, 200, and 500 ppm dose groups, respectively. Although no statistical significance was reported relative to the number of pups born live per litter and the number surviving to weaning, a dose response is suggested by these data. The interpretation of these data was compromised by the unusual number of pup deaths in the control group; however, overall postnatal pup mortality at 500 ppm (a total of 108 pup deaths, from 19 litters) was

clearly greater than the control value (a total of 60 pup deaths from 15 litters) and was judged to be a treatment-related effect.

Table 6A. F1 pup litter size and mortality [a]

Parameter	Dose level (ppm)				
	0	50	100	200	500
Mean (SD) no. live pups/litter: PND 0	15.9 ± 1.5	15.3 ± 2.5	14.8 ± 2.0	14.7 ± 3.5	14.5 ± 3.8
PND 1	14.6 ± 2.3	14.6 ± 3.1	14.3 ± 2.3	14.3 ± 3.2	13.0 ± 3.6
PND 4	14.4 ± 2.5	13.8 ± 3.1	14.0 ± 2.3	13.3 ± 3.2	11.9 ± 3.8
PND 7	14.2 ± 2.4	13.4 ± 2.9	13.5 ± 2.2	12.9 ± 3.3	11.5 ± 3.6
PND 14	14.0 ± 2.6	12.6 ± 3.1	13.0 ± 2.8	12.3 ± 3.5	11.0 ± 3.8
PND 21	13.9 ± 2.6	12.6 ± 3.1	13.0 ± 2.7	12.1 ± 3.5	11.0 ± 3.8
No. dead [stillborn] on PND 0 (litters)	36(8) [b]	14(10)	10(7)	6(4)	12(8)
No. dead pups (litters) - PND 0-4	51(13) [c]	52(16) [d]	34(15) [e]	38(13) [f]	60(19) [g]
No. dead pups - PND 4-7	2(2)	11(8)	11(9)	10(7)	11(7)
No. dead pups - PND 7-14	6(5)	21(7)	11(4)	18(9)	20(9)
No. dead pups - PND 14-21	1(1)	0(0)	1(1)	3(3)	15(1)
Dams with total litter loss	2	1	2	0	2

a Data were summarized from MRID 43869101, Table 23, p.64, and Appendices 22-23, pp. 217-226.
b Includes 2 litters with 13 and 16 deaths.
c Includes 2 litters with 11 and 19 deaths.
d Includes 2 litters with 12 and 14 deaths.
e Includes 1 litter with 15 deaths.
f Includes 1 litter with 11 deaths.
g Includes 2 litters with 9 deaths each.

Table 6B. F1 pup survival indices [a]

Parameter		Dose level (ppm)				
		0	50	100	200	500
Birth Index	Mean litter index (%)	93	88	89	91	87
	No. losing >2 pups	4	11	6	3	9
	No. litters	22	26	25	27	26
Live Birth Index	Mean litter index (%)	94	96	94	99	97
	No. losing >2 pups	2	3	2	2	4
	No. litters	23	26	25	27	26
Viability Index Days 0-4	Mean litter index (%)	87	87	90	92	84
	No. losing >2 pups	4	3	1	3	5
	No. litters	22	26	24	27	26
Lactation Index Days 4-21	Mean litter index (%)	97	92	93	91	89
	No. losing >2 pups	1	6	6	7	8
	No. litters	21	25	23	27	25
Overall Survival Index Days 0-21	Mean litter index (%)	79	78	79	83	74
	No. losing >2 pups	5	6	4	8	8
	No. litters	23	26	25	27	25

a Data were summarized from MRID 43869101, Table 24, p.65.

6. Pup body weight:

F1 pup body weight data are summarized in Table 7. F1 pup weights were significantly reduced at the 500 ppm dose level for both sexes on PND 1 ($p \leq 0.001$) and 4 ($p \leq 0.01$ M, $p \leq 0.05$ F), and for males on PND 7 ($p \leq 0.05$).

Table 7. Mean (±SD) F1 pup weight during lactation (g) [a]

Postnatal Day	Dose level (ppm)				
	0	50	100	200	500
	F1 males				
PND 1	6.7 ± 0.5	6.6 ± 0.6	6.7 ± 0.7	6.5 ± 0.8	5.6 ± 0.7***
PND 4	9.8 ± 1.3	9.7 ± 1.4	9.8 ± 1.5	9.5 ± 1.5	8.3 ± 1.7**
PND 7	14.5 ± 1.9	14.8 ± 2.0	15.1 ± 2.2	14.2 ± 2.4	13.0 ± 2.3*

PND 14	28.1 ± 3.0	29.2 ± 2.5	28.6 ± 3.2	29.2 ± 4.3	27.1 ± 4.1
PND 21	46.4 ± 6.1	50.2 ± 5.2	48.1 ± 6.1	50.1 ± 8.5	47.5 ± 6.8
	F1 females				
PND 1	6.3 ± 0.6	6.6 ± 0.5	6.4 ± 0.6	6.0 ± 0.7	5.3 ± 0.7***
PND 4	9.1 ± 1.3	9.3 ± 1.2	9.5 ± 1.3	8.7 ± 1.2	8.0 ± 1.7*
PND 7	13.7 ± 1.5	14.3 ± 1.8	14.5 ± 1.8	13.4 ± 1.8	12.6 ± 2.4
PND 14	26.5 ± 2.7	28.4 ± 3.4	27.8 ± 2.9	27.3 ± 3.8	26.8 ± 4.0
PND 21	43.8 ± 5.3	48.1 ± 6.7	46.3 ± 5.6	46.9 ± 7.3	47.0 ± 6.8

a Data were summarized from MRID 43869101, Table 25, p. 66.
* Significantly different from control value, $p \leq 0.05$.
** Significantly different from control value, $p \leq 0.01$
*** Significantly different from control value, $p \leq 0.001$.

7. Cesarean section data:

Uterine content and ovarian data that were derived from the cesarean section of F1 dams on gestation day 20 are summarized in Table 8. F2 fetal weights were significantly reduced ($p \leq 0.001$) at 500 ppm as compared to control. There were no apparent effects of treatment on mean corpora lutea or implantation data. Mean numbers of live implants, dead fetuses, and early or late resorptions were similar between control and treated groups.

Table 8. Cesarean section data - F1 parents/ F2 fetuses [a]

Parameter	Dose level (ppm)				
	0	50	100	200	500
No. pregnant	21	18	22	22	22
Total no. corpora lutea	369	325	399	380	355
Total no. implants	351	313	377	350	338
Pre-implantation loss (%)	5	4	6	8	5
Total live implant (%)	328 (93)	290 (93)	348 (92)	327 (93)	313 (93)
Total dead implants (%)	23 (7)	23 (7)	29 (8)	23 (7)	25 (7)
Total early resorptions	18 (5)	22 (7)	28 (7)	20 (6)	14 (4)

Total late resorptions (%)	4 (1)	1 (0.3)	1 (0.3)	2 (1)	5 (1)
Total fetal deaths (%)	1 (0.3)	0	0	1 (0.3)	6 (2)
Mean (±SD) corpora lutea	17.6 ± 2.8	18.1 ± 2.1	18.1 ± 2.5	17.3 ± 3.5	16.1 ± 2.2
Mean (±SD) implants	16.7 ± 2.6	17.4 ± 2.6	17.1 ± 2.7	15.9 ± 4.3	15.4 ± 2.6
Mean (±SD) live implants	15.6 ± 2.7	16.1 ± 3.0	15.8 ± 2.9	14.9 ± 4.1	14.2 ± 2.9
Mean (±SD) dead implants	1.1 ± 0.8	1.3 ± 1.0	1.3 ± 1.2	1.0 ± 1.0	1.1 ± 1.6
Mean (±SD) early resorptions	0.9 ± 0.9	1.2 ± 1.0	1.3 ± 1.2	0.9 ± 1.0	0.6 ± 0.8
Mean (±SD) late resorptions	0.2 ± 0.4	0.1 ± 0.2	0.05 ± 0.2	0.1 ± 0.3	0.2 ± 0.4
Mean (±SD) fetal deaths	0.05 ± 0.2	0	0	0.05 ± 0.2	0.3 ± 1.1
Mean (±SD) total uterus wt. (g)	92 ± 17	98 ± 17	92 ± 15	91 ± 15	81 ± 15
Mean (±SD) fetal weight (g)	3.69 ± 0.32	3.74 ± 0.35	3.55 ± 0.20	3.59 ± 0.26	3.28 ± 0.23***

a Data were summarized from MRID 43869101, Tables 25, pp. 67.
*** Significantly different from control value, $p \leq 0.001$.

8. Offspring sexual maturation:

The mean age of sexual maturation for F1 pups is presented in Table 9. The age of vaginal opening was delayed by approximately 4 days in females at 500 ppm, and there was an increase of vaginal threads at that dose. There was no effect of treatment on the age of balanopreputial separation in males.

The authors noted that the assessment of the onset of vaginal opening was complicated by the presence of vaginal threads, but any female offspring with vaginal threads (and therefore delayed vaginal patency) were excluded from the mean calculations. Although the study authors concluded that the incidence of vaginal threads did not indicate any effect on treatment, this conclusion is not justified or supported in the study report. Upon examination of the individual data (MRID 43869101, Appendix 28, pp. 244-245), Agency reviewers noted that the number of female pups with vaginal threads was 1, 0, 1, 2, and 6 in the 0, 50, 100, 200, and 500 ppm groups, respectively. The mean number of days to completion of vaginal patency for those female offspring with vaginal threads was 52.0, N/A, 49.0, 58.0, and 59.3, in the 0, 50, 100, 200, and 500 ppm groups, respectively. Including these female offspring in the calculation of mean age of vaginal opening revealed a delay of approximately 4 days for the 500 ppm F1 females as compared to control. Agency reviewers concluded that these findings were related to treatment.

Table 9. Mean (±SD) age of F1 sexual maturation (days) [a]

Parameter	Dose level (ppm)				
	0	50	100	200	500
	Males (N = 24)				
Age at preputial separation	44.0 ± 2.8	44.0 ± 2.1	43.5 ± 2.8	43.0 ± 1.6	43.6 ± 1.8
Weight (g) at preputial separation	224 ± 18	232 ± 19	223 ± 30	222 ± 22	215 ± 20
	Females (N = 24)				
Age at vaginal opening [b]	34.9 ± 3.8	34.5 ± 3.0	35.9 ± 3.5	34.0 ± 2.8	34.3 ± 2.4
Weight (g) at vaginal opening [b]	124 ± 17	130 ± 20	136 ± 25	123 ± 17	126 ± 13
Age (g) at vaginal opening [c]	37.8 ± 6.9	34.5 ± 2.4	39.0 ± 5.5	36.2 ± 7.4	33.7 ± 1.3

a Data were summarized from MRID 43869101, Table 27, p. 68.
b Excluding female pups with vaginal threads.
c Including female pups with vaginal threads. Number of affected pups presented in parentheses. Values calculated by reviewer; statistical analysis not performed.

5. Pathology:

a. Necropsy findings:

Necropsy findings did not reveal any apparent relationship to treatment.

b.Organ weights:

Mean relative male reproductive organ weight data are summarized in Table 10. In F0 males, the mean weights of the epididymides, seminal vesicles and testes were unaffected. F0 prostate weights were statistically significantly increased only at the 50 ppm dose level. Therefore, it is unlikely that this finding is associated with treatment.

In F1 males, statistically significant reductions in mean covariate adjusted prostate and testes weights were apparent at the 500 ppm dose levels (Table 10). Absolute epididymides weights were decreased ($p \leq 0.05$) at 500 ppm as compared to control (1.2820 g for 500 ppm F1 males versus 1.3811 g for controls), but relative epididymides weight (adjusted using terminal body weight as the covariate factor) demonstrated no significant difference from control for any treated group.

Table 10. Mean relative (covariate adjusted) male organ weight data (g) [a]

Organ		Dose level (ppm)				
		0	50	100	200	500
		F0				
Epididymides	Mean SE	1.4971 0.0262	1.4650 0.0262	1.4759 0.0267	1.4963 0.0262	1.5019 0.0262
Prostate	Mean SE	0.85 0.04	1.03** 0.04	0.87 0.04	0.86 0.04	0.94 0.04
Seminal vesicles	Mean SE	2.282 0.097	2.382 0.097	2.262 0.097	2.249 0.097	2.291 0.097
Testes	Mean SE	3.77 0.07	3.78 0.07	3.70 0.07	3.89 0.07	3.74 0.07
		F1				
Epididymides	Mean SE	1.3753 0.0242	1.3512 0.0242	1.3523 0.0242	1.3450 0.0242	1.3082 0.0242
Prostate	Mean SE	0.79 0.04	0.76 0.04	0.73 0.04	0.70 0.04	0.65* 0.04
Seminal vesicles	Mean SE	2.577 0.083	2.818 0.083	2.669 0.083	2.730 0.083	2.605 0.083
Testes	Mean SE	3.75 0.06	3.80 0.06	3.70 0.06	3.68 0.06	3.46** 0.06

a Data were summarized from MRID 43869101, Tables 29 and 31, p. 70 and 72. Organ weight analysis was conducted using body weight as the covariate factor.

* Significantly different from control value, $p \leq 0.01$.

** Significantly different from control value, $p \leq 0.01$.

c. Qualitative histopathology findings:

Histopathology findings on the male reproductive organs are presented in Table 11. These findings are of low incidence and for that reason were judged to be unrelated to administration of the test material.

Table 11. Incidence of histopathological findings in male reproductive organs [a]

Organ	Observation/Finding [b]	Dose level (ppm)	
		0	500
F0 Males			
Testes	Unilateral tubular atrophy	1	1
Testes	Focal tubular atrophy	0	1
Testes	Tubular epithelial sloughing	2	0
Epididymides	Lymphocytic infiltration	3	2
Epididymides	Inflammation	0	2
Prostate	Interstitial lymphocytic infiltration	2	0
Prostate	Interstitial inflammatory cell infiltrate	1	0
Seminal vesicles	Focal cystic dilatation	1	0
F1 Males			
Testes	Unilateral tubular atrophy	0	1
Testes	Focal tubular atrophy	0	1
Testes	Focal vaculitis	1	0
Epididymides	Lymphocytic infiltration	3	1
Epididymides	Focal inflammation	1	1
Prostate	Interstitial mononuclear cell infiltrate	6	5
Prostate	Interstitial inflammatory cell infiltrate	1	0
Prostate	Chronic inflammation	1	3

a Data were summarized from MRID 43869101, Tables 1 and 3, p. 42 and 44.
b Only control and 500 ppm (high-dose) animals were evaluated.

d. Sperm analysis:

Results of sperm analyses (epididymal sperm count, motility, and morphology assessments) are summarized in Table 12. No effects on sperm count, motility, percent progressively motile sperm, and VSL (straight line velocity) were apparent for F0 and F1 males at any dose level. Morphological assessment of control and high dose male sperm

revealed no increase in abnormalities, either including or excluding tail defects. Additionally, there were no differences between control and treated groups in the mean number of sperm tubules at stages 1 through 14. No effects were apparent in Stage VII tubule diameter.

Table 12. Mean (±SD) sperm assessment findings [a]

Parameter	Dose level (ppm)				
	0	50	100	200	500
	F0				
Sperm count (x 10^{-4})	3.3 ± 0.9	3.7 ± 1.0	3.2 ± 1.2	3.9 ± 1.3	3.5 ± 1.2
Motile (%)	91.3 ± 8.9	89.7 ± 8.5	89.5 ± 7.0	90.8 ± 6.9	87.7 ± 11.2
Progressively motile (%)	22.5 ± 4.1	19.9 ± 6.8	19.3 ± 3.8	22.2 ± 5.3	19.4 ± 8.3
Straight line velocity (µm.s^{-1})	125.6 ± 26.5	111.6 ± 25.3	116.6 ± 21.3	120.0 ± 25.7	112.1 ± 28.7
Stage VII tubule diameter	26.1 ± 1.3	NE	NE	NE	26.1 ± 1.1
Percent abnormal sperm (including tail defects)	0.09 ± 0.24	NE	NE	NE	0.05 ± 0.16
Percent abnormal sperm (excluding tail defects)	0.02 ± 0.09	NE	NE	NE	0.04 ± 0.13
	F1				
Sperm count (x 10^{-4})	3.8 ± 1.4	3.9 ± 1.1	3.7 ± 1.4	4.2 ± 1.4	3.2 ± 1.2
Motile (%)	88.2 ± 10.2	87.9 ± 10.5	88.4 ± 13.3	87.5 ± 8.1	87.3 ± 8.6
Progressively motile (%)	20.7 ± 9.8	23.2 ± 10.0	21.7 ± 10.8	18.4 ± 7.3	19.5 ± 8.3
Straight line velocity (µm.s^{-1})	92.4 ± 27.8	100.0 ± 33.2	95.0 ± 30.9	88.3 ± 30.8	91.9 ± 22.6
Stage VII tubule diameter	25.7 ± 1.0	NE	NE	NE	25.6 ± 1.0
Percent abnormal sperm (including tail defects)	0.19 ± 0.36	NE	NE	NE	0.10 ± 0.25
Percent abnormal sperm (excluding tail defects)	0.10 ± 0.25	NE	NE	NE	0.04 ± 0.14

a Data were summarized from MRID 43869101, Table 32 and 33, p. 73 and 74.
NE = Not evaluated.

e. Oocycte count:

A quantitative assessment of the ovary (summarized in Table 13) did not indicate any effects on the number of oocytes/follicles after evaluations of a single layer, multiple layers, and antral area. The procedures used in this evaluation were not clearly described.

Table 13. Mean (±SD) number of oocytes/follicles [a]

Oocytes/Follicles	F0		F1	
	Dose level (ppm)		Dose level (ppm)	
	0	500	0	500
Single layer	104 ± 57	110 ± 60	140 ± 53	134 ± 53
Multiple layer	32 ± 11	33 ± 15	20 ± 9	21 ± 6
Antral	24 ± 15	27 ± 20	67 ± 26	67 ± 23
Total	160 ± 66	170 ± 80	227 ± 70	221 ± 65

a Data were summarized from MRID 43869101, Table 34, p. 75.

III. DISCUSSION AND CONCLUSIONS

A. Systemic and Reproductive Toxicity:

No mortalities or clinical signs appeared associated with administration of the test material at any dose level.

No effects upon mean body weights or weight gain were apparent for F0 males and females. The mean weight gain for F1 females during weeks 4-16 at the high dose level (500 ppm) was reported as statistically significantly reduced ($p<0.01$) at 216 ± 18 grams while 244 ±34 grams was observed in the controls (89% of the control mean weight gain). No significant effects were noted during the gestation period. No effects upon food consumption were apparent at any dose level.

Mating and fertility were not affected at any treatment level.

F1 pup survival was decreased at 500 ppm. Decreases in the number of live pups per litter, which appeared to occur in a dose-dependant manner, were observed during the lactation period. Supporting this finding, the number of litters losing more than one pup was 1, 6, 6, 7, and 8 for the control, 50, 100, 200, and 500 ppm dose groups, respectively. Although no statistical significance was reported relative to the number of pups born live

per litter and the number surviving to weaning, a dose response is suggested by these data. The interpretation of these data was compromised by the unusual number of pup deaths in the control group; however, overall postnatal pup mortality at 500 ppm (a total of 108 pup deaths, from 19 litters) was clearly greater than the control value (a total of 60 pup deaths from 15 litters) and was judged to be a treatment-related effect. Decreased pup survival was also noted in the previous two-generation reproduction study in rats with sulfentrazone (MRID 43345408) at a dietary level of 500 ppm.

At 500 ppm, F1 mean pup weights per litter were significantly decreased at postnatal days 1, 4, and 7; and F2 fetal weights were significantly decreased at gestation day 20. No other treatment-related effects were observed at evaluation of F1 gestation day 20 uterine and ovarian data and F2 fetuses.

The age of vaginal opening was delayed by approximately 4 days in F1 females at 500 ppm, and there was an increase of vaginal threads at that dose. There was no effect of treatment on the age of balanopreputial separation in males. The authors noted that the assessment of the onset of vaginal opening was complicated by the presence of vaginal threads, but any female offspring with vaginal threads (and therefore delayed vaginal patency) were excluded from the mean calculations. Although the study authors concluded that the incidence of vaginal threads did not indicate any effect on treatment, this conclusion is not justified or supported in the study report. Upon examination of the individual data, Agency reviewers noted that the number of female pups with vaginal threads was 1, 0, 1, 2, and 6 in the 0, 50, 100, 200, and 500 ppm groups, respectively. The mean number of days to completion of vaginal patency for those female offspring with vaginal threads was 52.0, N/A, 49.0, 58.0, and 59.3, in the 0, 50, 100, 200, and 500 ppm groups, respectively. Including these female offspring in the calculation of mean age of vaginal opening revealed a delay of approximately 4 days for the 500 ppm F1 females as compared to control. Agency reviewers concluded that these findings were related to treatment.

In F0 males, the mean weights of epididymis, seminal vesicles and testes were unaffected. In F1 males, statistically significant reductions in mean covariate adjusted prostate and testes weights were apparent at the 500 ppm dose levels (Table 10). Absolute epididymides weights were decreased ($p \leq 0.05$) at 500 ppm as compared to control (1.2820 g for 500 ppm F1 males versus 1.3811 g for controls), but relative epididymides weight (adjusted using terminal body weight as the covariate factor) demonstrated no significant difference from control for any treated group.

No treatment-related histopathological effects were apparent.

No effects on sperm count, motility, percent progressively motile sperm, and VSL (straight line velocity) were apparent for F0 and F1 males at any dose level. Morphological assessment of control and high dose male sperm revealed no increase in

abnormalities, either including or excluding tail defects. Additionally, there were no differences between control and treated groups in the mean number of sperm tubules at stages 1 through 14. No effects were apparent in Stage VII tubule diameter.

A quantitative assessment of the ovary did not indicate any effects on the number of oocytes/follicles after evaluations of a single layer, multiple layers, and antral area.

In conclusion, **the NOAEL for parental (systemic) toxicity is 200 ppm (20 mg/kg/day) and the LOAEL is 500 (51 mg/kg/day) based upon a decrease in F1 female body weight gain.**

Offspring/reproductive toxicity is apparent at the high dose level based upon effects in F1 offspring. **The Offspring/Reproductive Toxicity NOAEL is at 200 ppm (16 mg/kg/day) and the Offspring/Reproductive LOAEL is at 500 ppm (40 mg/kg/day)** based upon reduced gestation day 20 fetal weights; decreased postnatal day 0, 4, and 7 pup weights; decreased pup survival; delayed vaginal patency; and reduced epididymides, prostate and testes weights.

B. Study Deficiencies:

This is a one-generation study, conducted to follow up on findings in the original reproduction study (FMC Study A92-3545; MRID 43345408). The study was terminated on day 20 of gestation to produce the F2 generation and therefore no F2 litter data were generated. This study can only regulatory requirements when considered with data generated in the primary study.

C. CLASSIFICATION:

The study is classified as **Acceptable/Non-guideline** and does not satisfy the guideline requirement for a reproduction study (OPPTS 870.3800; §83-4). However, the study data supports the conclusions of the two-generation reproduction study in rats with sulfentrazone (MRID 43345408; FMC Study A92-3545).