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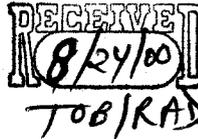
Glenn A. Gratz
Product Stewardship Manager
Safety, Health and Environment

8EHQ-0800-14300

ExxonMobil
Chemical

August 3, 2000

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U. S. Environmental Protection Agency
Attn: FYI Coordinator
Office of Pollution Prevention & Toxics
401 M Street, S.W.
Washington DC 20460-0001



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Re: FYI Submission: 8EHQ-98-14300

Dear Sir or Madam:

Under the "For Your Information" classification system, ExxonMobil Chemical Company is submitting the following information on a substance described as 1,2-benzenedicarboxylic acid, di-C9-11 branched alkyl esters, C10 rich (CAS RN 68515-49-1). This substance is currently being manufactured for commercial purposes as defined by TSCA.

This submission is provided as follow-up information for the TSCA Section 8(e) submission 8EHQ-98-14300 on this substance on October 16, 1998. The data presented are from a 2-generation reproductive toxicity study in rats that was conducted to clarify the results from the previous study submitted in 1998.

This new study confirmed the findings seen in the previous study, and an Offspring no observed adverse effect level (NOAEL) was determined to be 0.06% in the diet. Based on all ExxonMobil studies conducted on this substance, we can conclude:

- No effects on fertility were seen at levels up to 0.8% in the diet
- No effects seen on testicular development or sperm counts
- Significant reductions in offspring survival (days 1-4) in only the F2 generation at 0.2%, 0.4% and 0.8% levels in the diet.
- Significant reductions in weanling viability at 0.8%
- No alterations in developmental landmarks
- Significant reductions in adult body weight gain at 0.8%
- Increases in mean and relative liver and kidney weights at concentrations greater than 0.2%

If you have any questions or need additional information, please feel free to contact me at (281)-870-6899.

Sincerely yours,

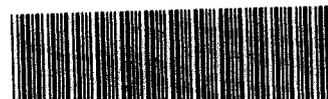
Glenn Gratz

MR 38429

Enclosure



BEHQ-98-14300



89000000282

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INTEROFFICE CORRESPONDENCE

DATE May 2, 2000

TO: V. Sinibaldi	REFERENCE: 00MRL 24
FROM: V. Fowler	SUBJECT: Final Report Number: 177535A

Attached is a copy of the report listed above. It has been sent electronically to files. Thank you.

Attachment

- c: Archives (original)
- Sponsor Representative - L. J. Hushka
- QA - signature page / statement page

ExxonMobil BIOMEDICAL SCIENCES, INC.

FINAL REPORT

PROJECT NUMBER: 177535A

MRD-94-775

**TWO GENERATION REPRODUCTION TOXICITY
STUDY IN RATS WITH MRD-94-775**

PERFORMED FOR:

EXXONMOBIL CHEMICAL COMPANY

**13501 Katy Freeway
Houston, Texas 77079**

and

EXXONMOBIL CHEMICAL EUROPE INC.

Machelen, Belgium

PERFORMED AT:

EXXON BIOMEDICAL SCIENCES, INC.

Toxicology Laboratory

Mettlers Road, East Millstone, New Jersey 08875-2350

(New address effective 12/99: 1545 Rte. 22 East, Annandale, NJ 08801-0971)

COMPLETION DATE: May 2, 2000

00MRL 24

Original

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PROJECT NUMBER: 177535A

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(New address effective 12/99: 1545 Rte. 22 East, Annandale, NJ 08801-0971)

COMPLETION DATE (DRAFT): February 28, 2000

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A**

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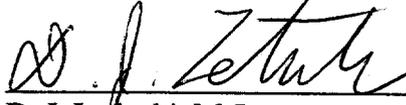
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APPROVAL SIGNATURES



J. J. Freeman, Ph.D., D.A.B.T.
Director of Laboratory Operations

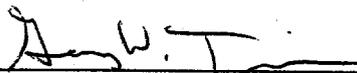
28 April 2000
Date



D. J. Letinski, M.S.
Analytical Chemistry Supervisor

28 Apr 00
Date

This study was conducted in compliance with the OECD Principles of Good Laboratory Practice.



G. W. Trimmer, B.A.
Study Director
P.O. Box 971, 1545 Route 22 East
Annandale, NJ 08801-0971

2/MAY/00
Date

QUALITY ASSURANCE STATEMENT

STUDY NUMBER: 177535A
 TEST SUBSTANCE: MRD-94-775
 STUDY SPONSOR(S): ExxonMobil Chemical Company and
 ExxonMobil Chemical Europe, Inc.

Listed below are the inspections performed by the Quality Assurance Unit of Exxon Biomedical Sciences, Inc., the date(s) of inspection, and the date(s) findings were reported to the Study Director and Management.

<u>Study Phase Inspected</u> Protocol	<u>Date(s) of Inspection</u>	<u>Reported to Study Director</u>	<u>Reported to Management</u>
	03,04 Dec 98	04 Dec 98	10,14 Dec 98
Analysis of Mixtures	11 Jan 99	19 Jan 99	20,21 Jan 99
Day 0 Gestation Body Weights	22 Feb 99 & 09 Mar 99	09 Mar 99	10,11 Mar 99
F1 Pup Necropsy (PND 21)	06,09 Apr 99	09 Apr 99	26,29 Apr 99
Clinical Observations	25 Jun 99	06 Jul 99	06,13 Jul 99
Watchdog System	23,24,29,30 Nov & 01 Dec 99	01 Dec 99	24,25 Feb 00
Final Report	01-16 Dec 99	16 Dec 99	15 Feb 00
	01 Dec 99 - 03 Jan 00	03 Jan 00	31 Jan 00
	17 Dec 99 - 04 Jan 00	04 Jan 00	08 Feb 00
	03-17 Jan 00	17 Jan 00	31 Jan 00
	04-13 Jan 00	13 Jan 00	17,18 Feb 00
	30 Jan - 01 Feb 00	02 Feb 00	22,23 Feb 00
	27 Jan - 03 Feb 00	03 Feb 00	09 Feb 00
	14 Jan 00 - 02 Feb 00	03 Feb 00	29 Feb 00
	04,07,09 Feb 00	10 Feb 00	17 Feb 00
	11-16 Feb 00	16 Feb 00	17,18 Feb 00
	17,18 Feb 00	18 Feb 00	28 Feb 00
	07-24 Feb 00	24 Feb 00	28,29 Feb 00
	28 Feb - 09 Mar 00	14 Mar 00	17,19 Apr 00
	02-03 Mar 00	03 Mar 00	17,19 Apr 00

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

QUALITY ASSURANCE STATEMENT (CONT'D)

STUDY NUMBER: 177535A
TEST SUBSTANCE: MRD-94-775
STUDY SPONSOR(S): ExxonMobil Chemical Company and
ExxonMobil Chemical Europe, Inc.

<u>Study Phase Inspected</u>	<u>Date(s) of Inspection</u>	<u>Reported to Study Director</u>	<u>Reported to Management</u>
Second Review of Final Report	21 Jan 00 - 11 Feb 00	11 Feb 00	17 Feb 00
	11,14,17 Feb 00	18 Feb 00	24 Feb 00
	22 Feb 00	22 Feb 00	28 Feb 00
	28,29 Feb 00	29 Feb 00	29 Feb 00
	17 Apr 00	17 Apr 00	17,19 Apr 00

The final report accurately reflects the methods, procedures and observations documented in the raw data.



W. James Bover, Ph.D.
Quality Assurance Section Head



Date

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A**

PERSONNEL

Study Director:	G. W. Trimmer, B.A. P.O. Box 971, 1545 Route 22 East Annandale, NJ 08801-0971
Sponsor:	Exxon Chemical Company ^a 13501 Katy Freeway Houston, Texas 77079-1398 and Exxon Chemical Europe Inc. ^b Machelen, Belgium
Sponsor Representative:	L. J. Hushka, Ph.D.
Director of Laboratory Operations:	J. J. Freeman, Ph.D., D.A.B.T.
Toxicology and Animal Care Supervisor:	R. C. Forgash, B.S.
Analytical Chemistry Supervisor:	D. J. Letinski, M.S.
Quality Assurance Section Head:	W. J. Bover, Ph.D.
Compound/Diet Preparation Supervisor:	R. W. Woods, B.S.
Statistician:	M. J. Nicolich, Ph.D.
Veterinarian:	R. L. Harris, D.V.M.
Consultant:	S. B. Harris, Ph.D.

^a - ExxonMobil Chemical Company beginning on December 3, 1999

^b - ExxonMobil Chemical Europe, Inc. beginning on December 3, 1999

GLOSSARY

The following are brief descriptions of some of the terms used in this report:

ABBREVIATIONS:	GD - Gestation Day PPD - Postpartum Day PND - Postnatal Day
P1 generation:	The adult animals purchased from Charles River Laboratories that were mated after 10 weeks of test material exposure.
F1 generation:	The offspring of the P1 generation.
P2 generation:	F1 generation animals chosen to mate.
F2 generation:	The offspring of the P2 generation.
Day 0 of the P2 generation:	The arbitrarily chosen first day of the second generation. This was within one week after the last offspring of the F1 generation reached PND 21 upon which the second-generation premating period was initiated.
P2 Selection Pool	The two F1 offspring/sex/litter selected on PND 21 to fill the P2 generation.
NOAEL:	No Observable Adverse Effect Level. The subsequent parameters were used to determine the following NOAELs:
Fertility NOAEL:	Male Mating and Female Fecundity Indices Male and Female Fertility Indices Gestational Index Mean Days of Gestation Mean Litter Size Percent Live and Dead Offspring Offspring Sex Ratio
Offspring NOAEL:	Offspring Survivorship Indices Offspring Body Weights Offspring Inlife and Gross Postmortem Observations Offspring Organ Weights (Absolute and Relative) Developmental Landmarks

SUMMARY

This study was a focused follow-up to a previously conducted two generation reproduction toxicity study, Study 177535, (EBSI, 1998). The objective of Study 177535 was to provide information concerning the potential effects of the test material on gonadal function, estrous cycle, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring in the rat. Study 177535 evaluated the reproductive toxicity endpoints found in the EPA and OECD test guidelines in effect at the time of the study. The current study (177535A) was conducted to clarify the dose response relationship of observations, primarily effects on offspring survival, made in Study 177535. Since the current study was a focused follow-up, it was not conducted to any specific regulatory testing guidelines, but followed the general study schedule outlined in OPPTS Guideline 870.3800 (EPA, 1998).

Doses for the present study were selected with the objective of identifying a No Observable Adverse Effect Level (NOAEL) and were based on the offspring survival results of Study 177535. Study 177535 indicated a possible adverse effect in the survivorship of the P2 offspring at birth, at Postnatal Day (PND) 1 and PND 4 at the lowest level tested (0.2%). However, in the mid dose group (0.4%) there was better survivorship in the P2 offspring at birth and PND 4 than in the 0.2% group. This response indicated there might have been something other than the test substance affecting survivorship in the 0.2% dose group. To further examine this observation, 0.4% was chosen as the high dose and 0.2% was chosen as the high mid dose for this present study. The low mid dose level (0.06%) and the low dose level (0.02%) for the current study were selected by applying an approximately three-fold difference between the dose levels.

Undiluted test material was blended in PMI Certified Rodent Diet 5002 (Meal) at a fixed concentration and mixed thoroughly to assure homogeneity. The test material-diet admixtures were administered ad libitum to 30 rats/sex/group at 4 dose levels. Group 1 served as a control and received carrier (PMI Certified Rodent Diet 5002 (Meal) only. Groups 2, 3, 4, and 5 received 0.02%, 0.06%, 0.2%, and 0.4% of the test material in feed, respectively. In addition to the 30 rats/sex/group, satellite groups of 25 female rats each were treated with the control diet and the high dose diet during the both generations. Blood samples were collected from the dams and offspring of these animals for possible future analysis. Additionally, milk samples were collected from the dams that delivered offspring. The data for the satellite animals will not be reported in this study. The satellite animal data will be reported separately if the blood and milk samples are analyzed.

SUMMARY (CONT'D)

P1 males and females received test material/diet mixture daily for at least ten weeks prior to mating and during the mating period. Additionally, P1 female animals received test material during the gestation and postpartum periods, until weaning of the F1 offspring on Postpartum Day (PPD) 21. P2 (F1) males were dosed from Postnatal Day (PND) 21 for at least 10 weeks before mating, through the mating period for F2 litters, and until sacrificed. The extra F1 offspring that were not selected for the P2 generation received test material from PND 21 until sacrificed after reaching vaginal patency or preputial separation.

P2 (F1) females were dosed from PND 21 for at least 10 weeks prior to mating, during mating, gestation, postpartum, and until they were sacrificed following weaning of the F2 animals on PPD 21. The F2 animals not selected for necropsy received the appropriate test substance/diet mixture until they were sacrificed after reaching vaginal patency (females) or until they were sacrificed on or after PND 56 (males).

Clinical inlife observations, body weight, and food consumption were recorded for all P1 and P2 animals at least weekly (Week 1 of the P1 generation was a 6-day value for the females; see protocol deviation) during the pre-mating and mating periods (food consumption was not measured during mating due to cohabitation). Clinical inlife observations and body weight were recorded for all P1 and P2 females on Gestation Days (GD) 0, 7, 14, and 21, and on PPD 0, 4, 7, 10, 14, and 21, and/or at least weekly until sacrificed. Food consumption was measured on the same schedule as body weights after Day 0 of each phase. Following their birth, the offspring were counted and examined externally daily from PND 0 to 21. Anogenital distance was measured on PND 0 and nipple retention was assessed on PND 13 or 14 for all offspring of both generations. Offspring were sexed and weighed on PND 0, 1, 4, 7, 14, and 21. Body weights and food consumption were measured on PND 28 and PND 35 for all F1 animals when these days occurred prior to Day 1 of the P2 generation. Vaginal patency or preputial separation as appropriate was evaluated for the F1 animals selected for the P2 selection pool, and for the F2 animals not selected for the PND 21 necropsy. Body weights also were recorded for animals on the day vaginal patency or preputial separation occurred (see protocol deviations).

Each P1/P2 male was sacrificed following the end of mating of the satellite animals, while females were sacrificed following weaning of their litters on PPD 21. A gross necropsy was performed on all adult animals, selected F1 and F2 neonates (one/sex/litter), and on all animals that succumbed (not euthanized) during the study. A full macroscopic examination was performed on these animals; liver and kidney weights were taken; and selected organs and tissues were collected. Histopathology was not performed.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A**

SUMMARY (CONT'D)

The ranges for the mean measured dose rate (mg/kg/day) for each parental animal during the pre-mating, gestation and postpartum periods were as follows:

Target Concentration in Diet	Mean Actual Dose in mg/kg/day During Premating (Weeks 1-10)			
	P1 Males	P1 Females	P2 Males	P2 Females
0.02%	23-12	21-14	26-11	25-14
0.06%	68-33	58-40	76-33	77-41
0.2%	225-114	202-139	254-114	266-137
0.4%	453-233	406-274	516-235	524-271
Target Concentration in Diet	Range of Mean Actual Dose in mg/kg/day for Females During Gestation (G) and Postpartum (PP) Period			
	P1 G	P1 PP	P2 G	P2 PP
0.02%	13-15	19-37	13-15	19-40
0.06%	39-43	57-112	38-44	52-114
0.2%	127-147	178-377	134-151	166-352
0.4%	254-295	356-744	256-286	356-747

The mean measured dose rate for the F1 offspring during postweaning in mg/kg/day was as follows:

Target Concentration in Diet (%)	Mean Actual Dose in mg/kg/day During PND 21-28 and PND 28-35	
	Males	Females
0.02%	33-30	33-30
0.06%	98-90	98-92
0.2%	325-301	324-302
0.4%	665-605	675-614

The test material was not considered to have any effect on fertility since there were no biologically significant differences between treated and control parental animals' reproductive indices (i.e., Mating, Fertility, Fecundity, or Gestational Indices). Additionally, there were no biologically significant differences in the onset of preputial separation or vaginal patency between treated and control F1 or F2 animals.

SUMMARY (CONT'D)

There were no treatment-related deaths or effects on body weight or food consumption in the parental animals, and the majority of P1 and P2 parental animals were free of abnormalities throughout the study. The only notable findings in the parental animals were increases in mean absolute and relative organ weights of the liver and kidneys in the treated animals in both generations. Both weight increases were expected and consistent with findings observed in the previously conducted multigeneration study 177535 (EBSI, 1998). Increased kidney weights were primarily male-specific and appeared consistent with male rat-specific nephropathy. Such findings are not relevant to human health (EPA, 1991). Hepatic weight increases were consistent with peroxisome proliferation (Boorman et al., 1990) and considered a physiological adaptation. Current literature suggests that compounds causing peroxisome proliferation in rodents have little, if any, effects on human liver (IARC, 1995). Increases in mean relative kidney weight in the 0.4% P1 females and in mean absolute kidney weight in the 0.2% and 0.4% P2 females were consistent with Study 177535. In Study 177535 there were no microscopic changes associated with these increases in weight. The increases female kidney weight also may be due to peroxisome proliferation.

No biologically significant effects were noted for any measure of fertility, offspring survival, or development in the P1/F1 offspring.

In the P2/F2 offspring, there were no biologically significant effects for any measure of fertility. However, a statistically significant decrease in survivorship was observed at PND 1 and PND 4 in the 0.2% and 0.4% groups. This appeared to be dose-related. Survivorship in the 0.4% offspring was substantially lower than the historical control range, while the survivorship in the 0.2% offspring was slightly below the low value of the historical control range. Decreased survival at the 0.2% and 0.4% groups were considered test material related. There was no effect observed in the live birth index. These findings are consistent with those of the previous study, 177535.

In the P2/F2 offspring there were no statistically significant differences in the mean body weights compared with the controls and there was no consistent dose response in these weights. However, lower body weights were observed. On PND 0, all treated male groups and the 0.02% and 0.4% dose female groups had mean body weights that were below the historical control range of this laboratory. The 0.2% dose group male PND 1 mean body weight also was marginally below the historical control range of this laboratory. These lower weights did not appear to be treatment-related, but rather were reflective of a generalized lower body weight for this population of animals.

SUMMARY (CONT'D)

However, in the P2/F2 generation there were statistically significant lower mean body weights compared with controls in the 0.4% males on PND 14, the 0.4% females on PNDs 14 and 21, and the 0.2% females on PND 14. This finding was inconsistent with observations made in Study 177535 (EBSI, 1998) and may be treatment related even though the weights were within the historical control range of the laboratory.

Nipple retention, anogenital distance, onset of vaginal patency, and preputial separation were comparable between treated and control offspring in both the F1 and F2 generations.

In conclusion, the test material was not considered to effect fertility since there were no biologically significant differences in fertility indices between control and treated parental animals of either generation. Additionally, there were no biologically significant differences in the onset of preputial separation or vaginal patency between control and treated F1 or F2 animals. Thus, the Fertility NOAEL (No Observable Adverse Effect Level) was established at 0.4%, the highest dose level tested under conditions of this study. In the offspring, there were treatment-related decreases in F2 offspring survivorship at PND 1 and PND 4 in the 0.2% and 0.4% group animals compared to the controls. Based on these findings, an Offspring NOAEL was established at 0.06%.

INTRODUCTION

This study was a focused follow-up for a previously conducted two-generation reproductive study with MRD-94-775, Study 177535, (EBSI, 1998) and was conducted to further investigate specific responses observed in the previous study. Therefore, this study did not follow any specific regulatory testing guidelines. However, the schedule (e.g., premating treatment period, mating period etc.) followed the study schedule outlined in OPPTS Guideline 870.3800 (EPA, 1998).

This study was conducted for Exxon Chemical Company, 13501 Katy Freeway, Houston, Texas 77079 and Exxon Chemical Europe Inc., Machelen, Belgium (subsequently referred to as the Sponsor) Effective December 3, 1999, these companies became ExxonMobil Chemical Company and ExxonMobil Chemical Europe Inc., respectively.

The study was conducted by Exxon Biomedical Sciences, Inc. (EBSI) Laboratory Operations, Mammalian Toxicology Laboratory at its facility at Mettlers Road, CN 2350, East Millstone, New Jersey 08875-2350. The EBSI Mammalian Toxicology Laboratory is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC International). Effective December 1999, the new address of the Laboratory Operations was 1545 Route 22 East, Annandale, New Jersey 08801-0971.

Study Initiation (Protocol Signature Date)

December 7, 1998

Inlife Test Period

December 7, 1998 to October 8, 1999

Justification for Selection of Test System

The rat is among the species of choice for reproduction and fertility testing according to the E.C. Dangerous Substances Directive (67/548/EEC), Annex V part B "Two-Generation Reproduction Toxicity Test" (EC, 1988), and the U.S. EPA TSCA test guidelines for reproduction and fertility effects (EPA, 1998).

Justification of Dosing Route

The dietary route is a preferred route of administration for non-volatile materials according to E.C. Dangerous Substances Directive Annex V, and U.S. EPA regulations. It also represents a likely route of human exposure.

INTRODUCTION (CONT'D)

Justification for Dose Selection

Doses for this study were selected based on the results of a previous conducted two-generation reproduction toxicity study in rats with the test material (EBSI study 177535). The dose levels tested in study 177535 were 0.2%, 0.4%, and 0.8%.

Doses for the present study were selected with the objective of identifying a No Adverse Effect Level (NOAEL) and were based on the offspring survival results of Study 177535. Study 177535 indicated a possible adverse effect in the survivorship of the P2 offspring at birth, at Postnatal Day (PND) 1 and PND 4 at the lowest level tested (0.2%). However, in the mid dose group (0.4%) there was better survivorship in the P2 offspring at birth and PND 4 than the 0.2% group. This response indicated there may have been something other than the test substance affecting survivorship in the 0.2% dose group. To further examine this observation, 0.4% was chosen as the high dose and 0.2% was chosen as the high mid dose for this present study. The low mid dose level (0.06%) and the low dose level (0.02%) for the current study were selected by applying an approximately three-fold difference between the dose levels.

Compliance

This study was conducted in general agreement with the following guidelines and standards:

Animal Welfare Act of 1966 (P.L. 89-544), as amended in 1970, 1976, and 1985.
Code of Federal Regulations, Title 9 [Animals and Animal Products], Subchapter A
-Animal Welfare Parts 1, 2, and 3.

Guide for the Care and Use of Laboratory Animals, Institute of Laboratory
Animal Resources, Commission on Life Sciences, National Research Council,
National Academy Press, Washington, D.C., 1996.

This study was conducted in compliance with the following standard:

OECD, Organization for Economic Cooperation and Development, Principles of
Good Laboratory Practice, C(97) 186/Final, 1997.

MATERIALS AND METHODS

TEST MATERIAL

Material Identification

EBSI Identification:	MRD-94-775
Supplier:	Exxon Chemical, Holland, BV
Date Received:	April 25, 1994
Expiration Date:	April 2000 ^a
CAS RN:	68515-49-1
Description:	Colorless liquid
Storage Condition:	Room temperature

The test material, as received, was considered the "pure" material for the purpose of dosing (the manufacturing specification was 99.5% purity, so the consequence of not correcting was negligible).

^a - The original expiration date assigned to the test substance was April 1999. However, prior to the experimental start date the Sponsor analyzed the test substance and confirmed the test substance was within the specifications for the product. The subsequent pre and post study characterization of the test substance confirmed the results of the Sponsor. Therefore, a new expiration date of April 2000 was assigned to the test substance.

Characterization of the Test Material

The testing laboratory performed analyses for the stability, identity, strength, purity, and composition or other characteristics that will appropriately identify the test material. This documentation is maintained at Exxon Biomedical Sciences, Inc. Toxicology Laboratory, P.O. Box 971, 1545 Route 22 East, Annandale, New Jersey 08801-0971.

TEST MATERIAL (CONT'D)

Analysis of Mixtures

The testing laboratory determined the homogeneity and stability of the test material.

Homogeneity of the test material for Study 177535A was determined at the low concentration (0.02% w/w). Triplicate samples were collected from the top, middle and bottom of the diet mixture. The concentration was the mean of all nine samples. The high dose concentration (0.4% w/w) was known to be homogeneous from Study 177535.

Stability was assessed by measuring the concentrations of selected samples of the low dose concentration (0.02%) for homogeneity analysis after room temperature and freezer storage. Stability analysis was performed on Day 3, Day 8, and Day 15. The high dose concentration was known from Study 177535 to be stable for 15 days.

Concentrations of test material-diet blends were checked by the testing laboratory at least once a month in order to assure continuing accuracy in mixing diets.

Solubility

Not applicable to this study.

Sample Retention

Two 10 ml samples of the undiluted test material were collected by the Compound Preparation Department and stored at room temperature.

Carrier

Purina Certified Rodent Diet 5002 (Meal)
Manufacturer: PMI Feeds, Inc.
Richmond, Indiana

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A**

TEST SYSTEM

Test Animal

Species:	Rat
Stock:	Males: CrI:CD [®] (SD)IGS BR Females: CrI:CD [®] BR - VAF/Plus
Supplier:	Charles River Laboratories, Inc. Raleigh facility, Raleigh, North Carolina (males) Portage facility, Portage, Michigan (females)
Area:	Males - R05; Females - P06

Animal Receipt Information:

Receipt Date:	November 24, 1998
Purchase Order Number:	8CR11129R

Quarantine and Acclimation Period

13 days; animals were checked for viability at least once daily.

Number and Sex

P1 Males:	150 virgin
P1 Females:	200 virgin

Age at Initiation of Test Material Administration

P1 Males:	Approximately 6-7 weeks
P1 Females:	Approximately 6-7 weeks

Body Weight at Initiation of Test Material Administration

P1 Males:	176 to 236 grams
P1 Females:	138 to 187 grams

Animal Identification

Ear tags and corresponding cage identification. Pups selected for growth from the F1 and F2 litters were eartagged on or after weaning.

TEST SYSTEM (CONT'D)

Selection

More animals than were required for the conduct of this study were purchased and acclimated. The P1 population was selected by exclusion of animals from the quarantine population (determined by the attending veterinarian, Study Director, and/or his designee) because of poor health, outlying body weights, or abnormalities. The selected P1 population was allocated randomly to groups by a computer-generated randomization procedure to most nearly equalize initial group mean body weight. Weight variation for individual animals was within $\pm 21.4\%$ of the mean body weight of their sex.

Housing

Room Numbers: 516 (The weaned F2 pups were placed in Room 515 from August 16, 1999 to September 2, 1999.)

Housing: Individually housed during the test period, except during the mating and postpartum periods. F1 littermates were double-housed by sex for one week after weaning or until Day 0 of the P2 generation (if less than one week after weaning), then individually housed. F2 littermates were double housed by sex for one week after weaning.

Caging: Suspended stainless steel and wire mesh with absorbent paper below cages. Stainless steel litter pans with bedding were provided for dams near parturition and during lactation.

Feed

Purina Certified Rodent Diet 5002 (Meal), ad libitum

Manufacturer: PMI Feeds Inc.
Richmond, Indiana

Analysis: Performed by PMI Feeds Inc. Copies of the feed analyses are maintained in the EBSI Toxicology Laboratory.

Contaminants: There were no known contaminants in the feed believed to have been present at levels that may have interfered with this study.

The availability of feed was checked daily for all animals.

TEST SYSTEM (CONT'D)

Water

Automatic watering system, ad libitum

Supplier: Elizabethtown Water Company
Bound Brook, New Jersey.

Analysis: Provided by Elizabethtown Water Company. Copies of the water analyses are maintained in the EBSI Toxicology Laboratory.

Contaminants: There were no known contaminants in the water believed to have been present at levels that may have interfered with this study.

The availability of water was checked daily for all animals.

Bedding (Direct)

Alpha-Dri

Manufacturer: Shepherd Specialty Papers, Inc.

Analysis: Provided by the Manufacturer. Copies of the analyses are maintained in the EBSI Toxicology Laboratory.

Contaminants: There were no known contaminants in the bedding believed to have been present at levels that may have interfered with this study.

Near parturition, Day 20 (± 1 day) of gestation, and during the postpartum period, mated females were provided with clean bedding as necessary, usually every two days.

Environmental Conditions

Temperature range: 68 to 76 degrees Fahrenheit

Humidity range: 40 to 70 percent relative humidity

Lighting: Approximately 12 hours light (0700-1900 hours) and 12 hours dark (1900-0700 hours) by automatic timer.

Monitored at least once daily.

EXPERIMENTAL DESIGN

Preparation of Animals

No special preparation of the animals was required prior to dose initiation.

Preparation of Test Material

Mixing of feed: The basal diet consisted of PMI Certified Rodent Diet 5002 (Meal). The test material was incorporated into the feed and mixed thoroughly to assure homogeneity. The test material diet admixtures were prepared as fixed concentrations of test material.

Fresh diets were prepared weekly, except when needed more frequently (e.g. lactation, postweaning). Prepared diets were covered and stored at room temperature following dispensing.

Diets were prepared at the following target concentrations, not to exceed stability data on the test material-dietary admixtures.

Experimental Groups

P1 and P2 GENERATIONS

Group	Target Concentration (%)	Anticipated Dose ^a (mg/kg/day)	Number of Main Study Animals		Number of Satellite Animals
			Male	Female	Female
1 (Control)	0	0	30	30	25 ^{b,c}
2 (Low)	0.02	16	30	30	0
3 (Low Mid)	0.06	48	30	30	0
4 (High Mid)	0.2	160	30	30	0
5 (High)	0.4	320	30	30	25 ^{b,c}

^a Average dose.

^b The satellite animals were treated in the same manner as the main study animals. However, the methods and data from the satellite animals will not be reported with Study 177535A.

^c P2 satellites: Group 1 contained 46 animals, Group 5 contained 40 animals.

EXPERIMENTAL DESIGN (CONT'D)

Administration of Test Material

The homogeneous blend of the test material, prepared as a mixture in PMI Certified Rodent Diet 5002 (Meal), was offered *ad libitum* to the treated rats of Groups 2, 3, 4, and 5. Control rats (Group 1) received PMI Certified Rodent Diet 5002 (Meal) *ad libitum* only. Feed jars containing diet were replaced at least once each week. The animals had access to the test or control feeders until the day of scheduled sacrifice.

The dosing regimen for all groups proceeded as follows: P1 males were dosed for at least 10 weeks prior to mating, through the mating period for F1 litters and until their sacrifice. P1 females were dosed for at least 10 weeks prior to mating, during the mating, gestation, and postpartum periods, until sacrificed. Males and females selected for the P2 generation were dosed from PND 21 until their death following the same dosing regimen as the P1 generation. The F1 female pups not selected for necropsy or the P2 generation were dosed from PND 21 through the day they achieved vaginal patency. The F1 male pups not selected for necropsy or the P2 generation were dosed from PND 21 through the day they achieved preputial separation. The F2 females were dosed from PND 21 through the day they achieved vaginal patency and were killed. The F2 males were dosed from PND 21 through the day they were killed (on or after PND 56).

Females that did not deliver or were not confirmed mated were dosed until sacrificed.

Experimental Evaluation

Inlife Procedures:

All animals were examined for viability twice daily Monday through Friday, and once daily on Saturdays, Sundays and holidays. Cage-side observations were performed daily on all P1 adults, except the days on which clinical observations were performed. Cage-side observations also were performed after weaning for all F1 offspring selected to be considered for the P2 generation.

EXPERIMENTAL DESIGN (CONT'D)

Experimental Evaluation (cont'd)

A clinical examination was given to each male prior to P1 selection, on the first day of dosing (Day 0), and at least weekly thereafter until sacrifice. Females received a clinical examination prior to P1 selection, on the first day of dosing (Day 0), and at least weekly thereafter until confirmation of mating, then on Gestation Day (GD) 0, 7, 14, and 21, and on Postpartum Day (PPD) 0, 4, 7, 10, 14, and 21. A clinical examination also was given to each P1 male and female on its day of sacrifice.

Male body weight was measured prior to P1 selection, on the first day of dosing, and at least weekly thereafter until sacrifice. Female body weight was measured prior to P1 selection, on the first day of dosing and at least weekly thereafter until confirmation of mating, then on GD 0, 7, 14, and 21 and on PPD 0, 4, 7, 10, 14, and 21, and/or at least weekly until sacrifice. Body weight also was measured on the day of sacrifice for all P1 males and females.

Food consumption was measured concurrently with body weight after Day 0, except during mating.

The inlife procedures detailed above were the same for the P2 generation.

Mating:

The P1 mating period began after at least 10 weeks of P1 dosing and ended when a female was confirmed mated or two weeks had elapsed. Each P1 male was assigned randomly (using animal reference numbers and a random numbers table) to be paired continuously with one P1 female of the same dose group to produce the F1 generation.

Mating was confirmed the morning following overnight pairing by observation of a copulatory plug (vaginal) and/or by the presence of sperm in a vaginal rinse. The day on which mating was confirmed was considered GD 0. After confirmation of mating, each animal was returned to its own cage.

On GD 20 (± 1 day), mated females were single housed in clean cages fitted with stainless steel litter pans and provided with fresh bedding material. Beginning on GD 21, mated females were examined at least twice daily for signs of parturition.

EXPERIMENTAL DESIGN (CONT'D)

Mating: (cont'd)

If a female was not confirmed as mated, a litter pan was provided 20 days after the first day vaginal smears were evaluated for sperm. After the litter pan was added, these females were examined for signs of parturition at least twice daily until 26 days after the last day of mating had elapsed.

The mating procedures detailed above were the same for the P2 generation.

Postnatal Evaluations

Dams were allowed to give birth. The duration of gestation was calculated and any difficulties occurring at parturition noted. The date of parturition was recorded as the dam's PPD 0.

Each morning and afternoon during the postnatal period, the litters were checked for dead offspring and unusual conditions, and the dams were examined for viability, nesting, and nursing behavior.

Dead pups were removed from the litter immediately after their discovery and subjected to a gross necropsy if their condition permitted.

On Postnatal Day (PND) 0, 1, 4, 7, 14, and 21 the offspring were counted, sexed, and each live pup was weighed. Pups were counted and examined externally on a daily basis during the postnatal period. Also, on PND 0 the anogenital distance of all live offspring was measured and on PND 13 or 14 (see protocol exceptions) the number of thoracic nipples was determined for all offspring.

On PND 4, after counting, sexing, weighing, and examination of pups, the size of each litter was adjusted by eliminating extra pups by random selection to yield, as nearly as possible, 4 males and 4 females per litter. Partial adjustment (e.g., 5 males and 3 females) was permitted whenever there were not enough pups to obtain 4 per sex per litter. Litters of eight pups or less were not adjusted. Culled pups were sacrificed. Culled pups that appeared normal were not subjected to further examination and tissues were not saved.

The postnatal evaluations detailed above were conducted for the F2 generation.

EXPERIMENTAL DESIGN (CONT'D)

Postnatal Evaluations (Cont'd)

At weaning (PND 21) of the F1 generation only, the offspring were examined externally and two offspring/sex/litter were selected randomly and group housed by sex to be considered for P2 generation adults. These offspring were observed and weighed on PNDs 28 and 35 (unless after Day 0 of the P2 generation).

From the remaining F1 offspring and all surviving F2 offspring on PND 21, one offspring/sex/litter in each group was selected randomly, sacrificed and examined for internal abnormalities. The remaining F1 offspring, if any, were discarded without further examinations. The remaining female F2 offspring were weighed and observed on PND 28. The remaining male F2 offspring were weighed and observed on PNDs 28, 35, 42, 49, and 56 before being discarded.

Beginning on PND 29, all surviving F1 and F2 female offspring were examined daily for vaginal opening. Beginning on PND 35, all surviving F1 and F2 male offspring were examined daily for preputial separation. The examinations continued until all animals reached criteria (i.e. vaginal opening or preputial separation). Offspring were weighed on the day they reached vaginal patency or preputial separation (see protocol deviation).

Study Termination

All animals (adults and offspring) were sacrificed by CO₂ asphyxiation and exsanguination.

Euthanasia was performed on animals for humane reasons and on moribund animals at the discretion of the Study Director or his designee.

All P1 and P2 males were sacrificed after the mating of the satellite females. P1 and P2 females were sacrificed after weaning of their litters. Confirmed mated females which did not give birth by presumed GD 26, or those females which had not been confirmed mated and did not give birth by 26 days after the last day of mating were sacrificed and received gross necropsies. Special attention was paid to the reproductive system. Any female whose entire litter succumbed or was euthanized was sacrificed after the last offspring succumbed.

EXPERIMENTAL DESIGN (CONT'D)

Study Termination (cont'd)

Vaginal smears were performed on each adult female (see protocol deviations) on their day of sacrifice to determine its stage in the estrous cycle. The stage of the estrous cycle was recorded.

If a dam died prior to PPD 21, all surviving offspring from that dam were sexed and examined externally, sacrificed, and discarded.

Necropsy:

Gross necropsies were performed on all adult animals, including those that were found dead or sacrificed. Body weight was recorded on the day of necropsy. The uterus of each female used for mating was examined grossly for evidence of implantations and those data were recorded. Additionally, the corpora lutea were counted and the number counted for each ovary were recorded (total count for the animal reported).

The following tissues and organs of all P1 and P2 adults surviving to termination were weighed prior to fixation:

liver

kidneys (paired)

The following organs and tissues of all P1 and P2 adults were preserved in 10% neutral buffered formalin (unless otherwise specified) for possible future analysis:

vagina	coagulating gland	mammary gland (females only)	
pituitary	ovaries	kidneys	adrenals
epididymides	liver ^c	seminal vesicles	spleen
prostate	testes ^a	oviducts	brain
thymus	uterus (with cervix)	stomach	
tissue masses/gross lesions ^b			

^a Both testes were preserved in Bouin's solution. The testes remained in Bouin's solution for approximately 24 hours then were rinsed and stored in 70 percent Ethyl Alcohol

^b Gross lesions retained at the discretion of the Study Director

^c After the appropriate sections for histopathological examination were collected, the remaining liver was flash frozen and stored at -70°C for possible future analysis.

EXPERIMENTAL DESIGN (CONT'D)

Study Termination (Cont'd)

Intact dead pups or pups sacrificed in moribund condition on PND 0 were examined by fresh visceral dissection using the Staples method (Staples, 1974). Dead pups and pups sacrificed as moribund after PND 0 were examined externally for anomalies and internally for gross visceral abnormalities. Culled pups (PND 4) with external abnormalities were subjected to a visceral examination at the discretion of the Study Director or his designee. Abnormal tissues were preserved in 10% neutral buffered formalin at the discretion of the Study Director.

Pups selected for necropsy on PND 21 were examined internally and the following tissues and organs were weighed prior to fixation:

liver kidneys (paired)

The following tissues were preserved in 10% neutral buffered formalin for possible future microscopic examination based on the effects seen in other parameters:

liver kidneys gross lesions (skin with alopecia not preserved)

After the appropriate liver sections for histopathological examination were preserved in 10% neutral buffered formalin, the remaining liver was flash frozen and stored at -70°C for possible future biochemical analysis.

Weaned pups that were not selected for necropsy or growth that succumbed were subjected to a gross postmortem examination. Organs were not weighed, but the tissues listed above were preserved.

The necropsy procedures detailed above were the same for the F2 generation.

Histopathology

Histopathology was not performed.

Records

A copy of the protocol, final report, raw data, computer-generated listings of raw data, supporting documentation, specimens, and one sample of the test material are maintained in the Archives of the EBSI Toxicology Laboratory.

EXPERIMENTAL DESIGN (CONT'D)

Statistical Analyses

- I. Continuous data were tested for statistical significance using the Bartlett's test of homogeneity of variance to determine if the groups have equivalent variances at the 1% level of significance (Snedecor and Cochran, 1989).

If the variances were equivalent, the hypothesis that there was no difference in response between the groups was tested using a standard one-way analysis of variance (ANOVA) (Snedecor and Cochran, 1989). If the ANOVA was significant, Dunnett's test was performed to determine which treated groups differed from control (Dunnett, 1964). A linear regression to test for a dose response also was performed and tested for lack of fit (Snedecor and Cochran, 1989). All tests were reported at the 5% or 1% level of significance.

If the variances were not equivalent, then a Kruskal-Wallis (non-parametric) test was performed to determine if the treatment effects are equivalent (Hollander and Wolfe, 1973). If there was a difference, Dunn's Rank Sum comparison was used to determine which treatment groups differed from control (Hollander and Wolfe, 1973). Jonckheere's test for ordered response also was performed (Hollander and Wolfe, 1973). All tests were reported at the 5% or 1% level of significance.

- II. Pup weight and anogenital distance was analyzed by a standard nested analysis of covariance (Snedecor and Cochran, 1989) with pups nested within dams and with dams nested within doses, and litter size (both sexes combined) as the covariate. If differences in groups were identified, the Least Significant Difference (LSD) technique was used to determine which groups differed from the control group (Snedecor and Cochran, 1989). Male and female pups were tested separately (the covariate was combined sexes in each analysis). All tests were reported at the 5% or 1% level of significance.
- III. Parental reproductive and offspring survival incidence data were analyzed for statistical significance. First, a standard chi-square analysis was performed to determine if the proportions of incidences differed between the groups tested (Snedecor and Cochran, 1989). In keeping with standard statistical practice, if any one cell had an expected value less than 5, this step was not reported. Next, each treatment group was compared to the control group using a 2 x 2 Fisher Exact test (Bradley, 1968). Thirdly, Armitage's test for linear trend in the dosage groups was performed (Snedecor and Cochran, 1989). All tests were reported at the 5% or 1% level of significance.

RESULTS

P1 GENERATION - PARENTAL RESULTS

1. PARENTAL SURVIVAL - P1

Summary of Survival: Table 1
Individual Survival Data: Appendix A

There were no treatment-related deaths. Two 0.06% dose females were found dead prior to scheduled termination. One female was found dead on Test Day 8 with a discolored and distended urinary bladder filled with brown liquid. A second female was found dead on Test Day 90, which was Gestation Day 12, with discolored lungs and red material in the thoracic cavity. Both animals were free of abnormalities at all scheduled observations intervals. These two deaths were considered incidental and unrelated to treatment with the test material.

2. PARENTAL CLINICAL INLIFE OBSERVATIONS - P1

Incidence of Inlife Observations: Tables 2-4
Individual Inlife Observations: Appendices B-D

There were no clinical signs judged to be directly related to treatment with the test material. The majority of animals in all groups had no adverse clinical signs during the premating/mating, postmating, gestation, and/or postpartum periods.

There was a very low incidence of insignificant observations in the male and/or female animals in one or more groups including controls. These included dental abnormalities, scabs/sores, alopecia, swollen snout/mouth, staining of the fur, ocular/oral discharge, soft stool, little sign of stool/food consumption, vaginal discharge, a single mass in the ventral cervical area, and/or a single abdominal mass. One female from the 0.06% dose group developed coarse tremors and/or convulsions during the changing of bedding on PND 5. These observations continued whenever the animal was handled during the remainder of the postpartum period. The animal was free of abnormalities during premating, mating and gestation, and maintained a normal litter. All observations were considered incidental and unrelated to treatment with the test material.

RESULTS (CONT'D)

3. PARENTAL BODY WEIGHT AND BODY WEIGHT CHANGE - P1

Mean Body Weight and Body Weight Change: Tables 5-8

Individual Body Weight and/or Body Weight Change: Appendices E-H

There were no statistically significant differences in mean body weight between the treated and control males or females during the P1 generation, including the gestation and postpartum intervals.

There were a few statistically significant differences (increases and decreases) in the mean body weight gain of males and females in all treatment groups compared with controls. However, in the absence of a clear pattern of response and correlating findings in absolute body weight, these sporadic differences were not considered biologically important.

4. PARENTAL FOOD CONSUMPTION - P1

Mean Food Consumption: Tables 9-11

Individual Food Consumption: Appendices I-K

There were no statistically significant differences in mean food consumption between the treated and control males or females during the P1 generation, including the gestation and postpartum intervals.

5. PARENTAL MEASURED DOSE RATE - P1

Mean Measured Dose Rate: Tables 12-14

Individual Measured Dose Rate: Appendix L

In general, the mean measured dose rate for the male and female animals during the pre mating period decreased over time, as expected. This trend is characteristic of fixed concentration dietary studies, since food consumption remains relatively constant while body weight continues to increase over the course of the study. The mean measured dose rate for each group during pre mating in mg/kg/day was as follows:

RESULTS (CONT'D)

Parental Measured Dose Rate - P1 (Cont'd):

TARGET CONCENTRATION IN DIET (%)	MEAN ACTUAL DOSE (mg/kg/day)		
	WEEK 1	WEEKS 2-9	WEEK 10
MALES: 0.02	23	19-12	12
MALES: 0.06	68	58-35	33
MALES: 0.2	225	194-120	114
MALES: 0.4	453	400-245	233
FEMALES: 0.02	20	21-15	14
FEMALES: 0.06	58	62-42	40
FEMALES: 0.2	191	202-142	139
FEMALES: 0.4	380	406-287	274

Mean measured dose rate during gestation was similar to the last two weeks of prepartum. During the postpartum period, there was a steady increase in mean measured dose rate. This is characteristic of fixed concentration dietary reproduction studies, since the dam's food consumption increases to fuel the increased energy expenditure of lactation while maintaining weight. Mean measured dose rate was greatest during the PPD 14-21 interval. For the convenience of the calculation, it was assumed that the dams ingested all food, and the data are presented this way. However, it is likely that a substantial amount of food was actually eaten by the offspring, particularly near the end of the lactational period. The mean gestation and postpartum measured dose rates were as follows:

TARGET CONCENTRATION IN DIET (%)	MEAN ACTUAL DOSE (mg/kg/day)	
	GESTATION	POSTPARTUM
FEMALES: 0.02	15-13	19-37
FEMALES: 0.06	43-39	57-112
FEMALES: 0.2	147-127	178-377
FEMALES: 0.4	295-254	356-744

RESULTS (CONT'D)

6. PARENTAL GROSS POSTMORTEM OBSERVATIONS - P1

Incidence of Gross Postmortem Observations: Table 15

Individual Gross Postmortem Observations: Appendix M

There were no gross postmortem observations judged to be related directly to treatment with the test material.

The majority of males throughout the groups were free of observable abnormalities at postmortem examination. There were single or low occurrences of discolored liver; dilated, discolored, abnormal contents, or cystic kidneys; abnormal contents in urinary bladder; small epididymides or seminal vesicles; small and/or flaccid testes; subcutaneous mass; and/or dry red ocular discharge, alopecia, dental abnormalities and scabs. These observations occurred in all groups including controls and were considered incidental.

In the females, there was an apparent dose-related increase in thick and/or discolored stomachs. This stomach irritation was attributed to ingestion of bedding materials since it was observed only in females and observed in all groups, including controls. The higher incidence in the treated animals may have been due to an interaction of the test material and the bedding. This observation was consistent with findings in the previously conducted two-generation reproductive study (EBSI, 1998) with this test material, where microscopically the stomachs had increased incidence of dilated glandular mucosa in females of all dose groups, and an increased incidence of erosions in the glandular mucosa and mixed or mononuclear inflammatory cell infiltration in females of higher dose levels.

Other postmortem observations in the females included single or low incidences of discolored kidneys, liver, lungs, or thymus; dilated kidneys; cystic ovary; subcutaneous mass; abnormal contents in a thick urinary bladder; abnormal contents in a distended uterus/vagina; alopecia, truncated tail, and/or dry red ocular discharge. One 0.06% female had a retained fetus. These observations were considered incidental.

One 0.06% female found dead on Test Day 8 had a discolored and distended urinary bladder filled with brown liquid. A second 0.06% female found dead on Test Day 90 (Gestation Day 12) had discolored lungs, thick red material in the thoracic cavity, dried red material around eyes and mouth, and anogenital staining. Both animals were free of abnormalities at all scheduled observations intervals. Although the cause of death could not be definitively determined, these two deaths were considered incidental and unrelated to treatment with the test material.

RESULTS (CONT'D)

7. PARENTAL ORGAN WEIGHT - P1

Mean Organ and Relative Organ Weights: Tables 16 and 17

Individual Organ and Relative Organ Weights: Appendices N and O

There were statistically significant increases in the mean absolute and relative liver weights of the 0.4% dose males (12% and 14%, respectively) and 0.4% dose females (12% and 13%, respectively) compared with controls. These increases were consistent with findings in the previously conducted two-generation reproductive study (EBSI, 1998), the known capability of certain phthalates to cause peroxisome proliferation (Boorman et al., 1990), and are considered to be a physiological adaptation.

There were statistically significant increases in mean absolute and relative kidney weights of the 0.4% males (14% and 18%, respectively). These increases were consistent with findings in the previously conducted two-generation reproductive study (EBSI, 1998).

There also was a statistically significant increase in the 0.4% female mean relative kidney weight (6%) compared with the controls.

8. REPRODUCTION INDICES - P1

Summary of Reproduction Data: Table 18

Individual Reproduction Data: Appendix P

Historical Control Data: Appendix BD

There were no statistically significant differences in Male Mating, Male Fertility, Female Fertility, Female Fecundity, or Female Gestational Indices between treated and control animals. Mean days of gestation and mean litter size of the treated and control groups were similar. Four control, one 0.02%, three 0.06%, four 0.2%, and six 0.4% dose females were not pregnant.

There were no statistically significant differences in the mean sex ratio of the treated offspring compared with controls. The percentages of live and dead offspring are discussed in detail in the following section (Offspring Survival).

RESULTS (CONT'D)

F1 GENERATION - OFFSPRING RESULTS

9. OFFSPRING SURVIVAL - F1

Summary of Offspring Survival: Table 19
 Individual Offspring Survival Data: Appendix Q
 Historical Control Data: Appendix BD

There were no statistically significant differences between the control and treated animals for post-implantation loss. There were no biologically significant differences in survivorship between treated and control offspring, and all survival indices were within the historical control range for this laboratory. Statistically significant differences were limited to an increase in the Live Birth Index of the 0.06% and 0.4% dose groups compared with controls. Increases in survival indices are not indicative of toxicity. Therefore, these increases were not considered biologically important.

F1 OFFSPRING SURVIVAL INDICES: TWO-GENERATION STUDY (177535A)

Group	Live Birth %	Day 1 Survival %	Day 4 Survival %	Day 7 Survival %	Day 14 Survival %	Day 21 Survival %	Viability at Weaning %
0%	96.3	97.8	96.2	99.5	100.0	100.0	99.5
0.02%	98.5	98.5	97.8	100.0	99.5	99.5	99.0
0.06%	99.2 *	98.4	95.9	99.5	100.0	100.0	99.5
0.2%	95.8	95.9	95.3	100.0	100.0	100.0	100.0
0.4%	99.2*	97.7	96.9	99.5	100.0	100.0	99.5
Historical Control	95.2-99.2	95.5-100	88.9-99.5	92.8-100	93.7-100	98.8-100	86.9-100

NOTE: * Mean significantly different from control mean (p < 0.05)

RESULTS (CONT'D)

10. OFFSPRING CLINICAL INLIFE OBSERVATIONS - F1

Incidence of Offspring Inlife Observations: Table 20
Individual Offspring Inlife Observations: Appendix R

There were no treatment-related clinical signs observed in the offspring of any group and the majority of offspring in all groups were free of observable abnormalities from PND 0-21. Some offspring across all groups were observed without milk in their stomachs, primarily during the first four days of the postnatal period, with the highest incidence occurring on PND 0.

Single or low incidences of lacerations; scabs; swollen hindpaw or hindleg; pale appearance; necrotic, filamentous, truncated or no tail; and/or umbilical hernia were observed in one or more groups, including controls. These observations were considered incidental and unrelated to treatment.

During the postweaning period, all animals were free of abnormalities with the exception of one 0.06% male offspring with a necrotic tail on PND 28.

RESULTS (CONT'D)

11. OFFSPRING BODY WEIGHT - F1

Mean Offspring Body Weight: Table 21
 Individual Offspring Body Weight: Appendix S
 Historical Control Data: Appendix BD

There were no statistically significant differences in mean body weights between treated and control animals of either sex. All values were within or greater than the historical control range of this laboratory as follows:

MEAN OFFSPRING BODY WEIGHT (GRAMS) - F1

MALE	PND 0	PND 1	PND 4	PND 7	PND 14	PND 21
0%	6.94	7.59h	10.92	17.44	35.52	56.65
0.02%	6.94	7.51h	10.55	17.43	35.87	56.87
0.06%	6.75	7.51h	10.58	17.15	34.95	55.64
0.2%	6.84	7.52h	10.80	17.71	34.72	55.60
0.4%	6.68	7.21	10.06	17.31	33.99	53.27
Historical Control	6.35-7.02	6.68-7.49	8.53-11.43	13.64-18.74	28.81-37.09	44.89-62.34
FEMALE	PND 0	PND 1	PND 4	PND 7	PND 14	PND 21
0%	6.57	7.24h	10.44	16.57	34.70	54.17
0.02%	6.51	7.11	10.08	16.62	34.77	54.10
0.06%	6.28	7.02	9.83	16.25	33.38	51.76
0.2%	6.38	7.09	10.23	16.87	33.57	53.05
0.4%	6.36	6.90	9.66	16.36	32.53	50.28
Historical Control	5.96-6.74	6.30-7.16	8.32-11.05	13.33-17.69	27.22-35.89	42.39-61.19

h – outside the historical control range for this laboratory

RESULTS (CONT'D)

12. OFFSPRING ANO-GENITAL DISTANCE - F1

Mean Anogenital Distance: Table 22

Individual Anogenital Distance: Appendix T

There were no statistically significant differences in mean PND 0 anogenital distance between treated and control animals of either sex.

13. OFFSPRING NIPPLE RETENTION - F1

Mean Nipple Retention: Table 23

Individual Nipple Retention: Appendix U

Nipple retention was similar between treated and control offspring of both sexes. The majority of females in all groups had six nipples retained on PND 13/14, while all males in all groups had zero.

14. OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F1

Incidence of Offspring Gross Postmortem Observations: Table 24

Individual Offspring Gross Postmortem Observations: Appendix V

In general, there were no gross postmortem observations in the F1 offspring judged to be related to treatment with the test material. The majority of animals selected for necropsy were free of observable abnormalities at the scheduled terminal sacrifice on PND 21. Observations were limited to single occurrences of truncated tail, discolored lungs, scabs on tail, or an apparent umbilical hernia. These single occurrences were considered incidental and unrelated to treatment.

The majority of animals that died prior to weaning (GD 22 - PND 21) also were free of observable abnormalities. There were single incidences of dilated renal pelvis/distended ureter (0.02%), club foot (0.02%), vascularized liver (0.02%), collapsed lung (0.2%), patent ductus arteriosus (0.2%), truncated tail (0.2%), and thick red material in thoracic cavity (control). Two animals also had discolored livers (0.02% and 0.06%). Due to their isolated incidence, all postmortem observations were considered incidental and unrelated to treatment with the test material.

RESULTS (CONT'D)

15. OFFSPRING ORGAN WEIGHTS - F1 (PND 21 SACRIFICE)

Mean Offspring Absolute Organ and Relative Organ Weights: Tables 25 and 26
Individual Offspring Organ Weights: Appendices W and X

There were no statistically significant differences in mean absolute or relative organ weights (kidney or liver) between treated and control animals of either sex.

16. POSTWEANING BODY WEIGHTS AND FOOD CONSUMPTION - F1

Mean Offspring Postweaning Body Weight: Table 27
Mean Offspring Postweaning Food Consumption: Table 28
Individual Offspring Postweaning Body Weight: Appendix Y
Individual Offspring Postweaning Food Consumption: Appendix Z

There were no statistically significant differences in mean body weight or mean food consumption between treated and control offspring of either sex during the two-week postweaning measurements.

17. POSTWEANING MEASURED DOSE RATE - F1

Mean Offspring Postweaning Measured Dose Rate: Table 29
Individual Offspring Postweaning Measured Dose Rate: Appendix AA

The mean measured dose rate during postweaning was similar between males and females and decreased over the two-week period, as expected. This trend is characteristic of fixed concentration dietary studies, since food consumption remains relatively constant while body weight continues to increase over the course of the study. The mean measured dose rate for each group during postweaning in mg/kg/day was as follows:

Target Concentration in Diet (%)	Mean Actual Dose (mg/kg/day)			
	PND 21- 28		PND 28 - 35	
	Males	Females	Males	Females
0.02%	33	33	30	30
0.06%	98	98	90	92
0.2%	325	324	301	302
0.4%	665	675	605	614

RESULTS (CONT'D)

18. DEVELOPMENTAL LANDMARKS - F1

Mean Time to Offspring Developmental Landmarks: Table 30
Individual Offspring Developmental Landmarks: Appendix AB

There were no statistically significant differences in age or weight at preputial separation between treated and control male offspring. There were no statistically significant differences in age or weight at vaginal patency between treated and control female offspring.

P2 GENERATION - PARENTAL RESULTS

1. PARENTAL SURVIVAL - P2

Summary of Survival: Table 31
Individual Survival Data: Appendix AC

There were no treatment-related deaths. One 0.4% male was found dead on Test Day 129 with a large, thick liver, dilated renal pelvis, and a misshapen heart with a large atrium. One 0.06% female was found dead on Test Day 84 (during the mating period). Postmortem examination revealed a distended uterine horn with purple gelatinous material, large spleen and liver, thick lungs, discolored thymus, and red vaginal discharge. While the exact cause of these deaths could not be determined, they were considered incidental and unrelated to treatment with the test material. All other animals survived to scheduled termination.

2. PARENTAL CLINICAL INLIFE OBSERVATIONS - P2

Incidence of Inlife Observations: Tables 32-34
Individual Inlife Observations: Appendices AD-AF

There were no clinical signs judged to be directly related to treatment with the test material. The majority of animals in all groups had no adverse clinical signs during the pre mating/mating, postmating, gestation, and/or postpartum periods. There was a very low occurrence of observations in the male and/or female animals and included dental abnormalities, scabs/sores, rings on tail, alopecia, dried red ocular discharge, and/or swollen snout. One female in the 0.4% dose group and one female in the 0.06% group exhibited an axillary mass during part of the postpartum period. All observations were considered incidental and unrelated to treatment with the test material.

RESULTS (CONT'D)

3. PARENTAL BODY WEIGHT AND BODY WEIGHT CHANGE - P2

Mean Body Weight and Body Weight Change: Tables 35-38

Individual Body Weight and/or Body Weight Change: Appendices AG-AJ

There were no statistically significant differences in mean body weight between the treated and control males or females during the P2 generation, including the gestation and postpartum intervals.

There were several statistically significant differences (increases and decreases) in the mean body weight gain of males and females in all treatment groups compared with controls. However, in the absence of a clear pattern of response and correlating findings in body weight, these sporadic differences were not considered biologically important.

4. PARENTAL FOOD CONSUMPTION - P2

Mean Food Consumption: Tables 39-41

Individual Food Consumption: Appendices AK-AM

There were no important differences in mean food consumption between the treated and control males or females during the P2 generation, including the gestation and postpartum intervals.

Statistically significant differences were limited to a decrease in mean food consumption of the 0.4% females during Week 7 of pre-mating followed by an increase during Week 8. This sporadic change in mean food consumption was not considered treatment-related.

RESULTS (CONT'D)

Parental Measured Dose Rate – P2 (Cont'd):

TARGET CONCENTRATION IN DIET (%)	MEAN ACTUAL DOSE (mg/kg/day)	
	GESTATION	POSTPARTUM
FEMALES: 0.02	15-13	19-40
FEMALES: 0.06	44-38	52-114
FEMALES: 0.2	150-134	166-352
FEMALES: 0.4	284-256	356-747

6. PARENTAL GROSS POSTMORTEM OBSERVATIONS - P2

Incidence of Gross Postmortem Observations: Table 45

Individual Gross Postmortem Observations: Appendix AO

Notable postmortem observations in the animals surviving to termination were limited to an increased incidence (8/29) of dilated renal pelves in the 0.4% dose males compared with controls. Dilated renal pelves also were observed in the other treated groups (2-5/30), but the incidence generally was similar to controls (3/30). Dilated renal pelves also were noted in several females.

There also was a low incidence of other postmortem observations in the animals surviving to termination which included abnormal kidney contents; depressed areas in kidney; discolored spleen, kidney, or thymus; malformed liver lobe; small/flaccid testes; small epididymides; cystic ovary; large heart; discolored stomach; alopecia; staining of the fur; dental abnormalities; and/or a scab. These observations were considered incidental and unrelated to treatment.

Postmortem observations in the 0.4% male found dead included a large, thick liver, dilated renal pelvis, and a misshapen heart with a large atrium. The 0.06% female found dead had a distended uterine horn with purple gelatinous material, large spleen and liver, thick lungs, discolored thymus, and red vaginal discharge. While the exact cause of these deaths could not be determined, they were considered incidental and unrelated to treatment of the test material.

RESULTS (CONT'D)

7. PARENTAL ORGAN WEIGHT - P2

Mean Organ and Relative Organ Weights: Tables 46 and 47

Individual Organ and Relative Organ Weights: Appendices AP and AQ

There were statistically significant increases in the mean absolute and relative liver weights of the 0.4% males (13% and 14%, respectively), 0.4% females (23% and 20%, respectively), and 0.2% females (17% and 9%, respectively) compared with controls. These increases were consistent with results observed in the previously conducted two-generation study with this test material (EBSI, 1998), the known capability of certain phthalates to cause peroxisome proliferation (Boorman et al., 1990).

In the kidneys, there were statistically significant increases in mean absolute and relative weights of the 0.4% dose males (20% and 19%, respectively), and the 0.2% males (10% and 7%, respectively) compared with controls.

There was a statistically significant increase in mean absolute kidney weight in the 0.2% females (13%) compared with controls.

8. REPRODUCTION INDICES - P2

Summary of Reproduction Data: Table 48

Individual Reproduction Data: Appendix AR

Historical Control Data: Appendix BD

There were no statistically significant differences in Male Mating, Male Fertility, Female Fertility, Female Fecundity, or Female Gestational Indices between treated and control animals. Mean days of gestation and mean litter size of the treated and control groups were similar. Five control, four 0.02%, five 0.06%, nine 0.2%, and three 0.4% dose females were not pregnant.

There were no statistically significant differences in the mean sex ratio of the treated offspring compared with controls. The percentages of live and dead offspring are discussed in detail in the following section (Offspring Survival).

RESULTS (CONT'D)

F2 GENERATION - OFFSPRING RESULTS

9. OFFSPRING SURVIVAL - F2

Summary of Offspring Survival: Table 49
Individual Offspring Survival Data: Appendix AS
Historical Control Data: Appendix BD

There was a dose-related decrease in the Day 1 and Day 4 survival indices, with statistically significant decreases being observed in the 0.2% dose group and 0.4% dose group compared with controls. Three of these values were outside the historical control range of this laboratory and were considered treatment-related.

F2 OFFSPRING SURVIVAL INDICES: TWO-GENERATION STUDY (177535A)

Group	Live Birth %	Day 1 Survival %	Day 4 Survival %	Day 7 Survival %	Day 14 Survival %	Day 21 Survival %	Viability at Weaning %
0%	97.7	99.0	97.7	98.5	95.4	100.0	94.0
0.02%	98.7	98.4	96.8	99.0	99.5*	100.0	98.5*
0.06%	97.4	97.4	96.6	99.0	100.0**	99.5	98.5*
0.2%	99.4h	95.2**h	92.3**	98.8	98.8	98.7h	96.3
0.4%	95.5	89.1**h	84.8**h	99.0	98.5	98.5h	96.0
Historical Control	95.2-99.2	95.5-100	88.9-99.5	92.8-100	93.7-100	98.8-100	86.9-100

NOTE: * Mean significantly different from control mean (p < 0.05)
** Mean significantly different from control mean (p < 0.01)
h Outside historical control range of this laboratory

There were no statistically significant differences between the control and treated animals for post-implantation loss. The live birth index for the 0.2% dose group was higher than the historical control and this was not considered biologically important. There were statistically significant increases in Day 14 and Viability at Weaning Indices of the 0.02% and 0.06% dose groups compared with controls. These increases were not considered biologically important. The Day 21 Survival Indices of the 0.2% and 0.4% dose groups were marginally outside the historical control range for this laboratory, but not statistically significantly different from the control. No biological importance was assigned to these observations.

RESULTS (CONT'D)

10. OFFSPRING CLINICAL INLIFE OBSERVATIONS - F2

Incidence of Inlife Observations: Table 50

Individual Inlife Observations: Appendix AT

There were no treatment-related clinical signs observed in the offspring of any group and the majority of offspring in all groups were free of observable abnormalities from PND 0-21. Some offspring across all groups were observed without milk in their stomachs, primarily during the first week of the postnatal period, with the highest incidence occurring on PND 0. Four control offspring were noted as emaciated on PND 10 and subsequently were euthanized.

Single or low incidences of lacerations; scabs; no apparent anus; partially cannibalized foreleg; necrotic, filamentous, truncated or no tail; truncated digits; and/or apparent broken leg were observed in one or more groups, including controls. These observations were considered incidental and unrelated to treatment.

During the postweaning period, all animals were free of abnormalities.

11. OFFSPRING BODY WEIGHT - F2

Mean Offspring Body Weight: Table 51

Individual Offspring Body Weight: Appendix AU

Historical Control Data: Appendix BD

On PND 0, all treated male groups and the 0.02% and 0.4% dose female groups had mean body weights that were outside the historical control range of this laboratory. The 0.2% dose group males PND 1 mean body weight also was marginally outside the historical control range of this laboratory. However, none of the values was statistically significantly different from controls and there is no consistent dose response. Additionally, the control values, particularly for the males, were in the lower half of the historical control range. These lower weights do not appear to be treatment-related.

There were statistically significant lower mean body weights in the 0.4% males on PND 14, the 0.4% females on PND 14 and 21, and the 0.2% females on PND 14 compared with controls. Although, these weights were within the historical control range of the laboratory these may have been a treatment-related effect (see discussion).

RESULTS (CONT'D)

Offspring Body Weight (Cont'd):

MEAN OFFSPRING BODY WEIGHT (GRAMS) - F2

MALE	PND 0	PND 1	PND 4	PND 7	PND 14	PND 21
0%	6.48	6.98	9.70	14.97	32.29	51.27
0.02%	6.23h	6.80	9.77	16.27	34.05	55.29*
0.06%	6.34h	6.81	9.76	15.73	32.43	52.18
0.2%	6.29h	6.64h	9.06	14.53	30.77	49.28
0.4%	6.27h	6.80	9.29	14.50	30.33*	48.32
Historical Control	6.35-7.02	6.68-7.49	8.53-11.43	13.64-18.74	28.81-37.09	44.89-62.34
FEMALE	PND 0	PND 1	PND 4	PND 7	PND 14	PND 21
0%	6.02	6.52	9.02	14.55	32.13	49.86
0.02%	5.86h	6.44	9.18	15.20	32.26	51.55
0.06%	5.97	6.42	9.14	14.96	31.10	48.55
0.2%	6.00	6.31	8.66	14.12	29.74*	47.31
0.4%	5.87h	6.43	8.93	13.92	29.29**	46.19*
Historical Control	5.96-6.74	6.30-7.16	8.32-11.05	13.33-17.69	27.22-35.89	42.39-61.19

NOTE: * Mean significantly different from control mean (p < 0.05)
 ** Mean significantly different from control mean (p < 0.01)
 h Outside historical control range of this laboratory

There also was a statistically significant increase in the 0.02% male mean body weight on PND 21. This increase was not considered biologically important.

RESULTS (CONT'D)

12. OFFSPRING ANO-GENITAL DISTANCE – F2

Mean Anogenital Distance: Table 52

Individual Anogenital Distance: Appendix AV

There were no statistically significant differences in mean anogenital distance between treated and control animals of either sex.

13. OFFSPRING NIPPLE RETENTION – F2

Mean Nipple Retention: Table 53

Individual Nipple Retention: Appendix AW

Nipple retention was similar between treated and control animals of both sexes. The majority of females in all groups had six nipples retained on PND 13, while all males in all groups had zero.

14. OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F2

Incidence of Offspring Gross Postmortem Observations: Table 54

Individual Offspring Gross Postmortem Observations: Appendix AX

There were no gross postmortem observations in the F2 offspring judged to be related to treatment with the test material. All animals were free of observable abnormalities at the scheduled terminal sacrifice on PND 21 with the exception of one 0.06% female observed with no apparent renal pelvis in one kidney. This observation was considered incidental and unrelated to treatment.

The majority of animals that died prior to scheduled termination (GD 22-PND 21) also were free of observable abnormalities. There were single or low incidences of compressed heart due to mechanical damage; missing/cannibalized foreleg; discolored kidney, liver, or intestines; scabs or lacerations; and/or lesions of the tail (truncated, partially cannibalized, mechanical injury and no tail). There were four control offspring that were emaciated. There was also a low incidence of offspring with no milk in stomach in the control, 0.2%, and 0.4% groups which were considered incidental and unrelated to treatment with the test material.

RESULTS (CONT'D)

15. OFFSPRING ORGAN WEIGHTS - F2 (PND 21 SACRIFICE)

Mean Offspring Organ and Relative Organ Weights: Tables 55 and 56
Individual Offspring Organ Weights: Appendices AY-AZ

There were no statistically significant differences in mean absolute or relative organ weights (kidney or liver) between treated and control animals of either sex with the exception of the 0.4% dose group female mean relative liver weight.

There was a statistically significant increase in the mean relative liver weight of the 0.4% dose group females compared with controls. In the absence of a similar trend in the respective absolute liver weight, this single difference was considered the result of the lower mean body weights of the 0.4% females at study termination and not treatment-related.

16. POSTWEANING BODY WEIGHT - F2

Mean Offspring Postweaning Body Weight: Table 57
Individual Offspring Postweaning Body Weight: Appendix BA

Mean postweaning body weights were significantly decreased compared to controls in the 0.4% dose males during PNDs 28 and 35, and in the 0.2% dose males at PND35 only. At PNDs 42, 49, and 56, an apparent recovery occurred in the 0.2% and 0.4% treated males and their mean body weights were no longer statistically different from controls.

There were no statistically significant differences in postweaning body weights between treated and control females on PND 28.

RESULTS (CONT'D)

17. DEVELOPMENTAL LANDMARKS – F2

Mean Time to Offspring Developmental Landmarks: Table 58
Individual Offspring Developmental Landmarks: Appendix BB

There was a statistically significant delay in preputial separation for the 0.4% males when compared to the control male offspring. This delay was small (1.2 days) and not considered biologically significant (EPA 1996). There were no statistically significant differences in the mean body weight at which preputial separation occurred between treated and control male offspring.

There were no statistically significant differences for age of vaginal patency between treated and control female offspring. However, there was a statistically significant decrease in the mean body weight at the time that the 0.4% females achieved vaginal patency compared with the control female offspring. This decrease was small (6%) and not considered biologically significant.

18. ANALYTICAL CHEMISTRY RESULTS

Analytical Chemistry Report: Appendix BC

The stability of MRD-94-775 in feed was evaluated in Study 177533 at 0.2% and 1.5%. The data showed the test material was stable at room temperature for at least 14 days. The stability for the low dose of the current study (0.02%) was evaluated prior to experimental start of the current study. The data showed the test material was stable at room temperature and freezer storage for at least 15 days. Homogeneity was evaluated during Study 177535 at 0.2% and 0.8%. Satisfactory homogeneity was observed with the relative standard deviation ranging from 2.79% to 3.04%. Homogeneity of the low dose of the current study (0.02%) was evaluated prior to experimental start of the current study. Satisfactory homogeneity was observed with a relative standard deviation of 5.03%. Concentration verification analysis indicated that all dose samples were within 15% of the nominal concentrations. Comparison of the pre and post characterization demonstrated that the neat material was stable.

DISCUSSION

This study was a focused follow-up for a previously conducted two-generation reproductive study with MRD-94-775, Study 177535, (EBSI, 1998) and was conducted to clarify specific responses observed in the Study 177535. Therefore, this study did not follow any specific regulatory testing guidelines. However, the schedule (e.g., pre-mating treatment period, mating period etc.) followed the study schedule outlined in OPPTS Guideline 870.3800 (EPA, 1998). Additionally, this study was designed to study the effect of the test material on specific developmental landmarks (anogenital distance, nipple retention in male offspring, preputial separation and vaginal patency).

Doses for this study were selected based on results of Study 177535 in which the doses were 0.2%, 0.4%, and 0.8%. The results of Study 177535 indicated a possible adverse effect in the survivorship of the P2 offspring at Postnatal Day (PND) 1 and PND 4 at the lowest level tested (0.2%). However in Study 177535, the decrease in survivorship in the 0.2% P2 offspring at PND 4 was greater than the decrease observed in the 0.4% group. This response indicated either the reduced survivorship in the 0.2% offspring or the greater survivorship in the 0.4% offspring was due to biological variation. Based on these results, 0.4% was chosen as the high dose and 0.2% was chosen as the high mid dose. The use of these dose levels was expected to clarify the results of offspring survivorship of these dose levels in Study 177535. The low mid dose level (0.06%) and the low dose level (0.02%) were selected by applying an approximately three-fold difference between the dose levels.

Administration of the test material via diet to Crl:CD[®]BR (Sprague Dawley-derived) rats in graded doses (0.02%, 0.06%, 0.2%, 0.4%) in the course of a two-generation reproduction toxicity study did not result in biologically significant effects on any parameter except for early offspring survivorship (PND 1 and PND 4) in the 0.2% and 0.4% groups of the F2 generation and decreases in the F2 offspring body weights at PND 14 and 21.

Similar to the previous study (177535) the test material produced no biologically significant signs of toxicity in any parameter at any dose level in either parental generation. The most notable parental findings were increases in absolute and relative weights of the liver and kidneys. These changes were expected since they were consistent with the results from studies with other phthalates (Gray et al., 1977; EBSI, 1982, 1986, 1996; BIBRA, 1985).

DISCUSSION (CONT'D)

The effects in the liver weights included statistically significant increases in the mean absolute and relative liver weights in the P1 and P2 treated males and females of the 0.4% group compared with controls. A statistically significant increase also was noted in the absolute and relative liver weights of the P2 females of the 0.2% group when compared with controls. In the previous study, Study 177535, these changes also were observed. The histopathology of Study 177535 revealed a dose-related increase in enlargement of the hepatocytes with an associated increase of cytoplasmic eosinophilia in both generations. This type of hepatocellular change, although not diagnostic, is seen with compounds that cause peroxisome proliferation (Boorman et al., 1990). The effects in liver and kidney weights found in this follow-up study are considered to be a consequence of the same process. The current literature suggests that compounds that cause peroxisome proliferation in rodents have little, if any, effects on human liver (IARC, 1995). Similar changes were observed in the livers of the F2 0.4% female offspring.

The effects in the kidney weights in this study were statistically significant increases in the mean absolute and relative kidney weights in the P1 and P2 treated males of the 0.4% group compared with controls. This increase also was noted in the 0.2% males of the P2 generation and an increase was noted in the relative kidney weights of the 0.4% females of the P1 generation and the absolute kidney weights of the 0.2% group females of the P2 generation. In the previous study, Study 177535, increased mean absolute and/or relative kidney weights compared with controls also were observed in all treated male groups of both generations. The microscopic examination of those animals revealed accumulations of dark orange or eosinophilic granular cytoplasmic pigment in the cortical tubules and cortical tubular degeneration. An increased incidence of granular casts in the renal tubules of the high dose parental males also was observed. These effects were consistent with male rat-specific nephropathy associated with accumulation of alpha_{2u}-globulin (α 2UG), a low molecular-weight protein. This phenomenon has been designated α 2UG nephropathy (EPA, 1991) and is induced by a wide range of chemicals. α 2UG is synthesized in male rats only under the control of testosterone. Female rats and other laboratory mammals administered the same chemicals do not accumulate α 2UG in the kidney nor the subsequent α 2UG nephropathy. Therefore, this finding was not regarded as relevant to human risk.

DISCUSSION (CONT'D)

No treatment-related microscopic changes were observed in the kidneys of the P1/P2 females in Study 177535, even though relative and/or absolute kidney weights were increased in a non-dose-dependent manner in the females of both generations. The similar effects observed in organ weights in this follow-up study (177535A) are considered the same effect. It has been suggested that the effect on kidney weights in the females may be due to peroxisome proliferation. Ward et al. (1998) found that when wild-type mice were fed di(2-ethylhexyl) phthalate (DEHP) there was an increase in kidney weights. However, when PPAR alpha deficient (knockout) mice were fed DEHP there was no increase in kidney weight. This suggests that the kidney weight effects in females were related to peroxisome proliferation and probably not relevant to humans. Additionally, peroxisome proliferation may be contributing to a portion of the increased kidney weight observed in the males. Given the lack of microscopic changes in the females at higher doses with similar organ weight changes in the previous study (177535A), the increases in female kidney weights were not considered adverse or biologically significant.

In the F1 offspring, no treatment-related effects were observed. In the F2 offspring statistically significant decreased survivorship was observed at PND 1 and PND 4 in the 0.2% and 0.4% groups. Survivorship in the 0.4% offspring was substantially lower than the historical control range, while survivorship in the 0.2% offspring was slightly below the low value of the historical control range.

The PND 0 body weights of the F2 offspring from all treated group males and the 0.02% and 0.4% dose group females were outside (lower) the historical control range of this laboratory. The 0.2% dose group males' PND 1 mean body weight also was marginally outside the historical control range of this laboratory. However, none of the values were statistically significantly different from controls and there was no consistent dose response. Additionally, the control values, particularly for the males, were in the lower half of the historical control range. These lower weights do not appear to be treatment-related.

DISCUSSION (CONT'D)

There also were statistically significant decreases in F2 offspring body weights on Days 14 and /or 21 in the 0.2% and/or 0.4% groups. These decreases were small and the values were within the historical control range of the laboratory. However, these lower body weights appear to be consistent with observations of lower offspring body weights at these intervals at a higher dose rate in Study 177535. It is noteworthy that by the Day 21 interval the offspring are consuming the test diet and this could contribute to the dose. Additionally, these animals (males and females) were weighed on PND 28 and the males were weighed on PNDs 35, 42, 49, and 56. No statistically significant differences were noted between the treated groups and the controls on PND 28 for the females and after PND 35 for the males. In the males the percent difference in body weight between the high dose and controls narrowed during this time. Thus, these decreases in body weight at PNDs 14 and 21 were transient and not biologically significant.

There were no statistically significant differences between the treated groups and the control group for nipple retention or ano-genital distance in either generation of offspring. Also, there were no statistically significant differences in the onset of vaginal patency or preputial separation in the F1 offspring. However, as some planned examinations were not made, the exact day of the onset of vaginal patency for a number of animals could not be determined in the F1 generation. Because the onset of vaginal patency was not determined precisely in the F1 generation, the day of onset of vaginal patency and preputial separation were determined for the F2 offspring. There was no statistically significant difference in the onset of vaginal patency in the F2 offspring. However, there was a statistically significant delay in preputial separation in the 0.4% group males compared to controls. This delay was small (1.2 days) and not considered biologically significant.

In conclusion, the test material was not considered a toxicant to fertility since there were no biologically significant differences between the control and treated parental animals for fertility indices from either generation. Thus, the fertility NOAEL (No Observable Adverse Effect Level) was established at 0.4%, the highest dose level tested under conditions of this study.

In the offspring, findings were limited to treatment-related decreases in F2 offspring survivorship at PND 1 and PND 4 in the 0.2% and 0.4% group animals compared to the controls. Based on these findings, an Offspring NOAEL was established at 0.06%.

PROTOCOL EXCEPTIONS

DAY 0 BODY WEIGHT: Fourteen females weighed less than the minimum acceptable weight (at least 150 grams) required by protocol at the initiation of test material administration for the P1 generation. The weight range for these animals was 138-149 grams.

FOOD CONSUMPTION: Food consumption for the females for Week 1 was a six-day value covering Days 1-7. This was due to the ability of the females to enter the adjacent cage. On Day 1 the females were transferred into different cages and new initial feeder weights were recorded.

TISSUE PRESERVATION AT PARENTAL NECROPSY: At the parental generations' necropsy, both epididymides were preserved from all males.

PPD 21 NECROPSY: Due to technician oversight, necropsies for dams IGG302 and IGG251 (P1 generation) as well as their offspring were not performed and/or documented properly. Organ weights were not collected for dam IGG251 or her offspring, nor were any tissues saved from the offspring. Additionally, no liver or kidney sections were flash-frozen from any of the animals.

CORPORA LUTEA COUNTS: Due to oversight corpora lutea were not counted for several P1 and P2 females. Corpora lutea cannot be counted after fixation due to color loss, which makes it impossible to distinguish them from other follicles.

EVALUATION OF P1 NIPPLE RETENTION: Nipple retention was not evaluated on PND 13 for several P1 offspring. These offspring were evaluated on PND 14 and reported as such. The data from these animals were used for the statistical evaluation.

SELECTION: The weight variation for the females was 21.4%. This was outside the acceptable range in the protocol.

PROTOCOL EXCEPTIONS (CONT'D)

PPD 21 VAGINAL SMEARS: Several dams (P1 and P2 generation) inadvertently did not have vaginal smears performed as required by protocol.

EVALUATION OF PREPUTIAL SEPARATION: Body weights were inadvertently not taken for F2 offspring that reached criteria on September 11, 1999. The affected animals can be found in the individual data in the appendices.

EVALUATION OF VAGINAL PATENCY: Due to an oversight vaginal patency was not performed on April 18, 1999. This affected the determination of the age of vaginal patency for many F1 females. Also, body weights were inadvertently not taken on any animals that reached criteria prior to April 20, 1999. The affected animal can be found in the individual data in the appendices.

DAY 0 OF THE P2 GENERATION: PND 28 or PND 35 observations, body weights, and food consumption were collected on Day 0 of the P2 generation although not required by the protocol. These values were collected to increase the size of the population being used to calculate postweaning test substance consumption. For several of these animals the observations and body weight were required as a Day 0 of the P2 generation measurement and only the food consumption measurement was additional.

It is unlikely that these protocol exceptions adversely affected the results or integrity of the study. In the case of the missed F1 vaginal patency evaluations on April 18, 1999, vaginal patency and preputial separation were evaluated for the F2 offspring.

No other circumstances occurred that would have affected the quality or integrity of the data.

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TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 1 - SUMMARY OF SURVIVAL - P1

DOSE	TOTAL PER GROUP	TOTAL SURVIVORS AT TERMINATION	ANIMAL NUMBER TYPE/DAY OF DEATH SIGNIFICANT POSTMORTEM FINDINGS	SURVIVAL INDEX
MALES				
0%	30	30		100%
0.02%	30	30		100%
0.06%	30	30		100%
0.2%	30	30		100%
0.4%	30	30		100%
FEMALES				
0%	30	30		100%
0.02%	30	30		100%
0.06%	30	28	IGG317F FOUND DEAD/TEST DAY 90 (GD 12) LUNGS DISCOLORED ANOGENITAL STAINING DRY RED MATERIAL AROUND BOTH EYES AND MOUTH RED MATERIAL THORACIC CAVITY	93%
0.2%	30	30		100%
0.4%	30	30	IGG285F FOUND DEAD/TEST DAY 8 URINARY BLADDER DISTENDED, DARK RED FILLED WITH BROWN LIQUID	100%
NOTE: GD - GESTATION DAY				

SURVIVAL INDEX (%) = $\frac{\text{TOTAL SURVIVORS AT TERMINATION}}{\text{TOTAL NUMBER OF ANIMALS IN GROUP}} \times 100$

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1

	MALES																
	D A Y	0	1	2	3	4	5	6	7	8	9	10	11	12			
SURVIVORS	0	7	1	2	2	3	4	4	5	6	7	7	8	9	1	1	2
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
GENERAL OBSERVATION WITHIN NORMAL LIMITS	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
RESPIRATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RED ORAL DISCHARGE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
APPEARANCE SOFT STOOL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SCABS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SWOLLEN: SNOUT OR MOUTH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1 (CONT'D)

		MALES																	
		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		0	7	1	2	2	3	4	4	4	5	6	7	7	8	9	1	1	2
MASS: VENTRAL CERVICAL	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.02%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.06%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.2%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SORES	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.02%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.06%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.2%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BROKEN: INCISOR (S)	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.02%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.06%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.2%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RED MATERIAL SEEN: SNOOUT	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.02%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.06%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.2%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LITTLE SIGN OF STOOL	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.02%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.06%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.2%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1 (CONT'D)

		MALES																
		D A Y																
		0	1	2	3	4	4	4	5	6	7	7	8	9	9	10	11	12
LITTLE SIGN OF FOOD CONSUMPTION		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.02%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.06%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MALOCCLUDED INCISORS		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.02%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.06%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ALOPECIA		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.02%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.06%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MISSING: INCISOR (S)		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.02%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.06%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR DRIED RED OCULAR DISCHARGE		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.02%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.06%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4%		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1 (CONT'D)

MALES

	D Y	A Y	A Y	D Y	D Y	A Y	A Y
SURVIVORS	1	1	2	3	1	1	3
	9	6					
	30	30	30	30	30	30	30
	30	30	30	30	30	30	30
	30	30	30	30	30	30	30
	30	30	30	30	30	30	30
GENERAL OBSERVATION WITHIN NORMAL LIMITS	24	24	24	26	23		
	27	27	27	27	27		
	29	29	29	30	30		
	27	27	27	27	28		
APPEARANCE SCABS	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
MASS: VENTRAL CERVICAL	1	1	1	1	1	1	1
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
SORES	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	1	1	1	1	1	1	1
	0	0	0	0	0	0	0
BROKEN: INCISOR (S)	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1 (CONT'D)

MALES

D A Y	D A Y	D A Y
1	1	1
2	2	3
9	6	3

MALOCCLUDED INCISORS

0%
0.02%
0.06%
0.2%
0.4%

1	1	1
1	1	1
2	2	2
0	2	0
2	2	1

ALOPECIA

0%
0.02%
0.06%
0.2%
0.4%

1	1	1
1	1	1
1	1	1
0	1	0
1	1	1

MISSING: INCISOR (S)

0%
0.02%
0.06%
0.2%
0.4%

2	2	2
1	1	2
0	0	0
0	0	0

OCULAR
DRIED RED OCULAR DISCHARGE

0%
0.02%
0.06%
0.2%
0.4%

4	4	4
2	2	2
0	0	0
0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1 (CONT'D)

		FEMALES																
		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		0	7	1	2	2	3	4	4	4	5	6	6	7	7	8	9	10
SURVIVORS		0	7	1	2	2	3	4	4	4	5	6	6	7	7	8	9	10
		30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
		30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
		30	30	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
		30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
GENERAL OBSERVATION WITHIN NORMAL LIMITS		0%	0.02%	0.06%	0.2%	0.4%												
APPEARANCE MALOCCLUDED INCISORS		0%	0.02%	0.06%	0.2%	0.4%												
ALOPECIA		0%	0.02%	0.06%	0.2%	0.4%												
OCULAR RED OCULAR DISCHARGE		0%	0.02%	0.06%	0.2%	0.4%												
DRIED RED OCULAR DISCHARGE		0%	0.02%	0.06%	0.2%	0.4%												

NOTE: AFTER DAY 70, SEE GESTATION/POSTPARTUM OBSERVATIONS AS FEMALES WERE CONFIRMED MATED AND/OR DELIVERED
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TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 3 - INCIDENCE OF GESTATION OBSERVATIONS - P1
FEMALES

	GESTATION DAY:			
	0	7	14	21
TOTAL (a)	25	25	25	25
0%	27	27	27	27
0.02%	23	23	22	22
0.06%	26	26	26	26
0.2%	21	21	21	21
0.4%				
GENERAL OBSERVATION WITHIN NORMAL LIMITS				
0%	24	23	23	23
0.02%	27	26	25	25
0.06%	23	23	22	21
0.2%	26	26	26	26
0.4%	20	19	19	19
APPEARANCE MALOCCLUDED INCISOR(S)				
0%	0	1	1	1
0.02%	0	0	0	0
0.06%	0	0	0	0
0.2%	0	0	0	0
0.4%	0	0	0	0
ALOPECIA				
0%	0	1	1	1
0.02%	0	0	0	0
0.06%	0	0	0	0
0.2%	0	0	0	0
0.4%	1	1	1	1
SCABS TRUNK				
0%	0	0	0	0
0.02%	0	0	0	0
0.06%	0	0	0	0
0.2%	0	0	0	0
0.4%	0	0	0	0
DRY RED OCULAR DISCHARGE				
0%	1	2	2	2
0.02%	0	0	1	0
0.06%	0	0	0	0
0.2%	0	0	0	0
0.4%	0	1	1	1

NOTE: (a) - TOTALS DO NOT INCLUDE NON-PREGNANT AND/OR NO CONFIRMED DATE OF MATING FEMALES

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 4 - INCIDENCE OF POSTPARTUM OBSERVATIONS - P1
FEMALES

	POSTPARTUM DAY:						
	0	4	7	1	4	7	2
TOTAL (a)	26	25	25	25	25	25	25
	28	28	28	28	28	28	28
	24	24	24	24	24	24	24
	26	26	26	26	26	26	26
	24	24	24	24	24	24	24
GENERAL OBSERVATION WITHIN NORMAL LIMITS							
0%	21	22	21	22	22	22	23
0.02%	25	25	25	26	26	26	26
0.06%	23	23	23	22	22	22	22
0.2%	25	26	26	26	26	26	26
0.4%	22	22	22	22	22	22	22
APPEARANCE MALOCCLUDED/BROKEN/MISSING INCISOR(S)							
0%	1	1	1	1	1	1	1
0.02%	0	0	0	0	0	0	0
0.06%	0	0	0	0	0	0	0
0.2%	0	0	0	0	0	0	0
0.4%	0	0	0	0	0	0	0
MASS: ABDOMINAL							
0%	0	0	1	1	1	1	1
0.02%	0	0	0	0	0	0	0
0.06%	0	0	0	0	0	0	0
0.2%	0	0	0	0	0	0	0
0.4%	0	0	0	0	0	0	0
ALOPECIA							
0%	0	0	0	0	0	0	0
0.02%	0	0	0	0	0	0	0
0.06%	0	0	0	0	0	0	0
0.2%	0	0	0	0	0	0	0
0.4%	0	0	0	0	0	0	0
DRY RED OCULAR DISCHARGE							
0%	2	2	2	1	1	1	0
0.02%	1	1	1	1	1	1	0
0.06%	0	0	0	0	0	0	0
0.2%	0	0	0	0	0	0	0
0.4%	1	1	1	1	1	1	1

NOTE: (a) - TOTALS DO NOT INCLUDE NON-PREGNANT AND/OR NO CONFIRMED DATE OF MATING FEMALES

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MRD-94-775: 177535A

TABLE 4 - INCIDENCE OF POSTPARTUM OBSERVATIONS - P1 (CONT'D)

FEMALES

	POSTPARTUM DAY:					
	0	4	7	10	14	21
VAGINAL DISCHARGE	4	1	1	0	4	2
0%	0	0	0	0	0	0
0.02%	0	0	0	0	0	0
0.06%	0	0	0	0	0	0
0.2%	1	0	0	0	0	0
0.4%	0	0	0	0	0	0
COARSE TREMORS/CONVULSIONS	0	0	0	0	0	0
0%	0	0	0	0	0	0
0.02%	0	0	0	0	0	0
0.06%	0	0	0	0	1	1
0.2%	0	0	0	0	0	0
0.4%	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MRD-94-775; 177535A

KEY A - STATISTICAL SYMBOLS AND ABBREVIATIONS

	No difference	p≤0.05	p≤0.01	Statistical Statement
(PARAMETRIC)				
A-		A	A+	No statistical difference among the means Significant difference among the means
L-		L	L+	No linear response to the dose levels Response is linearly related to dose
		Q	Q+	Linear response shows lack of fit
		*	**	Mean significantly different from control mean
(NONPARAMETRIC)				
K-		K	K+	No statistical difference among the means Means differ significantly
J-		J	J+	No ordered response to the dose levels An ordered response to the dose levels
		*	**	Mean significantly different from control mean

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 5 - MEAN BODY WEIGHT (GRAMS) - P1
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

MALE	A-L-																
	D A Y	A Y															
0 % MEAN STD.DEV. (N)	202.4 11.8 30	263.9 16.7 30	314.7 21.7 30	355.2 25.8 30	393.2 28.4 30	421.3 30.5 30	445.4 32.3 30	471.5 34.7 30	492.5 36.6 30	507.9 39.0 30	533.2 41.4 30	523.9 33.1 30	499.9 31.5 30	505.6 45.4 30	528.4 47.9 30	526.5 43.8 30	511.9 36.1 30
0.02 % MEAN STD.DEV. (N)	203.2 11.9 30	263.4 15.5 30	314.1 18.4 30	353.7 20.8 30	390.7 22.6 30	419.8 26.2 30	443.8 29.2 30	463.9 32.8 30	485.0 32.2 30	499.9 31.5 30	523.9 33.1 30	499.9 31.5 30	505.6 45.4 30	528.4 47.9 30	526.5 43.8 30	511.9 36.1 30	
0.06 % MEAN STD.DEV. (N)	204.2 10.8 30	265.6 15.8 30	316.1 21.5 30	356.0 25.7 30	389.7 30.5 30	423.5 33.5 30	449.9 35.7 30	471.4 39.1 30	489.9 42.0 30	505.6 45.4 30	528.4 47.9 30	499.9 31.5 30	505.6 45.4 30	528.4 47.9 30	526.5 43.8 30	511.9 36.1 30	
0.2 % MEAN STD.DEV. (N)	202.5 12.4 30	260.8 16.5 30	309.5 17.7 30	349.5 20.7 30	385.3 25.3 30	419.2 29.4 30	443.6 33.9 30	469.4 36.4 30	489.4 37.4 30	504.0 40.5 30	526.5 43.8 30	499.9 31.5 30	504.0 40.5 30	526.5 43.8 30	526.5 43.8 30	511.9 36.1 30	
0.4 % MEAN STD.DEV. (N)	203.5 11.7 30	264.0 14.4 30	312.4 17.5 30	352.5 21.1 30	384.5 23.6 30	413.8 24.9 30	436.4 27.7 30	459.9 30.5 30	479.0 32.9 30	490.9 34.2 30	511.9 36.1 30	499.9 31.5 30	490.9 34.2 30	526.5 43.8 30	526.5 43.8 30	511.9 36.1 30	

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 5 - MEAN BODY WEIGHT (GRAMS) - P1 (CONT'D)
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

FEMALE	A-L-															
	MEAN	STD. DEV.														
0 %	165.3	10.6	198.8	14.1	224.5	17.5	242.9	21.3	271.3	25.2	284.9	26.4	294.7	28.4	304.7	30.3
MEAN	197.3	13.1	223.3	15.5	243.9	17.8	272.0	21.4	285.0	22.1	297.8	25.0	306.5	27.4	300.7	27.4
STD. DEV.	10.6	30	15.5	30	17.8	30	21.4	30	22.1	30	25.0	30	27.4	30	27.4	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.02 %	163.7	9.0	193.3	10.5	219.6	13.2	236.3	16.4	264.9	17.7	278.7	20.0	289.0	23.0	297.9	22.5
MEAN	197.6	10.6	225.3	12.2	244.5	13.7	272.0	15.1	285.0	16.5	297.8	17.4	306.5	20.7	301.6	23.6
STD. DEV.	10.6	30	12.2	30	13.7	30	15.1	29	16.5	29	17.4	29	20.7	29	23.6	30
(N)	30	30	30	30	30	30	29	29	29	29	29	29	29	29	30	30
0.06 %	164.4	8.7	197.6	10.6	225.3	12.2	244.5	13.7	272.0	15.1	285.0	16.5	297.8	17.4	306.5	20.7
MEAN	197.3	13.1	223.3	15.5	243.9	17.8	272.0	21.4	285.0	22.1	297.8	25.0	306.5	27.4	300.7	27.4
STD. DEV.	10.6	30	15.5	30	17.8	30	21.4	30	22.1	30	25.0	30	27.4	30	27.4	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.2 %	165.3	10.6	197.3	13.1	223.3	15.5	243.9	17.8	272.0	21.4	285.0	22.1	297.8	25.0	306.5	20.7
MEAN	197.3	13.1	223.3	15.5	243.9	17.8	272.0	21.4	285.0	22.1	297.8	25.0	306.5	27.4	300.7	27.4
STD. DEV.	10.6	30	15.5	30	17.8	30	21.4	30	22.1	30	25.0	30	27.4	30	27.4	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.4 %	164.3	10.3	196.4	14.8	223.1	16.6	246.5	19.2	271.4	22.5	284.0	24.5	296.5	25.6	305.7	27.5
MEAN	196.4	14.8	223.1	16.6	246.5	19.2	271.4	22.5	284.0	24.5	296.5	25.6	305.7	27.5	310.9	27.5
STD. DEV.	10.3	30	14.8	30	16.6	30	19.2	30	22.5	30	24.5	30	25.6	30	27.5	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30

NOTE: AFTER DAY 70, SEE GESTATION/POSTPARTUM BODY WEIGHTS AS FEMALES WERE CONFIRMED MATED AND/OR DELIVERED

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 5 - MEAN BODY WEIGHT (GRAMS) - F1 (CONT'D)
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

MALE	A-L-													
	D A Y													
0 %	7	7	8	4	9	1	9	8	1	1	1	1	1	1
MEAN	523.3	545.8	555.2	560.4	574.7	586.7	597.7	602.3	609.4	601.6	601.6	601.6	601.6	601.6
STD. DEV.	43.7	47.9	44.4	45.6	45.0	46.0	50.3	49.4	56.7	49.1	49.1	49.1	49.1	49.1
(N)	30	30	30	30	30	30	30	30	24	30	30	30	30	24
0.02 %	7	7	8	4	9	1	9	8	1	1	1	1	1	1
MEAN	520.8	541.1	552.8	563.4	579.6	590.4	598.4	600.1	614.8	600.1	600.1	600.1	600.1	600.1
STD. DEV.	31.7	43.2	35.9	38.2	36.9	37.5	37.7	38.9	41.4	38.9	38.9	38.9	38.9	38.9
(N)	30	30	30	30	30	30	30	30	24	30	30	30	30	24
0.06 %	7	7	8	4	9	1	9	8	1	1	1	1	1	1
MEAN	522.3	522.9	551.9	564.5	577.0	587.2	599.1	601.6	621.5	601.6	601.6	601.6	601.6	601.6
STD. DEV.	48.0	63.3	50.9	53.7	54.0	56.5	56.7	55.9	55.1	55.9	55.9	55.9	55.9	55.9
(N)	30	30	30	30	30	30	30	30	24	30	30	30	30	24
0.2 %	7	7	8	4	9	1	9	8	1	1	1	1	1	1
MEAN	522.4	538.1	553.3	566.9	575.6	585.4	599.2	601.6	618.5	601.6	601.6	601.6	601.6	601.6
STD. DEV.	44.9	43.1	44.2	46.2	49.0	50.1	50.2	49.1	52.9	49.1	49.1	49.1	49.1	49.1
(N)	30	30	30	30	30	30	30	30	24	30	30	30	30	24
0.4 %	7	7	8	4	9	1	9	8	1	1	1	1	1	1
MEAN	507.9	525.8	535.5	542.5	551.4	564.4	573.8	583.6	609.5	583.6	583.6	583.6	583.6	583.6
STD. DEV.	37.2	38.0	40.0	44.1	42.8	44.3	44.3	45.3	38.7	45.3	45.3	45.3	45.3	45.3
(N)	30	30	30	30	30	30	30	30	24	30	30	30	30	24

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 6 - MEAN BODY WEIGHT CHANGE (GRAMS) - P1
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

MALE	0-7		7-14		14-21		21-28		28-35		35-42		42-49		49-56		56-63		63-70		70-77		77-84		
	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K+J+	K+J-	K+J-	A-L-	A-L-	KJ-	KJ-	K-J-	K-J-	A-L-	A-L-	A-L+	AL-Q	AL-Q	K+J-	K+J-			
0 %	61.5	60.2	61.4	58.3	60.6	61.5	60.2	61.4	58.3	60.6	61.5	60.2	61.4	58.3	60.6	61.5	60.2	61.4	58.3	60.6	61.5	60.2	61.4	58.3	60.6
MEAN	6.9	6.6	7.2	6.1	5.0	5.3	5.2	5.9	5.7	5.3	5.7	5.3	5.9	5.7	5.3	5.7	5.3	5.7	5.3	5.7	5.3	5.7	5.3	5.7	5.3
STD. DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.02 %	50.8	50.7	50.5	48.7	48.4	39.5	37.0	39.9	40.0	33.8	24.1	26.1	20.1	21.2	21.0	15.4	25.3	22.9	22.4	22.9	21.0	19.1	11.9	11.9	11.9
MEAN	7.1	6.9	7.6	6.2	5.0	5.3	4.5	6.1	7.4	9.3	5.7	5.9	10.8	8.6	4.9	6.0	5.7	5.9	5.9	5.7	4.9	4.1	4.5	4.5	4.5
STD. DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.06 %	50.8	50.7	50.5	48.7	48.4	39.5	37.0	39.9	40.0	33.8	24.1	26.1	20.1	21.2	21.0	15.4	25.3	22.9	22.4	22.9	21.0	19.1	11.9	11.9	11.9
MEAN	7.1	6.9	7.6	6.2	5.0	5.3	4.5	6.1	7.4	9.3	5.7	5.9	10.8	8.6	4.9	6.0	5.7	5.9	5.9	5.7	4.9	4.1	4.5	4.5	4.5
STD. DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.2 %	50.8	50.7	50.5	48.7	48.4	39.5	37.0	39.9	40.0	33.8	24.1	26.1	20.1	21.2	21.0	15.4	25.3	22.9	22.4	22.9	21.0	19.1	11.9	11.9	11.9
MEAN	7.1	6.9	7.6	6.2	5.0	5.3	4.5	6.1	7.4	9.3	5.7	5.9	10.8	8.6	4.9	6.0	5.7	5.9	5.9	5.7	4.9	4.1	4.5	4.5	4.5
STD. DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.4 %	50.8	50.7	50.5	48.7	48.4	39.5	37.0	39.9	40.0	33.8	24.1	26.1	20.1	21.2	21.0	15.4	25.3	22.9	22.4	22.9	21.0	19.1	11.9	11.9	11.9
MEAN	7.1	6.9	7.6	6.2	5.0	5.3	4.5	6.1	7.4	9.3	5.7	5.9	10.8	8.6	4.9	6.0	5.7	5.9	5.9	5.7	4.9	4.1	4.5	4.5	4.5
STD. DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
(N)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 6 - MEAN BODY WEIGHT CHANGE (GRAMS) - P1 (CONT'D)
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

FEMALE	0-7		7-14		14-21		21-28		28-35		35-42		42-49		49-56		56-63		63-70	
	A-L-	A-L-	A-L-	A-L-	A+L+	A+L+	A+L+	A-L-	A-L-	A-L-										
0 %	33.3	25.7	18.4	16.2	12.1	12.1	13.7	9.8	10.0	10.0	9.8	10.3	8.9	8.9	10.3	7.1	4.7	4.7	12.4	12.4
MEAN	6.1	6.1	6.4	7.2	6.3	6.3	4.7	7.3	8.6	8.6	7.3	5.5	4.9	4.9	5.5	7.1	7.1	7.1	8.3	8.3
STD.DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.02 %	29.6	26.3	16.7	15.7	12.8	12.8	13.9	10.3	11.1	11.1	13.0	10.3	8.9	8.9	10.3	3.7	3.7	3.7	11.6	11.6
MEAN	5.6	4.9	5.3	5.3	5.4	5.4	4.3	5.5	4.8	4.8	5.7	5.5	4.9	4.9	5.5	5.4	5.4	5.4	5.9	5.9
STD.DEV.	30	30	30	30	30	30	30	30	29	29	29	29	29	29	29	30	30	30	30	30
0.06 %	33.2	28.1	19.2	16.4	11.1	11.1	13.0	12.8	11.1	11.1	13.0	12.8	8.7	8.7	12.8	3.0	3.0	3.0	12.8	12.8
MEAN	6.0	5.2	5.2	4.8	4.8	4.8	5.7	5.2	4.8	4.8	5.7	5.2	6.7	6.7	5.2	5.5	5.5	5.5	12.4	12.4
STD.DEV.	30	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29
0.2 %	32.0	26.0	20.6	11.7	11.9	11.9	12.7	9.3	11.9	11.9	12.7	9.3	11.1	11.1	12.7	4.1	4.1	4.1	13.5	13.5
MEAN	6.0	4.7	4.7	6.8	6.8	6.8	4.4	6.8	5.2	5.2	4.4	6.8	6.4	6.4	4.4	5.7	5.7	5.7	7.0	7.0
STD.DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
0.4 %	32.1	26.7	23.4	12.5	12.4	12.4	12.6	12.5	12.4	12.4	12.6	12.5	9.2	9.2	12.6	5.2	5.2	5.2	11.0	11.0
MEAN	6.6	5.1	4.5	5.3	5.9	5.9	5.5	6.5	5.9	5.9	5.5	6.5	5.6	5.6	5.5	5.7	5.7	5.7	6.2	6.2
STD.DEV.	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30

NOTE: AFTER DAY 70 SEE GESTATION/POSTPARTUM BODY WEIGHTS AS FEMALES WERE CONFIRMED MATED AND/OR DELIVERED

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
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TABLE 6 - MEAN BODY WEIGHT CHANGE (GRAMS) - P1 CONT'D
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

MALE	84-91		91-98		98-105		105-112		112-119		119-126		126-133	
	K+J- A Y S	A+L-Q+ A Y S	A+L-Q+ A Y S	A+L+ A Y S	A-L- A Y S	K+J- A Y S	A+L+Q+ A Y S	A-L A Y S	K+J- A Y S	A+L+Q+ A Y S	A-L A Y S	A+L+Q+ A Y S	A-L A Y S	
0 %	8.4	5.2	14.2	12.0	11.1	4.6	6.8	12.1	11.1	4.6	6.8	11.1	4.6	
MEAN	12.1	8.2	7.5	5.6	13.4	7.3	7.6	33.4	8.0	1.7	2.9	11.1	4.6	
STD.DEV.	30	30	30	30	30	30	24	30	30	30	24	30	24	
0.02 %	11.7	10.5	16.3	10.8	8.0	1.7	2.9	33.4	5.3	6.6	5.6	11.1	4.6	
MEAN	37.4	8.7	6.4	6.4	5.3	3.0	5.6	30	30	30	24	30	24	
STD.DEV.	30	30	30	30	30	30	24	30	30	30	24	30	24	
0.06 %	29.0	12.6	12.5	10.2	11.9	2.5	8.5	37.4	4.6	7.1	5.8	11.9	2.5	
MEAN	30	30	30	30	30	30	24	30	30	30	24	30	24	
STD.DEV.	30	30	30	30	30	30	24	30	30	30	24	30	24	
0.2 %	15.1	13.6	8.8	9.8	13.8	2.4	11.0	30	5.9	6.0	6.1	13.8	2.4	
MEAN	5.3	5.0	6.0	6.7	5.9	3.0	6.1	30	30	30	24	30	24	
STD.DEV.	30	30	30	30	30	30	24	30	30	30	24	30	24	
0.4 %	9.7	7.0	9.0	12.9	9.5	9.8	11.5	30	6.1	5.7	5.3	9.5	9.8	
MEAN	7.5	8.9	10.5	8.6	6.1	5.7	5.3	30	30	30	24	30	24	
STD.DEV.	30	30	30	30	30	30	24	30	30	30	24	30	24	

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 7 - MEAN GESTATION BODY WEIGHT AND BODY WEIGHT CHANGE - P1
(SEE KEY A FOR STATISTICAL SYMBOLS AND ABBREVIATIONS)

FEMALE	GESTATION DAY:											
	0	7	14	21	28	35	42	49	56	63		
0 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K-J-	A-L-
MEAN	321.2	357.9	395.2	489.5	36.7	37.1	36.9	37.3	36.7	37.3	94.4	168.4
STD. DEV.	31.4	32.4	35.1	44.0	8.1	7.9	8.8	6.6	8.1	6.6	20.9	23.3
(N)	25	25	25	25	25	27	27	25	25	25	25	25
0.02 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	312.4	349.5	386.4	479.2	37.1	37.1	36.9	37.3	37.1	36.9	92.8	166.7
STD. DEV.	27.7	30.3	31.4	44.4	7.9	7.9	8.8	6.6	7.9	8.8	23.1	26.6
(N)	27	27	27	27	27	27	27	25	27	27	27	27
0.06 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	322.7	354.7	389.5	482.8	32.0	32.0	33.9	33.9	32.0	33.9	93.3	160.4
STD. DEV.	18.0	18.8	21.6	37.8	8.9	8.9	8.0	6.6	8.9	8.0	24.5	31.4
(N)	23	23	22	22	23	23	22	22	23	22	22	22
0.2 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	318.6	353.3	388.7	483.3	34.7	34.7	35.4	35.4	34.7	35.4	94.7	164.8
STD. DEV.	25.1	27.6	30.1	35.1	8.0	8.0	6.9	6.9	8.0	6.9	14.5	23.6
(N)	26	26	26	26	26	26	26	26	26	26	26	26
0.4 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	325.1	360.3	394.2	489.1	35.1	35.1	34.0	34.0	35.1	34.0	94.9	164.0
STD. DEV.	26.2	30.6	33.3	35.0	6.2	6.2	5.7	5.7	6.2	5.7	12.5	15.8
(N)	21	21	21	21	21	21	21	21	21	21	21	21

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 8 - MEAN POSTPARTUM BODY WEIGHT AND BODY WEIGHT CHANGE - P1
(GRAMS)
(SEE KEY A FOR STATISTICAL SYMBOLS AND ABBREVIATIONS)

FEMALE	POSTPARTUM DAY:													
	0	4	7	10	14	21	28	35	42	49				
0 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K-J-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	369.0	370.6	372.4	388.0	397.8	383.8	383.8	3.5	1.8	15.6	9.8	14.0	16.8	
STD. DEV.	43.7	35.1	29.2	31.2	29.3	32.0	32.0	26.2	14.0	13.4	13.0	14.3	22.3	
(N)	26	25	25	25	25	25	25	25	25	25	25	25	25	
0.02 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K-J-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	354.0	359.7	368.2	378.2	391.9	381.4	381.4	5.7	8.5	10.0	13.7	10.5	27.4	
STD. DEV.	30.8	25.2	24.3	27.5	22.8	21.9	21.9	16.5	7.7	13.6	12.5	13.6	22.6	
(N)	28	28	28	28	28	28	28	28	28	28	28	28	28	
0.06 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K-J-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	362.0	372.7	376.8	391.0	401.6	381.5	381.5	10.7	4.1	14.2	10.6	20.1	19.5	
STD. DEV.	20.5	20.6	22.8	19.3	18.2	20.0	20.0	14.4	10.5	13.9	8.0	12.6	13.0	
(N)	24	24	24	24	24	24	24	24	24	24	24	24	24	
0.2 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K-J-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	357.4	364.0	373.5	383.2	398.8	389.3	389.3	4.8	9.5	9.8	15.5	9.4	30.6	
STD. DEV.	34.6	25.9	26.7	21.9	26.6	26.7	26.7	16.0	8.4	14.6	10.2	13.0	20.3	
(N)	25	26	26	26	26	26	26	25	26	26	26	26	25	
0.4 %	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	K-J-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
MEAN	362.8	366.0	372.9	389.2	397.8	385.0	385.0	3.3	6.8	16.3	8.6	12.8	22.3	
STD. DEV.	34.4	30.4	28.3	27.0	25.2	24.5	24.5	13.7	8.9	9.5	12.1	14.2	24.3	
(N)	24	24	24	24	24	24	24	24	24	24	24	24	24	

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 9 - MEAN FOOD CONSUMPTION - P1
(GRAMS)
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

MALE	WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 5		WEEK 6		WEEK 7		WEEK 8		WEEK 9		WEEK 10		WEEK 16		
	A-L																						
0 % MEAN STD.DEV. (N)	181.8 13.4 30	189.5 16.9 30	197.0 17.1 30	206.5 15.6 27	211.2 16.8 27	209.1 16.6 26	208.9 17.6 28	210.3 16.9 27	212.2 15.0 28	210.3 16.9 27	208.9 17.6 28	209.1 16.6 26	207.7 15.2 27	210.3 16.9 27	208.9 17.6 28	210.3 16.9 27	212.2 15.0 28	207.7 15.2 27	206.9 17.7 30	207.6 15.4 30	207.7 15.2 27	206.9 17.7 30	199.2 13.8 29
0.02 % MEAN STD.DEV. (N)	183.4 12.8 30	195.2 13.5 30	199.1 13.0 30	206.8 12.3 30	211.2 13.8 29	205.0 18.9 27	200.7 18.2 28	203.5 16.9 29	207.7 15.2 27	203.5 16.9 29	200.7 18.2 28	205.0 18.9 27	207.7 15.2 27	203.5 16.9 29	200.7 18.2 28	203.5 16.9 29	207.7 15.2 27	206.9 17.7 30	206.9 17.7 30	207.6 15.4 30	207.7 15.2 27	206.9 17.7 30	201.3 12.2 29
0.06 % MEAN STD.DEV. (N)	185.2 13.5 30	195.6 16.6 30	200.2 17.6 30	204.5 15.7 29	209.8 15.8 30	207.8 15.0 30	202.8 17.3 29	204.0 21.2 29	202.6 21.1 29	204.0 21.2 29	202.8 17.3 29	207.8 15.0 30	202.8 17.3 29	204.0 21.2 29	202.8 17.3 29	204.0 21.2 29	202.6 21.1 29	202.6 21.1 29	199.6 17.2 30	199.6 17.2 30	199.6 17.2 30	199.6 17.2 30	199.1 18.2 28
0.2 % MEAN STD.DEV. (N)	182.4 17.2 30	193.2 16.0 29	197.7 16.3 30	203.4 17.6 30	206.1 17.2 28	207.8 19.0 30	207.0 17.0 29	206.3 15.5 30	208.2 17.9 29	206.3 15.5 30	207.0 17.0 29	207.8 19.0 30	207.0 17.0 29	206.3 15.5 30	208.2 17.9 29	206.3 15.5 30	208.2 17.9 29	208.2 17.9 29	205.9 16.7 30	205.9 16.7 30	205.9 16.7 30	205.9 16.7 30	203.9 19.5 29
0.4 % MEAN STD.DEV. (N)	185.2 11.7 30	201.4 12.6 29	205.1 15.4 30	208.4 14.4 28	207.4 14.7 29	209.5 15.7 29	205.2 15.3 30	206.3 14.7 29	207.4 14.7 29	206.3 14.7 29	205.2 15.3 30	209.5 15.7 29	205.2 15.3 30	206.3 14.7 29	207.4 14.7 29	206.3 14.7 29	208.0 15.5 29	208.0 15.5 29	204.3 16.3 30	204.3 16.3 30	204.3 16.3 30	204.3 16.3 30	207.8 13.8 25

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MRD-94-775: 177535A

TABLE 10 - MEAN GESTATION FOOD CONSUMPTION - P1
 (GRAMS)
 (SEE KEY A FOR STATISTICAL SYMBOLS AND ABBREVIATIONS)

GESTATION DAY:	0			1		
	A-L-	A-L-	A-L-	K-J-	A-L-	A-L-
0 %	175.8	193.0	202.9	567.8	567.8	567.8
MEAN	19.2	22.8	18.5	50.7	50.7	50.7
STD. DEV.	(N)	25	24	24	24	24
0.02 %	178.5	191.2	203.4	573.7	573.7	573.7
MEAN	17.2	19.0	19.9	52.7	52.7	52.7
STD. DEV.	(N)	27	26	27	26	26
0.06 %	170.9	187.7	198.2	558.3	558.3	558.3
MEAN	15.1	16.1	15.3	40.3	40.3	40.3
STD. DEV.	(N)	23	22	22	22	22
0.2 %	172.2	186.4	193.3	551.8	551.8	551.8
MEAN	17.8	18.0	33.5	59.6	59.6	59.6
STD. DEV.	(N)	26	26	26	26	26
0.4 %	176.6	189.0	196.1	561.0	561.0	561.0
MEAN	15.8	18.6	16.8	49.4	49.4	49.4
STD. DEV.	(N)	20	21	20	20	20

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 11 - MEAN POSTPARTUM FOOD CONSUMPTION - P1
(GRAMS)
(SEE KEY A FOR STATISTICAL SYMBOLS AND ABBREVIATIONS)

FEMALE	POSTPARTUM DAY:							K-J-	K-J-	K-J-
	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-			
0 %	0	4	7	7	1	4	0	4	0	
MEAN	134.6	133.3	163.7	163.7	266.4	516.1	1209.5	516.1	1209.5	
STD. DEV.	32.3	19.8	23.3	23.3	21.7	38.5	102.0	38.5	102.0	
(N)	25	25	23	23	24	24	22	24	22	
0.02 %	135.8	134.2	163.1	163.1	251.3	499.4	1164.5	499.4	1164.5	
MEAN	24.7	23.3	28.7	28.7	47.3	90.1	207.7	90.1	207.7	
STD. DEV.	28	27	26	26	27	28	24	28	24	
(N)										
0.06 %	140.6	138.6	166.6	166.6	256.1	509.3	1211.3	509.3	1211.3	
MEAN	24.9	19.8	15.9	15.9	36.6	60.1	129.1	60.1	129.1	
STD. DEV.	23	24	24	24	24	23	22	23	22	
(N)										
0.2 %	128.4	141.7	167.1	167.1	262.7	520.2	1224.2	520.2	1224.2	
MEAN	21.0	13.7	11.9	11.9	18.9	33.7	79.5	33.7	79.5	
STD. DEV.	25	25	25	25	24	24	21	24	21	
(N)										
0.4 %	129.7	135.2	166.2	166.2	257.0	509.5	1191.4	509.5	1191.4	
MEAN	23.8	17.0	16.9	16.9	19.7	39.8	96.0	39.8	96.0	
STD. DEV.	23	23	24	24	24	22	21	22	21	
(N)										

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 12 - MEAN MEASURED DOSE RATE - P1
(MG/KG/DAY)

	W E E K 1	W E E K 2	W E E K 3	W E E K 4	W E E K 5	W E E K 6	W E E K 7	W E E K 8	W E E K 9	W E E K 10	W E E K 16
MALE											
0.02 % MEAN STD.DEV. (N)	22.5 1.1 30	19.3 1.0 30	17.0 0.7 30	15.9 0.6 30	14.9 0.6 29	13.6 0.8 27	12.7 0.8 28	12.3 0.9 29	12.1 0.7 27	11.6 1.0 30	9.9 0.5 29
0.06 % MEAN STD.DEV. (N)	67.6 3.2 30	57.6 2.5 30	51.0 2.5 30	46.8 1.7 29	44.3 2.5 30	40.8 1.7 30	37.6 1.7 29	36.3 2.7 29	34.8 2.0 29	33.2 1.8 30	29.3 2.2 28
0.2 % MEAN STD.DEV. (N)	224.7 12.0 30	193.8 10.0 29	171.4 8.4 30	158.1 7.9 30	147.2 6.6 28	137.6 6.3 30	129.6 6.0 29	123.1 6.0 30	119.8 6.7 29	114.3 5.7 30	99.9 7.0 29
0.4 % MEAN STD.DEV. (N)	453.0 19.2 30	399.9 16.6 29	352.6 15.8 30	321.1 14.5 28	296.6 13.1 29	282.4 13.5 29	261.8 12.4 30	251.4 10.6 29	245.4 12.9 29	233.0 13.7 30	210.1 13.4 25

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH MRD-94-775: 177535A

TABLE 12 - MEAN MEASURED DOSE RATE - P1 (CONT'D)
(MG/KG/DAY)

	W E E K 1	W E E K 2	W E E K 3	W E E K 4	W E E K 5	W E E K 6	W E E K 7	W E E K 8	W E E K 9	W E E K 10
0.02 %	19.5	20.6	19.0	17.9	17.1	16.3	15.4	14.9	14.6	13.9
MEAN										
STD.DEV.	1.6	1.4	1.1	1.0	1.2	1.1	1.0	0.9	0.9	0.9
(N)	30	30	26	29	29	30	30	29	28	29
0.06 %	58.3	62.1	56.3	52.7	49.7	47.2	44.2	42.9	41.9	39.5
MEAN										
STD.DEV.	3.4	4.2	3.3	3.0	2.5	3.0	2.5	2.6	2.8	3.4
(N)	30	29	27	29	28	27	28	28	23	26
0.2 %	190.5	202.1	183.5	171.8	165.7	159.5	145.8	145.5	142.1	139.0
MEAN										
STD.DEV.	10.5	10.7	8.7	7.8	9.3	10.0	6.9	11.0	9.2	8.8
(N)	30	28	30	29	30	30	29	29	29	28
0.4 %	379.6	405.7	368.2	349.0	331.1	315.5	297.8	287.7	286.5	274.3
MEAN										
STD.DEV.	27.5	21.7	17.6	20.0	21.7	17.8	27.2	19.1	21.4	19.7
(N)	30	30	28	28	30	29	29	28	28	27

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MRD-94-775: 177535A

TABLE 13 - MEAN GESTATION MEASURED DOSE RATE - P1
 (MG/KG/DAY)

GESTATION DAY:	0		7		1	
	7	4	1	4	2	1
FEMALE						
0.02 % MEAN	15.4	14.8	13.4			
0.06 % MEAN	43.2	43.2	39.0			
0.2 % MEAN	146.5	143.6	126.7			
0.4 % MEAN	294.5	286.3	253.7			

FORMULA = BWF X FF X CONCENTRATION (mg/kg)

$$BWF = 1 / [(BW1 - BW2) \times 0.5] + BW2$$

1000

BODY WEIGHT CONVERSION FACTOR: MIDPOINT OF THE INTERVAL = 0.5

FF = FOOD CONSUMPTION (KG)/NUMBER OF DAYS IN FOOD CONSUMPTION INTERVAL

BW1 = MOST RECENT BODY WEIGHT

BW2 = PREVIOUS BODY WEIGHT

NOTE: CALCULATION OF THESE VALUES USING A CALCULATOR WILL NOT AGREE WITH THE VALUES PRESENTED DUE TO ROUNDING DIFFERENCES IN THE CALCULATION

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
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TABLE 14 - MEAN POSTPARTUM MEASURED DOSE RATE - P1
 (MG/KG/DAY)

POSTPARTUM DAY:	0	4	7	10	14
FEMALE	4	7	1	4	1
0.02 % MEAN	19.0	24.6	29.1	32.6	36.9
0.06 % MEAN	57.4	74.0	86.8	96.9	111.5
0.2 % MEAN	178.0	256.2	294.4	335.9	377.2
0.4 % MEAN	355.9	487.9	581.6	653.1	743.8

FORMULA = BWF X FF X CONCENTRATION (mg/kg)

BWF = $1 / [(BW1 - BW2) \times 0.5] + BW2$

1000

BODY WEIGHT CONVERSION FACTOR: MIDPOINT OF THE INTERVAL = 0.5

FF = FOOD CONSUMPTION (KG)/NUMBER OF DAYS IN FOOD CONSUMPTION INTERVAL

BW1 = MOST RECENT BODY WEIGHT

BW2 = PREVIOUS BODY WEIGHT

NOTE: CALCULATION OF THESE VALUES USING A CALCULATOR WILL NOT AGREE WITH THE VALUES PRESENTED DUE TO ROUNDING DIFFERENCES IN THE CALCULATIONS

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TABLE 15 - INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS - P1

DOSE:	MALES				
	0%	0.02%	0.06%	0.2%	0.4%
TOTAL AT SCHEDULED SACRIFICE:	30	30	30	30	30
NO OBSERVABLE ABNORMALITIES	23	26	25	25	26
EPIDIDYMIDES: Small	-	-	1	1	-
KIDNEY(S):					
Cystic	-	-	-	1	-
Discolored	-	1	-	-	2
Dilated pelvis/ abnormal contents	-	-	1	-	-
LIVER: Foci	-	1	-	-	-
MASS: (Subcutis, right thoracic)	1	-	-	-	-
TESTES: Small and/or flaccid	-	-	2	1	-
SEMINAL VESICLE (Right horn): Small	-	-	-	1	-
URINARY BLADDER: Abnormal contents	-	-	-	1	-
GENERAL CONDITION:					
Dried red ocular discharge	5	1	2	-	-
Alopecia	1	-	1	-	1
Maloccluded/missing incisors	3	2	2	-	1
Scabs	-	-	1	1	-

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TABLE 15 - INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS - P1 (CONT'D)

DOSE:	FEMALES					
	0%	0.02%	0.06%	0.2%	0.4%	
TOTAL AT SCHEDULED SACRIFICE:	30	30	28	30 (a)	30	
NO OBSERVABLE ABNORMALITIES	24	27	20	25	18	
KIDNEY(S):			1	-	-	
Dilated renal pelvis	-	-	1	1	-	
Discolored	-	-	-	-	1	
Focus	-	-	-	-	-	
LIVER: Striations	-	-	-	-	1	
LUNGS: Discolored	1	-	1	-	1	
Foci	-	-	1	-	-	
MASS: (Subcutis, posterior ventral)	1	-	-	-	-	
OVARY: Cyst	1	-	-	-	-	
STOMACH: Thick and/or discolored	2	2	3	4	5	
THYMUS: Foci	-	1	-	-	1	
URINARY BLADDER: Thick/ abnormal contents	-	-	1	-	-	
UTERUS/VAGINA: Contained one retained fetus	1	-	1	-	-	
Distended/abnormal contents	-	-	-	-	-	
GENERAL CONDITION						
Alopecia	-	-	2	-	2	
Truncated tail	1	-	-	-	-	
Dried red ocular discharge	-	-	-	-	1	
NOT PREGNANT	4	1	3	4	6	
DID NOT DELIVER	-	-	1	-	-	

NOTE: (a) - OBSERVATIONS FOR ONE FEMALE INADVERTENTLY NOT RECORDED

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TABLE 15 - INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS - P1 (CONT'D)

DOSE:	FEMALES (CONT'D)			
	0%	0.02%	0.06%	0.2%
FOUND DEAD	-	-	2	-
GENERAL CONDITION				
Anogenital staining	-	-	1	-
Dried red material around eyes and mouth	-	-	1	-
THORACIC CAVITY				
Abnormal contents	-	-	1	-
LUNGS				
Discolored	-	-	1	-
URINARY BLADDER				
Distended/abnormal contents	-	-	1	-

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KEY B - ORGAN ABBREVIATIONS

Abbreviation	Organ Name
-----	-----
TBW/BW	Terminal Body Weight
LIVER	Liver
KIDNEY/KIDNY	Kidneys (paired)

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TABLE 16 - MEAN ORGAN WEIGHT (GRAMS) - P1
(SEE KEYS A AND B FOR ABBREVIATIONS)

MALE	T B W		L I V E R		K I D N E Y	
	A-L-	A-L+	A-L-	A-L+	A-L-	A-L+
0 %	611.5	21.27	4.14			
MEAN	53.2	3.04	0.36			
STD. DEV.	(N)	30				
0.02 %	610.7	21.03	4.06			
MEAN	41.9	2.59	0.38			
STD. DEV.	(N)	30				
0.06 %	608.0	21.31	4.12			
MEAN	53.9	2.57	0.35			
STD. DEV.	(N)	30				
0.2 %	611.2	22.26	4.36			
MEAN	51.5	2.68	0.43			
STD. DEV.	(N)	30				
0.4 %	592.5	**	**			
MEAN	46.6	23.90	4.74			
STD. DEV.	(N)	30	2.70	0.45		
			0.30			

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MRD-94-775: 177535A

TABLE 16 - MEAN ORGAN WEIGHT (GRAMS) - P1 (CONT'D)
 (SEE KEYS A AND B FOR ABBREVIATIONS)

FEMALE	T B W		L I V E R		K I D N E Y	
	A-L-	A+L+	A+L-	A+L+	A+L-	A+L+
0 % MEAN STD. DEV. (N)	372.7 33.3 26	17.57 2.54 26	3.07 0.31 26			
0.02 % MEAN STD. DEV. (N)	363.1 23.8 29	16.95 2.37 29	2.97 0.19 29			
0.06 % MEAN STD. DEV. (N)	360.5 24.0 24	17.41 3.48 24	2.98 0.26 24			
0.2 % MEAN STD. DEV. (N)	365.2 36.2 26	18.21 2.68 25	3.07 0.30 25			
0.4 % MEAN STD. DEV. (N)	366.7 26.8 24	19.61 2.71 24	3.24 0.28 24			

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
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TABLE 17 - MEAN RELATIVE ORGAN WEIGHT - P1
(SEE KEYS A AND B FOR ABBREVIATIONS)

MALE	L I V E R / B W		K I D N E Y / B W	
	A+L+	A+L+	A+L+	A+L+
0 % MEAN STD. DEV. (N)	0.035 0.003 30	0.0068 0.0006 30		
0.02 % MEAN STD. DEV. (N)	0.034 0.003 30	0.0067 0.0005 30		
0.06 % MEAN STD. DEV. (N)	0.035 0.003 30	0.0068 0.0005 30		
0.2 % MEAN STD. DEV. (N)	0.036 0.002 30	0.0072 0.0007 30		
0.4 % MEAN STD. DEV. (N)	** 0.040 0.003 30	** 0.0080 0.0008 30		

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MRD-94-775: 177535A

TABLE 17 - MEAN RELATIVE ORGAN WEIGHT - P1 (CONT'D)
 (SEE KEYS A AND B FOR ABBREVIATIONS)

FEMALE	L I V E R / B W		K I D N E Y / B W	
	K+J+	A+L+	K+J+	A+L+
0 % MEAN STD. DEV. (N)	0.047 0.007 26	0.0083 0.0008 26		
0.02 % MEAN STD. DEV. (N)	0.047 0.005 29	0.0082 0.0005 29		
0.06 % MEAN STD. DEV. (N)	0.048 0.008 24	0.0083 0.0006 24		
0.2 % MEAN STD. DEV. (N)	0.050 0.004 25	0.0085 0.0005 25		
0.4 % MEAN STD. DEV. (N)	** 0.053 0.005 24	** 0.0088 0.0005 24		

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
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TABLE 18 - SUMMARY OF REPRODUCTION DATA - P1

Dose (%)	Male		Female		Gestational Index (%)	Mean Days Gestation (N)	Mean Litter Size (N)	Mean Live (N)	Mean Dead (N)	Percent Live (%)	Percent Dead (%)	Sex Ratio	
	Mating Index (%)	Fertility Index (%)	Fertility Index (%)	Index (%)								M (%)	F (%)
0	NSS 90.0	NSS 86.7	NSS 90.0	NSS 92.6	NSS 100.0	NT 22.6	NT 14.7	NT 14.2	NT 0.5	XX 96.3	XX 3.7	NSS 50.3	NSS 49.7
0.02	90.0	96.7	90.0	100.0	96.6	22.5	14.2	14.0	0.2	98.5	1.5	46.2	53.8
0.06	79.3	89.7	79.3	100.0	92.3	22.4	15.5	15.4	0.1	99.2	0.8	50.0	50.0
0.2	96.7	86.7	96.7	89.7	100.0	22.4	14.7	14.0	0.6	95.8	4.2	49.9	50.1
0.4	83.3	80.0	83.3	84.0	100.0	22.3	14.8	14.6	0.1	99.2	0.8	52.4	47.6

NOTE: X p<0.05 by Chi Square Analysis
 XX p<0.01 by Chi Square Analysis
 + Dose-response trend, p<0.05 by Armitage Test
 ++ Dose-response trend, p<0.01 by Armitage Test
 * p<0.05 by Fisher Exact Test
 ** p<0.01 by Fisher Exact Test
 NT NOT TESTED FOR STATISTICAL DIFFERENCES
 NSS NO STATISTICALLY SIGNIFICANT DIFFERENCES

Male Mating Index (MATING) = ----- X 100
 Number of males for which mating confirmed
 Number of males used for mating
 Male Fertility Index (FERTIL) = ----- X 100
 Number of males impregnating females
 Number of males used for mating
 Female Fertility Index (FERTIL) = ----- X 100
 Number of females for which mating confirmed
 Number of females paired
 Female Fecundity Index (FECUND) = ----- X 100
 Number of females pregnant (a)
 Number of females for which mating confirmed
 Gestational Index (GESTAT) = ----- X 100
 Number of females with live litters
 Number of females pregnant

NOTE: (a) - EXCLUDING FEMALES WITH NO CONFIRMED DATE OF MATING

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
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TABLE 19 - SUMMARY OF OFFSPRING SURVIVAL - F1

Dose (%)	Pl Post Implantation Loss (%)	Live Birth Index (%)	Day 1 Survival Index (%)	Day 4 Survival Index (%)	Day 7 Survival Index (%)	Day 14 Survival Index (%)	Day 21 Survival Index (%)	Viability at Weaning Index (%)
0	7.2	96.3	97.8	96.2	99.5	100.0	100.0	99.5
0.02	9.5	98.5	98.5	97.8	100.0	99.5	99.5	99.0
0.06	7.0	99.2	98.4	95.9	99.5	100.0	100.0	99.5
0.2	7.9	95.8	95.9	95.3	100.0	100.0	100.0	100.0
0.4	6.3	99.2	97.7	96.9	99.5	100.0	100.0	99.5

NOTE: X p<0.05 by Chi Square Analysis
 XX p<0.01 by Chi Square Analysis
 + Dose-response trend, p<0.05 by Armitage Test
 ++ Dose-response trend, p<0.01 by Armitage Test
 ** p<0.05 by Fisher Exact Test
 *** p<0.01 by Fisher Exact Test
 NT NOT TESTED FOR STATISTICAL DIFFERENCES
 NSS NO STATISTICALLY SIGNIFICANT DIFFERENCES
 K-J- SEE KEY A FOR STATISTICAL SYMBOLS

Post Implantation Loss Index (%) =	Number of pups born	X 100	Day 7 S.I. (%) =	Number of live pups at Day 7	X 100
Live Birth Index (%) =	Number of live pups at birth	X 100	Day 14 S.I. (%) =	Number of live pups at Day 14	X 100
Day 1 S. I. (%) =	Number of live pups at Day 1	X 100	Day 21 S.I. (%) =	Number of live pups at Day 21	X 100
Day 4 S. I. (%) =	Number of live pups at Day 4 (pre-cull)	X 100	Viability at Weaning Index (%) =	Number of live pups at Day 21	x 100

NOTE: S. I. - SURVIVAL INDEX

