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Chemical Category	1,2-BENZENEDICARBOXYLIC ACID, DI-C8-10-BRANCHED ALKYL ESTER*		

A.03

EXXON CHEMICAL COMPANY



11490

FYI-1098-1343

Safety and Environmental Affairs Department
David J. Johnson
MANAGER, SAFETY PROGRAMS

October 16, 1998

Contains No CBI

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Washington, D. C. 20460-0001



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92 OCT 19 PM 4:03

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Re: FYI Submission

Dear Sir or Madam:

Under the "For Your Information" classification system, Exxon Chemical Company is submitting the following information describing the toxicity of a substance described as 1,2-Benzenedicarboxylic acid, di-C₈,--branched alkyl esters, C₉-rich (CAS Registry Number 68515-98-0). This substance is currently being manufactured for commercial purposes as defined by TSCA.

This submission is provided as background information for a TSCA Section 8(e) submission on a related substance with CAS Registry Number 68515-49-1.

The data presented in this submission is from a two-generation reproductive toxicity study in rats. In brief, there were no effects on mating, fertility or fecundity and no pathological changes in any of the reproductive organs. Thus, the results of the study clearly demonstrate that the test substance is not a reproductive toxicant. In addition, there were no statistically significant reductions in live birth and early survival indices among the offspring. The results of this study are summarized in the attachment, with complete details in the enclosed report.

If you have any questions or need additional information, please feel free to contact me on (281) 870-6874.

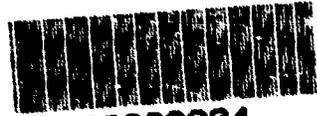
Sincerely yours,

Steven G. Hentges

SGH/jad
Attachment/Enclosure

92 OCT 30 PM 11:30

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84990000004

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Summary of Reproductive Toxicity Results

1,2-Benzenedicarboxylic acid, di-C₈₋₁₀-branched alkyl esters, C₉-rich

(CAS Registry Number 68515-48-0)

A definitive two-generation reproductive toxicity study was conducted with 1,2-Benzenedicarboxylic acid, di-C₈₋₁₀-branched alkyl esters, C₉-rich (CAS Registry Number 68515-48-0). The definitive study was preceded by a range-finding study.

In the first generation, adult male and female CD rats (P1 animals, 30 per dose group) were given dietary preparations containing 0, 0.2, 0.4 or 0.8% of the test substance beginning 10 weeks prior to mating, during the mating phase, and throughout gestation and lactation in the females. The dose levels were based on the results of the range-finding study. The dietary percentages corresponded to daily dosages of approximately 0, 170, 340 and 670 mg/kg/day, which increased during the lactation period. The offspring from this mating (the first generation or F1 animals) were exposed to the test substance throughout their entire life cycle; from the mothers during gestation and lactation, and from the diet from weaning until they had mated and produced a second generation of offspring. The second generation offspring (F2 animals) also received the test substance from their mothers during gestation and lactation and then were terminated at weaning (postnatal day 21).

In this study, there were no observed effects on mating, fertility or fecundity and no pathological changes in any of the reproductive organs. Thus, the results of the study clearly demonstrate that the test substance is not a reproductive toxicant. In addition, there were no statistically significant reductions in live birth and early survival indices among the offspring.

A 05

1,2 benzenedicarboxylic acid, di-C8, C9, C10 branched alkyl ester, C9 rich

CAS # 68515-48-0

EXXON BIOMEDICAL SCIENCES, INC.

FINAL REPORT

PROJECT NUMBER: 145535A

TEST MATERIAL: [REDACTED]
MRD-92-455

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MRD-92-455)

PERFORMED FOR:

EXXON CHEMICAL COMPANY
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and
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PERFORMED AT:

EXXON BIOMEDICAL SCIENCES, INC.
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DATE: February 29, 1996

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] MRD-92-485; 1455/5A**

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**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MIR-92-402); 14838A**

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**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRD-92-489; 14835A**

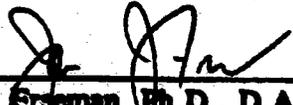
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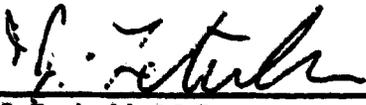
**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRD-92-489; 14833A**

APPROVAL SIGNATURES



**J. J. Freeman, Ph.D., D.A.B.T.
Mammalian Toxicology Laboratory Director**

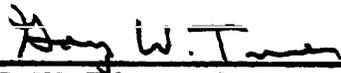
29 Feb 96
Date



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

29 Feb 96
Date

This study was conducted in accordance with OECD Principles of Good Laboratory Practice Regulations and the E.C. Council Decision on Good Laboratory Principles and the EPA Good Laboratory Practice Standards set forth in 40 CFR Part 792.



**G. W. Trimmer, B.A.
Study Director**

29 FEB 1996
Date

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-455; 14535A**

QUALITY ASSURANCE STATEMENT

STUDY NUMBER: 145535A

TEST SUBSTANCE/ARTICLE: MRD-92-455

STUDY SPONSOR: Exxon Chemical Company and Exxon Chemical Europe

Listed below are the dates that this study was inspected by the Quality Assurance Unit of Exxon Biomedical Sciences, Inc., and the dates findings were reported to the Study Director and Management.

<u>Date(s) of Inspection</u>	<u>Reported to Study Director</u>	<u>Reported to Management</u>
30 Nov 93	30 Nov 93	01,04 Dec 93
30 Nov 93	02 Dec 93	08,11 Dec 93
26 Dec 93	20 Dec 93	23,29 Dec 93
15 Mar 94	18 Mar 94	22,25 Mar 94
24,25 Mar 94	28 Mar 94	28 Mar, 02 Apr 94

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXX~~ MRD-92-455: 14535A**

QUALITY ASSURANCE STATEMENT (CONT.)

STUDY NUMBER: 145535A

TEST SUBSTANCE/ARTICLE: MRD-92-455

STUDY SPONSOR: Exxon Chemical Company and Exxon Chemical Europe

Listed below are the dates that this study was inspected by the Quality Assurance Unit of Exxon Biomedical Sciences, Inc., and the dates findings were reported to the Study Director and Management.

<u>Date(s) of Inspection</u>	<u>Reported to Study Director</u>	<u>Reported to Management</u>
25 Apr, 20 May 94	20 May 94	26 May, 05 Jun 94
30 Jun, 06 Jul 94	06 Jul 94	13,16 Jul 94
11,12 Jul 94	12 Jul 94	14,16 Jul 94
14,16 Sep 94	16 Sep 94	26 Sep, 01 Oct 94
15 Oct - 20 Nov 95	20 Nov 95	21,22 Feb 96
31 Jan -9,21 Feb 96	21 Feb 96	27 Feb 96


Joanne R. Jackson, B.S.
Quality Assurance Supervisor

21 Feb 96
Date

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~ NR-92-00: 14833A**

PERSONNEL

Study Director:

**December 9, 1993 to November 16, 1994:
As of November 16, 1994:**

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G. W. Trimmer, B.A.**

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R. C. Forgash, B.S.

Report Preparation Supervisor:

E. R. Frank, B.A.

Compound Preparation/Necropsy Supervisor:

M. A. Elliott, B.S.

Analytical Chemistry Supervisor:

D. J. Letinski, M.S.

Quality Assurance/Archives Supervisor:

J. R. Jackson, B.S.

Statistician:

M. J. Nicolich, Ph.D.

Maintenance Supervisor:

J. L. McGrath, A.S.

Veterinarian:

R. L. Harris, D.V.M.

Veterinary Pathologist:

**C. F. Morris, D.V.M.,
D.A.C.V.P.**

Consultant:

S. B. Harris, Ph.D.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRD-92-455; 14832A**

SUMMARY

This study was designed to provide general information concerning the potential effects of [REDACTED] (test material MRD-92-455), on gonadal function, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring in the rat.

Undiluted [REDACTED] was blended in Certified Rodent Chow at a fixed concentration and was mixed thoroughly to assure homogeneity. The test material-diet admixtures were administered *ad libitum* to 30 rats/sex/group at 3 dosage levels. Group 1 served as a control and received carrier (PMI Certified Rodent Chow) only. Groups 2, 3, and 4 received 0.2%, 0.4%, and 0.8% of [REDACTED] in food, respectively. Doses were selected based on findings from a One Generation Probe Study with [REDACTED] which resulted in lower body weight, suppression in body weight gain, lower food consumption, and increased liver and kidney weights compared with controls in parental animals at doses of 1.0% and 1.5% and suppression of body weight gain in the offspring at doses of 0.5%, 1.0%, and 1.5%. The offspring body weight reduction in the Probe study may have been the result of maternal stress, decreased milk consumption and/or due to direct exposure to DINP in the milk. However, the Probe study was terminated after only one generation since the pups in the mid and high dose groups were not thriving during the transition period from nursing to diet alone.

P1 males and females received test material 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 prior to mating and through the mating period for F2 litters, until sacrificed following delivery of their last litter sired. P2(F1) females were dosed from PND 21 for at least 10 weeks prior to mating, during mating, gestation, lactation, and until they were sacrificed following weaning of the F2 animals on PPD 21.

Clinical inlife observations, body weight, and food consumption were recorded for all P1 and P2 animals at least weekly during the pre-mating and mating periods (food consumption was not measured during mating due to cohabitation), and for 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. Following birth, the offspring were counted and examined externally daily from PND 0 to 21. Offspring were sexed and weighed on PND 0, 1, 4, 7, 14, and 21. P1/P2 males were sacrificed following the birth of their first litter sired, 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, and on all animals which died during the study. A full macroscopic examination was performed on these animals and selected organs and tissues were collected and weighed. A range of tissues were examined microscopically.

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; NRD-92-439; 14553A

SUMMARY (CONT'D)

There were no clinical signs which were judged to be directly related to treatment with [REDACTED]. The majority of P1 and P2 parental animals in all groups had no adverse clinical signs during the premating/mating, postmating, gestation, and/or postpartum periods.

There were no treatment-related deaths. Unscheduled mortality in the P1 parental animals was limited to one mid dose male (0.4%) and one low dose female (0.2%), both occurring prior to mating. Both deaths were considered incidental and unrelated to treatment with DINP. There were no unscheduled parental deaths in the P2 generation.

There were no biologically and/or statistically significant differences in P1 parental mean body weight or mean body weight change between the treated and control males and females during the majority of the study. Suppression in body weight gain was observed in the P1 high dose females during the postpartum period. In the P2 parental animals, there were several statistically significantly lower mean body weights in the high dose males and females compared with controls during the premating period. These significantly lower body weights compared with controls were most likely due to the lower mean body weight of the F1 pups during weaning which remained consistently lower and were evident at the beginning of the P2 generation (13% in males; 10% in females). In the absence of biologically significant differences in body weight gain between the treated and control animals, these lower mean body weights in the high dose animals compared with controls during the premating period were attributed to lower body weights of the P2 animals at the start of the P2 generation, rather than a treatment-related toxicological effect occurring during the P2 premating interval. During the postpartum period, there were statistically significant lower mean body weight of the high dose females compared with controls. These lower mean body weights (8-11%) during the postpartum period may be due, at least in part, to the lower body weight of the P2 females at the start of the P2 generation. Alternatively, these decreases may be due to maternal stress and increases in test material consumption during the postpartum period.

There were no biologically significant differences in mean food consumption between the treated and control males and females during the premating interval of either the P1 or P2 parental animals. During gestation, there was statistically significant lower mean food consumption in the P2 high dose females compared with controls. Additionally, there was significantly lower mean food consumption of both the P1 and P2 high dose females compared with controls during the postpartum interval.

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~; MSD-90-000; 14830A

SUMMARY (CONT'D)

In general, the mean measured dose rate for the males and females during pre-mating decreased over time, as expected. Also as expected, during the late gestation and the postpartum period, there was a steady increase in the mean measured dose rate in females. The mean measured dose rate (mg/kg/day) ranges for each group during the pre-mating, gestation and postpartum periods were as follows:

CONCENTRATION IN DIET	ACTUAL DOSE IN MG/KG/DAY DURING PREMATING PERIOD			
	P1 ♂	P1 ♀	P2 ♂	P2 ♀
0.2%	118-212	145-215	114-264	140-254
0.4%	236-426	278-425	235-523	271-522
0.8%	477-852	562-830	467-1090	544-1060

CONCENTRATION IN DIET	ACTUAL DOSE IN MG/KG/DAY DURING GESTATION (G) AND POSTPARTUM (PP) PERIOD			
	P1 G	P1 PP	P2 G	P2 PP
0.2%	139-153	159-356	133-153	174-395
0.4%	274-301	347-731	271-307	348-758
0.8%	543-571	673-1370	544-577	719-1541

There were biologically significant increases in the mean absolute and/or mean relative kidney weights of the P2 high and mid-dose males compared with controls. Additionally, there were statistically significant increases in the mean absolute and mean relative liver weights of both the P1 and P2 males and females at the high and/or mid dose levels compared with controls. These effects were substantiated by histopathological changes and thus, were considered treatment-related. No biologically significant effects were observed in the reproductive organs of any treated animals.

There were no gross postmortem findings in the P1 parental animals judged to be related to treatment with ~~XXXXXX~~. During the P2 generation, there was an increased incidence of dilated renal pelvis in the treated males compared with controls. This effect was substantiated at the histopathological examination (see below). Intestinal parasites, later diagnosed to be pinworms (*Syphacia muris*), were observed in the P1 and P2 males and/or females. These pinworms are commensal, relatively non-pathogenic and bacteria feeding. Pinworm parasites of laboratory rodents are generally non-pathogenic and infections are usually symptomless (Farrar et al., 1986). The origin of these parasites could not be determined, but were considered incidental and unrelated to treatment with DINP.

SUMMARY (CONT'D)

Treatment-related microscopic changes occurred in the liver of male and female rats of all treatment groups in both the P1 and P2 parental animals. Microscopic examination of the liver revealed a minimal to moderate increased cytoplasmic eosinophilia. The affected hepatocytes, although rarely enlarged microscopically, had a finely granular to homogenous cytoplasm which was intensely eosinophilic when stained with hematoxylin- and eosin, as compared with the controls. The intensity of this finding increased in a dose-related manner. This type of hepatocellular change, although not diagnostic, is seen with compounds which cause peroxisome proliferation. There was also an increased incidence of dilatation of the renal pelvis in the high and mid dose P2 males compared with controls. These changes were expected, since they were consistent with the results from studies with other phthalates (Gray et al., 1977) and DINP specifically (EBSI, 1982; BIBRA, 1985; EBSI, 1986). No treatment-related changes were observed in the kidneys of the P1 males or the P1/P2 females.

There were no statistically significant differences in Male Mating, Male Fertility, Female Fertility, Female Fecundity, or Female Gestational Indices between treated and control animals of either the P1 or P2 generation. Mean days of gestation of the P1/P2 treated and control groups were essentially equivalent. However in the F1 offspring, the mean litter size (15.1) and mean live offspring (14.8) of the high dose animals were greater than controls (12.5 and 12.2, respectively). This trend was not evident in the F2 offspring.

There were no biologically significant differences in the F1 or F2 offspring survival indices between the treated and control offspring. There were no treatment-related clinical findings observed in the offspring of any group. The majority of offspring in all groups were free of observable abnormalities from PND 0-21.

There were statistically significant lower mean offspring body weights in all treatment groups compared with controls during both the F1 and F2 generations. However, the weights of all F1 and F2 treated offspring at all intervals were within the historical control range of this laboratory, with the exception of the F2 high dose males and females on PND 0 and the F2 high dose males on PND 1. These findings in offspring appear to result from maternal stress and/or direct effects of DINP via exposure through lactation and are not indicative of developmental abnormalities or reproductive toxicity. An earlier developmental toxicity study of [REDACTED] (EBSI, 1994) demonstrated that exposure of pregnant female rats to doses up to 1000 mg/kg per day during gestation days (GD) 6-15, i.e., during organogenesis, did not result in developmental abnormalities or reduced fetal body weights. Other studies with phthalates concluded that these decreases were apparently due to decreased food consumption by the dams and changes in the quality or quantity of milk (Dostal et al., 1987). Thus, the lower body weights in the pups may have resulted from decreased milk consumption.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRID-98-459; 14935A**

SUMMARY (CONT'D)

In general, there were no gross postmortem findings in the F1 offspring judged to be related to treatment with [REDACTED]. The majority of animals were free of observable abnormalities at the scheduled terminal sacrifice on PND 21. Similarly, the majority of animals which died prior to scheduled termination (PND 0-20) were free of observable abnormalities, or were too autolyzed to be examined at the necropsy.

The test material was stable in feed at room temperature for at least 14 days and homogeneity was demonstrated. Concentration verification analysis indicated that all solutions were within 15% of the nominal concentrations.

In conclusion, findings in parental animals included microscopic changes in the kidneys of the P1 high dose (0.8%) and mid dose (0.4%) males and liver changes in both sexes of all treated groups (0.8%, 0.4%, and 0.2%), which correlated with increased mean absolute and/or relative kidney and liver weights in these groups. Changes in the liver and kidneys were expected, since they were consistent with the results from studies with other phthalates (Gray et al., 1977) and [REDACTED] specifically (EBSI, 1982; BIBRA, 1985; EBSI, 1986). There also was evidence of suppression in body weight gain and/or lower food consumption in the females during the postpartum interval. Lower mean body weight, body weight gain, and/or food consumption also were observed in the P2 males and females, but were considered to be related to the lower body weight of the F1 offspring (see below) which were present at the start of the P2 generation. Based on the microscopic liver changes in the low dose group, a parental systemic toxicity NOEL (No Observable Effect Level) could not be established, and a parental LOEL (Lowest Observable Effect Level) was established at 0.2% under the conditions of this study. There were no adverse effects on reproductive organs or parameters. There were no overt signs of toxicity observed in the offspring, as evidenced by the absence of adverse effects on survival or no adverse clinical signs. The mean body weights of the treated offspring were reduced in a dose-dependent manner on PND 0 and became further reduced during the postnatal period. Maternal exposure to DINP during the postpartum period was up to 2.8x greater than during the premating period due to increased food consumption in the lactating dams. Recovery of offspring body weights was evident after weaning. It is concluded the offspring body weights were reduced because of maternal stress, reduced milk quality and quantity, and possibly direct exposure to [REDACTED] in the milk resulting in decreased milk consumption by the offspring. As there were no reproductive effects in this study, the highest dose used, 0.8%, was judged to be the reproductive toxicity NOEL.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-455; 14533A**

INTRODUCTION

This study was designed to provide general information concerning the potential effects of [REDACTED], test material MRD-92-455, on gonadal function, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring in the rat.

This study was conducted for Exxon Chemical Company, 13501 Katy Freeway, Houston, Texas 77079 and Exxon Chemical Europe, Boulevard Du Souverain 280, B-1160 Auderghem, Belgium (subsequently referred to as the Sponsor).

The study was conducted by Exxon Biomedical Sciences, Inc. (EBSI) Toxicology Laboratory (an American Association for Accreditation of Laboratory Animal Care accredited facility and a Japanese Ministry of Agriculture, Forestry, and Fisheries certified facility), Mettlers Road, CN 2350, East Millstone, New Jersey 08875-2350.

Study Initiation (Protocol Signature Date)

December 9, 1993

Inlife Test Period

December 14, 1993 to September 25, 1994

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", and the U.S. EPA TSCA test guidelines for reproduction and fertility effects (40 CFR, Part 798).

Justification of Dosing Route

The dietary route is an accepted route of administration according to E.C. Dangerous Substances Directive Annex V, and U.S. EPA TSCA regulations, and represents a likely route of human exposure.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MERD-93-489; 14836A****INTRODUCTION (CONT'D)****Justification of Dose Level Selection**

Doses for this definitive Two Generation Reproduction Toxicity Study in Rats with [REDACTED] were selected based on findings from a One Generation Probe Study with [REDACTED]. In the probe study, findings were observed in the parental animals at dose levels of 1.0% and 1.5% and included lower body weight, suppression in body weight gain, lower food consumption, and increased liver and kidney weights compared with controls. There were no apparent effects on reproductive indices. The most common finding in the offspring from dams treated with either 0.5%, 1.0%, or 1.5% [REDACTED] was reduced body weights on PND 0 and significant suppression of body weight gain during the postnatal period. The offspring body weight reduction may have been the result of maternal stress, decreased milk consumption and/or due to direct exposure to [REDACTED] in the milk. However, the study was terminated after only one generation since the pups in the mid and high dose groups were not thriving during the transition period from nursing to diet alone.

This definitive multigeneration reproductive study of [REDACTED] was conducted to further evaluate the material, and clarify the results of the One Generation Probe Study with DINP. The doses selected were based on the findings observed in the probe study and were as follows:

1. 0.8%, selected as the high dose, should induce parental toxicity, but not mortality, and possibly also affect offspring body weights, but not offspring survival.
2. 0.4%, selected as the mid dose, should cause minimal parental effects (i.e. suppression in body weight or food consumption).
3. 0.2%, selected as the low dose, should not cause any observable adverse effects in the parents or offspring.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRD-92-455: 14533/A**

MATERIALS AND METHODS

TEST MATERIAL

Material Identification

EBSI Identification:	MRD-92-455
Sponsor Identification:	[REDACTED]
Supplier:	Exxon Chemical, Holland, BV CAS RN 67515-48-0
Date Received:	April 8, 1993
Expiration Date:	April 1998
Description:	Colorless liquid
Storage Condition:	Room temperature

The test material was assumed 100% pure for the purpose of dosing.

Characterization of the Test Material

The methods of synthesis, fabrication, and/or derivation of the test material are the responsibility of the Sponsor. Documentation is maintained at Exxon Chemical Europe, Boulevard Du Souverain 240, B-1160 Auderghem, Belgium.

Analysis of the Test Material

The stability, identity, strength, purity, and composition or other characteristics which will appropriately identify the test material were determined by the testing laboratory. Documentation is maintained at Exxon Biomedical Sciences, Inc., East Millstone, New Jersey.

TEST MATERIAL (CONT'D)

Analysis of Mixtures

The stability and homogeneity of the test material in feed was determined by the testing laboratory. Homogeneity was demonstrated as part of EBSI study #145535.

Stability was evaluated at a concentration of 0.2% (w/w) representing the lowest level expected during the study. A high dose of 1.5% was proven stable as part of EBSI study #145535.

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

One archival sample of the undiluted test material was collected by the Compound Preparation Department and stored at room temperature.

Carrier

PMI Certified Rodent Chow (S002 Meal)
Manufacturer: PMI Feeds, Inc.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~; MRD-92-499; 148335A****TEST SYSTEM****Test Animal**

Species:	Rat
Strain/Stock:	Cri:CD⁺BR - VAF/Plus^o
Supplier:	Charles River Breeding Laboratories, Inc. Kingston facility, Stone Ridge, New York.
Area:	Males - K92; Females - K83

Animal Receipt Information

Receipt Date:	November 30, 1993
Purchase Order Number:	3GM39449R

Quarantine and Acclimation Period

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

Number and Sex

P1 Males:	120 virgin
P1 Females:	120 virgin

Age at Initiation of Test Material Administration

P1 Males:	Approximately 7 weeks
	Approximate Date of Birth: October 26, 1993
P1 Females:	Approximately 6-7 weeks
	Approximate Date of Birth: October 29, 1993

Body Weight at Initiation of Test Material Administration

P1 Males:	221.8 to 298.9 grams
P1 Females:	149.7 to 199.4 grams

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH SUBSEQUENT PERINATAL LOSS; MSD-92-459; 14835A**

TEST SYSTEM (CONT'D)

Animal Identification

- P1/P2 Generations:** Ear tags and corresponding cage identification.
- F1/F2 Generations:** Pups selected from the F1 litters to serve as parents for the next generation (P2) were ear-tagged on or after weaning on Postnatal Day 21 (PND 21).

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, or his designee) because of poor health, outlying body weights, or abnormalities. The selected P1 population were allocated randomly to groups by a computer-generated randomization procedure to most nearly equalize initial group mean body weight.

Husbandry

Housing

- Room Number:** 502
- Housing:** Individually housed during the test period, except during the mating and postpartum periods. F1 and F2 littermates were housed by sex from PND 21 to 28.
- Caging:** Suspended stainless steel and wire mesh with absorbent paper below cages.

Feed

- PMI Certified Rodent Chow (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 at least once daily for all animals.

TEST SYSTEM (CONT'D)

Water

Automatic watering system, ad libitum

Supplier: Elizabethtown Water Company
Bound Brook, New Jersey.

Analysis: As 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 at least once daily for all animals.

Bedding (Direct)

CELLU-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 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.

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WTTB-~~XXXXXXXXXXXX~~; MRD-92-489; 14938A

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 Certified Rodent Chow (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. Prepared diets were covered and stored at room temperature following dispensing.

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

Experimental Groups

Group Number	Concentration in Diet (%)	Number of P1 Females	Number of P1 Males
1 Control	0	30	30
2 Low	0.2	30	30
3 Mid	0.4	30	30
4 High	0.8	30	30

Administration of Test Material

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

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRD-92-499; 14835A**

EXPERIMENTAL DESIGN (CONT'D)

The dosing regimen for all groups proceeded as follows: P1 males were dosed for at least 10 weeks prior to mating and through the mating period for F1 litters, until sacrificed following delivery of their last litter sired. P1 females were dosed for at least 10 weeks prior to mating, during the mating, gestation and postpartum periods, and until they were sacrificed following weaning of the F1 animals on PPD 21.

P2 (F1) males were dosed from PND 21 for at least 11 weeks prior to mating and through the mating period for F2 litters, until sacrificed following delivery of their last litter sired. P2 (F1) females were dosed from PND 21 for at least 11 weeks prior to mating and during mating, gestation, lactation, and until they were sacrificed following weaning of the F2 animals on PPD 21.

Experimental Evaluation

Inlife Procedures:

All animals were examined for viability at least once a day.

Male body weight was measured prior to P1/P2 selection, on the first day of dosing (Day 0), and at least weekly thereafter until sacrificed. Female body weight was measured prior to P1/P2 selection, on the first day of dosing and at least weekly thereafter until confirmation of mating, then on Gestation Days (GD) 0, 7, 14, and 21 and on Postpartum Days (PPD) 0, 4, 7, 10, 14, and 21.

Food consumption was measured concurrently with body weight during the test period, except that food consumption was not measured during mating.

A clinical examination was given to each male prior to P1/P2 selection, on the first day of dosing, and at least weekly thereafter until sacrificed. Females received a clinical examination prior to P1/P2 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.

Mating:

The P1 mating period began after at least 10 weeks of P1 dosing and ended when all females were confirmed mated or approximately 3 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.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~CHLOROPYRIFOS~~; MSD-98-09; 14835A**

EXPERIMENTAL DESIGN (CONT'D)

P2 (F1) mating was performed as described for the P1 generation, except that males and females which cohabited within each dose group were from different litters in order to avoid sibling mating.

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 the female's Day 0 of gestation (GD 0). After confirmation of mating, each animal was returned to its own cage.

On GD 20, mated females were placed in clean cages fitted with a stainless steel litter pan and provided with fresh bedding material. Beginning on GD 21, mated females were examined at least twice daily for signs of parturition.

If a female was not confirmed mated, a litter pan was provided after examination on the last scheduled day of mating. Non-confirmed mated females were examined at least twice daily for signs of parturition after insertion of litter pans in their cages. Several unconfirmed mated females were noted with red vaginal material approximately 2 weeks after overnight pairing. For husbandry purposes, these females were assumed to be at GD 14 and observations, body weight, and food consumption measurements were performed accordingly. These data are presented in the individual tables, however they are not included in gestation incidence or mean tables.

Postnatal Experimental Evaluation

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

Dead pups were removed from the litter immediately after their discovery. If intact, dead pups were examined externally and internally for anomalies. Dead pups discovered on PND 0 also were examined internally to determine whether they were stillborn.

On 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.

EXPERIMENTAL DESIGN (CONT'D)

On PND 4, after counting, weighing, and examining the 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 examined, then subsequently sacrificed and discarded.

Culled pups that appeared normal received only an external examination and tissues were not saved. Culled pups that appeared abnormal were subjected to a visceral examination.

At weaning (PND 21), the surviving neonates were examined as noted above and 10 male and 10 female offspring in each group were sacrificed and examined for internal abnormalities. The selection of the litters and the neonates within litters was done randomly. No more than one neonate of each sex was selected from any one litter.

From the remaining offspring, a maximum of 2/sex/litter were selected randomly and group housed by sex to be considered for F1 generation parents. Offspring which were retained in the F1 parental pool were given clinical examinations and body weights were measured at least weekly, following selection on PND 21 until designated Test Day 0 for the F₂ (F1) generation.

On the designated Test Day 0 (for the P2 generation), the number of animals to continue as P2 generation parents was standardized to a maximum of 30/sex/group. The selection process was random and allowed for at least 1 pup per sex from each litter to be represented in the P2 generation where possible. The remainder of the offspring were examined externally, sacrificed, and discarded.

Study Termination

Euthanasia was by CO₂ asphyxiation and exsanguination.

P1 and P2 (F1) males selected for mating were sacrificed after the birth of their last litter sired. P1 and P2 (F1) females were sacrificed after weaning (PPD 21) of the F1 and F2 litters, respectively. Confirmed mated P1 and P2 (F1) 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 completion of the mating period, were sacrificed and received gross necropsies. Special attention was paid to the reproductive system. Dams whose litters died (spontaneously or cannibalized) prior to weaning (PND 21) were sacrificed and necropsied.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED], MRD-93-485; 148E.SA**

EXPERIMENTAL DESIGN (CONT'D)

Offspring of dams which died prior to PND 21 were sexed and examined externally, sacrificed, and discarded. F1 pups not selected for mating were sacrificed after weaning. F2 litters were sacrificed after weaning.

Necropsy:

Gross necropsies were performed on all adult animals, including those that were found dead or were sacrificed. Body weight was recorded on the day of necropsy. The uteri of all females used for mating, but failed to deliver, were examined grossly for evidence of implantations and these data were recorded.

The following organs and tissues of all P1 and P2 (F1) animals used for mating were weighed:

- | | |
|---------------------------|---------------------------|
| kidneys (paired) | liver |
| testes (individual) | prostate/seminal vesicles |
| epididymides (individual) | ovaries (individual) |
| brain | |

The following organs and tissues of all P1 and P2 (F1) animals used for mating, as well as from the F1 and F2 neonates selected for necropsy, were preserved in 10% neutral buffered formalin. All tissues were retained, but not examined microscopically.

- | | | |
|------------------------------|------------------|-----------------------------|
| vagina | testes* | pituitary |
| uterus (with cervix) | epididymides | liver |
| ovaries | seminal vesicles | kidneys |
| coagulating gland | prostate | tissue masses/gross lesions |
| mammary gland (females only) | | |

- * The testes of P1 and P2 males were preserved in Bouin's solution. The testes remained in Bouin's solution for approximately 24 hours, then were rinsed and stored in 70% ethyl alcohol. Testes of F1 neonates were preserved in 10% neutral buffered formalin.

All F1 and F2 pups that died were subjected to a visceral examination. Abnormal tissues were not preserved as per the discretion of the Study Director.

Parental animals which succumbed prior to scheduled termination had tissues preserved but not weighed.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~; MRD-92-459; 14833A**

EXPERIMENTAL DESIGN (CONT'D)

Histopathology

Histological slides of the selected organs and tissues were prepared and evaluated for all high dose and control P1 and P2 (F1) animals used for mating. If abnormalities or equivocal results were seen at the high dose, then specimens from the mid-dose and, if necessary, those of the low dose will be evaluated for histopathology.

Records

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

Statistical Analyses

The following statistical methods were employed, where appropriate.

I. Continuous data were tested for statistical significance as follows:

Bartlett's test of homogeneity of variance was used 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 (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.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH SPINOSADEXEMIDE; MRD-92-483; 148836A**

EXPERIMENTAL DESIGN (CONT'D)

- II.** Pup weight 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 as follows:

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.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-455; 145335A**

RESULTS

P1 GENERATION - PARENTAL FINDINGS

1. PARENTAL CLINICAL INLIFE OBSERVATIONS - P1

Incidence of Inlife Observations: Tables 1 - 3

Individual Inlife Observations: Appendices A - C

There were no clinical signs judged to be directly related to treatment with [REDACTED]. 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 incidental findings observed in the male and/or female animals in one or more groups during the premating/mating, postmating, gestation, and/or postpartum periods. These findings included dental abnormalities, scabs/sores, soft stool, alopecia, staining of the fur, ocular discharge, nasal discharge, rales, and/or swollen abdomen. One low dose female had an inguinal mass on PPD 21 and one mid-dose female had a cervical mass on PPD 14 and 21. All findings were considered incidental and unrelated to treatment with [REDACTED].

2. PARENTAL SURVIVAL - P1

Summary of Parental Survival: Table 4

Individual Survival Data: Appendix D

There were no treatment-related deaths. Unscheduled mortality was limited to one mid dose male (0.4%) and one low dose female (0.2%), both occurring prior to mating. These deaths were considered incidental and unrelated to treatment with [REDACTED].

The mid dose male was sacrificed on Day 37. This animal was observed with dental abnormalities, a sore of the palate/mouth, swollen snout, emaciation, little sign of food consumption or stool, rales, and ocular discharge prior to euthanasia. This animal probably suffered an accidental injury to the snout which led to its subsequent poor health. This death was considered incidental and unrelated to treatment with [REDACTED].

The low dose female was found dead on Day 64. This animal was observed with soft stool, anogenital staining, and a swollen abdomen the day prior to death. Postmortem findings included enlarged liver and lymph nodes, as well as an enlarged, ruptured spleen. Due to the limited incidence, this death was considered incidental and unrelated to treatment with [REDACTED].

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-489; 14932A

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 biologically and/or statistically significant differences in mean body weight or mean body weight change between the treated and control males and females during the majority of the study, including gestation. There was evidence of body weight gain suppression in the high dose females during the postpartum period.

Statistically significant differences in mean body weight change were observed in the low and mid dose males compared with controls during the pre mating period. There was statistically significant suppression in body weight gain observed in the low dose males during the Day 21/28 interval and a statistically significant increase in mean body weight gain during the Day 49/56 interval. In the mid dose males, statistically significant suppression in body weight gain was observed during the Day 56/63 interval. In the absence of a clear consistent response over the test period, or a clear dose-related response, these limited differences were considered incidental and unrelated to treatment with [REDACTED]

Statistically significant body weight gain suppression was observed in the high dose females compared with controls during the Gestation Day (GD) 0/7 interval. There were no significant differences in absolute body weight during gestation or for the overall gestation interval (GD 0/21) between treated and control animals. Thus, in the absence of a consistent response during gestation, this limited finding was considered incidental.

During the postpartum period, there was evidence of body weight gain suppression in the high dose females. There was a statistically significant lower mean body weight in the high dose females compared with controls on postpartum days (PPD) 14 and 21. These differences from control were small (<8%) and generally would not be considered biologically important. However, there was statistically significant body weight gain suppression in the high dose females (84% decrease) compared with controls during the overall postpartum interval (PPD 0-21).

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-459; 148335A**

RESULTS (CONT'D)

4. PARENTAL FOOD CONSUMPTION - P1

Mean Food Consumption: Tables 9 - 11

Individual Food Consumption: Appendices I - K

There were no biologically and/or statistically significant differences in mean food consumption between the treated and control males and females during the majority of the study, including gestation. During the postpartum period, there was statistically significant lower mean food consumption in the high dose females compared with controls.

During the pre-mating period, significant differences from controls were limited to the low dose females. On three occasions (Weeks 4, 8, and 9), mean food consumption of the low dose females was statistically significantly greater than controls. Generally, increases in food consumption are not indicative of an adverse effect and thus, these small differences (<12%) were considered incidental.

There was a statistically significant lower mean food consumption in the high dose females during the GD 0-7 interval (7%). This small, isolated lower food consumption was not considered biologically important.

During the postpartum period, statistically significant lower mean food consumption values were observed in the high dose females compared with controls during the PPD 10/14 and 14/21 intervals (14% and 17%, respectively), as well as the overall postpartum period (9%).

In addition, there was a statistically significant increase in mean food consumption of the mid dose females compared with controls during the PPD 0/4 interval. This finding was considered incidental and unrelated to treatment with [REDACTED]

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITB [REDACTED], MRD-93-455; 145336A

RESULTS (CONT'D)

5. PARENTAL MEASURED DOSE RATE - P1

Mean Measured Dose Rate: Table 12
 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 measured dose rate for each group during pre-mating in mg/kg/day was as follows:

CONCENTRATION IN DIET (%)	ACTUAL DOSE (MG/KG/DAY)		
	WEEK 1	WEEKS 2-9	WEEK 10
MALES: 0.2	212	186-118	118
MALES: 0.4	426	369-236	236
MALES: 0.8	852	752-487	477
FEMALES: 0.2	215	200-145	148
FEMALES: 0.4	425	398-278	286
FEMALES: 0.8	830	799-562	562

Mean measured dose rate increased slightly during the GD 0-7 and 7-14 intervals and then decreased slightly during GD 14-21, but essentially was equivalent to the pre-mating measured dose rate. During the postpartum period, there was a steady increase in mean measured dose rate. This also was characteristic of fixed concentration dietary studies and was due to increases in food consumption to fuel the increased energy expenditure of lactation while the dams were maintaining weight. Mean measured dose rate was greatest during the PPD 14-21 interval. Near the end of this interval, pups may have been eating from the dam's feeder driving the food consumption values even higher. The mean measured dose rates during the gestation and postpartum periods were as follows:

CONCENTRATION IN DIET (%)	GESTATION MG/KG/DAY	POSTPARTUM MG/KG/DAY
FEMALES: 0.2	139.1-153.0	158.8-349.9
FEMALES: 0.4	273.5-301.0	346.6-730.7
FEMALES: 0.8	543.2-571.5	672.6-1379.4

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-659; 148335A**

RESULTS (CONT'D)

6. PARENTAL ORGAN WEIGHT - P1

Mean Organ Weight: Table 13

Mean Relative Organ Weight: Table 14

Individual Organ Weight: Appendix M

Individual Relative Organ Weight: Appendix N

There were statistically significant increases in the mean absolute and relative liver weights of the high dose males (16% and 16%, respectively) and females (22% and 28%, respectively) and the mid dose females (20% and 15%, respectively) compared with controls. The mean relative liver weight of the mid dose males also was statistically significantly increased (8%) compared with controls. Microscopically, there was increased cytoplasmic eosinophilia in these groups, thus, these changes were considered treatment-related.

In the kidneys, there were statistically significant increases in mean absolute and relative weights of the high dose (20% and 22%, respectively) and the mid dose males (14% and 17%, respectively) compared with controls. However, there were no microscopic changes observed in the kidneys of the P1 animals to support a treatment-related effect. Other changes in the kidneys included statistically significant increases in mean and relative weight of the high dose females (8% and 13%, respectively), mean relative weight of the low dose males (9%) and mean absolute weight of the mid (10%) and low (8%) dose females compared with controls. However, in the absence of correlating histopathological findings, these small increases (generally less than 10%) from controls were not considered biologically important.

Biologically significant differences in mean organ or relative organ weight of the reproductive organs were not observed between treated and control animals. There was a statistically significant decrease in the mean left ovary weight of the high dose females compared with controls. In the absence of a clear dose response, similar findings in the right ovary weights, consistent pattern of response between absolute and relative organ weights, or correlating microscopic findings, this single decrease was considered incidental and unrelated to treatment.

Other statistically significant differences included a decrease in the mean absolute brain weight of the low dose males and mean relative brain weight of the mid dose females compared with controls. In the absence of a clear dose response or consistent pattern of response between absolute and relative organ weights, these small decreases (<6%) were considered incidental and unrelated to treatment.

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MRD-92-457) 14835A

RESULTS (CONT'D)

7. PARENTAL GROSS POSTMORTEM OBSERVATIONS - P1

Incidence of Gross Postmortem Observations: Table 15

Individual Gross Postmortem Observations: Appendix O

There were no gross postmortem findings judged to be related to treatment with [REDACTED]

The majority of animals throughout the groups were free of observable abnormalities or had observations limited to intestinal parasites at postmortem examination. Approximately half of the females had intestinal parasites, later diagnosed to be pinworms (*Syphacia muris*). These pinworms are commensal, relatively non-pathogenic and bacteria feeding. Pinworm parasites of laboratory rodents are generally non-pathogenic and infections are usually symptomless (Farrar et al., 1986). The origin of these parasites could not be determined, but were considered incidental and unrelated to treatment with DINP. Additionally, there were single or low occurrences of discolored liver; dilated or discolored kidneys; foci on the lungs, kidneys, thymus, or colon; enlarged pituitary; distended uterus; white material in the urinary bladder; thickened/reddened small intestines; thickened stomach; alopecia; staining of the fur; dental abnormalities; and/or sores. One low dose and one mid dose female also had subcutaneous masses. These findings were considered incidental and unrelated to treatment.

Postmortem findings in the mid dose male which was sacrificed on Day 37 included a swollen snout, a sore of the palate, emaciation, dental abnormalities, and staining of the fur around the eyes. This animal was sacrificed following a probable accidental injury. Postmortem findings in the low dose female which was found dead on Day 64 included an enlarged liver and lymph nodes, as well as an enlarged, ruptured spleen. The cause of death for this animal is unknown. However, due to the limited incidence, this death was considered incidental and unrelated to treatment with [REDACTED]

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~; MRD-92-45; 14535A****RESULTS (CONT'D)****8. HISTOPATHOLOGY FINDINGS - P1****Histopathology Report: Appendix PP**

Treatment-related microscopic changes occurred in the liver of male and female rats of all treatment groups in the P1 generation. Microscopic examination of the liver revealed a minimal to moderate increased cytoplasmic eosinophilia in rats of both sexes in all treatment groups. The affected hepatocytes, although rarely enlarged microscopically, had a finely granular to homogenous cytoplasm which was intensely eosinophilic when stained with hematoxylin- and eosin, as compared with the controls. The intensity of this finding increased in a dose-related manner. This type of hepatocellular change, although not diagnostic, is seen with compounds which cause peroxisome proliferation.

All other microscopic changes observed in the P1 animals were considered to have occurred spontaneously, were typical of those which would be expected to occur in rats of this age, and were considered unrelated to treatment with DINP.

9. REPRODUCTION INDICES - P1

Summary of Reproduction Data: Table 16
Individual Reproduction Data: Appendix P

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 of the treated and control groups were essentially equivalent.

There were no statistically significant differences in mean percentage of live offspring, percentage of dead offspring, or sex ratio of the treated offspring compared with controls.

The mean litter size of the high dose offspring (15.1) was slightly higher than that of the controls (12.5). The mean litter size of the high dose group was within the laboratory historical control range (12.6-16.8), but the control group was slightly lower. Similarly, the mean live offspring per litter (14.8) of the high dose group was slightly higher than controls (12.2) but within historical control range (12.2-16.1), although the mean dead offspring were equal (0.3).

Three control, four low dose, five mid dose, and five high dose females were not pregnant.

RESULTS (CONT'D)

F1 GENERATION - OFFSPRING FINDINGS

10. OFFSPRING SURVIVAL - F1

**Summary of Offspring Survival: Table 17
Individual Offspring Survival Data: Appendix Q**

There were no statistically significant differences in offspring survival indices between the treated and control offspring with the exception of the mean Day 7 Survival Index of the low dose group which was statistically significantly increased (4%) compared with controls. In general, increases in survival or lactation indices are not indicative of toxicity. Therefore, this small increase was not considered biologically important.

11. OFFSPRING CLINICAL INLIFE OBSERVATIONS - F1

**Incidence of Inlife Observations: Table 18
Individual Inlife Observations: Appendix R**

There were no treatment-related clinical findings observed in the offspring of any group. 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.

Single or low incidences of swollen hindpaw, lacerations, scabs, truncated tail, missing digits (mechanically induced), hypothermia, and/or umbilical hernia were observed in one or more groups, including controls. These findings were considered incidental and unrelated to treatment.

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-455; 14535A

RESULTS (CONT'D)

12. OFFSPRING BODY WEIGHT - F1

Mean Offspring Body Weight: Table 19
Individual Offspring Body Weight: Appendix S

There were statistically significant lower mean offspring body weights in the mid and high dose males and females on PND 0, 7, 14, and 21; and in the low dose males and females on PND 21. The weights of all treated offspring at all intervals were within the historical control range of this laboratory. Additionally, the mean litter size of the control group (12.5) was smaller than the treated groups (14.8-15.1) and was lower than the historical control range for litter size in this laboratory (12.6-16.8). Thus, the differences in offspring body weight may have been due, at least in part, to the lower number of pups/litter in the control group and subsequent higher pup body weights of the control offspring compared to the other treated groups. Another variable which probably contributed to the lower offspring body weights in the high dose group may have been maternal stress, changes in the quality and quantity of milk, decreased milk consumption, and or possibly direct toxic actions of [REDACTED] (see discussion).

Group	MALE PND 0	MALE PND 1	MALE PND 4	MALE PND 7	MALE PND 14	MALE PND 21
0%	6.90	7.49	10.63	17.62	35.01	57.25
0.2%	6.78	7.39	10.26	16.44	33.28	51.40**
0.4%	6.48**	7.03	9.54	15.28**	30.43**	47.95**
0.8%	6.43**	7.05	9.74	15.67**	29.66**	46.52**
Historical Control	6.35-7.02	6.68-7.46	8.53-11.43	13.64-18.74	28.81-36.73	44.89-60.77

Group	FEMALE PND 0	FEMALE PND 1	FEMALE PND 4	FEMALE PND 7	FEMALE PND 14	FEMALE PND 21
0%	6.47	7.11	10.26	16.70	33.52	53.99
0.2%	6.36	6.96	9.61	15.54	31.89	49.19**
0.4%	6.16*	6.67	9.24	14.21**	29.14**	45.63**
0.8%	6.08*	6.70	9.36	15.03**	28.41**	44.68**
Historical Control	5.96-6.74	6.30-7.16	8.32-11.05	13.33-17.69	27.22-35.74	42.39-61.19

* Mean significantly different from control mean (p ≤ 0.05)
** Mean significantly different from control mean (p ≤ 0.01)

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~; NRD-92-499; 14935A

RESULTS (CONT'D)

13. OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F1

Incidence of Offspring Gross Postmortem Observations: Table 20
Individual Offspring Gross Postmortem Observations: Appendix T

In general, there were no gross postmortem findings in the F1 offspring judged to be related to treatment with ~~XXXXXX~~. The majority of animals were free of observable abnormalities at the scheduled terminal sacrifice on PND 21. Observations were limited to single occurrences of truncated tail, cyst-like structure in the mesentery, and a slightly enlarged spleen. These findings were considered incidental and unrelated to treatment.

The majority of animals which died prior to scheduled termination (PND 0-20) were free of observable abnormalities. There were single incidences of a tear in the abdominal wall, hematoma, discolored liver, distended urinary bladder, laceration, and dilated renal pelvis. Five animals in the control group, two animals in the low dose group, one animal in the mid dose, and four animals in the high dose group were stillborn. These postmortem findings were considered incidental and unrelated to treatment with the test material.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-459; 145335A**

RESULTS (CONT'D)

P2 GENERATION - PARENTAL FINDINGS

1. PARENTAL CLINICAL INLIFE OBSERVATIONS - P2

Incidence of Inlife Observations: Tables 21 - 23

Individual Inlife Observations: Appendices U - W

There were no clinical signs judged to be directly related to treatment with [REDACTED]. 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 incidental findings observed in the male and/or female animals in one or more groups during the premating/mating, postmating, gestation, and/or postpartum periods. These findings included dental abnormalities, scabs/sores, soft stool, kink in tail, truncated tail, alopecia, ocular discharge, ocular opacity, nasal discharge, emaciation, little sign of food consumption, red material vagina, and/or swollen snout/paw. One control female had a mass in the axial area, one low dose female had a mass in the ventral thoracic area, one high dose female had a mass in the anogenital area, and one low dose and one high dose female each had a mass in the cervical area. All findings were considered incidental and unrelated to treatment with [REDACTED].

2. PARENTAL SURVIVAL - P2

Summary of Parental Survival: Table 24

Individual Survival Data: Appendix X

There were no treatment-related deaths and all animals survived to scheduled terminal necropsy.

RESULTS (CONT'D)

3. PARENTAL BODY WEIGHT AND BODY WEIGHT CHANGE - P2

Mean Body Weight and Body Weight Change: Tables 25 - 28
Individual Body Weight and/or Body Weight Change: Appendices Y - BB

There were statistically significant lower mean body weights in the high dose males compared with controls at the majority of the intervals during the pre-mating period. These significant lower mean body weights were most likely due to the lower mean body weight of the F1 pups during weaning which remained consistently lower and was evident at the beginning of the P2 generation. At Day 0 of the P2 pre-mating period, the mean body weight of the high dose males was 13% lower than controls. However, the P2 animals appear to recover in that by the end of the pre-mating interval (Week 11), differences from controls were only 7%. Additionally, there were no biologically significant differences in body weight gain between the treated and control animals. Thus, the statistically significant lower mean body weights in the high dose males compared with controls during the pre-mating period was attributed to lower body weights of the P2 high dose males at the start of the P2 generation, rather than a treatment-related toxicological effect occurring during the pre-mating interval.

However, on two occasions, statistically significant differences in mean body weight change were observed in the mid and high dose males compared with controls during the pre-mating period (Day 42/49 and Day 63/70 intervals). In the absence of a clear consistent response over the test period or a clear dose-related response, these differences were considered incidental and unrelated to treatment with DINP.

There was a statistically significant lower mean body weight in the high dose females on Days 0, 7, and 14 of the pre-mating interval. These significantly lower body weights were most likely due to the lower mean body weight of the F1 pups during weaning which remained consistently lower and were evident at the beginning of the P2 generation. While the mean body weight of the high dose females remained lower than controls for the remainder of the pre-mating period, the decrease was not statistically significant at Day 21 and beyond thus indicating a recovery. Thus, the statistically significant lower mean body weights of the high dose females compared with controls during the beginning of the pre-mating period was attributed to lower body weights of the P2 high dose females at the start of the P2 generation, rather than a treatment-related toxicological effect occurring during the pre-mating interval.

RESULTS (CONT'D)

There was statistically significant lower mean body weight on GD 14 and body weight gain suppression during the GD 0/7 interval in the high dose females compared with controls. There were no significant differences in mean body weight gain for the overall gestation interval (GD 0/21) between treated and control animals. Thus, in the absence of a consistent response during gestation, these limited findings were considered incidental.

During the postpartum period, there were statistically significant lower mean body weights of the high dose females compared with controls on PPD 4, 7, 10, 14, and 21. However, there was no statistically significant differences in mean body weight gain in the high dose females compared with controls. Similarly, there were no differences in body weight gain between the high dose females and controls for the overall postpartum interval (PPD 0-21). Thus, these statistically significant lower mean body weight (8-11%) during the postpartum period may be due, at least in part, to the lower body weight of the P2 females at the start of the P2 generation. Additionally, these decreases may be due to maternal stress and increases in test material consumption during the postpartum period.

4. PARENTAL FOOD CONSUMPTION - P2

Mean Food Consumption: Tables 29 - 31

Individual Food Consumption: Appendices CC - EE

During the pre-mating period, there were a few small, but statistically significant, lower mean food consumption values in the treated animals compared with controls. The mean food consumption of the high dose males during Week 1 and high dose females during Weeks 9 and 11 were statistically significantly lower than controls. In the absence of a consistent pattern of response, these small differences (<8%) were considered incidental.

There was statistically significant lower (13-16%) mean food consumption in the high dose females during the GD 0/7 and 7/14 intervals, as well as the overall gestation interval (GD 0-21) compared with controls. Similarly, during the postpartum period there was statistically significant lower mean food consumption in the high dose females compared with controls during the PPD 7/10, 10/14, and 14/21 intervals (12%), as well as the overall postpartum period (9%).

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MKD-92-493; 14933A**

RESULTS (CONT'D)

5. PARENTAL MEASURED DOSE RATE - P2

Mean Measured Dose Rate: Table 32

Individual Measured Dose Rate: Appendix FF

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:

CONCENTRATION IN DIET (%)	ACTUAL DOSE (MG/KG/DAY)		
	WEEK 1	WEEKS 2-10	WEEK 11
MALES: 0.2	264	217-120	114
MALES: 0.4	523	440-243	235
MALES: 0.8	1090	923-489	467
FEMALES: 0.2	254	222-143	140
FEMALES: 0.4	522	450-283	271
FEMALES: 0.8	1060	916-577	544

Mean measured dose rate increased slightly during the GD 0-7 and 7-14 intervals and then decreased slightly during GD 14-21, but essentially was equivalent to the pre-mating measured dose rate. During the postpartum period, there was a steady increase in mean measured dose rate. This also was characteristic of fixed concentration dietary studies and was due to increases in food consumption to fuel the increased energy expenditure of lactation while the dams were maintaining weight. Mean measured dose rate was greatest during the PPD 14-21 interval. Near the end of this interval, pups may have been eating from the dam's feeder driving the food consumption values even higher. The mean measured dose rates during the gestation and postpartum periods were as follows:

CONCENTRATION IN DIET (%)	GESTATION MG/KG/DAY	POSTPARTUM MG/KG/DAY
FEMALES: 0.2	132.9-152.5	174.3-394.7
FEMALES: 0.4	270.6-307.1	347.6-757.8
MALES: 0.8	544.2-576.7	718.4-1541.3

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~ MRD-92-639: 148335A**

RESULTS (CONT'D)

6. PARENTAL ORGAN WEIGHT - P2

Mean Organ Weight: Table 33

Mean Relative Organ Weight: Table 34

Individual Organ Weight: Appendix GG

Individual Relative Organ Weight: Appendix HH

There were statistically significant increases in the mean relative liver weights of the high dose males (15%) and females (27%), as well as the mean absolute liver weight of the high dose females (18%) compared with controls. Microscopically, there was increased cytoplasmic eosinophilia in these groups, thus, these changes were considered treatment-related.

There was a statistically significant increase in mean absolute and relative kidney weight of the high dose males (14% and 23%, respectively) and mean relative kidney weight of the mid dose males (14%) compared with controls. Microscopically, there was an increased incidence of renal dilatation and thus, these changes were considered treatment-related.

The mean relative kidney weight of the high dose females was statistically significantly increased (10%) compared with controls. In the absence of correlating changes in relative organ weight or histopathological findings, this small increase was not considered biologically important.

In the reproductive organs, there was a statistically significant increase in the mean relative left and right epididymides weights (14% and 16%, respectively) of the high dose males compared with controls. In the absence of correlating findings in the absolute weights, microscopic changes which support an effect, or adverse effects in the male reproductive indices, these small increases were considered incidental and unrelated to treatment.

Other statistically significant differences included a decrease in the mean brain weight of the low dose and high dose males compared with controls. In the absence of a clear dose response or consistent pattern of response between absolute and relative organ weights, these small decreases (<4%) were considered incidental and unrelated to treatment.

RESULTS (CONT'D)

7. PARENTAL GROSS POSTMORTEM OBSERVATIONS - P2

Incidence of Gross Postmortem Observations: Table 35
Individual Gross Postmortem Observations: Appendix II

Probable treatment-related findings were limited to kidney abnormalities. There was an increased incidence of dilated renal pelves in all treated group males compared with controls. Dilated renal pelves also were observed in the treated female animals, but the incidence generally was similar to controls.

Approximately one-half of the males and females were observed intestinal parasites, later diagnosed to be pinworms (*syphacia muris*). These pinworms are commensal, relatively non-pathogenic and bacteria feeding. Pinworm parasites of laboratory rodents are generally non-pathogenic and infections are usually symptomless (Farrow et al., 1986). The origin of these parasites could not be determined, but were considered incidental and unrelated to treatment with [REDACTED]. Additionally, there were single or low occurrences of enlarged/thickened liver; no cleft in median lobe of liver; small or not apparent epididymides; cystic kidney; foci on the lungs; enlarged spleen; small, enlarged, flaccid, non-apparent, or misshapen testes; cystic, enlarged, or small ovaries; brown material in the urinary bladder; alopecia; staining of the fur; dental abnormalities; truncated tail; scabs and/or sores. One control, one low dose, and two high dose females had subcutaneous masses in the cervical, anogenital, or axillary areas. These findings were considered incidental and unrelated to treatment.

RESULTS (CONT'D)

8. HISTOPATHOLOGY FINDINGS - P2

Histopathology Report: Appendix PP

Treatment-related microscopic changes occurred in the liver of male and female rats of all treatment groups in the P2 generation. Microscopic examination of the liver revealed a minimal to moderate increased cytoplasmic eosinophilia in rats of both sexes in all treatment groups. The affected hepatocytes, although rarely enlarged microscopically, had a finely granular to homogenous cytoplasm which was intensely eosinophilic when stained with hematoxylin- and eosin, as compared with the controls. The intensity of this finding increased in a dose-related manner. This type of hepatocellular change, although not diagnostic, is seen with compounds which cause peroxisome proliferation.

In the kidneys, treatment-related changes consisted of an increased incidence of minimal to moderate amount of macroscopic and microscopic dilatation of the renal pelves which was mostly unilateral in the high and mid dose males compared with controls.

All other microscopic changes observed in the P2 animals were considered to have occurred spontaneously, were typical of those which would be expected to occur in rats of this age, and were considered unrelated to treatment with DINP.

9. REPRODUCTION INDICES - P2

Summary of Reproduction Data: Table 36
Individual Reproduction Data: Appendix JJ

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 of the treated and control groups were essentially equivalent.

There were no statistically significant differences in mean percentage of live offspring, percentage of dead offspring, or sex ratio of the treated offspring compared with controls. The mean litter size of the treated and control groups was essentially equivalent.

Eight control, nine low dose, nine mid dose, and eleven high dose females were not pregnant.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~CHLOROPYRIFOS METHYL~~ (RD-92-435): 14935A**

RESULTS (CONT'D)

F1 GENERATION - OFFSPRING FINDINGS

10. OFFSPRING SURVIVAL - F2

**Summary of Offspring Survival: Table 37
Individual Offspring Survival Data: Appendix KK**

There were no biologically significant differences in offspring survival indices between the treated and control offspring.

The mean Day 7 Survival and Viability at Weaning Indices of the mid dose group were statistically significantly decreased (5%) compared with controls. This significant decrease in survival was due to one litter (HCP078F) which had eight pups die between the Day 4 (postcull) and Day 7 intervals. The dam of this litter had dental abnormalities during gestation/lactation and subsequently was observed with poor food consumption and emaciation. Thus, this finding was considered incidental and unrelated to treatment.

11. OFFSPRING CLINICAL INLIFE OBSERVATIONS - F2

**Incidence of Inlife Observations: Table 38
Individual Inlife Observations: Appendix LL**

There were no treatment-related clinical findings observed in the offspring of any group. 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.

Single or low incidences of body discoloration, alopecia, lacerations, scabs, truncated or necrotic tail, hypothermia, and/or umbilical hernia were observed in one or more groups, including controls. These findings were considered incidental and unrelated to treatment. One mid dose female was observed with a missing hindleg on Day 0. This was most likely the result of cannibalization by the dam, rather than a malformation. In either case, this single occurrence was considered incidental and unrelated to treatment with ~~TABLE~~

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MRD-92-455): 145535A**

RESULTS (CONT'D)

12. OFFSPRING BODY WEIGHT - F2

Mean Offspring Body Weight: Table 39

Individual Offspring Body Weight: Appendix MM

There were statistically significant lower mean offspring body weights in the mid and high dose males on PND 7, 14, and 21; in the mid and high dose females on PND 0, 1, 4, 7, 14, and 21; in the low dose males on PND 7 and 21; and in the low dose females on PND 0, 4, 7, 14, and 21. The weights of all treated offspring at all intervals were within the historical control range of this laboratory, with the exception of the high dose males and females on PND 0 and the high dose males on PND 1 which were only slightly lower (0.7-2.6%) than controls.

The lower offspring body weights observed during the lactation period were probably related to maternal stress, changes in the quality and quantity of milk, decreased milk consumption, and or possibly direct toxic actions of [REDACTED] (see discussion).

Group	MALE PND 0	MALE PND 1	MALE PND 4	MALE PND 7	MALE PND 14	MALE PND 21
0%	6.67	7.30	10.63	18.08	37.09	62.34
0.2%	6.49	7.12	10.05	16.43*	34.80	57.89*
0.4%	6.55	7.08	9.73	15.48**	32.51**	54.82**
0.8%	6.18	6.64	9.05	14.70**	29.88**	49.12**
Historical Control	6.35-7.02	6.68-7.46	8.53-11.43	13.64-18.74	28.81-36.73	44.89-60.77
Group	FEMALE PND 0	FEMALE PND 1	FEMALE PND 4	FEMALE PND 7	FEMALE PND 14	FEMALE PND 21
0%	6.44	7.10	10.48	17.47	35.89	59.37
0.2%	6.13*	6.75	9.60*	15.72*	33.64*	55.50*
0.4%	6.11*	6.59*	9.05**	14.56**	31.22**	51.98**
0.8%	5.92*	6.41*	8.68**	13.76**	28.20**	46.20**
Historical Control	5.96-6.74	6.30-7.16	8.32-11.05	13.33-17.69	27.22-35.74	42.39-61.19

* Mean significantly different from control mean (p ≤ 0.05)

** Mean significantly different from control mean (p ≤ 0.01)

RESULTS (CONT'D)

13. OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F2

Incidence of Offspring Gross Postmortem Observations: Table 40

Individual Offspring Gross Postmortem Observations: Appendix NN

In general, there were no gross postmortem findings in the F1 offspring judged to be related to treatment with [REDACTED]. The majority of animals were free of observable abnormalities at the scheduled terminal sacrifice on PND 21. Three control, two low dose, and two mid dose animals had dilated renal pelves. One low dose male had a truncated tail and two high dose pups had umbilical hernias. These findings were considered incidental and unrelated to treatment.

The majority of animals which died prior to scheduled termination (PND 0-20) were free of observable abnormalities or were too autolyzed to be examined at the necropsy. Four mid dose pups from the same litter and one low dose pup were emaciated. Four low dose pups from the same litter and one control pup were stillborn. These postmortem findings were considered incidental and unrelated to treatment with the test material.

ANALYTICAL CHEMISTRY

Analytical Chemistry Report: Appendix OO

The stability of [REDACTED] in feed was evaluated at 0.2%. The data showed the test material was stable at room temperature for at least 14 days. A high dose of 1.5% was proven stable as part of EBSI study #145535.

Homogeneity was demonstrated as part of EBSI study #145535.

Concentration verification analysis indicated that all dose samples were within 15% of the nominal values.

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (EPA; MRD-92-459): 145535A**

DISCUSSION

This study was conducted in follow-up to a one generation reproductive toxicity study of [REDACTED] (EBSI Project 145535) to assess the potential effects of the substance on reproduction and development in the rat. The results of this study clarified findings made in the previous study and indicate that [REDACTED] is neither a reproductive nor a developmental toxicant. Animals directly exposed to [REDACTED] show responses consistent with findings from other toxicity studies with [REDACTED] (EBSI, 1982; BIBRA, 1985; EBSI, 1986).

Doses for this study (0.2%, 0.4%, and 0.8% of [REDACTED] in feed) were selected based on findings from a One Generation Probe Study with [REDACTED]. In the probe study, there was lower body weight, suppression in body weight gain, lower food consumption, and increased liver and kidney weights compared with controls in parental animals at doses of 1.0% and 1.5% and suppression of body weight gain in the offspring at doses of 0.5%, 1.0%, and 1.5%. The offspring body weight reduction in the Probe study may have been the result of maternal stress, decreased milk consumption and/or due to direct exposure to [REDACTED] in the milk. However, the Probe study was terminated after only one generation since the pups in the mid and high dose groups were not thriving during the transition period from nursing to diet alone.

Administration of [REDACTED] via diet to Cri:CD¹BR (Sprague Dawley-derived) rats in graded doses in the course of a two-generation reproductive toxicity study was associated with signs of toxicity in the parental animals. In the offspring, findings were limited to dose dependent reduction in body weights on PND 0, 1, 4, 7, 14, and 21 in both F1 and F2 generations. These offspring findings were probably related to maternal stress and/or direct effects of [REDACTED] via exposure during lactation and are not indicative of developmental abnormalities or reproductive toxicity. F1 generation body weights largely recovered after weaning (only 5-7% lower than controls at Week 11 of pre-mating), and reproductive indices in treated groups were similar to control. There were no signs of adverse effects on reproduction and no evidence of developmental toxicity in this study.

In the parental animals, microscopic and organ weight changes were observed in the kidney and liver. These changes were expected, since they were consistent with the results from studies with other phthalates (Gray et al., 1977) and [REDACTED] specifically (EBSI, 1982; BIBRA, 1985; EBSI, 1986). Microscopically, the liver revealed a minimal to moderate increased cytoplasmic eosinophilia in rats of both sexes in all treatment groups. The affected hepatocytes, although rarely enlarged microscopically, had a finely granular to homogenous cytoplasm which were intensely eosinophilic when stained compared with the controls. The intensity of this finding increased in a dose-related manner. This type of hepatocellular change, although not diagnostic, is seen with compounds which cause peroxisome proliferation. Increased liver weights compared with controls were observed in the P1 and/or P2 high- and/or mid-dose groups. In the kidneys, histomorphologic examination noted an increased incidence of dilatation of the

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-459; 14836A

DISCUSSION (CONT'D)

renal pelvis in the high and mid dose P2 males compared with controls. Statistically significant increases in the mean absolute and/or mean relative kidney weights were observed in the P2 high and mid-dose males. No treatment-related changes were observed in the kidneys of the P1 males or the P1/P2 females.

Female animals exhibited lower body weights (P1) and food consumption (P1/P2) compared with controls during the postpartum period. These findings were temporally associated and occurred during a study phase when the dose of [REDACTED] consumed by maternal animals exceeded the test material consumption during the pre-mating period (7-21%, 48-60%, 85-92%, 102-111%, and 137-155% increase over pre-mating values during PPD 0-4, 4-7, 7-10, 10-14, and 14-21, respectively in the P1 generation; and 25-32%, 56-74%, 98-102%, 132-143%, and 180-183% increase over pre-mating values during PPD 0-4, 4-7, 7-10, 10-14, and 14-21, respectively in the P2 generation) (Tables 12 and 32). This is a common occurrence in fixed dietary concentration reproductive studies because of increased maternal food consumption during the postpartum period, i.e., to provide for the lactating offspring. In a previous 1-generation reproductive toxicity study of [REDACTED], reduced body weights and food consumption were also observed in male and female animals at doses of 1% and 1.5% in the feed. It is likely that the added stress of lactation and nursing contributed to the onset of this effect in the current study. Statistically significant lower mean body weights were observed in P2 males and females compared with controls during the entire P2 generation. These reduced body weights were derived from effects observed during the F1 postnatal period, specifically reduced body weight growth during that period. Recovery occurred during the P2 pre-mating period. These F1/P2 pre-mating body weight findings are discussed further below.

There was no evidence of adverse effects on the reproductive system. Mating, fertility, fecundity, and gestational indices of the treated male and/or female animals were comparable with controls in both generations. There were no structural changes observed in the reproductive organs from either generation at macroscopic or microscopic evaluations. Similarly, there were no biologically significant differences in mean absolute or relative weight of the reproductive organs.

There was no evidence of reproductive or developmental toxicity from the offspring evaluations of either generation. The Live Birth, Survival, and Lactation Indices of the treated offspring were compared with controls, and there were no adverse clinical or postmortem findings in any group.

Offspring body weights were reduced in a dose dependent manner during the postnatal period in both generations, with statistically significant differences from controls noted in one or more dose groups at many, but not all of the postnatal intervals. This weight reduction became more evident in both generations during progression through the postnatal period. The mean F1 body weights of all groups were within the historical control range of this laboratory. In the F2 generation, high dose male and

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED]; MRD-92-085; 145335A

DISCUSSION (CONT'D)

female offspring body weights on PND 0, and high dose male offspring body weights on PND 1, were slightly lower (0.6-2.6%) than the historical control range of this laboratory. Examination of F1, P2, and F2 treated group body weights, as a percent of control, indicate that body weights of the high dose F1 offspring were reduced on PND 0 (6-7% lower than controls), become further reduced during the postnatal period (17-19% lower than controls on PND 21), and then largely recover following weaning (10-13% on Day 0) during the P2 premating period (only 5-7% lower than controls at the end of 11 weeks of premating). The F2 pups followed a similar trend, with body weights of the high dose offspring being reduced on PND 0 (7-8% lower than controls), become further reduced during the postnatal period (21-22% lower than controls on PND 21). It is during the postnatal period when maternal food consumption and body weights first become reduced in the high dose group (see above).

Studies of another phthalate, di(2-ethylhexyl)phthalate (DEHP), demonstrated that high doses affected milk quality and quantity in lactating dams (Dostal et al., 1987). These researchers concluded that the observed decreases in offspring body weight were due to decreased food consumption by the dams. DEHP was also found to be present in the milk of lactating dams (Dostal et al., 1987). It is considered likely that [REDACTED] is also transferred into the milk and that the lactating offspring were directly exposed to the substance. [REDACTED] also has an odor (as noted on the MSDS) which could be speculated to affect palatability of the milk to the offspring. Thus, it is likely that the lower F1 and F2 offspring body weights observed in this study during the lactation period may have resulted from changes in the quality and quantity of milk, decreased milk consumption, and possibly direct toxic action by [REDACTED]. F2 offspring body weight reductions in treated animals were probably greater because of the increased stress/lower maternal body weights of their dams.

The palatability of the milk may result in a delay in offspring suckling and thus, directly affect the treated offspring body weights on PND 0. Each morning and afternoon during the postnatal period, dams were checked for the completion of parturition and PND 0 offspring weights subsequently were measured. However, time of parturition is variable in dams and if parturition occurred during the evening, a significant period of time could have elapsed prior to the PND 0 weighing during which lactation and nursing would be expected to begin. During this time, decreased palatability of the milk may result in a reluctance of the treated offspring to nurse which would directly affect the presumed PND 0 offspring weights. Again, this decrease in PND 0 weights could occur secondarily to maternal stress, or differences in the quality and quantity of milk consumed by the offspring.

It is also possible that the offspring were exposed to [REDACTED] in utero, it appears unlikely that this would have resulted in reduced birth weights, e.g. via direct toxicity and a mechanism similar to that which occurs in parental animals. Measured dose rate during gestation was highest during the GD 7-14 interval at 153 mg/kg, 296-305 mg/kg,

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] MRD-92-483; 14836A

DISCUSSION (CONT'D)

and 572-577 mg/kg in the 0.2%, 0.4%, and 0.8% dose groups, respectively. A developmental study of [REDACTED] (EBSI, 1994) demonstrated that exposure of pregnant female rats to doses up to 1000 mg/kg per day during gestation days (GD) 6-15, i.e., during organogenesis, did not result in developmental abnormalities or reduced fetal body weights. Thus, the reduced PND 0 weights observed in the current study were attributed to postnatal rather than in utero effects.

In conclusion, findings in parental animals included microscopic changes in the kidneys of the P1 high dose (0.8%) and mid dose (0.4%) males and liver changes in both sexes of all treated groups (0.8%, 0.4%, and 0.2%), which correlated with increased mean absolute and/or relative kidney and liver weights in these groups. Changes in the liver and kidneys were expected, since they were consistent with the results from studies with other phthalates (Gray et al., 1977) and [REDACTED], specifically (EBSI, 1982; BIBRA, 1985; EBSI, 1986). There also was evidence of suppression in body weight gain and/or lower food consumption in the females during the postpartum interval. Lower mean body weight, body weight gain, and/or food consumption also were observed in the P2 males and females, but were considered to be related to the lower body weight of the F1 offspring which were present at the start of the P2 generation. Based on the microscopic liver changes in the low dose group, a parental systemic toxicity NOEL (No Observable Effect Level) could not be established, and a parental LOEL (Lowest Observable Effect Level) was established at 0.2% under the conditions of this study. There were no adverse effects on reproductive organs or parameters. There were no overt signs of toxicity observed in the offspring, as evidenced by the absence of adverse effects on survival or no adverse clinical signs. The mean body weights of the treated offspring were reduced in a dose-dependent manner on PND 0 and became further reduced during the postnatal period. Maternal exposure to [REDACTED] during the postpartum period was up to 2.8x greater than during the prepartum period due to increased food consumption in the lactating dams. Recovery of offspring body weights was evident after weaning. It is concluded the offspring body weights were reduced because of maternal stress, reduced milk consumption, reduced milk quality and quantity, and possibly direct exposure to [REDACTED] in the milk. As there were no reproductive effects in this study, the highest dose used, 0.8%, was judged to be the reproductive toxicity NOEL.

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WITH ~~SPERMATOCYTES~~; MED-99-489; 14833A**

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**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH ~~XXXXXXXXXXXXXXXXXXXX~~; MRD-98-459; 145335A**

PROTOCOL EXCEPTIONS

BODY WEIGHT: One P1 female weighed 149.7 grams (0.03 grams less than "at least 150 grams" as specified in the protocol) at initiation of test material administration (Day 0).

F1 CULLING (PND 4): The litter from dam HCO510 was culled from 6 males and 3 females to 4 males and 3 females. The litter should have been culled to 5 males and 3 females.

NECROPSY OF CULLED PUPS (PND 4): Culled pups with abnormalities inadvertently were not subjected to a gross necropsy as required by protocol.

F2 OFFSPRING NECROPSY: Pups J-M from the HCP078 litter inadvertently were not examined the day they were found dead. They were subsequently examined the next day.

F2 OFFSPRING SELECTION FOR NECROPSY: The protocol required 10 pups/sex/group be randomly selected for sacrifice and necropsy on PND 21 and that no more than one pup of each sex be selected from a litter. Two additional F2 pups (one male and one female) were selected for necropsy due to inlife abnormalities.

TISSUE PRESERVATION: Gross lesions discovered at necropsy were not preserved. The tissues in question were primarily lesions not associated with toxicity. In addition, P1 male HCO394 (Group 3) did not have its pituitary gland removed and preserved.

These protocol deviations did not adversely affect the study results or integrity.

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

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED]; NMB-92-(55): 145515A

TABLE 1 -- INCIDENCE OF INLIFE OBSERVATIONS -- F1

	MALES																	
	D A Y																	
SURVIVORS	0	7	1	2	2	3	4	4	5	6	6	7	8	9	1	2	3	3
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
GENERAL OBSERVATION WITHIN NORMAL LIMITS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
RESPIRATION DRY HALES	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
DRIED RED NASAL DISCHARGE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
APPEARANCE SOFT STOOL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
SCABS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
SORES	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	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 [REDACTED] AND-92-415; 145935A

TABLE 1 - 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	4	2	3	5	2	4	5	5	7	7	8	9	1	8	10
BROKEN INCISOR(S)	0%	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
	0.8%	0	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
	0.2%	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
	0.8%	0	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
	0.2%	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
	0.8%	0	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
	0.2%	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
	0.8%	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 [REDACTED] (MED-92-455): 145535A

TABLE 1 - 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	D	D
		A	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	Y
		0	7	1	4	1	2	2	3	4	4	5	6	7	7	8	9	9	9	9
ABDOMINAL STAINING	0%	0	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
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.8%	0	0	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
	0.2%	0	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	0
	0.8%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AMOEBNITAL STAINING	0%	0	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
	0.4%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.8%	0	0	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
	0.2%	0	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	0
	0.8%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NOTE: * - SEE GESTATION/POSTPARTUM OBSERVATIONS AS FEMALES ARE CONFIRMED MATED AND/OR DELIVER

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (CAS NO. 149531A)

TABLE 2 - INCIDENCE OF GESTATION OBSERVATIONS - F1
 FEMALES

TOTAL (A)	%	GESTATION DAY:			
		0	7	1	2
	0.25	26	26	26	26
	0.45	24	24	24	24
	0.85	24	24	24	24

GENERAL OBSERVATION WITHIN NORMAL LIMITS	%	25	24	24	23
	0.25	24	24	24	24
	0.45	24	24	24	24
	0.85	23	23	23	23

APPARANCE MALOCCLUDED/BROKEN INCISOR(S)	%	1	2	2	3
	0.25	0	0	0	0
	0.45	0	0	0	0
	0.85	0	0	0	0
ALOPECIA	%	0	0	0	0
	0.25	0	0	0	0
	0.45	0	0	0	0
	0.85	1	1	1	1

OCULAR DRY RED OCULAR DISCHARGE	%	1	1	1	1
	0.25	0	0	0	0
	0.45	0	0	0	0
	0.85	0	0	0	0

NOTE: (A) - TOTALS DO NOT INCLUDE NON-PREGNANT AND/OR UNCONFIRMED DATE OF MATING FEMALES

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MRD-92-455): 145535A

TABLE 3 -- INCIDENCE OF POSTPARTUM OBSERVATIONS -- ♀
FEMALES

	POSTPARTUM DAY:						
	0	4	7	10	14	21	28
TOTAL	27	27	26	26	26	26	26
GENERAL OBSERVATION WITHIN NORMAL LIMITS	24	24	24	24	24	24	24
0%	24	24	24	24	24	24	24
0.2%	24	24	24	24	24	24	24
0.4%	24	24	24	24	24	24	24
0.8%	24	24	24	24	24	24	24
APPEARANCE	24	24	23	23	24	24	24
MALOCCLUDED/BROKEN INCISOR(S)	24	24	24	24	24	24	24
0%	24	24	24	24	24	24	24
0.2%	24	24	24	24	24	24	24
0.4%	24	24	24	24	24	24	24
0.8%	24	24	24	24	24	24	24
ABOGENITAL STAINING	24	24	24	24	24	24	24
0%	24	24	24	24	24	24	24
0.2%	24	24	24	24	24	24	24
0.4%	24	24	24	24	24	24	24
0.8%	24	24	24	24	24	24	24
ALOPECIA	24	24	24	24	24	24	24
0%	24	24	24	24	24	24	24
0.2%	24	24	24	24	24	24	24
0.4%	24	24	24	24	24	24	24
0.8%	24	24	24	24	24	24	24
MASS (POSTERIOR VENTRAL OR CERVICAL AREA)	24	24	24	24	24	24	24
0%	24	24	24	24	24	24	24
0.2%	24	24	24	24	24	24	24
0.4%	24	24	24	24	24	24	24
0.8%	24	24	24	24	24	24	24
OCULAR	24	24	24	24	24	24	24
DRY RED OCULAR DISCHARGE	24	24	24	24	24	24	24
0%	24	24	24	24	24	24	24
0.2%	24	24	24	24	24	24	24
0.4%	24	24	24	24	24	24	24
0.8%	24	24	24	24	24	24	24

NOTE: TOTALS DO NOT INCLUDE FEMALES FOLLOWING LOSS OF LITTER
* - OBSERVATION FOR ONE ANIMAL INADVERTENTLY NOT RECORDED

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH MED-92-455; 145533A

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
L-	L	L+	No linear response to the dose levels
	Q	Q+	Linear response shows lack of fit
	*	* ₀	Mean significantly different from control mean
(NONPARAMETRIC)			
K-	K	K+	No statistical difference among the means
J-	J	J+	Means differ significantly
	*	**	No ordered response to the dose levels
	*	**	An ordered response to the dose levels
	*	**	Mean significantly different from control mean
NT			Data not tested

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] (MWD-22-485), 145235A

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

	D 0		D 1		D 2		D 3		D 4		D 5		D 6		D 7	
	A-L	A-L	A-L	A-L	A-L	A-L										
MALE																
0 ♀																
MEAN	194.2	248.0	305.1	348.7	385.8	418.6	451.2	471.7	493.9	510.2	527.8					
STD. DEV.	9.6	14.2	17.0	24.6	31.8	37.6	43.2	44.6	53.4	59.2	62.8					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.2 ♀																
MEAN	195.0	249.7	308.0	352.2	392.8	428.5	453.4	473.5	495.1	517.8	528.1					
STD. DEV.	9.7	11.7	14.6	18.2	23.2	28.8	30.5	33.7	35.4	38.1	39.7					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.4 ♀																
MEAN	194.1	248.0	306.7	348.6	382.6	414.6	443.8	465.0	488.5	507.8	519.6					
STD. DEV.	8.9	13.5	16.7	23.5	28.8	33.6	38.6	38.8	42.0	44.2	46.4					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.8 ♀																
MEAN	194.1	247.6	307.7	351.8	391.3	428.4	452.4	468.8	487.4	508.5	521.7					
STD. DEV.	9.3	11.6	14.6	19.0	24.8	29.6	33.7	36.8	39.8	42.1	44.5					
(N)	30	30	30	30	30	30	30	30	30	30	30					
FEMALE																
0 ♀																
MEAN	165.6	178.0	204.7	225.5	247.7	262.8	278.1	284.8	287.6	304.7	309.6					
STD. DEV.	7.8	10.1	12.5	16.1	18.6	18.6	20.0	20.4	21.4	21.1	23.8					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.2 ♀																
MEAN	167.1	180.3	208.7	229.9	254.1	270.5	289.2	294.7	305.2	316.0	323.3					
STD. DEV.	8.5	10.6	11.7	12.6	14.2	15.3	16.3	17.3	19.0	19.6	20.8					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.4 ♀																
MEAN	166.5	179.0	207.7	228.4	258.7	265.2	282.6	288.7	308.7	315.4	314.9					
STD. DEV.	7.8	9.8	13.4	17.7	19.1	22.6	21.8	25.6	27.5	27.5	30.5					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.8 ♀																
MEAN	165.6	178.0	208.0	228.8	258.4	266.2	281.0	289.2	297.7	308.2	311.9					
STD. DEV.	7.9	9.7	12.8	17.4	19.4	20.3	22.1	22.8	24.3	24.8	25.0					
(N)	30	30	30	30	30	30	30	30	30	30	30					

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] MRD-92-455): 45535A

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

	D			D			D			D		
	A	A	Y	A	A	Y	A	A	Y	A	A	Y
MALE	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
0 %	MEAN	546.9	551.4	565.1	577.4	589.0	589.0	589.0	589.0	589.0	589.0	589.0
	STD. DEV.	66.7	69.8	70.2	75.3	80.0	80.0	80.0	80.0	80.0	80.0	80.0
	(N)	30	30	30	30	30	30	30	30	30	30	30
0.2 %	MEAN	547.8	551.9	567.3	576.2	588.8	588.8	588.8	588.8	588.8	588.8	588.8
	STD. DEV.	61.3	62.8	65.4	66.7	68.5	68.5	68.5	68.5	68.5	68.5	68.5
	(N)	30	30	30	30	30	30	30	30	30	30	30
0.4 %	MEAN	536.0	543.6	555.3	569.2	579.2	579.2	579.2	579.2	579.2	579.2	579.2
	STD. DEV.	48.1	49.4	51.1	49.9	52.8	52.8	52.8	52.8	52.8	52.8	52.8
	(N)	29	29	29	29	29	29	29	29	29	29	29
0.8 %	MEAN	537.7	543.1	555.9	568.4	578.1	578.1	578.1	578.1	578.1	578.1	578.1
	STD. DEV.	67.2	51.5	57.3	53.7	54.9	54.9	54.9	54.9	54.9	54.9	54.9
	(N)	30	30	30	30	30	30	30	30	30	30	30
FEMALE	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
0 %	MEAN	318.2										
	STD. DEV.	24.1										
	(N)	30										
0.2 %	MEAN	332.5										
	STD. DEV.	22.3										
	(N)	29										
0.4 %	MEAN	323.6										
	STD. DEV.	30.7										
	(N)	30										
0.8 %	MEAN	320.5										
	STD. DEV.	26.7										
	(N)	30										

NOTE: (A) - SEE GESTATION/POSTPARTUM BODY WEIGHT TABLES AS FEMALES ARE CONFIRMED MATED AND/OR DELIVER

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (CAS NO. 52-455); 145535A**

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

DAY:	P		1		2		3		4		5		6		7	
	A-L	A-L	A-L	A-L	A-L	A-L										
0 ♀																
MEAN	53.7	57.2	43.6	36.8	33.1	32.6	29.4	23.2	16.4	17.5	19.1	4.5				
STD. DEV.	7.3	9.3	8.6	8.4	7.2	7.2	7.2	7.2	12.2	10.2	7.3	6.7				
(N)	30	30	30	30	30	30	30	30	30	30	30	30				
0.2 ♂																
MEAN	54.2	58.6	44.2	40.6	27.8	32.8	29.1	21.6	22.7	11.3	19.7	4.2				
STD. DEV.	3.6	6.7	4.2	6.8	5.4	6.9	5.5	3.7	5.8	8.7	7.5	7.8				
(N)	30	30	30	30	30	30	30	30	30	30	30	30				
0.4 ♂																
MEAN	53.8	58.7	41.9	34.8	32.8	29.3	19.6	22.5	19.5	11.6	18.4	5.7				
STD. DEV.	5.9	7.6	8.8	11.8	9.6	13.8	6.7	6.8	4.8	5.3	5.3	6.1				
(N)	30	30	30	30	30	30	30	30	30	30	30	30				
0.6 ♂																
MEAN	53.8	59.9	44.1	39.4	29.1	22.0	16.4	18.5	21.1	13.2	18.0	8.2				
STD. DEV.	6.5	7.2	7.5	7.6	7.2	5.7	5.2	6.2	5.8	4.2	5.3	6.3				
(N)	30	30	30	30	30	30	30	30	30	30	30	30				
FEMALES																
0 ♀																
MEAN	31.4	26.7	20.9	22.3	15.3	15.1	6.7	12.8	7.1	4.9	8.6	(A)				
STD. DEV.	5.6	7.6	6.2	9.7	7.4	6.6	6.0	6.3	7.8	7.5	6.8					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.2 ♀																
MEAN	33.2	28.4	21.2	24.2	16.5	18.7	5.5	10.5	10.8	7.4	11.2					
STD. DEV.	5.1	4.1	4.8	7.2	6.6	6.5	6.2	6.3	7.8	6.3	7.2					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.4 ♀																
MEAN	32.5	28.8	20.7	21.8	16.8	16.4	7.1	11.1	10.7	3.4	8.7					
STD. DEV.	5.6	7.1	6.3	4.7	6.5	6.3	6.7	6.7	6.1	5.9	6.2					
(N)	30	30	30	30	30	30	30	30	30	30	30					
0.6 ♀																
MEAN	32.4	29.8	20.7	21.6	15.8	14.8	8.2	8.5	10.5	3.7	8.6					
STD. DEV.	5.6	7.6	6.3	6.8	5.6	6.8	6.2	4.8	4.7	3.6	5.3					
(N)	30	30	30	30	30	30	30	30	30	30	30					

NOTE: (A) - SEE GESTATION/POSTPARTUM BODY WEIGHT TABLES AS FEMALES BECAME CONFIRMED MATED AND/OR DELIVER

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] MID-92-655; 145515A

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

	W		W		W		W		W		W		W		
	A-L														
0 ♀	204.6	214.3	216.1	217.1	217.4	221.4	216.7	212.8	219.9	219.9	219.9	219.9	219.9	219.9	219.9
MEAN	15.8	18.0	21.0	23.2	22.3	24.9	22.5	28.5	27.8	27.8	27.8	27.8	27.8	27.8	27.8
STD. DEV.	30	28	29	26	29	27	27	27	26	26	26	26	26	26	26
0.2 ♀	203.7	212.5	212.6	212.9	214.8	215.6	215.2	218.7	218.4	218.4	218.4	218.4	218.4	218.4	218.4
MEAN	15.5	14.4	14.9	17.2	17.8	16.2	16.6	18.1	17.2	17.2	17.2	17.2	17.2	17.2	17.2
STD. DEV.	29	29	33	26	28	28	28	26	28	28	28	28	28	28	28
0.4 ♀	203.9	208.4	209.0	212.0	212.9	213.4	212.8	214.0	213.7	213.7	213.7	213.7	213.7	213.7	213.7
MEAN	15.9	17.9	19.6	22.9	22.4	22.2	19.6	22.4	22.4	22.4	22.4	22.4	22.4	22.4	22.4
STD. DEV.	29	26	27	27	27	27	27	27	27	27	27	27	27	27	27
0.8 ♀	204.2	216.4	215.0	218.0	217.8	217.3	214.8	217.9	219.1	219.1	219.1	219.1	219.1	219.1	219.1
MEAN	15.6	15.8	18.5	20.4	20.1	19.6	20.7	22.4	22.2	22.2	22.2	22.2	22.2	22.2	22.2
STD. DEV.	29	28	28	28	29	30	28	27	28	28	28	28	28	28	28
FEMALE	A-L	A-L	A-L	A+L-Q	EQ	A-L	A-L	AL-Q	A+L-Q						
0 ♀	140.7	149.4	156.6	172.4	159.3	159.9	159.0	154.5	147.9	147.9	147.9	147.9	147.9	147.9	147.9
MEAN	10.6	11.1	12.7	16.1	12.3	12.3	14.1	18.3	16.7	16.7	16.7	16.7	16.7	16.7	16.7
STD. DEV.	27	28	27	29	26	25	27	26	25	25	25	25	25	25	25
0.2 ♀	145.0	151.5	160.3	170.5	165.0	163.1	161.8	164.7	165.5	165.5	165.5	165.5	165.5	165.5	165.5
MEAN	9.4	9.2	11.3	14.2	11.1	11.3	14.5	17.6	12.3	12.3	12.3	12.3	12.3	12.3	12.3
STD. DEV.	27	27	26	26	28	28	28	28	26	26	26	26	26	26	26
0.4 ♀	141.7	150.9	152.3	156.3	158.4	156.0	149.1	150.3	150.2	150.2	150.2	150.2	150.2	150.2	150.2
MEAN	10.8	13.8	13.4	17.9	20.1	20.0	20.7	16.3	16.0	16.0	16.0	16.0	16.0	16.0	16.0
STD. DEV.	28	26	26	26	27	24	27	28	25	25	25	25	25	25	25
0.8 ♀	139.4	152.1	153.0	145.0	156.1	157.7	157.1	154.5	153.1	153.1	153.1	153.1	153.1	153.1	153.1
MEAN	11.3	12.5	12.7	12.0	13.6	14.9	13.3	10.9	11.4	11.4	11.4	11.4	11.4	11.4	11.4
STD. DEV.	26	21	23	23	28	26	29	26	27	27	27	27	27	27	27

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] MED-92-455; 145535A

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

GESTATION DAY:	0		7		1		4		0	
	A+L+	A+L+Q	A-L-	AL	A+L+	A+L+Q	A-L-	AL	A+L+	A+L+Q
MEAN	181.4	196.6	207.2	583.5	177.1	16.3	15.0	43.6	184.9	207.0
STD. DEV.	17.1	16.3	15.0	23	18.0	20.2	20.3	55.5	179.0	193.9
(N)	24	25	25	20	23	21	24	20	24	23
0.2										
MEAN	184.9	207.0	218.2	609.1	180.0	20.2	20.3	55.5	179.0	193.9
STD. DEV.	18.0	20.2	20.3	20	19.6	16.1	19.9	45.0	168.5	185.4
(N)	23	21	24	20	24	23	24	23	24	24
0.1										
MEAN	179.0	193.9	208.4	578.1	168.5	185.4	203.0	558.0	13.2	16.1
STD. DEV.	16.6	16.1	19.9	23	13.2	16.1	27.8	50.0	24	24
(N)	24	23	24	20	24	24	22	22		
0.8										
MEAN	168.5	185.4	203.0	558.0	13.2	16.1	27.8	50.0		
STD. DEV.	13.2	16.1	27.8	22	24	24	22	22		
(N)	24	24	22	22						

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH (MID-92-455); 145515A

TABLE 11 - MEAN POSTPARTUM FOOD CONSUMPTION - F1
(SEE KEY A FOR STATISTICAL ABERRATIONS)

POSTPARTUM DAY:	0		4		7		14		21	
	A+LQ	A-L-	A+LQ	A-L-	A+LQ	A-L-	A+LQ	A-L-	A+LQ	A-L-
FEMALES										
08										
MEAN	186.0	120.4	154.0	246.3	530.3	1800.0				
STD. DEV.	26.5	18.1	25.8	43.8	78.9	191.2				
(N)	27	23	25	26	26	25				
0.25										
MEAN	121.0	125.4	141.9	246.7	496.6	1157.4				
STD. DEV.	21.9	15.1	33.8	35.0	52.2	117.4				
(N)	23	24	24	24	24	23				
0.49										
MEAN	128.1	126.7	156.0	235.4	512.2	1170.6				
STD. DEV.	28.4	19.8	17.5	28.3	61.8	93.0				
(N)	21	23	21	24	24	19				
0.99										
MEAN	122.3	122.0	142.5	211.9	448.2	1052.0				
STD. DEV.	34.0	18.4	17.3	23.4	57.6	112.0				
(N)	25	24	24	24	25	24				

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MED-92-455): 149535A

TABLE 12 - MEAN MEASURED DOSE RATE - P1 (CONT'D)

GESTATION DAY:	MEAN MEASURED DOSE RATE (MG/KG/DAY)	
	0	7
0.2 \$	7	4
MEAN	151.2	139.1
0.4 \$		
MEAN	201.0	273.5
0.6 \$		
MEAN	565.2	543.2

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (NBD-92-895); 145535A

TABLE 12 - MEAN MEASURED DOSE RATE - P1 (CONT'D)

POSTPARTUM DAY:	0	4	7	1	1
	4	7	1	1	2
0.2% MEAN	156.8	218.4	276.4	307.3	349.9
0.4% MEAN	346.6	450.3	550.6	604.3	730.7
0.8% MEAN	672.6	900.4	1037.9	1136.7	1379.4

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MD-97-455); 14935A

TABLE 12 - MEAN MEASURED DOSE RATE - 91 (CONT'D)

FORMULA USED =	$\frac{ff \times \text{Concentration (mg/kg)}}{BW7}$
BW7 =	$\frac{[(BW2-BW1) \times bf] + BW1}{1000}$
ff =	Food Consumption (kg)/number of days in interval
BW1 =	Body weight at beginning of interval
BW2 =	Body weight at end of interval
bf =	3/7
BW7 =	Body weight factor
ff =	Feed factor

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MD-92-455): 14535A

KEY B - ORGAN ABBREVIATIONS

Abbreviation	Organ Name
TSM/BW	Terminal Body Weight
LIVER	Liver
KIDNEY/KIDNY	Kidneys
BRAIN	Brain
LT TS	Left Testis
RT TS	Right Testis
LT EP	Left Epididymis
RT EP	Right Epididymis
PT+SV	Prostate and Seminal Vesicles
ROVAR	Right Ovary
LOVAR	Left Ovary

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] NRD-92-495; 14535A

TABLE 13 - MEAN ORGAN WEIGHT - F1 (GRAMS) (SEE KEYS A AND B FOR ABBREVIATIONS)

SEX	Dose	Organ Weights (g)									
		L	L	L	L	L	L	L	L	L	L
MALE	0	617.7	23.27	4.80	2.23	1.0633	1.0576	0.7988	0.0252	3.886	0.0252
	MEAN	30.0	4.33	0.46	0.12	0.1373	0.1421	0.0737	0.0793	0.581	0.0793
	STD. DEV.	(N)	30	30	30	30	30	30	30	30	30
	0.2	613.7	23.52	5.18	2.15	1.0615	1.0611	0.8239	0.0149	3.971	0.0149
MEAN	30.0	3.78	0.54	0.11	0.1742	0.1731	0.0851	0.0771	0.516	0.0771	
STD. DEV.	(N)	30	30	30	30	30	30	30	30	30	
0.4	604.6	24.68	5.47	2.16	1.0904	1.0138	0.8112	0.0203	3.584	0.0203	
MEAN	30.0	3.76	0.48	0.13	0.1547	0.1458	0.0828	0.1113	0.496	0.1113	
STD. DEV.	(N)	30	30	30	30	30	30	30	30	30	
0.8	604.0	26.04	5.75	2.17	1.0973	1.0028	0.8271	0.0309	3.895	0.0309	
MEAN	30.0	4.07	0.62	0.16	0.1725	0.1730	0.0808	0.0994	0.472	0.0994	
STD. DEV.	(N)	30	30	30	30	30	30	30	30	30	
FEMALE	0	379.5	17.58	3.18	1.03	1.03	1.03	0.0625	0.0625	0.0625	0.0625
	MEAN	30.0	2.44	0.32	0.11	0.11	0.11	0.0168	0.0168	0.0168	0.0168
	STD. DEV.	(N)	30	30	30	30	30	30	30	30	30
	0.2	392.0	19.42	3.36	1.01	1.01	1.01	0.0670	0.0670	0.0670	0.0670
MEAN	30.0	3.48	0.36	0.10	0.10	0.10	0.0165	0.0165	0.0165	0.0165	
STD. DEV.	(N)	30	30	30	30	30	30	30	30	30	
0.4	395.8	21.06	3.48	1.01	1.01	1.01	0.0679	0.0679	0.0679	0.0679	
MEAN	30.0	3.84	0.40	0.11	0.11	0.11	0.0177	0.0177	0.0177	0.0177	
STD. DEV.	(N)	30	30	30	30	30	30	30	30	30	
0.8	361.6	21.46	3.35	1.01	1.01	1.01	0.0599	0.0599	0.0599	0.0599	
MEAN	30.0	4.10	0.42	0.10	0.10	0.10	0.0155	0.0155	0.0155	0.0155	
STD. DEV.	(N)	30	30	30	30	30	30	30	30	30	

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] MID-92-455; 145512A

TABLE 14. - MEAN RELATIVE ORGAN WEIGHT - 91
 (SEE KEYS A AND B FOR ABBREVIATIONS)

	MALE				FEMALE			
	A+L+	A+L+Q	K-J-	A-L-	A+L+	A+L+Q	A-L-	A-L-
0 %								
MEAN	0.038	0.008	0.0037	0.00307	0.00318	0.00314	0.00140	0.00140
STD. DEV.	0.003	0.0006	0.0005	0.00042	0.00034	0.00016	0.00016	0.00016
(N)	30	30	30	30	30	30	30	30
0.2 %								
MEAN	0.038	0.0085	0.0035	0.00308	0.00309	0.00135	0.00132	0.00132
STD. DEV.	0.004	0.0006	0.0003	0.00031	0.00021	0.00013	0.00016	0.00016
(N)	30	30	30	30	30	30	30	30
0.4 %								
MEAN	0.041	0.0091	0.0036	0.00314	0.00318	0.00135	0.00138	0.00138
STD. DEV.	0.004	0.0007	0.0003	0.00032	0.00034	0.00019	0.00023	0.00023
(N)	29	29	29	29	29	29	29	29
0.8 %								
MEAN	0.044	0.0095	0.0036	0.00316	0.00314	0.00138	0.00140	0.00140
STD. DEV.	0.004	0.0006	0.0004	0.00034	0.00033	0.00016	0.00016	0.00016
(N)	30	30	30	30	30	30	30	30
FEMALE	A+L+	A+L+	A+L+Q	A-L-	A-L-	A-L-	A-L-	A-L-
0 %								
MEAN	0.046	0.0082	0.0056	0.00307	0.00318	0.00135	0.00140	0.00140
STD. DEV.	0.006	0.0007	0.0005	0.00034	0.00034	0.00016	0.00016	0.00016
(N)	30	30	30	30	30	30	30	30
0.2 %								
MEAN	0.049	0.0086	0.0052	0.00309	0.00318	0.00135	0.00140	0.00140
STD. DEV.	0.008	0.0009	0.0004	0.00034	0.00034	0.00016	0.00016	0.00016
(N)	29	29	29	29	29	29	29	29
0.4 %								
MEAN	0.053	0.0086	0.0051	0.00308	0.00318	0.00135	0.00140	0.00140
STD. DEV.	0.008	0.0008	0.0004	0.00034	0.00034	0.00016	0.00016	0.00016
(N)	30	30	30	30	30	30	30	30
0.8 %								
MEAN	0.059	0.0093	0.0055	0.00310	0.00318	0.00135	0.00140	0.00140
STD. DEV.	0.010	0.0010	0.0006	0.00034	0.00034	0.00016	0.00016	0.00016
(N)	29	29	29	29	29	29	29	29

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] MID-92-655; 145915A

TABLE 15 - INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS - F1

DOSE:	SEXES			
	0%	0.2%	0.4%	0.8%
TOTAL AT SCHEDULED SACRIFICE:	10	30	29	30
NO OBSERVABLE ABNORMALITIES	13	24	26	23
KIDNEY(S): Dilated pelvis Foci or Mottled	-	1 3	-	1 3
LIVER: Mottled	-	2	-	-
LUNGS: Foci	1	-	1	-
THYMUS: Foci	-	1	-	-
URINARY BLADDER: Contained white, fibrous material	4	5	1	2
GENERAL CONDITION: Dried red material around eye(s) Alopecia Maloccluded/broken incisors Seros palate Seros skin/subcutis	1 3 1 1 1 2	- - - - - -	2 2 2 - -	1 2 2 - -

PRETERMINAL DEATHS

NUMBER EUTHANASIED:	-	-	1(A)	-
---------------------	---	---	------	---

NOTE: (A) - ACCIDENTAL INJURY. ANIMAL EUTHANASIED. POSTMORTEM OBSERVATIONS INCLUDED SWOLLEN SNOUT, SORES PALATE, SLIGHT EMACIATION, MALOCCLUDED INCISORS, AND DRY RED MATERIAL AROUND EYES.

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (RAD-92-455): 14553/A

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

	FEMALES		
	04	0.28	0.48
DOSE:	04	0.28	0.48
TOTAL AT SCHEDULED SACRIFICE:	30	29	30
NO OBSERVABLE ABNORMALITIES	14	16	17
COLON: Red feci	-	1	-
ILEUM: Thickened and reddened	-	1	-
KIDNEY(S): Dilated pelvis	-	1	-
LARGE INTESTINES, CECUM, COLON, AND/OR RECTUM: Parasites, pinworms presumptive	11	12	13
PITUITARY: Enlarged	-	1	-
SKIN/SUBCUTIS: Mass	-	1	-
STOMACH: Thickened	-	-	1
UTERUS: Distended	-	1	-
GENERAL CONDITION			
Alopecia	-	-	1
Anogenital staining	-	-	1
Red material around eye(s)	1	-	-
Maloccluded/broken incisors	1	-	-
UTERUS: No evidence of implantation sites	3	4	5
PRETERMINAL DEATHS			
NUMBER FOUND DEAD:	-	1	-
LIVER: Enlarged and thickened	-	1	-
LYMPH NODES: Enlarged	-	1	-
SPLEEN: Enlarged, thickened, appears ruptured	-	1	-
GENERAL CONDITION: Anogenital staining	-	1	-

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH MHD-52-655: 145535A

TABLE 17 - SUMMARY OF OFFSPRING SURVIVAL - F1

Dose (%)	Live Birth		Day 1		Day 4		Day 7		Day 14		Day 21		Viability at Weaning	
	Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS
0.0	97.3	96.5	95.1	95.1	96.0	96.0	96.0	100.0	100.0	99.5	99.5	95.5	95.5	95.5
0.2	98.0	98.9	97.1	97.1	99.5	99.5	98.9	98.9	100.0	100.0	100.0	98.4	98.4	98.4
0.4	96.9	98.5	96.8	96.8	97.8	97.8	100.0	100.0	100.0	100.0	100.0	97.8	97.8	97.8
0.8	97.9	97.6	95.1	95.1	99.0	99.0	99.0	99.0	100.0	100.0	100.0	97.9	97.9	97.9

NOTE: * P<0.05 by Fischer Exact Test
 ** P<0.01 by Fischer Exact Test
 + Dose-response trend, P<0.05 by Armitage Test
 ++ Dose-response trend, P<0.01 by Armitage Test
 MSS NO STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN CONTROLS AND TREATED GROUPS AT P<0.05 OR P<0.01 BY FISCHER EXACT TEST

Live Birth (%) = Index	Number of live pups at birth	Day 14 S.I. (%) =	Number of live pups at Day 14
Day 1 S. I. (%) =	Number of pups born	Day 21 S.I. (%) =	Number of live pups at Day 21
Day 4 S. I. (%) =	Number of live pups at Day 1	Viability (%) = Index at Weaning	Number of live pups at Day 4 (postcull)
Day 7 S. I. (%) =	Number of live pups at Day 7		Number of live pups at Day 4 (postcull)
	Number of live pups at Day 0		
	Number of live pups at Day 4 (pre-cull)		
	Number of live pups at Day 0		
	Number of live pups at Day 7		
	Number of live pups at Day 4 (postcull)		

NOTE: S. I. - SURVIVAL INDICES
 ALL INDICES MULTIPLIED BY 100

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MRD-92-455): 14525A

TABLE 10 - INCIDENCE OF OUTSPRING INLIFE OBSERVATIONS - F1 (CONT'D)
 (PRE-WEANING OBSERVATIONS)

TIME *	P D																				
EUTHANIZED	0	0	0	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	0	0
0.4 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
WITHOUT MILK (b)																					
0 %	30	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2 %	31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4 %	37	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 %	30	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SWOLLEN HINDPAW																					
0 %	0	0	1	1	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	0	0
0.4 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LACERATION (AXIAL, CERVICAL, DORSAL, HEAD, HINDLEG, POSTERIOR DORSAL)																					
0 %	0	0	2	2	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	0	0
0.4 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 %	0	2	8	7	6	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2
MISSING DIGIT																					
0 %	0	0	0	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	0	0
0.4 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NOTE: PND - POSTNATAL DAY
 (a) - LITTERS CULLED AFTER PND 4 OBSERVATIONS
 (b) - MILK OBSERVATIONS DISCONTINUED AFTER PND 13 DUE TO PRESENCE OF HAIR COAT

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (FWD-92-455); 145535A

TABLE 16 - INCIDENCE OF OFFSPRING IN-LIFE OBSERVATIONS - F1 (CONT'D)
 (PRE-WEANING OBSERVATIONS)

TIME -	PND 0	PND 1	PND 2	PND 3	PND 4	PND 5	PND 6	PND 7	PND 8	PND 9	PND 10	PND 11	PND 12	PND 13	PND 14	PND 15	PND 16	PND 17	PND 18	PND 19	PND 20	PND 21	
0 ♀	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
0.2 ♀	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
0.4 ♀	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
0.8 ♀	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
SCABS (HEAD, DORSAL)	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	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	0	0	0	0
0.4 ♀	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 ♀	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UMBILICAL HERNIA	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	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	0	0	0	0
0.4 ♀	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 ♀	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HYPOTHERMIC	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	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	0	0	0	0
0.4 ♀	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.8 ♀	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NOTE: PND - POSTNATAL DAY
 (n) - LITTERS COLLECTED AFTER PND 4 OBSERVATIONS

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] MHD-92-655): 145535A

TABLE 19 - MEAN OFFSPRING BODY WEIGHT - F1 (GRAMS) (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

	0	1	4	7	1	2
----- MALE -----						
0%						
MEAN	6.90	7.49	10.63	17.62	35.01	57.25
STD. DEV.	0.62	0.81	1.94	2.35	3.94	6.73
(N)	163	161	155	97	97	96
0.2%						**
MEAN	6.78	7.39	10.26	16.44	33.28	51.40
STD. DEV.	0.57	0.77	1.53	2.85	4.52	8.52
(N)	168	165	162	94	94	94
0.4%	**			**	**	**
MEAN	6.48	7.03	9.54	15.28	30.42	47.95
STD. DEV.	0.63	0.80	1.72	3.19	4.36	7.94
(N)	177	175	162	90	90	90
0.8%	**			**	**	**
MEAN	6.43	7.05	9.74	15.67	29.66	46.52
STD. DEV.	0.45	0.62	1.25	1.74	2.55	5.15
(N)	176	172	160	94	92	92
----- FEMALE -----						
0%						
MEAN	6.47	7.11	10.26	16.70	33.52	53.99
STD. DEV.	0.52	0.73	1.52	2.15	3.70	6.17
(N)	166	163	158	92	96	96
0.2%						**
MEAN	6.36	6.96	9.61	15.54	31.82	49.19
STD. DEV.	0.58	0.78	1.52	2.79	4.57	7.54
(N)	182	181	178	94	93	93
0.4%	*			**	**	**
MEAN	6.16	6.67	9.24	14.21	28.14	45.63
STD. DEV.	0.59	0.75	1.65	3.21	4.50	7.31
(N)	182	179	170	95	94	94
0.8%	**			**	**	**
MEAN	6.08	6.70	9.36	15.03	28.41	44.68
STD. DEV.	0.52	0.70	1.30	1.72	3.10	5.68
(N)	193	188	183	97	97	97

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] AND-92-455); 145535A

TABLE 26 - INCIDENCE OF OFFSPRING CROSS FOSTERED OBSERVATIONS - F1

DOSE GROUP (a):	TERMINAL EUTHANASIA: FWD 21			
	0	0.2	0.4	0.6
N =	20	20	20	21
NO OBSERVABLE ABNORMALITIES	20	19	18	20
KIDNEY: Embedded focus, pale, and small	-	1	-	-
MESENTERY: Cyst-like structure	-	-	1	-
SPLEEN: Slightly enlarged	-	-	1	-
TAIL: Truncated	-	-	-	1 (a)

DOSE GROUP (b):	VISCERAL MASTITIS: CD 22 - FWD 20			
	0	0.2	0.4	0.6
NUTRITION	0	0	0	1 (c)
FOUND DEAD	21	16	16	17
NO OBSERVABLE ABNORMALITIES (b)	18	16	14	16
STILLSORE	5	2	1	4
NO MILK IN STOMACH	2	-	-	2
TOO CARNIVOROUS FOR ANY STIMULATION	-	-	2	-
ABDOMINAL WALL: Tear	1	-	-	-
HEAD: Mesentery (appeared mechanical)	-	-	-	1
LIVER: Discolored	1	-	-	-
KIDNEY: Dilated renal pelvis(es)	1	-	-	-
SKIN: Laceration posterior dorsal	-	-	-	1 (c)
URINARY BLADDER: Distended	1	-	-	-

NOTE: (a) - Additional pup selected for necropsy due to infill abnormality
 (b) - Includes animals that may have been too autolyzed or cannibalized to examine internally, determined stillborn, and/or without milk in stomach.
 (c) - Animal euthanized due to laceration CD - OBSERVATION DAY
 FWD - POSTNATAL DAY

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MD-92-455); 14535A

TABLE 21 - INCIDENCE OF INLIFE OBSERVATIONS - P2 (CONT'D)

		MALES																	
		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
		0	7	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
		Y	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
		0	7	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
TRUNCATED TAIL	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NAUCLIPED INCISORS	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.85	0	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
	0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MISSING INCISOR	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR RED OCULAR DISCHARGE	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DRIP RED OCULAR DISCHARGE	0%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IM RATS WITH [REDACTED] (MID-82-455): 15535A

TABLE 21 - INCIDENCE OF IMILFE OBSERVATIONS - P2 (CONT'D)

	MALES					
	D	A	A	D	D	D
SURVIVORS	0%	0.2%	0.4%	0.8%	1	1
GENERAL OBSERVATION WITHIN NORMAL LIMITS	0%	0.2%	0.4%	0.8%	1	1
APPEARANCE SCARS	0%	0.2%	0.4%	0.8%	1	1
SWOLLEN HINDPAW	0%	0.2%	0.4%	0.8%	1	1
SORES	0%	0.2%	0.4%	0.8%	1	1
BROKEN INCISOR(S)	0%	0.2%	0.4%	0.8%	1	1
TRUNCATED TAIL	0%	0.2%	0.4%	0.8%	1	1
MALOCCLUDED INCISORS	0%	0.2%	0.4%	0.8%	1	1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MD-92-855); (45535A)

TABLE 21 .. INCIDENCE OF INLIFE OBSERVATIONS - P2 (CONT'D)

MALES

	D	D	D	D
	A	A	A	A
	Y	Y	Y	Y
	1	1	1	1
	0	1	3	0

ALOPECIA

0%

0.2%

0.4%

0.8%

OCULAR
 DISCHARGES AND OCULAR DISCHARGES

0%

0.2%

0.4%

0.8%

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] MRD-93-455; 14535A

TABLE 21 - INCIDENCE OF IM-LIFE OBSERVATIONS - P2 (CONT'D)
 FEMALES

	D	A	D
	A	A	A
	Y	Y	Y
1	1	1	1
2	0	2	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	0	0
24	0	0	0
25	0	0	0
26	0	0	0
27	0	0	0
28	0	0	0
29	0	0	0
30	0	0	0
31	0	0	0
32	0	0	0
33	0	0	0
34	0	0	0
35	0	0	0
36	0	0	0
37	0	0	0
38	0	0	0
39	0	0	0
40	0	0	0
41	0	0	0
42	0	0	0
43	0	0	0
44	0	0	0
45	0	0	0
46	0	0	0
47	0	0	0
48	0	0	0
49	0	0	0
50	0	0	0
51	0	0	0
52	0	0	0
53	0	0	0
54	0	0	0
55	0	0	0
56	0	0	0
57	0	0	0
58	0	0	0
59	0	0	0
60	0	0	0
61	0	0	0
62	0	0	0
63	0	0	0
64	0	0	0
65	0	0	0
66	0	0	0
67	0	0	0
68	0	0	0
69	0	0	0
70	0	0	0
71	0	0	0
72	0	0	0
73	0	0	0
74	0	0	0
75	0	0	0
76	0	0	0
77	0	0	0
78	0	0	0
79	0	0	0
80	0	0	0
81	0	0	0
82	0	0	0
83	0	0	0
84	0	0	0
85	0	0	0
86	0	0	0
87	0	0	0
88	0	0	0
89	0	0	0
90	0	0	0
91	0	0	0
92	0	0	0
93	0	0	0
94	0	0	0
95	0	0	0
96	0	0	0
97	0	0	0
98	0	0	0
99	0	0	0
100	0	0	0

DRIED RED OCULAR DISCHARGE

0%
 0.2%
 0.4%
 0.8%

NOTE: SEE GESTATION/POSTPARTUM OBSERVATIONS AS FEMALES WERE CONFIRMED MATED AND/OR DELIVER

%

A 02

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MD-92-455); 14535A

TABLE 12 - INCIDENCE OF GESTATION OBSERVATIONS - F2
 FEMALES

TOTAL (A)	GESTATION DAY:				
	0	7	14	21	28
0%	21	21	21	21	21
0.25	21	21	21	21	21
0.48	20	20	20	20	20
0.88	17	17	17	17	17
GENERAL OBSERVATION WITHIN NORMAL LIMITS					
0%	17	16	16	16	16
0.25	20	20	17	17	16
0.48	17	18	17	17	17
0.88	16	16	15	15	15
APPEARANCE MISSING/MALOCCLUDED/BROKEN INCISOR(S)					
0%	2	2	2	2	2
0.25	2	1	1	1	1
0.48	0	0	0	0	0
0.88	0	0	0	0	0
MASS (ALVEOLAR, AXIAL, VENTRAL THORACIC)					
0%	0	0	0	0	0
0.25	0	0	0	0	0
0.48	1	1	1	1	1
0.88	0	0	0	0	0
SCABS/SORES					
0%	1	2	2	2	2
0.25	0	0	0	0	0
0.48	0	0	0	0	0
0.88	0	0	0	0	0
ALOPECIA					
0%	1	1	1	1	1
0.25	1	1	1	1	1
0.48	0	0	0	0	0
0.88	0	0	0	0	0
TRUNCATED TAIL					
0%	0	0	0	0	0
0.25	1	1	1	1	1
0.48	0	0	0	0	0
0.88	0	0	0	0	0
OCULAR DRY RED OCULAR DISCHARGE					
0%	0	0	0	0	0
0.25	0	0	0	0	0
0.48	0	0	0	0	0
0.88	0	0	0	0	0

NOTE: (A) - TOTALS DO NOT INCLUDE NON-PREGNANT AND/OR UNCONFIRMED DATE OF MATING FEMALES

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] MRD-92-455: 145535A

TABLE 23 - INCIDENCE OF POSTPARTUM OBSERVATIONS - F2

FEMALES

	POSTPARTUM DAY:							
	0	4	7	1	1	4	1	2
TOTAL	22	22	22	22	22	22	22	22
GENERAL OBSERVATION WITHIN NORMAL LIMITS	21	21	21	21	21	21	21	21
	21	21	20	20	20	20	20	20
	19	19	19	19	19	19	19	19
APPEARANCE MALOCCLUDED/MISSING/BROKEN INCISOR(S)	15	16	16	15	15	15	15	15
	17	16	16	16	17	17	17	17
	18	18	17	16	15	15	15	15
	16	16	16	15	15	16	16	15
SORES/SCABS	3	3	3	3	4	4	4	5
	1	1	1	2	2	2	2	4
	2	1	1	1	1	1	1	1
	2	1	1	0	0	0	0	0
	0	0	0	0	0	0	0	0
ALOPECIA	1	1	1	1	1	1	1	1
	3	4	4	4	3	3	3	3
	0	0	0	1	1	1	1	1
	1	0	1	1	1	1	1	1
MASS (AXIAL, ANOGENITAL, VENTRAL THORACIC, CERVICAL)	0	1	1	1	1	1	1	1
	1	0	2	1	1	1	1	1
	0	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1

NOTE: TOTALS DO NOT INCLUDE FEMALES FOLLOWING LOSS OF LITTER

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] MID-82-455): 145535A

TABLE 23 - INCIDENCE OF POSTPARTUM OBSERVATIONS - P2 (CONT'D)
 FEMALES

	POSTPARTUM DAY:									
	0	1	2	3	4	5	6	7	8	9
DRY RED BASAL DISCHARGE	0	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0	0	0
0.45	0	0	0	0	0	0	0	0	0	0
0.85	0	0	0	0	0	0	0	0	0	0
EMACIATED	0	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0	0	0
0.45	0	0	0	0	0	0	0	0	0	0
0.85	0	0	0	0	0	0	0	0	0	0
LITTLE SIGN OF FOOD CONSUMPTION	0	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0	0	0
0.45	0	0	0	0	0	0	0	0	0	0
0.85	0	0	0	0	0	0	0	0	0	0
RED MATERIAL VAGINA	1	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0	0	0
0.45	0	0	0	0	0	0	0	0	0	0
0.85	0	0	0	0	0	0	0	0	0	0
TRUNCATED TAIL	0	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0	0	0
0.45	0	0	0	0	0	0	0	0	0	0
0.85	0	0	0	0	0	0	0	0	0	0
OCULAR DRY RED OCULAR DISCHARGE	0	0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0	0	0
0.45	0	0	0	0	0	0	0	0	0	0
0.85	0	0	0	0	0	0	0	0	0	0

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (NIDDK-92-455); 165596A

TABLE 24 - SUMMARY OF PARENTAL SURVIVAL - P2

DOSE	TOTAL PER GROUP	TOTAL SURVIVORS AT TERMINATION	ANIMAL NUMBER TYPE/DATE OF DEATH SIGNIFICANT POSTMORTEM FINDINGS	SURVIVAL INDEX
			MALES	
0%	30	30		100%
0.2%	30	30		100%
0.4%	30	30		100%
0.8%	30	30		100%
			FEMALES	
0%	30	30		100%
0.2%	30	30		100%
0.4%	30	30		100%
0.8%	30	30		100%

SURVIVAL INDEX (%) " TOTAL SURVIVORS AT TERMINATION X 100
 TOTAL NUMBER OF ANIMALS IN GROUP

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (MED-22-455): 145355A

TABLE 25 - MEAN BODY WEIGHT - F2
(SEE KEY A FOR STATISTICAL ABERRATIONS)

SEX	Dose	0		1		2		3		4		5		6		7		
		Mean	Std. Dev.															
MALE	0	211.1	46.8	202.2	42.0	401.0	39.7	442.8	481.3	501.5	532.2	558.4	574.1	599.1	592.2	571.2	552.0	
	0.2	210.4	30.6	200.0	33.8	399.6	40.0	443.0	477.0	500.7	529.1	554.7	579.8	592.2	571.2	552.0	530.0	
	0.4	198.0	25.7	267.1	29.2	382.6	33.1	421.4	454.8	476.0	500.2	526.2	541.5	580.0	580.0	550.0	530.0	
	0.8	184.6	27.1	281.1	28.0	368.1	27.8	409.0	445.8	460.2	492.9	517.2	522.2	551.0	551.0	471.1	471.1	
	FEMALE	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+	443+
	0	167.5	33.4	201.2	27.3	250.0	26.2	266.0	290.1	289.4	302.6	312.0	318.1	327.9	327.9	310.1	310.1	
	0.2	165.6	20.6	198.0	19.2	282.4	23.0	271.0	285.8	292.9	307.2	316.1	321.5	327.9	327.9	310.1	310.1	
	0.4	197.1	15.2	189.4	14.8	243.0	16.6	261.5	277.9	286.8	301.7	309.5	315.0	320.9	320.9	310.1	310.1	
	0.8	150.3	18.9	165.6	18.9	237.5	23.5	254.4	271.2	278.2	289.1	299.3	303.3	310.3	310.3	280.6	280.6	

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH (REDACTED) (MD-92-455): 165535A

TABLE 25 - MEAN BODY WEIGHT - P2 (CONT'D)
(GRAMS)
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

	D		A		D		A		D		A		D		A	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
MALE	A-L	AL+	AL+	AL+	AL+	AL+	AL+	AL+								
0 %	MEAN	618.0	616.4	631.0	645.7	658.5	668.1	684.6	697.0	707.7						
	STD. DEV.	57.0	55.7	57.7	52.5	63.6	66.8	68.2	73.5	76.1						
	(N)	30	30	30	30	30	30	30	30	30						
0.2 %	MEAN	613.5	612.6	626.2	641.6	650.4	664.5	677.3	694.2	705.5						
	STD. DEV.	74.2	73.6	75.2	77.1	79.9	81.9	83.4	88.1	89.5						
	(N)	30	30	30	30	30	30	30	30	30						
0.4 %	MEAN	522.5	578.5	597.4	611.7	628.1	638.6	651.7	661.2	672.3						
	STD. DEV.	56.4	69.9	61.2	66.2	68.5	70.0	73.8	77.4	80.0						
	(N)	30	18	30	30	30	30	30	30	30						
0.8 %	MEAN	572.7	573.8	587.6	599.3	613.6	624.0	636.3	647.7	656.8						
	STD. DEV.	49.4	50.9	51.7	55.0	54.3	56.3	58.0	63.3	65.9						
	(N)	30	30	30	30	30	30	30	30	30						
FEMALE	A-L															
0 %	MEAN	334.8														
	STD. DEV.	29.9														
	(N)	30														
0.2 %	MEAN	337.6														
	STD. DEV.	33.3														
	(N)	30														
0.4 %	MEAN	331.3														
	STD. DEV.	31.7														
	(N)	30														
0.8 %	MEAN	318.6														
	STD. DEV.	32.9														
	(N)	30														

NOTE: (A) - SEE GESTATION/POSTPARTUM BODY WEIGHT TABLES AS FEMALES ARE CONFIRMED MATED AND/OR DELIVER

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] (CAS NO. 145535A)

TABLE 16 - MEAN BODY WEIGHT CHANGE - P2 (GRAMS) (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

SEX	DAY:	STATISTICAL ABBREVIATIONS												
		A-L	A-L	A-L	A-L	A-L	A-L	A-L	A-L	A-L	A-L			
0 ♀	MEAN	71.2	62.2	56.4	41.8	30.5	20.3	30.7	26.1	15.7	25.0	18.8	7.0	7.7
	STD. DEV.	6.4	7.6	10.3	9.3	9.9	6.8	7.6	9.1	6.2	10.4	9.2	6.0	6.0
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
0.2 ♀	MEAN	69.6	63.1	56.4	43.4	34.8	22.9	29.4	25.6	15.8	21.9	21.1	9.7	9.7
	STD. DEV.	7.6	9.3	8.2	9.0	9.4	7.2	7.6	7.5	7.2	6.7	5.9	7.3	7.3
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
0.4 ♀	MEAN	68.3	59.4	56.2	38.8	32.4	21.3	25.1	25.1	15.3	17.4	22.6	9.2	9.2
	STD. DEV.	6.8	7.4	6.3	8.1	6.4	7.0	7.6	7.6	6.2	7.6	6.5	9.8	9.8
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
0.8 ♀	MEAN	66.5	58.0	50.0	40.0	36.7	22.5	24.2	24.7	15.2	19.4	20.9	7.1	7.1
	STD. DEV.	6.2	5.7	8.2	13.1	9.5	7.6	7.6	9.2	6.2	5.7	6.4	7.3	7.3
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
FEMALES	MEAN	33.7	25.6	23.8	16.1	13.2	8.1	14.2	8.2	5.2	9.9	7.0	(A)	(A)
	STD. DEV.	12.1	12.0	11.3	7.8	8.0	6.1	7.3	8.6	5.8	9.2	6.2	30	30
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
0.2 ♀	MEAN	32.4	25.2	25.4	19.2	13.9	7.1	14.2	6.9	5.4	6.4	9.7	30	30
	STD. DEV.	7.1	5.6	5.1	5.1	7.1	6.3	7.3	6.8	5.6	6.2	6.7	30	30
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
0.4 ♀	MEAN	32.2	28.8	24.7	18.5	16.6	8.9	14.9	7.9	5.9	5.5	19.8	30	30
	STD. DEV.	7.7	6.3	6.3	5.1	8.6	6.8	6.6	10.0	8.1	6.3	7.8	30	30
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30
0.8 ♀	MEAN	35.5	27.6	24.2	16.8	16.8	7.0	10.0	4.2	4.1	7.0	8.2	30	30
	STD. DEV.	6.7	7.9	6.7	6.9	6.2	4.1	3.8	4.6	5.3	5.0	5.5	30	30
	(N)	30	30	30	30	30	30	30	30	30	30	30	30	30

NOTE: (A) - SEE GESTATION/POSTPARTUM BODY WEIGHT TABLES AS FEMALES WERE UNWEIGHED DATED APPROXIMATELY 10 DELIVERED

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] MID-82-853; 145535A

TABLE 27 - MEAN GESTATION BODY WEIGHT AND BODY WEIGHT CHANGE - F2
 (GRAMS)
 (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

GESTATION DAY:	0		7		14		21		28		35		42	
	A-L	A-L	A-L	A-L	A-L									
0 ♀	330.0	370.0	408.3	497.3	591.1	680.3	769.0	857.8	946.6	1035.4	1124.2	1213.0	1301.8	1390.6
MEAN	28.2	30.0	37.3	43.0	48.7	54.4	60.1	65.8	71.5	77.2	82.9	88.6	94.3	100.0
STD. DEV.	(N)	21	21	21	21	21	21	21	21	21	21	21	21	21
0.2 ♀	333.0	365.0	402.3	497.0	590.0	680.0	769.0	857.8	946.6	1035.4	1124.2	1213.0	1301.8	1390.6
MEAN	31.7	37.0	36.0	40.0	45.0	50.0	55.0	60.0	65.0	70.0	75.0	80.0	85.0	90.0
STD. DEV.	(N)	21	21	21	21	21	21	21	21	21	21	21	21	21
0.4 ♀	326.0	360.7	397.0	492.5	588.0	680.0	769.0	857.8	946.6	1035.4	1124.2	1213.0	1301.8	1390.6
MEAN	25.0	28.6	29.0	30.0	31.0	32.0	33.0	34.0	35.0	36.0	37.0	38.0	39.0	40.0
STD. DEV.	(N)	20	20	20	20	20	20	20	20	20	20	20	20	20
0.6 ♀	315.1	342.7	370.0	460.4	550.0	640.0	730.0	820.0	910.0	1000.0	1090.0	1180.0	1270.0	1360.0
MEAN	37.1	36.7	38.0	45.0	52.0	59.0	66.0	73.0	80.0	87.0	94.0	101.0	108.0	115.0
STD. DEV.	(N)	17	17	17	17	17	17	17	17	17	17	17	17	17

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] NRD-92-455): 145535A

TABLE 18 - MEAN POSTPARTUM BODY WEIGHT AND BODY WEIGHT CHANGE -- F2
 (GRAMS)
 (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

POSTPARTUM DAY:	0		4		7		1		1		2		4		7		10		14		17		21		
	A-L+	AL+	AL+	AL+	A-L+																				
0 ♀	382.4	381.9	387.9	393.5	407.9	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2	394.2
MEAN	40.3	36.2	35.8	30.0	27.7	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2
STD.DEV.	(N)	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22	22
0.2 ♀	375.5	376.0	377.9	388.4	398.7	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2	389.2
MEAN	38.7	34.9	34.8	34.1	37.2	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7	32.7
STD.DEV.	(N)	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21
0.4 ♀	374.6	364.1	368.1	360.4	364.3	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5	356.5
MEAN	35.1	38.1	37.8	27.5	28.2	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5
STD.DEV.	(N)	20	21	21	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
0.6 ♀	351.2	350.9	355.0	358.2	364.7	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2	362.2
MEAN	35.4	32.6	31.4	32.0	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1	33.1
STD.DEV.	(N)	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] (NID-02-155): 15535A

TABLE 29 - MEAN FOOD CONSUMPTION - 92
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)

SEX	AGE	WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 5		WEEK 6		WEEK 7		WEEK 8		WEEK 9		WEEK 10		
		MEAN	STD. DEV.	MEAN	STD. DEV.																	
MALE	0.6	217.9	23.5	239.1	23.7	243.5	23.8	243.8	23.8	243.8	23.8	243.8	23.8	243.8	23.8	243.8	23.8	243.8	23.8	243.8	23.8	243.8
		16.1	29.1	18.1	28.1	19.1	27.1	18.0	28.0	18.0	28.0	18.0	28.0	18.0	28.0	18.0	28.0	18.0	28.0	18.0	28.0	18.0
	0.2	218.6	23.8	249.1	23.8	249.6	23.8	249.6	23.8	249.6	23.8	249.6	23.8	249.6	23.8	249.6	23.8	249.6	23.8	249.6	23.8	249.6
		19.3	28.1	22.1	27.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1
	0.4	207.8	23.2	239.1	23.2	239.3	23.2	239.3	23.2	239.3	23.2	239.3	23.2	239.3	23.2	239.3	23.2	239.3	23.2	239.3	23.2	239.3
		19.0	28.3	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1
0.6	201.6	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	22.2	238.1	
	19.5	28.6	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1	18.1	27.1
FEMALE	0.6	197.9	161.2	167.4	167.4	162.9	162.9	167.1	167.1	168.2	168.2	162.9	162.9	168.2	168.2	168.2	168.2	168.2	168.2	168.2	168.2	168.2
		14.7	15.4	16.1	16.1	15.0	15.0	15.8	15.8	16.2	16.2	16.2	16.2	16.2	16.2	16.2	16.2	16.2	16.2	16.2	16.2	16.2
	0.2	198.3	163.7	174.4	174.4	172.0	172.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0	168.0
		10.1	17.0	18.1	18.1	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
	0.4	196.7	156.8	163.2	163.2	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0	164.0
		9.0	9.5	12.1	12.1	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7
0.8	192.3	158.5	159.7	159.7	162.2	162.2	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	161.1	
	10.5	18.4	13.5	13.5	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] NRD-92-455): 45535A

TABLE 25 - MEAN FOOD CONSUMPTION - P2 (CONT'D)
 (GRAMS)
 (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

	W E R		W E R		W E R	
	1 6	1 7	1 8	1 9	1 8	1 9
MALE	A-L-	A-L-	A-L-	A-L-	A-L-	A-L-
0 % MEAN	232.5	232.3	233.0	230.6	230.6	230.6
STD. DEV. (N)	24.4 28	25.5 30	24.7 28	23.7 29	23.7 29	23.7 29
0.2 % MEAN	231.0	232.3	231.8	236.2	236.2	236.2
STD. DEV. (N)	24.1 26	25.2 26	25.7 26	26.3 27 ^a	26.3 27 ^a	26.3 27 ^a
0.4 % MEAN	231.6	232.5	230.7	226.2	226.2	226.2
STD. DEV. (N)	23.1 28	25.1 27	24.8 28	23.8 30	23.8 30	23.8 30
0.8 % MEAN	226.6	226.6	229.8	227.4	227.4	227.4
STD. DEV. (N)	18.1 28	22.3 27	25.7 28	21.2 28	21.2 28	21.2 28

**TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] (CAS# 105535A)**

**TABLE 10 - MEAN GESTATION FOOD CONSUMPTION - F2
(GRAMS)
(SEE KEY A FOR STATISTICAL ABBREVIATIONS)**

SEX	GESTATION DAY:			
	0	7	14	21
MEAN	195.2	212.7	208.7	619.1
STD. DEV.	26.7	61.7	36.6	66.5
(N)	20	19	20	18
0.2 ♀	182.0	203.6	206.1	599.1
MEAN	17.3	17.6	19.4	52.2
STD. DEV.	2.0	1.9	1.9	1.8
(N)	20	19	20	18
0.4 ♀	187.2	201.2	207.6	591.4
MEAN	14.0	23.2	26.5	52.2
STD. DEV.	2.0	1.9	2.0	1.9
(N)	20	19	20	18
0.8 ♀	163.4	179.9	197.8	541.8
MEAN	14.5	16.2	16.6	45.6
STD. DEV.	1.6	1.7	1.7	1.6
(N)	16	17	17	16

END 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (CAS NO. 145535-01-0)
 NID-92-455; 145535A

TABLE 31 - MEAN POSTPARTUM FOOD CONSUMPTION - P2
 (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

POSTPARTUM DAY:	0		4		7		1		2		3	
	A-L	A+L	A-L	A+L	A-L	A+L	A-L	A+L	A-L	A+L	A-L	A+L
0 ♀	121.8	128.9	143.3	163.5	171.1	261.0	261.0	554.9	1218.9			
STD. DEV.	24.1	14.3	20.2	20.2	31.5	31.5	61.2	123.0				
(N)	19	21	21	18	22	22	22	22	15			
0.2 ♀	131.0	123.3	162.1	162.1	255.5	545.2	1217.2					
STD. DEV.	28.5	12.9	16.2	16.2	18.2	39.0	79.0					
(N)	21	21	21	21	21	21	21					
0.4 ♀	129.2	115.5	152.8	152.8	255.1	512.5	1169.8					
STD. DEV.	30.5	26.7	15.0	15.0	32.7	74.0	135.9					
(N)	19	21	19	19	20	19	18					
0.8 ♀	124.1	125.1	144.0	144.0	229.9	490.4	1110.1					
STD. DEV.	21.9	17.2	17.2	17.2	31.8	55.1	112.2					
(N)	18	18	18	18	18	18	17					

RUN 1

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] AND-92-655; 145535A

TABLE 32 - MEAN MEASURED DOSE RATE - P2 (MG/KG/DAY)

	W E E E	2	3	4	5	6	7	8	9	10	11
MALES											
0.2 g											
MEAN	263.4	217.1	195.0	171.7	154.2	143.0	136.2	126.3	122.3	119.6	116.4
STD. DEV.	21.6	19.5	13.8	10.6	6.2	6.8	6.2	5.5	6.6	6.6	5.7
(N)	27	26	26	27	26	27	27	28	28	28	28
0.4 g											
MEAN	523.3	439.6	391.4	345.3	308.1	291.7	276.0	253.4	249.7	243.3	235.2
STD. DEV.	106.4	83.9	61.0	45.2	30.6	19.7	16.9	18.2	17.5	16.7	15.3
(N)	30	30	28	29	28	30	30	30	28	29	28
0.7 g											
MEAN	1090.2	923.3	817.7	727.4	643.0	602.2	564.9	523.0	510.3	499.1	466.8
STD. DEV.	87.3	66.3	61.0	50.3	41.1	35.5	30.8	28.0	35.3	40.0	39.8
(N)	30	30	30	30	30	29	30	29	26	29	26
FEMALES											
0.2 g											
MEAN	254.1	221.0	200.8	191.6	176.6	167.3	161.7	151.0	148.0	142.6	139.9
STD. DEV.	25.1	23.0	19.2	14.8	11.3	8.5	7.3	6.5	6.1	6.1	6.2
(N)	28	28	28	28	28	27	27	26	26	26	26
0.4 g											
MEAN	521.5	480.5	488.1	383.2	350.8	340.4	326.3	299.5	296.4	282.5	271.0
STD. DEV.	32.0	30.5	27.5	25.0	23.0	19.0	18.0	22.6	22.7	19.7	23.3
(N)	28	26	28	28	29	29	28	28	28	27	28
0.5 g											
MEAN	1060.4	915.9	823.1	768.0	714.0	670.7	642.3	598.0	590.8	576.7	543.9
STD. DEV.	89.6	73.0	56.1	64.8	50.6	46.1	50.2	39.9	53.0	39.0	31.3
(N)	29	28	28	27	26	27	26	25	27	26	28

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
WITH [REDACTED] AND-92-455; 18535A

TABLE 32 -- MEAN MEASURED DOSE RATE - P2 (CONT'D)

GESTATION DAY:	0	7	14	21
0.2 \$	7	1	4	1
MEAN	149.8	152.5	132.9	
0.4 \$				
MEAN	307.1	305.3	270.6	
0.8 \$				
MEAN	571.2	576.7	564.2	

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TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS
 WITH [REDACTED] (MID-82-455); 145931A

TABLE 32 - MEAN MEASURED DOSE RATES - P2 (CONT'D)

POSTPARTUM DAY:	0	4	7	10	14
0-28 MEAN	174.3	218.1	262.0	324.6	394.7
0-42 MEAN	347.6	433.6	541.3	659.6	757.8
0-84 MEAN	718.4	945.2	1076.8	1272.1	1541.3

9

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH

NHD-92-455); 145535A

**TABLE 33 - MEAN ORGAN WEIGHT - P2
(GRAMS)
(SEE KEYS A AND B FOR ABBREVIATIONS)**

	Males		Females		Males		Females		Males		Females	
	AL+	A-L-	AL+	A-L-	AL	E-3-	E-3-	A-L-	A-L-	E-3-	E-3-	A-L-
0 % MEAN STD. DEV. (N)	716.8 76.7 30	28.05 4.05 30	5.21 0.71 30	2.28 0.13 30	1.8963 0.1774 30	1.9490 0.2525 30	0.8133 0.0978 30	0.0178 0.0021 30	0.221 0.659 30	0.0133 0.0978 30	0.0133 0.0978 30	0.0133 0.0978 30
0.2 % MEAN STD. DEV. (N)	713.2 84.6 30	0.06 5.16 30	5.53 0.58 30	2.20 0.13 30	1.8977 0.1626 30	2.0016 0.2423 30	0.0340 0.1411 30	0.0433 0.1415 30	4.118 0.604 30	0.0340 0.1411 30	0.0340 0.1411 30	0.0340 0.604 30
0.4 % MEAN STD. DEV. (N)	679.8 86.4 30	28.19 4.01 30	5.18 0.65 30	2.29 0.11 30	1.8793 0.3342 25	1.9642 0.4322 30	0.0225 0.1122 30	0.0239 0.0929 25	4.148 0.626 30	0.0225 0.1122 30	0.0225 0.1122 30	0.0225 0.626 30
0.8 % MEAN STD. DEV. (N)	667.0 66.4 30	29.77 3.27 30	5.85 0.59 30	2.28 0.10 30	2.0463 0.1806 30	2.0214 0.3326 30	0.0740 0.1393 30	0.0768 0.0893 30	4.056 0.666 30	0.0740 0.1393 30	0.0740 0.1393 30	0.0740 0.666 30
FEMALES												
0 % MEAN STD. DEV. (N)	379.8 27.0 30	18.12 2.97 30	3.27 0.41 30	2.09 0.08 30								A-L-O 0.0527 0.0137 30
0.2 % MEAN STD. DEV. (N)	378.3 34.1 30	19.77 5.09 30	3.47 0.52 30	2.03 0.14 30								A-L-O 0.0527 0.0137 30
0.4 % MEAN STD. DEV. (N)	376.4 35.1 30	20.43 4.26 30	3.46 0.51 30	2.04 0.12 30								A-L-O 0.0685 0.0182 30
0.8 % MEAN STD. DEV. (N)	352.6 32.6 30	21.44 4.92 30	3.43 0.44 30	2.02 0.12 30								A-L-O 0.0566 0.0186 30

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH MRD-92-455): 145535A

TABLE 34 - MEAN RELATIVE ORGAN WEIGHT - P2 (SEE KEYS A AND B FOR ABBREVIATIONS)

	A+L+		A-L-		A-L+		A+L+		A-L-	
	MEAN	STD. DEV.	MEAN	STD. DEV.	MEAN	STD. DEV.	MEAN	STD. DEV.	MEAN	STD. DEV.
0 %	0.039	0.0073	0.0032	0.00281	0.00274	0.00115	0.00114	0.00115	0.00114	0.00115
0.2 %	0.041	0.0078	0.0031	0.00285	0.00285	0.00120	0.00118	0.00120	0.00118	0.00120
0.4 %	0.041	0.0083	0.0033	0.00289	0.00290	0.00121	0.00122	0.00121	0.00122	0.00121
0.8 %	0.045	0.0090	0.0033	0.00309	0.00306	0.00131	0.00132	0.00131	0.00132	0.00131
FEMALE	0.048	0.0088	0.0055	0.0044	0.0044	0.0016	0.0016	0.0016	0.0016	0.0016
0.2 %	0.052	0.0092	0.0054	0.0046	0.0046	0.0016	0.0016	0.0016	0.0016	0.0016
0.4 %	0.055	0.0092	0.0055	0.0046	0.0046	0.0016	0.0016	0.0016	0.0016	0.0016
0.8 %	0.061	0.0097	0.0058	0.0049	0.0049	0.0016	0.0016	0.0016	0.0016	0.0016

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH ~~TESTES~~ AND-92-455; 145525A

TABLE 35 -- INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS -- P2

	MALES			0.88
	TERMINAL SUPRANASIA			
	06	0.26	0.46	
POSS:				
TOTAL AT SCHEDULED SACRIFICE:	30	30	30	30
NO OBSERVABLE ABNORMALITIES	17	8	7	9
CECUM, COLON AND/OR RECTUM:	10	16	14	13
Parasites, pinworms presumptive	-	1	1	1
SPIDERMIS:				
Small	-	-	1	-
Not apparent	-	-	-	-
KIDNEY(S):	2	7	8	10
Dilated pelvis	1	-	-	-
Cystic	-	-	-	-
LIVER:	1-2	1	1	-
Enlarged/thickened	-	-	-	-
No cleft median lobe	-	-	1	-
LUNGS: Fecl	-	-	-	-
TESTIS(ES):	1	-	2	1
Small	-	-	-	-
Enlarged	1	1	2	-
Flaccid	-	-	-	-
Not apparent:	-	-	1	-
Missshapen	-	-	1	-
URINARY BLADDER: Brown liquid	-	1	-	-
GENERAL CONDITION:				
Red material around eye(s)	-	1	1	3
Alpecia	-	1	1	-
Malescled/broken incisors	1	1	2	2
Scabs/sores skin/subcutis	1	1	-	-
Truncated tail	1	1	-	-

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH ~~CONTROLS~~ MSD-92-455; 145335A

TABLE 35 - SUMMARY OF REPRODUCTION DATA - F2

DOSE (%)	MALE		FEMALE		MEAN DAYS GESTAT. (%)	MEAN LITTER SIZE (M)	MEAN LIVE (M)	MEAN DEAD (M)	OFFSPRING			
	MATING (%)	FERTIL. (%)	FERTIL. (%)	RECUND. (%)					LIVE (%)	DEAD (%)	MALE (%)	FEMALE (%)
0	NS 90.0	NS 73.3	NS 90.0	NS 77.8	NS 100.0	NS 14.1	NS 13.9	NS 0.2	NS 98.7	NS 1.3	NS 52.3	NS 47.7
0.2	93.3	70.0	93.3	75.0	100.0	15.5	15.0	0.5	96.9	3.1	50.5	49.5
0.4	93.3	70.0	93.3	80.0	100.0	14.8	14.7	0.1	99.6	0.6	50.0	50.0
0.8	80.0	63.3	80.0	70.0	100.0	15.4	15.3	0.1	99.7	0.3	49.6	50.2

NOTE: * P<0.05 BY FISCHER EXACT TEST
 ** P<0.01 BY FISCHER EXACT TEST
 + DOSE-RESPONSE TREND, P<0.05 BY ARMITAGE TEST
 ++ DOSE-RESPONSE TREND, P<0.01 BY ARMITAGE TEST
 NS NO STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN CONTROLS AND TREATED GROUPS AT P<0.05 OR P<0.01 BY FISCHER EXACT TEST
 NT NOT TESTED FOR STATISTICAL DIFFERENCES

Male Mating Index (MATING) = Number of males for which mating confirmed ----- X 100
 Number of males used for mating ----- 100

Male Fertility Index (FERTIL) = Number of males impregnating females ----- X 100
 Number of males used for mating ----- 100

Female Fertility Index (FERTIL) = Number of females for which mating confirmed ----- X 100
 Number of females paired ----- 100

Female Fecundity Index (FECUND) = Number of females pregnant (a) ----- X 100
 Number of females for which mating confirmed ----- 100

Gestational Index (GESTAT) = Number of females with live litters ----- X 400
 Number of females pregnant ----- 400

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

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH MRD-92-455; 145535A

TABLE 37 - SUMMARY OF OFFSPRING SURVIVAL - F2

Dose (%)	Live Birth		Day 1		Day 4		Day 7		Day 14		Day 21		Viability at Weaning		
	Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Survival Index	MSS	Index
0.0	98.7		96.7		94.8		98.8		100.0		100.0		100.0		98.8
0.2	96.9		98.7		98.1		99.4		100.0		99.4		99.4		98.8
0.4	99.4		95.5		94.2		94.0		100.0		99.4		99.4		93.4
0.8	99.7		97.3		96.6		98.7		100.0		100.0		100.0		98.7

NOTE: * p<0.05 by Fischer Exact Test
 ** p<0.01 by Fischer Exact Test
 + Dose-response trend, p<0.05 by Armitage Test
 ++ Dose-response trend, p<0.01 by Armitage Test
 MSS NO STATISTICALLY SIGNIFICANT DIFFERENCES BETWEEN CONTROLS AND TREATED GROUPS AT P<0.05 OR P<0.01 BY FISHER EXACT TEST
 NT NOT TESTED FOR STATISTICAL DIFFERENCES

Live Birth (%) = Index	Number of live pups at birth	Day 16 S.I. (%) =	Number of live pups at Day 16
Day 1 S. I. (%) =	Number of pups born	Day 21 S.I. (%) =	Number of live pups at Day 7
Day 4 S. I. (%) =	Number of live pups at Day 1	Viability (%) = Index at Weaning	Number of live pups at Day 21
Day 7 S. I. (%) =	Number of live pups at Day 0		Number of live pups at Day 14
	Number of live pups at Day 4 (pre-cull)		Number of live pups at Day 21
	Number of live pups at Day 0		Number of live pups at Day 4 (post-cull)
	Number of live pups at Day 7		
	Number of live pups at Day 4 (post-cull)		

NOTE: S. I. - SURVIVAL INDICES
 ALL INDICES MULTIPLIED BY 100

TWO OPERATION REPRODUCTION FERTILITY STUDY IN RATS
 WITH [REDACTED], MD-92-459; 14533A

TABLE 36 - INCIDENCE OF OFFSPRING IN LIFE OBSERVATIONS - F2
 (F1E-MATING OBSERVATIONS)

TIME -	(a)												
	P	P	P	P	P	P	P	P	P	P	P	P	P
0.2	294	295	296	297	298	299	300	301	302	303	304	305	306
0.4	307	308	309	310	311	312	313	314	315	316	317	318	319
0.6	320	321	322	323	324	325	326	327	328	329	330	331	332
TOTAL SURVIVORS													
0.2	171	171	171	171	171	171	171	171	171	171	171	171	171
0.4	171	171	171	171	171	171	171	171	171	171	171	171	171
0.6	171	171	171	171	171	171	171	171	171	171	171	171	171
NO OBSERVABLE ABNORMALITIES													
0.2	171	171	171	171	171	171	171	171	171	171	171	171	171
0.4	171	171	171	171	171	171	171	171	171	171	171	171	171
0.6	171	171	171	171	171	171	171	171	171	171	171	171	171
TOTAL FOUND DEAD (P.B.)													
0.2	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
0.6	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL FOUND DEAD (P.B.)													
0.2	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
0.6	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL MISSING/PRESUMED CAMELISED													
0.2	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
0.6	0	0	0	0	0	0	0	0	0	0	0	0	0

NOTE: PBD - POSTNATAL DAY
 (a) - LITTERS CULLED AFTER PBD 4 OBSERVATIONS

TWO GENERATION REPRODUCTION TOXICITY STUDY IN RATS WITH [REDACTED] AND-92-455); 145535A

TABLE 39 - MEAN OFFSPRING BODY WEIGHT - F2 (GRAMS) (SEE KEY A FOR STATISTICAL ABBREVIATIONS)

		POSTNATAL DAY: 0 1 4 7 14 21					
MALE							
0%	MEAN	6.67	7.30	10.63	16.06	37.09	62.34
	STD. DEV.	0.78	1.01	1.90	3.16	4.88	7.88
	(N)	160	153	150	87	87	87
0.2%	MEAN	6.49	7.12	10.05	16.43	34.80	57.89
	STD. DEV.	0.59	0.82	1.36	2.34	3.47	6.56
	(N)	159	160	158	79(A)	82	79(A)
0.4%	MEAN	6.55	7.08	9.73	15.48	32.51	54.82
	STD. DEV.	0.51	0.84	1.70	2.80	4.33	7.45
	(N)	154	146	140	83	83	82
0.8%	MEAN	6.18	6.64	9.05	14.70	28.88	49.12
	STD. DEV.	0.67	0.88	1.62	3.00	4.00	7.38
	(N)	145	141	139	72	72	72
FEMALE							
0%	MEAN	6.44	7.10	10.48	17.47	35.99	59.37
	STD. DEV.	0.74	0.99	1.80	2.88	4.12	7.70
	(N)	146	143	140	84	84	84
0.2%	MEAN	6.13	6.75	9.60	15.72	33.64	55.50
	STD. DEV.	0.65	0.88	1.43	2.22	3.66	6.28
	(N)	156	151	151	80(A)	85	79(A)
0.4%	MEAN	6.11	6.59	9.05	14.56	31.23	51.98
	STD. DEV.	0.61	0.87	1.71	3.03	4.01	7.48
	(N)	154	148	146	73	73	73
0.8%	MEAN	5.92	6.41	8.68	13.76	28.20	46.20
	STD. DEV.	0.72	0.92	1.70	2.49	3.53	6.50
	(N)	146	142	141	78	78	78

NOTE: (A) - 4 MALE/4 FEMALE OFFSPRING EXCLUDED FROM CALCULATION DUE TO RECORDING ERROR: PUP WEIGHTS/SIX RECORDED DID NOT CORRESPOND WITH NUMBER, SEX OF SURVIVORS

C 04

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