

A 01

CODING FORMS FOR SRC INDEXING

Microfiche No.	OTS0559306-1		
New Doc ID	89990000098	Old Doc ID	8EHQ-0299-14185
Date Produced	12/15/98	Date Received	02/02/99
		TSCA Section	8E
Submitting Organization	EXXON CHEMICAL CO		
Contractor	EXXON CHEMICAL EUROPE INC		
Document Title	SUPPORT: FINAL REPORT, ONE GENERATION REPRODUCTION TOXICITY RANGEFINDING STUDY IN RATS WITH MRD-97-014, WITH COVER LETTER DATED 1/27/1999		
Chemical Category	HEXANOIC ACID, 3,5,5-TRIMETHYL-		

OFFICE OF TOXIC SUBSTANCES
CODING FORM FOR GLOBAL INDEXING

REV. 7/27/82

Microfiche No. (7) •		OTS 0559306		1		No. of Pages		2								
Doc I.D.			89990000098		3		Old Doc I.D.			8EQ-0299-14185 ⁴						
Case No.(s)										5						
Date Produced (6)			6		Date Rec'd (6)			7		Conf. Code •		8				
										N						
Check One: <input type="checkbox"/> Publication <input type="checkbox"/> Internally Generated <input type="checkbox"/> Externally Generated																
Pub/Journal Name										9						
										9						
Author(s)										10						
Organ. Name										11						
Dept/Div										12						
P.O. Box			13		Street No./Name							14				
City			15		State		16		Zip		17		Country		18	
MID No. (7)			19		D & B NO. (11)							20				
Contractor										21						
Doc Type										22						
										8.E						
Doc Title										23						
Chemical Name (300 per name)										25		CAS No. (10)		24		

A 04

EXXON CHEMICAL COMPANY

16491

RECEIVED
OPPT CBIC



99 FEB -2 AM 7:23

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

8EHQ - 0299 - 14185

January 27, 1999

pdcn 8898000152

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460-0001



8EHQ-98-14185

Re: Notification of Substantial Risk Under TSCA Section 8(e)

Dear Sir or Madam:

On May 22, 1998, Exxon Chemical Company submitted a notification of substantial risk under the provisions of TSCA Section 8(e). The initial submission (TSCA Section 8(e) Control Number 8EHQ-98-14185) described the preliminary results of a one-generation reproductive study in rats on a substance identified as Hexanoic acid, 3,5,5-trimethyl- (CAS Registry Number 3302-10-1). At the time of the submission, the study had been completed but the draft data had not passed through a quality assurance review and a final report was not available. The purpose of this submission is to complete the record on this study by providing a copy of the final report.

The results of this study were reported in summary form in the submission referenced above. Thus, a results summary has not been provided with this submission. In the report the test material is identified with the code name MRD-97-014, which corresponds to the substance identified by the chemical name and CASRN above.

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

Sincerely yours,

Steven G. Hentges



89990000098

SGH/jad
Enclosure

y:\data\sg\sg\1999\1004.doc

CONTAINS NO CBI

99 FEB 11 PM 12:56
RECEIVED
OPPT CBIC

P.O. Box 3272, Houston, Texas 77253-3272
Tel: (281) 870-6212 Fax: (281) 588-4795

A Division of Exxon Corporation



RECEIVED
OPPT CBIC

99 FEB -2 AM 7:23

EXXON BIOMEDICAL SCIENCES, INC.

FINAL REPORT

PROJECT NUMBER: 101433B

TEST MATERIAL: MRD-97-014

ONE GENERATION REPRODUCTION TOXICITY
RANGEFINDING STUDY IN RATS

PERFORMED FOR:

EXXON CHEMICAL EUROPE INC.
Boulevard Du Souverain 280, B-1160
Auderghem, Belgium

PERFORMED AT:

EXXON BIOMEDICAL SCIENCES, INC.
Laboratory Operations
Mettlers Road, CN 2350
East Millstone, New Jersey 08875-2350

COMPLETION DATE: December 15, 1998

CONTAINS NO CBI

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
 IN RATS WITH MRD-97-014: 101433B

TABLE OF CONTENTS

	PAGE
APPROVAL SIGNATURES	4
QUALITY ASSURANCE STATEMENT	5
PERSONNEL	6
SUMMARY	7-9
INTRODUCTION	10
MATERIALS AND METHODS	
TEST MATERIAL	11-12
TEST SYSTEM	13-15
EXPERIMENTAL DESIGN	16-22
RESULTS	23-29
DISCUSSION	30-31
PROTOCOL EXCEPTIONS	32
REFERENCES	33
TABLES	
TABLE 1 - SUMMARY OF SURVIVAL - P1	39
TABLE 2 - INCIDENCE OF INLIFE OBSERVATIONS - P1	40-45
TABLE 3 - INCIDENCE OF GESTATION OBSERVATIONS - P1	46
TABLE 4 - INCIDENCE OF POSTPARTUM OBSERVATIONS - P1	47
TABLE 5 - MEAN BODY WEIGHT - P1	49-52
TABLE 6 - MEAN BODY WEIGHT CHANGE - P1	53-55
TABLE 7 - MEAN GESTATION BODY WEIGHT AND BODY WEIGHT CHANGE - P1	56
TABLE 8 - MEAN POSTPARTUM BODY WEIGHT AND BODY WEIGHT CHANGE - P1	57
TABLE 9 - MEAN FOOD CONSUMPTION - P1	58-61
TABLE 10 - MEAN GESTATION FOOD CONSUMPTION - P1	62
TABLE 11 - MEAN POSTPARTUM FOOD CONSUMPTION - P1	63
TABLE 12 - MEAN MEASURED DOSE RATE - P1	64-66
TABLE 13 - MEAN GESTATION MEASURED DOSE RATE - P1	67
TABLE 14 - MEAN POSTPARTUM MEASURED DOSE RATE - P1	68
TABLE 15 - INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS - P1	69-70
TABLE 16 - MEAN ORGAN WEIGHT P1	72-73
TABLE 17 - MEAN RELATIVE ORGAN WEIGHT P1	74-75
TABLE 18 - SUMMARY OF REPRODUCTION DATA - P1	76
TABLE 19 - MEAN SPERM DATA P1	79-81
TABLE 20 - SUMMARY OF OFFSPRING SURVIVAL - F1	82
TABLE 21 - INCIDENCE OF OFFSPRING INLIFE OBSERVATIONS - F1	83-86
TABLE 22 - MEAN OFFSPRING BODY WEIGHT - F1	87-90
TABLE 23 - MEAN DEVELOPMENTAL LANDMARKS	91-92
TABLE 24 - INCIDENCE OF OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F1	93

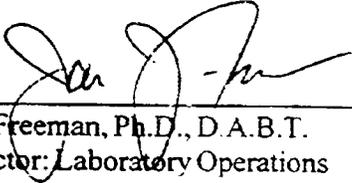
ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

TABLE OF CONTENTS (CONT'D)

KEYS	
KEY A - STATISTICAL SYMBOLS AND ABBREVIATIONS	48
KEY B - ORGAN ABBREVIATIONS	71
KEY C - SPERM ASSESSMENT METHODOLOGY	77-78
 APPENDICES	
APPENDIX A - INDIVIDUAL SURVIVAL DATA - P1	94-96
APPENDIX B - INDIVIDUAL INLIFE OBSERVATIONS - P1	97-111
APPENDIX C - INDIVIDUAL GESTATION OBSERVATIONS - P1	112-116
APPENDIX D - INDIVIDUAL POSTPARTUM OBSERVATIONS - P1	117-121
APPENDIX E - INDIVIDUAL BODY WEIGHT - P1	122-131
APPENDIX F - INDIVIDUAL BODY WEIGHT CHANGE - P1	132-141
APPENDIX G - INDIVIDUAL GESTATION BODY WEIGHT - P1	142-146
APPENDIX H - INDIVIDUAL POSTPARTUM BODY WEIGHT - P1	147-151
APPENDIX I - INDIVIDUAL FOOD CONSUMPTION - P1	152-161
APPENDIX J - INDIVIDUAL GESTATION FOOD CONSUMPTION - P1	162-166
APPENDIX K - INDIVIDUAL POSTPARTUM FOOD CONSUMPTION - P1	167-171
APPENDIX L - INDIVIDUAL MEASURED DOSE RATE - P1	172-179
APPENDIX M - INDIVIDUAL GROSS POSTMORTEM OBSERVATIONS - P1	180-184
APPENDIX N - INDIVIDUAL ORGAN WEIGHT P1	185-189
APPENDIX O - INDIVIDUAL RELATIVE ORGAN WEIGHT P1	190-194
APPENDIX P - INDIVIDUAL REPRODUCTION DATA - P1	195-196
APPENDIX Q - INDIVIDUAL SPERM DATA	197-211
APPENDIX R - INDIVIDUAL OFFSPRING SURVIVAL DATA - F1	212-213
APPENDIX S - INDIVIDUAL OFFSPRING INLIFE OBSERVATIONS - F1	214-278
APPENDIX T - INDIVIDUAL OFFSPRING BODY WEIGHT - F1	279-323
APPENDIX U - INDIVIDUAL DEVELOPMENTAL LANDMARKS	324-354
APPENDIX V - INDIVIDUAL OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F1	355-358
APPENDIX W - ANALYTICAL CHEMISTRY REPORT	359-366
APPENDIX X - STATISTICIAN'S REPORT	367-370
APPENDIX Y - HISTORICAL CONTROL DATA	371-385

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

APPROVAL SIGNATURES



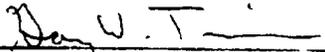
J. J. Freeman, Ph.D., D.A.B.T.
Director: Laboratory Operations

14 Dec 98
Date



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

15 Dec 98
Date



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

15/DEC/98
Date

**ONE GENERATION REPRODUCTION TOXICITY RANGEFINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

**EXXON BIOMEDICAL SCIENCES, INC.
METTLERS ROAD
CN 2350
EAST MILLSTONE, NEW JERSEY 08875-2350**

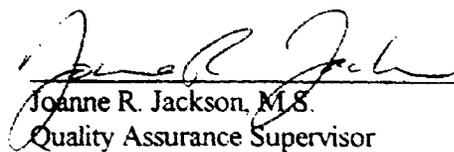
**QUALITY ASSURANCE STATEMENT
NON-REGULATORY STUDY**

STUDY NUMBER: 101433B

TEST SUBSTANCE/ARTICLE: MRD-97-014

STUDY SPONSOR: Exxon Chemical Europe, Inc.

All QA audits (including this final report) have been processed


Joanne R. Jackson, M.S. 14/Dec 98
Quality Assurance Supervisor Date

**ONE GENERATION REPRODUCTION TOXICITY RANGEFINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

PERSONNEL

Study Director:	G. W. Trimmer, B.A.
Sponsor:	Exxon Chemical Europe Inc. Boulevard Du Souverain 280, B1160 Auderghem, Belgium
Sponsor Representative:	J. L. Ambroso, Ph.D.
Director: Laboratory Operations:	J. J. Freeman, Ph.D., D.A.B.T.
Toxicology and Animal Care Supervisor:	R. C. Forgash, B.S.
Report Preparation Supervisor:	E. R. Frank, B.A.
Compound Preparation Supervisor:	M. A. Elliott, B.S.
Analytical Chemistry Supervisor:	D. J. Letinski, M.S.
Quality Assurance/Archives Supervisor:	J. R. Jackson, B.S.
Maintenance Supervisor:	J. L. McGrath, A.S.
Veterinarian:	R. L. Harris, D.V.M.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

SUMMARY

This study was designed to provide general information on the effect of dietary administration of MRD-97-014 on reproduction, and offspring development in the rat.

Undiluted test material 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 10 rats/sex/group at 4 dosage levels. Group 1 served as a control and received carrier (Purina Certified Rodent Chow) only. Groups 2, 3, 4, and 5 received 0.06%, 0.12%, 0.25% and 0.5% of MRD-97-014 in feed, respectively. 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) 28.

Clinical in-life observations, body weight, and food consumption were recorded for all P1 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 Postpartum Days (PPD) 0, 4, 7, 14, 21 and 28. Following birth, the offspring were counted and examined externally daily from Postnatal Day (PND) 0 to 28. Offspring were sexed and weighed on PND 0, 1, 4, 7, 14, 21 and 28. The offspring also were weighed and observed on PND 35, 42, and 49 (males only). The P1 males were euthanized after the end of mating (Test Day 119 or 120), while females were euthanized following weaning of their litters on PPD 28. A gross necropsy was performed on all adult animals and on all animals that died during the study. A full macroscopic examination was performed on these animals.

There were no treatment-related deaths or clinical signs noted in the parental animals during this study. There also were no treatment-related clinical signs noted for the offspring.

There were no treatment-related effects noted for the male reproductive parameters of sperm motility, total cauda sperm count, homogenization resistant spermatid count, sperm morphology, or the reproduction indices of mean male fertility, male mating, female fertility, fecundity, or gestational indices. There also were no treatment-related effects on the absolute or relative organ weights of the reproductive organs.

Decreases in food consumption were noted for the 0.5% males on Days 1 and 2 and for the 0.5% females on Day 1, and Weeks 1, 2, 4, and 6. These decreases were attributed to reduced palatability of the diet. There also were statistically significant decreases in food consumption in the 0.5% group females during the PPD 0/4 (46%), 7/14 (15%), and entire postpartum period (PPD 0-28) (17%).

Decreases in body weights were noted in the 0.5% females at Gestation Days (GD) 7 and 21 and at Postpartum Days (PPD) 4, 7, and 14.

ONE GENERATION REPRODUCTION TOXICITY RANGING STUDY
IN RATS WITH MRD-97-014: 101433B

SUMMARY (CONT'D)

Mean absolute and mean relative liver weights were increased in both sexes of the 0.5% group.

In offspring, reduced Live Birth Index (92.8%) and Day 1 (85.4%) and Day 4 (78.6%) survival indices were noted in the 0.5% group. Offspring body weights of both sexes of the 0.5% group were reduced compared with the controls during the entire postnatal period. Similar body weight observations were noted in the 0.25% male offspring at all postnatal intervals except PND 21 and in the 0.25% female offspring at PND 0, 1, 4, 7, 35, and 42.

The onset of eye opening appeared to be delayed in the male offspring, and pinna detachment appeared to be delayed in both sexes. However, while treatment related, these delays were considered secondary to reduced offspring body weight.

In conclusion, under the conditions of this study MRD-97-014 did not produce an adverse effect on fertility, fecundity, or reproductive organs. Evidence of maternal toxicity included decreased body weights during the gestation and postpartum periods and increases in the mean absolute and mean relative liver weights in the 0.25% and 0.5% groups. There were also indications of offspring toxicity in the 0.25% and 0.5% dose groups that may be related to maternal toxicity. The apparent NOAEL for both maternal and offspring effects in this study is the 0.12% level.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101-433B**

INTRODUCTION

This study was designed to provide general information concerning the potential effects of the test material on gonadal function, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring. The results of this study were used to select dose levels for a subsequent definitive reproduction study with the test material in the rat.

This study was conducted for Exxon Chemical Europe Inc., Boulevard Du Souverain 280, B-1160, Auderghem, Belgium (subsequently referred to as the Sponsor). The study was conducted by Exxon Biomedical Sciences, Inc. (EBSI) Laboratory Operations, Mettlers Road, CN 2350, East Millstone, New Jersey 08875-2350. The EBSI Toxicology Laboratory is an American Association for Accreditation of Laboratory Animal Care (AAALAC) accredited facility and a Japanese Ministry of Agriculture, Forestry, and Fisheries (JMAFF) certified facility.

Study Initiation (Protocol Signature Date)

September 24, 1997

In-life Test Period

September 25, 1997 to March 2, 1998

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), as adapted in 88/302/EEC part B "One-Generation Reproduction Toxicity Test" (EC, 1988).

Justification of Dosing Route

The dietary route is an accepted route of administration according to E.C. Dangerous Substances Directive (67/548/EEC), as adapted in 88/302/EEC part B "One-Generation Reproduction Toxicity Test" (EC, 1988) and represents a likely route of human exposure.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

INTRODUCTION (CONT'D)

Compliance

This study was conducted in compliance with the following:

EC, European Community, Council Decision on Principles of Good Laboratory Practice, (89/569/EEC), 1989.

OECD, Organization for Economic Cooperation and Development. Principles of Good Laboratory Practice, 1981.

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

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

Guide for the Care and Use of Laboratory Animals, 1985. Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, D.C., 1996.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

MATERIALS AND METHODS

TEST MATERIAL

Material Identification

EBSI Identification:	MRD-97-014
Supplier:	Exxon Chemical France
Date Received:	May 28, 1997; January 6, 1998; February 6, 1998
Expiration Date:	June 2002; May 1998
Description:	Colorless liquid
Storage Condition:	Room temperature (neat material and mixtures)

Adjustments in the dose calculations were not made to correct for the purity of the test material. The test material, as received, was considered the "pure" material for the purpose of dosing.

Characterization of the Test Material

Characterization and stability evaluations of the neat test material were performed by the testing laboratory. Documentation is maintained in the testing laboratory's archives.

Analysis of Materials

The stability and homogeneity of the test material in feed was determined by the testing laboratory prior to and/or concurrent with dose initiation. Homogeneity was evaluated at three concentrations. The sample representing the lowest level (0.06%) was analyzed during this study. Two samples (0.3% and 1.2% - representing the highest level dosed) were analyzed during a previous study (101433A). Triplicate samples were collected from the top, middle and bottom of each preparation (nine samples in total). The concentration was the mean of all nine samples.

Stability was assessed by measuring the concentrations of selected samples at room temperature.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

TEST MATERIAL (CONT'D)

Analysis of Mixtures (Cont'd)

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 from each container of the undiluted test material was collected by the Compound Preparation Department and stored at room temperature.

Carrier

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

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B****TEST SYSTEM*****Test Animal***

Species: Rat
Strain/Stock: Cri:CD®BR - VAF/Plus®
Supplier: Charles River Laboratories, Inc.
Males: Raleigh, North Carolina
Females: Kingston facility, Stone Ridge, New York.
Area: Males - R05; Females - K71

Animal Receipt Information:

Receipt Date: September 11, 1997
Purchase Order Number: 97GWT1132

Quarantine and Acclimation Period

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

Number and Sex

P1 Males: 50 virgin
P1 Females: 50 virgin

Age at Initiation of Test Material Administration

P1 Males: Approximately 7 weeks
Approximate Date of Birth: August 6, 1997
P1 Females: Approximately 7 weeks
Approximate Date of Birth: August 5, 1997

Body Weight at Initiation of Test Material Administration

P1 Males: 221 to 266 grams
P1 Females: 168 to 201 grams

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

TEST SYSTEM (CONT'D)

Animal Identification

P1 Generation: Ear tags and corresponding cage identification.

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 technical staff) 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. Weight variation for individual animals was within $\pm 20\%$ of the mean body weight of their sex.

Husbandry

Feed

PMI Certified Rodent Diet Meal 5002: ad libitum

Manufacturer: PMI Feeds Inc.
Richmond, Indiana

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

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

The availability of feed was checked daily for all animals.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

TEST SYSTEM (CONT'D)

Water

Automatic watering system: ad libitum
Supplier: Elizabethtown Water Company
Bound Brook, New Jersey.
Analysis: Periodic analysis is the responsibility of EBSI. A copy of the results is maintained at EBSI.
Contaminants: There were no known contaminants in the water believed to have been present at levels that may have interfered with this study.

The availability of water was checked daily for all animals.

Housing

Room Number: 507
Housing: Single housed during the test period, except during the mating and postpartum periods.
Caging: Suspended stainless steel and wire mesh with absorbent paper below cages. Stainless steel litterpans were provided with bedding for dams on Gestation Day 20 (± 1 day) and during the postpartum period.

Bedding (Direct)

Alpha-Dri
Manufacturer: Shepherd Specialty Papers, Inc.
Analysis: Provided by the Manufacturer. Copies of the analyses are maintained in the EBSI Toxicology Laboratory.
Contaminants: There were no known contaminants in the bedding believed to have been present at levels that may have interfered with this study.

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

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

TEST SYSTEM (CONT'D)

Environmental Conditions

Temperature: 68 to 76 degrees Fahrenheit
Humidity: 40 to 70 percent relative humidity
Lighting: Approximately 12 hours light (0700 to 1900 hours) and 12 hours dark (1900 to 0700 hours) by automatic timer.

Monitored continuously.

ONE GENERATION REPRODUCTION TOXICITY RANGEFINDING STUDY
IN RATS WITH MRD-97-014: 101433B

EXPERIMENTAL DESIGN (CONT'D)

Administration of Test Material

A homogeneous blend of test material, prepared as a mixture in PMI Certified Rodent Diet Meal #5002, was offered ad libitum to the treated rats of Groups 2, 3, 4 and 5. Control rats (Group 1) received PMI Certified Rodent Diet Meal #5002, 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.

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, and until their sacrifice. P1 females were dosed for at least 10 weeks prior to mating, during the mating, gestation and lactation periods, and until they were sacrificed following weaning of the F1 animals on PPD 28.

F1 pups were dosed from PND 28 through their day of sacrifice.

Experimental Evaluation

Inlife Procedures:

All animals were examined for viability at least twice daily Monday through Friday, and at least once daily on weekends and holidays.

Body weights were recorded for all males pretest, on the day of initiation of dosing (Day 0), on Days 4 and 7, and weekly until they were sacrificed. Body weights also were taken on the day of sacrifice for all males.

Body weights were recorded for all females pretest, at initiation of dosing (Day 0), on Days 4 and 7, and weekly until confirmation of mating or the end of the mating period. Body weights were recorded for confirmed-mated females on GDs 0, 7, 14, and 21, on PPDs 0, 4, 7, 14, and 21 and weekly after Postpartum Day 21. After the mating period, body weights were recorded weekly for females not confirmed mated until they were sacrificed. Confirmed-mated females which did not deliver by GD 26 were weighed weekly after GD 26 until sacrificed. Body weights also were recorded on the day of sacrifice for all females.

Food consumption was measured on Days 1, 2, 3, and 7, and then concurrently with body weight after Day 7, except during the mating period and on GD 0 and PPD 0 for the females when food consumption was not measured.

**ONE GENERATION REPRODUCTION TOXICITY RANGEFINDING STUDY
IN RATS WITH MRD-97-014: 101433B****EXPERIMENTAL DESIGN*****Preparation of Animals***

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

Preparation of Test Diets

Mixing of feed: The basal diet consisted of PMI Certified Rodent Diet Meal (#5002). 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 for the first 5 weeks and twice weekly thereafter. Prepared diets were covered and stored at room temperature following dispensing.

Diets were prepared at the target concentrations listed below. Fresh diets were prepared at a frequency determined by stability data on the test material-dietary admixtures.

Experimental Groups

Group Number	Target Concentration (%)	Number of P1 Females	Number of P1 Males
1 (Control)	0	10	10
2 (Low)	0.06	10	10
3 (Low Mid)	0.12	10	10
4 (High Mid)	0.25	10	10
5 (High)	0.5	10	10

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

EXPERIMENTAL DESIGN (CONT'D)

Administration of Test Material

A homogeneous blend of test material, prepared as a mixture in PMI Certified Rodent Diet Meal #5002, was offered ad libitum to the treated rats of Groups 2, 3, 4 and 5. Control rats (Group 1) received PMI Certified Rodent Diet Meal #5002, 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.

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, and until their sacrifice. P1 females were dosed for at least 10 weeks prior to mating, during the mating, gestation and lactation periods, and until they were sacrificed following weaning of the F1 animals on PPD 28.

F1 pups were dosed from PND 28 through their day of sacrifice.

Experimental Evaluation

Inlife Procedures:

All animals were examined for viability at least twice daily Monday through Friday, and at least once daily on weekends and holidays.

Body weights were recorded for all males pretest, on the day of initiation of dosing (Day 0), on Days 4 and 7, and weekly until they were sacrificed. Body weights also were taken on the day of sacrifice for all males.

Body weights were recorded for all females pretest, at initiation of dosing (Day 0), on Days 4 and 7, and weekly until confirmation of mating or the end of the mating period. Body weights were recorded for confirmed-mated females on GDs 0, 7, 14, and 21, on PPDs 0, 4, 7, 14, and 21 and weekly after Postpartum Day 21. After the mating period, body weights were recorded weekly for females not confirmed mated until they were sacrificed. Confirmed-mated females which did not deliver by GD 26 were weighed weekly after GD 26 until sacrificed. Body weights also were recorded on the day of sacrifice for all females.

Food consumption was measured on Days 1, 2, 3, and 7, and then concurrently with body weight after Day 7, except during the mating period and on GD 0 and PPD 0 for the females when food consumption was not measured.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

EXPERIMENTAL DESIGN (CONT'D)

Experimental Evaluation (cont'd)

A clinical examination was given to each male prior to P1 selection, on the first day of dosing, and at least weekly thereafter until euthanized. Females received a clinical examination prior to P1 selection, on the first day of dosing, and at least weekly thereafter until confirmation of mating, then on GD 0, 7, 14, and 21, and on PPD 0, 4, 7, 14 and 21.

Cageside observations were performed daily on all P1 adults and after weaning for all F1 offspring, except the days clinical observations were performed.

Mating:

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

Mating was confirmed the morning following overnight pairing by observation of a copulatory plug (vaginal) and/or by the presence of sperm in a vaginal rinse. The day on which mating was confirmed was 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 on the first Gestation Day 20. Non-confirmed mated females were examined at least twice daily for signs of parturition for 26 days after insertion of litter pans in their cages.

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).

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

EXPERIMENTAL DESIGN (CONT'D)

Postnatal Experimental Evaluation (cont'd)

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

Dead pups were removed from the litter immediately after their discovery. 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, 21, and 28 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. All animals were weighed on PND 35, 42, and 49 (males only were weighed on PND Day 49).

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 sacrificed. 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.

The pups from each litter were examined daily for pinna detachment (starting PND 1), hair growth (starting PND 3), righting reflex (starting PND 3), incisor eruption (starting PND 7), and eye opening (starting PND 11). The examinations continued for an individual landmark until the criterion for that landmark was attained. Additionally, beginning on PND 29, all surviving female offspring were examined daily for vaginal opening. Beginning on PND 35 all surviving male offspring were examined daily for preputial separation. The examinations continued until all animals reached criteria.

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

EXPERIMENTAL DESIGN (CONT'D)

Study Termination

All females (adults and offspring) and all male offspring were sacrificed by carbon dioxide asphyxiation and exsanguination. All P1 males were sacrificed by exsanguination following anesthesia with methoxyflurane.

All females were sacrificed after weaning their litters. P1 females that were not confirmed mated and did not give birth by presumed GD 26 or those that were not confirmed mated and did not give birth by 26 days after insertion of litter pans in their cages were sacrificed and received gross necropsies with special attention paid to the reproductive systems. Any female whose entire litter succumbed was sacrificed after the last offspring succumbed.

Vaginal smears were performed on each female on their day of sacrifice to determine its stage in the estrous cycle. The stage of the estrous cycle was recorded, but not used for estrous cycle calculations.

If a dam died prior to PPD 21, all offspring from that dam were sexed and examined externally, sacrificed, and discarded. These animals were not evaluated due to the fact that there is no control data to be compared to.

Surviving F1 females were sacrificed on PND 42 and surviving F1 males were sacrificed on PND 49 unless they had not met criteria for vaginal patency or preputial separation, respectively.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B****EXPERIMENTAL DESIGN (CONT'D)****Necropsy:**

Gross necropsies were performed on all adult animals that were found dead. Body weight was recorded on the day of necropsy. The uterus of each female used for mating, but failing to deliver, was examined grossly for evidence of implantations and these data were recorded.

A gross necropsy was performed on all adult animals surviving to termination. Body weights were recorded on the day of necropsy. The uterus of each female was examined grossly for evidence of implantation and the number of implantation sites was recorded.

Samples of sperm from the left distal cauda epididymis (or proximal vas deferens) were collected at necropsy and evaluated for the percentage of progressively motile sperm and sperm morphology. Also, the entire left cauda epididymis was minced in saline to enumerate the total number of sperm (cauda reserves).

The following organs and tissues of all adults were preserved in 10% neutral buffered formalin:

coagulating gland	right epididymis
seminal vesicles	prostate
testes ^a	uterus
liver	ovaries

^a The right testis was preserved in Bouin's solution. The right testis remained in Bouin's solution for approximately 24 hours. The right testis was then rinsed with tap water and stored in 70 percent Ethyl Alcohol. The left testis was frozen for enumeration of homogenization resistant spermatids.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

EXPERIMENTAL DESIGN (CONT'D)

Necropsy (cont'd):

The following tissues and organs of all males surviving to termination and all females were weighed prior to fixation:

ovaries (individual)	uterus
testes (individual)	prostate
liver	
right epididymis (total and cauda)	
seminal vesicles (with coagulating glands and their fluids)	

Intact dead pups or pups sacrificed in moribund condition on PND 0 were examined by fresh visceral dissection. Dead pups and pups sacrificed as moribund after PND 0 were examined externally for anomalies and internally for gross visceral abnormalities. Culled pups (PND 4) with external abnormalities were subjected to a visceral examination at the discretion of the Study Director or his designee.

Abnormal tissues were preserved in 10% neutral buffered formalin at the discretion of the Study Director or designee for possible future microscopic examination.

Records

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

Statistical Analyses

Group means and standard deviations were calculated, where appropriate (Snedecor and Cochran, 1989).

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS

P1 GENERATION - PARENTAL FINDINGS

1. PARENTAL SURVIVAL - P1

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

One 0.25% male was found dead on Test Day 91. Gross postmortem examination revealed no observable abnormalities. All other animals survived to study termination.

2. PARENTAL CLINICAL IN-LIFE OBSERVATIONS - P1

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

There were no treatment-related clinical signs. The majority of animals in all groups had no adverse clinical signs during the pre-mating/mating, post-mating, 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 pre-mating/mating, post-mating, gestation, and/or postpartum periods. These findings included dental abnormalities, alopecia, oral discharge and/or ocular discharge. One 0.5% male was observed to be emaciated with little sign of food consumption on Day 21, but was free of these signs for the remainder of the study. These findings were considered incidental and unrelated to treatment with the test material.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

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 significant differences in mean body weight or mean body weight change between the treated and control animals of either sex during the pre-mating, mating, and post-mating (males) periods.

Among males there were statistically significant increases in mean body weight gain in the 0.5% dose group at the Day 56/63 interval (41% higher than the controls) and in the 0.12% dose group at the Day 92/99 interval (192% higher than the controls). In the absence of a clear consistent response over the test period, these limited differences were considered incidental and unrelated to treatment with the test material.

Statistically significantly decreased mean body weights when compared with controls were observed in the 0.5% females on Gestation Day (GD) 7 (9%) and on GD 21 (11%) and on Postpartum Days (PPD) 4, 7, and 14 (17%, 12%, and 10%, respectively). Also, there was a corresponding statistically significant decrease in mean body weight change for the 0.5% group females at the PPD 0-4 interval (209%). There also was a statistically significantly decreased mean body weight compared with controls in the 0.25% females on PPD 4 (10%).

There also were statistically significant increases in mean body weight change in the 0.25 and 0.5% group females at the PPD 4/7 (470% and 567%, respectively), PPD 14/21 (154% and 235%, respectively), and in the 0.25% females on PPD 0/21 intervals (112%).

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

RESULTS (CONT'D)

4. PARENTAL FOOD CONSUMPTION - P1

Mean Food Consumption: Tables 9-11

Individual Food Consumption: Appendices I-K

There were statistically significant decreases in mean food consumption for the 0.5% group males at Days 1 (21%) and 2 (21%). There were statistically significant decreases in mean food consumption in the 0.25% group females at Day 1 (30%), Day 3 (18%), and Weeks 1 (13%), 2 (11%), 3 (21%), 4 (13%), and 6 (12%). There also were statistically significant decreases in mean food consumption for the 0.5% group females at Day 1 (47%) and Weeks 1 (15%), 2 (13%), 4 (11%), and 6 (10%). These decreases were considered to be due to reduced palatability of the diet mixtures.

There were no statistically significant differences in food consumption during the gestation period. However, statistically significant decreases in food consumption were noted in the 0.5% group females during the PPD 0/4 (46%), 7/14 (15%), and entire postpartum period (PPD 0-28) (17%).

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS (CONT'D)

5. PARENTAL MEASURED DOSE RATE - P1

Mean Measured Dose Rate: Tables 12-14
Individual Measured Dose Rate: Appendix L

In general, the mean measured dose rate for the male and female animals during the premating 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 in mg/kg/day was as follows:

	DOSE (%)	WEEK 1 (mg/kg/day)	WEEKS 2-9 (mg/kg/day)	WEEK 10 (mg/kg/day)	Gestation	Postpartum
M A L E S	0.06	59	33-51	32	Not Applicable	Not Applicable
	0.12	117	66-101	66		
	0.25	247	147-215	145		
	0.5	477	289-435	290		
F E M A L E S	0.06	57	40-56	40	37-42	57-126
	0.12	116	79-112	81	79-86	109-228
	0.25	231	168-224	167	165-185	241-500
	0.5	450	347-453	347	336-382	311-970

During gestation, mean measured dose rate was similar to Week 10 of the premating period, and slightly decreased at the end of gestation since maternal body weights significantly increase (although food consumption remains relatively constant) during the latter part of gestation.

During the postpartum period, mean measured dose rate exceeded the Week 10 premating values. This resulted from the steady increase in food consumption during the postpartum period, while body weights remained relatively constant. Food consumption measurements during the final week of the postpartum period are confounded since the pups begin eating from the dams' feeder during this time.

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS (CONT'D)

6. PARENTAL GROSS POSTMORTEM OBSERVATIONS - P1

Incidence of Gross Postmortem Observations: Table 15
Individual Gross Postmortem Observations: Appendix M

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

The majority of animals in all groups were free of observable abnormalities at postmortem examination. There were single or low occurrences of dental abnormalities, alopecia, discolored kidneys, dilated renal pelvis, misshapen kidneys, abnormal contents kidney or urinary bladder, flaccid kidney or testis, small seminal vesicles, liver adhered to kidney, and/or cystic ovary. These findings were considered incidental and unrelated to treatment.

7. ORGAN WEIGHT - P1

Mean Organ Weights and Relative Organ Weights: Tables 16-17
Individual Organ Weights and Relative Organ Weights: Appendices N-O

There were no statistically significant changes in the mean absolute or mean relative organ weights for the reproductive organs weighed during the study. There were statistically significant increases in the mean absolute and mean relative liver weights of the 0.5% males (15% and 21%, respectively) and 0.5% females (21% and 24%, respectively) and the 0.25% females mean absolute and relative liver weights (15% and 14%, respectively). The significance of the increases in the liver weights could not be determined because histopathology was not performed on the tissues.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

RESULTS (CONT'D)

8. REPRODUCTION INDICES - P1

Summary of Reproduction Data: Table 18
Individual Reproduction Data: Appendix P

There were no statistically significant differences between treated and control groups in mean male fertility and mating indices and female fertility, fecundity, or gestational indices.

There were no substantial differences between treated and control groups in mean days of gestation.

There was a statistically significant decrease in the mean percent live offspring (6%) and the corresponding increase in the mean percent dead offspring (700%) in the 0.5% dose group.

One control female, two 0.06% dose females, one 0.12% dose female, and one 0.25% dose female were not pregnant.

9. PARENTAL MALE REPRODUCTIVE ASSESSMENT - P1

Summary of Sperm Data: Table 19
Individual Sperm Data: Appendix Q

There were no statistically significant differences in homogenization resistant spermatid counts, total cauda sperm counts, progressive sperm motility or sperm morphology between the treated and control males.

F1 GENERATION - OFFSPRING FINDINGS

10. OFFSPRING SURVIVAL - F1

Summary of Offspring Survival: Table 20
Individual Offspring Survival Data: Appendix R

There were statistically significant decreases in 0.5% group offspring compared with the control offspring for the live birth index (6.0%), the Day 1 survival index (14%), and the Day 4 survival index (21%).

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS (CONT'D)

11. OFFSPRING CLINICAL IN-LIFE OBSERVATIONS - F1

Incidence of Offspring In-life Observations: Table 21

Individual Offspring In-life Observations: Appendix S

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 most groups were observed without milk in their stomachs during the first week of the postnatal period.

Single or low incidences of sores/scabs; truncated or necrotic tail; and purple discoloration were observed in one or more groups during the postpartum period. During the postweaning period, one 0.25% group male was observed with a large firm testis.

12. OFFSPRING BODY WEIGHT - F1

Mean Offspring Body Weight: Table 22

Individual Offspring Body Weight: Appendix T

Historical Control Data: Appendix Y

There were statistically significant differences in mean offspring body weight compared with the control group in the 0.5% group males and females at all preweaning and postweaning intervals.

There were statistically significant decreases in mean offspring body weights in the 0.25% group males and females at PND 0, 1, 4, 7, 35 and 42. There also were statistically significant decreases in mean offspring body weights in the 0.25% group males at PND 14, 28, and 49. The following tables show the actual mean weights:

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS (CONT'D)

MEAN OFFSPRING BODY WEIGHT - F1 (PREWEANING)

Group	MALE PND 0	MALE PND 1	MALE PND 4	MALE PND 7	MALE PND 14	MALE PND 21	MALE PND 28
0%	6.71	7.09	9.54	15.58	32.32	51.18	91.53
0.06%	6.82	7.31	10.13	16.70	34.12	53.06	93.88
0.12%	6.39	6.85	9.01	14.44	30.72	48.88	90.23
0.25%	5.76**h	5.95**h	7.98*h	12.55**h	28.64*h	46.23	81.65**
0.5%	5.66**h	5.73**h	7.67**h	11.07**h	23.31**h	39.18**h	72.63**
Historical Control	6.35-7.02	6.68-7.49	8.53-11.43	13.64-18.74	28.81-37.09	44.89-62.34	98.34
Group	FEMALE PND 0	FEMALE PND 1	FEMALE PND 4	FEMALE PND 7	FEMALE PND 14	FEMALE PND 21	FEMALE PND 28
0%	6.36	6.89	9.33	14.72	30.50	47.77	82.46
0.06%	6.51	7.00	9.67	15.35	31.89	49.18	83.84
0.12%	5.92h	6.40	8.78	13.81	28.79	46.18	81.83
0.25%	5.46**h	5.65**h	7.83**h	12.77*h	28.89	45.33	77.09
0.5%	5.65**h	5.65**h	7.55**h	11.10**h	23.47**h	38.59**h	69.34**
Historical Control	5.96-6.74	6.30-7.16	8.32-11.05	13.33-17.69	27.22-35.89	42.39-61.19	90.68

NOTE: All weights are in grams

* Mean significantly different from control mean (p 0.05)

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

h Outside historical control range for this laboratory

ONE GENERATION REPRODUCTION TOXICITY RANGEFINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS (CONT'D)

MEAN OFFSPRING BODY WEIGHT - F1 (POSTWEANING)

Group	MALE PND 35	MALE PND 42	MALE PND 49
0%	147.7	205.8	266.3
0.06%	151.0	211.4	272.4
0.12%	144.3	205.1	266.3
0.25%	128.4**	183.4**	242.1**
0.5%	119.8**	170.9**	227.6**
Group	FEMALE PND 35	FEMALE PND 42	FEMALE PND 49
0%	124.8	158.3	NA
0.06%	126.5	161.4	NA
0.12%	123.1	157.2	NA
0.25%	114.9**	148.6*	NA
0.5%	109.3**	140.9**	NA

NOTE: All weights are in grams

* Mean significantly different from control mean (p 0.05)

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

NA Not applicable

ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B

RESULTS (CONT'D)

13. OFFSPRING DEVELOPMENTAL LANDMARKS - F1

Mean Time to Offspring Developmental Landmarks: Table 23
Individual Offspring Developmental Landmarks: Appendix U

There were no statistically significant differences for hair growth. There was a statistically significant advance in incisor eruption in the 0.06% group females (1.5 days). Based on the lack of a dose response, and the fact that this was an advance rather than a retardation in this landmark, this difference was considered incidental and not related to treatment.

Also, there was a statistically significant advance in righting reflex in the 0.06% males (2.8 days) compared with the control. This difference was not considered biologically significant due to the lack of a dose response and also because this was an advance, rather than a retardation in the landmark. The following table is a tabulation of the PND 4, pre-cull, righting reflex data. Righting reflex was also advanced at this time point.

Males	# pups at criteria on PND 4	# pups evaluated on PND 4	% of pups at criteria on PND 4
0%	20	58	34.5
0.06%	33	45	73.3
0.12%	33	55	60.0
0.25%	37	60	61.7
0.5%	14	39	35.9
Females			
0%	7	54	13.0
0.06%	22	47	46.8
0.12%	19	58	32.8
0.25%	17	49	34.7
0.5%	19	42	45.2

There were statistically significant retardations in the male eye opening for the 0.5% group (0.7 days later), and the male and female pinna detachment in the 0.5% group (1.0 day later each). These findings are not biologically significant but rather reflect the normal maturation of these animals with the delays due to somewhat smaller body weights. This conclusion is consistent with data from studies where the control offspring weights were reduced (*i.e.* reproduction studies by the inhalation route).

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B****RESULTS (CONT'D)****13. OFFSPRING DEVELOPMENTAL LANDMARKS - F1 (cont'd)**

There was a statistically significant advance for preputial separation for the 0.06% group males (1.2 days) when compared with the controls. Due to the small size of this advance and the absence of a dose response, this difference was not considered biologically significant. There also was a statistically significant retardation of preputial separation for the 0.5% group males (2.1 days) compared with the control male offspring. In the females, the 0.5% group exhibited a statistically significant retardation (1.8 days) for vaginal patency compared with controls. These two findings are not biologically significant but rather reflect the normal maturation of these animals with the delays due to somewhat smaller body weights. This conclusion is consistent with data from studies where the control offspring weights were reduced (*i.e.* reproduction studies by the inhalation route).

14. OFFSPRING GROSS POSTMORTEM OBSERVATIONS - F1

Incidence of Offspring Gross Postmortem Observations: Table 24
Individual Offspring Gross Postmortem Observations: Appendix V

The majority of animals which died prior to scheduled termination (GD 21 - PND 28) were free of observable abnormalities or were too autolyzed/cannibalized to be examined at the necropsy. There were single or low incidences of no milk in the stomach, dilated renal pelvis, and discolored liver. Due to the very low incidence of findings, all were considered incidental and not treatment-related.

15. ANALYTICAL CHEMISTRY

Analytical Chemistry Report: Appendix W

Satisfactory homogeneity was observed at all 3 levels (0.06%, 0.3%, and 1.2%). The relative standard deviation (RSD) ranged from 0.991% to 4.29%. Stability data indicated the test material was stable in meal at ambient temperature for at least 4 days at 0.06% and at least 15 days at 0.3% and 1.2%. Concentration verification analysis indicated that all meal samples were within 10% of the nominal concentrations.

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

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B****DISCUSSION**

Administration of MRD-97-014 via diet at graded doses to one generation of CrI:CD®BR rats was associated with signs of overt toxicity at dose levels of 0.25% and 0.5%. The toxicity was most readily apparent in the offspring.

Overt signs of toxicity in the parental animals included decreased body weight, body weight gain suppression, and decreased food consumption in the female animals during the gestation and postpartum periods. The decreased body weight was noted at PPD 4 for the 0.25% group females and at GD 7 and 21 and PPDs 4, 7, and 14 for the 0.5% group females. However, it appears from the body weight change data that these groups begin to recover after PPD 4 with the body weight change being statistically significantly increased compared with controls at the PPD 4/7 and PPD 14/21 intervals in both groups. The PPD 0/21 body weight change also was increased compared with controls in both groups with the increase being statistically significant in the 0.25% group.

The decreased maternal body weights in the 0.5% group coincided with statistically significant decreased offspring survivorship in that group. Offspring survivorship was reduced as reflected by the live birth index and the PND 1 and PND 4 survivorship indices in the 0.5% group. Offspring survivorship was 100% in the 0.5% group after PND 4 which again coincided with the recovery in maternal body weights.

The decreased maternal body weights of the 0.25% and 0.5% groups also coincided with statistically significant decreased offspring body weights in the 0.25 and 0.5% groups. The offspring body weights were statistically significantly reduced at all intervals in both sexes of the 0.5% group and at all intervals except PND 21 in the males of the 0.25% group, and all intervals except PNDs 14, 21, and 28 in the 0.25% group females. However, beginning with the PND 14 body weights the offspring of both sexes of the 0.5% group show signs of recovery. The difference between the control and the 0.5% body weights is reduced by approximately 50% by study termination (PND 42 for the females and PND 49 for the males) compared with the difference observed at PND 7. The offspring body weights of both sexes of the 0.25% group also show similar signs of recovery beginning on PND 14 but the recovery occurs faster and then levels out.

It is possible that the offspring survivorship and body weight effects were the result of maternal toxicity during the late gestation and early postpartum periods. Maternal toxicity during late gestation could cause the decrease in the size of the offspring at birth and subsequent weighing intervals with the survivorship effects related to the decreased offspring body weights. The maternal toxicity was observed in the adults as reduced body weights.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

DISCUSSION (CONT'D)

In conclusion, under the conditions of this study administration of MRD-97-014 in the diet for 10 weeks prior to mating and during gestation and lactation, resulted in evidence of maternal toxicity and findings in offspring that may have been secondary to maternal toxicity. During the first few weeks of the pre-mating period there was a palatability problem with the diet that was apparent in the female animals in the 0.25% and 0.5% dose groups and males in the 0.5% group. Maternal toxicity was demonstrated by decreased body weight and food consumption during the gestation and postpartum periods, and increased absolute and relative liver weights in the 0.25% and 0.5% groups. Paternal effects were limited to increased absolute and relative liver weights in the 0.5% group. The differences between male and female adults in this study may be due to the somewhat higher dose rates observed in the females, especially during the postpartum period. Coincident with the maternal effects, offspring body weights were decreased in both sexes in the 0.25% and 0.5% groups, and offspring survival was decreased in the 0.5% dose group. There were also some small delays in developmental landmarks in the high dose offspring. These delays are likely secondary to the decreased offspring growth in this group.

There was no evidence of adverse effects on mating behavior, fertility, sperm parameters, or reproductive organ weights in the parental animals. Thus, the test material does not effect fertility at the dose levels tested. There were also no malformations observed in the offspring in this study. There were indications of offspring toxicity that may be related to maternal toxicity in the two highest doses. The apparent NOAEL for both maternal and offspring effects in this study is the 0.12% level.

**ONE GENERATION REPRODUCTION TOXICITY RANGE-FINDING STUDY
IN RATS WITH MRD-97-014: 101433B**

REFERENCES

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

EPA, U.S. Environmental Protection Agency, 40 CFR Part 792, Toxic Substance Control Act (TSCA), Good Laboratory Practice Standards (GLPs), Final Rule, 1989.

EPA, U.S. Environmental Protection Agency, 40 CFR Part 798, Toxic Substance Control Act (TSCA), Test Guidelines for Reproduction and Fertility Effects.

European Community (E.C.), Dangerous Substances Directive (67/548/EEC) Annex V, Part B, Methods for the Determination of Toxicity "Two-Generation Reproduction Toxicity Test".

European Community (E.C.), Council Decision on Good Laboratory Principles, (89/569/EEC); 1989.

Guide for the Care and Use of Laboratory Animals, 1985. Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, D.C., 1996.

OECD, Organization for Economic Cooperation and Development, Principles of Good Laboratory Practice, 1981.

Snedecor, G.W., and Cochran, W.G., Statistical Methods, 8th ed., Iowa State University Press, 1989.