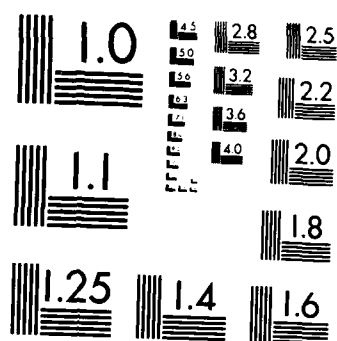


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C	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
D	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
E	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10
F	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
G	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10
H	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10
I	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10
J	J1	J2	J3	J4	J5	J6	J7	J8	J9	J10



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Institute Report No. 248

**Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl
Phosphinate (MPP) in Rats**

AD-A189 622

*Valerie G. Coppes, BS
Martha A. Hanes, DVM, CPT VC
and
Don W. Korte, Jr., PhD, MAJ MSC*

MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

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Toxicology Series: 63

OCTOBER 1987

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**Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP) in Rats
(Toxicology Series 63)--Coppes, Hanes, and Korte**

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 22 Oct 87

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The teratogenic potential of 4-nitrophenyl methyl phenyl phosphinate (MPP) was tested in pregnant Sprague-Dawley rats. MPP was administered by oral gavage on Days 6 through 15 of gestation. Dose levels tested were 0, 0.12, 1.25, and 3.12 mg/kg/day. The vehicle contained 21.5% Tween 80, 18.5% absolute ethanol, 37.5% 50 mM citrate buffer, and 22.5% distilled water. Fetuses were delivered by cesarean section on Day 20 and weighed, examined externally, and either processed in Bouin's solution for visceral examination or alizarin red stain for skeletal examination. MPP did not produce dose-related teratogenic or embryotoxic effects in Sprague-Dawley rats. (Keywords)					
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ABSTRACT

The teratogenic potential of 4-nitrophenyl methyl phenyl phosphinate (MPP) was tested in pregnant Sprague-Dawley rats. MPP was administered by oral gavage on Days 6 through 15 of gestation. Dose levels tested were 0, 0.12, 1.25, and 3.12 mg/kg/day. The vehicle contained 21.5% Tween 80, 18.5% absolute ethanol, 37.5% 50 mM citrate buffer, and 22.5% distilled water. Fetuses were delivered by cesarean section on Day 20 and weighed, examined externally, and either processed in Bouin's solution for visceral examination or alizarin red stain for skeletal examination. MPP did not produce dose-related teratogenic or embryotoxic effects in Sprague-Dawley rats.

KEY WORDS: Developmental Toxicology, Teratology, 4-Nitrophenyl Methyl Phenyl Phosphinate, Rat

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PREFACE

TYPE OF REPORT: Teratology GLP Study Report

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Letterman Army Institute of Research
Division of Toxicology
Presidio of San Francisco, CA 94129-6800

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Fort Detrick, MD 21701-5012

PROJECT: 35162772A875 Defense Against Chemical Agents
WU 304 Toxicity Testing of Phosphinate Compounds
APC TLO4

GLP STUDY NUMBER: 82021

STUDY DIRECTOR: Don W. Korte, Jr., PhD, MAJ MSC

PRINCIPAL INVESTIGATOR: Martha A. Hanes, DVM, CPT, VC

CO-INVESTIGATOR: Valerie G. Coppes, BS

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol, addenda, raw data, SOPs, and an aliquot of the test compound will be retained in the LAIR Archives. Alizarin specimens will be retained in LAIR Pathology Archives.

TEST SUBSTANCE: 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP)

INCLUSIVE STUDY DATES: 31 Aug 82- 15 March 83

OBJECTIVES: The purpose of this study was to determine the teratogenic and embryotoxic potential of MPP in pregnant Sprague-Dawley rats when administered orally during the period of organogenesis.

ACKNOWLEDGMENTS

SP5 Justo Rodriguez, BS; SP5 Thomas P. Kellner, BA; SP5 Lawrence Mullen, BS; SP5 Paul D. Mauk, BS; SP4 Evelyn Zimmerman, Carolyn M. Lewis, MS, and Yvonne C. Johnson, BS, assisted in the research; COL John Marshall, PhD, and COL John Fruin, DVM, PhD, gave professional guidance; and Claire Lieske, US Army Medical Research Institute of Chemical Defense, provided the test compound, advice, and support.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 82021 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte 23 Oct 87
DON W. KORTE, JR., PhD / DATE
MAJ, MSC
Study Director

Martha A. Hanes 23 Oct 87
MARTHA A. HANES, DVM / DATE
CPT, VC
Principal Investigator

Valerie G. Coppes 23 Oct 87
VALERIE G. COPPES, BS / DATE
DAC
Co-Principal Investigator



DEPARTMENT OF THE ARMY

LETTERMAN ARMY INSTITUTE OF RESEARCH
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7 Oct 87

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance

1. I hereby certify that in relation to LAIR GLP Study 82021, the following inspections were made.

Insemination Determination	(Phase II)	10 Feb 83
Dosing and Weighing	(Phase I)	19, 29 Oct 82
	(Phase II)	23, 24 Feb 83
Unscheduled Sacrifice	(Phase I)	26 Oct 83
Scheduled Sacrifice	(Phase I)	2 Nov 82
	(Phase II)	3 Mar 83
Fetal Visceral Observations	(Phase II)	21 Apr 83
Fetal Skeletal Observations	(Phase II)	5 Aug 84

2. The report entitled "Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP) in Rats," Toxicology Series 63, and the raw data were audited on 11 Jun 87, 24 Sep 87, and 5 Oct 87.

Carolyn M. Lewis
CAROLYN M. LEWIS
C, Quality Assurance

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Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate in Rats -- Coppes et al

Organophosphinate compounds are being evaluated as prophylactic agents in organophosphate poisoning because of several disadvantages associated with conventional carbamate prophylaxis. The spontaneous rate of reactivation of carbamylated cholinesterase is relatively rapid with a $t_{1/2}$ for hydrolysis of 15 to 30 minutes (1). Consequently, there is no significant oxime effect on spontaneous reactivation of the carbamylated enzyme (2). Phosphinylated cholinesterases are reactivated more slowly with a $t_{1/2}$ for hydrolysis of 105.0 to 278.1 minutes (3). Therefore, oxime therapy significantly accelerates the rate of spontaneous reactivation of the phosphinylated enzyme (2). One of the phosphinates, 4-nitrophenyl methyl phenyl phosphinate (MPP), was selected for toxicologic evaluation based on the results of efficacy studies. LAIR was tasked to conduct the acute, subchronic, and teratogenic testing of MPP. This report presents results of a study to assess the teratogenic potential of MPP.

Objective of the Study

The purpose of this study was to determine the teratogenic and embryotoxic potential of MPP in pregnant Sprague-Dawley rats when administered orally during the period of organogenesis.

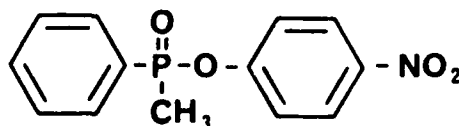
MATERIALS

Test Substance

Chemical Name: 4-Nitrophenyl Methyl Phenyl Phosphinate

Chemical Abstract Service Registry No.: None

Molecular Structure $C_{13}H_{12}NO_4P$



Molecular Weight: 277.2

Coppes -- 2

Source: Ash Stevens Inc.
Detroit, Michigan 48202

Lot No.: XL 1X-40

Contaminants: None detected

Physical State/Color: Fluffy white crystals

Stability: Unstable at neutral and basic pH. Stable in acidified solution.

Other test substance information is presented in Appendix A.

Rationale for Selection of the Vehicle

MPP is hydrolyzed in alkaline solutions. A vehicle was selected which would solubilize and stabilize the MPP. The vehicle selected was the same one used in the subchronic study (4). It contained 21.5% polysorbate 80 (Tween 80), 18.5% absolute ethanol, 37.5% 50 mM citrate buffer (pH 3.2), and 22.5% distilled water.

Additional information about the vehicle appears in Appendix A.

Animal Data

Young adult Sprague-Dawley rats were obtained from Bantin-Kingman, Fremont, CA. The study was conducted in two phases due to the number of animals required. Eighty-five female and 41 male Sprague-Dawley rats were assigned to Phase I and 103 females and 52 males to Phase II. Two females from Phase I and 6 females from Phase II were selected at random for quality control necropsy. Animals were identified by sequentially numbered metal eartags. The weight ranges of rats were as follows:

Phase	Receipt		Start of Breeding	
	Females (gm)	Males (gm)	Females (gm)	Males (gm)
I	250-296	249-286	261-331	406-504
II	193-308	223-299	240-327	391-589

A concurrently performed positive control study established the Sprague-Dawley rat as a sensitive test system for teratology studies at

LAIR (5). Historic data on sporadic malformations in rats have been well documented (6).

Husbandry

Upon arrival at LAIR, rats were housed individually in wire mesh rack cages with automatic water dispensers for the quarantine period. Animals were fed Purina Certified Rodent Chow 5002 (Ralston Purina Company, St Louis, MO) and tap water ad libitum throughout the study. No contaminants or naturally occurring substances were expected to influence the study. During breeding 1 male and 2 females were placed in polycarbonate cages with hardwood chip bedding, wire lids, and water bottles. After breeding the males were returned to the wire mesh rack cages; the females remained in the polycarbonate cages (2 females of the same dose group and breeding date per cage).

In Phase I, room temperature ranged between 64 and 74°F (17.8 and 23.3°C) and relative humidity between 58 and 77%. In Phase II, temperature ranged between 68 and 74°F (20.0 and 23.3°C) and relative humidity ranged between 47 and 70%. Several times during Phase II the relative humidity spiked to 90% for a short period of time. The fluctuation of relative humidity is not expected to have an impact on the outcome of the study. The photoperiod was 13 hours of light per day (0630-1930 hours).

METHODS

Methods used are described in detail in LAIR Teratology Testing Procedure OP-STX-40 (7) and were in accordance with Food and Drug Administration Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use (8).

Acclimation

Females were acclimatized before start of breeding for 8 and 18 days for Phases I and II, respectively. Males were acclimatized for at least 6 weeks.

Group Assignment

Females were assigned to groups according to LAIR OP-ISC-21 "Animal Randomization Procedure" (9) on the Data General ECLIPSE C/330 computer. Twenty random sequences of numbers corresponding to the number of dose groups were generated. When females became sperm positive, they were assigned to the dose group. Animals were selected for quality control necropsy according to a random number table.

Dose Levels

Dose levels tested were 0, 3.12, 1.25, and 0.12 mg/kg/day. Sperm-positive females were dosed daily between 0800-1200 hours from Day 6 through Day 15 of gestation by oral intubation using an 18-gauge, 3-inch gastric gavage needle (Popper and Sons, Inc, New Hyde Park, NY 11040). Dosing was conducted without sedation or anesthetization of the animals. The test compound was administered orally as this is the expected human exposure route. The dose for each female was based on the Day 6 (Day 0 was the day sperm were detected in vagina) body weight, and that dose was used throughout the dosing period. Doses were calculated by a program on a Hewlett-Packard 98A calculator. The vehicle control was given at a constant volume of 1 ml per animal. Phase I females were dosed from 19 Oct 82 through 30 Oct 82. Phase II females were dosed from 14 Feb 83 through 27 Feb 83.

Compound Preparation and Analysis

A quantity of vehicle sufficient for the entire dosing period of each phase was prepared. Stock solutions of 10 mg/ml test compound were prepared on 18, 22, and 28 Oct 82 for Phase I and on 13 and 18 Feb 83 for Phase II. These solutions were diluted with vehicle to obtain concentrations of 1.0 mg/ml for the high dose group, 0.4 mg/ml for the mid dose group, and 0.04 mg/ml for the low dose group. Aliquots of the dosing solutions and vehicle were pipetted into separate vials for each day of dosing and refrigerated to prevent contamination and decomposition. Before dosing the animals, the vials for that day were placed in a beaker of hot tap water for 15 to 30 minutes to bring the solutions to room temperature. The MPP solutions were assayed for hydrolyzed phosphinate by measuring its decomposition product, p-nitrophenol, with a Gilford Model 2400-S spectrophotometer (Appendix A).

Breeding

After the quarantine period, each male was placed in the breeding cage with 2 females. Females were checked each morning for evidence of insemination. Day 0 for each female was the day sperm were observed in her vaginal smear. Sperm-positive females were assigned to dose groups as previously described. Sperm-positive females were separated from the males and placed with another female of similar breeding date and same dose group.

The breeding period was 3 days for Phase I and 5 days for Phase II. Matings were terminated when adequate numbers of females were sperm positive. Those females which were not sperm positive at the completion of the breeding period were removed from the study.

Cesarean Section Procedure

Dams were weighed and euthanized with CO₂ gas on Day 20 of gestation. Non-pregnant females were examined and removed from the study. Gravid uteri were examined for number and placement of implantation sites, resorptions, and live and dead fetuses. Corpora lutea were not counted. The uterus and ovaries were removed, the dam examined for gross visceral signs of toxicity and reweighed. Fetuses were assigned alternately to either skeletal or visceral examination. Each fetus was sexed, weighed, and examined externally.

Fetuses assigned for skeletal examination were placed in 70% ethanol for several hours and eviscerated. They were then processed by the alizarin red S staining technique of Cray (10). After processing, the specimens were stored in glycerol with a few crystals of thymol to inhibit bacterial and mold growth. Fetuses assigned for visceral examination were placed in Bouin's solution. The body walls were pierced to allow penetration of the fixing solution.

Observations and Records

Pregnant females were weighed on Day 0 and every other day through Day 20. Males were weighed weekly. Females were observed daily from Day 0 through Day 20 for clinical signs of toxicity, abortion, or premature delivery. Clinical signs were not recorded for Phase I animals except at cesarean section. Date, time, and amount of dosing solution administered were recorded during the daily dosing on Days 6 through 15. At sacrifice, uterine data, body weight, and results from gross examination of the dam were recorded. The gravid maternal weight was termed the "Gravid Day 20" weight. The maternal weight after removal of the uterus and fetuses was termed the "Corrected Day 20" weight.

Fetal weight, sex, and external examination findings from live fetuses were recorded. Bouin's fetuses were examined under low magnification by the modified Wilson freehand razor blade sectioning technique (11). The alizarin skeletons were examined under low magnification on a light box for degree of ossification, malformations, and alignment. The numbers of ossified sternebrae, ribs, caudal vertebrae, metacarpals, and metatarsals were counted.

Schedule of Study Events

The study was divided into 2 phases to allow adequate time for animal care, fetal processing, and fetal examination. Upon arrival several animals from each phase were sent for quality control necropsy. The historical listing of study events is given in Appendix B.

Statistical Analysis

The data were analyzed with BMDP software on a Data General ECLIPSE C/330 computer (12). Methods used are described by Hollander and Wolfe (13). Data from both phases were combined for analysis. The litter or litter mean was used as the experimental unit. All tests were run at the .05 level of significance. In this report the term "significant" indicates a statistically significant difference.

The maternal body weights, weight changes (Corrected Day 20 - Day 0), and fetal weights were compared by one-way analysis of variance. The variability of groups was compared using Levene's test for equal variances. If a significant result was obtained with Levene's test, the Welch's test was performed. The fetal examination findings were compared by the Chi-Square analysis. When differences were obtained with the Chi-Square analysis, the Fisher's Exact test was used to compare each MPP dose group with the vehicle control. The number of implantations, percent resorptions, percent live fetuses, and ossification data were compared by the Kruskal-Wallis test.

Deviations from Original Protocol

Phase II deviated from the randomization as previously described, i.e. after sufficient animals had been assigned to 2 dose groups, these 2 numbers in the random sequence were skipped. Assignment of animals to the remaining 3 groups was continued in order to obtain a total of 20 pregnant females per dose group (total Phase I and Phase II). After combining Phase I and II the number of pregnant females per group ranged from 17 to 22.

The original protocol specified dosing from Day 6 through Day 17. However, in this study, animals were dosed from Day 6 through Day 15, the period of major organogenesis in the rat. The dose was calculated on the Day 6 body weight rather than Day 0 as stated in the protocol. Females were weighed every other day instead of every day. Pregnant females were housed 2 per cage rather than gang caged.

These deviations from the protocol did not affect the outcome of the study.

Animals Excluded from Study

Due to inadvertent destruction of Bouin's processed fetuses, 2 females, 82D00759 and 82D00688, were eliminated from Phase I. Data from the skeletal-processed fetuses from these females were not included in this report. However, these data will be archived with other raw data from GLP Study #82021.

Nine animals were misdosed and subsequently they were removed from the study. Misdosing was confirmed by necropsy findings. These animals are listed in Appendix D.

Raw Data and Final Report Storage

A copy of the final report, study protocol, addenda, raw data, SOPs, and an aliquot of test compound will be retained in the LAIR Archives. Alizarin specimens will be retained in LAIR Pathology Archives.

RESULTS

Quality Control Necropsy

Tissues from Phase I quality control rats were normal by microscopic examination. Microscopic examination of Phase II tissues revealed sinusitis in all 6 females. Since all other tissues were normal and weight gain of the females was normal, the remaining females from that shipment were used for Phase II. The sinusitis appeared to have no effect on the results of the study.

Maternal Data

The individual maternal weights are listed in Appendix C, and the group mean maternal weights are presented in Table 1. There were no significant differences in the weights or weight gains (Corrected Day 20 - Day 0) between the groups.

There were no maternal deaths in any of the dose groups. Individual maternal clinical signs are listed in Appendix D. Clinical signs for each dose group during the pretreatment (Day 0 through Day 5), treatment (Day 6 through Day 15) and posttreatment (Day 16 through Day 20) periods are found in Tables 2a, b, and c, respectively. The 3 MPP dose groups exhibited a dose-related increased incidence of clinical signs in comparison to the vehicle control group. Generally, these signs were seen in only a few animals per group, occurred randomly throughout the dosing period, and lasted 1 or 2 days. Clinical signs most frequently observed in the MPP dose groups included inactivity, yellow stained mouth, and ataxia.

The number of animals assigned to each group, number of animals that died during the study, and number and percent of animals that were pregnant are presented in Table 3. Pregnancy rate ranged from 68% in the vehicle control group to 96% in the MPP high dose group.

Cesarean/Fetal Data

The individual number of implantations, resorptions, percent resorptions, and number and percent of fetuses dead and live are listed in Appendix E. The number, sex, and mean fetal weight per litter are found in Appendix F. There were no differences in numbers of fetuses or fetal weights between groups. These data are summarized in Table 4.

Each fetus was examined for variations, retarded development, and anomalies both externally during the cesarean section delivery and again after visceral or skeletal processing. Descriptions of the examination findings were recorded. These descriptions with their corresponding incidences are listed in Appendices G, H, and I for the external, visceral, and skeletal examinations. Summaries for incidence of each anomaly and variant appear in Tables 5, 6, and 7. Fetuses with multiple anomalies and variants are listed in more than one descriptive category but are counted only once in the totals. Appendix J lists the number of fetuses per litter with anomalies and variants in the external, visceral, and skeletal examination findings. Appendix K shows the number of fetuses per litter with any anomalies and variants. Table 8 shows the group summary of the number of fetuses and the number of litters containing fetuses with anomalies and variants for the external, visceral, and skeletal examinations and a summary of number of fetuses and litters containing fetuses with any anomalies and variants. The MPP high and mid dose groups had significantly fewer fetuses with visceral variants, and the MPP high dose group had fewer fetuses with any variant than the vehicle control group. There were no significant differences in the number of fetuses with anomalies in the high, mid, and low MPP dose groups in comparison to the vehicle control group.

The litter mean numbers of sternbrae, caudal vertebrae, metacarpals, and metatarsals ossified are presented in Appendix L and the summaries by group are presented in Table 9. There were no group differences in the ossification data.

Table 1
Mean* Maternal Body Weights and Weight Changes†

Day	Dosage of MPP (mg/kg/day)			
	0	3.12	1.25	0.12
0	277.8 ± 22.1	276.6 ± 13.6	273.9 ± 14.1	284.0 ± 20.7
6	309.8 ± 21.6	308.4 ± 12.1	302.1 ± 14.8	314.2 ± 21.7
12	320.5 ± 23.5	320.1 ± 19.3	318.9 ± 19.0	327.1 ± 31.7
16	345.1 ± 25.0	351.5 ± 24.2	335.5 ± 23.3	355.1 ± 39.5
Gravid 20	400.8 ± 36.8	406.0 ± 29.9	388.3 ± 44.3	405.2 ± 44.9
Corrected 20	318.4 ± 33.8	314.2 ± 25.8	310.7 ± 23.8	315.5 ± 31.5
Weight change†	40.5 ± 19.6	37.6 ± 25.7	36.8 ± 20.5	31.6 ± 21.6

*Mean ± S.D. in g of pregnant animals.

†Group mean of [Corrected Day 20 weight - Day 0 weight].

Table 2a

Maternal Clinical Signs - Pretreatment (Days 0-5)

Signs	Dosage of MPP (mg/kg/day)			
	0	3.12	1.25	0.12
Slight weight loss	1	2		2
Blood, vaginal area		2	1	1

Table 2b

Maternal Clinical Signs - Treatment (Days 6-15)

Signs	Dosage of MPP (mg/kg/day)			
	0	3.12	1.25	0.12
Signs of abortion			1	
Blood				
mouth/nose	1	1	1	
vaginal area			1	
Cyanosis			1	
Foaming at mouth				
during misdosing	1			
Salivation		1		
Gasping		1		
Convulsion		1		
Hunched Posture			1	
Vomiting		1		
Ataxia				3
Inactive		5	3	2
Yellow stained mouth		3		
Yellow stained perianus		1		
Red stained nose/mouth	1	1		1
Sound production	2	3	2	1
Mass (axillary)			1	
Weight loss				1

Table 2c

Maternal Clinical Signs
 Posttreatment and at Sacrifice (Days 16-20)

Signs	Dosage of MPP (mg/kg/day)			
	0	3.12	1.25	0.12
Weight loss			1	
Sound production			1	
Mass (axillary):				
granulomatous tissue			1	
yellow fluid-filled			1	
Bladder stones			1	
Uterus:				
enlarged, fluid filled	1			
Blood on nose		1		
Cyanosis			1	
Inactive			1	

Table 3

Summary of Maternal Data

	Dosage of MPP (mg/kg/day)			
	0	3.12	1.25	0.12
Number of animals assigned	25	23	24	26
Number of animals died	0	0	0	0
Percent of animals died	0	0	0	0
Number of animals pregnant	17	22	20	21
Percent of animals pregnant	68	96	83	81

Table 4
Mean* Uterine and Litter Data

	Dosage of MPP (mg/kg/day)				
	0	3.12	1.25	0.12	
Number of litters	17	22	20	21	
Mean values per litter					
Number of implantations	14.1 + 4.9	15.8 + 2.2	14.2 + 4.2	14.7 + 3.1	
Number of resorptions	1.5 + 1.5	1.4 + 1.8	2.4 + 3.6	1.3 + 1.0	
Percent resorptions†	10.8 + 12.0	9.4 + 11.6	16.9 + 22.4	8.4 + 6.5	
Number of dead fetuses	0	0	0	0.1 + 0.2	
Percent dead fetuses§	0	0	0	0.3 + 1.3	
Number of live fetuses	12.6 + 5.1	14.3 + 2.8	11.9 + 5.2	13.3 + 2.8	
Percent live fetuses‡	89.2 + 12.0	90.5 + 11.6	83.1 + 22.4	91.3 + 6.9	
Live fetuses:					
Body weight (g)	4.3 + 1.0	4.1 + 0.8	4.0 + 0.7	4.2 + 1.0	
Body weight, male fetuses (g)	4.4 + 1.0	4.1 + 0.8	4.1 + 0.9	4.4 + 1.0	
Body weight, female fetuses (g)	4.0 + 0.8	4.0 + 0.8	4.0 + 0.6	4.2 + 1.0	
Number of male fetuses	6.9 + 3.2	7.6 + 2.2	6.6 + 3.6	6.7 + 2.6	
Percent male fetuses	57.5 + 17.8	53.9 + 13.9	48.3 + 20.4	49.9 + 16.8	

*Group mean + S.D.

†Group mean of [resorptions per litter/implantations per litter] x 100

§Group mean of [dead fetuses per litter/implantations per litter] x 100

‡Group mean of [live fetuses per litter/implantations per litter] x 100

Table 5

Coppes -- 13

Description and Incidence of Fetal External Examination Findings

	Dosage of MPP (mg/kg/day)							
	0		3.12		1.25		0.12	
	No.	%	No.	%	No.	%	No.	%
No. of fetuses examined	215		315		238		280	
Anomalies								
Domed cranium	1	0						
Cleft palate					1	0		
Protruding tongue	1	0						
Variants								
Hemorrhage on cranium			1	0				

Table 6

Description and Incidence of Fetal Visceral Examination Findings

	Dosage of MPP (mg/kg/day)							
	0		3.12		1.25		0.12	
	No.	%	No.	%	No.	%	No.	%
No. of fetuses examined	105		154		113		134	
Anomalies								
Cleft palate					1	1		
Variants								
Dilated brain ventricles	1	1						
Cerebral hemorrhage	3	3					2	1
Microphthalmia					1	1		
Small lens	1	1						
Dilated renal pelvis	11	11	9	6	8	7	18	13
Small kidney	6	6	1	1	2	2		

Table 7

Description and Incidence of Fetal Skeletal Examination Findings

	Dosage of MPP (mg/kg/day)							
	0		3.12		1.25		0.12	
	No.	%	No.	%	No.	%	No.	%
No. of fetuses examined	110		161		125		145	
Anomalies								
Domed cranium	1	1						
Short maxilla with long mandible	1	1						
Variants								
Incomplete ossification:								
Cranium	14	13	15	9	6	5	8	6
Vertebral centra	7	6	8	5	10	8	11	8
Pelvis			1	1	2	2		
Sternebrae:								
Fewer than 3 ossified							1	1
Large orbit	1	1						
Wavy ribs	2	2	3	2				
Short ribs							1	1
Lumbar rib			6	4	8	6		

Table 8
Summary of External, Visceral, and Skeletal Examination Findings

	Dosage of MPP (mg/kg/day)							
	0		3.12		1.25		0.12	
	No.	%	No.	%	No.	%	No.	%
External Exam								
Fetuses examined	215		315		238		280	
Litters examined	17		22		19		21	
Fetuses with anomalies	1	0	0	0	1	0	0	0
Fetuses with variants	0	0	1	0	0	0	0	0
Litters with anomalies	1	6	0	0	1	5	0	0
Litters with variants	0	0	1	5	0	0	0	0
Visceral Exam								
Fetuses examined	105		154		113		134	
Litters examined	16		22		19		21	
Fetuses with anomalies	0	0	0	0	1	1	0	0
Fetuses with variants	22	21	10*	6	11*	10	19	14
Litters with anomalies	0	0	0	0	1	5	0	0
Litters with variants	8	50	7	32	6	32	11	52
Skeletal Exam								
Fetuses examined	110		161		125		145	
Litters examined	17		22		19		21	
Fetuses with anomalies	1	1	0	0	0	0	0	0
Fetuses with variants	21	19	28	18	24	19	20	14
Litters with anomalies	1	6	0	0	0	0	0	0
Litters with variants	9	53	15	68	11	58	9	43
Summary of External, Visceral, Skeletal								
Fetuses examined	215		315		238		280	
Litters examined	17		22		19		21	
Fetuses with anomalies	1	1	0	0	1	0	0	0
Fetuses with variants	43	20	39*	13	35	15	39	14
Litters with anomalies	1	6	0	0	1	5	0	0
Litters with variants	11	65	17	77	13	68	15	71

*Significantly different from the control group.

Table 9
Summary of Ossification Data*

	Dosage of MPP (mg/kg/day)			
	0	3.12	1.25	0.12
Sternebrae	5.40 ± 0.49	5.45 ± 0.52	5.45 ± 0.52	5.19 ± 0.79
Caudal vertebrae	3.66 ± 1.12	3.52 ± 1.06	3.51 ± 0.89	3.70 ± 1.35
Metacarpals	6.60 ± 0.84	6.46 ± 0.70	6.44 ± 0.76	6.57 ± 0.90
Metatarsals	8.08 ± 0.52	8.09 ± 0.61	8.11 ± 0.65	8.17 ± 0.61

*Mean values calculated on a per litter basis.

DISCUSSION

This study was undertaken to evaluate the teratogenic and embryotoxic effects of 4-nitrophenyl methyl phenyl phosphinate (MPP). Dose levels were selected based upon results of acute and subchronic toxicity studies (14, 4). The high dose of MPP produced collapse, changes in respiratory rate and depth, tremors, gasping, excessive salivation, piloerection or rough coat, loss of equilibrium, humpback, red and yellow stains on anterior and posterior body sections, cyanosis, and vomiting in the 14-day subchronic toxicity study. Clinical signs of toxicity observed in this study were similar at comparable dose levels to those reported in the 14-day subchronic study. The dose levels selected for this study produced a dose-related increase in the incidence of clinical signs observed in the treated animals versus the controls.

Evidence for a teratogenic effect is considered to be a dose-related increase in frequency of major malformations in the test groups compared to the vehicle control group. For this study, major malformations, such as cleft palate, protruding tongue, abnormal cranium and mandible, were considered anomalies. Minor variations in the number or degree of ossification of sternebrae, caudal vertebrae, metatarsals, metacarpals, skull bones, vertebrae centra, dilated renal pelvis, dilated ventricles of the brain, cerebral hemorrhage, and ribs (wavy, short, and lumbar) were considered to be variants as they do not represent a specific malformation but a transient phase in development. However, if variants occurred at significantly higher frequencies in the test groups compared to the vehicle control group, this would be considered evidence of embryotoxicity. Decreased body size and edema also are manifestations of embryotoxicity. Fetal deaths or resorptions are considered manifestations of maternal toxicity, not evidence of teratogenicity (15).

MPP did not produce dose-related teratogenic or embryotoxic effects. The MPP dose groups contained 1 fetus with a major anomaly, cleft palate in the mid dose group. This represented a 0.42% anomaly rate for that group (total 238 fetuses) which is similar to that found in the vehicle control group. Visceral variant findings for the low dose group were similar to those found in the vehicle control group, with the mid and high dose groups having significantly fewer fetuses with variants. Skeletal variant findings were similar to the vehicle control with the exception that 6% in the mid and 4% in the high MPP dose groups had supernumerary lumbar ribs. The presence of supernumerary lumbar ribs is one of the most common variants in rats (6).

One vehicle control fetus had anomalies of the head characterized by domed-shaped cranium, protruding tongue, and short maxilla with long mandible. This represents a 0.47% anomaly rate for fetuses in that

group (total 215 fetuses). Palmer (6) reported an incidence of spontaneous malformations in the rat of 0.41% major malformations from 51,349 control fetuses.

The vehicle control and MPP dose groups had a higher incidence of nondose-related visceral and skeletal variants than published control data (6). The incidence of visceral variants was 21% in the vehicle control group and 6%, 10%, and 14% in the MPP high, mid, and low dose groups, respectively. Dilated renal pelvis occurred in 11% of the vehicle control fetuses and in 13% of the MPP low dose fetuses versus a published control incidence of 6 to 7%. However, this published control rate included renal dilation as a variant only when no pelvic projections were present (6), whereas in our study renal pelvic dilation was recorded as a variant even though some pelvic projections were present. Other visceral variants were small kidney, cerebral hemorrhage, dilated ventricles of brain, and microphthalmia. Likewise, 2 skeletal variants, incomplete ossification of cranium and vertebral centra, occurred at a higher frequency in all groups than in published control data (6).

Two factors may have contributed to the incidence of variants in the vehicle control and MPP dose groups. The vehicle contained 18.5% absolute ethanol. Fetal alcohol syndrome (FAS) is characterized by growth retardation and an increased frequency of major and minor malformations. Mice treated with alcohol (3.75 ml/kg) on Day 7 produced a high frequency of fetuses with defects of the head, microphthalmia, cleft palate, and a characteristic profile in which the maxilla failed to overlap the mandible (16). Even though rats in this study received a lower daily dose (0.58 ml/kg ETOH), they did receive it on Days 6 through 15. Thus, two fetuses in the vehicle control group, one fetus with a domed cranium, short maxilla, and long mandible and one fetus with small lens, and one fetus in the mid dose (MPP) group with cleft palate and microphthalmia may represent a fetal effect of the ethanol in the vehicle.

The vehicle also contained 21.5% Tween 80. The Tween component of the vehicle may not be inert in teratological experiments. Kocher-Becker et al (17) reported that Tween 20 when given to mice was not merely a solubilizing agent but a teratogen in itself. When given to Swiss mice as a single injection of 1.0 ml/kg on Day 9 of gestation, Tween 20 produced malformations and variants, mostly involving the vertebrae and ribs, in 11.8% of the fetuses in comparison to 0.8% in the control. At higher dose levels, Tween 20 produced malformations with striking similarities to those produced by thalidomide. Although the rats in this study received 0.67 ml Tween 80/kg on Days 6 through 15, variations in ribs and vertebral centra ossification possibly could be attributed to the Tween in the vehicle. In comparing Tween 20, Tween 40, Tween 60, and Tween 80, Bresch and Ockenfels (18) found that the 4 different Tween surfactants acted similarly and all 4 strongly

influenced development of the sea urchin embryo.

CONCLUSION

When given in daily oral doses of 0.12, 1.25, and 3.12 mg/kg/day from Days 6 through 15 of pregnancy, MPP did not produce dose-related teratogenic or embryotoxic effects in Sprague-Dawley rats.

RECOMMENDATION

If efficacy data warrant continued development, the teratogenic potential of MPP should be evaluated in a second species, preferably the rabbit, to confirm its low risk. If additional teratology studies are conducted, a new vehicle should be developed which would not only insure the stability of the test compound but also would be more compatible with teratologic evaluations.

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APPENDICES

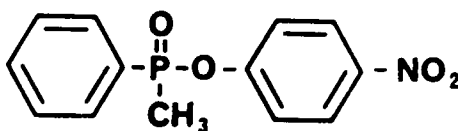
CHEMICAL DATA

Test Substance

Chemical Name: 4-Nitrophenyl Methyl Phenyl Phosphinate

Chemical Abstract Service Registry No.: None

Molecular Structure $C_{13}H_{12}NO_4P$



Source: Ash Stevens Inc.
Detroit, Michigan 48202

Lot No.: XL 1X-40

Contaminants: None detected

Molecular Weight: 277.2

Melting Point: 85-86°C

Physical State/Color: Fluffy white crystals

Stability: Unstable at neutral and basic pH. Stable in acidified solution. In preliminary studies MPP was relatively stable in vehicle for 8 days as determined by spectrophotometric measurement of p-nitrophenol (Spectrophotometric measure of p-nitrophenol for phosphinate determination. LAIR Standard Operating Procedure OP-STX-49. Letterman Army Institute of Research, Presidio of San Francisco, CA. 28 Dec 1981.)

Vehicle Substances

Chemical Name: Polysorbate 80 (Tween 80)

Chemical Abstract Service Registry No.: 9005-65-6

Source: Fisher Scientific Co.
Fairlawn, New Jersey 07410

Lot No.: 713137

Chemical Name: Ethanol, anhydrous

Chemical Abstract Service Registry No.: 64-17-5

Phase I

Source: U.S. Industrial Chemicals
Tuscola, Illinois 61953

Lot No.: 136

Phase II

Source: Aaper Alcohol and Chemical Co.
Louisville, Kentucky 40214

Lot No.: DSP-KY-73

Chemical Name: Citric acid, monohydrate

Chemical Abstract Service Registry No.: 77-92-9

Chemical Name: Sodium citrate

Chemical Abstract Service Registry No.: None

Analysis of Dosing Solution

Date of Preparation	Date of Analysis	Dosing Solution mg/ml	Intact Phosphinate* mg/ml
Phase I			
18 Oct 82	18 Oct 82	0.04	0.042
18 Oct 82	18 Oct 82	0.40	0.402
18 Oct 82	18 Oct 82	1.00	1.042
18 Oct 82	19 Oct 82	0.04	0.036
18 Oct 82	19 Oct 82	0.40	0.371
18 Oct 82	19 Oct 82	1.00	0.950
18 Oct 82	22 Oct 82	0.04	0.038
18 Oct 82	22 Oct 82	0.40	0.375
18 Oct 82	22 Oct 82	1.00	0.950
22 Oct 82	22 Oct 82	0.04	0.042
22 Oct 82	22 Oct 82	0.40	0.398
22 Oct 82	22 Oct 82	1.00	1.131
28 Oct 82	28 Oct 82	0.04	0.037
28 Oct 82	28 Oct 82	0.40	0.395
28 Oct 82	28 Oct 82	1.00	1.119
Phase II			
13 Feb 83	13 Feb 83	1.00	0.898
18 Feb 83	19 Feb 83	1.00	0.935

* Determined by spectrophotometric measurement of p-nitrophenol for phosphinate determination.

Historical Listing of Major Study Events

29 Jun 82	Date of protocol request.
31 Aug 82	41 male rats arrived at LAIR for Phase I.
5 Oct 82	85 females arrived at LAIR for Phase I.
12 - 15 Oct 82	Phase I breeding.
19 - 30 Oct 82	Sperm-positive females dosed.
2 - 4 Nov 82	Cesarean sections on sperm-positive females.
13 Dec 82	52 males arrived at LAIR for Phase II.
20 Jan 83	103 females arrived at LAIR for Phase II.
7 - 12 Feb 83	Phase II breeding.
14 - 27 Feb 83	Sperm-positive females dosed.
28 Feb - 4 Mar 83	Cesarean sections on sperm-positive females.

Individual Maternal Body Weights (Grams) - Vehicle Animals

Maternal ID	Day 0 Age	Date of Breeding	Date of Sacrifice	Preg- nant	Day of Gestation							Weight Change
					Gravid Correct							
					0	6	12	16	20	20	20	
82D000682	130	13 Oct 82	02 Nov 82	Yes	270	295	317	350	402	317	47	
82D000691	131	14 Oct 82	03 Nov 82	Yes	299	338	343	381	459	356	57	
82D000694	(132)	15 Oct 82	04 Nov 82	No	(311)	(318)	(318)	(307)	(313)	(313)	(2)	
82D000698	130	13 Oct 82	02 Nov 82	Yes	270	307	307	341	407	327	57	
82D000703	130	13 Oct 82	02 Nov 82	Yes	267	306	335	328	343	327	60	
82D000719	130	13 Oct 82	02 Nov 82	Yes	303	333	359	389	449	346	43	
82D000724	130	13 Oct 82	02 Nov 82	Yes	286	319	302	333	365	311	25	
82D000743	130	13 Oct 82	02 Nov 82	Yes	262	306	302	343	408	327	65	
82D000749	(131)	14 Oct 82	03 Nov 82	No	(291)	(320)	(328)	(329)	(316)	(316)	(25)	
82D000751	132	15 Oct 82	04 Nov 82	Yes	331	349	359	387	443	382	51	
83D000001	98	09 Feb 83	01 Mar 83	Yes	263	287	303	313	340	279	16	
83D000013	(97)	08 Feb 83	28 Feb 83	No	(277)	(278)	(289)	(296)	(302)	(302)	(25)	
83D000019	98	09 Feb 83	01 Mar 83	Yes	272	316	322	357	395	278	6	
83D000026	(97)	08 Feb 83	28 Feb 83	No	(314)	(331)	(325)	(314)	*	*	*	
83D000039	97	08 Feb 83	28 Feb 83	Yes	296	329	337	350	402	353	57	
83D000041	(98)	09 Feb 83	1 Mar 83	No	(282)	(324)	(317)	(313)	(300)	(300)	(18)	
83D000049	(100)	11 Feb 83	03 Mar 83	No	(281)	(309)	(298)	(297)	(290)	(290)	(9)	
83D000052	(97)	08 Feb 83	28 Feb 83	No	(285)	(314)	(317)	(328)	(332)	(332)	(47)	
83D000062	99	10 Feb 83	02 Mar 83	Yes	265	282	302	334	373	273	8	
83D000063	98	09 Feb 83	01 Mar 83	Yes	240	273	296	312	370	282	42	
83D000070	100	11 Feb 83	03 Mar 83	Yes	265	294	311	343	385	285	20	
83D000076	98	09 Feb 83	01 Mar 83	Yes	257	294	279	315	388	282	25	
83D000082	101	12 Feb 83	04 Mar 83	Yes	301	335	351	*	451	356	55	
83D000087	(100)	11 Feb 83	03 Mar 83	No	(262)	(295)	(297)	(293)	(286)	(286)	(24)	
83D000096	101	12 Feb 83	04 Mar 83	Yes	276	303	324	*	434	331	55	

* Weight not obtained.

Individual Maternal Body Weights (Grams) - 3.12 mg/kg/day MPP Animals

Maternal ID	Day 0 Age	Date of Breeding	Date of Sacrifice	Preg- nant	Day of Gestation						Gravid Correct 20	Correct 20	Weight Change
					0	6	12	16	20				
82D00681	130	13 Oct 82	02 Nov 82	Yes	284	313	330	369	438	314	314	30	
82D00696	130	13 Oct 82	02 Nov 82	Yes	298	329	325	366	431	352	352	54	
82D00699	131	14 Oct 82	03 Nov 82	Yes	269	308	320	348	406	356	356	87	
82D00704	131	14 Oct 82	03 Nov 82	Yes	274	305	312	347	424	321	321	47	
82D00706	130	13 Oct 82	02 Nov 82	Yes	264	307	338	373	426	343	343	79	
82D00723	130	13 Oct 82	02 Nov 82	Yes	279	300	317	339	401	306	306	27	
82D00728	131	14 Oct 82	03 Nov 82	Yes	293	314	315	352	392	316	316	23	
82D00734	130	13 Oct 82	02 Nov 82	Yes	274	308	334	373	416	318	318	44	
82D00739	130	13 Oct 82	02 Nov 82	Yes	286	324	348	390	448	337	337	51	
82D00750	131	14 Oct 82	03 Nov 82	Yes	290	321	335	378	445	342	342	52	
82D00752	130	13 Oct 82	02 Nov 82	Yes	277	309	350	394	447	340	340	63	
83D00010	98	09 Feb 83	01 Mar 83	Yes	258	291	314	335	362	271	271	13	
83D00016	97	08 Feb 83	28 Feb 83	Yes	252	286	292	310	388	292	292	40	
83D00020	97	08 Feb 83	28 Feb 83	Yes	254	289	319	355	430	328	328	74	
83D00024	98	09 Feb 83	01 Mar 83	Yes	266	312	331	349	386	287	287	21	
83D00040	(99)	10 Feb 83	02 Mar 83	No	(264)	(278)	(273)	(272)	(255)	(255)	(255)	(-9)	
83D00042	97	08 Feb 83	28 Feb 83	Yes	269	294	288	326	388	289	289	20	
83D00044	98	09 Feb 83	01 Mar 83	Yes	289	323	287	331	369	284	284	-5	
83D00047	99	10 Feb 83	02 Mar 83	Yes	278	303	287	297	346	265	265	-13	
83D00050	98	09 Feb 83	01 Mar 83	Yes	301	323	348	366	389	314	314	13	
83D00059	97	08 Feb 83	28 Feb 83	Yes	273	307	306	353	437	323	323	50	
83D00073	99	10 Feb 83	02 Mar 83	Yes	269	298	324	351	390	293	293	24	
83D00101	100	11 Feb 83	03 Mar 83	Yes	289	320	323	331	373	322	322	33	

Individual Maternal Body Weights (Grams) - 1.25 mg/kg/day MPP Animals

Maternal ID	Day 0 Age	Date of Breeding	Date of Sacrifice	Preg-nant	Day of Gestation						Gravid Correct	Weight Change
					0	6	12	16	20			
82D00684	(130)	13 Oct 82	02 Nov 82	No	(308)	(324)	(338)	(321)	(325)	(325)	(17)	
82D00689	132	15 Oct 82	04 Nov 82	Yes	291	312	318	344	396	338	47	
82D00697	132	15 Oct 82	04 Nov 82	Yes	271	300	290	338	416	313	42	
82D00700	130	13 Oct 82	02 Nov 82	Yes	287	314	345	376	454	335	48	
82D00705	(132)	15 Oct 82	04 Nov 82	No	(281)	(304)	(298)	(284)	(284)	(284)	(3)	
82D00708	(131)	14 Oct 82	03 Nov 82	No	(293)	(326)	(307)	(315)	(298)	(298)	(5)	
82D00710	130	13 Oct 82	02 Nov 82	Yes	276	302	332	354	418	330	54	
82D00715	130	13 Oct 82	02 Nov 82	Yes	282	316	337	366	447	347	65	
82D00731	131	14 Oct 82	03 Nov 82	Yes	261	307	304	320	402	306	45	
82D00735	130	13 Oct 82	02 Nov 82	Yes	278	293	319	324	355	325	47	
82D00740	132	15 Oct 82	04 Nov 82	Yes	303	331	320	336	366	317	14	
82D00745	130	13 Oct 82	02 Nov 82	Yes	268	292	313	353	416	302	34	
82D00763	131	14 Oct 82	03 Nov 82	Yes	280	303	312	338	392	317	37	
83D00003	101	12 Feb 83	04 Mar 83	Yes	266	292	292	*	365	279	13	
83D00014	97	08 Feb 83	28 Feb 83	Yes	262	301	301	311	344	305	43	
83D00029	98	09 Feb 83	01 Mar 83	Yes	294	322	357	292	285	285	-9	
83D00031	99	10 Feb 83	02 Mar 83	Yes	249	282	296	305	330	294	45	
83D00032	99	10 Feb 83	02 Mar 83	Yes	288	323	352	373	458	356	68	
83D00037	98	09 Feb 83	01 Mar 83	Yes	257	280	316	345	429	312	55	
83D00051	(97)	08 Feb 83	28 Feb 83	No	(279)	(311)	(297)	(292)	(292)	(292)	(13)	
83D00056	97	08 Feb 83	28 Feb 83	Yes	266	309	312	333	388	312	46	
83D00060	98	09 Feb 83	01 Mar 83	Yes	256	278	309	319	357	268	12	
83D00067	97	08 Feb 83	28 Feb 83	Yes	268	289	317	306	354	274	6	
83D00077	98	09 Feb 83	01 Mar 83	Yes	275	295	336	341	393	298	23	

* Weight not obtained.

Individual Maternal Body Weights (Grams) - 0.12 mg/kg/day MPP Animals

Maternal ID	Day 0 Age	Date of Breeding	Date of Sacrifice	Preg-nant	Day of Gestation						Gravid Correct	Weight Change
					0	6	12	16	20	20		
82D00686	(130)	13 Oct 82	02 Nov 82	No	(283)	(306)	(298)	(275)	(292)	(292)	(292)	(9)
82D00690	(131)	14 Oct 82	03 Nov 82	No	(286)	(295)	(316)	(305)	(304)	(304)	(304)	(18)
82D00693	131	14 Oct 82	03 Nov 82	Yes	288	320	334	368	431	336	336	48
82D00702	(131)	14 Oct 82	03 Nov 82	No	(282)	(312)	(300)	(304)	(285)	(285)	(285)	(3)
82D00714	130	13 Oct 82	02 Nov 82	Yes	310	338	365	407	482	352	352	42
82D00717	(130)	13 Oct 82	02 Nov 82	No	(276)	(306)	(315)	(293)	(285)	(285)	(285)	(9)
82D00727	130	13 Oct 82	02 Nov 82	Yes	308	346	370	416	510	395	395	87
82D00729	132	15 Oct 82	04 Nov 82	Yes	282	299	310	342	390	313	313	31
82D00741	(130)	13 Oct 82	02 Nov 82	No	(282)	(306)	(312)	(288)	(289)	(289)	(289)	(7)
82D00746	130	13 Oct 82	02 Nov 82	Yes	281	310	329	348	401	319	319	38
82D00764	131	14 Oct 82	03 Nov 82	Yes	261	298	267	285	326	286	286	25
83D00004	97	08 Feb 83	28 Feb 83	Yes	288	317	333	362	414	322	322	34
83D00011	100	11 Feb 83	03 Mar 83	Yes	265	285	292	318	378	299	299	34
83E00015	98	09 Feb 83	01 Mar 83	Yes	282	308	337	350	424	325	325	43
83D00023	97	08 Feb 83	28 Feb 83	Yes	266	301	322	339	394	316	316	50
83D00025	098	09 Feb 83	01 Mar 83	Yes	253	289	260	276	341	249	249	-4
83D00030	99	10 Feb 83	02 Mar 83	Yes	298	332	342	380	376	287	287	-11
83D00034	98	09 Feb 83	01 Mar 83	Yes	327	357	381	402	444	339	339	12
83D00038	99	10 Feb 83	02 Mar 83	Yes	288	328	358	390	448	338	338	50
83D00043	100	11 Feb 83	03 Mar 83	Yes	295	324	324	332	391	322	322	27
83D00054	97	08 Feb 83	28 Feb 83	Yes	293	317	324	357	407	315	315	22
83D00069	98	09 Feb 83	01 Mar 83	Yes	295	320	344	374	410	307	307	12
83D00075	99	10 Feb 83	02 Mar 83	Yes	254	287	313	309	355	290	290	36
83D00078	98	09 Feb 83	01 Mar 83	Yes	302	334	356	392	418	319	319	17
83D00080	101	12 Feb 83	04 Mar 83	Yes	245	270	289	*	346	261	261	16
83D00097	101	12 Feb 83	04 Mar 83	Yes	282	319	320	*	423	336	336	54

* Weight not obtained.

Misdosed Animals

MPP Dose	Maternal ID	Date Removed
0	82D00716	26 Oct 82
0	83D00033	16 Feb 83
3.12	83D00074	19 Feb 83
1.25	83D00018	18 Feb 83
1.25	83D00022	16 Feb 83
1.25	83D00057	19 Feb 83
0.12	82D00737	25 Oct 82
0.12	83D00035	21 Feb 83
0.12	83D00094	23 Feb 83

Maternal Clinical Signs - Vehicle Animals

Maternal ID	Study Day	Date	Signs
82D00691	14	28 Oct 82	Brief bleeding from mouth on introduction of gavage needle, not dosed
82D00703	20	2 Nov 82	Enlarged uterus, left horn filled with fluid at sacrifice
83D00039	15	23 Feb 83	Sound production
83D00062	11	21 Feb 83	Misdose, slight foaming at mouth
83D00063	7	16 Feb 83	Red stained nose
	14	23 Feb 83	Sound production
83D00082	0	12 Feb 83	Slight weight loss

Maternal Clinical Signs - 3.12 mg/kg/day MPP Animals

Maternal ID	Study Day	Date	Signs
82D00696	9	22 Oct 82	Gasping, salivation
83D00010	0	9 Feb 83	Bloody vaginal discharge
83D00016	0	8 Feb 83	Bloody vaginal discharge
	9	17 Feb 83	Inactive
	15	23 Feb 83	Sound production
83D00020	6	14 Feb 83	Blood in mouth during dosing
83D00024	8	17 Feb 83	Inactive
83D00042	0	8 Feb 83	Slight weight loss
83D00044	7	16 Feb 83	Yellow stained mouth
	8	17 Feb 83	Yellow stained mouth
83D00047	6	16 Feb 83	Misdose, vomiting
	7	17 Feb 83	Yellow stained mouth
	13	23 Feb 83	Red stained nose, sound production
	14	24 Feb 83	Convulsions, vomiting, inactive, sound production
	15	25 Feb 83	Red stained nose, sound production
83D00050	8	17 Feb 83	Inactive
83D00059	0	8 Feb 83	Slight weight loss
	8	16 Feb 83	Inactive
	15	23 Feb 83	Yellow stained perianal
	16	24 Feb 83	Blood on nose
83D00101	12	23 Feb 83	Yellow stained mouth, sound production

Maternal Clinical Signs - 1.25 mg/kg/day MPP Animals

Maternal ID	Study Day	Date	Signs
82D00735	9	22 Oct 82	Blood in mouth at dosing
82D00740	20	4 Nov 82	Yellow fluid filled mass in left axilla
83D00003	12	24 Feb 83	Inactive
83D00029	8	17 Feb 83	Bloody vaginal discharge, signs of abortion
	9	18 Feb 83	Clotted blood in vaginal area
	14	23 Feb 83	Bloody vaginal discharge, sound production, cyanosis
	15	24 Feb 83	Bloody vaginal discharge, sound production, inactive
	16	25 Feb 83	Sound production, cyanosis
	17	26 Feb 83	Inactive
83D00031	7	17 Feb 83	Inactive
83D00032	13	23 Feb 83	Mass in right axilla
	20	2 Mar 83	At sacrifice mass revealed granulomatous tissue
83D00056	9	17 Feb 83	Hunched posture
83D00067	15	23 Feb 83	Sound production
	16	24 Feb 83	Sharp weight loss
83D00077	0	9 Feb 83	Bloody vaginal discharge
	20	1 Mar 83	3 bladder stones at sacrifice

Maternal Clinical Signs - 0.12 mg/kg/day MPP Animals

Maternal ID	Study Day	Date	Signs
82D00686	14	27 Oct 82	Received partial dose
83D00011	0	11 Feb 83	Bloody vaginal discharge
83D00025	8	17 Feb 83	Weight loss
	15	24 Feb 83	Ataxia, inactive
83D00054	0	8 Feb 83	Slight weight loss
	12	20 Feb 83	Sound production
83D00078	8	17 Feb 83	Ataxia
83D00080	0	12 Feb 83	Slight weight loss
83D00097	6	18 Feb 83	Red stained mouth, nose
	7	19 Feb 83	Red stained mouth
	12	24 Feb 83	Ataxia, inactive

Individual Uterine and Litter Data - Vehicle Animals

Maternal ID	Implantations	Resorptions	Resorp.%	----- Number of Fetuses -----		
				Dead	Dead %	Live Live %
82D00682	14	5	36	0	0	9 64
82D00691	18	1	6	0	0	17 94
82D00698	14	0	0	0	0	14 100
82D00703	1	0	0	0	0	1 100
82D00719	16	1	6	0	0	15 94
82D00724	9	3	33	0	0	6 67
82D00743	15	3	20	0	0	12 80
82D00751	10	1	10	0	0	9 90
83D00001	13	4	31	0	0	9 69
83D00019	18	0	0	0	0	18 100
83D00039	7	0	0	0	0	7 100
83D00062	19	0	0	0	0	19 100
83D00063	15	1	7	0	0	14 93
83D00070	19	1	5	0	0	18 95
83D00076	18	1	6	0	0	17 94
83D00082	16	2	12	0	0	14 88
83D00096	18	2	11	0	0	16 89

Individual Uterine and Litter Data - 3.12 mg/kg/day MPP Animals

Maternal ID	Implantations	Resorptions	Resorp.%	---- Number of Fetuses ----		
				Dead	Dead %	Live Live %
82D00681	17	3	18	0	0	14 82
82D00696	15	2	13	0	0	13 87
82D00699	11	4	36	0	0	7 64
82D00704	17	0	0	0	0	17 100
82D00706	13	1	8	0	0	12 92
82D00723	17	1	6	0	0	16 94
82D00728	13	1	8	0	0	12 92
82D00734	12	0	0	0	0	12 100
82D00739	18	2	11	0	0	16 89
82D00750	16	0	0	0	0	16 100
82D00752	17	1	6	0	0	16 94
83D00010	16	1	6	0	0	15 94
83D00016	14	0	0	0	0	14 100
83D00020	18	0	0	0	0	18 100
83D00024	18	1	6	0	0	17 94
83D00042	18	2	11	0	0	16 89
83D00044	15	1	6	0	0	14 94
83D00047	16	2	12	0	0	14 88
83D00050	13	1	8	0	0	12 92
83D00059	18	1	6	0	0	17 94
83D00073	18	0	0	0	0	18 100
83D00101	17	8	47	0	0	9 53

Individual Uterine and Litter Data - 1.25 mg/kg/day MPP Animals

Maternal ID	Implantations	Resorptions	Resorp.%	----- Number of Fetuses -----		
				Dead	Dead %	Live Live /
82D00689	11	2	18	0	0	9 82
82D00697	17	0	0	0	0	17 100
82D00700	16	1	6	0	0	15 94
82D00710	15	2	13	0	0	13 87
82D00715	16	0	0	0	0	16 100
82D00731	16	0	0	0	0	16 100
82D00735	5	1	20	0	0	4 80
82D00740	11	4	36	0	0	7 64
82D00745	16	3	19	0	0	13 81
82D00763	14	2	14	0	0	12 86
83D00003	16	2	12	0	0	14 88
83D00014	8	3	38	0	0	5 62
83D00029	17	17	100	0	0	0 0
83D00031	5	0	0	0	0	5 100
83D00032	19	3	16	0	0	16 84
83D00037	19	0	0	0	0	19 100
83D00056	12	2	17	0	0	10 83
83D00060	17	2	12	0	0	15 88
83D00067	18	2	11	0	0	16 89
83D00077	17	1	6	0	0	16 94

Individual Uterine and Litter Data - 0.12 mg/kg/day MPP Animals

Maternal ID	Implantations	Resorptions	Resorp.%	---- Number of Fetuses ----		
				Dead	Dead %	Live %
82D00693	16	2	12	0	0	14 88
82D00714	16	1	6	0	0	15 94
82D00727	18	1	6	0	0	17 94
82D00729	13	1	8	0	0	12 92
82D00746	13	2	15	0	0	11 85
82D00764	6	0	0	0	0	6 100
83D00004	13	0	0	0	0	13 100
83D00011	13	0	0	0	0	13 100
83D00015	17	2	12	0	0	15 88
83D00023	13	1	8	0	0	12 92
83D00025	17	2	12	0	0	15 88
83D00030	17	0	0	0	0	17 100
83D00034	18	1	6	0	0	17 94
83D00038	16	3	19	0	0	13 81
83D00043	12	1	8	0	0	11 92
83D00054	13	2	15	0	0	11 85
83D00069	17	1	6	0	0	16 94
83D00075	10	0	0	0	0	10 100
83D00078	18	1	6	0	0	17 94
83D00080	18	3	16	1	6	14 78
83D00097	14	3	21	0	0	11 79

Fetal Sex and Weight - Vehicle Animals

Maternal ID	Sex		Mean Weight(g) ±S.D.	
	Males	Females	Fetal	Females
82D00682	7	2	6.16±.26	6.21±.27
82D00691	9	8	3.66±.57	3.98±.11
82D00698	6	8	3.55±.25	3.77±.12
82D00703	1	0	6.40	6.40
82D00719	11	4	4.47±.35	4.57±.20
82D00724	4	2	6.27±.29	6.40±.26
82D00743	6	6	4.18±.28	4.27±.27
82D00751	2	7	3.79±.33	4.20±.00
83D00001	4	5	4.16±.14	4.20±.16
83D00019	11	7	4.09±.22	4.20±.20
83D00039	5	2	4.19±.27	4.18±.33
83D00062	12	7	3.22±.27	3.25±.22
83D00063	7	7	3.83±.50	3.96±.54
83D00070	8	10	3.57±.20	3.70±.22
83D00076	11	6	3.88±.19	3.96±.16
83D00082	7	7	3.74±.44	3.96±.11
83D00096	7	9	3.49±.15	3.43±.17
				5.95±.07
				3.31±.68
				3.39±.19
				4.18±.53
				6.00±.14
				4.08±.28
				3.67±.27
				4.12±.13
				3.93±.14
				4.20±.14
				3.16±.36
				3.70±.46
				3.47±.12
				3.73±.15
				3.51±.54
				3.56±.10

Fetal Sex and Weight - 3.12 mg/kg/day MPP Animals

Maternal ID	Sex		Males(%)	Mean Weight(g) + S.D.		
	Males	Females		Fetal	Males	Females
82D00681	8	6	57	5.91+ .32	6.06+ .24	5.70+ .31
82D00696	3	10	23	3.66+ .28	3.47+ .40	3.72+ .22
82D00699	4	3	57	3.93+ .13	3.98+ .13	3.87+ .40
82D00704	9	8	53	3.83+ .31	4.02+ .22	3.61+ .26
82D00706	7	5	58	4.10+ .41	4.27+ .40	3.86+ .31
82D00723	6	10	37	3.93+ .30	3.98+ .39	3.89+ .24
82D00728	9	3	75	3.93+ .30	3.93+ .35	3.90+ .10
82D00734	7	5	58	6.02+ .24	6.10+ .26	5.90+ .16
82D00739	9	7	56	4.55+ .34	4.71+ .27	4.34+ .34
82D00750	10	6	62	3.61+ .44	3.81+ .11	3.28+ .59
82D00752	8	8	50	4.28+ .18	4.25+ .18	4.30+ .19
83D00010	12	3	80	3.78+ .19	3.81+ .20	3.67+ .12
83D00016	9	5	64	3.94+ .15	4.01+ .15	3.80+ .00
83D00020	8	10	44	3.44+ .29	3.45+ .26	3.43+ .32
83D00024	6	11	35	3.55+ .17	3.65+ .08	3.49+ .18
83D00042	10	6	62	3.78+ .23	3.77+ .28	3.80+ .14
83D00044	6	8	43	3.66+ .13	3.70+ .13	3.63+ .14
83D00047	7	7	50	3.81+ .24	3.94+ .26	3.73+ .12
83D00050	9	3	75	3.73+ .44	3.76+ .52	3.67+ .06
83D00059	6	11	35	5.87+ .18	5.93+ .22	5.84+ .14
83D00073	10	8	56	3.32+ .24	3.36+ .29	3.28+ .18
83D00101	5	4	56	3.31+ .26	3.48+ .22	3.10+ .08

Fetal Sex and Weight - 1.25 mg/kg/day MPP Animals

Maternal ID	Sex		Mean Weight(g) + S.D.	
	Males	Females	Fetal	Males
82D00689	3	6	3.89 $\pm$.27	4.00 $\pm$.20
82D00697	10	7	3.81 $\pm$.18	3.88 $\pm$.12
82D00700	11	4	5.56 $\pm$.23	5.65 $\pm$.18
82D00710	6	7	4.02 $\pm$.19	4.15 $\pm$.12
82D00715	9	7	3.90 $\pm$.19	3.84 $\pm$.32
82D00731	11	5	3.54 $\pm$.25	3.58 $\pm$.26
82D00735	1	3	4.35 $\pm$.38	4.60
82D00740	5	2	3.39 $\pm$.26	3.36 $\pm$.26
82D00745	10	3	*	*
82D00763	3	9	3.30 $\pm$.77	2.73 $\pm$ 1.4
83D00003	8	6	3.41 $\pm$.26	3.48 $\pm$.27
83D00014	0	5	4.06 $\pm$.40	4.06 $\pm$.40
83D00031	1	4	3.92 $\pm$.41	4.10
83D00032	7	9	3.81 $\pm$.29	3.99 $\pm$.17
83D00037	12	7	3.93 $\pm$.20	3.98 $\pm$.18
83D00056	6	4	5.95 $\pm$.50	6.23 $\pm$.12
83D00060	6	9	3.73 $\pm$.30	3.90 $\pm$.17
83D00067	8	8	4.88 $\pm$.27	4.96 $\pm$.21
83D00077	8	8	3.25 $\pm$.54	3.44 $\pm$.45
				3.64 $\pm$.23

* Fetuses not weighed.

Fetal Sex and Weight - 0.12 mg/kg/day MPP Animals

Maternal ID	Sex		Mean Weight(g) $\pm$ S.D.	
	Males	Females	Fetal	Males
82D00693	8	6	3.90 $\pm$.25	4.05 $\pm$.18
82D00714	8	7	5.75 $\pm$.19	5.80 $\pm$.19
82D00727	10	7	4.37 $\pm$.16	4.40 $\pm$.14
82D00729	6	6	3.86 $\pm$.28	4.02 $\pm$.32
82D00746	4	7	4.49 $\pm$.39	4.73 $\pm$.13
82D00764	5	1	3.90 $\pm$.32	3.86 $\pm$.34
83D00004	8	5	3.70 $\pm$.26	3.72 $\pm$.27
83D00011	4	9	3.73 $\pm$.16	3.88 $\pm$.15
83D00015	9	6	3.87 $\pm$.23	4.01 $\pm$.10
83D00023	7	5	4.08 $\pm$.35	4.04 $\pm$.45
83D00025	8	7	4.07 $\pm$.27	4.14 $\pm$.22
83D00030	11	6	3.21 $\pm$.18	3.24 $\pm$.20
83D00034	6	11	3.77 $\pm$.20	3.93 $\pm$.10
83D00038	8	5	5.70 $\pm$.40	5.84 $\pm$.35
83D00043	1	10	3.75 $\pm$.20	3.80
83D00054	5	6	7.44 $\pm$.55	7.74 $\pm$.20
83D00069	9	7	3.76 $\pm$.17	3.80 $\pm$.13
83D00075	6	4	4.24 $\pm$.25	4.30 $\pm$.17
83D00078	9	8	3.44 $\pm$.17	3.48 $\pm$.18
83D00080	6	8	3.27 $\pm$.26	3.50 $\pm$.14
83D00097	2	9	4.73 $\pm$.38	5.25 $\pm$.21
				3.70 $\pm$.19
				5.69 $\pm$.20
				4.33 $\pm$.18
				3.70 $\pm$.13
				4.39 $\pm$.44
				4.10
				3.66 $\pm$.25
				3.67 $\pm$.12
				3.67 $\pm$.22
				4.14 $\pm$.11
				3.99 $\pm$.32
				3.15 $\pm$.14
				3.68 $\pm$.19
				5.48 $\pm$.41
				3.74 $\pm$.21
				7.18 $\pm$.64
				3.71 $\pm$.21
				4.15 $\pm$.34
				3.39 $\pm$.17
				3.10 $\pm$.19
				4.61 $\pm$.31

Description and Incidence of Fetal External Examination Findings - Vehicle Animals

Maternal ID	Variants			Anomalies	
	No.*	No.†	No. and Description of Each Variant	No.§	No. and Description of Each Anomaly
82D00682	9	0		0	
82D00691	17	0		0	
82D00698	14	0		0	
82D00703	1	0		1	1 Domed cranium 1 Protruding tongue
82D00719	15	0		0	
82D00724	6	0		0	
82D00743	12	0		0	
82D00751	9	0		0	
83D00001	9	0		0	
83D00019	18	0		0	
83D00039	7	0		0	
83D00062	19	0		0	
83D00063	14	0		0	
83D00070	18	0		0	
83D00076	17	0		0	
83D00082	14	0		0	
83D00096	16	0		0	

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal External Examination Findings - 3.12 mg/kg/day MPP Animals

Maternal ID	No.*	No.†	Variants		Anomalies	
			No. and Description of Each Variant	No.‡	No. and Description of Each Anomaly	
82D00681	14	0		0		
82D00696	13	0		0		
82D00699	7	0		0		
82D00704	17	0		0		
82D00706	12	0		0		
82D00723	16	0		0		
82D00728	12	0		0		
82D00734	12	0		0		
82D00739	16	0		0		
82D00750	16	1	1 Hemorrhage on cranium	0		
82D00752	16	0		0		
83D00010	15	0		0		
83D00016	14	0		0		
83D00020	18	0		0		
83D00024	17	0		0		
83D00042	16	0		0		
83D00044	14	0		0		
83D00047	14	0		0		
83D00050	12	0		0		
83D00059	17	0		0		
83D00073	18	0		0		
83D00101	9	0		0		

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

Description and Incidence of Fetal External Examination Findings - 1.25 mg/kg/day MPP Animals

Maternal ID	Variants			Anomalies	
	No.*	No.†	No. and Description of Each Variant	No.§	No. and Description of Each Anomaly
82D00689	9	0		0	
82D00697	17	0		0	
82D00700	15	0		0	
82D00710	13	0		0	
82D00715	16	0		0	
82D00731	16	0		0	
82D00735	4	0		0	
82D00740	7	0		0	
82D00745	13	0		0	
82D00763	12	0		0	
83D00003	14	0		0	
83D00014	5	0		0	
83D00031	5	0		0	
83D00032	16	0		0	
83D00037	19	0		0	
83D00056	10	0		0	
83D00060	15	0		0	
83D00067	16	0		0	
83D00077	16	0		1	1 Cleft palate

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal External Examination Findings - 0.12 mg/kg/day MPP Animals

Maternal ID	Variants		Anomalies	
	No.*	No.† of Each Variant	No.§ of Each Anomaly	No. and Description of Each Anomaly
82D00693	14	0	0	
82D00714	15	0	0	
82D00727	17	0	0	
82D00729	12	0	0	
82D00746	11	0	0	
82D00764	6	0	0	
83D00004	13	0	0	
83D00011	13	0	0	
83D00015	15	0	0	
83D00023	12	0	0	
83D00025	15	0	0	
83D00030	17	0	0	
83D00034	17	0	0	
83D00038	13	0	0	
83D00043	11	0	0	
83D00054	11	0	0	
83D00069	16	0	0	
83D00075	10	0	0	
83D00078	17	0	0	
83D00080	11	0	0	
83D00097	11	0	0	

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - Vehicle Animals

Maternal ID	No.*	No.†	Variants		Anomalies	
			No. and Description of Each Variant	No.‡	No. and Description of Each Anomaly	
82D00682	4	0			0	
82D00691	8	1	1 Dilated brain ventricles		0	
82D00698	7	0			0	
82D00719	7	0			0	
82D00724	3	0			0	
82D00743	6	2	1 Dilated renal pelvis		0	
			1 Small kidney			
82D00751	5	2	1 Dilated renal pelvis		0	
			1 Small lens			
83D00001	4	0			0	
83D00019	9	4	1 Cerebral hemorrhage		0	
			3 Dilated renal pelvis			
83D00039	3	0			0	
83D00062	10	5	5 Small kidney		0	
83D00063	7	0			0	
83D00070	9	1	1 Dilated renal pelvis		0	
83D00076	8	0			0	
83D00082	7	5	5 Dilated renal pelvis		0	
83D00096	8	2	2 Cerebral hemorrhage		0	

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - 3.12 mg/kg/day MPP Animals

Maternal ID	Variants			Anomalies	
	No.*	No.†	No. and Description of Each Variant	No.‡	No. and Description of Each Anomaly
82D00681	7	1	1 Dilated renal pelvis	0	
82D00696	6	0		0	
82D00699	3	0		0	
82D00704	8	0		0	
82D00706	6	0		0	
82D00723	8	0		0	
82D00728	6	0		0	
82D00734	6	0		0	
82D00739	8	0		0	
82D00750	8	0		0	
82D00752	8	0		0	
83D00010	7	2	2 Dilated renal pelvis	0	
83D00016	7	0		0	
83D00020	9	0		0	
83D00024	8	0		0	
83D00042	8	0		0	
83D00044	7	1	1 Dilated renal pelvis	0	
83D00047	7	2	1 Dilated renal pelvis 1 Dilated renal pelvis 1 Small kidney	0	
83D00050	6	2	2 Dilated renal pelvis	0	
83D00059	8	1	1 Dilated renal pelvis	0	
83D00073	9	0		0	
83D00101	4	1	1 Dilated renal pelvis	0	

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - 1.25 mg/kg/day MPP Animals

Variants			Anomalies	
Maternal ID	No.*	No.†	No. and Description of Each Variant	No.§ No. and Description of Each Anomaly
82D00689	4	0		0
82D00697	8	0		0
82D00700	7	0		0
82D00710	6	5	5 Dilated renal pelvis	0
82D00715	8	0		0
82D00731	8	1	1 Small kidney	0
82D00735	2	0		0
82D00740	3	0		0
82D00745	6	0		0
82D00763	6	1	1 Small kidney	0
83D00003	7	0		0
83D00014	2	0		0
83D00031	2	1	1 Dilated renal pelvis	0
83D00032	8	0		0
83D00037	9	0		0
83D00056	5	1	1 Dilated renal pelvis	0
83D00060	7	0		0
83D00067	7	0		0
83D00077	8	2	1 Dilated renal pelvis 1 Microphthalmia	1 1 Cleft palate

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - 0.12 mg/kg/day MPP Animals

Maternal ID	Variants			Anomalies	
	No.*	No.†	No. and Description of Each Variant	No.‡	No. and Description of Each Anomaly
82D00693	7	1	1 Dilated renal pelvis	0	
82D00714	8	0		0	
82D00727	8	0		0	
82D00729	6	1	1 Dilated renal pelvis	0	
82D00746	5	2	2 Dilated renal pelvis	0	
82D00764	3	0		0	
83D00004	6	1	1 Dilated renal pelvis	0	
83D00011	6	1	1 Dilated renal pelvis	0	
83D00015	7	2	2 Cerebral hemorrhage	0	
			1 Dilated renal pelvis		
83D00023	6	1	1 Dilated renal pelvis	0	
83D00025	7	0		0	
83D00030	8	5	5 Dilated renal pelvis	0	
83D00034	8	0		0	
83D00038	6	0		0	
83D00043	5	0		0	
83D00054	5	2	2 Dilated renal pelvis	0	
83D00069	8	0		0	
83D00075	5	0		0	
83D00078	8	2	2 Dilated renal pelvis	0	
83D00080	7	1	1 Dilated renal pelvis	0	
83D00097	5	0		0	

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - Vehicle Animals

Variants			Anomalies	
Maternal ID	No.*	No.† No. and Description of Each Variant	No.§	No. and Description of Each Anomaly
82D00682	5	0	0	
82D00691	9	3 Incomplete ossification: 3 Cranium	0	
82D00698	7	0 1 Wavy ribs	0	
82D00703	1	1 Large orbit	1	1 Domed cranium 1 Short maxilla/long mandible
82D00719	8	0	0	
82D00724	3	0	0	
82D00743	6	5 Incomplete ossification: 5 Cranium	0	
82D00751	4	0	0	
83D00001	5	2 Incomplete ossification: 2 Cranium	0	
83D00019	9	2 1 Wavy ribs Incomplete ossification: 2 Vertebral centra	0	
83D00039	4	0	0	
83D00062	9	3 Incomplete ossification: 1 Cranium 3 Vertebral centra	0	

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - Vehicle Animals

Variants			Anomalies	
Maternal ID	No.*	No.† of Each Variant	No.‡ No. and Description of Each Anomaly	
83D00063	7	1	Incomplete ossification: 1 Cranium	0
83D00070	9	1	Incomplete ossification: 1 Vertebral centra	0
83D00076	9	0		0
83D00082	7	0		0
83D00096	8	3	Incomplete ossification: 2 Cranium 1 Vertebral centra	0

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 3.12 mg/kg/day MPP Animals

Variants			Anomalies	
Maternal ID	No.*	No.†	No. and Description of Each Variant	No.§ No. and Description of Each Anomaly
82D00681	7	1	1 Lumbar rib	0
82D00696	7	1	1 Lumbar rib	0
82D00699	4	0		0
82D00704	9	2	Incomplete ossification: 1 Vertebral centra 1 Lumbar rib	0
82D00706	6	1	Incomplete ossification: 1 Cranium	0
82D00723	8	3	Incomplete ossification: 1 Vertebral centra 1 Cranium	0
82D00728	6	1	2 Lumbar rib Incomplete ossification: 1 Vertebral centra	0
82D00734	6	0		0
82D00739	8	0		0
82D00750	8	4	Incomplete ossification: 2 Cranium 1 Vertebral centra 1 Lumbar rib	0
			1 Wavy ribs	
82D00752	8	3	Incomplete ossification: 3 Cranium 1 Wavy ribs	0

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 3.12 mg/kg/day MPP Animals

Maternal ID	No.*	No.†	Variants		Anomalies	
			No. and Description of Each Variant	No.‡	No. and Description of Each Anomaly	
83D00010	8	3	Incomplete ossification: 2 Cranium 1 Wavy ribs	0		
83D00016	7	0		0		
83D00020	9	3	Incomplete ossification: 3 Cranium	0		
83D00024	9	1	Incomplete ossification: 1 Cranium	0		
83D00042	8	0		0		
83D00044	7	0		0		
83D00047	7	1	Incomplete ossification: 1 Cranium	0		
83D00050	6	1	Incomplete ossification: 1 Vertebral centra	0		
83D00059	9	0		0		
83D00073	9	1	Incomplete ossification: 1 Cranium 1 Vertebral centra 1 Pelvis	0		
83D00101	5	2	Incomplete ossification: 2 Vertebral centra	0		

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 1.25 mg/kg/day MPP Animals

Maternal ID	Variants			Anomalies	
	No.*	No.†	No. and Description of Each Variant	No.§	No. and Description of Each Anomaly
82D00689	5	2	Incomplete ossification: 2 Vertebral centra	0	
82D00697	9	3	Incomplete ossification: 1 Cranium 1 Vertebral centra 1 Lumbar rib	0	
82D00700	8	0		0	
82D00710	7	2	Incomplete ossification: 1 Cranium 1 Lumbar rib	0	
82D00715	8	1	Incomplete ossification: 1 Vertebral centra	0	
82D00731	8	0		0	
82D00735	2	1	1 Lumbar rib	0	
82D00740	4	0		0	
82D00745	7	4	4 Lumbar rib	0	
82D00763	6	1	Incomplete ossification: 1 Cranium	0	
83D00003	7	0		0	
83D00014	3	1	Incomplete ossification: 1 Vertebral centra	0	

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 1.25 mg/kg/day MPP Animals

Variants			Anomalies	
Maternal ID	No.*	No.† No. and Description of Each Variant	No.§	No. and Description of Each Anomaly
83D00031	3	2 Incomplete ossification: 2 Vertebral centra	0	
83D00032	8	4 1 Lumbar rib Incomplete ossification: 3 Cranium 2 Vertebral centra	0	
83D00037	10	0	0	
83D00056	5	0	0	
83D00060	8	0	0	
83D00067	9	0	0	
83D00077	8	3 Incomplete ossification: 1 Vertebral centra 2 Pelvis	0	

* Number of fetuses examined.

† Number of fetuses with variants.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 0.12 mg/kg/day MPP Animals

Maternal ID	No.*	No.†	Variants		Anomalies	
			No. and Description of Each Variant	No.§	No. and Description of Each Anomaly	
82D00693	7	3	Incomplete ossification: 3 Vertebral centra	0		
82D00714	7	0		0		
82D00727	9	0		0		
82D00729	6	0		0		
82D00746	6	1	Incomplete ossification: 1 Vertebral centra	0		
82D00764	3	0		0		
83D00004	7	3	Incomplete ossification: 2 Cranium 1 Vertebral centra	0		
83D00011	7	2	Incomplete ossification: 2 Vertebral centra	0		
83D00015	8	2	Incomplete ossification: 2 Vertebral centra	0		
83D00023	6	0		0		
83D00025	8	0		0		
83D00030	9	0		0		

* Number of fetuses examined.

† Number of fetuses with variant.

§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 0.12 mg/kg/day MPP Animals

Maternal ID	Variants			No. and Description of Each Anomaly
	No.*	No.†	No.‡	
83D00034	9	2		Incomplete ossification: 2 Cranium 0
83D00038	7	2		Incomplete ossification: 2 Vertebral centra 0
83D00043	6	1		1 Short rib 0
83D00054	5‡	0		0 0
83D00069	8	4		Incomplete ossification: 4 Cranium 0
				Sternebrae: 1 Fewer than 3 ossified
83D00075	5	0		0
83D00078	9	0		0
83D00080	7	0		0
83D00097	6	0		0

* Number of fetuses examined.

† Number of fetuses with variants.

‡ Number of fetuses with anomalies.

§ One fetus lost during skeletal staining process.

Incidence of External, Visceral, and Skeletal Examination Findings - Vehicle Animals

Maternal ID	External			Visceral			Skeletal		
	Number Examined	Anomalies No.	Variants %	Number Examined	Anomalies No.	Variants %	Number Examined	Anomalies No.	Variants %
82D00682	9	0	0	0	0	0	5	0	0
82D00691	17	0	0	0	0	1 13	9	0	3 33
82D00698	14	0	0	0	0	0	7	0	0
82D00703	1	1 100	0	-	-	-	1	1 100	1 100
82D00719	15	0	0	0	0	0	8	0	0
82D00724	6	0	0	0	0	0	3	0	0
82D00743	12	0	0	0	0	2 33	6	0	5 83
82D00751	9	0	0	0	0	2 40	4	0	0
83D00001	9	0	0	0	0	0	5	0	2 40
83D00019	18	0	0	0	0	4 44	9	0	2 22
83D00039	7	0	0	0	0	0	4	0	0
83D00062	19	0	0	0	0	5 50	9	0	3 33
83D00063	14	0	0	0	0	0	7	0	1 14
83D00070	18	0	0	0	0	1 11	9	0	1 11
83D00076	17	0	0	0	0	0	9	0	0
83D00082	14	0	0	0	0	5 71	7	0	0
83D00096	16	0	0	0	0	2 25	8	0	3 38

Incidence of External, Visceral, and Skeletal Examination Findings - 3.12 mg/kg/day MPP Animals

Maternal ID	External			Visceral			Skeletal		
	Number Examined	Anomalies Variants		Number Examined	Anomalies Variants		Number Examined	Anomalies Variants	
		No.	%		No.	%		No.	%
82D00681	14	0	0	7	0	0	7	0	0
82D00696	13	0	0	6	0	0	7	0	0
82D00699	7	0	0	3	0	0	4	0	0
82D00704	17	0	0	8	0	0	9	0	0
82D00706	12	0	0	6	0	0	6	0	0
82D00723	16	0	0	8	0	0	8	0	0
82D00728	12	0	0	6	0	0	6	0	0
82D00734	12	0	0	6	0	0	6	0	0
82D00739	16	0	0	8	0	0	8	0	0
82D00750	16	0	0	8	0	0	8	0	0
82D00752	16	0	0	8	0	0	8	0	0
83D00010	15	0	0	7	0	0	8	0	0
83D00016	14	0	0	7	0	0	7	0	0
83D00020	18	0	0	9	0	0	9	0	0
83D00024	17	0	0	8	0	0	9	0	0
83D00042	16	0	0	8	0	0	8	0	0
83D00044	14	0	0	7	0	0	7	0	0
83D00047	14	0	0	7	0	0	7	0	0
83D00050	12	0	0	6	0	0	6	0	0
83D00059	17	0	0	8	0	0	9	0	0
83D00073	18	0	0	9	0	0	9	0	0
83D00101	9	0	0	4	0	0	5	0	0

Incidence of External, Visceral, and Skeletal Examination Findings - 1.25 mg/kg/day MPP Animals

Maternal ID	External			Visceral			Skeletal			
	Number Examined	Anomalies No. %	Variants No. %	Number Examined	Anomalies No. %	Variants No. %	Number Examined	Anomalies No. %	Variants No. %	
82D000689	9	0	0	4	0	0	5	0	2	40
82D000697	17	0	0	8	0	0	9	0	3	33
82D000700	15	0	0	7	0	0	8	0	0	0
82D000710	13	0	0	6	0	5	7	0	2	29
82D000715	16	0	0	8	0	0	8	0	1	13
82D000731	16	0	0	8	0	1	8	0	0	0
82D000735	4	0	0	2	0	0	2	0	1	50
82D000740	7	0	0	3	0	0	4	0	0	0
82D000745	13	0	0	6	0	0	7	0	4	57
82D000763	12	0	0	6	0	1	6	0	1	17
83D000003	14	0	0	7	0	0	7	0	0	0
83D000014	5	0	0	2	0	0	3	0	1	33
83D000031	5	0	0	2	0	1	3	0	2	66
83D000032	16	0	0	8	0	0	8	0	4	50
83D000037	19	0	0	9	0	0	10	0	0	0
83D000056	10	0	0	5	0	1	5	0	0	0
83D000060	15	0	0	7	0	0	8	0	0	0
83D000067	16	0	0	7	0	0	9	0	0	0
83D000077	16	1	6	8	1	13	8	0	3	38

Incidence of External, Visceral, and Skeletal Examination Findings - 0.12 mg/kg/day MPP Animals

Maternal ID	External			Visceral			Skeletal		
	Number Examined	Anomalies No.	Variants %	Number Examined	Anomalies No.	Variants %	Number Examined	Anomalies No.	Variants %
82D00693	14	0	0	0	0	0	7	0	3 43
82D00714	15	0	0	0	0	0	7	0	0 0
82D00727	17	0	0	0	0	0	9	0	0 0
82D00729	12	0	0	0	0	1 17	6	0	0 0
82D00746	11	0	0	0	0	2 40	6	0	1 17
82D00764	6	0	0	0	0	0 0	3	0	0 0
83D00004	13	0	0	0	0	1 17	7	0	3 43
83D00011	13	0	0	0	0	1 17	7	0	2 29
83D00015	15	0	0	0	0	2 29	8	0	2 25
83D00023	12	0	0	0	0	1 17	6	0	0 0
83D00025	15	0	0	0	0	0 0	8	0	0 0
83D00030	17	0	0	0	0	5 63	9	0	0 0
83D00034	17	0	0	0	0	0 0	9	0	2 22
83D00038	13	0	0	0	0	0 0	7	0	2 29
83D00043	11	0	0	0	0	0 0	6	0	1 17
83D00054	11	0	0	0	0	2 40	5*	0	0 0
83D00069	16	0	0	0	0	0 0	8	0	4 50
83D00075	10	0	0	0	0	0 0	5	0	0 0
83D00078	17	0	0	0	0	2 25	9	0	0 0
83D00080	14	0	0	0	0	1 14	7	0	0 0
83D00097	11	0	0	0	0	0 0	6	0	0 0

*One fetus lost during skeletal staining process.

Incidence of Anomalies and Variants
Vehicle Animals

Maternal ID	Number Examined	Anomalies		Variants	
		No.	%	No.	%
82D00682	9	0	0	0	0
82D00691	17	0	0	4	24
82D00698	14	0	0	0	0
82D00703	1	1	100	1	100
82D00719	15	0	0	0	0
82D00724	6	0	0	0	0
82D00743	12	0	0	7	58
82D00751	9	0	0	2	22
83D00001	9	0	0	2	22
83D00019	18	0	0	6	33
83D00039	7	0	0	0	0
83D00062	19	0	0	8	42
83D00063	14	0	0	1	7
83D00070	18	0	0	2	11
83D00076	17	0	0	0	0
83D00082	14	0	0	5	36
83D00096	16	0	0	5	31

Incidence of Anomalies and Variants
3.12 mg/kg/day MPP Animals

Maternal ID	Number Examined	Anomalies		Variants	
		No.	%	No.	%
82D00681	14	0	0	2	14
82D00696	13	0	0	1	8
82D00699	7	0	0	0	0
82D00704	17	0	0	2	12
82D00706	12	0	0	1	8
82D00723	16	0	0	3	19
82D00728	12	0	0	1	8
82D00734	12	0	0	0	0
82D00739	16	0	0	0	0
82D00750	16	0	0	5	31
82D00752	16	0	0	3	19
83D00010	15	0	0	5	33
83D00016	14	0	0	0	0
83D00020	18	0	0	3	17
83D00024	17	0	0	1	6
83D00042	16	0	0	0	0
83D00044	14	0	0	1	7
83D00047	14	0	0	3	21
83D00050	12	0	0	3	25
83D00059	17	0	0	1	6
83D00073	18	0	0	1	6
83D00101	9	0	0	3	33

Incidence of Anomalies and Variants
1.25 mg/kg/day MPP Animals

Maternal ID	Number Examined	Anomalies		Variants	
		No.	%	No.	%
82D00689	9	0	0	2	22
82D00697	17	0	0	3	18
82D00700	15	0	0	0	0
82D00710	13	0	0	7	54
82D00715	16	0	0	1	6
82D00731	16	0	0	1	6
82D00735	4	0	0	1	25
82D00740	7	0	0	0	0
82D00745	13	0	0	4	31
82D00763	12	0	0	2	17
83D00003	14	0	0	0	0
83D00014	5	0	0	1	20
83D00031	5	0	0	3	60
83D00032	16	0	0	4	25
83D00037	19	0	0	0	0
83D00056	10	0	0	1	10
83D00060	15	0	0	0	0
83D00067	16	0	0	0	0
83D00077	16	1	6	5	31

Incidence of Anomalies and Variants
0.12 mg/kg/day MPP Animals

Maternal ID	Number Examined	Anomalies		Variants	
		No.	%	No.	%
82D00693	14	0	0	4	29
82D00714	15	0	0	0	0
82D00727	17	0	0	0	0
82D00729	12	0	0	1	8
82D00746	11	0	0	3	27
82D00764	6	0	0	0	0
83D00004	13	0	0	4	31
83D00011	13	0	0	3	23
83D00015	15	0	0	4	27
83D00023	12	0	0	1	8
83D00025	15	0	0	0	0
83D00030	17	0	0	5	29
83D00034	17	0	0	2	12
83D00038	13	0	0	2	15
83D00043	11	0	0	1	9
83D00054	11*	0	0	2	18
83D00069	16	0	0	4	25
83D00075	10	0	0	0	0
83D00078	17	0	0	2	12
83D00080	14	0	0	1	7
83D00097	11	0	0	0	0

*One fetus lost during processing not
included in skeletal examination.

Fetal Ossification Data - Vehicle Animals

Maternal ID	No. Fetuses	Mean Number Ossified			
		Sternebrae	Caudal Vertebrae	Metacarpals	Metatarsals
82D00682	5	6.00	5.25	8.00	8.00
82D00691	9	5.78	3.56	6.44	7.78
82D00698	7	5.57	2.86	6.00	7.43
82D00703	1	6.00	4.00	8.00	8.00
82D00719	8	6.00	5.00	8.00	8.25
82D00724	3	6.00	6.67	8.00	10.00
82D00743	6	6.00	3.17	6.00	8.00
82D00751	4	4.75	3.25	6.00	8.00
83D00001	5	5.40	4.00	6.00	8.00
83D00019	9	5.22	3.00	6.44	8.00
83D00039	4	5.00	2.25	6.50	8.00
83D00062	9	4.89	2.33	6.00	8.00
83D00063	7	5.43	4.14	6.86	8.00
83D00070	9	4.89	3.00	6.00	8.00
83D00076	9	5.11	3.00	6.00	8.00
83D00082	7	5.14	3.43	6.00	7.86
83D00096	8	4.63	3.25	6.00	8.00

Fetal Ossification Data - 3.0 mg/kg/day MPP Animals

Maternal ID	No. Fetuses	Mean Number Ossified			
		Sternebrae	Caudal Vertebrae	Metacarpals	Metatarsals
82D000681	7	6.00	6.14	8.00	10.00
82D000696	7	5.57	3.14	6.57	8.00
82D000699	4	5.75	3.25	6.50	8.00
82D000704	9	6.00	3.33	6.89	8.00
82D000706	6	5.67	3.00	6.00	8.00
82D000723	8	5.88	3.38	7.00	8.00
82D000728	5	5.20	3.00	6.00	8.00
82D000734	6	6.00	6.67	8.00	9.67
82D000739	8	5.88	4.25	7.75	8.00
82D000750	8	5.50	3.38	6.25	8.00
82D000752	8	5.88	3.50	7.00	8.00
83D000010	8	5.00	3.12	6.00	8.00
83D000016	7	5.57	3.86	6.00	8.00
83D000020	9	4.89	4.00	6.00	8.00
83D000024	9	4.67	3.44	5.78	7.11
83D000042	8	5.00	3.00	6.00	7.50
83D000044	7	5.57	3.14	6.00	8.00
83D000047	7	5.14	3.00	6.00	8.00
83D000050	6	6.00	3.00	6.67	8.00
83D000059	9	5.78	3.56	6.00	8.00
83D000073	9	4.11	2.44	5.78	7.78
83D000101	5	4.80	1.80	6.00	8.00

Fetal Ossification Data - 1.25 mg/kg/day MPP Animals

Maternal ID	No. Fetuses	Mean Number Ossified			
		Sternebrae	Caudal Vertebrae	Metacarpals	Metatarsals
82D00639	5	5.80	3.80	6.00	8.00
82D00697	9	5.78	4.00	6.00	8.00
82D00700	8	6.00	4.88	8.00	9.75
82D00710	7	6.00	3.29	6.29	8.00
82D00715	8	6.00	3.13	6.00	8.00
82D00731	8	5.75	3.25	6.00	8.00
82D00735	2	6.00	3.50	8.00	8.00
82D00740	4	5.25	2.25	6.00	7.50
82D00745	7	6.00	6.29	8.00	10.00
82D00763	6	5.00	2.67	6.00	7.33
83D00003	7	4.86	3.29	6.00	8.00
83D00014	3	5.67	4.33	6.00	8.00
83D00031	3	5.33	3.00	7.33	8.00
83D00032	8	5.13	3.13	6.00	8.00
83D00037	10	5.60	3.40	6.00	8.00
83D00056	5	5.20	3.00	6.40	8.00
83D00060	8	5.13	3.25	6.00	8.00
83D00067	9	4.11	3.22	6.00	7.56
83D00077	8	5.00	3.00	6.25	8.00

Fetal Ossification Data 0.12 mg/kg/day NPP Animals

Maternal ID	No. Fetuses	Mean Number Ossified			
		Sternebrae	Caudal Vertebrae	Metacarpals	Metatarsals
82D000693	7	6.00	3.00	6.00	8.00
82D000714	7	6.00	6.14	8.00	10.00
82D000727	9	6.00	3.67	8.00	8.00
82D000729	6	5.50	3.00	6.00	8.00
82D000746	6	6.00	4.33	8.00	8.00
82D000764	3	6.00*	3.00	6.00	8.00
83D000004	7	5.00	6.00	6.00	8.00
83D000011	7	5.14	3.43	6.00	8.00
83D000015	8	4.38	3.00	6.25	8.00
83D000023	6	4.83	3.17	6.00	8.00
83D000025	8	5.38	3.88	6.50	8.00
83D000030	9	4.22	2.22	6.00	7.78
83D000034	9	4.22	2.44	5.56	7.78
83D000038	7	5.71	6.71	8.00	10.00
83D000043	6	5.67	2.17	6.67	8.00
83D000054	5	6.00	5.60	8.00	3.00
83D000069	8	4.00	3.13	5.63	8.00
83D000075	5	5.80	3.60	6.00	8.00
83D000078	9	4.11	2.00	6.00	8.00
83D000080	8	3.75	3.00	6.00	8.00
83D000097	6	5.33	4.17	7.33	8.00

*Sternebrae of 1 fetus damaged in processing not included in sternebrae litter mean.

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