Reproductive Parameters and Fetal Data from Reproductive Toxicity Studies in the Charles River Wistar Hannover [Crl:WI(Han)] Rat

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INTRODUCTION

This document reports data obtained using the Wistar Hannover rat, sometimes also called the Wistar Han or Han Wistar. It is important to distinguish between Wistar Hannover stocks and other Wistar stocks and strains, including the Wistar. When the term "Wistar rat" is used without modifier, it most often refers to an outbred stock distinct from the Wistar Hannover; the two terms are not synonymous.

A brief history of the Wistar and Wistar Hannover rats may be helpful. Outbred albino rats have been bred at the Wistar Institute since 1905 and were infused with additional rats from outside sources in 1918. From this early line of Wistar rats, animals were transferred to the UK in 1927. In 1964, Professor Rapp at the Hannover Institute received a small number of Wistar rats from the UK and began selective breeding for certain phenotypic characteristics. As a result, from their beginning the Hannover rats were selected to diverge from the progenitor Wistar stock. Thus, the Wistar Hannover has been bred as a distinct line divergent from the "regular" Wistar rats for more than 80 years, or more than 160 generations. As a result, the data presented in this document should be construed as representative only of Wistar Hannover rats, and not of Wistar rats in general. Additional information regarding the history of various stocks and strains of rats is available on the Charles River website (www.criver.com).

The data presented in this document were collected from control animals in 18 reproductive toxicity studies conducted between 1999 and 2008. The studies were conducted in Canada or the United States by contract laboratories or pharmaceutical toxicology facilities. All studies were conducted in accordance with the Standard Operating Procedures (SOPs) of the test facility and under the guidance of the facility's animal care and use committee. The majority of the studies mentioned were designed to support a research or marketing permit and were conducted in compliance with Good Laboratory Practice regulations, Fed. Reg., Vol. 43, 21 CFR Part 58, 22-Dec-1978, and all the subsequent amendments to these regulations. The majority of the studies were also performed according to the recommendations of the International Conference on Harmonization (ICH) guidelines on detection of toxicity to reproduction for medicinal products; availability; notice. Fed. Reg., Vol. 59, No. 183, 22-Sep-1994.

PURPOSE

The purpose of this document is two-fold: 1) to provide reference control data from developmental and reproductive toxicology studies conducted in the Charles River Wistar Hannover Crl:WI(Han) rat and 2) to establish a data foundation on which a much more comprehensive historical control database can be built.

COMMON STUDY PARAMETERS

All animals were obtained from Charles River in the United States and Canada. In some instances the test animals were received timed-pregnant and in others the rats were mated at the testing facility. Since all participating facilities conduct studies in compliance with current regulatory guidelines (see above), the studies included here can be assumed to meet or exceed those guidelines for animal handling, animal husbandry, and environmental conditions. The rats were fed an approved rodent diet and had free access to both food and

water. Feed and water were routinely analyzed for possible contaminants per facility SOPs. The animal rooms were generally maintained at 68-76° Fahrenheit with a relative humidity of 30-70%. A 12hr/12hr light/dark cycle was employed in all studies. Since these studies were conducted in different facilities over a period of several years, there was some variation in environmental conditions. The overall environmental conditions were not considered by those performing the studies to have had any effect on the quality or integrity of the studies.

TERMINOLOGY AND GENERAL INFORMATION

The tables presented in this document list reproductive parameters and fetal alterations (external gross, skeletal, and soft tissue). Only positive findings are presented. Since the data presented here were obtained from reproductive studies of differing protocol designs, all studies did not collect all parameters mentioned and, therefore, the "N" value for studies, fetuses, and litters may differ among tables. Information for some requested parameters was not provided by the testing facility and appears as "NA" or not available in the tables. Individual study data is generally reported to only one decimal point, as this is how it was received. Summary data is generally reported to two decimal points. The data is presented by individual study and is also summarized to show mean values, standard deviations, and minimum and maximum values for the various parameters. The terminology used in this document was established from the MARTA Glossary of terms (1993) distributed to the organization. Decisions to include, exclude, or combine findings were made by a panel of individuals all currently working in the field of reproductive toxicology and members of the Society of Toxicology or the Teratology Society.

ACKNOWLEDGEMENTS

Our special thanks to Joe Frank, the contributing laboratories, and the publication staff at Charles River, without whose help this publication would not have been possible.

REQUEST FOR DATA

This document is published to assist you, our clients, in evaluating your data. Our aim is to provide you with the data that you need to do your job well. This document is the first that we have compiled on reproductive parameters in the Charles River Wistar Hannover [Crl:WI(Han)] rat. Our hope is to expand this publication to include data from many more studies and information on postnatal development and male fertility. To this end, we invite you to participate in this project by sharing your control data. If you or someone in your laboratory is willing to participate, please contact Mary Giknis at mlagiknis@verizon.net.

Table 1: Summary of Individual Study Information

STUDY IDENTIFICATION	STRAIN IDENTIFICATION	GESTATIONAL DAY OF C-SECTION	DATE OF C-SECTION (MM/YYYY)
A	Crl:WI(Han)**	21	04/1999
B	Crl:WI(Han)**	20	09/1999
C	Crl:WI(Han)**	21	12/2003
D	Crl:WI(Han)**	20	01/2004
E	Crl:WI(Han)**	21	01/2004
F	Crl:WI(Han)**	20	01/2004
G	Crl:WI(Han)	21	10/2005
H	Crl:WI(Han)	21	12/2005
I	Crl:WI(Han)**	21	04/2006
J	Crl:WI(Han)**	21	01/2006
K	Crl:WI(Han)**	21	01/2007
L	Crl:WI(Han)**	21	01/2007
M	Crl:WI(Han)**	21	03/2007
N	Crl:WI(Han)**	21	09/2007
O	Crl:WI(Han)**	21	11/2007
P	Crl:WI(Han)**	21	12/2007
Q	Crl:WI(Han)**	21	12/2007
R	Crl:WI(Han)**	21	02/2008

** Crl:WI(Han) received, labeled with the old name of Wistar Han [CRL:WI(Glx/BRL/Han)IGS BR] at this facility

Table 2: Individual Study Reproductive Indices for All Studies Combined

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
# OF RATS TESTED	30	5	22	25	22	25	8	25	25	25	25	25	25	25	25	25	25	25
# OF RATS PREGNANT	25	5	22	24	20	22	8	24	25	23	19	22	24	25	22	24	22	23
% PREGNANT	83.3	100	100	96.0	90.9	88.0	100	96.0	100	92.0	76.0	88.0	96.0	100	88.0	96.0	88.0	92.0
# FOUND DEAD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
# ABORTED	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
# DELIVERED	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
# OF RATS PREGNANT AT																		
CAESAREAN-SECTIONING	23	5	22	22	20	22	8	24	25	23	19	22	24	25	22	24	22	21
# OF RATS WITH SINGLE																		
CONCEPTUS LITTER																		
LIVE:	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	1	0
RESORBED:	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
ABORTED:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CORPORA LUTEA																		
MEAN	12.6	10.6	13.0	14.3	12.7	13.7	13.5	12.8	11.2	11.1	12.0	10.7	11.7	11.8	11.3	11.6	11.3	13.5
S.D.	1.6	2.1	1.8	2.6	1.8	1.5	1.8	1.9	1.8	2.2	2.0	1.6	2.8	1.9	1.8	1.7	2.2	4.0
IMPLANTATIONS																		
MEAN	10.3	10.2	11.6	13.2	11.4	12.8	12.1	11.9	9.8	9.3	8.2	9.4	9.1	10.3	8.6	10.0	9.5	9.4
S.D.	2.4	1.9	2.0	2.8	1.9	1.4	1.6	2.0	2.2	3.3	3.4	2.8	2.6	2.2	3.5	2.4	2.8	2.8

Table 2: Individual Study Reproductive Indices for All Studies Combined

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
LITTER SIZES																		
LIVE CONCEPTUSES																		
(N)	230	47	246	261	222	265	90	272	237	197	149	196	210	237	179	226	201	184
MEAN	10.0	9.4	11.2	11.9	11.1	12.0	11.2	11.3	9.5	8.6	7.8	8.9	8.8	9.5	8.1	9.4	9.1	8.8
S.D.	2.6	1.5	1.9	3.3	1.9	1.6	1.8	2.0	2.3	3.5	3.4	2.8	2.5	2.4	3.6	2.4	2.8	3.1
DEAD CONCEPTUSES																		
(N)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
MEAN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.04
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TOTAL RESORPTIONS																		
(N)	8	4	10	29	5	17	7	14	7	16	7	10	9	21	11	15	7	13
MEAN	0.3	0.8	0.4	1.3	0.2	0.8	0.9	0.6	0.3	0.7	0.4	0.5	0.4	0.8	0.5	0.6	0.3	0.6
S.D.	0.6	0.8	0.8	1.6	0.4	0.8	1.1	1.2	0.5	0.9	0.6	0.7	0.6	1.0	0.7	0.8	0.8	0.7
EARLY RESORPTIONS																		
(N)	8	4	10	29	5	17	6	13	7	16	6	10	9	19	10	15	7	13
MEAN	0.3	0.8	0.4	1.3	0.2	0.8	0.8	0.5	0.3	0.7	0.3	0.5	0.4	0.8	0.5	0.6	0.3	0.6
S.D.	0.6	0.8	0.8	1.6	0.4	0.8	1.2	1.1	0.5	0.9	0.5	0.7	0.6	1.0	0.7	0.8	0.8	0.7
LATE RESORPTIONS																		
(N)	0	0	0	0	0	0	1	1	0	0	1	0	0	2	1	0	0	0
MEAN	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.2	0.0	0.0	0.2	0.0	0.0	0.3	0.2	0.0	0.0	0.0
DAMS WITH ANY RESORPTIONS																		
(N)	6	3	6	12	5	12	4	7	6	12	6	8	8	14	8	12	4	9
(%)	26.1	60.0	27.3	54.5	25.0	54.5	50.0	29.2	24.0	52.2	31.6	36.4	33.3	56.0	36.4	50.0	18.2	42.9

Table 2: Individual Study Reproductive Indices for All Studies Combined

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
DAMS WITH ALL																		
CONCEPTUSES RESORBED																		
(N)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
(%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4.5	0	0	4.8
DAMS WITH ONE OR MORE																		
LIVE FETUSES																		
(N)	23	5	22	22	20	22	8	24	25	23	19	22	24	25	21	24	22	20
(%)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	95.5	100	100	95.2
SEX RATIO (% MALES/LITTER)																		
MEAN	52.7	50.1	56.6	47.9	54.8	49.7	52.4	48.2	49.4	50.8	52.3	50.5	53.3	47.7	49.2	48.2	52.2	51.1
S.D.	16.6	14.1	16.3	13.3	13.7	16.8	18.4	14.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 3: Individual Study Reproductive Indices for All Studies with Gestational Day 20 C-Section

STUDY IDENTIFICATION	B	D	F
# OF RATS TESTED	5	25	25
# OF RATS PREGNANT	5	24	22
% PREGNANT	100.0	96.0	88.0
# FOUND DEAD	0	0	0
# ABORTED	0	0	0
# DELIVERED	0	1	0
# OF RATS PREGNANT AT			
CAESAREAN-SECTIONING	5	22	22
# OF RATS WITH SINGLE			
CONCEPTUS LITTER			
LIVE:	0	0	0
RESORBED:	0	0	0
ABORTED:	0	0	0
CORPORA LUTEA			
MEAN	10.6	14.3	13.7
S.D.	2.1	2.6	1.5
IMPLANTATIONS			
MEAN	10.2	13.2	12.8
S.D.	1.9	2.8	1.4

Table 3: Individual Study Reproductive Indices for All Studies with Gestational Day 20 C-Section

STUDY IDENTIFICATION	B	D	F
LITTER SIZES			
LIVE CONCEPTUSES			
(N)	47	261	265
MEAN	9.4	11.9	12.0
S.D.	1.5	3.3	1.6
DEAD CONCEPTUSES			
(N)	0	0	0
MEAN	0.0	0.0	0.0
S.D.	0.0	0.0	0.0
TOTAL RESORPTIONS			
(N)	4	29	17
MEAN	0.8	1.3	0.8
S.D.	0.8	1.6	0.8
EARLY RESORPTIONS			
(N)	4	29	17
MEAN	0.8	1.3	0.8
S.D.	0.8	1.6	0.8
LATE RESORPTIONS			
(N)	0	0	0
MEAN	0.0	0.0	0.0
S.D.	0.0	0.0	0.0
DAMS WITH ANY RESORPTIONS			
(N)	3	12	12
(%)	60.0	54.5	54.5

Table 3: Individual Study Reproductive Indices for All Studies with Gestational Day 20 C-Section

STUDY IDENTIFICATION	B	D	F
DAMS WITH ALL			
CONCEPTUSES RESORBED			
(N)	0	0	0
(%)	0.0	0.0	0.0
DAMS WITH ONE OR MORE			
LIVE FETUSES			
(N)	5	22	22
(%)	100.0	100.0	100.0
SEX RATIO (% MALES/LITTER)			
MEAN	50.1	47.9	49.7
S.D.	14.1	13.3	16.8

Table 4: Individual Study Reproductive Indices for All Studies with Gestational Day 21 C-Section

STUDY IDENTIFICATION	A	C	E	G	H	I	J	K	L	M	N	O	P	Q	R
# OF RATS TESTED	30	22	22	8	25	25	25	25	25	25	25	25	25	25	25
# OF RATS PREGNANT	25	22	20	8	24	25	23	19	22	24	25	22	24	22	23
% PREGNANT	83.3	100.0	90.9	100.0	96.0	100.0	92.0	76.0	88.0	96.0	100.0	88.0	96	88	92.0
# FOUND DEAD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
# ABORTED	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
# DELIVERED	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
# OF RATS PREGNANT AT															
CAESAREAN-SECTIONING	23	22	20	8	24	25	23	19	22	24	25	22	24	22	21
# OF RATS WITH SINGLE															
CONCEPTUS LITTER															
LIVE:	0	0	0	0	0	0	0	1	1	1	0	1	0	1	0
RESORBED:	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1
ABORTED:	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CORPORA LUTEA															
MEAN	12.6	13.0	12.7	13.5	12.8	11.2	11.1	12.0	10.7	11.7	11.8	11.3	11.6	11.3	13.5
S.D.	1.6	1.8	1.8	1.8	1.9	1.8	2.2	2.0	1.6	2.8	1.9	1.8	1.7	2.2	4.0
IMPLANTATIONS															
MEAN	10.3	11.6	11.4	12.1	11.9	9.8	9.3	8.2	9.4	9.1	10.3	8.6	10	9.5	9.4
S.D.	2.4	2.0	1.9	1.6	2.0	2.2	3.3	3.4	2.8	2.6	2.2	3.5	2.4	2.8	2.8

Table 4: Individual Study Reproductive Indices for All Studies with Gestational Day 21 C-Section

STUDY IDENTIFICATION	A	C	E	G	H	I	J	K	L	M	N	O	P	Q	R
LITTER SIZES															
LIVE CONCEPTUSES															
(N)	230	246	222	90	272	237	197	149	196	210	237	179	226	201	184
MEAN	10.0	11.2	11.1	11.2	11.3	9.5	8.6	7.8	8.9	8.8	9.5	8.1	9.4	9.1	8.8
S.D.	2.6	1.9	1.9	1.8	2.0	2.3	3.5	3.4	2.8	2.5	2.4	3.6	2.4	2.8	3.1
DEAD CONCEPTUSES															
(N)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
MEAN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.04
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TOTAL RESORPTIONS															
(N)	8	10	5	7	14	7	16	7	10	9	21	11	15	7	13
MEAN	0.3	0.4	0.2	0.9	0.6	0.3	0.7	0.4	0.5	0.4	0.8	0.5	0.6	0.3	0.6
S.D.	0.6	0.8	0.4	1.1	1.2	0.5	0.9	0.6	0.7	0.6	1.0	0.7	0.8	0.8	0.7
EARLY RESORPTIONS															
(N)	8	10	5	6	13	7	16	6	10	9	19	10	15	7	13
MEAN	0.3	0.4	0.2	0.8	0.5	0.3	0.7	0.3	0.5	0.4	0.8	0.5	0.6	0.3	0.6
S.D.	0.6	0.8	0.4	1.2	1.1	0.5	0.9	0.5	0.7	0.6	1.0	0.7	0.8	0.8	0.7
LATE RESORPTIONS															
(N)	0	0	0	1	1	0	0	1	0	0	2	1	0	0	0
MEAN	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0
S.D.	0.0	0.0	0.0	0.4	0.2	0.0	0.0	0.2	0.0	0.0	0.3	0.2	0.0	0.0	0.0
DAMS WITH ANY RESORPTIONS															
(N)	6	6	5	4	7	6	12	6	8	8	14	8	12	4	9
(%)	26.1	27.3	25.0	50.0	29.2	24.0	52.2	31.6	36.4	33.3	56.0	36.4	50.0	18.2	42.9

Table 4: Individual Study Reproductive Indices for All Studies with Gestational Day 21 C-Section

STUDY IDENTIFICATION	A	C	E	G	H	I	J	K	L	M	N	O	P	Q	R
DAMS WITH ALL															
CONCEPTUSES RESORBED															
(N)	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
(%)	0	0	0	0	0	0	0	0	0	0	0	4.5	0	0	4.8
DAMS WITH ONE OR MORE															
LIVE FETUSES															
(N)	23	22	20	8	24	25	23	19	22	24	25	21	24	22	20
(%)	100	100	100	100	100	100	100	100	100	100	100	95.5	100	100	95.2
SEX RATIO (% MALES/LITTER)															
MEAN	52.7	56.6	54.8	52.4	48.2	49.4	50.8	52.3	50.5	53.3	47.7	49.2	48.2	52.2	51.1
S.D.	16.6	16.3	13.7	18.4	14.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 5: Summary of Reproductive Indices for All Studies Combined

STUDY IDENTIFICATION	Mean	SD	Min	Max
# OF RATS TESTED	22.89	6.19	5	30
# OF RATS PREGNANT	21.06	5.57	5	25
% PREGNANT	92.79	6.73	76	100
# FOUND DEAD	0.00	0.00	0	0
# ABORTED	0.00	0.00	0	0
# DELIVERED	0.17	0.51	0	2
# OF RATS PREGNANT AT				
CAESAREAN-SECTIONING	20.72	5.43	5	25
# OF RATS WITH SINGLE				
CONCEPTUS LITTER				
LIVE:	0.28	0.46	0	1
RESORBED:	0.17	0.38	0	1
ABORTED:	0.00	0.00	0	0
CORPORA LUTEA				
MEAN	12.19	1.11	10.60	14.30
IMPLANTATIONS				
MEAN	10.39	1.45	8.20	13.20
LITTER SIZES				
LIVE CONCEPTUSES				
(N)	202.72	58.83	47	272
MEAN	9.81	1.31	7.80	12.00
DEAD CONCEPTUSES				
(N)	0.06	0.24	0	1
MEAN	0.00	0.01	0.00	0.04
TOTAL RESORPTIONS				
(N)	11.67	6.28	4	29
MEAN	0.58	0.27	0.20	1.30
EARLY RESORPTIONS				
(N)	11.33	6.20	4	29
MEAN	0.56	0.27	0.20	1.30
LATE RESORPTIONS				
(N)	0.33	0.59	0	2
MEAN	0.02	0.04	0.00	0.10

Table 5: Summary of Reproductive Indices for All Studies Combined

STUDY IDENTIFICATION	Mean	SD	Min	Max
DAMS WITH ANY RESORPTIONS				
(N)	7.89	3.29	3	14
(%)	39.31	13.27	18.20	60.00
DAMS WITH ALL				
CONCEPTUSES RESORBED				
(N)	0.11	0.32	0	1
(%)	0.52	1.50	0.00	4.80
DAMS WITH ONE OR MORE				
LIVE FETUSES				
(N)	20.61	5.42	5	25
(%)	99.48	1.50	95.20	100.00
SEX RATIO (% MALES/LITTER)				
MEAN	50.95	2.47	47.70	56.60

Table 6: Summary of Reproductive Indices for All Studies with Gestational Day 20 C-Section

STUDY IDENTIFICATION	Mean	SD	Min	Max
# OF RATS TESTED	18.33	11.55	5	25
# OF RATS PREGNANT	17.00	10.44	5	24
% PREGNANT	94.67	6.11	88.0	100.0
# FOUND DEAD	0.00	0.00	0	0
# ABORTED	0.00	0.00	0	0
# DELIVERED	0.33	0.58	0	1
# OF RATS PREGNANT AT				
CAESAREAN-SECTIONING	16.33	9.81	5	22
# OF RATS WITH SINGLE				
CONCEPTUS LITTER				
LIVE:	0.00	0.00	0	0
RESORBED:	0.00	0.00	0	0
ABORTED:	0.00	0.00	0	0
CORPORA LUTEA				
MEAN	12.87	1.99	10.60	14.30
IMPLANTATIONS				
MEAN	12.07	1.63	10.20	13.20
LITTER SIZES				
LIVE CONCEPTUSES				
(N)	191.00	124.72	47	265
MEAN	11.10	1.47	9.40	12.00
DEAD CONCEPTUSES				
(N)	0.00	0.00	0	0
MEAN	0.00	0.00	0.00	0.00
TOTAL RESORPTIONS				
(N)	16.67	12.50	4	29
MEAN	0.97	0.29	0.80	1.30
EARLY RESORPTIONS				
(N)	16.67	12.50	4	29
MEAN	0.97	0.29	0.80	1.30
LATE RESORPTIONS				
(N)	0.00	0.00	0	0
MEAN	0.00	0.00	0.00	0.00

Table 6: Summary of Reproductive Indices for All Studies with Gestational Day 20 C-Section

STUDY IDENTIFICATION	Mean	SD	Min	Max
DAMS WITH ANY RESORPTIONS				
(N)	9.00	5.20	3	12
(%)	56.33	3.18	54.50	60.00
DAMS WITH ALL				
CONCEPTUSES RESORBED				
(N)	0.00	0.00	0	0
(%)	0.00	0.00	0.00	0.00
DAMS WITH ONE OR MORE				
LIVE FETUSES				
(N)	16.33	9.81	5	22
(%)	100.00	0.00	100.00	100.00
SEX RATIO (% MALES/LITTER)				
MEAN	49.23	1.17	47.90	50.10

Table 7: Summary of Reproductive Indices for All Studies with Gestational Day 21 C-Section

STUDY IDENTIFICATION	Mean	SD	Min	Max
# OF RATS TESTED	23.80	4.71	8	30
# OF RATS PREGNANT	21.87	4.22	8	25
% PREGNANT	92.41	6.98	76.0	100.0
# FOUND DEAD	0.00	0.00	0	0
# ABORTED	0.00	0.00	0	0
# DELIVERED	0.13	0.52	0	2
# OF RATS PREGNANT AT				
CAESAREAN-SECTIONING	21.60	4.14	8	25
# OF RATS WITH SINGLE				
CONCEPTUS LITTER				
LIVE:	0.33	0.49	0	1
RESORBED:	0.20	0.41	0	1
ABORTED:	0.00	0.00	0	0
CORPORA LUTEA				
MEAN	12.05	0.90	10.70	13.50
IMPLANTATIONS				
MEAN	10.06	1.20	8.20	12.10
LITTER SIZES				
LIVE CONCEPTUSES				
(N)	205.07	44.11	90	272
MEAN	9.55	1.16	7.80	11.30
DEAD CONCEPTUSES				
(N)	0.07	0.26	0	1
MEAN	0.00	0.01	0.00	0.04
TOTAL RESORPTIONS				
(N)	10.67	4.37	5	21
MEAN	0.50	0.20	0.20	0.90
EARLY RESORPTIONS				
(N)	10.27	4.13	5	19
MEAN	0.48	0.19	0.20	0.80
LATE RESORPTIONS				
(N)	0.40	0.63	0	2
MEAN	0.02	0.04	0.00	0.10

Table 7: Summary of Reproductive Indices for All Studies with Gestational Day 21 C-Section

STUDY IDENTIFICATION	Mean	SD	Min	Max
DAMS WITH ANY RESORPTIONS				
(N)	7.67	2.99	4	14
(%)	35.90	11.74	18.20	56.00
DAMS WITH ALL				
CONCEPTUSES RESORBED				
(N)	0.13	0.35	0	1
(%)	0.62	1.64	0.00	4.80
DAMS WITH ONE OR MORE				
LIVE FETUSES				
(N)	21.47	4.16	8	25
(%)	99.38	1.64	95.20	100.00
SEX RATIO (% MALES/LITTER)				
MEAN	51.29	2.54	47.70	56.60

Table 8: Fetal Body Weight (Grams) by Individual Study - Gestational Day 20 C-Section

STUDY IDENTIFICATION	B	D	F
# OF RATS TESTED	5	25	25
LIVE FETAL BODY WEIGHTS			
MEAN	2.46	3.56	3.52
S.D.	0.30	0.35	0.20
MALE FETUSES			
MEAN	2.52	3.67	3.58
S.D.	0.35	0.40	0.23
FEMALE FETUSES			
MEAN	2.42	3.48	3.46
S.D.	0.28	0.31	0.22

Table 9: Fetal Body Weight (Grams) by Individual Study - Gestational Day 21 C-Section

STUDY IDENTIFICATION	A	C	E	G	H	I	J	K	L	M	N	O	P	Q	R
# OF RATS TESTED	30	22	22	8	25	25	25	25	25	25	25	25	25	25	25
LIVE FETAL BODY WEIGHTS															
MEAN	5.01	5.11	4.94	5.27	5.21	5.20	5.20	5.10	5.30	5.30	5.10	5.30	5.20	5.30	5.20
S.D.	0.29	0.23	0.27	0.31	0.23	0.30	0.40	0.50	0.20	0.40	0.30	0.40	0.30	0.30	0.40
MALE FETUSES															
MEAN	5.12	5.21	5.06	5.42	5.35	5.40	5.40	5.20	5.40	5.40	5.30	5.40	5.30	5.40	5.30
S.D.	0.33	0.24	0.32	0.36	0.27	0.30	0.40	0.50	0.20	0.40	0.40	0.40	0.30	0.30	0.40
FEMALE FETUSES															
MEAN	4.88	4.97	4.80	5.12	5.07	5.00	5.10	5.00	5.10	5.10	5.10	5.10	5.10	5.10	5.00
S.D.	0.25	0.23	0.30	0.25	0.23	0.30	0.50	0.40	0.20	0.40	0.30	0.40	0.40	0.30	0.40

Table 10: Summary of Fetal Body Weight (Grams) - Gestational Day 20 C-Section

STUDY IDENTIFICATION	Mean	SD	Min	Max
# OF RATS TESTED	18.33	11.55	5	25
LIVE FETAL BODY WEIGHTS				
(GESTATION DAY 20)				
GRAMS/LITTER				
MEAN	3.18	0.62	2.46	3.56
MALE FETUSES				
MEAN	3.26	0.64	2.52	3.67
FEMALE FETUSES				
MEAN	3.12	0.61	2.42	3.48

Table 11: Summary of Fetal Body Weight (Grams) - Gestational Day 21 C-Section

STUDY IDENTIFICATION	Mean	SD	Min	Max
# OF RATS TESTED	23.00	5.90	8	30
LIVE FETAL BODY WEIGHTS				
(GESTATION DAY 20)				
GRAMS/LITTER				
MEAN	5.20	0.12	4.94	5.33
MALE FETUSES				
MEAN	5.33	0.12	5.06	5.44
FEMALE FETUSES				
MEAN	5.05	0.10	4.80	5.22

Table 12: Fetal External Alterations: Individual Study Data*

STUDY IDENTIFICATION		F	H	J	K	M	N	O	P
LITTERS EVALUATED		22	24	23	19	24	25	21	24
FETUSES EVALUATED		265	272	197	149	210	237	179	226
FINDINGS									
AGNATHIA									
FETAL INCIDENCE	N	0	0	0	1	0	0	0	0
	%	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	1	0	0	0	0
	%	0.0	0.0	0.0	5.3	0.0	0.0	0.0	0.0
ASTOMIA									
FETAL INCIDENCE	N	0	0	0	1	0	0	0	0
	%	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	1	0	0	0	0
	%	0.0	0.0	0.0	5.3	0.0	0.0	0.0	0.0
ANENCEPHALY									
FETAL INCIDENCE	N	0	0	0	0	0	1	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	0	1	0	0
	%	0.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0
CLEFT PALATE									
FETAL INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
EARS MALPOSITIONED									
FETAL INCIDENCE	N	0	0	0	0	0	1	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	0	1	0	0
	%	0.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0
FOREPAW DIGIT MISSING									
FETAL INCIDENCE	N	1	0	0	0	0	0	0	0
	%	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	1	0	0	0	0	0	0	0
	%	4.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0

*Data on external alterations were provided for the eight studies presented here. The incidence, if any, of external alternations in other studies included in this document was not available.

Table 12: Fetal External Alterations: Individual Study Data*

STUDY IDENTIFICATION		F	H	J	K	M	N	O	P
GASTROSCHISIS									
FETAL INCIDENCE	N	0	0	0	0	1	0	0	0
	%	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	1	0	0	0
	%	0.0	0.0	0.0	0.0	4.2	0.0	0.0	0.0
LIMBS MALROTATED									
FETAL INCIDENCE	N	0	0	10	0	0	0	1	0
	%	0.0	0.0	5.1	0.0	0.0	0.0	0.6	0.0
LITTER INCIDENCE	N	0	0	5	0	0	0	1	0
	%	0.0	0.0	21.7	0.0	0.0	0.0	4.8	0.0
MENINGOCELE									
FETAL INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MICROGNATHIA									
FETAL INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OMPHALOCELE									
FETAL INCIDENCE	N	0	0	0	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4
LITTER INCIDENCE	N	0	0	0	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.2
TONGUE PROTRUDING									
FETAL INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
UMBILICAL HERNIA									
FETAL INCIDENCE	N	0	1	0	0	0	0	0	0
	%	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0
LITTER INCIDENCE	N	0	1	0	0	0	0	0	0
	%	0.0	4.2	0.0	0.0	0.0	0.0	0.0	0.0

*Data on external alterations were provided for the eight studies presented here. The incidence, if any, of external alternations in other studies included in this document was not available.

Table 12: Fetal External Alterations: Individual Study Data*

STUDY IDENTIFICATION		F	H	J	K	M	N	O	P
TOTAL FETAL EXTERNAL MALFORMATIONS									
FETAL INCIDENCE	N	1	1	10	1	1	1	1	1
	%	0.4	0.4	5.1	0.7	0.5	0.4	0.6	0.4
LITTER INCIDENCE	N	1	1	5	1	1	1	1	1
	%	4.5	4.2	21.7	5.3	4.2	4.0	4.8	4.2

*Data on external alterations were provided for the eight studies presented here. The incidence, if any, of external alternations in other studies included in this document was not available.

Table 13: Fetal Skeletal Alterations - Individual Study Data*

STUDY IDENTIFICATION		A	H
# LITTERS EXAMINED		24	24
# FETUSES EXAMINED		125	143
ALTERATION			
SKULL			
FRONTALS: INCOMPLETELY OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
PARIETALS: INCOMPLETELY OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
MANDIBLES: SHORT			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
PALATE: INCOMPLETELY OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
VERTEBRAE			
THORACIC: CENTRUM, BIFID			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0

* Data on fetal skeletal alterations were provided for the two studies presented here. The incidence, if any, of skeletal alterations in other studies included in this document was unavailable.

Table 13: Fetal Skeletal Alterations - Individual Study Data*

STUDY IDENTIFICATION		A	H
RIBS			
CERVICAL RIB(S) PRESENT			
FETAL INCIDENCE	N	7	5
	%	5.6	3.5
LITTER INCIDENCE	N	4	5
	%	16.7	20.8
ONE OR MORE, WAVY			
FETAL INCIDENCE	N	5	4
	%	4.0	2.8
LITTER INCIDENCE	N	4	3
	%	16.7	12.5
CLAVICULAE			
WAVY			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
STERNEBRAE			
ONE OR MORE INCOMPLETELY OSSIFIED OR NOT OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
PELVIS			
PUBES, INCOMPLETELY OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
PUBES, NOT OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0

* Data on fetal skeletal alterations were provided for the two studies presented here. The incidence, if any, of skeletal alterations in other studies included in this document was unavailable.

Table 13: Fetal Skeletal Alterations - Individual Study Data*

STUDY IDENTIFICATION		A	H
ISCHIA, INCOMPLETELY OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
ISCHIA, NOT OSSIFIED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
ILIA, IRREGULARLY SHAPED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
SCAPULAE			
SMALL AND IRREGULARLY SHAPED			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
HINDLIMB(S)			
FEMUR, FIBULA AND TIBIA, SHORT			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0

* Data on fetal skeletal alterations were provided for the two studies presented here. The incidence, if any, of skeletal alterations in other studies included in this document was unavailable.

Table 14: Fetal Soft Tissue Alterations - Individual Study Data*

STUDY IDENTIFICATION		A	H
# LITTERS EXAMINED		24	24
# FETUSES EXAMINED		108	129
ALTERATION			
EYE(S)			
RETINA FOLDED			
FETAL INCIDENCE	N	0	1
	%	0.0	0.8
LITTER INCIDENCE	N	0	1
	%	0.0	4.2
VESSELS			
UMBILICAL ARTERY, DESCENDS TO LEFT OF URINARY BLADDER			
FETAL INCIDENCE	N	7	3
	%	6.5	2.3
LITTER INCIDENCE	N	7	3
	%	29.2	12.5
KIDNEY(S)			
PELVIS, MODERATE DILATION			
FETAL INCIDENCE	N	0	0
	%	0.0	0.0
LITTER INCIDENCE	N	0	0
	%	0.0	0.0
INTESTINES			
PROTRUDE THROUGH UMBILICUS			
FETAL INCIDENCE	N	0	1
	%	0.0	0.8
LITTER INCIDENCE	N	0	1
	%	0.0	4.2

* Data on the fetal soft tissue alterations were provided for the two studies presented here. The incidence, if any, of soft tissue alterations in other studies included in this document was not available.

NOTES