

Reproductive and Juvenile Toxicology

Historical Control Data in Rats



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Contacts:

	Louise Pouliot, BSc, DESS Tox Director, Reproductive Toxicology Charles River Laboratories Montréal ULC
Tel:	514.630.2435
Fax:	514.630.8230
Email:	louise.pouliot@crl.com
	Keith J. Robinson, BSc, DABT Director Developmental and Juvenile Toxicology Charles River Laboratories Montréal ULC
Tel:	514.630.8204
Fax:	514.630.8230
Email:	keith.robinson@crl.com

¹ Additional HCD endpoints and years are available upon request.

HISTORICAL CONTROL DATA
RAT - CD® IGS (CrI:CD[SD]), 2006 - 2018@
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT		
GROUP PARENTAL PERFORMANCE++		
Parameter	Minimum*	Maximum*
COMBINATION OF GESTATION DAY 13 AND 20		
Mating Index (%)	73.9	100.0
Fertility Index (%)	62.5	100.0
Conception Rate (%)	75.0	100.0

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT			
GROUP UTERINE FINDINGS+			
Parameter	Average	Minimum*	Maximum*
GESTATION DAY 13 &			
Total Corpora Lutea / Rat	18.1	15.9	20.5
Total Implantation Site / Litter	16.6	14.3	18.9
Live Embryos / Litter	15.5	13.5	17.9
Dead Embryos / Litter	0.03	0.0	0.3
Early Resorptions / Litter	0.99	0.5	2.0
Combined Early Resorptions + Dead / Litter	1.02	0.5	2.0
Pre-Implantation Loss (%) / Litter	8.2	2.4	20.8
Post-Implantation Loss (%) / Litter	6.4	2.8	11.9
GESTATION DAY 20			
Total Corpora Lutea / Rat	18.2	16.9	19.4
Total Implantation Sites / Litter	16.3	15.0	17.1
Total Live Male Fetuses / Litter	7.7	6.6	8.4
Total Live Female Fetuses / Litter	7.5	6.2	8.3
Sex Ratio (% Males)	50.9	44.3	58.5
Total Live Fetuses / Litter	15.2	13.6	16.3
Dead Fetuses / Litter	0.00	0.0	0.0
Early Resorptions / Litter	0.98	0.5	1.4
Late Resorptions / Litter	0.02	0.0	0.1
Total Resorptions / Litter	1.02	0.5	1.4
Pre-Implantation Loss (%) / Litter	10.3	5.5	17.4
Post-Implantation Loss (%) / Litter	6.6	3.4	12.4

- * Study ranges, based on the group incidence, group percentage or group mean
 & Includes up to gestation day 15
 + Includes data from 84 studies
 ++ Includes data from 101 studies

@ The year (s) dosing was initiated on the studies

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FERTILITY AND EARLY EMBRYONIC DEVELOPMENT		
MALE REPRODUCTIVE ASSESSMENTS		
Parameter	Minimum*	Maximum*
ORGAN WEIGHTS +		
Left Testis (g)	1.690	2.058
Right Testis (g)	1.699	2.068
Left Epididymis (g)	0.549	0.780
Right Epididymis (g)	0.540	0.800
SPERM EVALUATION ++		
Cauda Epididymis Weight (g)	0.256	0.358
Cauda Spermatozoa Per Gram (Millions)	337.6	989.9
Cauda Motility (%)	60.3	75.6
Vas Deferens Motility (%)	60.3	90.6
CAUDA SPERMATOZOA MORPHOLOGY +++		
Abnormality (%)	2.5	14.2

* Study ranges, based on the group percentage or group mean

+ Includes data from 46 studies

++ Includes data from 32 studies

+++ Includes data from 29 studies

@ The year (s) dosing was initiated on the studies

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PRE AND POSTNATAL STUDIES		
GROUP MATERNAL PERFORMANCE +		
Parameter	Minimum*	Maximum*
Gestation Index (%)	88.9	100.0
Length of Gestation (Days)	21.3	22.0
Sex Ratio (% Males)	42.5	60.6
No. of Live Pups at Birth	11.3	16.4
No. of Dead Pups at Birth	0.0	1.0
No. of Implant Scars	12.6	17.2
Live Birth Index (%)	84.8	95.5

PRE AND POSTNATAL STUDIES		
VIABILITY (%) ++		
Parameter	Minimum*	Maximum*
Viability Index (%) - Day 4 Post Partum (Pre Cull)	91.1	100.0
Survival Index (%) - Day 7 Post Partum	95.5	100.0
Survival Index (%) - Day 14 Post Partum	94.9	100.0
Lactation Index (%) - Day 21 Post Partum	94.1	100.0

PRE AND POSTNATAL STUDIES		
SEXUAL MATURATION +++		
Parameter	Minimum*	Maximum*
Vaginal Opening (Days)	30.7	34.3
Preputial Separation (Days)	40.6	45.6

- * Study ranges, based on the group incidence, group percentage or group mean
+ Includes data from 36 studies
++ Includes data from 33 studies
+++ Includes data from 29 studies

@ The year (s) dosing was initiated on the studies

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PRE AND POSTNATAL STUDIES			
PUP BODY WEIGHTS (G) ++			
Parameter	Average	Minimum*	Maximum*
<u>Day 0 Post Partum Body Weights</u>			
Males	7.0	6.6	7.5
Females	6.6	6.2	7.1
Total	6.8	6.4	7.3
<u>Day 4 Post Partum Body Weights (Post Cull)</u>			
Males	11.5	10.3	12.6
Females	11.1	9.9	12.0
Total	11.3	10.1	12.3
<u>Day 7 Post Partum Body Weights</u>			
Males	18.5	15.8	20.0
Females	17.7	15.1	19.2
Total	18.1	15.4	19.6
<u>Day 14 Post Partum Body Weights</u>			
Males	36.9	28.7	40.6
Females	35.6	27.7	38.7
Total	36.3	28.2	39.6
<u>Day 21 Post Partum Body Weights</u>			
Males	60.7	48.7	66.2
Females	58.4	46.9	63.1
Total	59.5	47.8	64.4

* Study ranges, based on the group incidence, group percentage or group mean

++ Includes data from 37 studies

@ The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
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EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP MATERNAL FINDINGS			
Parameter	Total	Minimum*	Maximum*
No. of Rats Mated	1526	20	30
No. of Rats Pregnant	1483	18	30
No. of Rats Pregnant by Ammonium Sulfide Staining	1	0	1
No. of Rats Dying or Unscheduled Euthanasia on Study	2	0	1
No. of Rats with Total Resorption	1	0	1
No. of Rats Littering Prior to Scheduled Cesarean	1	0	1
Pregnancy Rate (%)	-	84.0	100.0

EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP OVARIAN AND UTERINE FINDINGS			
Parameter	Average	Minimum*	Maximum*
Total Corpora Lutea / Rat	15.7	13.9	20.1
Total Implantation Sites / Litter	13.9	11.6	17.6
Sex Ratio (% Males)	49.7	42.3	57.0
Total Live Fetuses / Litter	13.2	11.1	16.6
Dead Fetuses / Litter	0.002	0.0	0.1
Early Resorptions / Litter	0.69	0.2	1.4
Late Resorptions / Litter	0.02	0.0	0.3
Total Resorptions / Litter	0.72	0.0	1.5
Pre-Implantation Loss (%) / Litter	11.3	3.3	19.2
Post-Implantation Loss (%) / Litter	5.3	1.6	10.4

* Study ranges, based on the group incidence, group percentage or group mean

@ The year (s) dosing was initiated on the studies

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EMBRYO-FETAL DEVELOPMENT STUDIES			
FETAL WEIGHTS - SUMMARY DATA			
Parameter	Average	Minimum*	Maximum*
Fetal Weight (g) - Males	5.92	5.37	6.47
Fetal Weight (g) - Females	5.62	5.05	6.11
Fetal Weight (g) - Total	5.77	5.38	6.28

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) SKELETAL (SKE) TECHNIQUE OF WILSON (WT)	Litters examined		Total no. of studies/groups 69	
	1501			
	1501			
	1500			
		1501		
MALFORMATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Cleft palate/lip (EXT,WT)	2	0.13	0.00	4.76
Cranium: Exencephaly (EXT,WT,SKE)	1	0.07	0.00	4.17
Cranium: Meningoencephalocele (EXT,WT)	1	0.07	0.00	4.17
Brain: Hydrocephaly (EXT,WT)	2	0.13	0.00	4.55
Eye(s): Anophthalmia (EXT,WT)	2	0.13	0.00	4.55
Eye(s): Macrophthalmia (WT)	1	0.07	0.00	4.55
Eye(s): Microphthalmia (WT)	2	0.13	0.00	4.76
Eye(s): Open (EXT,WT)	1	0.07	0.00	4.17
Face: Aglossia (EXT,WT)	2	0.13	0.00	4.55
Face: Agnathia (EXT,WT)	2	0.13	0.00	4.55
Face: Astomia (EXT,WT)	1	0.07	0.00	4.55
Face: Maxillary micrognathia (EXT,WT)	1	0.07	0.00	4.17
Face: Mandibular micrognathia (EXT)	1	0.07	0.00	4.17
Nasopharyngeal Tract: Misshapen (WT)	1	0.07	0.00	4.00
Face: Nares small (EXT,WT)	1	0.07	0.00	4.55
Face: Palate; absent (WT)	1	0.07	0.00	4.55
Face: Split tongue (WT)	1	0.07	0.00	4.55
Heart: Ventricular septal defect (VIS)	3	0.20	0.00	5.00
Heart: Aortic arch, right-sided (VIS)	1	0.07	0.00	4.55
Heart: Transposition of major vessels (VIS)	2	0.13	0.00	4.55
Heart: Globular heart (VIS)	1	0.07	0.00	5.00
Heart: Ringed aorta (VIS)	1	0.07	0.00	4.76
Heart: Misshapen (VIS)	1	0.07	0.00	5.00
Heart: Truncus arterious, persistent (VIS)	1	0.07	0.00	4.76
Heart: Subclavian retroesophageal (VIS)	2	0.13	0.00	5.26
Vein: Posterior (caudal) vena cava, malpositioned (VIS)	1	0.07	0.00	5.26
Gonad: Ovary, absent (VIS)	1	0.07	0.00	5.56
Gonad: Uterus horn, absent (VIS)	1	0.07	0.00	5.56
Diaphragm: Diaphragmatic hernia (VIS)	1	0.07	0.00	4.76
Lungs: Lung lobes; absent (VIS)	3	0.20	0.00	5.00
Lungs: Lung lobes; fused (VIS)	4	0.27	0.00	5.00
Lungs: All lung lobes reduced/small (VIS)	2	0.13	0.00	4.76

* Study ranges, based on the group incidence

@ The year (s) dosing was initiated on the studies

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
MALFORMATIONS (CONT'D)	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Lungs and thymus: Lung lobe(s); supernumerary (VIS)	1	0.07	0.00	4.00
Vertebral column: Multiple fusions and variants in vertebral column (SKE)	1	0.07	0.00	4.76
Vertebral column: Caudal vertebra absent (SKE)	1	0.07	0.00	4.17
Vertebral column: Sacral vertebra Absent (SKE)	1	0.07	0.00	4.17
Thoracic: Situs inversus (VIS)	3	0.20	0.00	10.53
Liver: Liver lobe(s); absent (VIS)	1	0.07	0.00	4.76
Adrenal gland(s): Absent (VIS)	1	0.07	0.00	4.55
Trunk: Anus absent (Anal atresia) (EXT)	1	0.07	0.00	5.00
Trunk: Anus small (EXT)	1	0.07	0.00	4.00
Abdomen: Gastroschisis (EXT)	3	0.20	0.00	5.56
Abdomen: Situs inversus (VIS)	1	0.07	0.00	5.00
Abdomen: Omphalocele (EXT)	6	0.40	0.00	9.09
Abdomen: Abdominal muscles herniated (EXT)	1	0.07	0.00	4.17
Ribs: Multiple variants in ribs (SKE)	3	0.20	0.00	5.00
Tail: Absent (Acaudia) (EXT)	1	0.07	0.00	5.00
Tail: Microcaudia (EXT)	2	0.13	0.00	4.76
Tail: Tail thread-like (EXT)	1	0.07	0.00	4.00
Limb(s): Ectrodactyly (EXT)	2	0.13	0.00	4.76
Limb(s): Brachydactyly (EXT)	1	0.07	0.00	4.76
Limb(s): Abnormal flexure/hyperflexion of hindlimb(s) (EXT)	5	0.33	0.00	8.00
Limb(s): Abnormal flexure/hyperflexion of forelimb(s) (EXT)	1	0.07	0.00	5.00
Limb(s): Femur bent (SKE)	2	0.13	0.00	5.00
Limb(s): Fibula absent (SKE)	1	0.07	0.00	4.55
Limb(s): Radius bent (SKE)	1	0.07	0.00	5.00
Limb(s): Ulna bent (SKE)	1	0.07	0.00	5.00
Limb(s): Tibia misshapen (SKE)	1	0.07	0.00	4.55
General: Situs inversus (VIS)	7	0.47	0.00	10.53
Gross exam: Anasarca (EXT)	2	0.13	0.00	5.00
General: Conjoined twins (EXT,VIS,SKE)	1	0.07	0.00	4.55

* Study ranges, based on the group incidence

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) TECHNIQUE OF WILSON (WT)	Litters examined 1501 1501 1501		Total no. of studies/groups 69	
EXTERNAL AND VISCERAL VARIATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Moderate dilatation of olfactory bulb (WT)	1	0.07	0.00	4.55
Cranium: Moderate dilatation of the third ventricle (WT)	2	0.13	0.00	4.55
Cranium: Moderate dilatation of the lateral ventricles (WT)	2	0.13	0.00	4.55
Cranium: Subcutaneous edema (EXT)	2	0.13	0.00	4.55
Face: Protruding tongue (EXT)	1	0.07	0.00	4.17
Heart: Innominate artery absent (VIS)	1	0.07	0.00	5.26
Thorax: Subcutaneous edema (EXT)	1	0.07	0.00	4.55
Lungs: Lung lobe reduced/small (VIS)	1	0.07	0.00	5.00
Liver: Discoloration pale (VIS)	1	0.07	0.00	4.35
Liver: Vestigial lobe (VIS)	3	0.20	0.00	9.52
Spleen: Small (VIS)	2	0.13	0.00	4.76
Pancreas: Supernumerary (VIS)	1	0.07	0.00	4.00
Intestine: Short (VIS)	1	0.07	0.00	4.55
Stomach Cyst (VIS)	1	0.07	0.00	5.26
Kidney(s): Malpositioned (VIS)	1	0.07	0.00	4.55
Kidney(s): Small/reduction of renal papilla(e) (VIS)	16	1.07	0.00	9.52
Kidney(s): Reduced (VIS)	1	0.07	0.00	4.55
Ureter(s): Convoluted (VIS)	3	0.20	0.00	14.29
Ureter(s): Dilation (VIS)	77	5.13	0.00	23.53
Ureter(s): Megaureter (VIS)	10	0.67	0.00	5.88
Adrenal gland(s): Hemorrhage (VIS)	1	0.07	0.00	4.76
Testes: Malpositioned (VIS)	1	0.07	0.00	4.76
Tail: Kinked (EXT)	5	0.33	0.00	4.76

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL (SKE)	Litters examined 1500	Total no. of studies/groups 69		
SKELETAL VARIATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Frontal bone(s): Incomplete ossification	35	2.33	0.00	16.67
Parietal bone(s): Incomplete ossification	267	17.80	0.00	52.38
Parietal: Unossified line	1	0.07	0.00	5.26
Supraoccipital bone: Incomplete ossification	91	6.07	0.00	28.57
Interparietal bones: Increased ossification	1	0.07	0.00	5.00
Interparietal: Unossified line	2	0.13	0.00	4.76
Interparietal bone: Incomplete ossification	801	53.40	9.09	80.95
[Interparietal bone: Reduced ossification]	1	0.07	0.00	4.00
Interparietal bone: Misshapen	1	0.07	0.00	4.55
Hyoid bone: Unossified	56	3.73	0.00	22.73
Hyoid bone: Incomplete ossification/bipartite	647	43.13	4.00	86.36
Extra suture(s) in frontal/parietal/interparietal bone(s)	1	0.07	0.00	4.76
Nasal bone(s): Incomplete ossification	4	0.27	0.00	5.26
Maxilla: Incomplete ossification	1	0.07	0.00	4.55
Premaxilla: Incomplete ossification	20	1.33	0.00	42.86
Zygomatic bone(s): Incomplete ossification	31	2.07	0.00	44.00
VERTEBRAL COLUMN				
Cervical vertebral arch(es): Ossification center	4	0.27	0.00	5.88
Cervical vertebral arch(es): Fused	2	0.13	0.00	4.55
Cervical vertebral arch(es): Incomplete ossification	1	0.07	0.00	4.17
Cervical vertebral arch(es): Absent	2	0.13	0.00	8.33
Cervical vertebra(e): Absent	1	0.07	0.00	4.76
Cervical vertebra(e) arches: Misaligned	1	0.07	0.00	4.76
Cervical 7th and thoracic 1st vertebral arch(es): Fused	1	0.07	0.00	4.17
Extra pre-sacral vertebra(e)	7	0.47	0.00	5.00
25 pre-sacral vertebrae	10	0.67	0.00	9.52
Lumbar centrum: Bipartite	1	0.07	0.00	5.56
Lumbar centrum: Semi-bipartite/dumbbell	17	1.13	0.00	5.88
Lumbar centrum: Fused	1	0.07	0.00	4.76
Lumbar vertebral arch(es): Ossification center	101	6.73	0.00	62.50

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL VARIATIONS (CONT'D)	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN (CON'T)				
Lumbar arch , misshapen	1	0.07	0.00	5.26
Lumbar vertebral arch(es): Irregular/incomplete ossification	3	0.20	0.00	5.56
Lumbar vertebral arch(es): Fused	1	0.07	0.00	4.55
Ossification center on 1st lumbar vertebra or 14th thoracic vertebra	447	29.80	0.00	81.82
Ossification center on 4th lumbar vertebra	1	0.07	0.00	4.55
Sacral centrum: Unossified	1	0.07	0.00	4.76
Sacral centrum: Incomplete ossification	1	0.07	0.00	4.76
Sacral vertebra(e): Reduced no.	1	0.07	0.00	4.76
Sacral vertebral arch(es): Absent	1	0.07	0.00	4.76
Sacral vertebral arch(es): Incomplete ossification	2	0.13	0.00	4.76
Sacral vertebral centrum: Bipartite	1	0.07	0.00	5.56
Caudal vertebra(e): Reduced no.	3	0.20	0.00	4.76
Caudal vertebra(e): Bipartite	2	0.13	0.00	5.00
Caudal vertebra(e): Misaligned	1	0.07	0.00	5.00
Thoracic centrum: Misaligned	2	0.13	0.00	4.76
Thoracic vertebral centrum: Bipartite	18	1.20	0.00	15.79
Thoracic vertebral centrum: Semi-bipartite/dumbbell	270	18.00	0.00	95.83
Thoracic vertebral centrum: Incomplete ossification	10	0.67	0.00	14.29
Thoracic vertebral arch(es): Ossification center	3	0.20	0.00	4.76
Thoracic vertebral centrum: Displaced	2	0.13	0.00	4.55
Thoracic vertebral centrum: Fused	2	0.13	0.00	4.55
Thoracic vertebral arch(es): Fused	2	0.13	0.00	4.55
Thoracic vertebral arch(es): Absent	3	0.20	0.00	4.76
Thoracic vertebral arch(es): Incomplete ossification	1	0.07	0.00	4.35
STERNEBRAL COLUMN				
Sternebra(e): Incomplete ossification	71	4.73	0.00	42.86
Sternebra(e): Misshapen	6	0.40	0.00	14.29
Sternebra(e): Unossified	9	0.60	0.00	13.64
Sternebra(e): Bipartite	2	0.13	0.00	4.55
Sternebra(e): Semi-bipartite/dumbbell	2	0.13	0.00	5.88
Extra	6	0.40	0.00	8.00
Fused	4	0.27	0.00	5.00
Misaligned	3	0.20	0.00	5.00
CLAVICLE				
Misshapen/irregular	1	0.07	0.00	5.00

* Study ranges, based on the group incidence

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL VARIATIONS (CONT'D)	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
SCAPULA				
Bent	1	0.07	0.00	5.00
Short	1	0.07	0.00	4.55
RIBS				
Absent	3	0.20	0.00	5.00
Fused	4	0.27	0.00	4.55
Reduced	1	0.07	0.00	4.55
Nodule(s)	17	1.13	0.00	13.64
Supernumerary rib: Thoracolumbar, Short (Rudimentary 14th rib)	90	6.00	0.00	36.36
Supernumerary rib: Thoracolumbar, extra (full)	10	0.67	0.00	8.70
Supernumerary rib: Cervical, short	1	0.07	0.00	5.56
Wavy	21	1.40	0.00	9.52
Cervical	1	0.07	0.00	4.17
Ossification center(s) on 7th cervical vertebra(e)	49	3.27	0.00	18.18
Ossification center(s) on 5th cervical vertebra(e)	1	0.07	0.00	4.17
Rib(s) on 7th cervical vertebra(e)	14	0.93	0.00	12.00
Rib(s): Incomplete ossification	56	3.73	0.00	23.81
Rib(s): Irregular ossification	1	0.07	0.00	5.56
Rib fused with vertebral arch	1	0.07	0.00	5.56
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	7	0.47	0.00	5.26
Ischial bone(s): Incomplete ossification	6	0.40	0.00	5.26
Iliac bone(s): Misshapen	1	0.07	0.00	5.26
LIMBS				
Hindlimb: Tarsal bone, Increased ossification	34	2.27	0.00	35.29
Forelimb: Metacarpal bones, absent	2	0.13	0.00	5.00
Forelimb: Metacarpal bones, unossified	1	0.07	0.00	4.00
Reduced no. of phalange(s) in forepaw(s)	20	1.33	0.00	28.00
Reduced no. of phalange(s) in hindpaw(s)	1	0.07	0.00	4.55
Femur: Incomplete ossification	123	8.20	0.00	57.14
Humerus: Incomplete ossification	2	0.13	0.00	4.35

* Study ranges, based on the group incidence

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ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT)	Fetuses examined Total no. of studies/groups			
VISCERAL (VIS)				
SKELETAL (SKE)				
TECHNIQUE OF WILSON (WT)				
MALFORMATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Cleft palate/lip (EXT,WT)	2	0.01	0.00	0.36
Cranium: Exencephaly (EXT,WT,SKE)	1	0.01	0.00	0.32
Cranium: Meningoencephalocele (EXT,WT)	1	0.01	0.00	0.32
Brain: Hydrocephaly (EXT,WT)	2	0.01	0.00	0.35
Eye(s): Anophthalmia (EXT,WT)	2	0.01	0.00	0.35
Eye(s): Macrophthalmia (WT)	1	0.01	0.00	0.70
Eye(s): Microphthalmia (WT)	2	0.02	0.00	0.66
Eye(s): Open (EXT,WT)	1	0.01	0.00	0.32
Face: Aglossia (EXT,WT)	2	0.01	0.00	0.34
Face: Agnathia (EXT,WT)	2	0.01	0.00	0.34
Face: Astomia (EXT,WT)	1	0.01	0.00	0.34
Face: Maxillary micrognathia (EXT,WT)	1	0.01	0.00	0.32
Face: Mandibular micrognathia (EXT)	1	0.01	0.00	0.32
Nasopharyngeal Tract: Misshapen (WT)	1	0.01	0.00	0.63
Face: Nares small (EXT,WT)	1	0.01	0.00	0.34
Face: Palate; absent (WT)	1	0.01	0.00	0.68
Face: Split tongue (WT)	1	0.01	0.00	0.61
Heart: Ventricular septal defect (VIS)	3	0.03	0.00	0.74
Heart: Aortic arch, right-sided (VIS)	1	0.01	0.00	0.76
Heart: Transposition of major vessels (VIS)	2	0.02	0.00	0.76
Heart: Globular heart (VIS)	1	0.01	0.00	0.61
Heart: Ringed aorta (VIS)	1	0.01	0.00	0.69
Heart: Misshapen (VIS)	1	0.01	0.00	0.74
Heart: Truncus arterious, persistent (VIS)	1	0.01	0.00	0.66
Heart: Subclavian retroesophageal (VIS)	2	0.02	0.00	0.85
Vein: Posterior (caudal) vena cava, malpositioned (VIS)	1	0.01	0.00	0.79
Gonad: Ovary, absent (VIS)	1	0.01	0.00	0.87
Gonad: Uterus horn, absent (VIS)	1	0.01	0.00	0.87
Diaphragm: Diaphragmatic hernia (VIS)	1	0.01	0.00	0.74
Lungs: Lung lobes; absent (VIS)	3	0.03	0.00	0.74
Lungs: Lung lobes; fused (VIS)	4	0.04	0.00	0.74
Lungs: All lung lobes reduced/small (VIS)	2	0.02	0.00	0.74
Lungs and thymus: Lung lobe(s); supernumerary (VIS)	1	0.01	0.00	0.56

* Study ranges, based on the group incidence

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
MALFORMATIONS (CONT'D)	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Vertebral column: Multiple fusions and variants in vertebral column (SKE)	1	0.01	0.00	0.72
Vertebral column: Caudal vertebra absent (SKE)	1	0.01	0.00	0.60
Vertebral column: Sacral vertebra Absent (SKE)	1	0.01	0.00	0.60
Thoracic: Situs inversus (VIS)	3	0.03	0.00	1.64
Liver: Liver lobe(s); absent (VIS)	1	0.01	0.00	0.74
Adrenal gland(s): Absent (VIS)	1	0.01	0.00	0.68
Trunk: Anus absent (Anal atresia) (EXT)	1	0.01	0.00	0.37
Trunk: Anus small (EXT)	1	0.01	0.00	0.31
Abdomen: Gastroschisis (EXT)	3	0.02	0.00	0.45
Abdomen: Situs inversus (VIS)	1	0.01	0.00	0.73
Abdomen: Omphalocele (EXT)	6	0.03	0.00	0.68
Abdomen: Abdominal muscles herniated (EXT)	1	0.01	0.00	0.31
Ribs: Multiple variants in ribs (SKE)	4	0.04	0.00	1.43
Tail: Absent (Acaudia) (EXT)	1	0.01	0.00	0.37
Tail: Microcaudia (EXT)	2	0.01	0.00	0.37
Tail: Tail thread-like (EXT)	1	0.01	0.00	0.31
Limb(s): Ectrodactyly (EXT)	2	0.01	0.00	0.37
Limb(s): Brachydactyly (EXT)	1	0.01	0.00	0.37
Limb(s): Abnormal flexure/hyperflexion of hindlimb(s) (EXT)	5	0.03	0.00	0.64
Limb(s): Abnormal flexure/hyperflexion of forelimb(s) (EXT)	2	0.01	0.00	0.78
Limb(s): Femur bent (SKE)	3	0.03	0.00	1.55
Limb(s): Fibula absent (SKE)	1	0.01	0.00	0.69
Limb(s): Radius bent (SKE)	2	0.02	0.00	1.55
Limb(s): Ulna bent (SKE)	2	0.02	0.00	1.55
Limb(s): Tibia misshapen (SKE)	1	0.01	0.00	0.69
General: Situs inversus (VIS)	7	0.07	0.00	1.64
Gross exam: Anasarca (EXT)	2	0.01	0.00	0.35
General: Conjoined twins (EXT,VIS,SKE)	1	0.01	0.00	0.34

* Study ranges, based on the group incidence

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) TECHNIQUE OF WILSON (WT)	Fetuses examined Total no. of studies/groups 19814 69 9912 9911			
EXTERNAL AND VISCERAL VARIATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Moderate dilatation of olfactory bulb (WT)	1	0.01	0.00	0.70
Cranium: Moderate dilatation of the third ventricle (WT)	2	0.02	0.00	0.70
Cranium: Moderate dilatation of the lateral ventricles (WT)	2	0.02	0.00	0.64
Cranium: Subcutaneous edema (EXT)	2	0.01	0.00	0.33
Face: Protruding tongue (EXT)	1	0.01	0.00	0.32
Heart: Innominate artery absent (VIS)	1	0.01	0.00	0.85
Thorax: Subcutaneous edema (EXT)	1	0.01	0.00	0.33
Lungs: Lung lobe reduced/small (VIS)	1	0.01	0.00	0.74
Liver: Discoloration pale (VIS)	1	0.01	0.00	0.67
Liver: Vestigial lobe (VIS)	3	0.03	0.00	1.29
Spleen: Small (VIS)	2	0.02	0.00	0.74
Pancreas: Supernumerary (VIS)	1	0.01	0.00	0.63
Intestine: Short (VIS)	1	0.01	0.00	0.68
Stomach Cyst (VIS)	1	0.01	0.00	0.82
Kidney(s): Malpositioned (VIS)	1	0.01	0.00	0.68
Kidney(s): Small/reduction of renal papilla(e) (VIS)	18	0.18	0.00	1.94
Kidney(s): Reduced (VIS)	1	0.01	0.00	0.68
Ureter(s): Convoluted (VIS)	4	0.04	0.00	2.58
Ureter(s): Dilation (VIS)	94	0.95	0.00	4.24
Ureter(s): Megaureter (VIS)	10	0.10	0.00	0.87
Adrenal gland(s): Hemorrhage (VIS)	1	0.01	0.00	0.69
Testes: Malpositioned (VIS)	1	0.01	0.00	0.69
Tail: Kinked (EXT)	5	0.03	0.00	0.36

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL (SKE)	Fetuses examined 9921		Total no. of studies/groups 69	
SKELETAL VARIATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Frontal bone(s): Incomplete ossification	39	0.39	0.00	2.68
Parietal bone(s): Incomplete ossification	419	4.22	0.00	18.57
Parietal: Unossified line	1	0.01	0.00	0.80
Supraoccipital bone: Incomplete ossification	120	1.21	0.00	6.76
Interparietal bones: Increased ossification	1	0.01	0.00	0.76
Interparietal: Unossified line	2	0.02	0.00	0.63
Interparietal bone: Incomplete ossification	1802	18.16	2.27	44.29
[Interparietal bone: Reduced ossification]	1	0.01	0.00	0.56
Interparietal bone: Misshapen	1	0.01	0.00	0.67
Hyoid bone: Unossified	73	0.74	0.00	5.26
Hyoid bone: Incomplete ossification/bipartite	1247	12.57	0.67	32.14
Extra suture(s) in frontal/parietal/interparietal bone(s)	1	0.01	0.00	0.71
Nasal bone(s): Incomplete ossification	5	0.05	0.00	1.08
Maxilla: Incomplete ossification	1	0.01	0.00	0.67
Premaxilla: Incomplete ossification	29	0.29	0.00	11.51
Zygomatic bone(s): Incomplete ossification	48	0.48	0.00	11.61
VERTEBRAL COLUMN				
Cervical vertebral arch(es): Ossification center	4	0.04	0.00	0.81
Cervical vertebral arch(es): Fused	2	0.02	0.00	0.69
Cervical vertebral arch(es): Incomplete ossification	1	0.01	0.00	0.63
Cervical vertebral arch(es): Absent	2	0.02	0.00	1.27
Cervical vertebra(e): Absent	1	0.01	0.00	0.72
Cervical vertebra(e) arches: Misaligned	1	0.01	0.00	0.72
Cervical 7th and thoracic 1st vertebral arch(es): Fused	1	0.01	0.00	0.63
Extra pre-sacral vertebra(e)	7	0.07	0.00	0.79
25 pre-sacral vertebrae	14	0.14	0.00	3.57
Lumbar centrum: Bipartite	1	0.01	0.00	0.90
Lumbar centrum: Semi-bipartite/dumbbell	18	0.18	0.00	0.84
Lumbar centrum: Fused	1	0.01	0.00	0.72
Lumbar vertebral arch(es): Ossification center	178	1.79	0.00	16.27

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL VARIATIONS (CONT'D)	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN (CONT'D)				
Lumbar arch , misshapen	1	0.01	0.00	0.80
Lumbar vertebral arch(es): Irregular/incomplete ossification	3	0.03	0.00	0.92
Lumbar vertebral arch(es): Fused	1	0.01	0.00	0.69
Ossification center on 1st lumbar vertebra or 14th thoracic vertebra	805	8.11	0.00	34.48
Ossification center on 4th lumbar vertebra	1	0.01	0.00	0.72
Sacral centrum: Unossified	1	0.01	0.00	0.72
Sacral centrum: Incomplete ossification	1	0.01	0.00	0.72
Sacral vertebra(e): Reduced no.	1	0.01	0.00	0.68
Sacral vertebral arch(es): Absent	1	0.01	0.00	0.72
Sacral vertebral arch(es): Incomplete ossification	2	0.02	0.00	0.72
Sacral vertebral centrum: Bipartite	1	0.01	0.00	0.90
Caudal vertebra(e): Reduced no.	3	0.03	0.00	0.72
Caudal vertebra(e): Bipartite	2	0.02	0.00	0.75
Caudal vertebra(e): Misaligned	1	0.01	0.00	0.78
Thoracic centrum: Misaligned	2	0.02	0.00	0.72
Thoracic vertebral centrum: Bipartite	21	0.21	0.00	2.96
Thoracic vertebral centrum: Semi-bipartite/dumbbell	761	7.67	0.00	45.16
Thoracic vertebral centrum: Incomplete ossification	10	0.10	0.00	2.07
Thoracic vertebral arch(es): Ossification center	3	0.03	0.00	0.65
Thoracic vertebral centrum: Displaced	2	0.02	0.00	0.69
Thoracic vertebral centrum: Fused	2	0.02	0.00	0.69
Thoracic vertebral arch(es): Fused	2	0.02	0.00	0.69
Thoracic vertebral arch(es): Absent	3	0.03	0.00	0.69
Thoracic vertebral arch(es): Incomplete ossification	1	0.01	0.00	0.68
STERNEBRAL COLUMN				
Sternebra(e): Incomplete ossification	92	0.93	0.00	12.21
Sternebra(e): Misshapen	6	0.06	0.00	1.96
Sternebra(e): Unossified	13	0.13	0.00	2.27
Sternebra(e): Bipartite	2	0.02	0.00	0.76
Sternebra(e): Semi-bipartite/dumbbell	2	0.02	0.00	0.81
Extra	6	0.06	0.00	1.08
Fused	4	0.04	0.00	0.78
Misaligned	3	0.03	0.00	0.78
CLAVICLE				
Misshapen/irregular	2	0.02	0.00	1.55

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL VARIATIONS (CONT'D)	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
SCAPULA				
Bent	2	0.02	0.00	1.55
Short	1	0.01	0.00	0.69
RIBS				
Absent	3	0.03	0.00	0.78
Fused	4	0.04	0.00	0.76
Reduced	1	0.01	0.00	0.69
Nodule(s)	18	0.18	0.00	2.76
Supernumerary rib: Thoracolumbar, Short (Rudimentary 14th rib)	108	1.09	0.00	7.80
Supernumerary rib: Thoracolumbar, extra (full)	10	0.10	0.00	1.36
Supernumerary rib: Cervical, short	1	0.01	0.00	0.92
Wavy	28	0.28	0.00	2.76
Cervical	1	0.01	0.00	0.60
Ossification center(s) on 7th cervical vertebra(e)	53	0.53	0.00	3.36
Ossification center(s) on 5th cervical vertebra(e)	1	0.01	0.00	0.63
Rib(s) on 7th cervical vertebra(e)	14	0.14	0.00	1.61
Rib(s): Incomplete ossification	79	0.80	0.00	7.44
Rib(s): Irregular ossification	1	0.01	0.00	0.90
Rib fused with vertebral arch	1	0.01	0.00	0.90
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	10	0.10	0.00	2.48
Ischial bone(s): Incomplete ossification	7	0.07	0.00	1.65
Iliac bone(s): Misshapen	1	0.01	0.00	0.80
LIMBS				
Hindlimb: Tarsal bone, Increased ossification	65	0.66	0.00	15.32
Forelimb: Metacarpal bones, absent	5	0.05	0.00	2.42
Forelimb: Metacarpal bones, unossified	1	0.01	0.00	0.61
Reduced no. of phalange(s) in forepaw(s)	37	0.37	0.00	9.09
Reduced no. of phalange(s) in hindpaw(s)	1	0.01	0.00	0.69
Femur: Incomplete ossification	205	2.07	0.00	18.57
Humerus: Incomplete ossification	2	0.02	0.00	0.68

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HISTORICAL CONTROL DATA
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NEONATAL AND JUVENILE STUDIES CLINICAL PATHOLOGY RANGES HEMATOLOGY DATA																
Parameter	Age	Sex	Mean	SD	Range		Normal Range			Sex	Mean	SD	Range		Normal Range	
					Min	Max	Lower	Upper					Min	Max	Lower	Upper
WBC (10 ³ /μL)	Day 10 to 19	M	4.125	0.978	2.28	6.05	3.73	4.52		-						
	Day 20 to 29	M	5.708	2.634	1.04	13.80	5.09	6.33		F	5.523	2.474	1.15	14.70	4.93	6.12
	Day 30 to 39	M	5.407	2.723	0.98	12.76	4.75	6.06		F	4.951	2.318	1.74	13.19	4.38	5.52
	Day 40 to 49	M	7.874	3.171	2.82	17.21	7.38	8.36		F	6.929	2.475	1.24	14.98	6.54	7.32
RBC (10 ⁶ /μL)	Day 10 to 19	M	4.058	0.290	3.53	4.60	3.94	4.18		-						
	Day 20 to 29	M	4.964	0.567	3.81	6.38	4.83	5.10		F	4.996	0.562	3.74	6.16	4.86	5.13
	Day 30 to 39	M	5.901	0.390	5.02	6.70	5.81	5.99		F	6.034	0.397	5.16	6.68	5.94	6.13
	Day 40 to 49	M	6.819	0.610	5.54	8.38	6.72	6.91		F	7.065	0.678	4.73	8.71	6.96	7.17
HGB (g/dL)	Day 10 to 19	M	8.78	1.05	6.9	10.7	8.4	9.2		-						
	Day 20 to 29	M	10.07	1.25	7.4	12.8	9.8	10.4		F	10.17	1.18	7.4	12.6	9.9	10.5
	Day 30 to 39	M	12.36	0.71	10.9	13.7	12.2	12.5		F	12.34	0.75	9.4	13.9	12.2	12.5
	Day 40 to 49	M	14.37	1.24	11.7	17.2	14.2	14.6		F	14.58	1.35	9.3	17.6	14.4	14.8
HCT (%)	Day 10 to 19	M	28.79	3.12	22.5	34.4	27.5	30.1		-						
	Day 20 to 29	M	31.59	4.54	21.8	41.1	30.5	32.7		F	31.93	4.45	22.4	41.9	30.9	33.0
	Day 30 to 39	M	39.26	2.62	33.4	44.1	38.6	39.9		F	39.06	2.60	32.3	45.4	38.4	39.7
	Day 40 to 49	M	44.02	4.11	36.0	55.4	43.4	44.7		F	43.30	4.06	28.0	51.9	42.7	43.9

Legend:

WBC = White blood cell count

HCT = Hematocrit

RBC = Red blood cell count

HGB = Hemoglobin

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NEONATAL AND JUVENILE STUDIES CLINICAL PATHOLOGY RANGES HEMATOLOGY DATA																
Parameter	Age	Sex	Mean	SD	Range		Normal Range			Sex	Mean	SD	Range		Normal Range	
					Min	Max	Lower	Upper					Min	Max	Lower	Upper
PLT (10 ³ /µL)	Day 10 to 19	M	1192.2	211.6	582	1587	1106	1279		-						
	Day 20 to 29	M	1049.7	183.6	631	1437	1006	1093		F	1069.3	182.3	701	1509	1025	1113
	Day 30 to 39	M	1425.1	207.1	896	1779	1375	1475		F	1478.3	251.2	821	2605	1416	1540
	Day 40 to 49	M	1377.0	194.9	775	1933	1347	1407		F	1452.4	243.4	916	2317	1414	1491
RETIC (10 ⁹ /L)	Day 10 to 19	M	502.55	93.79	374.7	671.9	464.2	540.9		-						
	Day 20 to 29	M	919.11	165.99	630.9	1390.0	871.7	966.6		F	884.42	143.66	428.8	1140.0	842.0	926.9
	Day 30 to 39	M	578.60	89.47	309.5	728.5	556.8	600.3		F	463.53	67.03	322.2	598.3	446.7	480.4
	Day 40 to 49	M	450.75	78.87	272.7	688.3	438.2	463.3		F	301.68	84.38	144.6	600.1	288.0	315.3
PT (sec)	Day 10 to 19	M	-	-	-	-	-	-		-						
	Day 20 to 29	M	16.67	1.64	14.7	23.4	16.1	17.3		F	16.67	1.35	14.8	20.5	16.1	17.2
	Day 30 to 39	M	14.81	1.69	12.8	22.1	14.4	15.2		F	14.44	1.32	12.6	17.9	14.1	14.8
	Day 40 to 49	M	13.97	1.55	11.9	19.7	13.6	14.3		F	13.78	1.79	9.6	19.1	13.3	14.2
APTT (sec)	Day 10 to 19	M	-	-	-	-	-	-		-						
	Day 20 to 29	M	15.11	2.70	9.6	20.0	14.1	16.1		F	15.41	3.14	10.0	22.2	14.2	16.6
	Day 30 to 39	M	17.96	3.66	12.0	33.7	17.1	18.8		F	16.78	2.95	11.0	27.7	16.1	17.5
	Day 40 to 49	M	17.58	2.47	12.1	31.4	17.0	18.2		F	16.48	3.63	9.1	29.4	15.6	17.4

Legend:

PLT = Platelet count

APPT = Activated partial thromboplastin time

RETIC = Absolute reticulocyte count

PT = Prothrombin time

@ The year (s) studies were initiated

HISTORICAL CONTROL DATA
RAT - CD® IGS (CrI:CD[SD]) , 1998 - 2018@
CHARLES RIVER LABORATORIES PRECLINICAL SERVICES MONTREAL

NEONATAL AND JUVENILE STUDIES CLINICAL PATHOLOGY RANGES CLINICAL CHEMISTRY DATA																
Parameter	Age	Sex	Mean	SD	Range		Normal Range			Sex	Mean	SD	Range		Normal Range	
					Min	Max	Lower	Upper					Min	Max	Lower	Upper
AST (U/L)	Day 10 to 19	M	88.7	9.6	73	107	85	93		-						
	Day 20 to 29	M	117.9	20.3	94	217	113	123		F	113.9	24.4	80	243	108	120
	Day 30 to 39	M	113.8	21.1	71	166	109	119		F	101.7	22.7	61	165	97	107
	Day 40 to 49	M	143.5	42.7	68	454	137	150		F	127.7	34.0	66	279	123	133
ALT (U/L)	Day 10 to 19	M	17.2	2.8	12	23	16	18		-						
	Day 20 to 29	M	44.9	13.1	17	80	42	48		F	40.7	10.5	19	62	38	43
	Day 30 to 39	M	39.8	13.2	22	73	37	43		F	32.1	10.7	19	71	30	35
	Day 40 to 49	M	41.5	9.8	23	75	40	43		F	34.3	7.8	20	67	33	36
ALP (U/L)	Day 10 to 19	M	328.7	45.1	253	436	310	347		-						
	Day 20 to 29	M	331.4	73.8	180	531	313	350		F	311.9	83.0	205	601	293	331
	Day 30 to 39	M	308.9	76.6	174	612	291	326		F	249.6	59.1	118	400	236	263
	Day 40 to 49	M	305.5	69.3	152	556	295	316		F	209.7	57.6	103	416	201	219
TBIL (mg/dL)	Day 10 to 19	M	0.174	0.049	0.09	0.28	0.15	0.19		-						
	Day 20 to 29	M	0.147	0.097	0.04	0.52	0.12	0.17		F	0.156	0.128	0.05	0.69	0.12	0.19
	Day 30 to 39	M	0.094	0.042	0.03	0.19	0.08	0.10		F	0.089	0.049	0.00	0.25	0.08	0.10
	Day 40 to 49	M	0.075	0.025	0.02	0.17	0.07	0.08		F	0.077	0.026	0.01	0.17	0.07	0.08

Legend:

AST = Aspartate aminotransferase

TBIL = Total bilirubin

ALT = Alanine aminotransferase

ALP = Alkaline phosphatase

@ The year (s) studies were initiated

HISTORICAL CONTROL DATA
RAT - CD® IGS (CrI:CD[SD]) , 1998 - 2018@
CHARLES RIVER LABORATORIES PRECLINICAL SERVICES MONTREAL

NEONATAL AND JUVENILE STUDIES																
CLINICAL PATHOLOGY RANGES																
CLINICAL CHEMISTRY DATA																
Parameter	Age	Sex	Mean	SD	Range		Normal Range			Sex	Mean	SD	Range		Normal Range	
					Min	Max	Lower	Upper					Min	Max	Lower	Upper
CREAT (mg/dL)	Day 10 to 19	M	0.16	0.06	0.1	0.3	0.1	0.2		-						
	Day 20 to 29	M	0.32	0.14	0.2	0.6	0.3	0.4		F	0.32	0.14	0.2	0.6	0.3	0.4
	Day 30 to 39	M	0.27	0.12	0.1	0.6	0.2	0.3		F	0.29	0.10	0.1	0.5	0.3	0.3
	Day 40 to 49	M	0.28	0.09	0.1	0.5	0.3	0.3		F	0.31	0.08	0.2	0.5	0.3	0.3
GLUC (mg/dL)	Day 10 to 19	M	180.0	12.9	146	199	175	185		-						
	Day 20 to 29	M	197.6	45.7	127	370	186	209		F	208.6	43.2	116	368	199	219
	Day 30 to 39	M	140.7	61.7	61	331	127	155		F	148.3	77.4	71	378	131	166
	Day 40 to 49	M	114.0	59.5	51	332	105	123		F	123.7	58.4	61	357	115	133
CHOL (mg/dL)	Day 10 to 19	M	150.4	24.5	97	201	140	160		-						
	Day 20 to 29	M	73.9	18.0	39	134	69	78		F	77.4	17.0	42	134	74	81
	Day 30 to 39	M	57.7	12.8	27	86	55	61		F	63.1	13.5	34	96	60	66
	Day 40 to 49	M	69.6	15.2	39	114	67	72		F	72.0	16.7	32	120	69	75
TRIG (mg/dL)	Day 10 to 19	M	166.9	84.1	61	373	133	201		-						
	Day 20 to 29	M	87.8	56.5	13	326	74	102		F	81.5	58.6	15	364	68	95
	Day 30 to 39	M	47.4	32.7	13	187	40	55		F	48.6	34.5	15	247	41	56
	Day 40 to 49	M	65.1	35.5	10	204	60	71		F	43.3	20.5	13	158	40	46

Legend:

CREAT = Creatinine

GLUC = Glucose

CHOL = Cholesterol

TRIG = Triglycerides

@ The year (s) studies were initiated

HISTORICAL CONTROL DATA
RAT - CD® IGS (CrI:CD[SD]) , 1998 - 2018@
CHARLES RIVER LABORATORIES PRECLINICAL SERVICES MONTREAL

NEONATAL AND JUVENILE STUDIES CLINICAL PATHOLOGY RANGES CLINICAL CHEMISTRY DATA																
Parameter	Age	Sex	Mean	SD	Range		Normal Range			Sex	Mean	SD	Range		Normal Range	
					Min	Max	Lower	Upper					Min	Max	Lower	Upper
TPROT (g/dL)	Day 10 to 19	M	4.14	0.29	3.6	4.8	4.0	4.3		-						
	Day 20 to 29	M	4.63	0.25	4.0	5.1	4.6	4.7		F	4.66	0.30	4.0	5.3	4.6	4.7
	Day 30 to 39	M	4.98	0.23	4.4	5.6	4.9	5.0		F	5.20	0.25	4.7	5.8	5.1	5.3
	Day 40 to 49	M	5.55	0.43	4.7	6.5	5.5	5.6		F	5.79	0.45	4.9	6.7	5.7	5.9
ALB (g/dL)	Day 10 to 19	M	2.77	0.17	2.5	3.2	2.7	2.8		-						
	Day 20 to 29	M	3.40	0.40	2.2	4.0	3.3	3.5		F	3.47	0.40	2.3	4.3	3.4	3.6
	Day 30 to 39	M	3.79	0.30	2.8	4.4	3.7	3.9		F	4.01	0.30	2.9	4.6	3.9	4.1
	Day 40 to 49	M	3.94	0.29	3.3	4.7	3.9	4.0		F	4.22	0.34	3.5	4.9	4.2	4.3
PHOS (mg/dL)	Day 10 to 19	M	9.95	0.51	8.8	10.9	9.7	10.2		-						
	Day 20 to 29	M	10.42	0.94	8.5	12.7	10.2	10.7		F	10.27	1.12	8.6	13.3	10.0	10.6
	Day 30 to 39	M	11.15	1.40	8.9	15.0	10.8	11.5		F	11.15	1.16	8.8	13.9	10.9	11.4
	Day 40 to 49	M	10.21	1.12	7.8	13.9	10.0	10.4		F	9.61	1.32	6.4	17.5	9.4	9.8

Legend:

TPROT = Total protein

ALB = Albumin

PHOS = Phosphorus

@ The year (s) studies were initiated

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2003 - 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT		
GROUP PARENTAL PERFORMANCE +		
Parameter	Minimum*	Maximum*
Mating Index (%)	90.9	100.0
Fertility Index (%)	84.0	100.0
Conception Rate (%)	87.5	100.0

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT			
GROUP UTERINE FINDINGS ++			
Parameter	AVERAGE	Minimum*	Maximum*
COMBINATION OF GESTATION DAY 13 AND 20			
Total Corpora Lutea / Rat	13.3	11.8	14.7
Total Implantation Sites / Litter	12.0	9.8	13.7
Total Live Fetuses/Embryos / Litter	11.4	9.3	12.8
Dead Fetuses/Embryos / Litter	0.02	0.0	0.5
Total Resorptions / Litter	0.67	0.3	1.2
Pre-Implantation Loss (%) / Litter	9.7	5.2	22.4
Post-Implantation Loss (%) / Litter	6.1	2.7	16.6

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT		
MALE REPRODUCTIVE ASSESSMENTS		
Parameter	Minimum*	Maximum*
ORGAN WEIGHTS +++		
Left Testis (g)	1.784	1.963
Right Testis (g)	1.739	1.991
Left Epididymis (g)	0.589	0.731
Right Epididymis (g)	0.577	0.767
EPIDIDYMAL SPERM EVALUATION ++++		
Cauda Epididymis Weight (g)	0.200	0.268
Cauda Spermatozoa Per Gram (Millions)	362.4	1079.9
Cauda Casa Motility (%)	73.2	80.8
Vas Deferens Casa Motility (%)	67.8	90.3

* Study ranges, based on the group incidence, group percentage or group mean

+ Includes data from 43 studies

++ Includes data from 42 studies

+++ Includes data from 13 studies

++++ Includes data from 12 studies

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2003 - 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

PRE AND POSTNATAL STUDIES		
GROUP MATERNAL PERFORMANCE +		
Parameter	Minimum*	Maximum*
Gestation Index (%)	95.5	100.0
Length of Gestation (Days)	21.2	21.9
Sex Ratio (% Males)	44.1	55.1
No. of Live Pups at Birth	8.4	11.8
No. of Dead Pups at Birth	0.0	0.2
No. of Implant Scars	8.8	12.6
Live Birth Index (%)	90.2	100.0

PRE AND POSTNATAL STUDIES		
SEXUAL MATURATION ++		
Parameter	Minimum*	Maximum*
Vaginal Opening (Days)	31.0	33.7
Preputial Separation (Days)	41.2	43.8

PRE AND POSTNATAL STUDIES		
VIABILITY (%) +++		
Parameter	Minimum*	Maximum*
Viability Index (%) - Day 4 Post Partum	94.4	100.0
Survival Index (%) - Day 7 Post Partum	99.6	100.0
Survival Index (%) - Day 14 Post Partum	99.2	100.0
Lactation Index (%) - Day 21 Post Partum	98.8	100.0

* Study ranges, based on the group incidence, group percentage or group mean

+ Includes data from 19 studies

++ Includes data from 27 studies

+++ Includes data from 18 studies

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2003 - 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

PRE AND POSTNATAL STUDIES			
PUP BODY WEIGHTS (G) ++			
Parameter	Average	Minimum*	Maximum*
<u>BODY WEIGHTS[#]:</u>			
Day 0 Post Partum			
Males	6.1	5.4	6.4
Females	5.8	5.2	6.1
Total	5.9	5.3	6.3
Day 4 Post Partum			
Males	10.6	10.0	11.5
Females	10.2	9.6	11.1
Total	10.4	9.9	11.3
Day 7 Post Partum			
Males	15.6	12.9	17.3
Females	15.0	12.5	16.9
Total	15.3	12.7	17.1
Day 14 Post Partum			
Males	29.3	24.3	34.0
Females	28.5	23.6	33.5
Total	28.9	24.0	33.8
Day 21 Post Partum			
Males	44.8	37.2	53.2
Females	43.5	36.2	51.9
Total	44.2	36.8	52.5

* Study ranges, based on the group incidence, group percentage or group mean

Litters uncultured

++ Includes data from 21 studies

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP MATERNAL FINDINGS			
Parameter	Total	Minimum*	Maximum*
No. of Rats Mated	663	22	25
No. of Rats Pregnant	636	18	24
No. of Rats Pregnant by Ammonium Sulfide Staining	0	0	0
No. of Rats Dying or Unscheduled Euthanasia on Study	1	0	1
No. of Rats with Total Resorption	1	0	1
No. of Rats Littering Prior to Scheduled Cesarean	3	0	1
Pregnancy Rate (%)	-	81.8	100.0

EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP OVARIAN AND UTERINE FINDINGS			
Parameter	Average	Minimum*	Maximum*
Total Corpora Lutea / Rat	12.5	11.0	13.7
Total Implantation Sites / Litter	11.2	10.0	12.6
Sex Ratio (% Males)	50.5	41.2	61.4
Total Live Fetuses / Litter	10.7	9.4	11.9
Dead Fetuses / Litter	0.0	0.0	0.0
Early Resorptions / Litter	0.54	0.2	0.9
Late Resorptions / Litter	0.01	0.0	0.1
Total Resorptions / Litter	0.56	0.2	0.9
Pre-Implantation Loss (%) / Litter	10.2	4.7	16.7
Post-Implantation Loss (%) / Litter	5.1	2.1	10.5

* Study ranges, based on the group incidence, group percentage or group mean

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES			
FETAL WEIGHTS - SUMMARY DATA			
Parameter	Average	Minimum*	Maximum*
Fetal Weight (g) - Males	5.44	5.18	5.79
Fetal Weight (g) - Females	5.17	4.95	5.55
Fetal Weight (g) - Total	5.31	5.06	5.66

* Study ranges, based on the group incidence, group percentage or group mean

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) SKELETAL (SKE) TECHNIQUE OF WILSON (WT)	Litters examined			
	633	Total no. of		
	633	studies/groups used		
	633	29		
MALFORMATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Cleft palate (EXT,WT)	1	0.16	0.00	4.76
Eye(s): Retina fold (WT)	1	0.16	0.00	4.55
Eye(s): Lens(es) misshapen (WT)	2	0.32	0.00	4.55
Face: Aglossia (EXT,WT)	1	0.16	0.00	4.76
Face: Agnathia (EXT,WT)	1	0.16	0.00	4.76
Face: Astomia (EXT,WT)	1	0.16	0.00	4.76
Heart: Aortic arch absent (VIS)	1	0.16	0.00	5.00
Heart: Descending aorta absent (VIS)	1	0.16	0.00	5.00
Heart: Misshapen (VIS)	1	0.16	0.00	5.00
Diaphragm: Diaphragmatic hernia (VIS)	1	0.16	0.00	4.17
Lungs: Lung lobes, absent (VIS)	1	0.16	0.00	4.17
Vertebral column: Thoracic vertebra, Absent (SKE)	1	0.16	0.00	4.55
Ribs: Multiple variants in rib(s) (SKE)	3	0.47	0.00	9.09
Rib(s): Absent (SKE)	2	0.32	0.00	5.26
Rib(s): Fused (SKE)	2	0.32	0.00	4.76
Rib(s): Branched (SKE)	1	0.16	0.00	5.00
Abdomen: Gastroschisis (EXT)	1	0.16	0.00	4.35
Limb(s): Abnormal flexure/hyperflexure/ hyperextension of hindlimb(s) (EXT)	6	0.95	0.00	9.09
Limb(s): Abnormal flexure/hyperflexure of forelimb(s) (EXT)	1	0.16	0.00	4.35
Limb(s): Bent radius (SKE)	1	0.16	0.00	4.76
Limb(s): Bent ulna (SKE)	1	0.16	0.00	4.76
Gross exam: Anasarca (EXT)	1	0.16	0.00	4.35

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (Crl:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) TECHNIQUE OF WILSON (WT)	Litters examined			
	633	Total no. of		
	633	studies/groups used		
	633	29		
EXTERNAL AND VISCERAL VARIATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Area(s) of subcutaneous edema (lower jaw) (EXT)	1	0.16	0.00	4.55
Head: Moderate dilatation of the lateral ventricles (WT)	1	0.16	0.00	5.26
Liver: Discoloration pale (VIS)	5	0.79	0.00	9.09
Liver: Supernumerary lobes/vestigial lobe (VIS)	9	1.42	0.00	11.11
Kidney(s): Renal papilla(e) absent (VIS)	1	0.16	0.00	4.17
Ureter(s): Dilation (VIS)	7	1.11	0.00	8.33
General: Subcutaneous hematoma (EXT)	1	0.16	0.00	4.17

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL (SKE)	Litters examined 633	Total no. of studies/groups used 29		
SKELETAL VARIATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Frontal bone(s): Incomplete ossification	22	3.48	0.00	9.52
Parietal bone(s): Incomplete ossification	166	26.22	0.00	50.00
Supraoccipital bone: Incomplete ossification	56	8.85	0.00	27.27
Interparietal bone: Incomplete ossification	279	44.08	13.04	76.19
Nasal bone(s): Incomplete ossification	4	0.63	0.00	4.55
Hyoid bone: Incomplete ossification	57	9.00	0.00	34.78
Hyoid bone: Unossified	2	0.32	0.00	8.70
Zygomatic bone(s): Incomplete ossification	27	4.27	0.00	27.27
Premaxilla bone(s): Incomplete ossification	2	0.32	0.00	9.09
VERTEBRAL COLUMN				
Extra pre-sacral vertebrae	28	4.42	0.00	18.18
Cervical vertebral arch(es): Irregular ossification	1	0.16	0.00	4.17
Cervical vertebral arch(es): Incomplete ossification	1	0.16	0.00	4.17
Cervical vertebral arch(es): Absent	1	0.16	0.00	4.17
Cervical vertebral arch(es): Ossification center	18	2.84	0.00	22.73
Lumbar vertebra: Ossification center	2	0.32	0.00	9.09
Lumbar vertebral arch(es): Ossification center	132	20.85	0.00	81.82
Lumbar vertebral arch(es): Incomplete ossification	2	0.32	0.00	4.76
Lumbar centrum: Semi-bipartite	2	0.32	0.00	4.76
Ossification center on 1st lumbar vertebra or 14th thoracic vertebra	338	53.40	0.00	95.65
Ossification center on 6th lumbar vertebra	1	0.16	0.00	4.35
Sacral vertebral centrum: Incomplete ossification	1	0.16	0.00	5.56
Sacral vertebral arch(es): Malpositioned	1	0.16	0.00	5.00
Sacral vertebral arch(es) irregular ossification	3	0.47	0.00	13.64
Thoracic vertebral arch(es): Ossification center	43	6.79	0.00	55.00
Thoracic vertebral centrum: Semi-bipartite/dumbbell	62	9.79	0.00	52.38
Thoracic vertebral centrum: Bipartite	4	0.63	0.00	8.70
Thoracic vertebral centrum: Misshapen	1	0.16	0.00	4.55
Thoracic vertebral centrum: Fused	1	0.16	0.00	4.17
STERNEBRAL COLUMN				
Extra sternebrae	2	0.32	0.00	5.56
Sternebrae: Fused	1	0.16	0.00	5.00
Sternebrae: Misaligned	1	0.16	0.00	4.17
Sternebra(e):Semi-bipartite/dumbbell ossification	1	0.16	0.00	4.76

* Study ranges, based on the group incidence

@ The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (Crl:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL VARIATIONS (CONT'D)	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
STERNEBRAL COLUMN (CONT'D)				
Sternebra(e): Bipartite ossification	2	0.32	0.00	9.52
Sternebra(e): Incomplete ossification	25	3.95	0.00	26.09
Sternebra(e): Unossified	1	0.16	0.00	5.00
Sternebra(e): Misshapen	7	1.11	0.00	17.39
RIBS				
Malpositioned	1	0.16	0.00	4.55
Nodulated	12	1.90	0.00	10.00
Detached	1	0.16	0.00	4.76
Supernumerary rib: Thoracolumbar, full (extra)	105	16.59	0.00	36.36
Supernumerary rib: Thoracolumbar, short (rudimentary 14th rib)	418	66.03	39.13	104.76
Supernumerary rib: Cervical (full)	8	1.26	0.00	5.00
Supernumerary rib: Cervical (short)	18	2.84	0.00	10.00
Wavy	22	3.48	0.00	27.27
Ossification center(s) on 7th cervical vertebra	31	4.90	0.00	19.05
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	1	0.16	0.00	4.55
Ischial bone(s): Incomplete ossification	1	0.16	0.00	4.55
LIMBS				
Reduced no. of phalange(s) in forepaw(s)	4	0.63	0.00	4.76
Femur: Incomplete ossification	1	0.16	0.00	4.55

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RAT - Wistar Han IGS (CrI:WI [Han]), 2006 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) SKELETAL (SKE) TECHNIQUE OF WILSON (WT)	Fetuses examined			
	6771	Total no. of		
	3384	studies/groups used		
	3393	29		
3383				
MALFORMATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Cleft palate (EXT,WT)	3	0.04	0.00	1.36
Eye(s): Retina fold (WT)	1	0.03	0.00	0.82
Eye(s): Lens(es) misshapen (WT)	2	0.06	0.00	0.88
Face: Aglossia (EXT,WT)	1	0.01	0.00	0.45
Face: Agnathia (EXT,WT)	1	0.01	0.00	0.45
Face: Astomia (EXT,WT)	1	0.01	0.00	0.45
Heart: Aortic arch absent (VIS)	1	0.03	0.00	0.87
Heart: Descending aorta absent (VIS)	1	0.03	0.00	0.87
Heart: Misshapen (VIS)	1	0.03	0.00	0.87
Diaphragm: Diaphragmatic hernia (VIS)	1	0.03	0.00	0.76
Lungs: Lung lobes, absent (VIS)	1	0.03	0.00	0.71
Vertebral column: Thoracic vertebra, Absent (SKE)	1	0.03	0.00	1.01
Ribs: Multiple variants in rib(s) (SKE)	3	0.09	0.00	1.74
Rib(s): Absent (SKE)	2	0.06	0.00	1.01
Rib(s): Fused (SKE)	2	0.06	0.00	1.01
Rib(s): Branched (SKE)	1	0.03	0.00	0.91
Abdomen: Gastroschisis (EXT)	1	0.01	0.00	0.40
Limb(s): Abnormal flexure/hyperflexure/ hyperextension of hindlimb(s) (EXT)	7	0.10	0.00	1.39
Limb(s): Abnormal flexure/hyperflexure of forelimb(s) (EXT)	1	0.01	0.00	0.37
Limb(s): Bent radius (SKE)	3	0.09	0.00	2.73
Limb(s): Bent ulna (SKE)	3	0.09	0.00	2.73
Gross exam: Anasarca (EXT)	3	0.04	0.00	1.30

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL (EXT) VISCERAL (VIS) TECHNIQUE OF WILSON (WT)	Fetuses examined Total no. of studies/groups used 6771 3384 3383 29			
EXTERNAL AND VISCERAL VARIATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Area(s) of subcutaneous edema (lower jaw) (EXT)	1	0.01	0.00	0.41
Head: Moderate dilatation of the lateral ventricles (WT)	1	0.03	0.00	0.89
Liver: Discoloration pale (VIS)	6	0.18	0.00	1.64
Liver: Supernumerary lobes/vestigial lobe (VIS)	12	0.35	0.00	2.46
Kidney(s): Renal papilla(e) absent (VIS)	1	0.03	0.00	0.76
Ureter(s): Dilation (VIS)	7	0.21	0.00	1.52
General: Subcutaneous hematoma (EXT)	1	0.01	0.00	0.38

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CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL (SKE)	Fetuses examined 3393		Total no. of studies/groups used 29	
SKELETAL VARIATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Frontal bone(s): Incomplete ossification	24	0.71	0.00	2.80
Parietal bone(s): Incomplete ossification	284	8.37	0.00	20.75
Supraoccipital bone: Incomplete ossification	72	2.12	0.00	9.73
Interparietal bone: Incomplete ossification	562	16.56	2.24	34.91
Nasal bone(s): Incomplete ossification	4	0.12	0.00	1.01
Hyoid bone: Incomplete ossification	83	2.45	0.00	10.24
Hyoid bone: Unossified	2	0.06	0.00	1.49
Zygomatic bone(s): Incomplete ossification	32	0.94	0.00	6.60
Premaxilla bone(s): Incomplete ossification	2	0.06	0.00	1.74
VERTEBRAL COLUMN				
Extra pre-sacral vertebrae	35	1.03	0.00	3.36
Cervical vertebral arch(es): Irregular ossification	1	0.03	0.00	0.75
Cervical vertebral arch(es): Incomplete ossification	1	0.03	0.00	0.75
Cervical vertebral arch(es): Absent	1	0.03	0.00	0.75
Cervical vertebral arch(es): Ossification center	19	0.56	0.00	4.42
Lumbar vertebra: Ossification center	2	0.06	0.00	2.02
Lumbar vertebral arch(es): Ossification center	255	7.52	0.00	36.36
Lumbar vertebral arch(es): Incomplete ossification	2	0.06	0.00	0.94
Lumbar centrum: Semi-bipartite	2	0.06	0.00	0.91
Ossification center on 1st lumbar vertebra or 14th thoracic vertebra	719	21.19	0.00	45.52
Ossification center on 6th lumbar vertebra	1	0.03	0.00	0.75
Sacral vertebral centrum: Incomplete ossification	1	0.03	0.00	1.19
Sacral vertebral arch(es): Malpositioned	2	0.06	0.00	1.82
Sacral vertebral arch(es) irregular ossification	3	0.09	0.00	2.61
Thoracic vertebral arch(es): Ossification center	53	1.56	0.00	12.73
Thoracic vertebral centrum: Semi-bipartite/dumbbell	80	2.36	0.00	13.21
Thoracic vertebral centrum: Bipartite	4	0.12	0.00	1.71
Thoracic vertebral centrum: Misshapen	1	0.03	0.00	1.01
Thoracic vertebral centrum: Fused	1	0.03	0.00	0.75

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL VARIATIONS (CONT'D)	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
STERNEBRAL COLUMN				
Extra sternebrae	2	0.06	0.00	1.19
Sternebrae: Fused	1	0.03	0.00	0.90
Sternebrae: Misaligned	1	0.03	0.00	0.73
Sternebra(e): Semi-bipartite/dumbbell ossification	1	0.03	0.00	0.93
Sternebra(e): Bipartite ossification	2	0.06	0.00	1.87
Sternebra(e): Incomplete ossification	26	0.77	0.00	5.13
Sternebra(e): Unossified	1	0.03	0.00	0.91
Sternebra(e): Misshapen	7	0.21	0.00	3.42
RIBS				
Malpositioned	1	0.03	0.00	0.83
Nodulated	15	0.44	0.00	2.73
Detached	1	0.03	0.00	0.93
Supernumerary rib: Thoracolumbar, full (extra)	122	3.60	0.00	8.41
Supernumerary rib: Thoracolumbar, short (rudimentary 14th rib)	668	19.69	7.46	35.71
Supernumerary rib: Cervical (full)	8	0.24	0.00	1.01
Supernumerary rib: Cervical (short)	20	0.59	0.00	2.54
Wavy	31	0.91	0.00	7.07
Ossification center(s) on 7th cervical vertebra	33	0.97	0.00	3.64
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	1	0.03	0.00	0.78
Ischial bone(s): Incomplete ossification	1	0.03	0.00	0.78
LIMBS				
Reduced no. of phalange(s) in forepaw(s)	5	0.15	0.00	2.02
Femur: Incomplete ossification	1	0.03	0.00	0.88

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