

Historical Control Data in Rats



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¹ Additional HCD endpoints and years are available upon request.

Historical Control Data**Rat Crl: OFA.SD.****Maternal body weight gain (g) during gestation**

Study	Year	Dams with live foetuses	Gestation days 0 to 6		Gestation days 0 to 3		Gestation days 3 to 6		Gestation days 6 to 9		Gestation days 9 to 12		Gestation days 12 to 15		Gestation days 15 to 18		Gestation days 6 to 18		Gestation days 18 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	22	39.4	7.0					12.1	5.0	17.0	4.1	17.2	5.0	38.5	9.5	84.7	15.6	46.2	12.1
B18	2018	21	35.8	9.5					9.4	6.1	16.7	5.8	18.7	6.0	36.9	9.9	81.8	16.2	50.1	13.6
C18	2018	6	41.9	10.3					13.0	3.5	14.3	7.4	21.1	6.8	39.0	6.7	87.4	14.8	47.9	4.5
D18	2018	22			15.4	4.9	15.6	4.9	13.7	3.5	17.8	4.9	21.5	5.2	38.9	5.6	92.0	10.9	50.2	10.8
E18	2018	6	38.5	6.8					13.7	5.1	19.5	4.1	20.5	5.9	36.3	5.5	90.0	16.8	48.7	7.8
F18	2018	6			25.0	4.0	15.2	4.1	15.9	4.7	14.5	3.2	22.3	3.3	29.8	6.7	82.4	7.0	50.9	2.8
G18	2018	21			15.9	6.8	16.0	5.6	14.2	5.4	18.7	5.2	21.1	4.6	35.8	8.5	89.8	15.0	55.8	11.4
H18	2018	6			26.4	3.3	13.9	4.7	12.8	6.7	19.7	4.0	18.2	4.2	38.4	7.9	89.1	15.0	49.7	7.4
I18	2018	21			20.3	5.9	15.2	4.8	16.2	6.4	18.4	3.9	22.5	6.1	39.8	8.2	96.9	16.3	53.1	11.6
J18	2018	21			22.2	5.3	16.7	3.5	13.2	5.6	20.2	3.8	20.2	3.9	37.5	9.0	91.1	15.2	50.1	7.4
K18	2018	6			16.3	7.0	19.4	3.1	10.0	5.3	22.0	2.1	17.7	3.1	34.8	4.0	84.6	10.5	53.0	5.6
L18	2018	22			20.5	4.1	18.5	4.6	13.4	4.8	18.7	4.2	23.3	5.4	40.8	6.9	96.3	12.9	53.0	10.4
M18	2018	6			18.1	4.0	16.0	5.5	15.1	2.6	14.4	4.9	16.8	4.2	35.0	6.2	81.3	10.9	44.5	8.7
N18	2018	6			22.1	4.4	19.4	3.7	14.2	4.6	18.3	3.5	24.5	2.7	33.0	7.5	90.0	12.0	50.5	7.7
O18	2018	6			22.9	8.2	15.2	4.4	9.3	5.2	18.0	2.2	16.0	6.6	34.5	7.4	77.8	18.3	45.7	17.2
P18	2018	21			22.2	4.9	17.9	5.5	14.1	6.6	19.7	4.9	21.4	6.2	36.0	11.5	91.2	19.5	48.6	12.9
Q18	2018	6			20.3	6.4	14.2	1.7	12.8	4.4	27.1	3.3	21.7	3.6	36.4	8.0				
R18	2018	22			13.2	6.3	11.6	4.6	12.1	4.0	15.9	4.7	19.9	5.6	42.1	7.6	90.0	12.2	56.3	7.6
Total Mean SD		247	38.2	8.4	19.1	6.5	16.0	5.0	13.1	5.4	18.2	4.9	20.5	5.5	37.8	8.4	89.4	15.1	51.0	10.8
2015 to 2017		375	37.2	10.8	0.0	0.0	0.0	0.0	12.9	5.5	17.6	4.8	19.5	5.8	39.2	7.8	89.5	14.4	NA	NA

Historical Control Data

Rat Crl: OFA.SD.

Maternal food consumption (g/day) during gestation

Study	Year	Dams with live foetuses	Gestation days 0 to 6		Gestation days 0 to 3		Gestation days 3 to 6		Gestation days 6 to 9		Gestation days 9 to 12		Gestation days 12 to 15		Gestation days 15 to 18		Gestation days 6 to 18		Gestation days 18 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	22	21.5	3.7					23.7	3.0	25.1	3.0	26.6	3.0	28.2	3.1	25.9	2.9	27.8	3.8
B18	2018	21	20.1	1.8					23.9	2.6	25.0	2.7	25.7	2.8	26.6	3.2	25.3	2.5	26.7	4.8
C18	2018	6	22.9	2.2					24.3	2.5	25.2	3.5	27.5	3.1	30.3	2.8	26.8	2.8	30.3	2.1
D18	2018	22			17.6	2.5	22.3	2.2	24.5	2.2	26.4	1.9	28.7	2.1	29.9	2.3			30.7	2.3
E18	2018	6	20.9	1.6					24.0	2.0	25.9	2.7	27.1	3.4	27.6	3.5	26.2	2.7	28.9	2.9
F18	2018	6			16.7	1.9	21.9	3.1	22.1	2.8	23.0	3.2	23.9	1.7	24.8	2.3	23.5	2.3	25.6	2.3
G18	2018	21			16.8	2.7	21.2	2.9	22.4	2.7	24.4	3.3	26.4	3.0	28.1	3.8	25.4	3.0	28.6	3.4
H18	2018	6			17.4	0.6	23.1	1.4	23.1	2.4	25.6	2.3	25.7	3.4	28.5	3.6	25.7	2.8	27.4	3.1
I18	2018	21			17.4	2.1	21.7	3.3	24.1	2.9	25.8	2.6	27.3	2.8	29.2	3.6	26.4	2.9	26.0	11.5
J18	2018	21			18.6	2.6	23.5	2.7	23.6	2.5	25.7	2.6	27.5	2.3	28.7	3.6	26.4	2.5	28.9	3.9
K18	2018	6			17.3	2.7	21.3	2.2	22.2	2.1	23.2	2.7	26.1	2.5	26.6	3.7	24.5	2.3	25.6	2.7
L18	2018	22			18.2	2.2	23.7	3.9	24.1	2.4	25.7	2.3	27.9	2.6	29.2	2.8	26.7	2.2	29.8	3.1
M18	2018	6			15.9	2.5	21.8	1.3	21.3	1.9	22.6	2.3	22.3	1.5	25.8	1.7	23.0	1.6	26.6	2.4
N18	2018	6			20.6	2.0	23.2	0.9	24.8	0.9	27.4	1.3	27.7	2.1	30.3	2.7	27.5	1.5	30.0	3.0
O18	2018	6			17.9	3.3	21.8	3.6	22.0	4.7	23.1	3.1	23.3	3.0	23.4	3.1	22.9	3.3	25.8	4.4
P18	2018	21			19.1	2.3	24.0	2.6	23.3	3.0	24.9	3.2	27.3	3.5	28.2	3.3	25.8	2.8	30.8	3.4
Q18	2018	6			16.2	2.5	21.4	2.4	22.7	2.8	24.0	1.9	26.9	2.7	29.1	2.8				
R18	2018	22			22.5	2.3	24.2	2.1	25.9	2.6	27.1	2.5	28.0	2.1	29.5	2.3			30.3	1.9
Total Mean SD		247	21.0	2.8	18.3	2.9	22.8	2.9	23.7	2.8	25.3	2.8	26.9	2.9	28.4	3.3	25.7	2.7	28.6	4.8
2015 to 2017		375	20.9	4.6	0.1	0.0	0.1	0.0	23.6	2.8	24.8	2.9	26.3	3.4	27.8	3.3	26.0	2.8	NA	NA

Historical Control Data

Rat Crl: OFA.SD.

Caesarean data collected on day 21 of gestation

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Study	Year	Number of females			Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Early resorptions per dam		Late resorptions per dam		Post-implantation loss %	
		Mated	Pregnant	With live foetuses	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	22	22	22	14.6	1.4	13.9	1.7	5.1	9.1	1.7	2.7	0.0	0.0	12.2	19.7
B18	2018	22	21	21	15.2	1.9	14.4	2.1	5.7	7.2	1.0	1.1	0.9	2.7	13.6	20.5
C18	2018	6	6	6	13.8	0.8	13.3	1.4	3.6	8.8	1.3	0.5	0.2	0.4	11.2	3.6
D18	2018	22	22	22	14.5	1.9	13.6	2.7	7.3	11.8	0.9	1.1	0.0	0.0	6.8	8.2
E18	2018	6	6	6	14.3	2.1	12.8	1.7	10.0	8.2	1.3	0.8	0.2	0.4	11.6	8.2
F18	2018	6	6	6	13.7	1.4	12.7	0.8	6.8	8.2	1.3	0.8	0.0	0.0	10.6	6.8
G18	2018	22	21	21	14.4	1.6	13.3	2.2	7.8	13.2	1.1	1.2	0.0	0.2	8.5	8.8
H18	2018	6	6	6	14.7	1.2	13.5	1.4	7.8	7.6	1.0	0.9	0.0	0.0	7.4	6.8
I18	2018	22	21	21	14.7	2.2	14.0	2.1	4.0	5.9	1.2	2.1	0.0	0.0	8.5	13.8
J18	2018	22	21	21	14.7	2.2	14.0	2.2	4.9	6.4	1.9	1.8	0.0	0.0	13.6	13.2
K18	2018	6	6	6	13.2	1.5	12.7	1.4	3.7	4.1	0.0	0.0	0.2	0.4	1.5	3.7
L18	2018	22	22	22	14.1	1.8	13.9	2.1	2.0	4.9	0.8	1.0	0.2	0.6	7.3	7.3
M18	2018	6	6	6	14.3	1.4	13.0	1.7	9.3	8.5	1.3	1.2	0.0	0.0	10.1	9.7
N18	2018	6	6	6	13.0	1.3	12.2	0.8	5.8	9.3	1.2	1.2	0.0	0.0	9.2	9.0
O18	2018	6	6	6	13.5	1.4	13.2	1.5	2.5	3.9	1.2	2.0	0.0	0.0	10.1	18.4
P18	2018	22	21	21	14.6	2.0	13.1	3.2	11.5	16.8	1.0	1.3	0.1	0.3	9.7	11.1
Q18	2018	6	6	6	13.8	2.0	13.2	2.3	5.1	6.3	0.8	0.8	1.2	2.9	13.7	20.1
R18	2018	22	22	22	16.4	2.4	15.4	2.2	5.4	8.3	0.9	1.0	0.0	0.0	5.8	7.2
Total		252	247 98%	247 98%												
Mean					14.6		13.7		6.0		1.1		0.1		9.5	
SD						2.0		2.2		9.5		1.5		1.0		12.6
2015 to 2017		307	299 97%	299 97%	14.6	2.3	13.9	2.4	5.0	9.8	1.2	1.4	0.0	0.3	8.9	11.5

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Historical Control Data

Rat Crl: OFA.SD.

Caesarean data collected on day 21 of gestation

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Study	Year	Number of females			Dead foetuses Total	Live litter size		Foetal weight (g) on GD21		Gravid uterus weigh (g) on GD21		Sex ratio % males
		Mated	Pregnant	With live foetuses		Mean	SD	Mean	SD	Mean	SD	
A18	2018	22	22	22	0	12.2	3.2	5.70	0.3	92.7	22.4	46.9
B18	2018	22	21	21	0	12.5	3.9	5.35	0.7	95.7	22.0	45.0
C18	2018	6	6	6	0	11.8	1.2	5.89	0.2	94.1	10.8	50.1
D18	2018	22	22	22	0	12.7	2.9	5.64	0.3	95.8	19.3	48.7
E18	2018	6	6	6	0	11.3	1.8	6.03	0.3	91.5	14.1	44.9
F18	2018	6	6	6	0	11.3	1.2	5.62	0.5	84.7	7.9	50.7
G18	2018	22	21	21	0	12.1	2.1	5.78	0.2	93.7	16.6	53.5
H18	2018	6	6	6	0	12.5	1.5	5.55	0.4	94.5	6.8	42.0
I18	2018	22	21	21	0	12.8	2.6	5.64	0.3	97.1	21.3	50.2
J18	2018	22	21	21	0	12.0	2.6	5.72	0.4	92.2	16.2	47.1
K18	2018	6	6	6	0	12.5	1.6	5.77	0.4	98.4	9.5	44.7
L18	2018	22	22	22	0	12.9	2.4	5.67	0.3	98.8	16.7	49.8
M18	2018	6	6	6	0	11.7	1.9	5.57	0.5	88.4	14.7	33.7
N18	2018	6	6	6	0	11.0	0.6	5.92	0.2	88.9	4.5	44.2
O18	2018	6	6	6	0	12.0	3.3	5.40	0.4	89.7	27.6	55.5
P18	2018	22	21	21	0	12.0	3.4	5.75	0.4	92.6	26.0	44.1
Q18	2018	6	6	6	0	11.2	2.6					52.1
R18	2018	22	22	22	0	14.5	2.4	5.62	0.3	107.9	16.4	48.1
Total		252	247 98%	247 98%	0							
Mean						12.4		5.67		95.7		47.8
SD							2.7		0.4		18.6	
2015 to 2017		307	299 97%	299 97%	0	11.6	5.8	NA	NA	NA	NA	49.4

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Historical Control Data**Rat Crl: OFA.SD.****Malformations (external, internal and skeletal)**

Study	Year	Number of litters examined	Number of fetuses examined	Number of litters with malformed fetuses	Litter Incidence %	Number of malformed fetuses	Foetal Incidence %	Type of malformation by foetus
A18	2018	22	268	0	-	0	-	
B18	2018	21	263	1	4.76	1	0.38	Malformed limb, paw, pelvis and vertebral column; anal atresia, absent genital tubercle, fleshy tail tab; absent kidneys, ureters, urinary bladder and right testis; malpositioned left testis
C18	2018	6	71	0	-	0	-	
D18	2018	22	279	1	4.55	1	0.36	Omphalocele
E18	2018	6	68	0	-	0	-	
F18	2018	6	68	0	-	0	-	
G18	2018	21	254	1	4.76	1	0.39	Retroesophageal subclavian artery
H18	2018	6	75	1	16.67	1	1.33	Cleft palate
I18	2018	21	269	0	-	0	-	
J18	2018	21	253	0	-	0	-	
K18	2018	6	75	0	-	0	-	
L18	2018	22	284	0	-	0	-	
M18	2018	6	70	0	-	0	-	
N18	2018	6	66	0	-	0	-	
O18	2018	6	72	0	-	0	-	
P18	2018	21	251	1	4.76	1	0.40	Malformed lumbar vertebrae
Q18	2018	6	67	1	16.67	1	1.49	Brachydactyly (absence of phalanx and metatarsal), gastroschisis and cleft palate
R18	2018	22	320	2	9.09	2	0.63	1rst: Anophthalmia and retinal fold / 2nd: Malformed lumbar vertebrae
Total 2018		247	3073	8	3.24%	8	0.26%	
2015 to 2017		299	3802	10	3.34%	10	0.26%	

Study nos. C18, E18, F18, H18, K18, M18, N18 and O18: Dose Range Finding studies with external examination only.

Study no. Q18: Dose Range Finding study with external and skeletal examinations only.

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - EXTERNAL EXAMINATION ON DAY 20 OR 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	13		32	
Number of fetuses examined	2285		5803	
OBSERVATION	N	%	N	%
Kyphosis	1	0.04	0	0.00
Trunk: small	1	0.04	0	0.00
Omphalocele	0	0.00	1	0.02
Gastroschisis	0	0.00	2	0.03
Thoracoschisis	0	0.00	1	0.02
Head/neck: malformed	0	0.00	1	0.02
Exencephaly	1	0.04	0	0.00
Micrognathia	1	0.04	0	0.00
Clef palate	1	0.04	1	0.02
Tongue: protruding	1	0.04	0	0.00
Limb: malformed	0	0.00	1	0.02
Limb: malrotated	1	0.04	1	0.02
Brachydactyly	0	0.00	1	0.02
Acaudia	2	0.09	0	0.00
Tail, fleshy tab	0	0.00	1	0.02
Genital tubercle: absent	2	0.09	1	0.02
Anal atresia	2	0.09	1	0.02

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - FRESH VISCERAL EXAMINATION OF BODY ON DAY 20 OR 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	6		18	
Number of fetuses examined	1008		2566	
OBSERVATION	N	%	N	%
Situs inversus	0	0.00	1	0.04
Heart: malformed	0	0.00	1	0.04
Aortic arch: narrowed	0	0.00	1	0.04
Persistent truncus arteriosus	0	0.00	1	0.04
Inominate artery: absent	1	0.10	16	0.62
Azygos vein: absent	1	0.10	0	0.00
Azygos vein: transposed	0	0.00	1	0.04
Umbilical artery: transposed	17	1.70	108	4.21
Subclavian artery: retroesophageal	0	0.00	1	0.04
Intestine: distended	0	0.00	1	0.04
Liver: lobe misshapen	0	0.00	1	0.04
Adrenal gland: absent	1	0.10	0	0.00
Multiple urogenital abnormalities	1	0.10	0	0.00
Kidney: absent	26	2.58	22	0.86
Kidney: dilated renal pelvis	26	2.58	55	2.14
Ureter: absent	249	24.70	339	13.21
Ureter: dilated	249	24.70	501	19.52
Ureter: dilated (marked)	15	1.49	5	0.19
Ureter: convoluted	175	17.36	339	13.21
Ureter: convoluted (marked)	6	0.60	3	0.12
Ureter: fused	1	0.10	0	0.00
Urinary bladder: absent	0	0.00	1	0.04
Testis: absent	0	0.00	1	0.04
Testis: malpositioned	0	0.00	1	0.04
Testis: cyst	0	0.00	2	0.08

File name: I.1.1-RAT_SD_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - FIXED VISCERAL EXAMINATION
OF HEAD ON DAY 20 OR 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	7		18	
Number of foetuses examined	894		2304	
OBSERVATION	N	%	N	%
Hydrocephaly	0	0.00	1	0.04
Brain: malformed	1	0.11	0	0.00
Brain: dilated ventricles	0	0.00	2	0.09
Anophthalmia	0	0.00	2	0.09
Eye: discolored	0	0.00	1	0.04
Retina: Fold	0	0.00	1	0.04

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - SKELETAL EXAMINATION OF
BODY ON DAY 20 OF GESTATION - page 1/4**

PERIOD	2013-2015		2016-2018	
Number of studies included	7		8	
Number of foetuses examined	1014		1052	
OBSERVATION	N	%	N	%
Metacarpals: advanced ossification	14	1.38	0	0.00
Metacarpals: incomplete ossification, 2nd to 4th digits	6	0.59	3	0.29
Metacarpals: incomplete ossification, 2nd and 5th digits	11	1.08	0	0.00
Metacarpals: unossified, 2nd to 4th digits	0	0.00	2	0.19
Metacarpals: unossified, 5th digit	143	14.10	124	11.79
Metatarsals: incomplete ossification	5	0.49	10	0.95
Metatarsals: unossified	3	0.30	7	0.67
Metatarsals: absent	3	0.30	7	0.67
Phalanx: absent, forepaws	0	0.00	1	0.10
Limbs: malformed	0	0.00	1	0.10
Clavicle: bent	0	0.00	1	0.10
Scapula: misshapen	0	0.00	1	0.10
Pubis: incomplete ossification	7	0.69	6	0.57
Pubis: unossified	0	0.00	4	0.38
Ischium: incomplete ossification	0	0.00	2	0.19
Ribs: number of full ribs = 12/12	0	0.00	4	0.38
Ribs: number of full ribs = 12/13	2	0.20	1	0.10
Ribs: number of full ribs = 13/14	1	0.10	0	0.00
Rib: supernumerary cervical	4	0.39	17	1.62
Rib: supernumerary lumbar	3	0.30	5	0.48
Rib: supernumerary lumbar (short)	88	8.68	106	10.08

Historical Control Data

Rat Crl: OFA.SD.

**FOETAL EXAMINATION - SKELETAL EXAMINATION OF
BODY ON DAY 20 OF GESTATION - page 2/4**

PERIOD	2013-2015		2016-2018	
Number of studies included	7		8	
Number of fetuses examined	1014		1052	
OBSERVATION	N	%	N	%
Rib: short	2	0.20	1	0.10
Rib: unilateral rudimentary 14th	9	0.89	0	0.00
Rib: bilateral rudimentary 14th	5	0.49	0	0.00
Rib: bent	0	0.00	1	0.10
Rib: thick	0	0.00	1	0.10
Sternebrae: incomplete ossification of 1st/3rd	23	2.27	13	1.24
Sternebrae: incomplete ossification of 2nd/4th	45	4.44	23	2.19
Sternebrae: incomplete ossification of 6th	31	3.06	46	4.37
Sternebrae: unossified	0	0.00	1	0.10
Sternebrae: unossified 1st/3rd	1	0.10	3	0.29
Sternebrae: unossified 2nd/4th	5	0.49	7	0.67
Sternebrae: unossified 5th	61	6.02	60	5.70
Sternebrae: unossified 6th	8	0.79	9	0.86
Sternebrae: asymmetric	3	0.30	5	0.48
Hemisternebrae	1	0.10	0	0.00
Sternebrae: bipartite	4	0.39	2	0.19
Sternebrae: split	1	0.10	0	0.00
Sternebrae: minor fusion	0	0.00	1	0.10
Sternebrae: malformed	0	0.00	1	0.10

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - SKELETAL EXAMINATION OF
BODY ON DAY 20 OF GESTATION - page 3/4**

PERIOD	2013-2015		2016-2018	
Number of studies included	7		8	
Number of foetuses examined	1014		1052	
OBSERVATION	N	%	N	%
Vertebral column: malformed	1	0.10	1	0.10
Vertebrae, presacral vertebral arches = 27	3	0.30	2	0.19
Vertebrae, cervical: malformed	1	0.10	1	0.10
Vertebrae, cervical: advanced ossification	112	11.05	0	0.00
Vertebrae, cervical: increased ossification 1st centrum	157	15.48	208	19.77
Vertebrae, cervical: incomplete ossification of arches	0	0.00	3	0.29
Vertebrae, cervical: small arch	1	0.10	0	0.00
Vertebrae, thoracic: number = 12	0	0.00	4	0.38
Vertebrae, thoracic: incomplete ossification of 1-4th centrum	7	0.69	0	0.00
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	36	3.55	38	3.61
Vertebrae, thoracic: incomplete ossification of 9-13th centrum	9	0.89	0	0.00
Vertebrae, thoracic: unossified centrum	2	0.20	1	0.10
Vertebrae, thoracic: unossified 1-9th centrum	9	0.89	8	0.76
Vertebrae, thoracic: bipartite centrum	6	0.59	8	0.76
Vertebrae, thoracic: misaligned centrum	0	0.00	1	0.10
Vertebrae, lumbar: number = 5	0	0.00	3	0.29
Vertebrae, lumbar: number = 7	2	0.20	5	0.48
Vertebrae, lumbar: incomplete ossification of centrum	0	0.00	4	0.38
Vertebrae, lumbar: bipartite centrum	1	0.10	1	0.10
Vertebrae, lumbar: hemicentric centrum	0	0.00	1	0.10
Vertebrae, lumbar: small centrum	0	0.00	1	0.10

Historical Control Data

Rat Crl: OFA.SD.

**FOETAL EXAMINATION - SKELETAL EXAMINATION OF
BODY ON DAY 20 OF GESTATION - page 4/4**

PERIOD	2013-2015		2016-2018	
Number of studies included	7		8	
Number of foetuses examined	1014		1052	
OBSERVATION	N	%	N	%
Vertebrae, sacral: incomplete ossification of centrum	0	0.00	4	0.38
Vertebrae, sacral: incomplete ossification of arches	47	4.64	21	2.00
Vertebrae, sacral: unossified	0	0.00	4	0.38
Vertebrae, sacral: unossified centrum	1	0.10	0	0.00
Vertebrae, sacral: unossified arches	0	0.00	1	0.10
Vertebrae, sacral: hemicentric centrum	0	0.00	1	0.10
Vertebrae, caudal: unossified	9	0.89	8	0.76
Vertebrae, caudal: unossified arches - region 1-2	115	11.34	154	14.64

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - SKELETAL EXAMINATION OF
HEAD ON DAY 20 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	7		8	
Number of foetuses examined	960		1052	
OBSERVATION	N	%	N	%
Skull: malformed	0	0.00	1	0.10
Generalised incomplete ossification	0	0.00	3	0.29
Frontal: incomplete ossification	0	0.00	1	0.10
Parietal: incomplete ossification	14	1.46	13	1.24
Interparietal: incomplete ossification	44	4.58	35	3.33
Supraoccipital: incomplete ossification	21	2.19	3	0.29
Supraoccipital: unossified line	1	0.10	0	0.00
Squamosal: incomplete ossification	7	0.73	3	0.29
Tympanic annulus: incomplete ossification	0	0.00	1	0.10
Nasal: incomplete ossification	2	0.21	1	0.10
Zygomatic: incomplete ossification	2	0.21	0	0.00
Zygomatic: misshapen	1	0.10	0	0.00
Maxilla: small	1	0.10	0	0.00
Mandible: short	1	0.10	0	0.00
Mandible: long	1	0.10	0	0.00
Palatine: absent	0	0.00	1	0.10
Palatine: split	0	0.00	1	0.10
Hyoid: incomplete ossification	4	0.42	0	0.00
Hyoid: unossified	12	1.25	6	0.57
Presphenoid: incomplete ossification	2	0.21	1	0.10
Presphenoid: unossified	0	0.00	1	0.10
Basisphenoid: misshapen	0	0.00	1	0.10

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY
ON DAY 21 OF GESTATION - page 1/2**

PERIOD	2017-2018	
Number of studies included	11	
Number of fetuses examined	1674	
OBSERVATION	N	%
Metacarpals: incomplete ossification, 5th digit	27	1.61
Metacarpals: unossified, 5th digit	4	0.24
Metatarsals: incomplete ossification	1	0.06
Metatarsals: unossified, 1st digit	86	5.14
Phalanx: unossified, forepaws	94	5.62
Phalanx: unossified, hindpaws	302	18.04
Paw: malformed	1	0.06
Femur: short	1	0.06
Humerus: incomplete ossification	8	0.48
Scapula: bent	1	0.06
Pelvis: malformed	1	0.06
Ribs: absent	2	0.12
Ribs: number of full ribs = 12/13	1	0.06
Rib: supernumerary cervical	26	1.55
Rib: supernumerary lumbar	4	0.24
Rib: supernumerary lumbar (short)	143	8.54
Rib: short	4	0.24
Rib: wavy	3	0.18
Rib: incomplete ossification	2	0.12

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY****ON DAY 21 OF GESTATION - page 2/2**

PERIOD	2017-2018	
Number of studies included	11	
Number of fetuses examined	1674	
OBSERVATION	N	%
Sternebrae: extra ossification site	3	0.18
Sternebrae: incomplete ossification of 1st/3rd	4	0.24
Sternebrae: incomplete ossification of 2nd/4th	9	0.54
Sternebrae: incomplete ossification of 6th	4	0.24
Sternebrae: unossified 5th	11	0.66
Sternebrae: unossified 6th	3	0.18
Sternebrae: asymmetric	6	0.36
Vertebral column: malformed	1	0.06
Vertebrae, presacral vertebral arches = 27	6	0.36
Vertebrae, presacral vertebral arches = 25	3	0.18
Vertebrae, cervical: incomplete ossification of arches	3	0.18
Vertebrae, cervical: unossified odontoid process	959	57.29
Vertebrae, cervical: unossified centrum	988	59.02
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	10	0.60
Vertebrae, thoracic: incomplete ossification of 10-13th centrum	62	3.70
Vertebrae, thoracic: unossified 1-9th centrum	2	0.12
Vertebrae, lumbar: malformed	2	0.12
Vertebrae, lumbar: number = 5	1	0.06
Vertebrae, lumbar: number = 7	5	0.30
Vertebrae, lumbar: incomplete ossification of centrum	3	0.18
Vertebrae, sacral: incomplete ossification of arches	1	0.06
Vertebrae, caudal: number < 5	13	0.78
Vertebrae, caudal: malpositioned	1	0.06

File name: I.1.1-RAT_SD_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - SKELETAL EXAMINATION OF HEAD
ON DAY 21 OF GESTATION**

PERIOD	2017-2018	
Number of studies included	11	
Number of fetuses examined	1549	
OBSERVATION	N	%
Cranium: sutural bone	4	0.26
Cranium: extra ossification site	1	0.06
Frontal: incomplete ossification	2	0.13
Parietal: incomplete ossification	6	0.39
Interparietal: incomplete ossification	67	4.33
Interparietal: unossified area	2	0.13
Supraoccipital: incomplete ossification	2	0.13
Squamosal: incomplete ossification	5	0.32
Nasal: incomplete ossification	2	0.13
Zygomatic: incomplete ossification	3	0.19
Zygomatic: misshapen	2	0.13
Mandible: incomplete ossification	59	3.81
Hyoid: incomplete ossification	8	0.52
Hyoid: unossified	3	0.19

Historical Control Data**Rat Crl: OFA.SD.****Maternal body weight gain (g) during lactation**

Study	Year	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
M17	2017	21	10.5	8.8	5.9	8.7	6.6	6.2	3.0	7.7	1.8	8.2	-14.3	13.9
F16	2016	6	9.2	6.0	8.0	4.7								
I16	2016	24	17.2	11.3	7.6	9.7	5.3	5.4	2.4	8.9	-1.4	8.5	-12.1	11.0
J16	2016	23	9.5	8.4	7.7	6.5	6.9	5.6	5.1	6.6	-0.7	8.5	-16.3	11.0
K16	2016	5	13.7	7.1	5.0	6.8								
F15	2015	10	6.4	6.9	4.3	6.0	5.1	6.4	0.1	9.9	-0.6	6.4	-11.1	13.8
A13-1	2013	23	13.3	8.1	8.7	7.9								
Total		112												
Mean			12.0		7.1		6.1		3.1		-0.2		-13.8	
SD			9.3		7.8		5.7		8.1		8.1		12.1	
2007-2011		115	13.3	9.9	8.5	7.5	NA	NA	NA	NA	NA	NA	NA	NA

Historical Control Data**Rat Crl: OFA.SD.****Maternal food consumption (g/day) during lactation**

Study	Year	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
M17	2017	21	34.4	4.0	42.9	5.7	49.9	4.7	58.5	6.0	61.5	7.0	70.2	7.1
F16	2016	6	34.4	8.7	43.1	5.3								
I16	2016	24	37.6	4.5	48.2	4.4	53.2	4.3	61.0	3.5	62.7	5.5	72.9	7.5
J16	2016	23	34.9	4.7	45.9	4.2	52.1	4.3	60.0	4.9	61.8	5.7	70.1	6.7
K16	2016	5	41.6	3.4	49.8	4.9								
F15	2015	10	32.1	8.5	41.6	10.3	45.0	10.1	49.3	10.6	53.1	15.3	58.0	15.5
A13-1	2013	23	37.2	6.7	48.6	5.3								
<i>Total</i>		<i>112</i>												
<i>Mean</i>			<i>35.9</i>		<i>46.0</i>		<i>50.9</i>		<i>58.5</i>		<i>60.9</i>		<i>69.4</i>	
<i>SD</i>				<i>5.9</i>		<i>6.1</i>		<i>5.9</i>		<i>6.8</i>		<i>8.2</i>		<i>9.6</i>
2007-2011		<i>115</i>	<i>40.0</i>	<i>6.5</i>	<i>50.2</i>	<i>5.7</i>	<i>NA</i>	<i>NA</i>	<i>NA</i>	<i>NA</i>	<i>NA</i>	<i>NA</i>	<i>NA</i>	<i>NA</i>

Historical Control Data**Rat Crl: OFA.SD.****Post-partum litter data**

Study	Year	Number of females				Gestation length (days)		Number of uterine implants		Number of pups born		Pre-birth loss index %	Live birth index %	Pup viability index %	Pup weaning index %
		Mated	Pregnant	With liveborn	With pups at weaning	Mean	SD	Mean	SD	Mean	SD				
M17	2017	22	21	21	21	22.1	0.3	15.5	1.6	14.8	2.0	4.64	100	98.1	98.8
F16	2016	6	6	6	NA	22.5	0.5	14.7	1.9	13.8	2.6	6.32	96.4	100	
I16	2016	24	24	24	24	22.0	0.0	13.3	2.3	12.0	1.9	9.35	99.3	99.3	99.5
J16	2016	25	24	23	23	22.0	0.4	13.2	2.5	11.8	2.7	10.42	95.7	99.3	100
K16	2016	5	5	5	NA	22.4	0.5	15.6	1.7	15.0	1.4	3.69	100	98.7	
F15	2015	10	10	10	10	22.2	0.4	12.2	3.9	10.8	3.9	13.57	95.4	100	98.6
A13-1	2013	25	25	23	23	22.0	0.2	13.6	1.9	12.1	2.1	11.00	99.6	100	99.5
<i>Total %</i>		<i>117</i>	<i>115 98%</i>	<i>112 96%</i>	<i>101 95%</i>										
<i>Mean SD</i>						<i>22.1</i>	<i>0.3</i>	<i>13.8</i>	<i>2.5</i>	<i>12.6</i>	<i>2.7</i>	<i>9.03</i>	<i>98.3</i>	<i>99.3</i>	<i>99.4</i>
2007-2011		<i>125</i>	<i>121 97%</i>	<i>118 94%</i>	<i>114 91%</i>	<i>21.5</i>	<i>3.5</i>	<i>13.4</i>	<i>1.4</i>	<i>12.0</i>	<i>2.9</i>	<i>NR</i>	<i>97.3</i>	<i>97.6</i>	<i>98.7</i>

NR: not recorded

Historical Control Data**Rat Crl: OFA.SD.****Post-partum data - pup weights (g)**

Study	Year	Number of litters	Postnatal day 1				Postnatal day 4				Postnatal day 7				Postnatal day 14				Postnatal day 21			
			Males		Females		Males		Females		Males		Females		Males		Females		Males		Females	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
M17	2017	21	6.8	0.7	6.5	0.6	9.7	1.2	9.4	1.0	16.1	1.7	15.4	1.7	34.1	2.9	32.8	3.1	57.7	5.6	54.6	5.3
F16	2016	6	7.3	0.3	6.9	0.6	10.2	0.8	9.9	1.3	16.1	1.3	16.0	1.7								
I16	2016	24	7.6	0.6	7.2	0.6	11.4	1.1	10.8	1.1	18.2	1.5	17.4	1.5	36.2	2.4	35.0	2.7	59.8	3.6	57.7	3.6
J16	2016	23	7.4	0.4	7.2	0.5	11.0	0.9	10.7	1.2	18.0	1.2	17.7	1.6	36.1	1.9	35.6	2.3	59.0	3.9	58.2	4.4
K16	2016	5	7.5	0.6	7.1	0.7	10.8	1.3	10.3	1.2	18.5	1.9	18.1	1.9								
F15	2015	10	7.7	0.6	7.6	0.6	11.4	1.2	11.0	1.5	18.0	1.9	17.5	2.5	35.6	3.8	33.7	6.3	57.7	5.2	53.6	11.9
A13-1	2013	23	7.6	0.5	7.2	0.4	11.2	0.9	10.8	0.8	18.4	1.4	17.7	1.2	38.1	2.5	36.9	2.4	61.2	3.9	59.1	3.9
<i>Total Mean</i>		<i>112</i>	<i>7.4</i>		<i>7.1</i>		<i>10.8</i>		<i>10.5</i>		<i>17.7</i>		<i>17.1</i>		<i>36.1</i>		<i>35.0</i>		<i>59.3</i>		<i>57.1</i>	
<i>SD</i>			<i>0.6</i>		<i>0.6</i>		<i>1.2</i>		<i>1.2</i>		<i>1.7</i>		<i>1.8</i>		<i>2.9</i>		<i>3.4</i>		<i>4.5</i>		<i>5.7</i>	
2007-2011		123	7.6		7.3		11.1		10.7		18.0		17.4		36.2		35.3		59.6		57.6	
			<i>0.7</i>		<i>0.7</i>		<i>1.2</i>		<i>1.3</i>		<i>1.6</i>		<i>1.5</i>		<i>3.2</i>		<i>2.9</i>		<i>5.5</i>		<i>4.8</i>	

Historical Control Data**Rat Crl: OFA.SD.****Pre-weaning development - % of pups positive**

Study	Year	Number of litters	Pinna unfolding				Incisor eruption									Eye opening					
			PND1	PND2	PND3	PND4	PND7	PND8	PND9	PND10	PND11	PND12	PND13	PND14	PND15	PND12	PND13	PND14	PND15	PND16	PND17
M17	2017	21	5	81	100	100	0	1	7	46	85	97	99	100	100	0	8	47	95	100	100
I16	2016	24	0	84	99	100	2	4	23	60	96	99	100	100	100	0	0	24	80	99	100
J16	2016	23	1	60	96	100	0	0	9	21	60	94	98	100	100	0	2	50	92	100	100
F15	2015	10	5	70	100	100	0	4	10	53	96	100	100	100	100	0	7	59	94	100	100
A13-1	2013	23	0	69	99	100	0	1	10	34	78	97	100	100	100	0	3	69	96	100	100
H12-1	2012	3	33	71	96	100	0	0	22	43	78	91	100	100	100	26	61	83	96	100	100
H12-2	2012	3	0	29	92	100	0	0	17	29	58	71	96	100	100	0	17	58	100	100	100
I12-1	2012	4	0	25	84	100	0	0	0	44	47	88	100	100	100	0	6	34	100	100	100
I12-2	2012	4	0	6	100	100	0	0	0	3	25	84	100	100	100	0	0	53	81	100	100
<i>Total Mean %</i>		<i>115</i>	<i>2</i>	<i>68</i>	<i>98</i>	<i>100</i>	<i>0</i>	<i>2</i>	<i>12</i>	<i>40</i>	<i>78</i>	<i>95</i>	<i>99</i>	<i>100</i>	<i>100</i>	<i>1</i>	<i>5</i>	<i>49</i>	<i>91</i>	<i>100</i>	<i>100</i>
2007-2011		172	1	53	95	100	0	2	16	54	90	99	100	100	100	0	4	49	85	95	97

PND = postnatal day

Historical Control Data**Rat Crl: OFA.SD.****Post-weaning development**

Study	Year	Vaginal opening					Balano-preputial skinfold cleavage				
		PND of occurrence			Body weight (g)		PND of occurrence			Body weight (g)	
		Mean	SD	N	Mean	SD	Mean	SD	N	Mean	SD
I16	2016	34	2	20	124	15	42	2	20	199	15
J16	2016	35	2	20	130	14	44	2	19	218	16
F15	2015	35	1	10	127	14	44	1	10	221	26
A13-1	2013	35	3	25	139	17	44	3	25	235	27
H12-2	2012	33	2	12	132	18	43	1	12	231	24
I12-1	2012	34	2	16	125	13	46	2	16	242	26
I12-2	2012	36	2	16	141	13	43	2	16	219	18
<i>Total</i>				<i>119</i>					<i>118</i>		
<i>Mean</i>		<i>35</i>			<i>132</i>		<i>44</i>			<i>223</i>	
<i>SD</i>			<i>2</i>		<i>16</i>		<i>2</i>			<i>26</i>	
2007-2011		34	2	253	122	14	44	3	254	221	24

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Water Maze (VideoTrack 3.2)

Study Year N	MALES							
	Time (s)				Distance (cm)			
	A13-1	I16	J16	Overall	A13-1	I16	J16	Overall
	2013	2016	2016		2013	2016	2016	
	25	20	20		25	20	20	
Trial 1								
Mean	33	28	28	30	404	358	394	387
SD	19	20	14	18	199	215	164	192
Trial 2								
Mean	19	15	14	16	235	212	197	216
SD	11	8	7	9	112	170	105	130
Trial 3								
Mean	15	11	9	12	177	162	145	163
SD	11	7	4	8	107	86	67	89
Trial 4								
Mean	20	15	9	15	221	216	137	193
SD	16	10	6	12	130	137	67	121
Trial 5								
Mean	40	36	37	38	509	547	550	533
SD	22	21	27	23	310	323	343	320
Trial 6								
Mean	26	26	19	24	275	337	250	287
SD	13	16	10	13	120	200	152	160
Trial 7								
Mean	23	16	12	17	268	185	150	204
SD	12	10	5	11	128	99	86	117

File name: I.1.2-RAT_SD_post partum_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Water Maze (VideoTrack 3.2)

Study Year N	FEMALES							
	Time (s)				Distance (cm)			
	A13-1	I16	J16	Overall	A13-1	I16	J16	Overall
	2013	2016	2016		2013	2016	2016	
	25	20	20		25	20	20	
Trial 1								
Mean	30	26	25	27	392	407	344	382
SD	17	11	8	13	204	159	127	169
Trial 2								
Mean	20	12	15	16	275	197	206	230
SD	13	8	7	10	146	105	102	125
Trial 3								
Mean	14	12	10	12	187	173	118	161
SD	10	8	4	8	140	79	37	102
Trial 4								
Mean	15	8	11	12	180	128	144	153
SD	10	4	7	8	95	35	77	78
Trial 5								
Mean	40	28	37	35	529	448	538	507
SD	25	17	26	23	334	241	339	308
Trial 6								
Mean	27	19	25	24	307	277	328	304
SD	19	16	15	17	127	186	165	158
Trial 7								
Mean	21	14	13	16	217	188	159	190
SD	14	12	9	12	117	94	83	102

File name: I.1.2-RAT_SD_post partum_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Open Field (VideoTrack 3.2)

Study	Year	N	MALES														
			Total time (s) engaged in:						Total distance travelled (cm)		Time (s) spent in:						
			Ambulatory activity		Small movements		Inactivity				Corner regions		Centre region		Lateral regions		
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
I16	2016	20	49	9	35	3	96	10	975	132	96	18	11	7	73	14	
J16	2016	20	53	9	36	4	90	12	1051	148	95	15	12	6	73	12	
A13-1	2013	25	52	11	35	5	92	14	1060	210	93	16	15	12	72	13	
Total Mean		65	51		35		93		1031		95		13		73		
SD			10		4		12		172		16		9		13		

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Open Field (VideoTrack 3.2)

Study	Year	N	FEMALES													
			Total time (s) engaged in:						Total distance travelled (cm)		Time (s) spent in:					
			Ambulatory activity		Small movements		Inactivity				Corner regions		Centre region		Lateral regions	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I16	2016	20	48	21	27	10	105	30	1008	407	115	26	9	12	55	19
J16	2016	20	58	9	36	5	86	13	1174	158	96	18	13	11	71	11
A13-1	2013	25	60	12	36	5	84	15	1221	238	106	11	9	5	65	10
Total		65														
Mean			56		33		91		1141		106		10		64	
SD				15		8		22		294		20		10		15

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Startle (version II)

Study	Year	Pup Age	N	MALES													
				Block 1		Block 2				Block 3				Block 4			
				AVeN		AVeN		Habituation (%)		AVeN		Habituation (%)		AVeN		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
J16	2016	10W	20	0.425	0.166	0.319	0.154	-25.4	23.3	0.279	0.147	-33.8	23.3	0.271	0.131	-35.2	19.5
Total Mean SD			20	0.425	0.166	0.319	0.154	-25.4	23.3	0.279	0.147	-33.8	23.3	0.271	0.131	-35.2	19.5

W: week

Historical Control Data**Rat Crl: OFA.SD.****Post-weaning behaviour tests - Startle (version II)**

Study	Year	Pup Age	N	MALES			
				Block 5			
				AVeN		Habituation (%)	
				Mean	SD	Mean	SD
J16	2016	10W	20	0.258	0.081	-35.3	19.7
<i>Total</i>			<i>20</i>				
<i>Mean</i>				<i>0.258</i>		<i>-35.3</i>	
<i>SD</i>					<i>0.081</i>		<i>19.7</i>

W: week

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Startle (version II)

Study	Year	Pup Age	N	FEMALES													
				Block 1		Block 2				Block 3				Block 4			
				AVeN		AVeN		Habituation (%)		AVeN		Habituation (%)		AVeN		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
J16	2016	10W	20	0.322	0.144	0.228	0.127	-28.3	29.1	0.198	0.100	-35.6	27.5	0.205	0.129	-35.4	29.5
Total			20														
Mean				0.322		0.228		-28.3		0.198		-35.6		0.205		-35.4	
SD				0.144		0.127		29.1		0.100		27.5		0.129		29.5	

W: week

Historical Control Data**Rat Crl: OFA.SD.****Post-weaning behaviour tests - Startle (version II)**

Study	Year	Pup Age	N	FEMALES			
				Block 5			
				AVeN		Habituation (%)	
				Mean	SD	Mean	SD
J16	2016	10W	20	0.194	0.110	-36.6	27.8
<i>Total</i>			20				
<i>Mean</i>				0.194		-36.6	
<i>SD</i>					0.110		27.8

W: week

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Startle (version 6.11)

Study	Year	Pup Age	N	MALES													
				Habituation													
				Trial 1		Trial 2		Trial 3		Trial 4		Trial 5		Trial 6		Trial 7	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I16	2016	10	20	6.150	4.509	6.501	3.242	5.214	2.340	4.880	2.053	4.624	3.349	3.557	2.043	3.339	2.482
<i>Total</i>			<i>20</i>	<i>6.150</i>		<i>6.501</i>		<i>5.214</i>		<i>4.880</i>		<i>4.624</i>		<i>3.557</i>		<i>3.339</i>	
<i>Mean</i>																	
<i>SD</i>					<i>4.509</i>		<i>3.242</i>		<i>2.340</i>		<i>2.053</i>		<i>3.349</i>		<i>2.043</i>		<i>2.482</i>

W: week

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Startle (version 6.11)

Study	Year	Pup Age	N	MALES															
				Habituation								Pre-pulse inhibition							
				Trial 8		Trial 9		Trial 10		Habituation (%)		No PP		PP 68 db		PP 71 db		PP 77 db	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I16	2016	10	20	2.264	1.362	1.977	1.058	2.478	1.599	57	51	2.511	1.014	2.135	0.985	1.706	1.047	1.143	0.826
Total			20	2.264		1.977		2.478		57		2.511		2.135		1.706		1.143	
Mean																			
SD				1.362		1.058		1.599		51		1.014		0.985		1.047		0.826	

W: week

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Startle (version 6.11)

Study	Year	Pup Age	N	FEMALES													
				Habituation													
				Trial 1		Trial 2		Trial 3		Trial 4		Trial 5		Trial 6		Trial 7	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I16	2016	10	20	4.972	2.434	3.775	1.704	5.265	3.120	4.149	2.331	4.234	1.781	3.489	1.893	3.477	2.473
Total			20	4.972		3.775		5.265		4.149		4.234		3.489		3.477	
Mean																	
SD																	
					2.434		1.704		3.120		2.331		1.781		1.893		2.473

W: week

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Startle (version 6.11)

Study	Year	Pup Age	N	FEMALES															
				Habituation								Pre-pulse inhibition							
				Trial 8		Trial 9		Trial 10		Habituation (%)		No PP		PP 68 db		PP 71 db		PP 77 db	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I16	2016	10	20	2.191	1.321	2.245	1.312	2.417	1.756	52	31	2.429	1.232	2.002	1.162	1.415	0.882	0.899	0.658
Total			20																
Mean				2.191		2.245		2.417		52		2.429		2.002		1.415		0.899	
SD				1.321		1.312		1.756		31		1.232		1.162		0.882		0.658	

W: week

Historical Control Data

Rat Crl: OFA.SD.

Maternal body weight gain (g) during gestation

Study	Year	Dams with live fetuses	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD
S18	2018	6	26.1	4.4	15.6	4.2	27.6	7.7
T18	2018	19	21.4	6.2	16.0	5.8	25.4	5.7
I17	2017	20	16.8	6.2	14.7	4.8	24.3	3.5
J17	2017	17	20.6	4.9	16.7	3.1	26.0	5.1
K17-2	2017	18	21.2	8.8	17.2	6.5	23.5	7.2
A16	2016	13	15.3	6.6	14.0	3.9	21.0	7.5
B16	2016	22	14.4	8.0	14.5	6.4	22.4	4.7
I16	2016	16	21.7	4.7	16.3	4.5	20.8	6.0
J16	2016	16	22.7	6.8	16.1	4.9	26.0	10.7
G15	2015	17	17.8	6.2	14.6	5.5	24.2	6.2
K15	2015	14	15.5	6.3	12.8	4.8	17.1	4.4
L15	2015	14	17.8	10.2	15.3	7.2	22.7	5.8
D14	2014	15	22.4	6.6	17.0	4.9	26.9	6.0
Total Mean		207	19.1	7.4	15.5	5.3	23.6	6.6
SD								
2010-2013		306	20.9	7.2	15.8	5.5	25.1	5.9

Historical Control Data**Rat Crl: OFA.SD.****Maternal food consumption (g/day) during gestation**

Study	Year	Dams with live fetuses	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 0 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
S18	2018	6	24.5	1.4	26.1	1.4	25.3	1.2		
T18	2018	19	23.8	2.7	25.3	2.5	24.5	2.6	27.2	2.7
I17	2017	20	21.2	3.0	22.7	2.8	21.9	2.9	23.8	2.4
J17	2017	17	21.3	2.3	23.0	2.0			24.6	2.1
K17-2	2017	18	24.2	2.5	25.5	3.2	24.8	2.7	26.0	3.3
A16	2016	13					21.5	2.2	23.3	2.0
B16	2016	22	21.5	1.8	23.1	2.5	22.3	1.9	24.5	2.0
G15	2015	17					23.3	2.4	24.7	2.5
K15	2015	14	22.8	3.2	24.8	2.9			25.1	2.9
L15	2015	14	22.4	2.4	24.9	2.4	23.7	2.1	24.3	2.0
D14	2014	15	25.3	2.5	28.6	2.3			29.9	3.1
<i>Total Mean</i>		<i>175</i>	<i>22.8</i>		<i>24.6</i>		<i>23.2</i>		<i>25.3</i>	
<i>SD</i>				<i>2.8</i>		<i>3.0</i>		<i>2.6</i>		<i>3.0</i>
2010-2013		184	24.2	3.2	26.2	2.9	24.8	2.3	26.8	2.8

Historical Control Data**Rat Ctrl: OFA.SD.****Oestrous cycle - before treatment**

Study	Year	Females evaluated	Cycle length (days)		Irregularity index		Oestrous days (%)		Females acyclic or with acyclic period
		N	Mean	SD	Mean	SD	Mean	SD	%
G15	2015	17	3.9	0.4	0.2	0.3	30.7	9.0	15
G9	2009	15	3.5	0.6	0.0	0.0	34.2	8.8	25
C7	2007	18	4.1	0.3	0.0	0.1	24.8	3.8	10
<i>Total</i>		<i>50</i>							
<i>Mean</i>			<i>3.9</i>		<i>0.1</i>		<i>29.6</i>		<i>16</i>
<i>SD</i>				<i>0.5</i>		<i>0.2</i>		<i>8.3</i>	

Historical Control Data

Rat Crl: OFA.SD.

Oestrous cycle - during treatment (pre-mating period)

Study	Year	Females evaluated	Cycle length (days)		Irregularity index		Oestrous days (%)		Females acyclic or with acyclic period
		N	Mean	SD	Mean	SD	Mean	SD	%
R18	2018	22	3.9	0.5	0.3	0.2	35.2	10.3	0
I17	2017	19	4.2	0.5	0.4	0.3	33.8	9.8	10
K17-2	2017	16	4.0	0.5	0.2	0.2	30.8	8.1	20
A16	2016	8	4.1	0.4	0.4	0.1	37.5	4.7	60
B16	2016	12	4.5	0.5	0.3	0.4	26.7	7.0	50
G15	2015	13	3.9	0.4	0.1	0.2	33.0	10.3	35
H15	2015	23	4.1	0.4	0.2	0.3	27.8	7.1	4
K15-1	2015	14	4.1	0.4	0.4	0.3	29.5	8.1	13
K15-2	2015	5	4.3	0.3	0.4	0.1	31.7	7.9	69
L15-1	2015	12	4.3	0.5	0.4	0.2	35.1	7.0	0
L15-2	2015	11	4.2	0.5	0.4	0.2	34.2	5.1	31
D14	2014	20	4.1	0.3	0.2	0.2	30.7	7.0	0
F9	2009	19	3.9	0.4	0.4	0.3	32.6	7.7	5
G9	2009	20	4.0	0.4	0.1	0.2	28.6	8.7	0
B8	2008	18	4.1	0.3	0.1	0.2	27.8	7.0	10
B7	2007	19	4.4	0.6	0.2	0.3	30.5	7.8	5
C7	2007	18	4.3	0.6	0.1	0.1	28.1	4.9	10
<i>Total Mean SD</i>		269	4.1	0.5	0.3	0.3	31.1	8.2	13

File name: I.1.3-RAT_SD_G13_sperm_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****Caesarean data collected on, or close to, day 13 of gestation**

Study	Year	Number of females		Pre-coital interval (days)		Number of females		Fertility index %	Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Post-implantation loss %		Live embryos	
		Paired	Mated	Mean	SD	Pregnant	With live embryos		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
S18	2018	6	6	2.5	1.4	6	6	100	17.3	2.3	16.2	0.8	5.8	8.8	1.0	2.4	16.0	0.6
T18	2018	20	20	2.9	1.2	19	19	95	16.1	2.3	15.8	2.6	2.5	6.0	3.8	5.8	15.3	2.9
I17	2017	21	21	3.4	3.4	21	21	100	16.0	2.1	15.5	1.9	3.1	4.4	6.0	5.7	14.6	2.2
J17	2017	20	19	2.4	0.8	19	19	100	16.4	1.5	16.1	1.4	1.6	2.7	5.8	5.6	15.2	1.5
K17-1	2017	20	20	2.8	1.4	20	20	100	16.3	1.8	14.8	3.6	9.1	19.7	4.3	6.3	14.2	3.8
K17-2	2017	20	20	2.6	1.3	18	18	90	16.7	3.6	16.3	4.0	5.2	16.0	2.8	4.8	15.8	3.8
A16	2016	20	18	3.1	2.7	16	16	89	16.0	1.7	15.4	1.9	3.9	6.1	4.5	4.6	14.7	2.0
B16	2016	24	23	3.8	3.0	23	23	100	14.9	2.3	14.3	2.5	4.3	8.2	5.8	7.5	13.4	2.6
I16	2016	20	20	2.7	1.2	17	17	85	16.2	2.3	16.1	2.4	1.2	2.6	7.7	15.6	14.9	3.7
J16	2016	20	20	3.2	2.3	17	17	85	16.7	2.0	15.7	2.0	5.8	8.2	8.2	12.3	14.5	2.6
G15	2015	20	20	2.3	1.0	18	18	90	16.5	2.5	14.9	3.8	10.8	21.4	4.9	6.4	14.1	3.7
K15	2015	16	16			15	15	94	14.1	2.5	13.3	4.1	7.8	23.1	8.3	8.4	12.1	3.8
L15	2015	16	16	3.6	2.9	16	16	100	16.2	2.5	15.1	2.6	6.2	11.2	8.2	13.0	13.9	3.3
D14	2014	20	20	3.3	2.9	15	15	75	18.1	2.2	17.6	2.0	2.8	4.3	4.7	5.3	16.8	2.3
Total		263	259 98%			240 93%	240 93%											
Mean				3.0					16.2		15.4		4.9		5.6		14.6	
SD					2.2					2.4		2.9		12.2		8.2		3.1
2010-2013		334	333 100%	3.2	3.0	313 94%	312 94%		16.8	2.8	15.8	2.7	5.6	8.7	5.7	10.9	14.9	3.1

Historical Control Data**Rat Crl: OFA.SD.****Sperm Analysis - number in epididymis and motility**

Study	Year	Number of males	Number of sperm in epididymis		% motile		Progressive sperm %	
			Mean	SD	Mean	SD	Mean	SD
T18	2018	20	1015	308	97.5	1.4	69.8	4.1
I17	2017	21	919	238	95.0	3.2	64.1	5.2
J17	2017	20	917	295	96.6	1.6	69.9	2.5
K17	2017	20	1081	292	94.6	5.2	62.6	9.1
L17	2017	22	842	275	91.8	4.4	62.8	4.5
B16	2016	24	908	307	93.3	3.8	63.0	5.3
G15	2015	20	987	372	95.0	3.0	65.0	7.0
H15	2015	24	1080	261	92.0	3.0	59.0	6.0
K15-1	2015	15	1126	232	94.0	4.0	59.0	12.0
K15-2	2015	15	1145	275	94.0	3.0	60.0	4.0
D14	2014	20	1027	277	90.0	21.0	59.0	14.0
<i>Total</i>		<i>221</i>						
<i>Mean</i>			<i>996</i>		<i>93.9</i>		<i>63.2</i>	
<i>SD</i>				<i>296</i>		<i>7.3</i>		<i>8.1</i>
2010-2013		<i>124</i>	<i>933</i>	<i>454</i>	<i>90.6</i>	<i>12.3</i>	<i>NA</i>	<i>NA</i>

Historical Control Data**Rat Crl: OFA.SD.****Sperm Analysis - number in testis**

Study	Year	Number of males	Testis weight (g)		10 ⁶ Sperm per g of testis	
			Mean	SD	Mean	SD
T18	2018	20	1.90	0.18	115	14.3
I17	2017	21	2.01	0.16	131	20.2
J17	2017	20	1.87	0.19	105	13.7
K17	2017	20	1.99	0.14	146	26.3
L17	2017	22	1.98	0.11	97.9	18.2
B16	2016	24	1.84	0.11	141	25.5
G15	2015	20	1.88	0.16	129	37.5
H15	2015	24	1.94	0.17	111	22.1
K15-1	2015	15	1.88	0.18	131	16.7
K15-2	2015	15	2.10	0.27	102	20.0
D14	2014	20	1.86	0.29	125	30.1
<i>Total Mean</i>		<i>221</i>	<i>1.93</i>	<i>0.19</i>	<i>121</i>	<i>27.5</i>
2010-2013		<i>124</i>	<i>1.96</i>	<i>0.19</i>	<i>128</i>	<i>22.7</i>

Historical Control Data**Rat Crl: OFA.SD.****Sperm Analysis - number in the cauda epididymis**

Study	Year	Number of males	Cauda epididymis weight (g)		10 ⁶ Sperm per g of cauda epididymis	
			Mean	SD	Mean	SD
G15	2015	20	0.33	0.03	778	216
H15	2015	24	0.32	0.03	599	256
D14	2014	20	0.31	0.04	777	394
<i>Total</i>		<i>64</i>				
<i>Mean</i>			<i>0.32</i>		<i>710</i>	
<i>SD</i>				<i>0.03</i>		<i>304</i>

Historical Control Data**Rat Crl: OFA.SD.****Maternal body weight gain (g) during gestation: females treated by continuous IV infusion**

Study	Year	Infusion volume mL/kg/day	Dams with live foetuses	Gestation days 0 to 6		Gestation days 6 to 9		Gestation days 9 to 12*		Gestation days 12 to 15*		Gestation days 15 to 18		Gestation days 6 to 18		Gestation days 18 to 20		Gestation days 18 to 21	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A17	2017	24	6	25.3	7.1	12.6	2.4	15.6	3.7	18.1	7.5	29.3	10.6			23.1	8.0		
B17	2017	24	5	31.4	12.8	18.2	5.4	24.0	4.7	23.2	5.1	30.8	9.7			25.5	9.9		
C17	2017	5 [#]	21	35.8	9.5	9.4	6.1	16.7	5.8	18.7	6.0	36.9	9.9	81.8	16.2			50.1	13.6
A16	2016	24	6	33.1	4.5	22.2	4.2	15.2	6.4	20.0	1.8	20.0	14.4			25.2	10.6		
J12	2012	15	25	32.4	6.5	15.3	8.7	17.9	5.1	21.0	5.4	40.4	6.7			32.1	6.7		
C11	2011	5 [#]	6	20.9	9.7	13.8	5.0	22.1	4.2	16.8	9.6	26.7	10.1			35.1	9.0		
D11	2011	5 [#]	25	22.2	14.8	15.4	3.8	19.3	7.0	23.0	5.6	35.7	9.3			31.7	12.3		
E11	2011	5 [#]	6	27.2	7.4	8.8	6.5	25.4	2.0	15.1	3.8	33.1	6.2			34.4	4.3		
F11	2011	60	24	27.2	8.7	15.8	4.6	18.2	6.9	21.2	6.5	40.0	7.4			29.7	6.3		
G11	2011	15	6	28.1	5.3	14.8	3.1	16.5	4.4	17.6	3.8	34.9	5.9			28.3	3.6		
A10	2010	60	7	27.4	6.1	15.9	4.0	16.9	6.0	18.9	5.4	32.8	5.1			27.4	4.8		
Total			137																
Mean				28.7		14.4		18.4		20.3		35.7		81.8		30.3		50.1	
SD					10.5		6.3		6.1		6.0		9.7		16.2		8.6		13.6
Non-infusion studies 2018																			
			247	8.5	38.5	13.1	5.4	18.2	4.9	20.5	5.5	37.8	8.4	89.4	15.1	NA	NA	51.0	10.8

[#] Infusion volume per administration.

* Day 12 instead of 11 for study A10.

Historical Control Data**Rat Crl: OFA.SD.****Maternal food consumption (g/day) during gestation: females treated by continuous IV infusion**

Study	Year	Infusion volume mL/kg/day	Dams with live fetuses	Gestation days 0 to 6		Gestation days 6 to 9		Gestation days 9 to 12*		Gestation days 12* to 15*		Gestation days 15 to 18		Gestation days 6 to 18		Gestation days 18 to 20		Gestation days 18 to 21	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A17	2017	24	6	19.8	2.1	23.8	2.0	23.8	2.1	24.3	3.9	28.2	3.0			28.3	2.7		
B17	2017	24	5	20.2	3.3	27.4	1.1	27.5	1.6	27.9	3.4	30.7	3.1			28.4	3.1		
C17	2017	5 [#]	21	20.1	1.8	23.9	2.6	25.0	2.7	25.7	2.8	26.6	3.2	25.3	2.5			26.7	4.8
A16	2016	24	6	18.7	1.4	24.9	2.1	23.6	3.3	26.9	1.4	28.6	2.6			27.4	1.9		
J12	2012	15	25	20.7	1.6	25.2	3.1	26.7	2.4	27.2	2.7	29.4	2.7			30.9	2.8		
C11	2011	5 [#]	6	21.4	2.5	26.0	3.0	30.7	2.5	30.7	3.7	31.6	3.5			29.9	2.8		
D11	2011	5 [#]	25	21.2	4.0	27.0	4.0	29.7	3.6	31.2	3.4	32.7	4.5			31.1	6.2		
E11	2011	5 [#]	6	22.6	2.5	27.3	2.6	33.1	5.0	30.9	3.0	30.7	3.2			30.5	2.2		
F11	2011	60	24	19.2	2.6	24.5	2.6	25.9	3.2	27.1	3.4	29.5	3.1			29.9	4.0		
G11	2011	15	6	18.2	1.7	23.5	2.2	25.4	2.3	26.5	2.8	26.2	1.6			28.8	2.5		
A10	2010	60	7	22.9	1.6	28.8	1.8	31.5	3.3	30.3	3.3	28.4	4.4			26.5	5.1		
<i>Total Mean</i>			137	20.4		25.4		27.3		28.0		29.5		25.3		29.9		26.7	
<i>SD</i>					2.7		3.2		3.9		3.7		3.8		2.5		4.2		4.8
<i>Non-infusion studies 2018</i>																			
			247	21.0	2.8	23.7	2.8	25.3	2.8	26.9	2.9	28.4	3.3	25.7	2.7	NA	NA	28.6	4.8

[#] Infusion volume per administration.

* Day 12 instead of 11 for study A10.

Historical Control Data

Rat Crl: OFA.SD.

Caesarean data collected on day 20 or 21 of gestation: females treated by continuous IV infusion during gestation

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Study	Year	Rate of infusion ml/kg/day	Number of females			Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Early resorptions per dam		Late resorptions per dam		Post-implantation loss %	
			Mated	Pregnant	With live fetuses	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C17	2017	5*	22	21	21	15.2	1.9	14.4	2.1	5.7	7.2	1.0	1.1	0.9	2.7	13.6	20.5
C11	2011	5*	6	6	6	15.3	2.1	13.5	2.1	11.8	8.8	1.8	1.8	0.5	0.5	18.3	19.3
D11	2011	5*	25	25	25	14.8	2.0	13.9	2.0	6.2	9.8	1.0	1.1	0.0	0.2	7.7	9.8
E11	2011	5*	6	6	6	14.8	2.3	13.8	1.5	6.1	5.8	1.5	1.0	0.0	0.0	10.8	7.2
A7	2007	33	30	29	29	14.7	2.0	12.7	1.5	12.4	10.3	1.1	1.1	0.0	0.0	8.7	8.5
B7	2007	30	6	6	6	16.3	3.7	14.5	2.9	10.5	7.2	1.7	1.6	0.0	0.0	1.7	1.6
C7	2007	30	6	5	5	12.8	1.6	12.4	1.1	2.7	6.0	1.4	0.5	0.0	0.0	11.1	3.5
D7	2007	30	25	25	25	14.5	2.2	12.6	3.1	13.4	17.0	1.3	1.4	0.0	0.2	11.2	11.3
A6	2006	24	6	6	6	14.8	2.3	13.2	2.1	11.1	6.7	1.5	1.0	0.2	0.4	12.9	9.8
B6	2006	24	6	6	6	14.3	2.5	12.2	3.1	16.1	10.3	1.5	1.5	0.0	0.0	11.2	11.7
Total			138	135	135												
Mean				98%	98%	14.8		13.3		9.7		1.2		0.2		10.3	
SD							2.2	2.3		11.2		1.2		1.1		12.4	
Non-infusion studies 2018																	
			252	247	247	14.6	2.0	13.7	2.2	6.0	9.5	1.1	1.5	0.1	1.0	9.5	12.6
				98%	98%												

* Infusion volume per administration.

Historical Control Data

Rat Crl: OFA.SD.

Caesarean data collected on day 20 or 21 of gestation: females treated by continuous IV infusion during gestation

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Study	Year	Rate of infusion ml/kg/day	Number of females			Dead foetuses Total	Live litter size		Foetal weight (g) on G20		Gravid uterus weight (g) on G20		Foetal weight (g) on G21		Gravid uterus weight (g) on G21		Sex ratio % males
			Mated	Pregnant	With live foetuses		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
C17	2017	5*	22	21	21	0	12.5	3.9					5.35	0.7	95.7	22.0	45.0
C11	2011	5*	6	6	6	0	11.2	3.5	4.1	0.4							48.3
D11	2011	5*	25	25	25	0	12.9	2.5	4.0	0.4							50.8
E11	2011	5*	6	6	6	0	12.3	1.5	4.1	0.2							50.0
A7	2007	33	30	29	29	0	11.6	1.8	4.1	0.3							53.4
B7	2007	30	6	6	6	0	12.6	2.1	3.6	0.7	71.2	9.3					51.8
C7	2007	30	6	5	5	0	11.0	0.7	3.8	0.2	66.3	5.9					48.1
D7	2007	30	25	25	25	0	11.3	3.1	4.0	0.3	68.9	19.0					53.1
A6	2006	24	6	6	6	0	11.5	2.5	4.0	0.4							44.1
B6	2006	24	6	6	6	0	10.7	2.6	3.6	0.9							35.7
Total			138	135	135	0											
Mean				98%	98%		11.9		4.0		68.9		5.35		95.7		49.7
SD								2.7	0.4		16.3		0.7		22.0		
Non-infusion studies 2018																	
			252	247	247	0	12.4	2.7	NA	NA	NA	NA	5.67	0.4	95.7	18.6	47.8
				98%	98%												

* Infusion volume per administration.

Historical Control Data

Rat Crl: OFA.SD.

Malformations (external, internal and skeletal) - females treated by continuous IV infusion during gestation

Study	Year	Number of litters examined	Number of fetuses examined	Number of litters with malformed fetuses	Litter Incidence %	Number of malformed fetuses	Foetal Incidence %	Type of malformation by foetus
C17	2017	21	263	1	4.76	1	0.38	Malformed limbs, pelvis and vertebral column, anal atresia, fleshy tab tail, absent genital tubercle, testis, kidneys, ureter and urinary bladder, malpositioned testis
C11	2011	6	67	0	-	0	-	
D11	2011	25	322	1	4.00	1	0.31	Anal atresia, acaudia, malformed vertebral column
E11	2011	6	74	0	-	0	-	
A7	2007	29	337	0	-	0	-	
B7	2007	6	77	0	-	0	-	
C7	2007	5	55	0	-	0	-	
D7	2007	25	282	0	-	0	-	
A6	2006	6	69	0	-	0	-	
B6	2006	6	64	0	-	0	-	
Total 2006 to 2018		135	263	2	1.48%	2	0.76%	
Non-infusion studies 2018		247	3073	8	3.24%	8	0.26%	

Study nos. B6, A6, C7, B7, C11 and E11: Dose Range Finding studies with external examination only.

Historical Control Data**Rat Crl: OFA.SD.****FOETAL EXAMINATION - EXTERNAL EXAMINATION ON DAY 20 OR 21 OF GESTATION
females treated by continuous IV infusion during gestation**

PERIOD	Continuous IV infusion		Non-infusion	
	2006 to 2018		2016-2018	
Number of studies included	10		32	
Number of foetuses examined	1610		5803	
OBSERVATION	N	%	N	%
Head/neck: malformed	0	0.00	1	0.02
Cleft Palate	0	0.00	1	0.02
Trunk: local oedema	12	0.75	0	0.00
Trunk: short	1	0.06	0	0.00
Omphalocele	0	0.00	1	0.02
Gastroschisis	0	0.00	2	0.03
Thoracoschisis	0	0.00	1	0.02
Limbs: malformed	1	0.06	1	0.02
Limbs: malrotated	0	0.00	1	0.02
Brachydactyly	0	0.00	1	0.02
Genital tubercule: absent	1	0.06	1	0.02
Anal atresia	2	0.12	1	0.02
Acaudia	1	0.06	0	0.00
Tail: fleshy tab	1	0.06	1	0.02

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

FOETAL EXAMINATION - FIXED VISCERAL EXAMINATION OF BODY ON DAY 20 OF GESTATION
females treated by continuous IV infusion during gestation

PERIOD	Continuous IV infusion		Non-infusion studies	
	2006 to 2018		2011 to 2013	
Number of studies included	3		7	
Number of foetuses examined	451		878	
OBSERVATION	N	%	N	%
Kidney: dilated renal pelvis	1	0.22	15	1.71
Kidney: dilated renal pelvis (slight)	0	0.00	4	0.46
Kidney: malpositioned	0	0.00	2	0.23
Testis: malpositioned	0	0.00	1	0.11
Ureter: dilated (slight)	62	13.75	154	17.54
Ureter: dilated (moderate)	0	0.00	2	0.23
Ureter: convoluted	75	16.63	208	23.69

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

FOETAL EXAMINATION - FRESH VISCERAL EXAMINATION OF BODY ON DAY 20 OR 21 OF GESTATION
females treated by continuous IV infusion during gestation

PERIOD	Continuous IV infusion		Non-infusion studies	
	2017 to 2018		2016 to 2018	
Number of studies included	1		18	
Number of fetuses examined	263		2566	
OBSERVATION	N	%	N	%
Situs inversus	0	0.00	1	0.04
Heart: malformed	0	0.00	1	0.04
Aortic arch: narrowed	0	0.00	1	0.04
Persistent truncus arteriosus	0	0.00	1	0.04
Inominate artery: absent	1	0.38	16	0.62
Azygos vein: transposed	0	0.00	1	0.04
Subclavian artery: transposed	0	0.00	1	0.04
Umbilical artery: transposed	24	9.13	108	4.21
Intestine: distended	0	0.00	1	0.04
Liver: lobe misshapen	0	0.00	1	0.04
Kidney: absent	1	0.38	22	0.86
Kidney: dilated renal pelvis	13	4.94	55	2.14
Ureter: absent	1	0.38	339	13.21
Ureter: dilated	28	10.65	501	19.52
Ureter: dilated (marked)	4	1.52	5	0.19
Ureter: convoluted	30	11.41	339	13.21
Ureter: convoluted (marked)	3	1.14	3	0.12
Urinary bladder: absent	1	0.38	1	0.04
Testis: absent	1	0.38	1	0.04
Testis: malpositioned	1	0.38	1	0.04
Testis: cyst	0	0.00	2	0.08

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

FOETAL EXAMINATION - FIXED VISCERAL EXAMINATION OF HEAD ON DAY 20 OR 21 OF GESTATION
females treated by continuous IV infusion during gestation

PERIOD	Continuous IV infusion		Non-infusion studies	
	2006 to 2018		2016 to 2018	
Number of studies included	4		18	
Number of fetuses examined	576		2304	
OBSERVATION	N	%	N	%
Hydrocephaly	0	0.0	1	0.04
Brain: dilated ventricles	1	0.2	2	0.09
Anophthalmia	0	0.0	2	0.09
Eye(s): discolored	0	0.0	1	0.04
Retina: fold	0	0.0	1	0.04

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION****- page 1/3****females treated by continuous IV infusion during gestation**

PERIOD	Continuous IV infusion		Non-infusion	
	2006 to 2018		2016 to 2018	
Number of studies included	3		8	
Number of foetuses examined	490		1052	
OBSERVATION	N	%	N	%
Metacarpals: incomplete ossification, 3rd or 4th digit	1	0.20	0	0.00
Metacarpals: incomplete ossification, 2nd to 4th digit	0	0.00	3	0.29
Metacarpals: incomplete ossification, 2nd or 5th digit	69	14.08	0	0.00
Metacarpals: unossified, 2nd to 4th digits	0	0.00	2	0.19
Metacarpals: unossified, 5th digit	0	0.00	124	11.79
Metatarsals: advanced ossification	36	7.35	0	0.00
Metatarsals: incomplete ossification	8	1.63	10	0.95
Metatarsals: unossified	1	0.20	7	0.67
Metatarsals: absent	0	0.00	7	0.67
Phalanx: absent, forepaws	0	0.00	1	0.10
Limbs: malformed	0	0.00	1	0.10
Clavicle: bent	0	0.00	1	0.10
Scapula: misshapen	0	0.00	1	0.10
Pubis: incomplete ossification	4	0.82	6	0.57
Pubis: unossified	0	0.00	4	0.38
Ischium: incomplete ossification	1	0.20	2	0.19
Ribs: number of full ribs = 12/12	0	0.00	4	0.38
Ribs: number of full ribs = 12/13	0	0.00	1	0.10
Rib: supernumerary cervical	0	0.00	17	1.62
Rib: supernumerary lumbar	0	0.00	5	0.48
Rib: supernumerary lumbar (short)	0	0.00	106	10.08
Rib: short	0	0.00	1	0.10

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION****page 2/3****females treated by continuous IV infusion during gestation**

PERIOD	Continuous IV infusion		Non-infusion	
	2006 to 2018		2016 to 2018	
Number of studies included	3		8	
Number of foetuses examined	490		1052	
OBSERVATION	N	%	N	%
Rib: unilateral rudimentary 14th	20	4.08	0	0.00
Rib: bilateral rudimentary 14th	13	2.65	0	0.00
Rib: wavy	2	0.41	0	0.00
Rib: bent	0	0.00	1	0.10
Rib: thick	0	0.00	1	0.10
Sternebrae: incomplete ossification of 1st/3rd	34	6.94	13	1.24
Sternebrae: incomplete ossification of 2nd/4th	52	10.61	23	2.19
Sternebrae: incomplete ossification of 6th	52	10.61	46	4.37
Sternebrae: unossified	0	0.00	1	0.10
Sternebrae: unossified of 1st or 3rd	1	0.20	3	0.29
Sternebrae: unossified of 2nd or 4th	3	0.61	7	0.67
Sternebrae: unossified 5th	20	4.08	60	5.70
Sternebrae: unossified 6th	2	0.41	9	0.86
Sternebrae: malformed	0	0.00	1	0.10
Sternebrae: asymmetric	6	1.22	5	0.48
Sternebrae: minor fusion	0	0.00	1	0.10
Sternebrae: bipartite	11	2.24	2	0.19
Vertebral column: malformed	1	0.20	1	0.10
Vertebrae, presacral vertebral arches = 27	0	0.00	2	0.19
Vertebrae, cervical: malformed	0	0.00	1	0.10
Vertebrae, cervical: advanced ossification	316	64.49	0	0.00
Vertebrae, cervical: increased ossification 1st centrum	0	0.00	208	19.77
Vertebrae, cervical: incomplete ossification of arches	1	0.20	3	0.29

File name: IL.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION****page 3/3****females treated by continuous IV infusion during gestation**

PERIOD	Continuous IV infusion		Non-infusion	
	2006 to 2018		2016 to 2018	
Number of studies included	3		8	
Number of foetuses examined	490		1052	
OBSERVATION	N	%	N	%
Vertebrae, thoracic: number = 12	0	0.00	4	0.38
Vertebrae, thoracic: incomplete ossification of 1-4th centrum	9	1.84	0	0.00
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	0	0.00	38	3.61
Vertebrae, thoracic: incomplete ossification of 9-13th centrum	58	11.84	0	0.00
Vertebrae, thoracic: unossified centrum	0	0.00	1	0.10
Vertebrae, thoracic: unossified 1-4th centrum	7	1.43	0	0.00
Vertebrae, thoracic: unossified 1-9th centrum	0	0.00	8	0.76
Vertebrae, thoracic: bipartite centrum	2	0.41	8	0.76
Vertebrae, thoracic: misaligned centrum	0	0.00	1	0.10
Vertebrae, lumbar: number = 5	0	0.00	3	0.29
Vertebrae, lumbar: number = 7	1	0.20	5	0.48
Vertebrae, lumbar: incomplete ossification of centrum	2	0.41	4	0.38
Vertebrae, lumbar: bipartite centrum	0	0.00	1	0.10
Vertebrae, lumbar: hemicentric centrum	0	0.00	1	0.10
Vertebrae, lumbar: small centrum	0	0.00	1	0.10
Vertebrae, sacral: incomplete ossification of centrum	1	0.20	4	0.38
Vertebrae, sacral: incomplete ossification of arches	10	2.04	21	2.00
Vertebrae, sacral: unossified	1	0.20	4	0.38
Vertebrae, sacral: unossified arches	0	0.00	1	0.10
Vertebrae, sacral: hemicentric centrum	0	0.00	1	0.10
Vertebrae, caudal: unossified	2	0.41	8	0.76
Vertebrae, caudal: unossified arches - region 1-2	40	8.16	154	14.64
Vertebrae, caudal: unossified centrum - region 1-2	1	0.20	0	0.00

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL SKELETAL EXAMINATION OF HEAD ON DAY 20 OF GESTATION**
females treated by continuous IV infusion during gestation**page 1/1**

PERIOD	Continuous IV infusion		Non-infusion	
	2006 to 2018		2016 to 2018	
Number of studies included	3		8	
Number of foetuses examined	490		1052	
OBSERVATION	N	%	N	%
Skull: malformed	0	0.00	1	0.10
Generalised incomplete ossification	0	0.00	3	0.29
Frontal: incomplete ossification	1	0.20	1	0.10
Parietals: incomplete ossification	31	6.33	13	1.24
Interparietal: incomplete ossification	97	19.80	35	3.33
Supraoccipital: incomplete ossification	53	10.82	3	0.29
Squamosal: incomplete ossification	18	3.67	3	0.29
Tympanic annulus: incomplete ossification	0	0.00	1	0.10
Nasal: incomplete ossification	0	0.00	1	0.10
Zygomatic: incomplete ossification	3	0.61	0	0.00
Palatine: absent	0	0.00	1	0.10
Palatine: split	0	0.00	1	0.10
Hyoid: incomplete ossification	8	1.63	0	0.00
Hyoid: unossified	17	3.47	6	0.57
Presphenoid: incomplete ossification	2	0.41	1	0.10
Presphenoid: unossified	0	0.00	1	0.10
Basisphenoid: incomplete ossification	4	0.82	0	0.00
Basisphenoid: misshapen	0	0.00	1	0.10

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data**Rat Crl: OFA.SD.****FOETAL SKELETAL EXAMINATION OF BODY ON DAY 21 OF GESTATION****- page 1/3****females treated by continuous IV infusion during gestation**

PERIOD	Continuous IV infusion		Non-infusion	
	2017 to 2018		2017 to 2018	
Number of studies included	1		11	
Number of fetuses examined	263		1674	
OBSERVATION	N	%	N	%
Femur: short	1	0.38	1	0.06
Humerus: incomplete ossification	0	0.00	8	0.48
Scapula: bent	0	0.00	1	0.06
Paws: malformed	1	0.38	1	0.06
Metacarpals: incomplete ossification, 5th digit	4	1.52	27	1.61
Metacarpals: unossified	0	0.00	0	0.00
Metacarpals: unossified, 5th digit	3	1.14	4	0.24
Metatarsals: incomplete ossification	0	0.00	1	0.06
Metatarsals: unossified, 1st digit	24	9.13	86	5.14
Phalanx: unossified, forepaws	10	3.80	94	5.62
Phalanx: unossified, hindpaws	0	0.00	302	18.04
Phalanx: unossified, proximal 2nd to 5th digits, hindpaws	26	9.89	0	0.00
Pelvis: malformed	1	0.38	1	0.06
Ribs: number of full ribs = 12/13	0	0.00	1	0.06
Rib: supernumerary cervical	9	3.42	26	1.55
Rib: supernumerary lumbar	0	0.00	4	0.24
Rib: supernumerary lumbar (short)	16	6.08	143	8.54
Rib: absent	2	0.76	2	0.12
Rib: short	3	1.14	4	0.24
Rib: wavy	0	0.00	3	0.18
Rib; incomplete ossification	0	0.00	2	0.12

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

FOETAL SKELETAL EXAMINATION OF BODY ON DAY 21 OF GESTATION
females treated by continuous IV infusion during gestation

page 2/3

PERIOD	Continuous IV infusion		Non-infusion	
	2017 to 2018		2017 to 2018	
Number of studies included	1		11	
Number of fetuses examined	263		1674	
OBSERVATION	N	%	N	%
Sternebrae: extra ossification site	0	0.00	3	0.18
Sternebrae: incomplete ossification of 1st/3rd	2	0.76	4	0.24
Sternebrae: incomplete ossification of 2nd/4th	4	1.52	9	0.54
Sternebrae: incomplete ossification of 6th	2	0.76	4	0.24
Sternebrae: unossified of 1st or 3rd	0	0.00	0	0.00
Sternebrae: unossified of 2nd or 4th	0	0.00	0	0.00
Sternebrae: unossified 5th	6	2.28	11	0.66
Sternebrae: unossified 6th	2	0.76	3	0.18
Sternebrae: asymmetric	2	0.76	6	0.36
Sternebrae: misaligned	0	0.00	0	0.00
Hemisternebra	0	0.00	0	0.00
Sternoschisis	0	0.00	0	0.00
Sternebrae: minor fusion	0	0.00	0	0.00
Sternebrae: bipartite	0	0.00	0	0.00
Sternebrae: split	0	0.00	0	0.00

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

FOETAL SKELETAL EXAMINATION OF BODY ON DAY 21 OF GESTATION
females treated by continuous IV infusion during gestation

page 3/3

PERIOD	Continuous IV infusion		Non-infusion	
	2017 to 2018		2017 to 2018	
Number of studies included	1		11	
Number of foetuses examined	263		1674	
OBSERVATION	N	%	N	%
Vertebral column: malformed	1	0.38	1	0.06
Vertebrae, presacral: number = 25	2	0.76	3	0.18
Vertebrae, presacral: number = 27	0	0.00	6	0.36
Vertebrae, cervical: incomplete ossification of arches	0	0.00	3	0.18
Vertebrae, cervical: unossified odontoid process	99	37.64	959	57.29
Vertebrae, cervical: unossified centrum	128	48.67	988	59.02
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	3	1.14	10	0.60
Vertebrae, thoracic: incomplete ossification of 10-13th centrum	10	3.80	62	3.70
Vertebrae, thoracic: unossified 1-9th centrum	1	0.38	2	0.12
Vertebrae, lumbar: malformed	0	0.00	2	0.12
Vertebrae, lumbar: number = 5	1	0.38	1	0.06
Vertebrae, lumbar: number = 7	0	0.00	5	0.30
Vertebrae, lumbar: incomplete ossification of centrum	2	0.76	3	0.18
Vertebrae, sacral: incomplete ossification of arches	0	0.00	1	0.06
Vertebrae, caudal: number <5	3	1.14	13	0.78
Vertebrae, caudal: malpositioned	0	0.00	1	0.06

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

**FOETAL SKELETAL EXAMINATION OF HEAD ON DAY 21 OF GESTATION
females treated by continuous IV infusion during gestation**

PERIOD	Continuous IV infusion		Non-infusion	
	2017 to 2018		2017 to 2018	
Number of studies included	1		11	
Number of foetuses examined	138		1549	
OBSERVATION	N	%	N	%
Cranium: sutural bone	0	0.00	4	0.26
Cranium: extra ossification site	0	0.00	1	0.06
Frontal: incomplete ossification	0	0.00	2	0.13
Parietals: incomplete ossification	0	0.00	6	0.39
Interparietal: incomplete ossification	4	2.90	67	4.33
Interparietal: unossified area	0	0.00	2	0.13
Supraoccipital: incomplete ossification	0	0.00	2	0.13
Squamosal: incomplete ossification	0	0.00	5	0.32
Nasal: incomplete ossification	0	0.00	2	0.13
Zygomatic: incomplete ossification	0	0.00	3	0.19
Zygomatic: misshapen	0	0.00	2	0.13
Mandible: incomplete ossification	0	0.00	59	3.81
Hyoid: incomplete ossification	0	0.00	8	0.52
Hyoid: unossified	0	0.00	3	0.19

File name: II.1.1-RAT_SD_PERFUSION_G20-G21_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

Maternal body weight gain (g) during lactation for dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A17	2017	24	6	13.0	4.6	10.0	8.0	5.8	7.8	10.0	5.0	-1.5	10.0	-18.7	8.7
A16	2016	24	5	8.5	16.6	8.1	2.7	13.2	3.4	4.8	6.1	0.0	13.2	1.2	9.4
J12	2012	15	24	13.8	4.9	8.6	7.3								
F11	2011	60	23	16.2	7.8	11.6	7.6								
G11	2011	15	6	14.1	4.1	11.4	7.4								
A3	2003	48	24	11.4	8.6	9.2	7.4								
A99	1999	100	19	12.2	9.5	3.9	7.6								
B99	1999	200	24	8.9	5.4	9.3	5.4								
C99	1999	200	6	5.6	8.1	12.1	4.2								
A97	1997	40	23	10.1	10.3	10.3	6.7								
Total Mean			160	11.8		9.2		9.2		7.6		-0.8		-9.6	
SD					8.3		7.1		7.1		5.9		10.9		13.4
<i>Non-infusion studies 2013 to 2018</i>															
			112	12.0	9.3	7.1	7.8	6.1	5.7	3.1	8.1	-0.2	8.1	-13.8	12.1

Historical Control Data

Rat Crl: OFA.SD.

Maternal food consumption (g/day) during lactation for dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A17	2017	24	6	33.4	3.5	43.7	4.7	50.0	2.7	59.4	3.8	60.9	4.4	67.2	4.5
A16	2016	24	5	32.6	10.3	41.6	9.0	45.9	10.0	56.1	14.2	55.3	15.5	66.7	16.8
J12	2012	15	24	39.5	6.5	47.7	5.7								
F11	2011	60	23	38.8	6.4	44.9	7.4								
G11	2011	15	6	35.8	2.5	49.5	7.4								
A3	2003	48	24	37.3	7.5	44.9	7.9								
A99	1999	100	19	39.0	5.2	45.1	5.5								
B99	1999	200	24	35.4	5.7	44.1	5.0								
C99	1999	200	6	35.0	6.2	42.8	5.7								
A97	1997	40	23	33.1	6.5	42.7	9.3								
Total Mean SD			160	36.7	6.6	44.9	7.0	48.1	7.0	57.9	9.5	58.3	10.7	67.0	11.1
Non-infusion studies 2013 to 2018															
			112	35.9	5.9	46.0	6.1	50.9	5.9	58.5	6.8	60.9	8.2	69.4	9.6

Historical Control Data

Rat Crl: OFA.SD.

Post-partum litter data for dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Number of females				Gestation length (days)		Number of uterine implants		Number of pups born		Pre-birth loss index %	Live birth index %	Pup viability index %	Pup weaning index %
			Mated	Pregnant	With liveborn	With pups at weaning	Mean	SD	Mean	SD	Mean	SD				
A17	2017	24	6	6	6	6	22.3	0.5	12.3	2.8	10.5	3.7	15.75	95.2	98.3	100
A16	2016	24	6	5	5	5	22.0	0.0	11.6	4.8	10.0	4.8	15.74	92.0	100	100
J12	2012	15	25	25	24	24	21.9	0.3	14.0	2.1	12.7	2.7	9.29	94.3	98.3	98.9
F11	2011	60	24	24	23	23	22.0	0.3	13.1	2.9	12.6	3.0	4.10	99.3	88.3	94.3
G11	2011	15	6	6	6	NA	22.0	0.0	13.7	1.0	11.7	2.3	14.60	100	98.6	NA
A10	2010	60	7	7	7	NA	21.9	0.4	14.4	0.8	13.0	1.2		100	95.6	NA
A3	2003	48	25	24	24	24	22.0	0.3	12.8	2.5	10.6	3.9		98.4	98.4	100
A99	1998	100	25	22	21	20	22.0	0.0	14.3	2.7	12.3	2.3		98.0	98.0	90.0
B99	1998	200	25	24	24	24	22.0	0.0	13.6	2.5	11.4	2.4		98.0	98.0	98.0
C99	1998	200	6	6	6	6	22.0	0.0	13.8	2.9	11.8	2.6		100	98.0	100
A97	1997	40	25	23	23	22	21.7	0.4	13.8	2.7	12.2	3.3		96.0	84.0	93.0
Total			180	172 96%	169 94%	154 92%										
Mean							22.0		13.5		11.9		9.03	97.4	94.9	97.6
SD								0.3		2.6		3.0				
Non-infusion studies 2013 to 2018																
			117	115 98%	112 96%	101 95%	22.1	0.3	13.8	2.5	12.6	2.7	9.03	98.3	99.3	99.4

NA: not applicable

Historical Control Data

Rat Crl: OFA.SD.

Post-partum data - pup weights (g) for dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Number of litters	Postnatal day 1				Postnatal day 4				Postnatal day 7				Postnatal day 14				Postnatal day 21			
				Males		Females		Males		Females		Males		Females		Males		Females		Males		Females	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A17	2017	24	6	7.4	0.9	7.3	0.9	11.5	1.9	11.4	2.0	18.1	2.6	17.9	2.5	36.2	4.1	35.9	3.3	60.5	5.3	60.6	4.0
A16	2016	24	5	7.3	0.8	6.9	0.6	10.4	1.0	9.9	0.8	16.3	1.7	15.8	1.4	33.1	4.9	32.2	5.2	55.2	8.1	54.3	9.5
J12	2012	15	24	7.0	0.6	6.6	0.6	9.9	1.2	9.4	1.2	16.1	2.1	15.3	2.1	33.3	3.5	32.2	3.7	53.8	6.8	51.7	6.5
F11	2011	60	24	6.8	0.9	6.5	0.8	9.3	1.8	8.9	1.7	15.0	3.0	14.4	2.6	33.0	3.5	31.3	4.7	53.3	5.8	51.0	7.2
G11	2011	15	6	7.2	0.6	7.1	0.6	10.1	1.1	9.8	1.3	14.7	1.4	14.4	1.8								
A10	2010	60	7	6.4	0.5	6.1	0.5	8.5	1.3	7.9	1.0												
A3	2003	48	24	7.6	0.7	7.1	0.5	10.9	1.0	10.4	0.8	17.1	2.0	16.4	1.5	35.0	3.7	34.3	2.3	54.6	7.0	53.7	3.9
A99	1999	100	19	7.1	0.6	6.8	0.6	10.1	1.1	10.0	1.2	16.2	1.8	16.1	1.7	32.2	4.2	32.0	4.0	53.1	6.9	52.8	6.2
B99	1999	200	24	7.3	0.7	7.0	0.6	10.6	0.9	10.1	1.0	16.5	1.5	16.1	1.5	32.7	2.6	32.4	3.1	53.9	4.3	52.8	4.8
C99	1999	200	6	6.7	0.6	6.8	0.8	9.8	1.3	9.8	1.6	15.2	1.5	14.8	1.9	31.0	3.0	30.6	2.3	49.1	4.7	49.2	3.3
A97	1997	40	22	6.5	0.8	6.2	0.8	8.4	1.5	8.0	1.5	13.0	1.9	12.2	2.2	27.7	3.2	25.6	4.0	45.2	5.7	41.7	8.8
Total Mean			167	7.0		6.7		9.9		9.5		15.7		15.2		32.5		31.5		52.7		51.1	
SD				0.8		0.7		1.5		1.5		2.4		2.4		4.1		4.5		6.9		7.5	
<i>Non-infusion studies 2013 to 2018</i>																							
			112	7.4	0.6	7.1	0.6	10.8	1.2	10.5	1.2	17.7	1.7	17.1	1.8	36.1	2.9	35.0	3.4	59.3	4.5	57.1	5.7

Historical Control Data**Rat Crl: OFA.SD.****Pre-weaning development for litters of dams infused throughout gestation, parturition and lactation**

Study	Year	Rate of Infusion mL/kg/day	Number of litters	Pinna unfolding (% of pups positive)						Incisor eruption (% of pups positive)								
				PND1	PND2	PND3	PND4	PND5	PND6	PND7	PND8	PND9	PND10	PND11	PND12	PND13	PND14	PND15
J12	2012	15	24	0	37	96	100	100	100	0	2	9	30	64	92	98	99	100
F11	2011	60	23	1	42	87	94	95	100	0	0	10	46	84	98	100	100	100
A3	2003	48	24	1	76	99	100	100	100	0	9	45	91	100	100	100	100	100
A99	1999	100	19	0	83	99	100	100	100	0	1	22	87	98	100	100	100	100
B99	1999	200	24	3	88	100	100	100	100	0	3	22	84	99	100	100	100	100
A97	1997	40	23	0	29	75	95	100	100	2	5	15	45	84	98	100	100	100
<i>Total</i>			<i>137</i>															
<i>Mean %</i>				<i>1</i>	<i>59</i>	<i>93</i>	<i>98</i>	<i>99</i>	<i>100</i>	<i>0</i>	<i>3</i>	<i>21</i>	<i>63</i>	<i>88</i>	<i>98</i>	<i>100</i>	<i>100</i>	<i>100</i>
<i>Non-infusion studies 2012 to 2018</i>			<i>115</i>	<i>2</i>	<i>68</i>	<i>98</i>	<i>100</i>	<i>100</i>	<i>100</i>	<i>0</i>	<i>2</i>	<i>12</i>	<i>40</i>	<i>78</i>	<i>95</i>	<i>99</i>	<i>100</i>	<i>100</i>

PND = postnatal day

Historical Control Data

Rat Crl: OFA.SD.

Pre-weaning development for litters of dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Number of litters	Eye opening (% of pups positive)					
				PND12	PND13	PND14	PND15	PND16	PND17
J12	2012	15	24	1	4	61	97	100	100
F11	2011	60	23	0	14	77	99	100	100
A3	2003	48	24	0	16	79	100	100	100
A99	1999	100	19	1	13	79	99	100	100
B99	1999	200	24	2	27	87	100	100	100
A97	1997	40	23	0	5	31	70	97	100
<i>Total</i>			<i>137</i>						
<i>Mean %</i>				<i>1</i>	<i>13</i>	<i>69</i>	<i>94</i>	<i>99</i>	<i>100</i>
<i>Non-infusion studies 2012 to 2018</i>			<i>115</i>	<i>1</i>	<i>5</i>	<i>49</i>	<i>91</i>	<i>100</i>	<i>100</i>

PND = postnatal day

Historical Control Data**Rat Crl: OFA.SD.****Post-weaning development (dams infused throughout gestation, parturition and lactation)**

Study	Year	Vaginal opening					Balano-preputial skinfold cleavage				
		Day of occurrence			Body weight (g)		Day of occurrence			Body weight (g)	
		Mean	SD	N	Mean	SD	Mean	SD	N	Mean	SD
J12	2012	33	2	25	111	10	43	2	25	215	19
F11	2011	35	3	25	116	21	45	4	25	217	29
<i>Total</i>				50					50		
<i>Mean</i>		34			114		44			216	
<i>SD</i>			3			16		3			24
<i>Non-infusion studies</i>											
<i>2012 to 2018</i>		35	2	119	132	16	44	2	118	223	26

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Water Maze (VideoTrack 3.2)
(dams infused throughout gestation, parturition and lactation)

Study Year N	MALES				Non-infusion studies	
	Time (s)		Distance (cm)		Time (s)	Distance (cm)
	J12 2012 25	Overall	J12 2012 25	Overall	2013 to 2018 65 65	
Trial 1						
Mean	31	31	387	387	30	387
SD	12	12	159	159	18	192
Trial 2						
Mean	18	18	223	223	16	216
SD	11	11	148	148	9	130
Trial 3						
Mean	16	16	186	186	12	163
SD	9	9	95	95	8	89
Trial 4						
Mean	14	14	161	161	15	193
SD	6	6	85	85	12	121
Trial 5						
Mean	36	36	463	463	38	533
SD	12	12	164	164	23	320
Trial 6						
Mean	30	30	348	348	24	287
SD	13	13	143	143	13	160
Trial 7						
Mean	19	19	212	212	17	204
SD	12	12	137	137	11	117

File name: II.1.2-RAT_SD_PERFUSION_postpartum_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Water Maze (VideoTrack 3.2)**(dams infused throughout gestation, parturition and lactation)**

Study Year N	FEMALES				Non-infusion studies	
	Time (s)		Distance (cm)		Time (s)	Distance (cm)
	J12 2012 25	Overall	J12 2012 25	Overall	2013 to 2018 65 65	
Trial 1						
Mean	29	29	361	361	27	382
SD	14	14	166	166	13	169
Trial 2						
Mean	20	20	241	241	16	230
SD	12	12	130	130	10	125
Trial 3						
Mean	14	14	170	170	12	161
SD	10	10	103	103	8	102
Trial 4						
Mean	11	11	146	146	12	153
SD	5	5	85	85	8	78
Trial 5						
Mean	37	37	526	526	35	507
SD	24	24	342	342	23	308
Trial 6						
Mean	24	24	290	290	24	304
SD	16	16	191	191	17	158
Trial 7						
Mean	20	20	265	265	16	190
SD	12	12	168	168	12	102

File name: II.1.2-RAT_SD_PERFUSION_postpartum_2018_OK.xls

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Open Field (VideoTrack 3.2)
(dams infused throughout gestation, parturition and lactation)

Study	Year	N	MALES													
			Total time (s) engaged in:						Total distance travelled (cm)		Time (s) spent in:					
			Ambulatory activity		Small movements		Inactivity		Mean	SD	Corner regions		Centre region		Lateral regions	
			Mean	SD	Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
A12	2012	25	54	8	37	4	88	10	1074	152	88	14	18	10	74	10
<i>Total Mean</i>		25	54		37		88		1074		88		18		74	
<i>SD</i>				8		4		10		152		14		10		10
<i>Non-infusion studies 2013 to 2018</i>																
		65	51	10	35	4	93	12	1031	172	95	16	13	9	73	13

Historical Control Data

Rat Crl: OFA.SD.

Post-weaning behaviour tests - Open Field (VideoTrack 3.2)
(dams infused throughout gestation, parturition and lactation)

Study	Year	N	FEMALES													
			Total time (s) engaged in:						Total distance travelled (cm)		Time (s) spent in:					
			Ambulatory activity		Small movements		Inactivity		Mean	SD	Corner regions		Centre region		Lateral regions	
			Mean	SD	Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
A12	2012	25	62	14	35	7	83	20	1262	285	102	20	15	8	64	15
<i>Total</i>		25														
<i>Mean</i>			62		35		83		1262		102		15		64	
<i>SD</i>				14		7		20		285		20		8		15
<i>Non-infusion studies 2013 to 2018</i>																
		65	56	15	33	8	91	22	1141	294	106	20	10	10	64	15

Historical Control Data

Rat Crl: OFA.SD.

Maternal body weight gain (g) during gestation (females treated by continuous IV infusion)

Study	Year	Dams with live fetuses	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD
F13	2013	18	18.1	5.6	14.2	5.0		
J12	2012	24	23.0	6.6	12.8	3.9	23.7	6.2
B11	2011	17	14.9	10.7	15.5	4.7	23.2	4.9
B8	2008	20	20.0	6.1	14.4	5.5	25.0	7.3
F3	2003	19	17.5	4.8	8.1	4.2	23.3	6.7
<i>Total</i>		98						
<i>Mean</i>			19.0		12.9		23.8	
<i>SD</i>				7.3		5.2		6.3
<i>Non-infusion studies 2014 to 2018</i>								
		207	19.1	7.4	15.5	5.3	23.6	6.6

Historical Control Data

Rat Crl: OFA.SD.

Maternal food consumption (g/day) during gestation (females treated by continuous IV infusion)

Study	Year	Dams with live fetuses	Gestation days 0 to 8		Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
F13	2013	18			28.8	3.0	29.9	2.9		
B11	2011	16	28.3	2.0					28.9	2.0
B8	2008	20	29.7	2.4					31.7	3.0
F3	2003	19	27.3	2.5					27.9	3.2
<i>Total</i>		73								
<i>Mean</i>			28.5		28.8		29.9		29.6	
<i>SD</i>				2.5		3.0		2.9		3.3
<i>Non-infusion studies 2014 to 2018</i>										
		175	23.2	2.6	22.8	2.8	24.6	3.0	25.3	3.0

Historical Control Data

Rat Ctrl: OFA.SD.

Oestrous cycle - before treatment (females treated by continuous IV infusion)

Study	Year	Females evaluated	Cycle length (days)		Irregularity index		Oestrous days (%)		Females acyclic or with acyclic period
		N	Mean	SD	Mean	SD	Mean	SD	%
B11	2011	12	4.2	0.7	0.0	0.0	32.3	8.4	0
B8	2008	17	4.2	0.8	0.0	0.1	27.3	7.9	15
<i>Total</i>		29							
<i>Mean</i>			4.2		0.0		29.4		9
<i>SD</i>				0.7		0.1		8.3	
<i>Non-infusion studies 2007 to 2018</i>									
		50	3.9	0.5	0.1	0.2	29.6	8.3	16

Historical Control Data

Rat Crl: OFA.SD.

Oestrous cycle - during treatment (pre-mating period) (females treated by continuous IV infusion)

Study	Year	Females evaluated	Cycle length (days)		Irregularity index		Oestrous days (%)		Females acyclic or with acyclic period
		N	Mean	SD	Mean	SD	Mean	SD	%
F13	2013	18	4.4	0.5	0.3	0.3	31.9	7.1	10
B11	2011	19	4.3	0.6	0.2	0.3	30.1	6.1	5
B8	2008	19	4.0	0.6	0.4	0.3	31.9	4.8	5
F3	2003	11	4.1	0.2	0.2	0.2	25.6	3.1	45
<i>Total</i>		67							
<i>Mean</i>			4.2		0.3		30.4		13
<i>SD</i>				0.5		0.3		6.0	
<i>Non-infusion studies 2007 to 2018</i>									
		269	4.1	0.5	0.3	0.3	31.1	8.2	13

Historical Control Data

Rat Crl: OFA.SD.

Caesarean data collected on, or close to, day 13 of gestation: females treated by continuous IV infusion

Study	Year	Number of females		Pre-coital interval (days)		Number of females		Fertility index %	Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Post-implantation loss %		Live embryos	
		Paired	Mated	Mean	SD	Pregnant	With live embryos		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
F13	2013	20	20	3.63	1.83	19	19	95	16.6	2.0	15.5	2.3	6.7	9.9	6.1	4.8	14.5	2.3
J12	2012	25	25	2.54	1.1	25	25	100	16.2	3.2	15.0	3.4	7.5	10.5	5.6	7.2	14.2	3.5
B11	2011	20	20	4.40	3.65	18	17	90	14.6	3.6	13.3	3.7	10.7	19.3	10.5	22.7	12.6	3.8
B8	2008	20	20	3.10	2.29	20	20	100	16.8	2.9	15.8	2.0	6.6	8.1	3.1	5.3	15.3	2.3
F3	2003	20	20	2.40	1.39	19	19	95	17.0	4.0	15.0	2.0	12.1	4.0	4.5	1.0	15.0	2.0
D98	1998	20	19			16	15	79	16.4	3.8	14.7	3.4	9.2	17.6	12.3	24.4	13.4	4.2
E98	1998	25	24			24	24	100	14.9	2.3	13.9	2.0	6.1	10.5	5.7	7.6	13.1	2.2
C97	1997	25	25			23	23	92	18.1	2.6	15.5	2.3	13.4	13.4	4.5	5.3	14.8	2.4
Total		175	173 99%			164 95%	162 94%											
Mean				1.90					16.3		14.9		9.0		6.2		14.1	
SD					2.6					3.2		2.7		12.2		11.7		3.0
Non-infusion studies 2014 to 2018																		
		263	259 98%	3.0	2.2	240 93%	240 93%		16.2	2.4	15.4	2.9	4.9	12.2	5.6	8.2	14.6	3.1

Historical Control Data

Rat Crl: OFA.SD.

Sperm Analysis - number in epididymis and motility (males treated by continuous IV infusion)

Study	Year	Number of males	Number of sperm in epididymis		% motile		Progressive sperm %	
			Mean	SD	Mean	SD	Mean	SD
G13	2013	18	1389	464	94.4	3.4		
A11	2011	20	794	368	82.6	10.6		
<i>Total</i>		38						
<i>Mean</i>			1076		88.2		NR	
<i>SD</i>				509		9.9		NR
<i>Non-infusion studies 2014 to 2018</i>								
		221	996	296	93.9	7.3	63.2	8.1

NR: not recorded

Historical Control Data**Rat Crl: OFA.SD.****Sperm Analysis - number in testis (males treated by continuous IV infusion)**

Study	Year	Number of males	Testis weight (g)		10 ⁶ Sperm per g of testis	
			Mean	SD	Mean	SD
G13	2013	18	1.87	0.14	131	28.9
A11	2011	20	1.90	0.10	125	25.4
<i>Total</i>		38				
<i>Mean</i>			1.89		128	
<i>SD</i>				0.12		27.0
<i>Non-infusion studies 2014 to 2018</i>						
		221	1.93	0.19	121	27.5

Historical Control Data

Rat Wistar : Crl-WI

Maternal body weight gain (g) during gestation

Study	Year	Dams with live foetuses	GD 0 to 6		GD 6 to 9		GD 9 to 12		GD 12 to 15		GD 15 to 18		GD 6 to 18		GD 18 to 20		GD 6 to 21		GD 18 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	21	31.7	7.2	6.5	3.9	13.6	3.7	14.6	3.3	32.2	6.6	66.8	9.5	24.5	4.4				
B18	2018	9	31.4	6.5	10.1	3.1	15.7	4.1	15.0	4.4	29.1	8.3	69.9	5.6					38.0	5.9
C18	2018	21	35.3	7.9	12.6	5.4	15.4	4.5	13.9	11.5	35.2	10.4	77.1	8.0	26.2	6.2				
D18	2018	6	32.5	5.3	8.9	4.2	14.2	4.2	14.9	3.6	28.6	6.4	66.5	13.0					34.4	8.0
E18	2018	22	30.5	8.8	12.4	5.4	16.1	3.8	17.5	5.4	31.1	4.4	77.1	11.3					38.7	6.1
F18	2018	6	30.1	8.0	12.0	4.1	12.8	2.3	19.6	4.4	29.5	6.9	73.9	10.2	26.0	6.1				
G18	2018	18	28.2	6.3	12.5	3.5	12.5	5.0	14.7	4.5	32.8	6.5	72.5	9.2					31.5	8.3
H18	2018	5	29.2	6.9	9.2	4.9	17.8	4.4	12.5	3.7	33.0	6.6	72.5	18.6					31.3	9.8
K18	2018	6	30.8	6.9	13.9	3.7	15.4	2.0	14.3	3.0	35.5	6.6			20.4	6.0				
L18	2018	21	31.1	5.9	11.8	3.2	18.2	2.9	15.5	5.2	31.8	5.4			22.7	7.1				
M18	2018	5	29.4	5.2	10.7	4.5	13.5	10.0	19.2	4.8	27.2	2.5			28.1	2.8				
N18	2018	6			2.3	6.5	15.7	2.6	18.0	2.5	33.6	4.0			26.8	4.4				
A17	2017	22	31.9	6.2	11.4	4.8	15.9	3.4	16.1	3.7	32.0	6.7	75.5	11.3			112.6	18.2	37.1	7.9
B17	2017	5	32.9	8.4	14.1	2.6	14.1	4.8	18.4	3.9	29.4	11.9	76.0	17.0			110.0	24.9	34.1	8.2
C17	2017	22	25.3	5.2	9.9	4.1	15.3	3.6	16.7	4.5	31.7	5.9	73.7	11.6	24.2	5.5				
D17	2017	6	27.9	6.8	13.8	5.8	12.9	3.5	15.4	3.3	34.7	5.7	76.7	10.6	25.2	2.8				
E17	2017	9	27.6	8.8	13.1	4.2	16.3	4.5	14.4	5.0	34.8	2.9	78.5	6.5	24.9	4.1				
F17	2017	21	32.4	6.7	9.3	4.2	14.9	3.8	18.0	4.0	31.6	3.7	73.8	9.2	25.0	4.5				
H17	2017	6	30.1	8.0	12.0	4.1	12.8	2.3	19.6	4.4	29.5	6.9	73.9	10.2	26.0	6.1				
I17	2017	24	33.9	6.9	18.1	3.2	15.4	3.3	20.1	3.9	32.0	5.3	85.7	9.0					40.9	7.0
J17	2017	24	33.5	5.8	17.8	5.0	14.2	3.7	23.6	4.0	30.9	5.8	86.5	11.5	26.8	4.7				
K17	2017	6	27.0	7.4	11.1	3.4	17.5	3.7	12.8	2.1	35.4	5.3					116.4	7.8	39.8	3.3
L17	2017	22	32.1	6.4	11.3	3.9	16.2	4.6	16.9	4.0	33.5	4.9					116.6	10.9	38.9	4.6
M17	2017	6	34.2	4.4	10.8	3.4	11.9	24.7	26.5	22.4	35.9	3.2					124.6	9.9	39.5	6.4
N17	2017	22	31.3	6.2	10.1	3.0	15.9	3.9	17.2	5.7	32.7	7.0					107.5	14.2	31.7	5.5
O17	2017	6	40.2	7.5	10.0	2.2	23.5	3.4	12.6	6.3	34.7	4.3					120.0	11.4	39.3	4.0
P17	2017	22	29.6	6.7	13.0	4.7	17.6	4.0	17.0	3.7	32.7	4.6					113.7	13.0	33.5	5.9
V17	2017	24	33.5	7.4	12.0	5.3	15.7	4.0	15.3	4.6	31.4	4.2			26.3	5.8				
Total Mean		393	31.4		11.9		15.5		16.9		32.2		76.2		25.2		113.7		36.4	
SD			7.1		5.1		5.0		6.1		6.1		11.6		5.4		14.5		7.2	
2014 to 2016		627	29.4	13.5	11.3	4.5	15.6	4.6	16.0	4.8	31.7	6.7	75.5	11.7	24.6	5.9	111.9	17.1	35.6	8.1

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data

Rat Wistar : Crl-WI

Maternal food consumption (g/day) during gestation

Study	Year	Dams with live foetuses	GD 0 to 6		GD 6 to 9		GD 9 to 12		GD 12 to 15		GD 15 to 18		GD 6 to 18		GD 18 to 20		GD 6 to 21		GD 18 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	21	18.9	2.3	21.2	2.9	22.3	2.6	24.0	2.6	25.0	2.7	23.1	2.5	25.8	2.6				
B18	2018	9	20.8	2.6	25.8	6.4	24.5	2.9	26.3	3.3	27.2	2.4	26.0	3.1					26.3	2.5
C18	2018	21	19.7	2.9	23.1	2.8	24.5	3.1	24.9	3.3	27.6	2.4	25.0	2.3	28.1	3.3				
D18	2018	6	19.1	1.6	22.0	3.5	25.0	2.9	25.1	2.8	26.3	2.6	24.6	2.7					26.0	2.6
E18	2018	22	18.3	2.8	22.5	3.1	23.0	3.3	24.9	3.3	25.5	2.7	24.0	3.0					25.5	2.7
F18	2018	6	18.2	2.0	21.0	2.2	22.8	1.8	24.3	1.9	25.7	2.1	23.5	1.9	28.4	2.5				
G18	2018	18	18.6	2.6	20.0	2.3	21.8	2.9	24.3	2.2	25.1	2.5	22.8	2.3					25.0	3.3
H18	2018	5	16.0	1.9	21.0	4.2	21.2	4.4	24.0	4.0	25.2	2.5	22.8	3.6					24.9	2.8
K18	2018	6	18.3	1.9	21.1	4.6	20.9	3.3	23.2	3.3	26.0	3.5			25.8	3.2				
L18	2018	21	17.8	2.3	19.7	1.9	20.5	2.4	23.1	2.0	24.1	2.6			24.9	2.8				
M18	2018	5	18.6	3.3	17.8	4.9	25.3	1.7	23.2	3.7	28.0	3.8			28.4	4.2				
N18	2018	6			22.4	1.6	22.9	0.9	25.0	1.6	25.8	0.9			27.5	1.0				
A17	2017	22	20.3	2.6	24.6	2.7	25.6	3.1	26.6	2.8	27.8	2.9	26.2	2.7			26.4	2.7	27.5	2.8
B17	2017	5	21.3	2.2	25.5	2.0	25.9	3.7	26.8	2.5	29.0	1.4	26.8	2.1			26.6	2.0	25.7	1.9
C17	2017	22	19.2	2.0	23.0	2.1	24.4	2.3	26.2	2.1	27.2	2.8	25.2	2.0	26.8	2.9				
D17	2017	6	18.5	2.6	20.7	2.4	21.4	1.5	22.5	1.5	24.5	1.9	22.3	1.7	25.4	1.5				
E17	2017	9	18.8	2.8	21.8	3.3	23.0	3.4	24.1	3.2	25.6	3.1	23.6	3.2	25.7	3.5				
F17	2017	21	19.9	2.6	22.8	2.9	23.6	2.9	26.1	2.5	25.8	2.4	24.6	2.5	26.3	3.0				
G17	2017	8	21.3	1.3	23.1	1.6	23.8	2.2	24.3	2.2	25.8	2.5	24.3	2.0	26.0	1.8				
H17	2017	6	18.2	2.0	21.0	2.2	22.8	1.8	24.3	1.9	25.7	2.1	23.5	1.9	28.4	2.5				
I17	2017	24	19.7	2.7	24.5	2.3	26.2	2.5	26.8	2.6	28.8	2.7	26.6	2.3					26.6	2.7
J17	2017	24	20.6	2.7	23.8	2.5	26.3	3.1	26.3	3.0	28.8	3.2	26.3	2.8	27.8	3.5				
K17	2017	6	17.8	2.3	21.1	1.6	21.9	2.1	23.2	2.0	24.6	1.9					23.3	1.4	25.6	1.7
L17	2017	22	19.6	2.2	22.8	2.3	22.7	2.4	25.0	2.1	26.5	2.5					24.6	2.0	26.0	2.2
M17	2017	6	20.5	1.5	21.6	1.0	20.1	6.0	25.1	2.0	26.5	1.4					23.8	1.3	25.9	1.3
N17	2017	22	19.9	2.7	20.2	2.6	20.4	2.9	23.5	2.5	25.7	2.8					23.0	2.2	25.0	3.0
O17	2017	6	20.1	2.1	19.8	0.8	21.4	1.2	23.7	1.5	23.4	1.9					22.5	1.0	23.9	0.6
P17	2017	22	18.7	2.6	20.1	2.2	21.4	2.2	23.1	2.1	23.9	2.2					22.5	1.8	24.0	2.3
V17	2017	24	19.6	2.2	23.3	2.4	23.5	2.8	25.0	2.8	26.5	3.1			26.8	3.6				
Total		401																		
Mean			19.3		22.2		23.3		24.9		26.3		24.8		26.7		24.1		25.7	
SD				2.6		3.1		3.3		2.8		3.0		2.8		3.1		2.5		2.7
2014 to 2016		627	19.0	2.4	21.9	2.9	22.9	3.1	24.5	2.9	25.6	3.0	24.0	2.6	26.1	3.2	23.5	2.5	25.0	2.8

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data

Rat Wistar : Crl-WI

Caesarean data collected on day 20 or 21 of gestation - page 1/3

Study	Year	Number of females			Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Early resorptions per dam		Late resorptions per dam		Post-implantation loss %	
		Mated	Pregnant	With live fetuses	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	22	21	21	13.2	1.6	12.1	1.6	8.5	8.5	1.0	1.2	0.0	0.0	9.0	10.1
B18	2018	9	9	9	13.0	1.5	12.1	1.9	7.0	7.2	1.4	1.3	0.0	0.0	12.8	13.0
C18	2018	22	21	21	13.4	1.6	12.7	1.9	5.5	8.6	1.2	1.1	0.0	0.0	9.5	8.6
D18	2018	6	6	6	12.8	2.7	11.3	1.9	10.5	13.0	1.8	1.3	0.2	0.4	17.3	12.8
E18	2018	22	22	22	13.0	1.1	12.2	1.6	6.8	7.2	0.9	0.7	0.0	0.2	7.7	5.7
F18	2018	6	6	6	13.2	2.8	11.5	2.8	13.1	10.3	1.0	0.9	0.5	0.5	15.7	15.0
G18	2018	20	18	18	12.9	1.3	11.5	1.7	10.8	9.6	0.6	0.8	0.0	0.0	5.2	7.3
H18	2018	6	5	5	11.6	2.3	10.4	3.9	13.3	21.7	1.0	1.0	0.0	0.0	7.9	7.5
A17	2017	22	22	22	13.1	2.1	11.8	2.9	10.8	16.4	0.9	1.0	0.1	0.3	8.2	9.7
B17	2017	6	5	5	12.4	2.1	10.8	4.4	16.2	28.4	0.8	0.8	0.2	0.4	7.7	7.7
C17	2017	22	22	22	13.3	1.9	12.2	2.7	8.1	15.8	0.8	0.9	0.0	0.2	6.3	7.3
D17	2017	6	6	6	13.2	1.9	12.8	1.7	2.3	3.6	0.3	0.8	0.2	0.4	4.0	6.5
E17	2017	9	9	9	13.4	1.2	12.4	1.2	7.2	7.2	0.6	1.0	0.0	0.0	4.1	7.0
F17	2017	22	21	21	13.8	1.5	12.2	1.5	11.0	9.8	1.0	1.3	0.1	0.4	9.9	11.8
G17	2017	8	8	8	12.9	4.0	12.1	4.7	9.1	17.0	1.4	1.1	0.0	0.0	14.1	11.8
H17	2017	6	6	6	13.2	2.8	11.5	2.8	13.1	10.3	1.0	0.9	0.5	0.5	15.7	15.0
I17	2017	24	24	24	13.0	1.7	11.8	1.8	8.6	9.0	1.1	1.1	0.0	0.2	9.9	9.8
J17	2017	24	24	24	13.3	2.2	12.6	1.7	5.1	6.8	1.1	1.2	0.0	0.2	8.7	8.6
K17	2017	6	6	6	13.7	1.0	13.0	1.3	5.0	3.9	0.3	0.8	0.0	0.0	2.4	5.8
L17	2017	22	22	22	13.6	1.8	12.5	1.6	8.2	9.4	1.0	1.6	0.0	0.0	8.1	12.3
M17	2017	6	6	6	13.5	1.4	13.3	1.6	1.4	3.4	0.8	1.2	0.0	0.0	6.5	9.0
N17	2017	22	22	22	12.3	1.8	10.9	2.1	11.5	11.9	0.8	1.0	0.0	0.2	8.2	9.4
O17	2017	6	6	6	14.3	1.9	13.8	0.8	2.8	6.8	1.2	1.0	0.0	0.0	8.5	7.3
P17	2017	22	22	22	13.2	1.6	12.3	2.0	7.0	8.9	1.2	1.0	0.1	0.4	11.0	9.7
Total		346	339 98%	339 98%												
Mean SD					13.2	1.8	12.1	2.2	8.4	11.0	1.0	1.1	0.0	0.3	8.8	9.7
2014 to 2016		536	514 96%	508 95%	12.8	1.9	11.7	2.6	7.8	12.5	0.9	1.2	0.1	0.5	9.0	13.4

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****Caesarean data collected on day 20 or 21 of gestation - page 2/3**

Study	Year	Number of females			Dead foetuses Total	Live litter size		Litter weight (g) on GD 20		Foetal weight (g) on GD 20		Uterus weight (g) on GD 20	
		Mated	Pregnant	With live foetuses		Mean	SD	Mean	SD	Mean	SD	Mean	SD
A18	2018	22	21	21	0	11.0	2.1	39.0	8.1	3.53	0.33	61.1	11.0
B18	2018	9	9	9	0	10.7	2.7						
C18	2018	22	21	21	0	11.4	1.9	41.2	7.5	3.60	0.19	64.0	10.8
D18	2018	6	6	6	0	9.3	2.0						
E18	2018	22	22	22	0	11.2	1.5						
F18	2018	6	6	6	0	10.0	3.6	36.1	13.2	3.64	0.27	57.3	19.4
G18	2018	20	18	18	0	10.9	1.7						
H18	2018	6	5	5	0	9.4	3.2						
A17	2017	22	22	22	0	10.8	3.1						
B17	2017	6	5	5	0	9.8	3.8						
C17	2017	22	22	22	0	11.4	2.6	39.2	8.5	3.45	0.20	61.7	13.0
D17	2017	6	6	6	0	12.3	2.0	45.0	7.1	3.66	0.23	68.9	9.8
E17	2017	9	9	9	0	11.9	0.9	41.3	3.0	3.48	0.16	63.9	4.8
F17	2017	22	21	21	0	11.0	2.0	40.0	7.9	3.63	0.24	63.0	10.6
G17	2017	8	8	8	0	10.8	4.8	33.7	12.1	3.55	0.26	58.3	24.0
H17	2017	6	6	6	0	10.0	3.6	36.1	13.2	3.64	0.27	57.3	19.4
I17	2017	24	24	24	0	10.7	2.0						
J17	2017	24	24	24	0	11.5	1.7	40.9	6.2	3.58	0.23	65.0	9.7
K17	2017	6	6	6	0	12.7	1.2						
L17	2017	22	22	22	0	11.4	1.9						
M17	2017	6	6	6	0	12.5	2.2						
N17	2017	22	22	22	0	10.0	2.2						
O17	2017	6	6	6	0	12.7	1.4						
P17	2017	22	22	22	0	11.0	2.4						
Total		346	339 98%	339 98%	0								
Mean SD						11.0 2.3		39.7 8.3		3.56 0.24		62.6 12.4	
2014 to 2016		536	514 96%	508 95%	0	10.8	2.5	38.5	8.4	3.52	0.25	60.8	12.5

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data

Rat Wistar : Crl-WI

Caesarean data collected on day 20 or 21 of gestation - page 3/3

Study	Year	Number of females			Litter weight (g) on GD 21		Foetal weight (g) on GD 21		Uterus weight (g) on GD 21		Sex ratio
		Mated	Pregnant	With live foetuses							% males
					Mean	SD	Mean	SD	Mean	SD	
A18	2018	22	21	21							53.2
B18	2018	9	9	9	52.6	12.9	4.94	0.31	72.9	16.2	42.7
C18	2018	22	21	21							47.1
D18	2018	6	6	6	46.5	10.3	4.98	0.23	64.6	13.0	52.1
E18	2018	22	22	22	57.2	6.5	5.11	0.24	77.1	8.6	45.0
F18	2018	6	6	6							58.9
G18	2018	20	18	18	54.8	8.8	5.04	0.19	74.9	10.7	51.1
H18	2018	6	5	5	48.2	17.5	5.08	0.27	65.0	22.1	45.7
A17	2017	22	22	22	54.0	14.8	5.03	0.31	74.4	19.3	48.5
B17	2017	6	5	5	50.7	21.0	5.07	0.38	70.4	27.5	55.0
C17	2017	22	22	22							52.5
D17	2017	6	6	6							48.0
E17	2017	9	9	9							43.5
F17	2017	22	21	21							47.5
G17	2017	8	8	8							40.6
H17	2017	6	6	6							58.9
I17	2017	24	24	24	55.8	10.4	5.24	0.25	77.1	13.2	53.8
J17	2017	24	24	24							45.6
K17	2017	6	6	6	64.4	5.6	5.09	0.33	86.8	7.4	49.5
L17	2017	22	22	22	58.7	8.8	5.17	0.24	79.4	11.0	49.2
M17	2017	6	6	6	60.9	10.7	4.87	0.35	82.2	13.3	52.9
N17	2017	22	22	22	51.5	10.9	5.15	0.32	71.4	14.2	48.8
O17	2017	6	6	6	64.5	6.1	5.10	0.13	85.7	7.9	56.1
P17	2017	22	22	22	55.1	11.0	5.03	0.30	75.0	14.3	54.4
Total		346	339 98%	339 98%							
Mean					55.3		5.09		75.6		49.6
SD						11.2		0.28		14.3	
2014 to 2016		536	514 96%	508 95%	54.4	11.4	5.02	0.25	74.9	15.1	51.2

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data

Rat Wistar : Crl-WI

Malformations (external, internal and skeletal)

Study	Year	Number of litters examined	Number of fetuses examined	Number of litters with malformed fetuses	Litter incidence %	Number of malformed fetuses	Foetal incidence %	Type of malformation by foetus
A18	2018	21	232	1	4.76	1	0.43	Malformed cervical and thoracic vertebrae, and ribs
B18	2018	9	96	1	11.11	1	1.04	Narrowed aortic arch
C18	2018	21	240	0	-	0	-	
D18	2018	6	56	0	-	0	-	
E18	2018	22	247	0	-	0	-	
F18	2018	6	60	0	-	0	-	
G18	2018	18	196	0	-	0	-	
H18	2018	5	47	0	-	0	-	
A17	2017	22	238	2	9.09	2	0.84	1st: Situs inversus, abnormal lobation of lung 2nd: Situs inversus, abnormal lobation of lung, transposed great vessels
B17	2017	5	49	0	-	0	-	
C17	2017	22	251	2	9.09	2	0.80	1st: Cleft lip and palate; 2nd: Malformed thoracic vertebrae
D17	2017	6	74	1	16.67	1	1.35	Agnathia
E17	2017	9	107	0	-	0	-	
F17	2017	21	231	0	-	0	-	
G17	2017	8	86	0	-	0	-	
H17	2017	6	60	0	-	0	-	
I17	2017	24	256	0	-	0	-	
J17	2017	24	275	2	8.33	2	0.73	1st: Microphthalmia; 2nd: Proboscis (malformed skull)
K17	2017	6	76	0	-	0	-	
L17	2017	22	251	1	4.55	1	0.40	Proboscis
M17	2017	6	75	0	-	0	-	
N17	2017	22	221	0	-	0	-	
O17	2017	6	76	0	-	0	-	
P17	2017	22	242	0	-	0	-	
Total 2017 and 2018		339	3742	10	2.95%	10	0.27%	
Total 2014 to 2016		508	5539	25	4.92%	25	0.45%	

Study nos. B17, D17, H17, Q17, S17, U17, D18, F18 and H18: Dose Range Finding studies with external examination only

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - EXTERNAL EXAMINATION ON DAY 20 OR 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	30		39	
Number of foetuses examined	4672		6077	
OBSERVATION	N	%	N	%
Anasarca	1	0.02	0	0.00
Exencephaly	2	0.04	0	0.00
Head/neck: malformed	1	0.02	0	0.00
Eye(s): malformed	0	0.00	1	0.02
Eye(s): absent bulge	0	0.00	1	0.02
Agnathia	0	0.00	2	0.03
Astomia	0	0.00	1	0.02
Micrognathia	2	0.04	2	0.03
Cleft palate	0	0.00	1	0.02
Cleft lip	0	0.00	1	0.02
Nose: single naris	1	0.02	0	0.00
Proboscis	0	0.00	3	0.05
Limbs: malrotated	1	0.02	0	0.00
Trunk: omphalocele	1	0.02	0	0.00
Umbilicus: hernia	1	0.02	0	0.00
Gastroschisis	1	0.02	0	0.00
Anal atresia	2	0.04	0	0.00
Tail: thread-like	1	0.02	0	0.00

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - FRESH VISCERAL EXAMINATION OF BODY ON DAY 20 OR 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	17		23	
Number of foetuses examined	1857		2716	
OBSERVATION	N	%	N	%
Situs inversus	4	0.22	1	0.04
Great blood vessels: malformed	1	0.05	2	0.07
Great blood vessels: transposition	0	0.00	1	0.04
Carotid artery: narrowed	1	0.05	0	0.00
Pulmonary artery: malpositioned	1	0.05	0	0.00
Subclavian artery: retroesophageal	1	0.05	0	0.00
Umbilical artery: transposed	239	12.87	345	12.70
Azygos vein: transposed	0	0.00	1	0.04
Aortic arch: narrowed	0	0.00	1	0.04
Lungs: abnormal lobation	0	0.00	2	0.07
Lungs: lobe absent	1	0.05	1	0.04
Thyroid gland: small	0	0.00	1	0.04
Thorax: tissue-mass	0	0.00	1	0.04
Diaphragm: absent	1	0.05	0	0.00
Intestine: distended	0	0.00	1	0.04
Stomach: narrowed	0	0.00	1	0.04
Pancreas: large	0	0.00	1	0.04
Pancreas: malpositioned	0	0.00	1	0.04
Spleen: small	0	0.00	1	0.04
Spleen: discolored	0	0.00	1	0.04
Liver: discolored lobe	1	0.05	4	0.15
Liver: abnormal lobation	1	0.05	1	0.04
Adrenal gland(s): discolored	1	0.05	0	0.00
Kidney(s): renal pelvic dilatation	0	0.00	1	0.04
Kidney(s): malpositioned	1	0.05	0	0.00
Kidney(s): large	2	0.11	0	0.00
Kidney: absent	1	0.05	0	0.00
Ureter(s): dilated	59	3.18	24	0.88
Ureter(s): convoluted	20	1.08	9	0.33
Testis: malpositioned	2	0.11	0	0.00
Testis: cyst	1	0.05	9	0.33

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - FIXED VISCERAL EXAMINATION OF HEAD ON DAY 20 OR 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	18		23	
Number of foetuses examined	1664		2407	
OBSERVATION	N	%	N	%
Head: multiple visceral abnormalities	0	0.00	1	0.04
Microphthalmia	0	0.00	1	0.04
Anophthalmia	2	0.12	0	0.00
Aphakia	0	0.00	1	0.04
Retinal fold	0	0.00	1	0.04
Brain: dilated lateral ventricles	6	0.36	6	0.25

Historical Control Data

Rat Wistar : Crl-WI

FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 1/3

PERIOD	2013-2015		2016-2018	
Number of studies included	15		14	
Number of foetuses examined	1642		1645	
OBSERVATION	N	%	N	%
Generalised incomplete ossification	1	0.06	0	0.00
General: multiple skeletal abnormalities	1	0.06	0	0.00
Humerus: bent	1	0.06	0	0.00
Humerus: thick	0	0.00	1	0.06
Scapula: misshapen	1	0.06	0	0.00
Scapula: bent	0	0.00	1	0.06
Metacarpals: incomplete ossification (2nd or 5th digits)	14	0.85	0	0.00
Metacarpals: incomplete ossification (2nd to 4th digits)	9	0.55	5	0.30
Metacarpals: unossified (5th digit)	216	13.15	208	12.64
Metacarpals: unossified (2nd to 4th digits)	0	0.00	1	0.06
Metatarsals: advanced ossification	22	1.34	0	0.00
Metatarsals: incomplete ossification	6	0.37	7	0.43
Metatarsals: unossified	3	0.18	6	0.36
Pubis: incomplete ossification	11	0.67	4	0.24
Pubis: unossified	2	0.12	2	0.12
Ischium: incomplete ossification	1	0.06	0	0.00
Ischium: unossified	0	0.00	1	0.06
Ribs: number of full ribs = 12/12	0	0.00	1	0.06
Ribs: number of full ribs = 12/13	1	0.06	0	0.00
Ribs: number of full ribs = 14/14	1	0.06	0	0.00
Rib: incomplete ossification	4	0.24	3	0.18
Rib: irregular ossification	10	0.61	0	0.00
Rib: unilateral rudimentary 14th	27	1.64	0	0.00
Rib: bilateral rudimentary 14th	49	2.98	0	0.00
Rib: supernumerary cervical	23	1.40	7	0.43
Rib: supernumerary lumbar	27	1.64	60	3.65
Rib: supernumerary lumbar (short)	716	43.61	753	45.78

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data

Rat Wistar : Crl-WI

FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 2/3

PERIOD	2013-2015		2016-2018	
Number of studies included	15		14	
Number of foetuses examined	1642		1645	
OBSERVATION	N	%	N	%
Rib: branched	0	0.00	1	0.06
Rib: wavy	47	2.86	25	1.52
Rib: thick	41	2.50	84	5.11
Rib: intercostal	0	0.00	1	0.06
Sternebrae: incomplete ossification of 1st/3rd	23	1.40	19	1.16
Sternebrae: incomplete ossification of 2nd/4th	88	5.36	34	2.07
Sternebrae: incomplete ossification of 6th	370	22.53	322	19.57
Sternebrae: unossified 1st/3rd	4	0.24	5	0.30
Sternebrae: unossified 2nd/4th	12	0.73	8	0.49
Sternebrae: unossified 5th	106	6.46	86	5.23
Sternebrae: unossified 6th	60	3.65	39	2.37
Sternebrae: asymmetric	17	1.04	6	0.36
Sternebrae: bipartite ossification	6	0.37	1	0.06
Sternebrae: hemisternebra	3	0.18	0	0.00
Sternebrae: minor fusion	1	0.06	0	0.00
Sternebrae: misshapen	1	0.06	2	0.12
Vertebral column: malformed	2	0.12	0	0.00
Vertebrae, presacral arches = 27	15	0.91	10	0.61
Vertebrae, cervical: advanced ossification	140	8.53	0	0.00
Vertebrae, cervical: incomplete ossification of arch	0	0.00	11	0.67
Vertebrae, cervical: increased ossification 1st centrum	395	24.06	397	24.13
Vertebrae, cervical: absent arch	1	0.06	1	0.06

Historical Control Data

Rat Wistar : Crl-WI

FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 3/3

PERIOD	2013-2015		2016-2018	
Number of studies included	15		14	
Number of foetuses examined	1642		1645	
OBSERVATION	N	%	N	%
Vertebrae, thoracic: malformed	2	0.12	3	0.18
Vertebrae, thoracic: incomplete ossification of centrum	5	0.30	1	0.06
Vertebrae, thoracic: incomplete ossification of 1-4th centrum	2	0.12	0	0.00
Vertebrae, thoracic: incomplete ossification of 9-13th centrum	12	0.73	0	0.00
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	10	0.61	13	0.79
Vertebrae, thoracic: unossified centrum	0	0.00	1	0.06
Vertebrae, thoracic: unossified 1-9th centrum	5	0.30	3	0.18
Vertebrae, thoracic: bipartite ossification of centrum	14	0.85	19	1.16
Vertebrae, thoracic: centrum hemicentric	3	0.18	1	0.06
Vertebrae, thoracic: small centrum	0	0.00	2	0.12
Vertebrae, thoracic: misaligned centrum	0	0.00	1	0.06
Vertebrae, thoracic: number = 12	0	0.00	1	0.06
Vertebrae, lumbar: incomplete ossification of centrum	5	0.30	7	0.43
Vertebrae, lumbar: unossified centrum	0	0.00	1	0.06
Vertebrae, lumbar: number = 7	25	1.52	14	0.85
Vertebrae, lumbar: centrum bipartite	0	0.00	1	0.06
Vertebrae, lumbar: incomplete ossification of arches	7	0.43	4	0.24
Vertebrae, sacral: unossified arches	3	0.18	5	0.30
Vertebrae, sacral: incomplete ossification of arches	76	4.63	57	3.47
Vertebrae, sacral: unossified centrum	1	0.06	0	0.00
Vertebrae, sacral: unossified	5	0.30	3	0.18
Vertebrae, sacral: incomplete ossification of centrum	3	0.18	3	0.18
Vertebrae, caudal: unossified arches - region 1-2	552	33.62	548	33.31
Vertebrae, caudal: unossified centrum - region 1-2	4	0.24	4	0.24
Vertebrae, caudal: unossified	21	1.28	20	1.22

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF HEAD ON DAY 20 OF GESTATION - page 1/2**

PERIOD	2013-2015		2016-2018	
Number of studies included	15		14	
Number of foetuses examined	1544		1594	
OBSERVATION	N	%	N	%
Generalised incomplete ossification	2	0.13	2	0.13
Skull: malformed	2	0.13	2	0.13
Head: malformed	0	0.00	1	0.06
Nasal: incomplete ossification	9	0.58	3	0.19
Frontal: incomplete ossification	11	0.71	15	0.94
Parietal: incomplete ossification	171	11.08	191	11.98
Parietals: unossified area	2	0.13	0	0.00
Interparietal: incomplete ossification	192	12.44	162	10.16
Supraoccipital: incomplete ossification	124	8.03	100	6.27
Supraoccipital: bipartite ossification	2	0.13	0	0.00
Supraoccipital: unossified	0	0.00	2	0.13
Fontanelle: enlarged	1	0.06	1	0.06
Squamosal: incomplete ossification	57	3.69	83	5.21
Zygomatic arch: incomplete ossification	26	1.68	19	1.19
Hyoid: unossified	17	1.10	15	0.94
Basioccipital: unossified area	1	0.06	0	0.00
Basioccipital: incomplete ossification	2	0.13	0	0.00
Palatine: split	2	0.13	0	0.00
Presphenoid: incomplete ossification	1	0.06	4	0.25
Presphenoid: unossified	1	0.06	2	0.13
Presphenoid: small	1	0.06	0	0.00
Alisphenoid: incomplete ossification	3	0.19	0	0.00
Basisphenoid: incomplete ossification	1	0.06	1	0.06
Mandible: fused	1	0.06	1	0.06
Mandible: short	2	0.13	1	0.06
Maxilla: short	2	0.13	0	0.00
Maxilla: split	1	0.06	0	0.00
Maxilla: multiple abnormalities	1	0.06	0	0.00

File name: I.2.1-RAT_WISTAR_G20-G21_2018_OK.xls

Historical Control Data

Rat Wistar : Crl-WI

FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 21 OF GESTATION - Page 1/2

PERIOD	2013-2015		2016-2018	
Number of studies included	2		9	
Number of foetuses examined	233		1096	
OBSERVATION	N	%	N	%
Metacarpals: incomplete ossification (5th digit)	1	0.43	7	0.64
Metatarsals: unossified, 1st digit	7	3.00	11	1.00
Phalanx: unossified (2nd to 5th digits), forepaws	21	9.01	0	0.00
Phalanx: unossified, forepaws	0	0.00	110	10.04
Phalanx: unossified, hindpaws	0	0.00	30	2.74
Phalanx: unossified (2nd to 5th digits), hindpaws	54	23.18	236	21.53
Rib: supernumerary cervical	4	1.72	21	1.92
Rib: supernumerary lumbar	2	0.86	39	3.56
Rib: supernumerary lumbar (short)	121	51.93	491	44.80
Rib: short	0	0.00	1	0.09
Rib: wavy	17	7.30	11	1.00
Rib: thick	8	3.43	39	3.56
Sternebrae: incomplete ossification of 1st/3rd	1	0.43	2	0.18
Sternebrae: incomplete ossification of 2nd/4th	2	0.86	12	1.09
Sternebrae: incomplete ossification of 6th	2	0.86	2	0.18
Sternebrae: unossified 5th	1	0.43	1	0.09
Sternebrae: unossified 6th	1	0.43	0	0.00
Sternebrae: extra ossification site	0	0.00	2	0.18
Sternebrae: asymmetric	5	2.15	7	0.64
Sternebrae: split	1	0.43	0	0.00
Sternebrae: misshapen	0	0.00	1	0.09

Historical Control Data

Rat Wistar : Crl-WI

FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 21 OF GESTATION - page 2/2

PERIOD	2013-2015		2016-2018	
Number of studies included	2		9	
Number of foetuses examined	233		1096	
OBSERVATION	N	%	N	%
Vertebrae, presacral arches = 27	2	0.86	3	0.27
Vertebrae, cervical: incomplete ossification of arch	0	0.00	2	0.18
Vertebrae, cervical: unossified odontoid process	21	9.01	153	13.96
Vertebrae, cervical: unossified centrum	57	24.46	344	31.39
Vertebrae, cervical: bipartite centrum	0	0.00	27	2.46
Vertebrae, thoracic: incomplete ossification of centrum	0	0.00	3	0.27
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	3	1.29	7	0.64
Vertebrae, thoracic: incomplete ossification of 10-13th centrum	14	6.01	24	2.19
Vertebrae, thoracic: fused arch	0	0.00	1	0.09
Vertebrae, thoracic: bipartite ossification of centrum	6	2.58	3	0.27
Vertebrae, thoracic: centrum hemicentric	0	0.00	1	0.09
Vertebrae, thoracic: misaligned centrum	0	0.00	1	0.09
Vertebrae, thoracic: absent centrum	0	0.00	1	0.09
Vertebrae, thoracic: small centrum	0	0.00	1	0.09
Vertebrae, lumbar: number = 5	0	0.00	1	0.09
Vertebrae, lumbar: number = 7	2	0.86	9	0.82
Vertebrae, lumbar: incomplete ossification of centrum	0	0.00	1	0.09
Vertebrae, sacral: incomplete ossification of arches	1	0.43	0	0.00
Vertebrae, caudal number < 5	7	3.00	39	3.56

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF HEAD ON DAY 21 OF GESTATION**

PERIOD	2013-2015		2016-2018	
Number of studies included	2		9	
Number of fetuses examined	233		1050	
OBSERVATION	N	%	N	%
Parietal: incomplete ossification	9	3.86	38	3.62
Interparietal: incomplete ossification	23	9.87	80	7.62
Supraoccipital: incomplete ossification	6	2.58	8	0.76
Cranium: Sutural bone	2	0.86	2	0.19
Squamosal: incomplete ossification	4	1.72	7	0.67
Zygomatic arch: incomplete ossification	2	0.86	9	0.86
Hyoid: incomplete ossification	0	0.00	7	0.67
Mandible: incomplete ossification	0	0.00	15	1.43

Historical Control Data**Rat Wistar: Crl-WI****Maternal body weight gain (g) during lactation**

Study	Year	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
K18	2018	6	14.9	5.7	3.8	6.0	16.3	7.0	0.1	3.6				
L18	2018	21	13.3	6.3	6.3	8.8	7.2	5.8	10.2	6.7	0.2	7.2	-14.0	6.1
M18	2018	5	12.4	8.5	7.1	3.1								
N18	2018	6	15.5	9.3	13.2	9.9								
V17	2017	23	10.2	10.0	8.7	6.1	2.7	5.6	7.8	6.5	-1.2	8.3	-17.2	9.9
U16	2016	5	6.6	2.5	1.2	5.3								
V16	2016	21	9.1	6.4	10.2	3.8	8.0	5.4	6.6	7.1	4.5	7.3	-12.8	6.4
W16	2016	21	17.6	10.4	9.1	4.9	8.5	5.5	6.5	5.8	1.6	5.7	-10.7	7.5
X16	2016	7	2.6	7.2										
I15	2015	22	13.9	9.9	5.2	6.8	8.1	6.4	2.5	7.1	-4.1	7.4	-10.4	6.2
J15	2015	24	10.5	7.0	8.3	6.4	8.8	5.8	4.5	4.3	2.8	6.3	-12.8	7.6
K15-1	2015	22	12.9	6.8	7.4	5.6								
K15-2	2015	22	11.2	6.0	10.0	5.9								
L15	2015	10	21.2	11.3										
M15	2015	9	18.8	5.3										
Total Mean		224	12.7		8.0		7.6		6.0		0.6		-13.0	
SD				8.6		6.5		6.3		6.6		7.5		7.7
2012-2014		92	8.1	7.6	7.2	5.7	7.6	5.8	6.0	6.7	1.3	7.2	-7.0	9.5

Historical Control Data**Rat Wistar: Crl-WI****Maternal food consumption (g/day) during lactation**

Study	Year	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21		Lactation days 14 to 21	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
K18	2018	6	32.0	6.7	39.1	4.5	49.3	3.4	53.2	4.3						
L18	2018	21	31.5	4.9	38.1	6.4	45.4	6.4	55.7	8.9	54.8	5.5	62.7	6.2		
M18	2018	5	37.8	5.8	45.5	6.5										
N18	2018	6	37.1	3.7	50.7	4.4										
V17	2017	23	35.2	4.7	43.3	3.8	50.3	4.5	57.5	4.1	62.3	5.0	68.0	6.2		
U16	2016	5	24.4	4.0	31.5	5.2										
V16	2016	21	28.5	4.8	39.5	5.7	45.4	6.6	52.1	9.4	56.2	9.3	65.2	11.3		
W16	2016	21	31.2	5.5	43.0	6.2	48.4	7.4	57.0	9.1	58.0	10.3	66.6	10.9		
X16	2016	7	24.5	2.8												
I15	2015	22	34.4	5.2	44.0	4.4	51.7	4.0	55.3	5.1	58.4	4.5	65.1	5.5	52.4	4.3
J15	2015	24	30.8	4.0	40.6	3.9	48.4	4.5	53.8	4.6	59.2	4.6	64.0	4.5	50.4	3.9
K15-1	2015	22	30.6	3.9	40.1	2.8									59.9	4.1
K15-2	2015	22	27.6	4.5	38.4	3.8									56.7	3.7
L15	2015	10	38.2	5.3												
M15	2015	9	36.1	4.5												
Total Mean		224	31.7		41.0		48.4		55.2		58.2		65.3		54.7	
SD				5.7		5.6		5.9		7.1		7.1		7.8		5.4
2012-2014		92	31.6	4.9	41.6	5.0	48.7	5.5	55.4	6.1	59.3	7.5	62.5	6.3	62.2	4.0

Historical Control Data**Rat Wistar: Crl-WI****Post-partum litter data**

Study	Year	Number of females				Gestation length (days)		Number of uterine implants		Number of pups born		Pre-birth loss index %	Live birth index %	Pup viability index %	Pup weaning index %
		Mated	Pregnant	With liveborn	With pups at weaning	Mean	SD	Mean	SD	Mean	SD				
K18	2018	6	6	6	NA	22.5	0.5	11.5	1.9	10.7	2.4	7.2	100.0	98.4	NA
L18	2018	22	21	21	21	22.3	0.5	11.7	2.5	10.7	2.2	8.3	99.1	97.7	100.0
M18	2018	6	5	5	NA	22.2	0.4	11.6	1.5	10.8	1.6	6.7	100.0	100.0	NA
N18	2018	6	6	6	NA	22.2	0.4	13.3	1.4	12.8	1.2	3.3	100.0	98.7	NA
V17	2017	24	24	23	23	22.4	0.5	12.6	1.5	11.0	2.1	12.3	96.2	98.8	99.4
U16	2016	6	5	5	NA	22.8	0.8	10.2	3.6	8.0	3.4	18.7	100	100	NA
V16	2016	21	21	21	21	22.5	0.6	11.3	2.1	9.9	2.3	13.6	99.5	97.1	100
W16	2016	22	22	21	21	22.4	0.5	11.0	4.0	10.3	3.5	10.7	99.1	99.5	100
X16	2016	10	9	7	NA	22.6	0.8	11.9	5.3	10.6	3.6	20.7	100	100	NA
I15	2015	24	22	22	22	22.2	0.4	12.8	1.5	11.5	1.3	10.1	98.4	99.6	100
J15	2015	24	24	24	24	22.4	0.5	11.9	1.8	10.6	1.7	10.4	99.6	98.0	100
K15-1	2015	24	22	22	22	22.2	0.4	12.8	1.6	11.8	1.4	7.8	98.8	98.8	100
K15-2	2015	24	24	22	22	22.2	0.4	11.9	2.1	11.3	2.2	5.1	96.0	96.2	100
L15	2015	10	10	10	NA	22.3	0.5	15.0	1.5	13.6	1.6	9.1	97.1	100	NA
M15	2015	9	9	9	NA	22.0	0.0	14.2	3.6	13.9	3.3	2.0	100	100	NA
Total %		238	230	224	176										
Mean			97%	94%	95%	22.3		12.2		11.1		10.0	98.5	98.5	99.9
SD						0.5		2.6		2.5					
2012-2014		100	98	98	92	22.1	0.4	10.9	3.3	10.5	2.0		99.1	98.3	100.0
			98%	98%	98%										

NA = Not Applicable

Historical Control Data**Rat Wistar: Crl-WI****Post-partum data - pup weights (g)****Page 1/2**

Study	Year	Number of litters	Postnatal day 1				Postnatal day 4				Postnatal day 7				Postnatal day 14			
			Males		Females		Males		Females		Males		Females		Males		Females	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
K18	2018	6	7.3	0.6	6.8	0.7	11.3	1.2	10.8	1.4	17.6	1.9	17.0	2.0	34.1	2.2	33.3	2.7
L18	2018	21	7.1	0.9	6.8	0.8	11.1	1.2	10.7	1.3	17.3	1.8	16.9	1.7	33.7	3.2	32.9	3.1
M18	2018	5	7.1	1.1	6.7	0.9	10.9	2.1	10.5	1.9	17.6	3.4	17.1	3.0				
N18	2018	6	6.8	0.2	6.6	0.3	10.8	0.6	10.5	0.6	15.9	0.5	15.4	0.5				
V17	2017	23	7.2	0.9	6.9	0.8	11.3	1.4	11.1	1.4	18.3	1.5	17.7	1.6	35.6	2.3	34.8	2.5
U16	2016	5	7.4	1.3	7.0	1.3	11.5	2.3	11.2	2.5	17.5	2.6	17.0	2.9				
V16	2016	21	7.4	0.8	7.0	0.6	11.4	1.0	10.9	0.9	17.4	1.1	16.5	1.5	33.3	2.0	31.9	3.0
X16	2016	7	7.0	1.4	6.6	1.1	10.5	2.3	10.2	2.3								
W16	2016	21	6.7	1.0	6.4	1.0	10.5	1.9	10.1	2.0	16.9	2.2	16.4	2.3	34.1	2.5	33.1	2.6
I15	2015	22	7.0	0.7	6.8	0.7	11.1	1.0	10.9	1.1	17.9	1.4	17.4	1.5	34.2	2.4	33.3	2.1
J15	2015	24	7.3	0.9	6.9	0.9	11.2	1.1	10.8	1.2	17.3	1.5	16.7	1.5	33.4	2.4	32.6	2.5
K15-1	2015	22	6.6	0.5	6.4	0.5	10.3	1.0	10.0	1.0	16.8	1.1	16.1	1.1	33.5	1.6	32.6	1.8
K15-2	2015	22	6.8	0.9	6.5	0.8	10.2	1.5	9.9	1.5	15.8	1.8	15.4	1.8	31.1	3.0	30.7	2.9
L15	2015	10	6.7	0.5	6.4	0.6	10.2	1.0	9.7	1.0								
M15	2015	9	6.4	0.6	6.0	0.5	9.8	1.2	9.4	1.1								
Total Mean		224	7.0		6.7		10.8		10.5		17.2		16.6		33.6		32.8	
SD				0.8		0.8		1.4		1.4		1.8		1.8		2.7		2.8
2012-2014		98	6.9	0.7	6.6	0.7	10.7	1.2	10.3	1.3	16.9	1.7	16.4	1.8	32.8	2.6	32.0	2.6

Historical Control Data**Rat Wistar: Crl-WI****Post-partum data - pup weights (g) Page 2/2**

Study	Year	Number of litters	Postnatal day 21			
			Males		Females	
			Mean	SD	Mean	SD
K18	2018	6				
L18	2018	21	53.6	5.5	52.2	4.9
M18	2018	5				
N18	2018	6				
V17	2017	23	57.6	3.8	56.0	4.4
U16	2016	5				
V16	2016	21	55.1	3.3	52.5	5.0
X16	2016	7				
W16	2016	21	56.0	3.8	53.9	3.8
I15	2015	22	54.2	4.1	52.8	3.7
J15	2015	24	53.8	3.5	52.3	3.7
K15-1	2015	22	53.5	2.7	51.5	3.0
K15-2	2015	22	49.7	4.5	48.8	4.1
L15	2015	10				
M15	2015	9				
<i>Total</i>		224				
<i>Mean</i>			54.2		52.5	
<i>SD</i>				4.5		4.5
2012-2014		98	51.2	4.3	49.6	4.1

Historical Control Data**Rat Wistar: Crl-WI****Pre-weaning development - % of pups positive**

Study	Year	Number of litters	Pinna unfolding					Incisor eruption								Eye opening					
			PND1	PND2	PND3	PND4	PND5	PND7	PND8	PND9	PND10	PND11	PND12	PND13	PND14	PND12	PND13	PND14	PND15	PND16	PND17
L18	2018	21	10	48	100	100	100	0	3	10	39	66	99	100	100	1	15	77	100	100	100
V17	2017	23	18	73	100	100	100	0	0	2	43	81	98	100	100	1	20	84	99	100	100
V16	2016	21	25	79	100	100	100	0	1	8	23	61	93	99	100	1	14	73	97	100	100
W16	2016	21	7	59	99	100	100	1	2	16	46	84	97	99	100	3	11	56	94	100	100
I15	2015	22	4	43	98	100	100	0	4	11	50	89	99	100	100	0	25	85	99	100	100
J15	2015	24	9	71	99	100	100	0	1	7	47	87	100	100	100	1	18	83	100	100	100
Total Mean %		132	12	62	99	100	100	0	2	9	42	78	98	100	100	1	17	77	98	100	100
2012-2014		79	7	58	98	100	100	0	2	13	43	83	98	99	100	1	14	72	99	100	100

PND: postnatal day

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning development**

Study	Year	Vaginal opening					Balano-preputial skinfold cleavage				
		Postnatal Day of occurrence			Body weight (g)		Postnatal Day of occurrence			Body weight (g)	
		Mean	SD	N	Mean	SD	Mean	SD	N	Mean	SD
L18	2018	33.3	1.4	20	117	10	47.5	3.9	20	230	27
V17	2017	33.6	2.3	20	120	14	45.5	2.5	20	214	21
V16	2016	33.4	3.5	20	118	18	47.0	4.5	20	220	25
W16	2016	32.7	1.6	20	112	8	44.1	3.1	20	202	22
I15	2015	32.8	1.8	20	110	9	44.6	2.1	20	209	19
J15	2015	33.6	2.1	20	117	13	41.7	0.9	20	190	14
K15-2	2015	33.0	3.0	24	108	13	43.0	2.0	24	181	13
<i>Total</i>				<i>144</i>					<i>144</i>		
<i>Mean</i>		<i>33.2</i>			<i>114</i>		<i>44.7</i>			<i>206</i>	
<i>SD</i>			<i>2.3</i>			<i>13</i>		<i>3.4</i>			<i>26</i>
2012-2014		33.6	2.3	101	108	15	43.2	2.0	101	186	21

Historical Control Data

Rat Wistar: Crl-WI

Post-weaning behaviour tests - Water Maze (manual record)

		MALES						
		Time (s)			Number of error			
		V17 2017 20	L18 2018 20		Overall	V17 2017 20	L18 2018 20	Overall
Age		8-9W	8-9W			8-9W	8-9W	
Straight channel								
Trial 1								
	Mean	26.6	28.1		27	NA	NA	-
	SD	13.4	21.1		17	NA	NA	-
	N	20	20		40	NA	NA	-
Trial 2								
	Mean	8.0	7.9		8	NA	NA	-
	SD	3.7	3.8		4	NA	NA	-
	N	20	20		40	NA	NA	-
Trial 3								
	Mean	4.7	6.0		5	NA	NA	-
	SD	1.8	2.4		2	NA	NA	-
	N	20	20		40	NA	NA	-
Trial 4								
	Mean	4.2	5.2		5	NA	NA	-
	SD	2.0	1.7		2	NA	NA	-
	N	20	20		40	NA	NA	-
Learning								
Trial 1								
	Mean	79.3	91.0		86	5.1	5.4	5.3
	SD	41.8	43.5		42	2.3	2.6	2.4
	N	12	17		29	12	17	29
Trial 2								
	Mean	48.4	67.1		58	3.1	4.3	3.7
	SD	32.9	33.2		34	2.3	2.2	2.3
	N	16	18		34	16	18	34
Trial 3								
	Mean	47.2	60.7		54	2.9	3.8	3.4
	SD	40.2	43.7		42	3.1	2.4	2.8
	N	18	18		36	18	18	36
Trial 4								
	Mean	27.3	44.3		36	1.4	2.4	1.9
	SD	15.7	28.4		24	1.0	1.9	1.6
	N	18	19		37	18	19	37
Trial 5								
	Mean	29.8	37.5		34	2.0	2.2	2.1
	SD	24.2	24.3		24	1.7	1.5	1.6
	N	20	19		39	20	19	39
Memory								
Trial 6								
	Mean	42.1	43.3		43	1.9	2.8	2.4
	SD	31.7	33.7		32	1.6	2.1	1.9
	N	19	20		39	19	20	39

W: Week

- : Not Applicable

File name: I.2.2-RAT_WISTAR_post partum_2018_OK.xls

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Water Maze (manual record)**

		FEMALES						
		Time (s)			Number of error			
		V17	L18		Overall	V17	L18	Overall
Study	Year	2017	2018			2017	2018	
N		20	20			20	20	
Age		8-9W	8-9W			8-9W	8-9W	
Straight channel								
Trial 1								
	Mean	35.1	23.0		29	NA	NA	-
	SD	17.1	13.2		16	NA	NA	-
	N	20	20		40	NA	NA	-
Trial 2								
	Mean	7.5	7.5		8	NA	NA	-
	SD	3.5	4.1		4	NA	NA	-
	N	20	20		40	NA	NA	-
Trial 3								
	Mean	5.0	5.1		5	NA	NA	-
	SD	1.5	2.5		2	NA	NA	-
	N	20	20		40	NA	NA	-
Trial 4								
	Mean	5.0	5.1		5	NA	NA	-
	SD	1.5	2.9		2	NA	NA	-
	N	20	20		40	NA	NA	-
Learning								
Trial 1								
	Mean	65.2	71.1		68	3.9	4.1	4.0
	SD	29.8	43.3		37	1.4	2.7	2.1
	N	15	16		31	15	16	31
Trial 2								
	Mean	58.8	68.6		64	3.2	5.0	4.1
	SD	41.8	44.5		43	2.6	3.4	3.1
	N	18	20		38	18	20	38
Trial 3								
	Mean	44.0	44.3		44	2.9	2.9	2.9
	SD	38.3	26.4		32	2.4	2.3	2.3
	N	18	19		37	18	19	37
Trial 4								
	Mean	36.0	43.6		40	2.4	3.0	2.7
	SD	21.9	38.8		31	1.6	3.6	2.8
	N	19	19		38	19	19	38
Trial 5								
	Mean	25.5	38.6		32	2.1	2.3	2.2
	SD	15.9	36.5		29	1.8	2.9	2.4
	N	20	20		40	20	20	40
Memory								
Trial 6								
	Mean	37.7	36.1		37	1.9	2.5	2.2
	SD	31.6	21.6		27	1.9	1.5	1.7
	N	20	19		39	20	19	39

W: Week

- : Not Applicable

File name: I.2.2-RAT_WISTAR_post partum_2018_OK.xls

Historical Control Data

Rat Wistar: Crl-WI

Post-weaning behaviour tests - Motor Activity - Fine Movements

Page 1/2

Study	Year	Pup Age	N	MALES													
				Interval 1		Interval 2				Interval 3				Interval 4			
				Count		Count		Habituation (%)		Count		Habituation (%)		Count		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	882	256	558	212	-34	27	505	191	-41	20	453	260	-47	26
Total			20	882		558		-34		505		-41		453		-47	
Mean																	
SD					256		212		27		191		20		260		26

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Motor Activity - Fine Movements****Page 2/2**

Study	Year	Pup Age	N	MALES									
				Interval 5				Interval 6				Total	
				Count		Habituation (%)		Count		Habituation (%)		Count	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	347	237	-58	32	300	246	-65	29	3044	804
<i>Total</i>			<i>20</i>										
<i>Mean</i>				<i>347</i>		<i>-58</i>		<i>300</i>		<i>-65</i>		<i>3044</i>	
<i>SD</i>					<i>237</i>		<i>32</i>		<i>246</i>		<i>29</i>		<i>804</i>

W: week

Historical Control Data

Rat Wistar: Crl-WI

Post-weaning behaviour tests - Motor Activity - Ambulation

Page 1/2

Study	Year	Pup Age	N	MALES													
				Interval 1		Interval 2				Interval 3				Interval 4			
				Count		Count		Habituation (%)		Count		Habituation (%)		Count		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	231	108	127	73	-36	53	114	65	-45	31	84	54	-57	31
Total			20														
Mean				231		127		-36		114		-45		84		-57	
SD					108		73		53		65		31		54		31

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Motor Activity - Ambulation****Page 2/2**

Study	Year	Pup Age	N	MALES									
				Interval 5				Interval 6				Total	
				Count		Habituation (%)		Count		Habituation (%)		Count	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	77	64	-60	41	59	54	-70	33	692	251
<i>Total</i>			<i>20</i>										
<i>Mean</i>				77		-60		59		-70		692	
<i>SD</i>					64		41		54		33		251

W: week

Historical Control Data

Rat Wistar: Crl-WI

Post-weaning behaviour tests - Motor Activity - Fine Movements

Page 1/2

Study	Year	Pup Age	N	FEMALES													
				Interval 1		Interval 2				Interval 3				Interval 4			
				Count		Count		Habituation (%)		Count		Habituation (%)		Count		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	951	301	540	176	-41	16	411	208	-55	23	360	211	-58	29
Total			20	951		540		-41		411		-55		360		-58	
Mean																	
SD					301		176		16		208		23		211		29

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Motor Activity - Fine Movements****Page 2/2**

Study	Year	Pup Age	N	FEMALES									
				Interval 5				Interval 6				Total	
				Count		Habituation (%)		Count		Habituation (%)		Count	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	234	195	-72	24	203	159	-77	18	2698	645
<i>Total</i>			<i>20</i>										
<i>Mean</i>				234		-72		203		-77		2698	
<i>SD</i>					195		24		159		18		645

W: week

Historical Control Data

Rat Wistar: Crl-WI

Post-weaning behaviour tests - Motor Activity - Ambulation

Page 1/2

Study	Year	Pup Age	N	FEMALES													
				Interval 1		Interval 2				Interval 3				Interval 4			
				Count		Count		Habituation (%)		Count		Habituation (%)		Count		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	349	156	180	103	-46	20	131	136	-65	23	93	75	67	34
Total			20	349		180		-46		131		-65		93		67	
Mean																	
SD					156		103		20		136		23		75		34

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Motor Activity - Ambulation****Page 2/2**

Study	Year	Pup Age	N	FEMALES									
				Interval 5				Interval 6				Total	
				Count		Habituation (%)		Count		Habituation (%)		Count	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	51	52	-81	23	58	65	-80	22	862	406
<i>Total</i>			<i>20</i>										
<i>Mean</i>				51		-81		58		-80		862	
<i>SD</i>					52		23		65		22		406

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Startle (version II)****Page 1/2**

Study	Year	Pup Age	N	MALES													
				Block 1		Block 2				Block 3				Block 4			
				AVeN		AVeN		Habituation (%)		AVeN		Habituation (%)		AVeN		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	0.530	0.184	0.469	0.210	-12.2	16.1	0.417	0.159	-20.1	17.0	0.418	0.166	-20.0	17.3
V17	2017	10-11W	19	0.584	0.188	0.498	0.230	-16.6	19.9	0.396	0.145	-31.6	18.6	0.392	0.137	-31.8	19.1
<i>Total</i>			39	<i>0.556</i>		<i>0.483</i>		<i>-14.3</i>		<i>0.407</i>		<i>-25.7</i>		<i>0.406</i>		<i>-25.7</i>	
<i>Mean</i>																	
<i>SD</i>					<i>0.185</i>		<i>0.218</i>		<i>17.9</i>		<i>0.151</i>		<i>18.5</i>		<i>0.151</i>		<i>18.9</i>

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Startle (version II) - Page 2/2**

Study	Year	Pup Age	N	MALES			
				Block 5			
				AVeN		Habituation (%)	
				Mean	SD	Mean	SD
L18	2018	10W	20	0.435	0.190	-17.5	17.1
V17	2017	10-11W	19	0.381	0.150	-33.9	18.5
<i>Total</i>			39				
<i>Mean</i>				0.408		-25.5	
<i>SD</i>					0.172		19.4

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Startle (version II)****Page 1/2**

Study	Year	Pup Age	N	FEMALES													
				Block 1		Block 2				Block 3				Block 4			
				AVeN		AVeN		Habituation (%)		AVeN		Habituation (%)		AVeN		Habituation (%)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L18	2018	10W	20	0.425	0.158	0.399	0.200	-8.5	18.1	0.313	0.122	-25.2	16.6	0.305	0.109	-26.2	17.1
V17	2017	10-11W	20	0.449	0.183	0.374	0.195	-18.0	16.4	0.339	0.144	-23.6	14.6	0.318	0.115	-27.4	14.4
<i>Total</i>			<i>40</i>														
<i>Mean</i>				<i>0.437</i>		<i>0.386</i>		<i>-13.3</i>		<i>0.326</i>		<i>-24.4</i>		<i>0.311</i>		<i>-26.8</i>	
<i>SD</i>					<i>0.169</i>		<i>0.195</i>		<i>17.7</i>		<i>0.132</i>		<i>15.5</i>		<i>0.111</i>		<i>15.6</i>

W: week

Historical Control Data**Rat Wistar: Crl-WI****Post-weaning behaviour tests - Startle (version II) - Page 2/2**

Study	Year	Pup Age	N	FEMALES			
				Block 5			
				AVeN		Habituation (%)	
				Mean	SD	Mean	SD
L18	2018	10W	20	0.296	0.103	-27.4	18.6
V17	2017	10-11W	20	0.306	0.102	-29.1	14.4
<i>Total</i>			<i>40</i>				
<i>Mean</i>				<i>0.301</i>		<i>-28.3</i>	
<i>SD</i>					<i>0.102</i>		<i>16.4</i>

W: week

Historical Control Data

Rat Wistar : Crl-WI

Maternal body weight gain (g) during gestation

Study	Year	Dams with live embryos	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD
I18	2018	19	17.0	4.0	16.8	3.3	26.1	4.1
J18	2018	16	12.6	3.5				
L18	2018	19	15.1	3.2	15.7	3.6	21.8	4.6
Q17	2017	16	12.5	5.6	14.9	3.6	24.1	3.9
R17	2017	16	18.1	4.5	17.0	4.0	28.2	4.0
T17	2017	21	22.9	3.0	16.0	4.9	29.7	3.4
U17	2017	20	15.7	4.4	14.0	3.8	22.4	3.9
V17	2017	16	16.6	7.3	12.8	4.6	23.4	4.4
B16	2016	18	16.7	4.5	13.2	4.6	21.3	4.4
C16	2016	20	15.6	3.6	14.6	3.5	20.2	4.6
D16	2016	19	15.4	2.9	12.3	4.0	26.0	6.0
E16	2016	17	17.5	4.1	15.1	4.3	23.5	3.8
F16	2016	18	14.1	3.8	13.2	5.0	24.0	4.0
Y16	2016	19	12.7	4.1	9.5	3.1	20.7	4.8
A15	2015	20	16.9	5.6	14.6	3.3	26.3	4.2
I15	2015	19	16.7	6.7	14.6	3.8	23.2	6.0
J15	2015	19	19.0	5.3	16.1	4.5	21.8	4.8
<i>Total</i>		<i>312</i>						
<i>Mean</i>			<i>16.3</i>		<i>14.4</i>		<i>23.9</i>	
<i>SD</i>				<i>5.1</i>		<i>4.3</i>		<i>5.1</i>
2012 to 2014		<i>143</i>	<i>13.9</i>	<i>4.5</i>	<i>9.7</i>	<i>8.0</i>	<i>19.9</i>	<i>12.5</i>

Historical Control Data

Rat Wistar : Crl-WI

Maternal food consumption (g/day) during gestation

Study	Year	Dams with live embryos	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 0 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
I18	2018	19	20.0	1.8	22.7	2.2	21.4	1.9	25.2	1.8
J18	2018	16	18.3	1.6						
L18	2018	19	19.9	1.3	22.3	1.5			25.2	1.6
Q17	2017	16					21.3	1.8	23.5	1.9
R17	2017	16	19.7	1.4	21.4	2.0			23.8	2.0
T17	2017	21	19.4	1.6	21.8	2.3			23.4	2.1
U17	2017	20	21.0	1.7	22.1	2.3	21.6	1.8	25.2	2.6
A16	2016	21	19.4	3.7	21.3	2.5	20.3	2.7	22.4	2.5
B16	2016	18	18.4	2.0	20.3	2.1	19.3	2.0	21.0	1.9
C16	2016	20	18.6	1.7	21.1	1.8	19.9	1.7	22.9	2.4
D16	2016	19	17.9	2.9	18.8	2.1	18.3	2.4	21.2	2.3
E16	2016	17	18.5	2.0	21.2	2.7	19.8	2.2	23.5	2.2
F16	2016	18	18.9	2.1	20.5	2.1			21.4	2.4
Y16	2016	19	18.3	2.0	20.9	2.2			20.7	2.0
A15	2015	20					20.0	1.9	23.8	2.0
Total		279								
Mean			19.1		21.3		20.2		23.2	
SD				2.2		1.8		2.2		2.2
2012 to 2014		72	19.0	2.2	20.0	2.2	19.2	2.0	22.1	2.3

Historical Control Data**Rat Wistar : Crl-WI****Caesarean data collected on, or close to, day 13 of gestation - page 1/2**

Study	Year	Number of females		Pre-coital interval (days)		Number of females		Fertility index %	Number of corpora lutea		Number of uterine implants	
		Paired	Mated	Mean	SD	Pregnant	With live embryos		Mean	SD	Mean	SD
I18	2018	20	20	2.2	1.3	19	19	95	14.1	1.7	13.1	2.3
J18	2018	19	19	3.4	3.0	17	16	89	13.2	3.3	12.6	3.3
L18	2018	20	20	2.3	1.2	20	20	100	13.9	1.5	12.5	2.8
Q17	2017	19	19	2.7	2.7	17	17	89	14.9	1.8	13.9	1.7
R17	2017	20	19	4.1	3.9	17	17	89	13.5	2.5	12.7	3.4
T17	2017	22	22	2.9	2.6	21	21	95	15.0	1.2	14.6	1.3
U17	2017	20	20	2.8	1.0	20	20	100	14.9	1.9	13.7	2.3
V17	2017	20	19	2.7	2.5	16	16	84	14.9	2.1	14.2	2.9
A16	2016	22	22	2.5	0.9	21	21	95	14.0	1.6	13.1	1.5
B16	2016	20	18	2.4	1.2	18	18	100	13.8	1.9	13.1	2.4
C16	2016	20	20	3.1	2.6	20	20	100	14.4	2.5	11.7	4.8
D16	2016	20	20	2.3	1.2	20	19	100	12.8	3.6	12.0	3.9
E16	2016	22	19	1.9	1.0	18	18	95	14.2	2.0	12.5	3.9
F16	2016	25	25	3.2	3.6	19	18	88	13.2	2.7	11.8	3.7
V16	2016	20	20	2.7	1.2	20	20	100	14.8	2.2	13.8	2.9
Y16	2016	20	20	2.5	1.2	20	20	100	14.3	2.2	13.5	2.3
A15	2015	20	20	4.2	5.0	20	20	100	14.2	2.1	13.4	2.2
I15	2015	20	20	3.3	3.3	19	19	95	14.8	1.8	14.4	2.4
J15	2015	20	19	2.7	1.2	19	19	100	16.0	2.4	14.3	2.2
<i>Total</i>		<i>389</i>	<i>381</i> <i>98%</i>			<i>361</i> <i>95%</i>	<i>358</i> <i>94%</i>					
<i>Mean</i>				<i>2.8</i>					<i>14.3</i>		<i>13.2</i>	
<i>SD</i>					<i>2.5</i>					<i>2.3</i>		<i>2.9</i>
2012 to 2014		<i>150</i>	<i>150</i> <i>100%</i>	<i>2.77</i>	<i>2.0</i>	<i>144</i> <i>96%</i>	<i>144</i> <i>96%</i>		<i>13.9</i>	<i>2.3</i>	<i>12.8</i>	<i>2.7</i>

File name: I.2.3-RAT_WISTAR_G13_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****Caesarean data collected on, or close to, day 13 of gestation - page 2/2**

Study	Year	Number of females		Pre-implantation loss %		Post-implantation loss %		Live embryos	
		Pregnant	With live embryos	Mean	SD	Mean	SD	Mean	SD
I18	2018	19	19	7.6	10.6	6.8	8.4	12.2	2.5
J18	2018	17	16	4.2	5.8	10.4	23.6	11.9	3.6
L18	2018	20	20	10.8	16.2	5.0	7.3	11.9	3.0
Q17	2017	17	17	6.8	9.0	5.8	7.4	13.1	2.1
R17	2017	17	17	8.1	20.4	3.9	6.9	12.2	3.4
T17	2017	21	21	2.8	4.4	4.8	8.1	13.9	1.6
U17	2017	20	20	8.1	8.6	8.3	7.4	12.5	2.1
V17	2017	16	16	5.1	12.1	6.4	9.2	13.4	3.4
A16	2016	21	21	5.8	7.0	3.2	3.9	12.7	1.5
B16	2016	18	18	5.2	11.1	4.5	6.3	12.5	2.4
C16	2016	20	20	21.5	24.8	5.6	9.0	11.0	4.6
D16	2016	20	19	9.1	13.3	9.5	22.5	11.3	3.8
E16	2016	18	18	13.5	20.7	5.3	5.4	11.8	3.8
F16	2016	19	18	13.3	21.7	11.8	22.9	11.0	3.9
V16	2016	20	20	6.7	11.7	4.6	8.4	13.2	2.9
Y16	2016	20	20	6.2	7.8	7.8	6.6	12.4	2.2
A15	2015	20	20	5.0	9.6	7.2	7.8	12.4	2.1
I15	2015	19	19	3.6	10.4	4.9	8.0	13.6	2.5
J15	2015	19	19	10.2	10.9	2.3	4.9	13.9	2.0
<i>Total</i>		<i>361</i>	<i>358</i>						
		<i>95%</i>	<i>94%</i>						
<i>Mean</i>				<i>8.1</i>		<i>6.2</i>		<i>12.5</i>	
<i>SD</i>					<i>13.9</i>		<i>11.1</i>		<i>3.0</i>
2012 to 2014		<i>144</i>	<i>144</i>	<i>7.6</i>	<i>12.5</i>	<i>4.8</i>	<i>5.9</i>	<i>12.2</i>	<i>2.7</i>
		<i>96%</i>	<i>96%</i>						

File name: I.2.3-RAT_WISTAR_G13_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****Oestrous cycle - before treatment**

Study	Year	Females evaluated	Cycle length (days)		Irregularity index		Oestrous days (%)		Females acyclic or with acyclic period
		N	Mean	SD	Mean	SD	Mean	SD	%
Q17	2017	20	3.8	0.3	0.2	0.2	31.8	6.3	0
U17	2017	19	3.9	0.2	0.3	0.2	30.5	4.0	5
I13	2013	17	3.9	0.3	0.3	0.2	31.4	7.4	15
J13	2013	20	4.1	0.3	0.2	0.3	29.3	8.5	0
<i>Total</i>		76							
<i>Mean</i>			3.9		0.2		30.7		5
<i>SD</i>				0.3		0.2		6.7	

Historical Control Data**Rat Wistar : Crl-WI****Oestrous cycle - during treatment (pre-mating period)**

Study	Year	Females evaluated	Cycle length (days)		Irregularity index		Oestrous days (%)		Females acyclic or with acyclic period
		N	Mean	SD	Mean	SD	Mean	SD	%
J18	2017	16	4.0	0.2	0.1	0.2	28.7	5.8	20
Q17	2017	17	4.2	0.23	0.3	0.28	30.7	6.1	15
U17	2017	20	4.1	0.5	0.3	0.3	32.1	6.8	0
A16	2016	20	4	0.3	0.3	0.2	32.0	5.6	9
B16	2016	19	3.8	0.3	0.2	0.2	27.4	6.2	5
F16	2016	21	3.9	0.2	0.2	0.3	28.6	5.1	5
Y16	2016	16	3.9	0.5	0.3	0.3	32.1	5.6	24
A15	2015	20	3.8	0.3	0.3	0.2	32.7	4.3	0
K15-1	2015	16	4.1	0.2	0.2	0.2	31.3	4.7	33
K15-2	2015	23	3.9	0.2	0.2	0.2	31.4	3.9	4
<i>Total</i>		<i>188</i>							
<i>Mean</i>			<i>4.0</i>		<i>0.2</i>		<i>30.7</i>		<i>10</i>
<i>SD</i>				<i>0.3</i>		<i>0.2</i>		<i>5.6</i>	

Historical Control Data

Rat Wistar: Crl-WI

Sperm Analysis - number in epididymis and motility

Study	Year	Number of males	Number of sperm in epididymis		% motile		% progressive	
			Mean	SD	Mean	SD	Mean	SD
J18	2018	20	937	219	93	8	64.0	10.0
Q17	2017	20	874	303	97	1	68.0	4.6
R17	2017	10	974	322	90	6	60.0	6.0
T17	2017	10	797	270	91	14	56.0	15.0
U17	2017	20	746	227	95	2	68.0	4.0
C16	2016	20	705	302	90	6	61.9	7.8
D16	2016	19	738	335	88	6	58.9	4.4
E16	2016	10	681	307	85	30	60.0	22.0
A15	2015	20	624	279	91	5	62.0	12.0
I15	2015	20	838	244	93	3	63.0	4.0
K15-1	2015	24	737	234	92	8	59.0	9.0
K15-2	2015	24	992	317	91	9	58.0	11.0
<i>Total Mean</i>		217	804		92		61.9	
<i>SD</i>				296		9		9.9
2010 to 2014		119	796	312	88	12	-	-

Historical Control Data**Rat Wistar: Crl-WI****Sperm Analysis - number in testis**

Study	Year	Number of males	Testis weight (g)		10 ⁶ Sperm per g of testis	
			Mean	SD	Mean	SD
J18	2018	20	1.78	0.17	116	12
Q17	2017	20	1.90	0.13	147	27
R17	2017	10	1.92	0.14	124	29
T17	2017	10	1.81	0.12	130	22
C16	2016	20	1.84	0.15	105	27
D16	2016	19	1.72	0.11	126	38
E16	2016	10	1.87	0.15	132	29
A15	2015	20	1.75	0.13	123	25
I15	2015	20	1.98	0.12	123	23
K15-1	2015	24	1.82	0.18	135	26
K15-2	2015	24	1.87	0.14	130	18
<i>Total</i>		<i>197</i>				
<i>Mean</i>			<i>1.84</i>		<i>126</i>	
<i>SD</i>				<i>0.16</i>		<i>27</i>
2010 to 2014		119	1.86	0.17	126	28

Historical Control Data

Rat Wistar: Crl-WI

Sperm Analysis - number in epididymis

Study	Year	Number of males	Cauda epididymis weight (g)		10 ⁶ Sperm per g of cauda epididymis	
			Mean	SD	Mean	SD
R17	2017	10	0.30	0.04	414	133
U17	2017	20	0.28	0.03	533	112
K15-1	2015	24	0.27	0.03	631	350
K15-2	2015	24	0.26	0.03	465	188
<i>Total</i>		78				
<i>Mean</i>			0.27		527	
<i>SD</i>				0.03		242

Historical Control Data**Rat Wistar : Crl-WI****Maternal body weight gain (g) during gestation: females treated by continuous IV infusion**

Study	Year	Infusion volume mL/kg/day	Dams with live foetuses	Gestation days 0 to 6		Gestation days 6 to 9		Gestation days 9 to 12		Gestation days 12 to 15		Gestation days 15 to 18		Gestation days 6 to 18		Gestation days 18 to 20	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A15	2015	8	22	22.4	8.6	7.6	6.9	11.5	7.7	16.1	4.1	26.8	7.8	61.9	13.1	20.5	5.8
B15	2015	2	22	26.6	9.9	13.1	10.0	16.7	5.0	17.4	5.3	31.6	6.3	78.7	14.7	26.9	6.1
A11	2011	60	8	10.4	5.4	13.4	4.6	12.9	3.3	12.9	2.9	28.3	4.0			26.1	5.4
A10	2010	120	6	17.1	6.6	10.3	5.3	16.6	3.1	13.9	3.6	24.7	3.3			33.8	8.0
A8	2008	24	6	19.6	6.4					10.7	4.4	15.9	17.2			19.1	11.1
B8	2008	24	22	18.9	6.4	10.4	3.3	14.5	4.3	13.7	4.8	24.9	6.7			22.3	6.9
<i>Total</i>			86														
<i>Mean</i>				20.9		10.7		14.3		15.0		26.8		70.3		23.9	
<i>SD</i>					9.0		7.1		5.8		4.8		8.4		16.2		7.6
<i>Non-infusion studies 2017 and 2018</i>																	
			393	31.4	7.1	11.9	5.1	15.5	5.0	16.9	6.1	32.2	6.1	76.2	11.6	25.2	5.4

Study A8 was recorded on days 0, 6, 11, 15, 18 and 20 of gestation.

Historical Control Data

Rat Wistar : Crl-WI

Maternal food consumption (g/day) during gestation: females treated by continuous IV infusion

Study	Year	Infusion volume mL/kg/day	Dams with live foetuses	Gestation days 0 to 6		Gestation days 6 to 9		Gestation days 9 to 12		Gestation days 12 to 15		Gestation days 15 to 18		Gestation days 6 to 18		Gestation days 18 to 20	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A15	2015	8	22	16.1	3.4	19.6	4.2	20.4	3.8	23.6	3.4	23.2	3.7	21.7	3.5	24.9	3.3
B15	2015	2	22	17.9	2.6	22.9	3.3	23.1	3.2	27.0	3.5	27.7	3.8	25.2	3.0	28.6	2.9
A11	2011	60	8	17.3	3.1	24.6	1.4	25.2	1.4	28.4	2.0	30.2	1.2			28.3	2.0
A10	2010	120	6	19.8	1.8	23.9	4.4	28.4	2.3	29.5	1.2	30.5	0.9			29.8	2.4
A8	2008	24	6	20.2	2.2					26.3	0.9	23.6	6.7			24.4	3.7
B8	2008	24	22	19.2	2.0	23.3	2.3	25.0	2.8	26.0	2.2	27.2	2.2			24.8	4.4
<i>Total</i>			86														
<i>Mean</i>				18.0		22.4		23.5		26.1		26.6		23.4		26.4	
<i>SD</i>					3.0		3.7		3.8		3.3		4.1		3.6		3.9
<i>Non-infusion studies 2017 and 2018</i>																	
			401	19.3	2.6	22.2	3.1	23.3	3.3	24.9	2.8	26.3	3.0	24.8	2.8	26.7	3.1

Study A8 was recorded on days 0, 6, 11, 15, 18 and 20 of gestation.

Historical Control Data

Rat Wistar : Crl-WI

Caesarean data collected on day 20 or 21 of gestation: females treated by continuous IV infusion

Study	Year	Infusion volume mL/kg/day	Number of females			Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Early resorptions per dam		Late resorptions per dam		Post-implantation loss %	
			Mated	Pregnant	With live foetuses	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A15	2015	8	22	22	22	11.1	2.7	10.6	2.8	5.7	8.4	1.9	2.9	0.1	0.3	19.9	23.0
B15	2015	2	22	22	22	12.9	1.8	12.0	1.9	7.1	10.4	1.0	1.4	0.0	0.0	8.8	13.4
A11	2011	60	8	8	8	12.3	1.0	11.3	2.3	8.1	17.3	0.5	0.5	0.1	0.4	5.2	6.2
A10	2010	120	6	6	6	13.2	1.3	12.7	1.8	4.1	4.5	0.5	0.5	0.0	0.0	3.7	4.1
A8	2008	24	6	6	6	11.8	1.5	9.8	1.0	16.5	7.3	0.5	0.5	0.0	0.0	5.0	5.5
B8	2008	24	25	22	22	12.6	1.9	11.9	1.8	5.9	6.6	1.1	1.0	0.0	0.2	9.9	7.7
<i>Total</i>			89	86	86												
<i>Mean</i>				97%	97%	12.3		11.4		7.0		1.1		0.0		10.9	
<i>SD</i>						2.1		2.2		9.6		1.8		0.2		15.1	
Non-infusion studies 2017 and 2018																	
			346	339	339	13.2	1.8	12.1	2.2	8.4	11.0	1.0	1.1	0.0	0.3	8.8	9.7
				98%	98%												

Historical Control Data

Rat Wistar : CrI-WI

Caesarean data collected on day 20 or 21 of gestation: females treated by continuous IV infusion

Study	Year	Infusion volume mL/kg/day	Number of females			Dead foetuses Total	Live litter size on GD 20		Foetal weight on GD 20 (g)		Placental weight on GD 20 (g)		Uterus weight on GD 20 (g)		Sex ratio % males
			Mated	Pregnant	With live foetuses		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
A15	2015	8	22	22	22	0	8.6	3.5	3.4	0.4			49.4	18.7	57.4
B15	2015	2	22	22	22	0	11.0	2.4	3.5	0.3			61.3	12.1	44.1
A11	2011	60	8	8	8	0	10.6	2.1	3.9	0.3					51.6
A10	2010	120	6	6	6	0	12.2	1.5	3.7	0.3					46.9
A8	2008	24	6	6	6	0	9.3	1.0	3.8	0.6					43.8
B8	2008	24	25	22	22	0	10.7	1.8	3.8	0.3	0.49	0.05			51.6
<i>Total</i>			89	86 97%	86 97%	0									
<i>Mean</i>							10.2		3.6		0.49		55.4		50.3
<i>SD</i>							2.7		0.4		0.05		16.7		
Non-infusion studies 2017 and 2018															
			346	339 98%	339 98%	0	11.0	2.3	3.56	0.24	NR	NR	62.6	12.4	49.6

NR: not recorded

Historical Control Data**Rat Wistar : Crl-WI****Malformations (external, internal and skeletal): females treated by continuous IV infusion**

Study	Year	Number of litters examined	Number of fetuses examined	Number of litters with malformed fetuses	Litter Incidence %	Number of malformed fetuses	Foetal Incidence %	Type of malformation by foetus
A15	2015	22	190	2	9.09	2	1.05	1: Multiple abnormalities of great vessels 2: Absent supraoccipital
B15	2015	22	241	1	4.55	1	0.41	1: Agnathia; absent mandible
A11	2011	8	85	1	12.50	1	1.18	1: Enlarged ventricular chamber with thin wall (bilateral)
A10	2010	6	73	0	-	0	-	-
A8	2008	6	56	0	-	0	-	-
B8	2008	22	235	1	4.55	1	0.43	1: Absent kidneys
Total		86	880	5	5.81%	5	0.57%	
Non-infusion studies 2017-2018								
		339	3742	10	2.95%	10	0.27%	

Study no. A8: Dose Range Finding study with external examination only

Study no. A10: Dose Range Finding study with external and visceral examinations only

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - EXTERNAL EXAMINATION ON DAY 20 OR 21 OF GESTATION
females treated by continuous IV infusion during gestation**

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2016		2016-2018	
Number of studies included	6		39	
Number of fetuses examined	880		6077	
OBSERVATION	N	%	N	%
Eye(s): malformed	0	0.00	1	0.02
Eye(s): absent bulge	0	0.00	1	0.02
Agnathia	1	0.11	2	0.03
Astomia	0	0.00	1	0.02
Micrognathia	0	0.00	2	0.03
Cleft palate	0	0.00	1	0.02
Cleft lip	0	0.00	1	0.02
Proboscis	0	0.00	3	0.05

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - FIXED VISCERAL - BODY - females treated by continuous IV infusion during gestation**

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2013		2011 to 2013	
Number of studies included	3		39	
Number of foetuses examined	227		542	
OBSERVATION	N	%	N	%
Major blood vessels: malformed	0	0.00	2	0.37
Heart: dilated ventricle(s) / ventricular chamber enlarged	1	0.44	0	0.00
Heart: ventricular wall thin	1	0.44	0	0.00
Kidney: absent	1	0.44	0	0.00
Ureter: slightly dilated	0	0.00	15	2.77
Ureter: convoluted	1	0.44	4	0.74
Testis: malpositioned	0	0.00	1	0.18

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - FRESH VISCERAL EXAMINATION OF BODY ON DAY 20 OR 21 OF GESTATION
females treated by continuous IV infusion during gestation**

	Continuous IV infusion		Non-infusion studies	
PERIOD	2017 to 2018		2016 to 2018	
Number of studies included	2		23	
Number of fetuses examined	226		2716	
OBSERVATION	N	%	N	%
Situs inversus	0	0.00	1	0.04
Great blood vessels: malformed	1	0.44	2	0.07
Great blood vessels: transposed	0	0.00	1	0.04
Umbilical artery: transposed	35	15.49	345	12.70
Azygos vein: transposed	0	0.00	1	0.04
Aortic arch: narrowed	0	0.00	1	0.04
Thyroid gland: small	0	0.00	1	0.04
Thorax: tissue-mass	0	0.00	1	0.04
Lungs: lobe absent	0	0.00	1	0.04
Lungs: abnormal lobation	0	0.00	2	0.07
Intestine: distended	0	0.00	1	0.04
Stomach: narrowed	0	0.00	1	0.04
Pancreas: large	0	0.00	1	0.04
Pancreas: malpositioned	0	0.00	1	0.04
Spleen: small	0	0.00	1	0.04
Spleen: discolored	0	0.00	1	0.04
Liver: lobe discolored	0	0.00	4	0.15
Liver: abnormal lobation	0	0.00	1	0.04
Kidney(s): renal pelvic dilatation	0	0.00	1	0.04
Ureter(s): dilated	9	3.98	24	0.88
Ureter(s): convoluted	5	2.21	9	0.33
Testis: cyst	0	0.00	9	0.33

File name: II.2.1-RAT_WISTAR_PERFUSION_G20_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - FIXED VISCERAL EXAMINATION OF HEAD ON DAY 20 OR 21 OF GESTATION
females treated by continuous IV infusion during gestation**

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	5		23	
Number of foetuses examined	432		2407	
OBSERVATION	N	%	N	%
Head: multiple visceral abnormalities	0	0.00	1	0.04
Microphthalmia	0	0.00	1	0.04
Aphakia	0	0.00	1	0.04
Retina: fold	0	0.00	1	0.04
Brain: dilated lateral ventricles	3	0.69	6	0.25

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 1/4**
females treated by continuous IV infusion during gestation

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	4		14	
Number of foetuses examined	392		1645	
OBSERVATION	N	%	N	%
Humerus: thick	0	0.00	1	0.06
Scapula: bent	0	0.00	1	0.06
Metacarpals: incomplete ossification (2nd or 5th digits)	12	3.06	0	0.00
Metacarpals: incomplete ossification (2nd to 4th digits)	4	1.02	5	0.30
Metacarpals: unossified (2nd to 4th digits)	3	0.77	1	0.06
Metacarpals: unossified (5th digit)	53	13.52	208	12.64
Metatarsals: advanced ossification	23	5.87	0	0.00
Metatarsals: incomplete ossification	1	0.26	7	0.43
Metatarsals: unossified	1	0.26	6	0.36
Pubis: incomplete ossification	3	0.77	4	0.24
Pubis: unossified	2	0.51	2	0.12
Ischium: unossified	1	0.26	1	0.06
Ribs: number of full ribs = 12/12	2	0.51	1	0.06
Ribs: number of full ribs = 13/14	9	2.30	0	0.00
Ribs: number of full ribs = 14/14	10	2.55	0	0.00
Rib: incomplete ossification	0	0.00	3	0.18
Rib: irregular ossification	26	6.63	0	0.00
Rib: unilateral rudimentary 14th	40	10.20	0	0.00
Rib: bilateral rudimentary 14th	68	17.35	0	0.00
Rib: supernumerary cervical	4	1.02	7	0.43
Rib: supernumerary lumbar	7	1.79	60	3.65
Rib: supernumerary lumbar (short)	87	22.19	753	45.78
Rib: branched	0	0.00	1	0.06

File name: II.2.1-RAT_WISTAR_PERFUSION_G20_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 2/4**
females treated by continuous IV infusion during gestation

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	4		14	
Number of foetuses examined	392		1645	
OBSERVATION	N	%	N	%
Rib: wavy	15	3.83	25	1.52
Rib: thick	13	3.32	84	5.11
Rib: intercostal	0	0.00	1	0.06
Sternebrae: incomplete ossification of 1st/3rd	13	3.32	19	1.16
Sternebrae: incomplete ossification of 2nd/4th	30	7.65	34	2.07
Sternebrae: incomplete ossification of 6th	111	28.32	322	19.57
Sternebrae: unossified	1	0.26	0	0.00
Sternebrae: unossified 1st/3rd	1	0.26	5	0.30
Sternebrae: unossified 2nd/4th	4	1.02	8	0.49
Sternebrae: unossified 5th	19	4.85	86	5.23
Sternebrae: unossified 6th	11	2.81	39	2.37
Sternebrae: asymetric	2	0.51	6	0.36
Sternebrae: bipartite ossification	3	0.77	1	0.06
Sternebra: misshapen	0	0.00	2	0.12
Vertebrae, presacral arches = 27	2	0.51	10	0.61
Vertebrae, cervical: advanced ossification	161	41.07	0	0.00
Vertebrae, cervical: increased ossification 1st centrum	15	3.83	397	24.13
Vertebrae, cervical: incomplete ossification of arch	3	0.77	11	0.67
Vertebrae, cervical: absent arch	0	0.00	1	0.06

File name: II.2.1-RAT_WISTAR_PERFUSION_G20_2018_OK.xls

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 3/4**
females treated by continuous IV infusion during gestation

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	4		14	
Number of foetuses examined	392		1645	
OBSERVATION	N	%	N	%
Vertebrae, thoracic: malformed	0	0.00	3	0.18
Vertebrae, thoracic: incomplete ossification of arch	2	0.51	0	0.00
Vertebrae, thoracic: incomplete ossification of centrum	0	0.00	1	0.06
Vertebrae, thoracic: incomplete ossification of 1-4th centrum	1	0.26	0	0.00
Vertebrae, thoracic: incomplete ossification of 5-8th centrum	1	0.26	0	0.00
Vertebrae, thoracic: incomplete ossification of 9-13th centrum	7	1.79	0	0.00
Vertebrae, thoracic: incomplete ossification of 1-9th centrum	2	0.51	13	0.79
Vertebrae, thoracic: unossified centrum	0	0.00	1	0.06
Vertebrae, thoracic: unossified 10-13th centrum	1	0.26	0	0.00
Vertebrae, thoracic: unossified 1-9th centrum	1	0.26	3	0.18
Vertebrae, thoracic: bipartite centrum	0	0.00	19	1.16
Vertebrae, thoracic: centrum hemicentric	0	0.00	1	0.06
Vertebrae, thoracic: small centrum	0	0.00	2	0.12
Vertebrae, thoracic: misaligned centrum	0	0.00	1	0.06
Vertebrae, thoracic: number = 12	2	0.51	1	0.06
Vertebrae, lumbar: incomplete ossification of centrum	2	0.51	7	0.43
Vertebrae, lumbar: unossified centrum	1	0.26	1	0.06
Vertebrae, lumbar: number = 7	3	0.77	14	0.85
Vertebrae, lumbar: centrum bipartite	0	0.00	1	0.06
Vertebrae, lumbar: incomplete ossification of arches	1	0.26	4	0.24

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF BODY ON DAY 20 OF GESTATION - page 4/4**
females treated by continuous IV infusion during gestation

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	4		14	
Number of foetuses examined	392		1645	
OBSERVATION	N	%	N	%
Vertebrae, sacral: unossified arches	0	0.00	5	0.30
Vertebrae, sacral: incomplete ossification of arches	32	8.16	57	3.47
Vertebrae, sacral: unossified centrum	0	0.00	0	0.00
Vertebrae, sacral: unossified	1	0.26	3	0.18
Vertebrae, sacral: incomplete ossification of centrum	1	0.26	3	0.18
Vertebrae, caudal: unossified arches - region 1-2	117	29.85	548	33.31
Vertebrae, caudal: unossified centrum - region 1-2	0	0.00	4	0.24
Vertebrae, caudal: unossified	8	2.04	20	1.22

Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF HEAD ON DAY 20 OF GESTATION****Page 1/2****females treated by continuous IV infusion during gestation**

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	4		14	
Number of foetuses examined	392		1594	
OBSERVATION	N	%	N	%
Generalised incomplete ossification	1	0.26	2	0.13
Skull: malformed	0	0.00	2	0.13
Head: malformed	0	0.00	1	0.06
Nasals: incomplete ossification	0	0.00	3	0.19
Frontals: incomplete ossification	8	2.04	15	0.94
Parietals: incomplete ossification	97	24.74	191	11.98
Parietals: unossified area	1	0.26	0	0.00
Interparietal: incomplete ossification	105	26.79	162	10.16
Supraoccipital: incomplete ossification	69	17.60	100	6.27
Supraoccipital: unossified	0	0.00	2	0.13
Supraoccipital: absent	1	0.26	0	0.00
Fontanelle: enlarged	0	0.00	1	0.06
Squamosal: incomplete ossification	38	9.69	83	5.21
Zygomatic arch: incomplete ossification	15	3.83	19	1.19
Hyoid: incomplete ossification	2	0.51	0	0.00
Hyoid: unossified	22	5.61	15	0.94
Presphenoid: incomplete ossification	3	0.77	4	0.25
Presphenoid: unossified	1	0.26	2	0.13
Basisphenoid: incomplete ossification	0	0.00	1	0.06

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Historical Control Data**Rat Wistar : Crl-WI****FOETAL EXAMINATION - SKELETAL EXAMINATION OF HEAD ON DAY 20 OF GESTATION****Page 2/2****females treated by continuous IV infusion during gestation**

	Continuous IV infusion		Non-infusion studies	
PERIOD	2008 to 2018		2016 to 2018	
Number of studies included	4		14	
Number of foetuses examined	392		1594	
OBSERVATION	N	%	N	%
Mandible: fused	0	0.00	1	0.06
Mandible: short	0	0.00	1	0.06
Mandible: absent	1	0.26	0	0.00

Historical Control Data**Rat Wistar: Crl-WI.****Maternal body weight gain (g) during lactation (dams infused throughout gestation, parturition and lactation)**

Study	Year	Rate of Infusion mL/kg/day	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
S14	2014	20	5	13.1	5.4	4.3	4.4	11.3	4.4	4.6	5.1	-0.3	5.4	-4.2	6.7
T14	2014	20	5	16.0	8.6	9.8	7.1	11.1	9.8	10.0	6.9	3.7	6.9	-5.3	10.2
U14	2014	20	21	17.6	9.7	6.9	4.5	8.6	3.9	3.8	5.3	2.3	5.5	-6.2	7.9
<i>Total</i>			31												
<i>Mean</i>				16.6		6.9		9.5		5.0		2.1		-5.8	
<i>SD</i>					8.9		5.0		5.2		5.8		5.6		7.8
<i>Non-infusion studies 2015 to 2018</i>															
			224	12.7	8.6	8.0	6.5	7.6	6.3	6.0	6.6	0.6	7.5	-13.0	7.7

Historical Control Data**Rat Wistar: Crl-WI.****Maternal food consumption (g/day) during lactation (dams infused throughout gestation, parturition and lactation)**

Study	Year	Rate of Infusion mL/kg/day	Dams with litters	Lactation days 1 to 4		Lactation days 4 to 7		Lactation days 7 to 10		Lactation days 10 to 14		Lactation days 14 to 17		Lactation days 17 to 21	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
S14	2014	20	5	31.9	5.7	40.4	5.6	42.9	4.5	53.4	9.0	56.1	10.6	59.8	6.5
T14	2014	20	5	35.1	7.2	41.2	3.2	45.5	4.7	54.9	6.2	55.7	4.7	65.4	3.1
U14	2014	20	21	34.6	4.8	42.0	4.0	48.1	5.5	54.2	6.7	58.3	5.9	61.7	6.8
<i>Total</i>			<i>31</i>												
<i>Mean</i>				34.2		41.6		46.8		54.2		57.5		62.0	
<i>SD</i>					5.3		4.1		5.5		6.8		6.5		6.3
<i>Non-infusion studies 2015 to 2018</i>															
			224	31.7	5.7	41.0	5.6	48.4	5.9	55.2	7.1	58.2	7.1	65.3	7.8

Historical Control Data**Rat Wistar: Crl-WI.****Post-partum litter data (dams infused throughout gestation, parturition and lactation)**

Study	Year	Rate of Infusion mL/kg/day	Number of females				Gestation length (days)		Number of uterine implants		Number of pups born		Pre-birth loss index %	Live birth index %	Pup viability index %	Pup weaning index %
			Mated	Pregnant	With liveborn	With pups at weaning	Mean	SD	Mean	SD	Mean	SD				
S14	2014	20	6	6	5	5	22.3	0.8	9.5	3.5	8.0	3.9	22.5	97.9	97.9	100
T14	2014	20	6	6	5	4	22.0	0.0	13.2	1.1	12.6	0.9	4.6	100	100	80.0
U14	2014	20	25	23	22	21	22.0	0.0	12.3	1.6	11.5	2.3	6.2	99.6	100	94.8
<i>Total</i>			37	35	32	30										
<i>Mean</i>				95%	86%	94%	22.0		12.0		11.1		8.5	99.4	99.7	99.5
<i>SD</i>								0.3		2.2		2.8				
<i>Non-infusion studies 2015 to 2018</i>			238	230	224	176	19.7	7.2	10.9	4.6	9.9	4.3	9.1	87.3	87.1	100
				97%	94%	95%										

NA: not applicable

Historical Control Data

Rat Wistar: Crl-WI.

Post-partum data - pup weights (g) for dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Number of litters	Postnatal day 1				Postnatal day 4				Postnatal day 7				Postnatal day 14				Postnatal day 21			
				Males		Females		Males		Females		Males		Females		Males		Females		Males		Females	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
S14	2014	20	5	6.9	0.4	6.6	0.3	10.2	0.5	10.1	0.7	15.9	1.3	15.6	1.4	30.4	3.7	29.7	3.1	47.9	5.0	47.3	4.5
T14	2014	20	5	6.0	0.5	5.7	0.3	8.3	1.0	8.0	0.9	13.4	2.1	13.0	1.4	27.5	3.5	26.6	3.1	47.3	2.6	44.9	3.8
U14	2014	20	22	6.6	0.5	6.3	0.5	9.8	1.2	9.4	1.0	15.9	1.7	15.2	1.4	31.3	2.3	30.4	2.0	49.9	3.4	48.6	3.1
Total Mean SD			32	6.5	0.5	6.2	0.5	9.6	1.2	9.3	1.1	15.5	1.9	14.9	1.6	30.6	3.0	29.6	2.7	49.2	3.7	47.8	3.5
Non-infusion studies 2015 to 2018																							
			224	7.0	0.8	6.7	0.8	10.8	1.4	10.5	1.4	17.2	1.8	16.6	1.8	33.6	2.7	32.8	2.8	54.2	4.5	52.5	4.5

Historical Control Data

Rat Wistar: Crl-WI.

Pre-weaning development for litters of dams infused throughout gestation, parturition and lactation

Study	Year	Rate of Infusion mL/kg/day	Number of litters	Pinna unfolding (% of pups positive)				Incisor eruption (% of pups positive)								Eye opening (% of pups positive)				
				PND1	PND2	PND3	PND4	PND7	PND8	PND9	PND10	PND11	PND12	PND13	PND14	PND12	PND13	PND14	PND15	PND16
U14	2014	20	22	0	58	100	100	0	0	3	26	69	99	100	100	1	8	70	99	100
Total			22																	
Mean %				0	58	100	100	0	0	3	26	69	99	100	100	1	8	70	99	100
Non-infusion studies 2015 to 2018			132	12	62	99	100	0	2	9	42	78	98	100	100	1	17	77	98	100

PND = postnatal day

Historical Control Data**Rat Wistar: Crl-WI.****Post-weaning development (dams infused throughout gestation, parturition and lactation)**

Study	Year	Vaginal opening					Balano-preputial skinfold cleavage				
		Day of occurrence			Body weight (g)		Day of occurrence			Body weight (g)	
		Mean	SD	N	Mean	SD	Mean	SD	N	Mean	SD
U14	2014	32	1	24	102	13	47	3	25	210	21
<i>Total</i>				24					25		
<i>Mean</i>		32			102		47			210	
<i>SD</i>			1			13		3			21
<i>Non-infusion studies</i>											
<i>2015 to 2018</i>		33.2	2.3	144	114	13	44.7	3.4	144	206	26

Historical Control Data

Rat Wistar : Crl-WI

Maternal body weight gain (g) during gestation (females treated by continuous IV infusion)

Study	Year	Dams with live embryos	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD
C15	2015	17	16.9	7.1	13.4	5.7	20.2	6.0
K12	2012	20	15.1	4.3	9.8	5.2	22.6	4.1
L12	2012	18	16.8	4.0	14.8	3.5	24.7	4.8
<i>Total</i>		55						
<i>Mean</i>			16.2		12.5		22.5	
<i>SD</i>				5.2		5.3		5.2
<i>Non-infusion studies 2015 to 2018</i>								
		312	16.3	5.1	14.4	4.3	23.9	5.1

Historical Control Data

Rat Wistar : Crl-WI

Maternal food consumption (g/day) during gestation (females treated by continuous IV infusion)

Study	Year	Dams with live embryos	Gestation days 0 to 4		Gestation days 4 to 8		Gestation days 0 to 8		Gestation days 8 to 13	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
C15	2015	17	21.6	1.7	23.9	3.3	22.7	2.3	23.6	2.4
K12	2012	20	23.2	1.8	23.3	1.8			25.0	2.1
L12	2012	18					20.8	1.7	23.2	2.1
<i>Total</i>		55								
<i>Mean</i>			22.5		23.6		21.7		24.0	
<i>SD</i>				1.9		2.6		2.2		2.3
<i>Non-infusion studies 2015 to 2018</i>										
		279	19.1	2.2	21.3	1.8	20.2	2.2	23.2	2.2

Historical Control Data

Rat Wistar : Crl-WI

Caesarean data collected on, or close to, day 13 of gestation (females treated by continuous IV infusion)

Study	Year	Number of females		Pre-coital interval (days)		Number of females		Number of corpora lutea		Number of uterine implants		Pre-implantation loss %		Post-implantation loss %		Live embryos	
		Paired	Mated	Mean	SD	Pregnant	With live embryos	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C15	2015	20	20	3.1	1.6	18	18	13.4	1.7	12.5	2.4	7.1	12.0	12.4	20.5	11.3	3.5
K12	2012	20	20	3.2	2.1	20	20	13.1	1.4	12.1	1.2	7.4	6.8	4.6	4.3	11.5	1.3
L12	2012	20	19	2.5	1.4	18	18	13.3	2.8	12.4	3.2	7.3	15.6	3.3	4.5	12.0	3.1
<i>Total</i>		60	59 98%			56 95%	56 95%										
<i>Mean</i>				2.9				13.3		12.3		7.3		6.7		11.6	
<i>SD</i>					1.7				2.0		2.3		11.7		12.6		2.7
<i>Non-infusion studies 2015 to 2018</i>																	
		389	381 98%	2.8	2.5	361 95%	358 94%	14.3	2.3	13.2	2.9	8.1	13.9	6.2	11.1	12.5	3.0

Historical Control Data**Rat Wistar: CrI-WI****Sperm Analysis - number in epididymis and motility (males treated by continuous IV infusion)**

Study	Year	Number of males	Number of sperm in epididymis		% motile		% progressive sperm	
			Mean	SD	Mean	SD	Mean	SD
C15	2015	20	932.0	317.0	92.0	4.0	58.0	9.0
L12	2012	20	779.9	323.3	88.3	18.8		
<i>Total</i>		40						
<i>Mean</i>			856.0		90.2		29.0	
<i>SD</i>				325.3		13.5		52.3
<i>Non-infusion studies 2015 to 2018</i>								
		217	804	296	92	9	61.9	9.9

Historical Control Data**Rat Wistar: Crl-WI****Sperm Analysis - number in testis (males treated by continuous IV infusion)**

Study	Year	Number of males	Testis weight (g)		10 ⁶ Sperm per g of testis	
			Mean	SD	Mean	SD
C15	2015	20	1.72	0.14	148	52
L12	2012	20	1.70	0.10	143	24
<i>Total</i>		<i>40</i>				
<i>Mean</i>			<i>1.71</i>		<i>145</i>	
<i>SD</i>				<i>0.12</i>		<i>40</i>
<i>Non-infusion studies 2015 to 2018</i>						
		<i>197</i>	<i>1.84</i>	<i>0.16</i>	<i>126</i>	<i>27</i>

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