

## Summary of results (Di-(2-ethylhexyl)phthalate)

Generation			Dam: F0 Offspring: F1						
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )			0	10	50	250	1250	100000	
Number of pregnant females			14	15	15	15	14	14	
Number of complete litter loss			0	0	1	0	0	0	
Found dead			0	0	0	0	0	0	
F0	Gestation Period	Clinical findings		–	–	–	–	–	–
		Body weights (g)	Day 0	243.5 $\pm 11.7$	242.3 $\pm 9.0$	238.7 $\pm 9.0$	243.1 $\pm 12.0$	242.9 $\pm 12.2$	244.3 $\pm 11.5$
			Day 7	279.2 $\pm 13.0$	277.0 $\pm 9.6$	271.7 $\pm 12.7$	277.2 $\pm 13.1$	276.7 $\pm 14.1$	276.0 $\pm 15.3$
			Day 10	293.6 $\pm 14.6$	289.8 $\pm 11.4$	283.7 $\pm 12.8$	290.4 $\pm 13.7$	290.7 $\pm 15.4$	291.5 $\pm 15.4$
			Day 14	315.7 $\pm 19.5$	314.1 $\pm 12.0$	308.7 $\pm 14.4$	313.6 $\pm 14.1$	314.9 $\pm 18.5$	318.0 $\pm 17.4$
			Day 21	404.3 $\pm 21.9$	399.8 $\pm 17.9$	395.8 $\pm 19.1$	399.0 $\pm 16.6$	402.6 $\pm 23.8$	405.8 $\pm 22.3$
		Body weight gains(g)	Day 0-7	35.7 $\pm 6.7$	34.7 $\pm 6.2$	33.0 $\pm 7.0$	34.0 $\pm 5.4$	33.8 $\pm 5.9$	31.7 $\pm 7.7$
			Day 0-10	50.4 $\pm 8.4$	47.5 $\pm 7.8$	45.0 $\pm 8.5$	47.2 $\pm 6.0$	47.8 $\pm 6.6$	47.2 $\pm 8.6$
			Day 0-21	160.8 $\pm 16.5$	157.5 $\pm 14.7$	157.1 $\pm 14.0$	155.8 $\pm 8.0$	159.7 $\pm 16.5$	161.6 $\pm 15.6$
		Food consumption (g)	Day 0-1	20.4 $\pm 1.6$	19.9 $\pm 2.4$	19.4 $\pm 3.8$	20.3 $\pm 2.7$	21.5 $\pm 2.2$	19.9 $\pm 3.2$
			Day 7-8	26.8 $\pm 2.8$	25.3 $\pm 3.0$	25.5 $\pm 1.8$	26.1 $\pm 1.9$	25.4 $\pm 2.4$	25.4 $\pm 2.3$
			Day 14-15	26.9 $\pm 3.2$	26.2 $\pm 2.9$	25.9 $\pm 3.1$	26.7 $\pm 2.3$	27.3 $\pm 2.3$	27.5 $\pm 3.1$
			Day 20-21	16.5 $\pm 2.5$	17.3 $\pm 3.8$	18.2 $\pm 3.1$	17.7 $\pm 2.7$	16.5 $\pm 3.6$	18.2 $\pm 4.4$
		Lactation Period	Clinical findings : Dystocia		0	0	0	0	0
	Body weights (g)		Day 0	285.9 $\pm 16.2$	282.7 $\pm 17.2$	286.6 $\pm 16.6$	284.0 $\pm 24.2$	281.6 $\pm 13.8$	290.5 $\pm 26.1$
			Day 4	294.8 $\pm 13.8$	296.2 $\pm 17.7$	291.0 $\pm 16.6$	290.1 $\pm 15.2$	296.3 $\pm 17.2$	295.4 $\pm 20.0$
			Day 10	312.5 $\pm 21.7$	314.8 $\pm 14.2$	306.7 $\pm 10.7$	309.2 $\pm 14.4$	314.9 $\pm 19.5$	321.9 $\pm 19.1$
			Day 14	331.4 $\pm 20.9$	330.4 $\pm 12.5$	321.2 $\pm 13.3$	327.4 $\pm 14.5$	326.7 $\pm 20.2$	333.9 $\pm 24.9$
			Autopsy day	327.5 $\pm 16.8$	327.6 $\pm 16.0$	324.0 $\pm 13.2$	323.8 $\pm 9.8$	323.4 $\pm 16.0$	336.6 $\pm 22.7$
	Body weight gains(g)		Day 0-7	18.7 $\pm 18.2$	23.5 $\pm 18.1$	13.2 $\pm 18.5$	14.5 $\pm 17.9$	21.8 $\pm 17.6$	17.3 $\pm 15.8$
Day 0-10			26.6 $\pm 22.0$	32.0 $\pm 15.8$	20.1 $\pm 18.6$	25.2 $\pm 17.8$	33.3 $\pm 16.8$	31.4 $\pm 15.6$	
Day 0-21			41.5 $\pm 14.7$	44.8 $\pm 12.2$	37.3 $\pm 15.1$	39.8 $\pm 23.1$	41.8 $\pm 13.3$	46.1 $\pm 15.3$	
Food consumption (g)			Day 3-4	38.1 $\pm 3.8$	36.1 $\pm 5.5$	36.6 $\pm 4.8$	34.5 $\pm 5.0$	37.7 $\pm 4.9$	35.0 $\pm 4.3$
Food consumption (g)	Day 6-7		37.4 $\pm 5.4$	37.4 $\pm 4.5$	38.1 $\pm 3.6$	37.0 $\pm 3.8$	38.1 $\pm 4.6$	38.0 $\pm 6.8$	
	Day 9-10		46.9 $\pm 9.1$	46.4 $\pm 4.9$	45.4 $\pm 4.3$	47.7 $\pm 5.5$	49.5 $\pm 5.2$	48.9 $\pm 4.7$	

H or **H** : Significantly higher than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

L or **L** : Significantly lower than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

– : No treatment-related alterations.

D or I : Decreasing or increasing tendency.

#: Not examined.

## Summary of results (continued-1)

Generation			Dam: F0 Offspring: F1					
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )			0	10	50	250	1250	100000
Number of pregnant females			14	15	15	15	14	14
Number of complete litter loss			0	0	1	0	0	0
F0	Delivery and maternal behavior	Delivery index(%)	100	100	100	100	100	100
		Gestation length (day)	21.7 $\pm 0.5$	21.9 $\pm 0.4$	21.6 $\pm 0.8$	21.9 $\pm 0.4$	21.8 $\pm 0.4$	21.9 $\pm 0.5$
		Number of implantation sites	17.2 $\pm 1.3$	16.5 $\pm 1.9$	15.9 $\pm 4.3$	16.9 $\pm 1.6$	16.6 $\pm 1.7$	17.2 $\pm 1.1$
		Number of pups delivered	15.8 $\pm 1.5$	15.7 $\pm 2.0$	14.9 $\pm 4.1$	15.7 $\pm 2.0$	16.1 $\pm 2.1$	15.9 $\pm 1.8$
	Absolute organ weights	Pituitary (mg)	10.0 $\pm 0.9$	10.1 $\pm 1.7$	10.1 $\pm 1.3$	9.7 $\pm 1.0$	9.9 $\pm 0.9$	10.4 $\pm 0.9$
		Thyroid (mg)	14.3 $\pm 2.5$	14.1 $\pm 2.4$	13.0 $\pm 2.9$	14.2 $\pm 2.5$	13.9 $\pm 3.3$	14.1 $\pm 2.7$
		Liver (g)	15.41 $\pm 1.09$	15.36 $\pm 1.14$	15.57 $\pm 0.99$	15.26 $\pm 1.27$	15.59 $\pm 1.25$	17.05 <b>H</b> $\pm 1.65$
		Adrenal (mg)	67.1 $\pm 7.7$	60.8 $\pm 6.1$	62.5 $\pm 4.3$	61.3 $\pm 6.4$	64.5 $\pm 5.7$	64.0 $\pm 6.3$
		Ovary (mg)	83.3 $\pm 6.4$	83.8 $\pm 9.1$	80.3 $\pm 9.3$	81.0 $\pm 8.3$	78.3 $\pm 7.9$	80.8 $\pm 5.2$
		Uterus (g)	237.5 $\pm 37.7$	240.1 $\pm 43.9$	243.6 $\pm 40.6$	222.9 $\pm 49.9$	221.9 $\pm 40.0$	233.3 $\pm 52.2$
	Relative organ weights	Pituitary ( $10^{-3}$ %)	3.1 $\pm 0.3$	3.1 $\pm 0.5$	3.1 $\pm 0.4$	3.0 $\pm 0.3$	3.0 $\pm 0.2$	3.1 $\pm 0.2$
		Thyroid ( $10^{-3}$ %)	4.4 $\pm 0.7$	4.3 $\pm 0.8$	4.0 $\pm 0.8$	4.4 $\pm 0.7$	4.3 $\pm 1.0$	4.2 $\pm 0.9$
		Liver (%)	4.70 $\pm 0.25$	4.69 $\pm 0.30$	4.81 $\pm 0.23$	4.71 $\pm 0.33$	4.81 $\pm 0.22$	5.07 <b>H</b> $\pm 0.27$
		Adrenal ( $10^{-3}$ %)	20.5 $\pm 2.4$	18.6 $\pm 1.8$	19.3 $\pm 1.6$	18.9 $\pm 1.8$	20.0 $\pm 1.6$	19.1 $\pm 1.7$
		Ovary ( $10^{-3}$ %)	25.5 $\pm 1.9$	25.6 $\pm 2.8$	24.8 $\pm 2.8$	25.0 $\pm 2.4$	24.2 $\pm 2.2$	24.1 $\pm 1.4$
		Uterus (%)	73.8 $\pm 11.6$	72.7 $\pm 13.8$	75.1 $\pm 10.1$	68.7 $\pm 14.6$	69.6 $\pm 11.2$	69.4 $\pm 15.2$
	Gross findings	Liver: Enlargement	0	0	0	0	0	2
		Histopathological findings	Pituitary: Remnant, Rathke's pouch	0	0	0	0	1
	Liver: Hypertrophy, hepatocyte, centrilobular		0	#	#	#	0	3
	Liver: Increase, eosinophilic granule, hepatocyte		0	#	#	#	0	6
	Ovary		-	-	-	-	-	-
	Uterus		-	-	-	-	-	-
		Vagina	-	-	-	-	-	-

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L or **L**: Significantly lower than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

- : No treatment-related alterations.

D or I: Decreasing or increasing tendency.

#: Not examined.

## Summary of results (continued-2)

Generation			Dam: F0 Offspring: F1						
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )			0	10	50	250	1250	100000	
Number of litters			14	15	14	15	14	14	
<b>F1</b>	Sex ratio (Male/male + female)		0.486	0.481	0.511	0.523	0.48	0.477	
	Clinical findings		–	–	–	–	–	–	
	Viability (%)	LD 0	98.5 $\pm 3.0$	99.6 $\pm 1.6$	100	100	100	98.6 $\pm 2.8$	
		LD 4	96.1 $\pm 7.2$	96.9 $\pm 4.4$	91.8 $\pm 25.8$	96.3 $\pm 4.3$	98.7 $\pm 2.6$	93.2 $\pm 6.8$	
		LD 21	100	100	99.1 $\pm 3.3$	100	100	100	
	Body weights (g)	Male	Day 0	5.9 $\pm 0.4$	5.9 $\pm 0.4$	5.9 $\pm 0.4$	5.7 $\pm 0.8$	5.9 $\pm 0.3$	5.8 $\pm 0.4$
			Day 7	14.1 $\pm 1.0$	14.1 $\pm 1.1$	13.5 $\pm 1.4$	14.2 $\pm 1.3$	14.5 $\pm 1.4$	14.2 $\pm 1.4$
			Day 14	29.6 $\pm 1.7$	29.2 $\pm 2.1$	28.8 $\pm 2.1$	29.7 $\pm 2.0$	30.1 $\pm 1.5$	29.5 $\pm 2.0$
			Autopsy day	46.7 $\pm 2.6$	46.4 $\pm 3.0$	44.1 $\pm 3.9$	46.9 $\pm 3.1$	46.4 $\pm 2.9$	46.2 $\pm 4.2$
		Female	Day 0	5.5 $\pm 0.4$	5.6 $\pm 0.4$	5.4 $\pm 0.3$	5.5 $\pm 0.4$	5.5 $\pm 0.3$	5.4 $\pm 0.4$
			Day 7	13.6 $\pm 1.0$	13.3 $\pm 1.1$	13.0 $\pm 1.4$	13.4 $\pm 1.2$	13.8 $\pm 1.2$	13.4 $\pm 1.2$
			Day 14	28.6 $\pm 1.7$	27.7 $\pm 2.1$	27.8 $\pm 2.0$	28.2 $\pm 2.0$	29.0 $\pm 1.6$	28.3 $\pm 1.8$
			Autopsy day	44.7 $\pm 2.3$	43.5 $\pm 3.2$	43.2 $\pm 3.6$	44.2 $\pm 2.9$	44.6 $\pm 3.4$	43.6 $\pm 2.9$
	Anogenital distances (mm)	LD 0	Male	3.24 $\pm 0.33$	3.24 $\pm 0.31$	3.26 $\pm 0.48$	3.46 $\pm 0.23$	3.33 $\pm 0.17$	3.35 $\pm 0.32$
			Female	1.48 $\pm 0.19$	1.48 $\pm 0.19$	1.43 $\pm 0.19$	1.52 $\pm 0.23$	1.51 $\pm 0.13$	1.54 $\pm 0.16$
	Corrected anogenital distances (AGD/BW <sup>1/3</sup> )	LD 0	Male	1.80 $\pm 0.17$	1.79 $\pm 0.17$	1.82 $\pm 0.24$	1.92 $\pm 0.12$	1.85 $\pm 0.10$	1.87 $\pm 0.16$
			Female	0.84 $\pm 0.10$	0.84 $\pm 0.11$	0.82 $\pm 0.11$	0.86 $\pm 0.13$	0.86 $\pm 0.08$	0.88 $\pm 0.09$
	Nipples/areolas	Male	LD 0	–	–	–	–	–	–
			LD 12	–	–	–	–	–	–
		Female	LD 0	–	–	–	–	–	–
LD 12			–	–	–	–	–	–	
External anomaly	Live pups		0	0	0	0	0	0	
	Dead pups: Short snout		1	0	0	0	0	0	
	Dead pups: Thread-like tail and anal atresia		1	0	0	0	0	0	
Gross findings of culling pups on LD 4	Kidney: Hydronephrosis		0	1	0	0	0	0	
	Kidney: Dilatation, renal pelvis		0	0	0	1	0	0	

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L or **L**: Significantly lower than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

–: No treatment-related alterations.

D or I: Decreasing or increasing tendency.

#: Not examined.

**Summary of results (continued-3)**

Generation				Dam: F0 Offspring: F1					
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )				0	10	50	250	1250	100000
Number of litters				14	15	14	15	14	14
F1	Male (LD 21)	Absolute organ weights	Liver (g)	1.72 $\pm 0.15$	1.71 $\pm 0.19$	1.61 $\pm 0.15$	1.74 $\pm 0.20$	1.71 $\pm 0.15$	1.72 $\pm 0.22$
			Testis (mg)	180.3 $\pm 21.0$	184 $\pm 17.5$	169.5 $\pm 17.2$	187.7 $\pm 14.0$	178.3 $\pm 17.0$	180.2 $\pm 19.5$
			Epididymis (mg)	31.5 $\pm 3.1$	31.3 $\pm 3.8$	29.9 $\pm 3.6$	32.5 $\pm 2.9$	30.4 $\pm 2.4$	30.8 $\pm 3.6$
			Accessory sex organs (mg)	42.9 $\pm 4.1$	44.5 $\pm 3.5$	42.4 $\pm 6.7$	45.4 $\pm 6.0$	40.0 $\pm 6.3$	45.1 $\pm 4.4$
			Prostate (mg)	14.0 $\pm 2.7$	15.1 $\pm 3.1$	12.8 $\pm 2.5$	14.7 $\pm 3.2$	12.6 $\pm 2.6$	14.4 $\pm 3.6$
			Seminal vesicle (mg)	9.6 $\pm 1.5$	10.3 $\pm 1.4$	9.2 $\pm 1.0$	9.0 $\pm 1.4$	8.9 $\pm 1.0$	9.4 $\pm 1.2$
		Relative organ weights	Liver (%)	1.72 $\pm 0.15$	1.71 $\pm 0.19$	1.61 $\pm 0.15$	1.74 $\pm 0.20$	1.71 $\pm 0.15$	1.72 $\pm 0.22$
			Testis (%)	180.3 $\pm 21.0$	184 $\pm 17.5$	169.5 $\pm 17.2$	187.7 $\pm 14.0$	178.3 $\pm 17.0$	180.2 $\pm 19.5$
			Epididymis ( $10^{-3}\%$ )	31.5 $\pm 3.1$	31.3 $\pm 3.8$	29.9 $\pm 3.6$	32.5 $\pm 2.9$	30.4 $\pm 2.4$	30.8 $\pm 3.6$
			Accessory sex organs ( $10^{-3}\%$ )	42.9 $\pm 4.1$	44.5 $\pm 3.5$	42.4 $\pm 6.7$	45.4 $\pm 6.0$	40.0 $\pm 6.3$	45.1 $\pm 4.4$
			Prostate ( $10^{-3}\%$ )	14.0 $\pm 2.7$	15.1 $\pm 3.1$	12.8 $\pm 2.5$	14.7 $\pm 3.2$	12.6 $\pm 2.6$	14.4 $\pm 3.6$
			Seminal Vesicle ( $10^{-3}\%$ )	9.6 $\pm 1.5$	10.3 $\pm 1.4$	9.2 $\pm 1.0$	9.0 $\pm 1.4$	8.9 $\pm 1.0$	9.4 $\pm 1.2$
	Female (LD 21)	Absolute organ weights	Liver (g)	1.65 $\pm 0.10$	1.62 $\pm 0.18$	1.59 $\pm 0.18$	1.63 $\pm 0.16$	1.67 $\pm 0.21$	1.59 $\pm 0.15$
			Ovary (mg)	6.9 $\pm 1.0$	6.6 $\pm 1.4$	6.0 $\pm 1.0$	6.5 $\pm 1.1$	6.5 $\pm 1.6$	6.8 $\pm 1.6$
			Uterus (mg)	26.3 $\pm 2.1$	26.5 $\pm 3.2$	25.1 $\pm 3.1$	25.5 $\pm 2.5$	26.2 $\pm 2.6$	25.4 $\pm 2.5$
		Relative organ weights	Liver (%)	3.72 $\pm 0.20$	3.75 $\pm 0.18$	3.68 $\pm 0.14$	3.72 $\pm 0.22$	3.74 $\pm 0.21$	3.66 $\pm 0.40$
			Ovary ( $10^{-3}\%$ )	15.6 $\pm 2.6$	15.7 $\pm 2.8$	13.9 $\pm 1.7$	14.9 $\pm 2.4$	14.6 $\pm 3.0$	15.6 $\pm 3.5$
			Uterus ( $10^{-3}\%$ )	59.6 $\pm 5.5$	61.8 $\pm 7.2$	58.2 $\pm 7.3$	58.3 $\pm 5.4$	59.2 $\pm 4.5$	58.3 $\pm 5.7$

**Summary of results (continued-4)**

Generation			Dam: F0 Offspring: F1						
Dose(µg/kg/day)			0	10	50	250	1250	100000	
Number of litters			14	15	14	15	14	14	
F1	Gross findings (LD 21)		Male	-	-	-	-	-	-
			Female	-	-	-	-	-	-
	Histopathological Findings (LD 21)	Male	Liver: Extramedullary hematopoiesis	15/26	#	#	#	#	15/29
			Testis	-	#	#	#	#	-
		Female	Liver: Extramedullary hematopoiesis	12/30	#	#	#	#	8/28
			Ovary: Atresia, folliculi	0/30	1/33	0/26	0/29	0/28	0/27
	Hormone concentrations (LD 21)	Male	Testosterone (ng/mL)	0.08 ±0.02	0.08 ±0.02	0.07 ±0.01	0.07 ±0.02	0.07 ±0.02	0.08 ±0.02
			FSH (ng/mL)	6.88 ±1.32	8.55 ±1.85	8.31 ±1.77	7.69 ±1.66	8.66 ±1.47	7.32 ±1.97
			LH (ng/mL)	1.34 ±0.47	1.51 ±0.70	1.88 ±1.07	1.89 ±1.25	1.74 ±0.91	1.35 ±0.32
		Female	FSH (ng/mL)	24.39 ±6.86	28.13 ±10.38	35.46 <b>H</b> ±8.67	30.33 ±9.15	32.36 ±11.95	32.22 ±6.85
			LH (ng/mL)	6.09 ±2.62	6.36 ±4.03	6.46 ±3.25	8.75 ±4.84	7.95 ±7.37	7.16 ±5.70

H or **H**: Significantly higher than the control (p < 0.05 and p < 0.01, respectively).

L or **L**: Significantly lower than the control (p < 0.05 and p < 0.01, respectively).

- : No treatment-related alterations.

D or I: Decreasing or increasing tendency.

#: Not examined

### Summary of results (continued-5)

Generation			Dam: F0 Offspring: F1						
Dose( $\mu$ g/kg/day)			0	10	50	250	1250	100000	
Number of litters			14	15	14	15	14	14	
Number of offspring (post weaning)		Male	28	30	28	30	28	28	
		Female	28	30	28	30	28	28	
<b>F1</b>	Clinical findings		-	-	-	-	-	-	
	Body weights (g)	Male	Day 28	82.5 $\pm$ 4.6	82.3 $\pm$ 4.7	79.9 $\pm$ 5.9	83.5 $\pm$ 5.0	82.9 $\pm$ 4.9	80.2 $\pm$ 7.0
			Day 35	137.1 $\pm$ 7.5	136.3 $\pm$ 7.6	132.5 $\pm$ 8.6	137.9 $\pm$ 7.2	138.7 $\pm$ 6.9	133.7 $\pm$ 9.6
			Day 42	198.5 $\pm$ 11.6	197.3 $\pm$ 9.9	194.8 $\pm$ 11.7	201.3 $\pm$ 8.3	201.9 $\pm$ 7.9	194.9 $\pm$ 14.1
			Day 49	260.7 $\pm$ 14.7	258.6 $\pm$ 13.2	257.8 $\pm$ 14.1	264.2 $\pm$ 12.4	264.3 $\pm$ 8.8	256.9 $\pm$ 18.1
			Day 56	328.6 $\pm$ 16.7	323.9 $\pm$ 13.3	323.6 $\pm$ 13.7	332.3 $\pm$ 14.9	334.2 $\pm$ 10.6	323.2 $\pm$ 18.2
			Day 63	381.2 $\pm$ 20.2	372.2 $\pm$ 12.8	371.9 $\pm$ 12.0	380.7 $\pm$ 19.6	383.2 $\pm$ 13.3	371.8 $\pm$ 18.4
			Day 70	419.7 $\pm$ 21.7	407.6 $\pm$ 12.7	407.6 $\pm$ 12.5	415.5 $\pm$ 22.8	419.2 $\pm$ 15.2	408.3 $\pm$ 18.9
			Day 77	443.9 $\pm$ 22.1	435.0 $\pm$ 14.3	430.4 $\pm$ 14.9	440.0 $\pm$ 27.0	443.5 $\pm$ 16.5	432.7 $\pm$ 18.8
			Day 84	472.5 $\pm$ 21.6	462.5 $\pm$ 14.0	455.8 $\pm$ 16.1	465.9 $\pm$ 30.3	472.1 $\pm$ 17.2	459.6 $\pm$ 19.7
			Day 91	494.1 $\pm$ 23.3	483.6 $\pm$ 14.9	480.5 $\pm$ 15.4	484.9 $\pm$ 29.8	495.8 $\pm$ 18.7	482.2 $\pm$ 21.3
			Autopsy day (13 weeks old)	513.1 $\pm$ 26.3	502.8 $\pm$ 16.2	497.9 $\pm$ 15.6	504.0 $\pm$ 35.1	511.5 $\pm$ 18.7	500.4 $\pm$ 22.9
	Female	Day 28	75.0 $\pm$ 4.0	74.8 $\pm$ 5.6	72.9 $\pm$ 5.7	76.8 $\pm$ 5.3	75.6 $\pm$ 5.2	75.4 $\pm$ 4.8	
		Day 35	121.3 $\pm$ 5.9	118.4 $\pm$ 7.6	117.4 $\pm$ 7.4	122.2 $\pm$ 6.9	121.2 $\pm$ 7.2	120.9 $\pm$ 6.9	
		Day 42	162.3 $\pm$ 6.2	157.6 $\pm$ 7.9	158.6 $\pm$ 9.3	162.0 $\pm$ 7.5	162.0 $\pm$ 8.0	160.4 $\pm$ 8.2	
		Day 49	191.7 $\pm$ 6.1	187.0 $\pm$ 9.6	190.0 $\pm$ 9.5	192.4 $\pm$ 10.3	191.4 $\pm$ 10.1	190.5 $\pm$ 11.0	
		Day 56	220.6 $\pm$ 9.7	214.3 $\pm$ 9.7	220.1 $\pm$ 10.6	220.8 $\pm$ 13.9	218.5 $\pm$ 12.5	218.0 $\pm$ 13.9	
		Day 63	241.8 $\pm$ 11.8	234.2 $\pm$ 11.5	242.6 $\pm$ 9.8	242.9 $\pm$ 14.0	241.3 $\pm$ 13.7	240.2 $\pm$ 15.1	
		Day 70	259.1 $\pm$ 13.6	251.5 $\pm$ 11.4	259.2 $\pm$ 10.5	262.5 $\pm$ 15.7	259.5 $\pm$ 14.7	259.8 $\pm$ 17.9	
	Body weight gains (g)	Male	Day 21-42	151.6 $\pm$ 10.3	150.6 $\pm$ 8.1	149.4 $\pm$ 9.7	154.1 $\pm$ 6.3	154.9 $\pm$ 5.8	148.2 $\pm$ 11.5
			Day 21-63	334.3 $\pm$ 18.3	325.6 $\pm$ 11.6	326.5 $\pm$ 10.6	333.5 $\pm$ 17.3	336.1 $\pm$ 12.2	325.1 $\pm$ 16.0
			Day 21-91	447.3 $\pm$ 21.7	436.9 $\pm$ 14.6	435.2 $\pm$ 14.0	437.7 $\pm$ 27.5	448.8 $\pm$ 17.5	435.5 $\pm$ 20.5
		Female	Day 21-42	117.1 $\pm$ 4.7	113.5 $\pm$ 6.3	115.4 $\pm$ 7.4	117.3 $\pm$ 4.8	117.2 $\pm$ 6.3	116.7 $\pm$ 7.6
Day 21-70			213.8 $\pm$ 12.3	207.3 $\pm$ 10.8	216.0 $\pm$ 10.3	217.8 $\pm$ 13.5	214.6 $\pm$ 13.3	211.0 $\pm$ 17.8	

H or **H** : Significantly higher than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

L or **L** : Significantly lower than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

- : No treatment-related alterations.

D or I: Decreasing or increasing tendency.

**Summary of results (continued-6)**

Generation			Dam: F0 Offspring: F1						
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )			0	10	50	250	1250	100000	
Number of litters			14	15	14	15	14	14	
Number of offspring (post weaning)		Male	28	30	28	30	28	28	
		Female	28	30	28	30	28	28	
<b>F1</b>	Sexual development (day)	Preputial separation (day)	46.4 $\pm 1.5$	45.6 $\pm 1.2$	45.7 $\pm 1.6$	45.4 $\pm 0.8$	45.3 $\pm 1.0$	46.1 $\pm 1.4$	
		Body weights (g)	235.4 $\pm 12.6$	228.2 $\pm 11.0$	226.9 $\pm 13.7$	232.5 $\pm 9.1$	231.9 $\pm 8.4$	229.9 $\pm 15.4$	
		Vaginal opening (day)	30.9 $\pm 1.4$	30.3 $\pm 1.5$	30.9 $\pm 1.4$	30.4 $\pm 0.9$	30.1 $\pm 1.1$	30.2 $\pm 1.1$	
		Body weights (g)	91.3 $\pm 6.9$	88.7 $\pm 7.2$	91.4 $\pm 10.2$	92.8 $\pm 7.0$	89.1 $\pm 6.7$	89.1 $\pm 6.6$	
	Estrus cycle	Normal estrus cycle	100	100	100	100	100	100	
		Estrus cycle length • iday • j	4.06 $\pm 0.05$	4.09 $\pm 0.07$	4.05 $\pm 0.05$	4.04 $\pm 0.03$	4.06 $\pm 0.05$	4.07 $\pm 0.07$	
		Total days examined	44.1 $\pm 1.5$	44.5 $\pm 1.7$	44.4 $\pm 1.7$	44.2 $\pm 1.6$	44.7 $\pm 1.3$	44.4 $\pm 1.8$	
		Number of diestrus	22.6 $\pm 0.7$	22.9 $\pm 1.0$	22.7 $\pm 1.0$	22.7 $\pm 1.0$	23.3 $\pm 1.2$	22.3 $\pm 0.9$	
		Number of proestrus	10.3 $\pm 0.6$	10.3 $\pm 0.8$	10.2 $\pm 0.4$	10.3 $\pm 0.8$	10.2 $\pm 0.8$	10.5 $\pm 0.9$	
		Number of estrus	11.1 $\pm 0.9$	11.3 $\pm 0.9$	11.5 $\pm 0.7$	11.3 $\pm 0.6$	11.2 $\pm 1.0$	11.6 $\pm 0.7$	
	Reproductive performance	Copulation index (%)	100	100	96.4	90.0	96.4	96.4	
		Fertility index (%)	92.9	93.3	100	100	96.3	100	
	Gestation period	Body weights(g)	Day 0	275.5 $\pm 19.5$	265.4 $\pm 13.4$	277.9 $\pm 14.4$	273.3 $\pm 15.7$	273.8 $\pm 15.8$	273.3 $\pm 19.0$
			Day 13	342.7 $\pm 18.0$	329.2 $\pm 15.1$	344.2 $\pm 15.2$	340.0 $\pm 20.4$	340.8 $\pm 17.5$	336.7 $\pm 18.3$
		Body weight gain (g)	Day 0-13	67.1 $\pm 6.7$	63.9 $\pm 9.3$	66.3 $\pm 8.0$	66.8 $\pm 9.3$	67.0 $\pm 6.4$	63.4 $\pm 5.3$
	Observations at terminal sacrifice (GD 13)	Number of corpora lutea	17.9 $\pm 0.8$	17.3 $\pm 1.7$	18.3 $\pm 1.5$	18.3 $\pm 1.8$	16.5 $\pm 2.4$	17.5 $\pm 1.0$	
		Number of implants	16.9 $\pm 1.0$	16.0 $\pm 1.6$	16.8 $\pm 1.8$	16.6 $\pm 1.5$	15.1 $\pm 2.3$	16.1 $\pm 1.5$	
		Fetal mortality (%)	3.9 $\pm 4.2$	7.5 $\pm 5.0$	6.5 $\pm 3.9$	9.3 $\pm 8.1$	7.4 $\pm 8.8$	5.4 $\pm 3.9$	
	Absolute organ weights (GD 13)	Pituitary (mg)	9.9 $\pm 1.1$	9.6 $\pm 1.0$	10.7 $\pm 1.3$	10.1 $\pm 0.9$	10.2 $\pm 1.0$	10.2 $\pm 1.6$	
		Thyroid (mg)	14.9 $\pm 2.3$	15.0 $\pm 2.4$	15.5 $\pm 2.0$	15.3 $\pm 2.2$	15.6 $\pm 2.3$	15.0 $\pm 1.8$	
		Adrenal (mg)	74.3 $\pm 6.0$	69.8 $\pm 5.8$	71.6 $\pm 6.6$	72.1 $\pm 4.9$	70.5 $\pm 6.3$	72.5 $\pm 9.8$	
	Relative organ weights (GD 13)	Pituitary ( $10^{-3}\%$ )	2.9 $\pm 0.3$	2.9 $\pm 0.3$	3.1 $\pm 0.3$	3.0 $\pm 0.2$	3.0 $\pm 0.3$	3.1 $\pm 0.4$	
		Thyroid ( $10^{-3}\%$ )	4.4 $\pm 0.5$	4.6 $\pm 0.6$	4.5 $\pm 0.6$	4.5 $\pm 0.6$	4.6 $\pm 0.7$	4.5 $\pm 0.5$	
		Adrenal ( $10^{-3}\%$ )	21.7 $\pm 1.7$	21.2 $\pm 1.7$	20.8 $\pm 1.6$	21.2 $\pm 1.1$	20.7 $\pm 1.9$	21.6 $\pm 2.7$	

## Summary of results (continued-7)

Generation			Dam: F0 Offspring: F1					
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )			0	10	50	250	1250	100000
Number of litters			14	15	14	15	14	14
Number of offspring (post weaning)		Male	28	30	28	30	28	28
		Female	28	30	28	30	28	28
Gross findings (GD 13)			-	-	-	-	-	-
Histopatho- logical findings	Pituitary: Remnant, Rathke's pouch		0	0	2	2	1	2
	Ovary		-	-	-	-	-	-
mRNA expression	Uterus	ER- $\alpha$	0.0885 $\pm 0.0281$	0.0908 $\pm 0.0243$	0.0791 $\pm 0.0324$	0.1131 $\pm 0.0191$	0.1022 $\pm 0.0369$	0.0723 $\pm 0.0165$
		ER- $\beta$	0.0008 $\pm 0.0012$	0.0008 $\pm 0.0009$	0.0010 $\pm 0.0007$	0.0015 <b>H</b> $\pm 0.0009$	0.0006 $\pm 0.0005$	0.0008 $\pm 0.0006$
		AR	0.0081 $\pm 0.0014$	0.0104 $\pm 0.0029$	0.0098 $\pm 0.0031$	0.0098 $\pm 0.0017$	0.0093 $\pm 0.0021$	0.0082 $\pm 0.0025$
		IGF-1	0.0324 $\pm 0.0074$	0.0371 $\pm 0.0086$	0.0291 $\pm 0.0070$	0.0299 $\pm 0.0054$	0.0335 $\pm 0.0069$	0.0318 $\pm 0.0075$
Male (13 weeks old)	Absolute organ weights	Pituitary (mg)	10.2 $\pm 0.9$	10.5 $\pm 1.2$	10.4 $\pm 0.6$	10.2 $\pm 0.7$	10.4 $\pm 0.6$	10.3 $\pm 1.0$
		Thyroid (mg)	18.4 $\pm 2.1$	19.2 $\pm 2.0$	19.1 $\pm 2.4$	18.7 $\pm 1.5$	19.3 $\pm 3.2$	18.3 $\pm 2.5$
		Adrenal (mg)	57.2 $\pm 5.3$	57.4 $\pm 4.2$	56.0 $\pm 3.0$	58.1 $\pm 4.7$	59.5 $\pm 3.6$	26.9 $\pm 5.1$
		Liver (g)	22.16 $\pm 2.26$	21.34 $\pm 1.40$	20.92 $\pm 1.25$	21.02 $\pm 2.19$	21.67 $\pm 1.27$	21.26 $\pm 2.04$
		Testis (g)	2.98 $\pm 0.21$	3.05 $\pm 0.17$	3.06 $\pm 0.21$	3.05 $\pm 0.14$	3.00 $\pm 0.15$	3.08 $\pm 0.09$
		Epididymis (g)	1.15 $\pm 0.05$	1.17 $\pm 0.07$	1.19 $\pm 0.05$	1.17 $\pm 0.04$	1.15 $\pm 0.06$	1.17 $\pm 0.06$
		Cosgulating gland (mg)	203.9 $\pm 39.9$	210.4 $\pm 49.0$	212.4 $\pm 38.3$	231.4 $\pm 37.3$	206.5 $\pm 42.8$	217.3 $\pm 43.6$
		Seminal vesicle (g)	1.60 $\pm 0.11$	1.70 $\pm 0.19$	1.70 $\pm 0.18$	1.74 $\pm 0.17$	1.69 $\pm 0.11$	1.62 $\pm 0.13$
		Prostate (mg)	591.7 $\pm 94.9$	588.0 $\pm 55.4$	590.7 $\pm 72.2$	598.8 $\pm 79.3$	626.6 $\pm 90.8$	572.6 $\pm 76.4$
	Relative organ weights	Pituitary ( $10^{-3}\%$ )	2.0 $\pm 0.2$	2.1 $\pm 0.2$	2.1 $\pm 0.1$	2.1 $\pm 0.1$	2.0 $\pm 0.1$	2.1 $\pm 0.2$
		Thyroid ( $10^{-3}\%$ )	3.6 $\pm 0.4$	3.8 $\pm 0.4$	3.8 $\pm 0.4$	3.8 $\pm 0.3$	3.8 $\pm 0.6$	3.7 $\pm 0.5$
		Adrenal ( $10^{-3}\%$ )	11.2 $\pm 1.1$	11.5 $\pm 0.8$	11.3 $\pm 0.5$	11.6 $\pm 0.9$	11.6 $\pm 0.6$	11.4 $\pm 0.9$
		Liver (%)	4.31 $\pm 0.29$	4.24 $\pm 0.18$	4.21 $\pm 0.21$	4.16 $\pm 0.22$	4.24 $\pm 0.16$	4.24 $\pm 0.29$
		Testis (%)	0.59 $\pm 0.05$	0.61 $\pm 0.03$	0.62 $\pm 0.05$	0.61 $\pm 0.04$	0.59 $\pm 0.03$	0.62 $\pm 0.04$
		Epididymis (%)	0.23 $\pm 0.01$	0.23 $\pm 0.01$	0.24 $\pm 0.02$	0.23 $\pm 0.01$	0.23 $\pm 0.01$	0.24 $\pm 0.02$
		Seminal vesicle (%)	39.8 $\pm 7.2$	42.1 $\pm 9.8$	42.8 $\pm 8.0$	46.4 $\pm 8.5$	40.5 $\pm 8.7$	43.7 $\pm 9.2$
		Cosgulating gland (mg)	0.32 $\pm 0.03$	0.34 $\pm 0.04$	0.35 $\pm 0.04$	0.35 $\pm 0.04$	0.33 $\pm 0.03$	0.33 $\pm 0.03$
Prostate ( $10^{-3}\%$ )		115.7 $\pm 18.4$	117.3 $\pm 13.7$	118.9 $\pm 15.0$	119.1 $\pm 14.8$	122.8 $\pm 18.2$	114.8 $\pm 16.5$	

H or **H** : Significantly higher than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

L or **L** : Significantly lower than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

- : No treatment-related alterations.

D or I: Decreasing or increasing tendency.



## Summary of results (continued-8)

Generation			Dam: F0 Offspring: F1						
Dose( $\mu\text{g}/\text{kg}/\text{day}$ )			0	10	50	250	1250	100000	
Number of litters			14	15	14	15	14	14	
Number of offspring (post weaning)		Male	28	30	28	30	28	28	
		Female	28	30	28	30	28	28	
<b>F1</b>	Gross findings	Kidney: Dilatation, renal pelvis		1	0	1	0	1	0
		Histo-pathological findings	Pituitary: Remnant, Rathoke's pouch		1	4	3	2	2
	Testis: Loss of germ cell, seminiferous tubule		1	0	0	0	0	0	
	Testis: Multinucleated giant cell, seminiferous tubule		1	0	0	0	0	0	
	Epididymis		–	–	–	–	–	–	
	Sperm examination	Number of epidermal Sperm( $\times 10^6/\text{g}$ cauda)		1045.1 $\pm 155.1$	1103.0 $\pm 168.3$	1126.0 $\pm 162.1$	1136.4 $\pm 202.1$	1076.6 $\pm 128.5$	1066.3 $\pm 147.8$
		Motility (%)		91.4 $\pm 5.9$	91.7 $\pm 5.2$	88.8 $\pm 9.4$	92.4 $\pm 3.8$	90.1 $\pm 5.1$	92.0 $\pm 5.1$
	mRNA expression (%)	Prostate	ER $\alpha$	0.0019 $\pm 0.0005$	0.0018 $\pm 0.0006$	0.0016 $\pm 0.0006$	0.0019 $\pm 0.0006$	0.0018 $\pm 0.0007$	0.0014 $\pm 0.0004$
			ER $\beta$	0.2095 $\pm 0.0282$	0.2320 $\pm 0.0312$	0.2114 $\pm 0.0418$	0.2450 $\pm 0.0529$	0.2279 $\pm 0.0265$	0.1914 $\pm 0.0509$
			AR	0.2030 $\pm 0.0348$	0.2136 $\pm 0.354$	0.1984 $\pm 0.0303$	0.2104 $\pm 0.0334$	0.1982 $\pm 0.0396$	0.1725 $\pm 0.0573$
IGF-1			0.0258 $\pm 0.0057$	0.0270 $\pm 0.0070$	0.0267 $\pm 0.0084$	0.0280 $\pm 0.0053$	0.0227 $\pm 0.0063$	0.0231 $\pm 0.0074$	

H or **H**: Significantly higher than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

L or **L**: Significantly lower than the control ( $p < 0.05$  and  $p < 0.01$ , respectively).

– : No treatment-related alterations.

D or I: Decreasing or increasing tendency.