

Summary of results (Diethyl phthalate)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg}$)			0	0.4	2	10	50	2,000,000
Number of pregnant females			15	15	15	14	14	15
Found dead			0	0	0	0	0	0
F0	Gestation Period	Clinical findings		-	-	-	-	-
		Dead		0/15	0/15	0/15	0/14	0/14
		Body weights (g)	Day 0	241.4 ±6.8	242.0 ±7.5	241.0 ±11.4	241.8 ±7.1	241.9 ±7.8
			Day 7	277.1 ±7.7	279.2 ±9.1	280.6 ±11.2	276.1 ±9.4	279.5 ±9.2
			Day 14	317.3 ±10.6	320.6 ±11.8	321.0 ±12.6	317.5 ±13.1	322.7 ±11.0
			Day 18	365.0 ±13.0	371.5 ±13.2	370.2 ±12.6	368.3 ±18.0	371.7 ±13.2
			Day 21	399.2 ±15.1	409.3 ±16.2	408.4 ±15.5	403.9 ±19.9	406.2 ±18.3
	Food Consumption (g)	Body weight gains(g)	Day 0-21	157.8 ±15.7	167.3 ±13.8	167.4 ±9.9	162.1 ±14.1	164.3 ±14.7
			Day 0-7	22.8 ±1.2	23.4 ±1.6	23.4 ±1.5	23.0 ±1.6	23.4 ±1.3
		Day 7-14	26.0 ±1.5	26.1 ±2.1	26.7 ±1.9	26.5 ±1.5	26.6 ±1.5	23.6 L ±1.5
	Lactation Period	Day 14-21	24.6 ±1.9	25.5 ±2.6	25.6 ±2.9	26.2 ±2.3	26.5 ±2.3	21.3 L ±1.2
		Body weights (g)	Day 0	273.9 ±15.7	276.6 ±13.0	276.3 ±17.1	274.6 ±13.1	281.4 ±20.4
			Day 21	323.2 ±12.2	320.9 ±12.8	324.3 ±12.3	320.2 ±14.4	327.1 ±11.3
		Food consumption (g)	Day 0-21	49.3 ±14.2	44.4 ±14.1	48.1 ±12.3	45.6 ±14.8	45.7 ±15.9
			Day 0-4	25.5 ±5.7	29.8 ±2.5	27.6 ±4.6	26.6 ±5.6	25.5 ±6.3
			Day 4-7	28.2 ±2.8	28.5 ±2.3	29.1 ±2.5	28.6 ±2.1	27.1 ±3.1
			Day 7-14	51.2 ±4.0	51.5 ±2.8	51.9 ±2.9	52.4 ±2.8	52.2 ±3.5
			Days 14-21	62.5 ±4.7	61.5 ±3.5	62.5 ±3.2	64.1 ±4.2	63.6 ±3.7

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.

Summary of results (continued - 1)

Generation		Dam: F0 Offspring: F1					
Dose (µg/kg/day)		0	0.4	2	10	50	2,000,000
Number of pregnant females		15	15	15	14	14	15
F0	Delivery and maternal behavior	Defective delivery	1/15 (delayed birth)	0/15	0/15	0/14	0/14
		Abnormality of lactation	0/15	0/15	0/15	0/14	3/15 (annihilation of pups)
		Gestation index (%)	100.0	100.0	100.0	100.0	100.0
		Gestation length (day)	22.1 ±0.5	22.1 ±0.3	22.1 ±0.3	22.0 ±0.0	22.1 ±0.3
		Number of implantation sites	16.6 ±2.3	16.9 ±1.6	16.9 ±2.0	17.1 ±2.6	16.5 ±2.2
	Number of dams		15	15	15	14	14
	Gross findings		—	—	—	—	—
	Absolute organ weights	Adrenal (mg)	76.0 ±7.3	74.2 ±6.6	73.7 ±9.4	72.8 ±7.5	73.2 ±9.7
		Pituitary (mg)	14.9 ±1.4	13.2 L ±1.9	12.8 L ±1.4	12.2 L ±1.7	13.2 L ±1.4
		Thyroid (mg)	24.4 ±4.8	21.4 ±4.7	21.7 ±3.0	19.5 L ±2.9	19.5 L ±2.6
		Liver (mg)	15495.1 ±2113.0	15202.8 ±1643.0	15302.2 ±1456.6	14630.5 ±1737.4	15375.1 ±1400.1
		Kidney (mg)	2529.4 ±235.3	2482.0 ±133.0	2485.0 ±149.9	2419.0 ±146.3	2518.5 ±124.9
		Ovary (mg)	93.3 ±13.3	98.9 ±13.3	96.3 ±11.8	92.1 ±13.8	97.8 ±10.5
		Uterus (mg)	408.9 ±93.3	444.5 ±146.6	403.7 ±103.9	411.3 ±117.5	445.7 ±106.9
	Relative organ weight	Adrenal (%)	0.0235 ±0.0017	0.0232 ±0.0024	0.0228 ±0.0031	0.0227 ±0.0020	0.0224 ±0.0029
		Pituitary (%)	0.0046 ±0.0005	0.0041 L ±0.0006	0.0039 L ±0.0004	0.0038 L ±0.0005	0.0040 L ±0.0004
		Thyroid (%)	0.0076 ±0.0015	0.0067 ±0.0015	0.0067 ±0.0010	0.0061 L ±0.0007	0.0060 L ±0.0008
		Liver (%)	4.7944 ±0.6546	4.7322 ±0.4339	4.7196 ±0.4241	4.5600 ±0.4043	4.6985 ±0.3744
		Kidney (%)	0.7829 ±0.0743	0.7745 ±0.0502	0.7669 ±0.0499	0.7558 ±0.0374	0.7709 ±0.0495
		Ovary (%)	0.0146 ±0.0031	0.0154 ±0.0024	0.0152 ±0.0024	0.0143 ±0.0026	0.0144 ±0.0021
		Uterus (%)	0.1267 ±0.0296	0.1387 ±0.0459	0.1247 ±0.0323	0.1280 ±0.0358	0.1364 ±0.0328
	Histopathological findings	Liver: Eosinophilic, granular change(+)	0/15	0/15	0/15	0/14	0/14
							12/15

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—: No treatment-related alterations.

Summary of results (continued - 2)

Generation		Dam: F0 Offspring: F1							
Dose ($\mu\text{g}/\text{kg}/\text{day}$)		0	0.4	2	10	50	2,000,000		
Number of litters		15	15	15	14	14	12		
F1	Number of pups delivered		15.4 ±2.4	15.5 ±1.2	15.8 ±1.7	15.8 ±2.7	15.5 ±3.1	14.5 ±3.0	
	Delivery index (%)		93.1 ±8.0	91.7 ±7.0	93.6 ±4.8	92.2 ±7.9	83.3 ±8.4	87.6 ±12.3	
	Birth index (%)		91.7 ±12.3	91.7 ±7.0	93.6 ±4.8	92.2 ±7.9	87.4 ±8.3	80.3 ±20.0	
	Sex ratio (Male/ female)		1.30 ±0.53	0.95 ±0.58	1.29 ±0.68	0.90 ±0.47	1.09 ±0.48	1.26 ±0.58	
	Number of live pups	LD 0		15.1 ±2.6	15.5 ±1.2	15.8 ±1.7	15.8 ±2.7	15.4 ±3.1	13.3 ±3.8
		LD 4		14.0 ±2.6	15.3 ±1.2	15.2 ±1.5	15.4 ±2.3	14.8 ±2.9	8.7 L ±5.7
	Viability (%)	LD 0		98.1 ±7.4	100.0 ±0.0	100.0 ±0.0	100.0 ±0.0	99.0 ±2.4	90.8 L ±16.2
		LD 4		92.9 ±1.2	98.7 ±2.6	96.4 ±5.3	98.1 ±3.4	95.4 ±6.3	68.1 L ±36.9
		LD 21		100.0 ±0.0	99.2 ±3.2	99.2 ±3.2	100.0 ±0.0	100.0 ±0.0	99.0 ±3.5
	Number of malformations	Male	Hypo-spadias	0	0	0	0	0	1
		Female	Cleft palate	0	0	0	0	1	0
	Clinical findings		Male	–	–	–	–	–	–
	Female		–	–	–	–	–	–	–

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–: No treatment-related alterations.

Summary of results (continued - 3)

Generation			Dam: F0 Offspring: F1						
Dose (µg/kg/day)			0	0.4	2	10	50	2,000,000	
Number of litters			15	15	15	14	14	12	
F 1	Body weights (g)	Male	Day 0	5.8 ±0.3	6.1 • c ±0.3	5.9 ±0.4	6.0 ±0.3	6.0 ±0.4	5.0 L ±0.3
			Day 4	8.8 ±1.3	9.3 ±0.5	8.8 ±1.3	9.0 ±0.8	8.9 ±1.1	7.6 L ±1.0
			Day 7	14.2 ±1.6	14.4 ±1.0	14.3 ±1.2	14.1 ±1.2	13.9 ±1.7	11.2 L ±2.0
			Day 14	29.6 ±3.5	29.8 ±1.6	30.0 ±2.1	30.1 ±1.8	29.2 ±2.5	23.2 L ±3.4
			Day 21	48.1 ±4.1	49.0 ±2.7	48.7 ±2.5	49.4 ±3.3	48.1 ±3.5	36.9 L ±5.4
		Female	Day 0	5.4 ±0.3	5.6 ±0.3	5.5 ±0.3	5.5 ±0.3	5.6 ±0.3	4.7 L ±0.3
			Day 4	8.3 ±1.3	8.5 ±0.6	8.4 ±0.7	8.3 ±0.9	8.4 ±1.1	7.1 L ±0.7
			Day 7	13.1 ±1.7	13.5 ±1.0	13.3 ±1.2	13.5 ±1.4	13.3 ±1.6	10.6 L ±1.4
			Day 14	26.9 ±2.5	28.1 ±1.5	28.6 ±1.9	28.8 ±2.3	28.0 ±2.5	22.5 L ±2.4
			Day 21	44.7 ±4.3	45.7 ±2.5	46.0 ±2.7	47.1 ±3.7	45.4 ±3.5	35.6 L ±3.9
	Body weight gains (g)	Male	Day 0-4	3.0 ±1.1	3.1 ±0.4	2.9 ±1.2	2.9 ±0.7	2.9 ±0.9	2.5 ±0.8
			Day 0-7	8.4 ±1.5	8.3 ±0.9	8.4 ±1.0	8.1 ±1.1	7.9 ±1.4	6.1 L ±1.8
			Day 0-14	23.8 ±3.4	23.7 ±1.5	24.2 ±2.0	24.1 ±1.7	23.3 ±2.2	18.1 L ±3.4
			Day 0-21	42.3 ±4.0	42.8 ±2.6	42.8 ±2.4	43.4 ±3.2	42.1 ±3.2	31.8 L ±5.3
		Female	Day 0-4	2.9 ±1.2	3.0 ±0.4	2.9 ±0.6	2.8 ±0.8	2.9 ±1.0	2.3 ±0.7
			Day 0-7	7.7 ±1.6	7.9 ±0.9	7.8 ±1.0	8.0 ±1.2	7.7 ±1.4	5.8 ±1.4
			Day 0-14	21.5 ±2.4	22.5 ±1.4	23.1 ±1.9	23.3 ±2.1	22.5 ±2.3	17.7 L ±2.4
			Day 0-21	39.3 ±4.3	40.1 ±2.4	40.5 ±2.6	41.6 ±3.5	39.9 ±3.4	30.8 L ±3.9
			AGD (mm)	2.64 ±0.20	2.75 ±0.14	2.78 ±0.18	2.73 ±0.25	2.75 ±0.19	2.81 ±0.25
	Anogenital distances (LD 0)	Male	AGD/ ³ • ªBW	1.47 ±0.11	1.50 ±0.07	1.54 ±0.09	1.50 ±0.14	1.52 ±0.12	1.64 H ±0.16
			Female	AGD (mm)	1.21 ±0.05	1.24 ±0.06	1.26 ±0.07	1.27 • c ±0.08	1.25 ±0.06
		Female	AGD/ ³ • ªBW	0.69 ±0.03	0.70 ±0.04	0.71 ±0.04	0.72 ±0.04	0.71 ±0.04	0.82 H ±0.14
			Presence of nipple (LD 12)	Male	0/120	0/120	0/120	0/112	0/112
		Female		120/120	119/119	119/119	112/112	112/112	98/98

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

Summary of results (continued - 4)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg/day}$)			0	0.4	2	10	50	2,000,000
Number of litters			15	15	15	14	14	12
F1	Reflex responses (day)	Male	Surface righting	1.2 ± 0.4	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.5	1.2 ± 0.5
			Cliff aversion	4.2 ± 0.7	4.3 ± 0.8	4.5 ± 0.9	3.9 ± 0.5	4.2 ± 0.6
			Negative geotaxis	7.7 ± 1.1	7.5 ± 1.1	7.5 ± 1.2	8.3 ± 0.8	7.8 ± 1.2
		Female	Surface righting	1.4 ± 0.7	1.4 ± 0.6	1.4 ± 0.6	1.1 ± 0.4	1.3 ± 0.6
			Cliff aversion	4.2 ± 0.9	4.5 ± 0.9	4.6 ± 1.0	4.0 ± 0.8	4.3 ± 0.7
	Postnatal development (day)	Male	Negative geotaxis	7.8 ± 1.2	7.6 ± 1.1	7.9 ± 1.1	8.2 ± 1.1	8.2 ± 1.1
			Incisor eruption	10.3 ± 0.7	10.1 ± 0.6	9.8 ± 1.8	10.5 ± 0.6	10.4 ± 0.8
			Ear opening	13.0 ± 0.7	13.1 ± 0.3	13.1 ± 0.3	13.3 ± 0.5	13.0 ± 0.4
		Female	Eye opening	17.7 ± 0.7	17.5 ± 0.6	17.7 ± 0.5	17.6 ± 0.5	17.6 ± 0.6
			Incisor eruption	10.2 ± 0.7	10.2 ± 0.8	10.3 ± 0.5	10.4 ± 0.5	10.4 ± 0.8
			Ear opening	13.0 ± 0.7	13.1 ± 0.4	13.1 ± 0.3	13.1 ± 0.4	13.1 ± 0.5
			Eye opening	17.8 ± 0.7	17.5 ± 0.5	17.7 ± 0.6	17.6 ± 0.5	17.7 ± 0.6

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).

Summary of results (continued - 5)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg/day}$)			0	0.4	2	10	50	2,000,000
Number of litters			15	15	15	14	14	12
Number of animals			LD 21	Male	32	29	27	26
F 1	Male	Gross findings	Hydro-nephrosis	0	0	1	0	0
		Absolute organ weights	Thymus (mg)	201.5 ±33.1	205.0 ±21.9	203.2 ±23.6	197.3 ±30.3	193.8 ±28.2
			Adrenal (mg)	10.0 ±2.0	10.0 ±1.8	10.0 ±1.7	10.3 ±1.7	9.6 ±1.9
			Pituitary (mg)	1.6 ±0.4	1.7 ±0.7	2.0 ±1.0	1.5 ±0.7	1.6 ±0.5
			Thyroid (mg)	6.4 ±1.9	5.9 ±2.1	6.8 ±1.9	6.4 ±2.2	5.7 ±1.9
			Liver (mg)	1760.4 ±268.2	1790.9 ±195.1	1781.6 ±163.8	1802.4 ±204.8	1751.7 ±200.3
			Kidney (mg)	526.7 ±55.7	538.1 ±51.5	543.4 ±98.3	534.5 ±54.7	527.1 ±53.2
			Testis (mg)	183.1 ±24.0	190.4 ±19.3	186.2 ±18.0	183.2 ±24.9	178.0 ±21.7
			Epididymis (mg)	35.5 ±4.3	35.4 ±5.0	36.0 ±5.2	35.0 ±2.9	34.3 ±4.4
			Prostate (mg)	33.4 ±8.3	33.2 ±8.6	33.3 ±8.3	29.9 ±7.1	30.2 ±7.2
	Female	Relative organ weights	Seminal vesicle + Coagulation gland (mg)	14.5 ±3.2	14.9 ±3.6	15.4 ±4.0	15.6 ±4.2	14.1 ±3.9
			Levator ani + Bulbocavernosus muscles (mg)	33.9 ±6.2	32.9 ±4.1	34.1 ±3.5	33.1 ±7.0	32.9 ±6.7
			Thymus (%)	0.4288 ±0.0570	0.4161 ±0.0426	0.40165 ±0.0457	0.4035 ±0.0458	0.4094 ±0.0483
			Adrenal (%)	0.0214 ±0.0044	0.0203 ±0.0036	0.0207 ±0.0026	0.0211 ±0.0035	0.0202 ±0.0039
			Pituitary (%)	0.0034 ±0.0011	0.0035 ±0.0015	0.0039 ±0.0018	0.0031 ±0.0015	0.0035 ±0.0013
			Thyroid (%)	0.0139 ±0.0051	0.0121 ±0.0041	0.0140 ±0.0033	0.0132 ±0.0048	0.0122 ±0.0041
			Liver (%)	3.7266 ±0.2779	3.6504 ±0.1665	3.6522 ±0.2176	3.6878 ±0.2010	3.6962 ±0.2200
			Kidney (%)	1.1208 ±0.0661	1.0952 ±0.0456	1.1254 ±0.1632	1.0949 ±0.0571	1.1139 ±0.0648
			Testis (%)	0.3895 ±0.0392	0.3874 ±0.0241	0.3863 ±0.0285	0.3751 ±0.0383	0.3756 ±0.0283
			Epididymis (%)	0.0758 ±0.0084	0.0728 ±0.0109	0.0756 ±0.0107	0.0720 ±0.0067	0.0726 ±0.0083
			Prostate (%)	0.0723 ±0.0227	0.0671 ±0.0174	0.0691 ±0.0164	0.0612 ±0.0134	0.0635 ±0.0131
			Seminal vesicle + Coagulation gland (%)	0.0313 ±0.0085	0.0305 ±0.0069	0.0319 ±0.0081	0.0322 ±0.0094	0.0299 ±0.0083
			Levator ani + Bulbocavernosus muscles (%)	0.0729 ±0.0168	0.0675 ±0.0080	0.0708 ±0.0062	0.0681 ±0.0146	0.0701 ±0.0160

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

Summary of results (continued - 6)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg}/\text{day}$)			0	0.4	2	10	50	2,000,000
Number of litters			15	15	15	14	14	12
Number of animals			LD 21	Female	28	30	29	29
F1	Female	Gross findings	Hydro-nephrosis	0	0	1	0	1
		Absolute organ weights	Thymus (mg)	195.1 ± 32.0	195.3 ± 23.1	201.3 ± 28.5	203.9 ± 21.2	190.9 ± 26.6
			Adrenal (mg)	13.4 ± 3.2	13.8 ± 2.3	13.1 ± 2.0	13.5 ± 1.6	13.8 ± 2.3
			Pituitary (mg)	1.5 ± 0.6	1.8 ± 0.7	1.7 ± 0.7	1.6 ± 0.5	1.6 ± 0.6
			Thyroid (mg)	6.4 ± 2.4	6.8 ± 2.7	5.9 ± 2.5	6.0 ± 1.6	6.4 ± 1.9
			Liver (mg)	1643.9 ± 226.6	1669.3 ± 139.4	1648.9 ± 183.0	1770.3 H ± 174.4	1694.5 ± 171.7
			Kidney (mg)	496.4 ± 60.2	501.2 ± 45.5	500.9 ± 65.1	522.9 ± 50.5	510.1 ± 57.5
		Relative organ weights	Ovary (mg)	5.6 ± 2.2	6.8 ± 2.8	6.5 ± 2.2	6.4 ± 1.7	5.9 ± 2.3
			Uterus (mg)	29.0 ± 5.4	28.9 ± 4.9	28.5 ± 5.0	28.9 ± 4.9	28.5 ± 4.8
			Thymus (%)	0.4418 ± 0.0498	0.4328 ± 0.0395	0.4443 ± 0.0554	0.4343 ± 0.0353	0.4205 ± 0.0447
			Adrenal (%)	0.0304 ± 0.0062	0.0304 ± 0.0047	0.0289 ± 0.0038	0.0288 ± 0.0034	0.0305 ± 0.0044
			Pituitary (%)	0.0035 ± 0.0012	0.0041 ± 0.0015	0.0039 ± 0.0015	0.0035 ± 0.0011	0.0035 ± 0.0012
			Thyroid (%)	0.0146 ± 0.0055	0.0152 ± 0.0059	0.0132 ± 0.0051	0.0127 ± 0.0036	0.0143 ± 0.0044
			Liver (%)	3.7246 ± 0.1422	3.6966 ± 0.1783	3.6330 ± 0.2144	3.7658 ± 0.1753	3.7404 ± 0.2062
		Relative organ weights	Kidney (%)	1.1273 ± 0.0440	1.1101 ± 0.0516	1.1075 ± 0.1345	1.1152 ± 0.0679	1.1236 ± 0.0716
			Ovary (%)	0.0127 ± 0.0046	0.0148 ± 0.0060	0.0144 ± 0.0049	0.0137 ± 0.0033	0.0130 ± 0.0047
			Uterus (%)	0.0664 ± 0.0130	0.0639 ± 0.0101	0.0627 ± 0.0104	0.0617 ± 0.0102	0.0624 ± 0.0085
								0.0749 H ± 0.0098

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

Summary of results (continued - 7)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg}/\text{day}$)			0	0.4	2	10	50	2,000,000
Number of litters			15	15	15	14	14	12
Number of animals	LD 21	Male	32	29	29	27	27	26
		Female	28	30	30	29	29	17
F1	Male	Histopathological findings	Testis : Decrease in number of germ cells with elongated nuclear cells					
		(2+)	0/32	0/29	0/29	0/27	0/27	4/26
		(3+)	0/32	0/29	0/29	0/27	0/27	4/26
		Significant difference						<u>H</u>
		Normal organs: Thymus, Adrenal, Pituitary, Thyroid, Liver, Kidney, Epididymis, Prostate, Seminal vesicle, Coagulation gland, Levator ani muscle, Bulbocavernosus muscle						
		Hormone concentrations ¹⁾	Testosterone (ng/mL) ± 0.05	0.10 ± 0.02	0.09 ± 0.02	0.08 ± 0.02	0.09 ± 0.03	0.07 ± 0.02
			FSH (ng/mL) ± 2.82	7.40 ± 2.59	7.29 ± 2.59	8.21 ± 3.34	8.34 ± 3.48	6.78 ± 3.51
			LH (ng/mL) ± 0.84	1.42 ± 0.29	1.13 ± 0.29	1.37 ± 0.46	1.52 ± 1.05	1.16 ± 0.34
	Female	Histopathological findings	Normal organs: Thymus, Adrenal, Pituitary, Thyroid, Liver, Kidney, Uterus, Ovary, Vagina					
		Hormone concentrations	FSH (ng/mL) ± 7.60	26.27 ± 6.66	21.61 ± 6.66	22.61 ± 6.75	27.53 ± 7.80	29.81 ± 22.40
			LH (ng/mL) ± 0.037	1.48 ± 1.54	1.85 ± 1.54	1.44 ± 0.67	1.65 ± 0.74	1.47 ± 0.46
			Estradiol (pg/mL) ± 17.6	51.1 ± 12.2	43.7 ± 12.2	47.7 ± 23.6	47.2 ± 14.5	41.9 ± 17.9
			Prolactin (ng/mL)	-	-	-	-	-

1) : Data lower than detection limit (Testosterone : 0.05ng/mL, FSH : 1.6ng/mL, LH : 0.8ng/mL, Estradiol:2.5pg/mL, Prolactin:0.78ng/mL) were excluded.

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).

Summary of results (continued - 8)

Generation			Dam: F0 Offspring: F1						
Dose ($\mu\text{g}/\text{kg}/\text{day}$)			0	0.4	2	10	50	2,000,000	
Number of litters			15	15	15	14	14	12	
Number of animals			Male	30	30	28	28	24	
			Female	30	30	28	28	23	
F 1	Body weights (g)	Male	Day 28	84.7 ± 8.9	83.9 ± 8.1	83.8 ± 5.8	85.5 ± 8.7	84.0 ± 6.3	67.6 <u>L</u> ± 10.3
			Day 35	141.1 ± 12.7	140.2 ± 10.8	140.4 ± 7.7	144.2 ± 12.3	141.0 ± 9.7	114.6 <u>L</u> ± 15.8
			Day 42	201.2 ± 16.6	201.3 ± 12.5	200.8 ± 8.7	206.1 ± 13.1	201.0 ± 12.5	166.1 <u>L</u> ± 20.2
			Day 49	260.8 ± 20.1	263.3 ± 15.0	263.5 ± 10.8	268.2 ± 17.5	262.4 ± 17.3	217.6 <u>L</u> ± 26.4
			Day 56	325.1 ± 25.4	326.4 ± 17.1	329.2 ± 13.1	331.9 ± 19.7	325.9 ± 20.6	274.0 <u>L</u> ± 31.4
			Day 63	373.6 ± 25.3	370.5 ± 21.5	376.7 ± 16.2	377.3 ± 21.7	374.8 ± 22.2	322.7 <u>L</u> ± 34.3
			Day 70	406.8 ± 24.7	404.5 ± 18.2	412.2 ± 20.2	408.3 ± 25.2	410.1 ± 24.2	357.4 <u>L</u> ± 34.2
	Female		Day 28	76.3 ± 8.5	77.2 ± 6.6	77.4 ± 3.8	79.1 ± 6.5	76.0 ± 8.3	63.1 <u>L</u> ± 8.9
			Day 35	122.2 ± 12.1	122.7 ± 7.6	123.4 ± 5.5	123.7 ± 10.2	121.4 ± 9.7	102.3 <u>L</u> ± 14.1
			Day 42	159.4 ± 14.0	161.3 ± 8.1	161.8 ± 7.1	162.5 ± 11.8	162.2 ± 10.1	138.5 <u>L</u> ± 16.3
			Day 49	189.3 ± 17.8	192.9 ± 9.1	192.8 ± 8.5	193.8 ± 14.3	192.8 ± 10.7	168.0 <u>L</u> ± 19.3
			Day 56	217.4 ± 20.8	220.0 ± 10.6	217.6 ± 12.7	217.9 ± 18.1	217.6 ± 12.5	194.5 <u>L</u> ± 21.6
			Day 63	237.3 ± 21.5	239.3 ± 11.2	240.5 ± 10.9	241.3 ± 19.8	241.9 ± 13.0	218.7 <u>L</u> ± 22.3
			Day 70	253.8 ± 21.6	255.7 ± 13.0	258.0 ± 13.5	257.6 ± 18.5	259.8 ± 14.1	237.2 <u>L</u> ± 22.7

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).

Summary of results (continued - 9)

Generation			Dam: F0 Offspring: F1						
Dose (µg/kg/day)			0	0.4	2	10	50	2,000,000	
Number of litters			15	15	15	14	14	12	
Number of animals			Male	30	30	28	28	24	
			Female	30	30	28	28	23	
F1	Body weight gains (g)	Male	Day 28-35	56.4 ±4.8	56.3 ±3.6	56.7 ±3.1	58.6 ±5.0	57.0 ±4.4	47.1 L ±6.0
			Day 28-42	116.4 ±9.5	117.4 ±5.9	117.1 ±6.0	120.5 ±6.9	117.0 ±7.7	98.5 L ±10.5
			Day 28-49	176.1 ±13.4	179.4 ±9.0	179.7 ±8.5	182.7 ±11.5	178.4 ±13.0	150.1 L ±17.0
			Day 28-56	240.3 ±18.7	242.5 ±11.7	245.5 ±11.2	246.3 ±13.7	241.9 ±16.3	206.5 L ±22.4
			Day 28-63	288.9 ±19.6	286.7 ±17.4	292.9 ±15.7	291.7 ±16.7	290.8 ±18.8	255.2 L ±25.7
			Day 28-70	322.1 ±20.4	320.6 ±15.1	328.4 ±18.6	322.8 ±21.2	326.1 ±21.0	289.9 L ±26.6
	Female	Female	Day 28-35	45.8 ±5.4	45.5 ±3.4	46.0 ±3.7	44.6 ±5.1	45.5 ±3.9	39.2 L ±5.9
			Day 28-42	83.1 ±8.4	84.1 ±6.0	84.4 ±6.8	83.4 ±7.6	86.2 ±6.5	75.5 L ±9.2
			Day 28-49	113.0 ±12.1	115.6 ±7.8	115.4 ±8.1	114.7 ±10.7	116.8 ±6.7	104.9 L ±12.5
			Day 28-56	141.0 ±15.8	142.8 ±9.8	140.2 ±13.1	138.8 ±15.4	141.6 ±9.1	131.4 L ±14.3
			Day 28-63	161.0 ±17.2	162.1 ±10.9	163.1 ±10.9	162.2 ±16.6	165.9 ±9.7	155.7 ±15.8
			Day 28-70	177.5 ±17.3	178.5 ±12.5	180.6 ±13.6	178.6 ±15.5	183.9 ±11.0	174.2 ±16.6

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).

Summary of results (continued - 10)

Generation				Dam: F0 Offspring: F1					
Dose (µg/kg/day)				0	0.4	2	10	50	2,000,000
Number of litters				15	15	15	14	14	12
F 1	Clinical findings	Male	-	-	-	-	-	-	-
		Female	Hemophthalmia • @exophthalmos	0	0	1	0	0	0
	Sexual development (day)	Male	Preputial separation	45.2 ±1.8	46.0 ±1.6	46.0 ±1.5	45.6 ±2.1	46.2 H ±1.4	49.8 <u>H</u> ±2.8
		Female	Vaginal opening	29.6 ±1.3	30.5 ±1.4	29.9 ±1.2	30.5 ±1.6	30.1 ±1.4	30.5 ±1.5
	Motor activity (8-9 weeks old) (count)	Male	Horizontal movement (short)	8009 ±1823	7326 ±2109	8677 ±1961	7169 ±1197	8436 ±2190	7876 ±1787
			Horizontal movement (long)	4966 ±1250	4578 ±1607	5603 ±1532	4327 ±839	5363 ±1659	4831 ±1271
			Vertical movement	67 ±37	64 ±33	72 ±23	67 ±17	68 ±37	75 ±22
		Female	Horizontal movement (short)	11054 ±2587	11003 ±2724	10861 ±1762	10220 ±1802	9981 ±2363	8913 ±1283
			Horizontal movement (long)	7645 ±2016	7448 ±2074	7453 ±1323	6825 ±1378	6786 ±1861	5929 L ±924
			Vertical movement	113 ±45	108 ±32	103 ±32	92 ±22	92 ±38	74 L ±23

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.

Summary of results (continued - 11)

Generation		Dam: F0 Offspring: F1						
Dose ($\mu\text{g}/\text{kg}/\text{day}$)		0	0.4	2	10	50	2,000,000	
Number of litters		15	15	15	14	14	12	
Number of animals		Female	30	30	28	28	23	
F1	Reproductive performance	Estrus cycle length (day)	4.13 ±0.07	4.15 ±0.12	4.15 ±0.08	4.25 ±0.45	4.15 ±0.25	4.13 ±0.15
		Pairing days until copulation	3.20 ±2.58	2.97 ±2.22	2.44 ±1.42	2.89 ±1.97	2.12 ±1.53	3.00 ±1.91
		Copulation index (%)	90.0	100.0	90.0	100.0	92.9	95.7
		Fertility index (%)	96.3	100.0	100.0	100.0	100.0	86.4
		Number of corpora lutea	16.9 ±1.4	17.4 ±1.5	17.6 ±2.0	17.3 ±1.3	17.6 ±1.3	16.2 ±1.8
		Number of implantation sites	14.4 ±2.0	15.8 H ±1.7	15.6 ±1.8	14.8 ±3.1	15.5 ±2.7	13.7 ±1.8
	Body weight (g)	Implantation loss (%)	5.4 ±5.8	5.8 ±5.7	5.5 ±6.7	5.0 ±4.9	10.3 ±18.0	4.8 ±4.0
		GD 0	256.8 ±25.5	257.6 ±14.2	258.4 ±14.8	257.6 ±19.9	258.8 ±14.6	236.8 L ±24.5
		GD 7	294.8 ±28.5	297.1 ±16.1	297.7 ±16.3	297.4 ±20.5	297.6 ±17.1	273.8 L ±25.0
		GD 13	326.6 ±31.3	330.2 ±23.9	332.9 ±19.0	332.6 ±21.6	334.2 ±20.9	305.3 L ±27.3
	Body weight gains (g)	GD 0-7	38.0 ±7.4	39.5 ±7.2	39.3 ±6.8	39.8 ±7.5	38.9 ±8.0	37.0 ±5.7
		GD 7-13	31.7 ±8.2	33.1 ±17.0	35.2 ±6.8	35.1 ±8.5	36.6 ±7.1	31.5 ±5.9

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).

Summary of results (continued - 12)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg}/\text{day}$)			0	0.4	2	10	50	2,000,000
Number of litters			15	15	15	14	14	12
Number of animals		Female	30	30	30	28	28	23
F₁	Female	Gross findings	Hydro-nephrosis	0	1	0	0	0
			Eye: red	0	0	1	0	0
		Absolute organ weights	Thymus (mg)	539.1 ±89.5	522.8 ±81.2	583.3 ±126.0	541.2 ±83.0	555.7 ±90.7
			Adrenal (mg)	68.7 ±9.9	73.4 ±12.9	72.2 ±8.7	73.8 ±7.3	73.6 ±10.6
			Pituitary (mg)	9.5 ±2.1	9.8 ±1.8	9.9 ±1.4	9.9 ±1.2	9.5 ±1.4
			Thyroid (mg)	19.1 ±4.9	18.2 ±3.6	19.5 ±3.7	18.5 ±3.4	18.9 ±5.1
			Liver (mg)	17954.9 ±2781.0	18592.2 ±1764.4	18084.4 ±2569.8	19495.6 ±1832.0	19141.7 ±2129.7
			Kidney (mg)	2275.8 ±271.9	2587.6 ±1680.2	2325.6 ±162.0	2279.2 ±165.4	2247.7 ±183.1
			Ovary (mg)	116.5 ±13.9	122.8 ±10.7	123.0 ±9.7	119.9 ±9.9	122.9 ±12.4
			Uterus (mg)	2129.3 ±828.0	2501.7 H ±246.0	2325.6 ±732.6	2394.1 ±479.0	2260.4 ±662.7
		Relative organ weights	Thymus (%)	0.1655 ±0.0264	0.1584 ±0.0215	0.1768 ±0.0383	0.1622 ±0.0244	0.1672 ±0.0284
			Adrenal (%)	0.0210 ±0.0023	0.0223 ±0.0043	0.0219 ±0.0024	0.0221 ±0.0023	0.0221 ±0.0029
			Pituitary (%)	0.0029 ±0.0006	0.0030 ±0.0007	0.0030 ±0.0004	0.0030 ±0.0003	0.0029 ±0.0004
			Thyroid (%)	0.0059 ±0.0014	0.0055 ±0.0011	0.0059 ±0.0011	0.0055 ±0.0011	0.0057 ±0.0016
			Liver (%)	5.4801 ±0.6130	5.6398 ±0.4843	5.4569 ±0.5519	5.8351 H ±0.4097	5.7384 ±0.5015
			Kidney (%)	0.6976 ±0.0683	0.7927 ±0.5554	0.6727 ±0.0383	0.6825 ±0.0324	0.6740 ±0.0313
			Ovary (%)	0.0359 ±0.0044	0.0373 ±0.0035	0.0373 ±0.0030	0.0359 ±0.0028	0.0369 ±0.0032
			Uterus (%)	0.6489 ±0.2349	0.7613 ±0.0956	0.6998 ±0.2145	0.7168 ±0.1348	0.6786 ±0.2000
Histopathological findings		Normal organs: Thymus, Adrenal, Pituitary, Thyroid, Liver, Kidney, Uterus, Ovary, Vagina						

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).

Summary of results (continued - 13)

Generation			Dam: F0 Offspring: F1					
Dose ($\mu\text{g}/\text{kg}/\text{day}$)			0	0.4	2	10	50	2,000,000
Number of litters			15	15	15	14	14	12
Number of animals		Male	30	30	30	28	28	24
F1	Male	Gross findings	Hydro-nephrosis	0	0	2	1	1
		Absolute organ weights	Thymus (mg)	597.9 ±120.3	605.0 ±119.4	651.6 ±150.1	556.3 ±83.9	594.0 ±91.8
			Adrenal (mg)	57.7 ±4.9	55.5 ±6.0	56.0 ±6.6	55.6 ±6.2	56.3 ±7.7
			Pituitary (mg)	10.5 ±1.6	10.6 ±1.4	10.1 ±1.3	10.3 ±1.1	10.2 ±1.2
			Thyroid (mg)	21.0 ±2.9	19.9 ±3.0	20.4 ±2.9	20.4 ±3.4	19.3 ±3.2
			Liver (mg)	21060.4 ±2088.7	20625.1 ±1830.8	20757.5 ±2892.5	20185.9 ±2066.5	20994.4 ±2142.9
			Kidney (mg)	3669.5 ±256.3	3637.9 ±300.4	3624.1 ±231.4	3666.2 ±290.0	3705.0 ±328.8
			Testis (mg)	2886.3 ±144.8	2958.7 H ±190.3	2974.2 H ±162.4	2916.8 ±158.8	2963.9 H ±158.7
			Epididymis (mg)	1120.7 ±56.8	1131.0 ±63.1	1125.6 ±43.9	1139.2 ±65.6	1135.8 ±64.7
			Prostate (mg)	1302.2 ±155.2	1276.9 ±177.4	1315.6 ±161.4	1307.9 ±154.0	1303.9 ±133.9
	Female	Absolute organ weights	Seminal vesicle + Coagulation gland (mg)	1703.6 ±183.0	1721.2 ±203.4	1767.8 ±248.9	1831.7 ±185.9	1782.0 ±148.7
			Levator ani + Bulbocavernosus muscles (mg)	1040.8 ±82.4	1045.2 ±79.0	1040.2 ±84.8	1066.7 ±87.6	1049.7 ±97.2
		Relative organ weights	Thymus (%)	0.1275 ±0.0260	0.1285 ±0.0247	0.1372 ±0.0298	0.1183 ±0.0148	0.1253 ±0.0147
			Adrenal (%)	0.0123 ±0.0012	0.0118 ±0.0011	0.0118 ±0.0014	0.0119 ±0.0013	0.0119 ±0.0014
			Pituitary (%)	0.0022 ±0.0003	0.0022 ±0.0003	0.0021 ±0.0003	0.0022 ±0.0002	0.0022 ±0.0003
			Thyroid (%)	0.0045 ±0.0006	0.0042 ±0.0006	0.0043 ±0.0006	0.0043 ±0.0007	0.0041 ±0.0007
			Liver (%)	4.4744 ±0.3195	4.3740 ±0.2777	4.3567 ±0.4269	4.2910 ±0.2565	4.4389 ±0.2920
			Kidney (%)	0.7800 ±0.0284	0.7720 ±0.0516	0.7639 ±0.0427	0.7805 ±0.0353	0.7836 ±0.0391
			Testis (%)	0.6151 ±0.0399	0.6287 ±0.0424	0.6275 ±0.0398	0.6266 ±0.0405	0.6261 ±0.0432
			Epididymis (%)	0.2387 ±0.0126	0.2403 ±0.0133	0.2376 ±0.0150	0.2431 ±0.0163	0.2409 ±0.0139
			Prostate (%)	0.2773 ±0.0324	0.2710 ±0.0367	0.2778 ±0.0365	0.2794 ±0.0353	0.2772 ±0.0342
			Seminal vesicle + Coagulation gland (%)	0.3626 ±0.0359	0.3655 ±0.0420	0.3725 ±0.0499	0.3908 ±0.0394	0.3786 ±0.0387
			Levator ani + Bulbocavernosus muscles (%)	0.2215 ±0.0150	0.2219 ±0.0140	0.2195 ±0.0198	0.2274 ±0.0162	0.2225 ±0.0198

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).

Summary of results (continued - 14)

Generation		Dam: F0 Offspring: F1						
Dose (µg/kg/day)		0	0.4	2	10	50	2,000,000	
Number of litters		15	15	15	14	14	12	
Number of animals		Male	30	30	28	28	24	
F1	Hormone concentrations	Testosterone (ng/mL)	1.90 ±0.50	2.18 ±0.86	2.16 ±0.71	2.54 ±0.92	2.37 ±0.91	2.32 ±0.89
		FSH (ng/mL)	10.69 ±1.46	10.50 ±1.81	11.28 ±1.86	11.72 ±1.06	11.90 ±2.31	14.97 H ±11.96
		LH (ng/mL)	2.17 ±0.52	2.01 ±0.42	2.00 ±0.45	2.03 ±0.43	2.18 ±0.52	2.28 ±0.51
	Histopathological findings	Testis : Tubular atrophy: focal						
		(+)	0/30	0/30	0/30	0/28	0/28	2/24
		(2+)	0/30	0/30	0/30	0/28	0/28	4/24
		(3+)	0/30	0/30	0/30	0/28	0/28	2/24
		Significant difference						H
	Testis : Interstitial cell hyperplasia							
	(+)	0/30	0/30	0/30	0/28	0/28	2/24	
	Epididymis	Debris of spermatic elements						
		(+)	0/30	0/30	0/30	0/28	0/28	6/24 H
Normal organs:								
Thymus, Adrenal, Pituitary, Thyroid, Liver, Kidney, Prostate, Seminal vesicle, Coagulation gland, Levator ani muscle, Bulbocavernosus muscle								
Sperm examination	Sperm examination	Motility (%)	88 ±5	90 ±4	89 ±5	91 ±3	90 ±4	84 ±12
		Progressive (%)	71 ±6	73 ±6	71 ±7	71 ±9	71 ±9	64 ±13
		Path velocity (µm/sec)	135.4 ±11.5	134.1 ±10.6	131.3 ±12.1	138.4 ±12.4	133.5 ±11.9	130.6 ±11.9
		Straight line velocity (µm/sec)	87.9 ±8.7	86.9 ±6.4	85.0 ±7.2	87.4 ±6.0	85.2 ±6.4	81.9 L ±7.3
		Curvilinear velocity (µm/sec)	282.0 ±27.9	276.8 ±27.0	270.4 ±25.1	284.8 ±25.2	271.5 ±26.7	268.5 ±25.0
		Amplitude of lateral head displacement (µm)	19.1 ±1.4	19.0 ±1.5	18.6 ±1.6	19.5 ±1.8	18.7 ±1.6	18.9 ±1.9
		Beat cross frequency (Hz)	23.7 ±2.7	23.3 ±2.2	23.4 ±2.4	23.0 ±1.9	23.6 ±1.8	23.5 ±2.4
		Straightness (%)	67 ±4	66 ±3	66 ±4	65 ±5	66 ±4	65 ±6
		Linearity (%)	33 ±2	33 ±2	33 ±2	32 ±3	33 ±2	32 ±3
		Elongation (%)	20 ±2	21 ±2	21 ±3	21 ±2	21 ±2	20 ±3
		Area (µm²)	358.2 ±34.5	358.4 ±47.5	353.1 ±61.2	357.7 ±49.9	356.1 ±60.5	346.2 ±48.9
		Number of epidermal sperm ($\times 10^6/g$ cauda)	597.3 ±102.3	628.2 ±103.3	586.6 ±97.7	601.6 ±74.8	590.4 ±80.6	496.8 ±169
		Daily sperm production ($\times 10^6/g$ testis)	22.9 ±2.3	22.1 ±1.9	22.1 ±1.6	21.5 ±2.4	22.1 ±1.9	21.9 ±3.0

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).