

Table 27 (continued) Autopsy findings in F0 and F1 parental female rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Item	HBCD (ppm)															
		Control				150				1500				15000			
		A	B	C	T	A	B	C	T	A	B	C	T	A	B	C	T
F1	Number of animals examined	22	1	1	24	22	1	1	24	20	1	3	24	13	8	3	24
	Number of animals with abnormal findings	2	0	0	2	2	0	0	2	4	0	0	4	0	0	3	3
	Findings <sup>a</sup>																
	Incisor: Malocclusion	0	0	0	0	0	0	0	0	2	0	0	2	0	0	0	0
	Nasal bone: Deformity	0	0	0	0	0	0	0	0	2	0	0	2	0	0	0	0
	Thyroid: Aplasia (unilateral)	1	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0
	Glandular stomach: Black patch, mucosa	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
	Liver: Hepatodiaphragmatic nodule	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Kidney: Dilatation, renal pelvis	1	0	0	1	1	0	0	1	1	0	0	1	0	0	0	0
	Deformity	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
	Fine white granule, renal pelvis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Uterus: Dilatation, lumen	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Retention, yellowish white fluid	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Vagina: Dilatation, lumen	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Retention, yellowish white fluid	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1

Statistical analyses were made based on the total number of animals examined.

Fate: A, animals that had weanlings; B, animals that did not produce viable pups or weanlings; C, animals that were not pregnant; T, total (A+B+C).

a: Values represent the number of animals that showed abnormal findings.

Table 28 Absolute and relative organ weights in F0 and F1 parental male rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Group	Number of animals		Body weight		Brain			Pituitary gland		Thyroid <sup>a</sup>		Thymus		Liver		Kidney <sup>a</sup>		Spleen	
				g	g	g	%	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	g	%	g	%	mg	10 <sup>-3</sup> %	
F0	Control	24	Mean	566.0	2.18	0.386	13.2	2.33	24.2	4.28	323	57.4	18.31	3.23	3.51	0.619	848	150		
			S.D.	36.5	0.09	0.022	1.6	0.20	3.8	0.71	88	16.7	2.24	0.26	0.36	0.044	136	19		
	HBCD 150 ppm	24	Mean	584.2	2.17	0.374	13.4	2.30	24.3	4.17	305	52.3	19.50	3.33	3.55	0.610	828	142		
			S.D.	44.3	0.08	0.026	1.6	0.26	4.5	0.77	82	14.0	2.29	0.24	0.27	0.046	109	21		
	HBCD 1500 ppm	24	Mean	597.7 *	2.18	0.369 <sup>5</sup>	13.2	2.22	24.3	4.09	299	50.3	20.49 *	3.41 *	3.58	0.601	855	143		
			S.D.	55.7	0.08	0.041	1.5	0.25	4.2	0.73	64	10.6	3.24	0.31	0.43	0.068	160	25		
	HBCD 15000 ppm	22	Mean	572.5	2.15	0.378	12.6	2.20	29.6 **	5.17 **	315	54.8	23.27 **	4.06 **	3.65	0.640	843	148		
			S.D.	43.6	0.08	0.027	1.2	0.15	5.9	1.00	71	10.6	2.34	0.22	0.27	0.059	248	46		
	F1	Control	24	Mean	605.6	2.19	0.363	13.1	2.16	24.3	4.03	344	56.7	19.83	3.27	3.74	0.618	885	146	
				S.D.	41.9	0.08	0.028	1.5	0.22	4.9	0.79	72	10.8	2.06	0.18	0.34	0.037	168	26	
		HBCD 150 ppm	24	Mean	576.7	2.22	0.388 *	13.6	2.37 **	24.2	4.22	305	52.8	19.36	3.34	3.59	0.625	840	146	
				S.D.	59.0	0.08	0.036	1.6	0.23	3.0	0.63	92	14.3	3.13	0.26	0.36	0.052	147	22	
HBCD 1500 ppm		22	Mean	613.3	2.18	0.358	13.2	2.17	25.4	4.15	368	59.8	20.73	3.37	3.77	0.619	878	143		
			S.D.	59.2	0.09	0.034	1.4	0.22	4.7	0.72	100	14.4	3.01	0.25	0.33	0.074	163	22		
HBCD 15000 ppm		24	Mean	584.4	2.11 **	0.363	13.3	2.28	29.0 <sup>55</sup>	4.96 **	341	58.3	22.61 **	3.86 **	3.77	0.645	851	146		
			S.D.	54.9	0.07	0.032	1.2	0.23	5.6	0.87	76	11.1	3.04	0.28	0.58	0.080	113	17		

(to be continued)

a: Values represent the total weights of the organs of both sides.

\*: Significantly different from the control at  $p \leq 0.05$  by Dunnett's test.

\*\* : Significantly different from the control at  $p \leq 0.01$  by Dunnett's test.

<sup>5</sup>: Significantly different from the control at  $p \leq 0.05$  by Mann-Whitney U-test.

<sup>55</sup>: Significantly different from the control at  $p \leq 0.01$  by Mann-Whitney U-test.

Table 28 (continued) Absolute and relative organ weights in F0 and F1 parental male rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Group	Number of animals		Adrenal <sup>a</sup>		Testis <sup>a</sup>		Epididymis <sup>a</sup>		Seminal vesicle		Prostate		
				mg	10 <sup>-3</sup> %	g	%	mg	10 <sup>-3</sup> %	g	%	mg	10 <sup>-3</sup> %	
F0	Control	24	Mean	53.4	9.4	3.34	0.592	1300	230	2.39	0.423	734	130	
			S.D.	9.6	1.4	0.32	0.065	172	33	0.29	0.056	109	21	
	HBCD 150 ppm	24	Mean	55.1	9.5	3.38	0.582	1268	218	2.30	0.394	722	124	
			S.D.	7.9	1.4	0.64	0.116	194	35	0.35	0.051	165	28	
	HBCD 1500 ppm	24	Mean	54.8	9.2	3.47	0.585	1299	219	2.20	0.369 **	755	126	
			S.D.	9.2	1.7	0.25	0.066	89	22	0.29	0.044	173	25	
	HBCD 15000 ppm	22	Mean	54.6	9.6	3.29	0.579	1272	224	2.20	0.385 *	735	129	
			S.D.	6.9	1.3	0.36	0.082	115	30	0.28	0.052	144	25	
	F1	Control	24	Mean	59.7	9.9	3.63	0.602	1346	223	2.36	0.391	834	137
				S.D.	11.0	1.6	0.33	0.069	107	24	0.26	0.051	195	28
		HBCD 150 ppm	24	Mean	63.1	10.9	3.52	0.614	1328	232	2.28	0.398	779	135
				S.D.	15.8	2.3	0.27	0.049	104	24	0.22	0.050	217	34
HBCD 1500 ppm		22	Mean	60.3	9.9	3.51	0.576	1282	210	2.33	0.382	803	131	
			S.D.	10.7	1.8	0.35	0.062	109	19	0.29	0.051	175	30	
HBCD 15000 ppm		24	Mean	59.4	10.2	3.45	0.593	1357	234	2.38	0.409	789	135	
			S.D.	6.7	1.1	0.36	0.065	104	23	0.22	0.045	159	22	

a: Values represent the total weights of the organs of both sides.

\*: Significantly different from the control at  $p \leq 0.05$  by Dunnett's test.

\*\* : Significantly different from the control at  $p \leq 0.01$  by Dunnett's test.

Table 29 Absolute and relative organ weights in F0 and F1 parental female rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Group	Number of animals		Body weight g	Brain		Pituitary gland		Thyroid <sup>a</sup>		Thymus		Liver		Kidney <sup>a</sup>		Spleen		
					g	%	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	g	%	g	%	mg	10 <sup>-3</sup> %	
F0	Control	24	Mean	310.5	2.04	0.658	15.6	5.04	19.7	6.38	232	75.2	14.52	4.69	2.44	0.787	588	189	
			S.D.	18.2	0.06	0.043	2.5	0.79	2.3	0.89	38	13.2	1.51	0.52	0.24	0.056	75	19	
	HBCD 150 ppm	21	Mean	309.3	2.04	0.664	16.1	5.21	18.5	5.99	238	77.3	14.66	4.76	2.34	0.759	577	187	
			S.D.	22.7	0.07	0.045	2.2	0.65	4.2	1.27	63	20.9	1.68	0.65	0.18	0.062	83	24	
	HBCD 1500 ppm	20	Mean	304.8	2.04	0.673	16.3	5.37	19.6	6.47	252	82.6	14.82	4.88	2.36	0.777	570	188	
			S.D.	25.8	0.07	0.051	1.8	0.58	3.6	1.32	73	21.3	1.50	0.48	0.21	0.056	89	28	
	HBCD 15000 ppm	17	Mean	313.4	2.00	0.643	15.3	4.90	22.5 <sup>§</sup>	7.20	200	64.4	19.01 **	6.07 **	2.39	0.764	584	187	
			S.D.	24.2	0.07	0.052	1.8	0.46	4.1	1.30	64	21.1	2.16	0.47	0.20	0.045	72	22	
	F1	Control	22	Mean	322.9	2.07	0.645	14.7	4.56	19.3	6.01	250	77.4	13.49	4.18	2.36	0.732	632	195
				S.D.	25.9	0.09	0.045	1.5	0.43	3.3	1.01	62	17.4	1.59	0.42	0.23	0.054	124	33
		HBCD 150 ppm	22	Mean	327.0	2.06	0.634	15.8	4.83	19.8	6.08	233	71.6	14.30	4.39	2.31	0.710	595	183
				S.D.	24.8	0.07	0.053	2.7	0.81	3.5	1.05	62	19.9	1.29	0.44	0.19	0.068	68	24
HBCD 1500 ppm		20	Mean	328.6	2.06	0.630	15.5	4.72	21.5	6.54	276	83.8	14.35	4.38	2.39	0.729	624	190	
			S.D.	20.2	0.08	0.045	1.8	0.59	4.6	1.36	80	21.8	1.41	0.47	0.18	0.070	93	27	
HBCD 15000 ppm		13	Mean	307.8	1.97 **	0.646	14.3	4.62	23.9 **	7.76 **	259	83.9	15.58 **	5.05 **	2.23	0.726	578	188	
			S.D.	30.5	0.06	0.056	3.0	0.68	4.5	1.36	76	22.2	2.38	0.50	0.26	0.051	70	16	

(to be continued)

a: Values represent the total weights of the organs of both sides.

\*\* : Significantly different from the control at  $p \leq 0.01$  by Dunnett's test.

§ : Significantly different from the control at  $p \leq 0.01$  by Mann-Whitney U-test.

65-05

Table 29 (continued) Absolute and relative organ weights in F0 and F1 parental female rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Group	Number of animals		Adrenal <sup>a</sup>		Ovary <sup>a</sup>		Uterus		
				mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	
F0	Control	24	Mean	65.7	21.2	101.9	32.8	959	309	
			S.D.	8.0	2.7	14.9	4.3	154	46	
	HBCD 150 ppm	21	Mean	66.9	21.8	103.1	33.4	960	313	
			S.D.	10.0	3.8	13.2	4.3	151	62	
	HBCD 1500 ppm	20	Mean	69.1	22.7	106.3	35.0	978	323	
			S.D.	9.0	2.5	13.2	4.4	151	57	
	HBCD 15000 ppm	17	Mean	72.5 *	23.2	111.4	35.7	920	296	
			S.D.	8.4	3.0	16.6	5.6	179	66	
	F1	Control	22	Mean	70.8	22.0	102.4	31.8	966	299
				S.D.	10.4	3.1	12.9	4.2	216	64
		HBCD 150 ppm	22	Mean	73.9	22.6	106.4	32.6	913	282
				S.D.	10.5	3.1	13.2	3.9	188	65
HBCD 1500 ppm		20	Mean	74.8	22.8	108.6	33.1	955	291	
			S.D.	9.6	2.8	18.0	5.3	204	64	
HBCD 15000 ppm		13	Mean	71.7	23.3	104.9	34.1	949	313	
			S.D.	13.4	3.5	16.9	4.2	156	69	

a: Values represent the total weights of the organs of both sides.

\*: Significantly different from the control at  $p \leq 0.05$  by Dunnett's test.

Table 30 Histopathological findings in F0 and F1 parental male rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Item	HBCD (ppm)															
		Control				150				1500				15000			
		A	B	C	T	A	B	C	T	A	B	C	T	A	B	C	T
F0	Number of animals examined	24	0	0	24	22	2	0	24	20	4	0	24	18	5 <sup>d</sup>	1	24 <sup>e</sup>
	Findings in organs/tissues examined <sup>a,b,c</sup>																
	Liver: Microgranuloma	11	-	-	11	-	0	-	0	0	1	-	1	11	4	0	15
	Congestion	0	-	-	0	-	0	-	0	0	0	-	0	0	0	1	1
	Fatty change, periportal	1	-	-	1	-	0	-	0	0	0	-	0	0	0	0	0
	Focal necrosis, granulation and mineralization	0	-	-	0	-	0	-	0	1	0	-	1	0	0	0	0
	Thyroid: Small size, follicle	0	-	-	0	0	0	-	0	6	0	-	6*	15	5 <sup>d</sup>	-	20**
	Hypertrophy of follicular cell	0	-	-	0	0	0	-	0	3	0	-	3	1	0	-	1
	Bone marrow: Hyperplasia, myeloid	0	-	-	0	-	0	-	0	-	0	-	0	1	0	0	1
	Testis: Atrophy of seminiferous tubule	1	-	-	1	-	1	-	1	-	0	-	0	0	0	0	0
	Hyperplasia of interstitial cell	0	-	-	0	-	1	-	1	-	0	-	0	0	0	0	0
	Necrosis and retention in spermatid	0	-	-	0	-	0	-	0	-	0	-	0	1	0	0	1
	Decrease in spermatid	0	-	-	0	-	0	-	0	-	0	-	0	2	0	0	2
	Multinucleated giant cell formation	0	-	-	0	-	0	-	0	-	0	-	0	1	0	0	1
	Edema in interstitium	1	-	-	1	-	0	-	0	-	0	-	0	1	0	0	1
	Epididymis: Decrease in spermatozoa	0	-	-	0	-	1	-	1	-	0	-	0	0	0	0	0
	Cell debris in lumen	0	-	-	0	-	1	-	1	-	0	-	0	1	0	0	1
	Hypoplasia	1	-	-	1	-	0	-	0	-	0	-	0	0	0	0	0
	Prostate: Cellular infiltration of inflammatory cell	14	-	-	14	-	1	-	1	-	2	-	2	5	2	1	8
	Pituitary gland: Cyst on pars nervosa	1	-	-	1	-	-	-	-	-	-	-	-	0	0	0	0
	Findings in organs/tissues in which abnormal findings were grossly observed <sup>d</sup>																
	Number of animals examined	0	0	0	0	1	0	0	1	3	0	0	3	2	0	1	3
	Cerebrum: Dilatation of ventricle	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-
	Harderian gland: Purulent inflammation	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1
	Kidney: Dilatation of renal pelvis	-	-	-	-	1	-	-	1	2	-	-	2	1	-	-	1
	Calculus in renal pelvis and hyperplasia of renal pelvic mucosa	-	-	-	-	0	-	-	0	0	-	-	0	1	-	-	1
	Mineralization in papilla	-	-	-	-	1	-	-	1	0	-	-	0	0	-	-	0
	Pyelitis	-	-	-	-	0	-	-	0	1	-	-	1	0	-	-	0
	Cervical adipose tissue: Cellular infiltration of inflammatory cell and edema	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1

(to be continued)

Fate: A, animals that impregnated a female; B, animals that unsuccessfully mated or did not impregnate a female; C, animals that died during the study; T, total (A+B+C).

a: Values represent the number of animals that showed abnormal findings.

b: Statistical analyses were made between the control and 15000 ppm groups, except for the thyroid between the control and all treated groups, based on the total number of animals examined.

c: Organs/tissues examined were the liver, thymus, thyroids, spleen, adrenals, bone marrow (femur), mesenteric lymph node, Peyer's patch, testis, epididymis, seminal vesicles, coagulating glands, prostate, mammary gland and pituitary gland.

d: Including the animal that was euthanized in treatment week 13 because of fracture of the nasal bone due to an accident in the cage.

e: The number of animals examined on the thyroids was 23 due to autolysis.

-: Not applicable.

\*: Significantly different from the control at  $p \leq 0.05$  by Fisher's exact probability test.

\*\* : Significantly different from the control at  $p \leq 0.01$  by Fisher's exact probability test.

Table 30 (continued) Histopathological findings in F0 and F1 parental male rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Generation	Item	HBCD (ppm)															
		Control				150				1500				15000			
		A	B	C	T	A	B	C	T	A	B	C	T	A	B	C	T
F1	Number of animals examined	23	1	0	24	23	1	0	24	19	3	2	24 <sup>d</sup>	21	3	0	24
	Findings in organs/tissues examined <sup>a,b,c</sup>																
	Liver: Microgranuloma	14	1	-	15	-	0	-	0	-	3	1	4	12	1	-	13
	Congestion	0	0	-	0	-	0	-	0	-	0	1	1	0	0	-	0
	Focal fibrosis	0	0	-	0	-	0	-	0	-	0	0	0	0	1	-	1
	Thyroid: Small size, follicle	0	0	-	0	0	0	-	0	2	0	-	2	10	1	-	11**
	Spleen: Atrophy of white pulp	0	0	-	0	-	0	-	0	-	0	1	1	0	0	-	0
	Testis: Atrophy of seminiferous tubule, spermatid granuloma and edema in interstitium	1	0	-	1	-	0	-	0	-	0	-	0	0	0	-	0
	Epididymis: Decrease in spermatozoa and cell debris in lumen	1	0	-	1	-	0	-	0	-	0	-	0	0	0	-	0
	Prostate: Cellular infiltration of inflammatory cell	12	1	-	13	-	1	-	1	-	3	-	3	9	2	-	11
	Pituitary gland: Tubular structure, pars intermedia	0	0	-	0	-	-	-	-	-	-	-	-	1	0	-	1
	Findings in organs/tissues in which abnormal findings were grossly observed <sup>d</sup>																
	Number of animals examined	4	1	0	5	0	0	0	0	6	2	0	8	12	2	0	14
	Eyeball: Deposit of hemosiderin and fibrosis in cornea	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1
	Adhesion between cornea and iris, and mineralization in lens	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1
	Kidney: Dilatation of renal pelvis	2	1	-	3	-	-	-	-	5	2	-	7	10	1	-	11
	Mineralization in renal pelvic mucosa/cortex/cortico-medullary junction	0	0	-	0	-	-	-	-	1	0	-	1	2	1	-	3
	Hyperplasia of renal pelvic mucosa	1	0	-	1	-	-	-	-	2	0	-	2	1	0	-	1
	Dilatation of tubule	0	0	-	0	-	-	-	-	2	0	-	2	1	0	-	1
	Regeneration of tubular epithelium	1	0	-	1	-	-	-	-	2	1	-	3	3	1	-	4
	Cellular infiltration of inflammatory cell in renal pelvic mucosa/cortex	0	1	-	1	-	-	-	-	0	1	-	1	1	0	-	1
	Hyaline droplet in proximal tubular epithelium	3	1	-	4	-	-	-	-	3	2	-	5	11	2	-	13
	Eosinophilic body in proximal tubular epithelium	0	0	-	0	-	-	-	-	3	1	-	4	9	2	-	11
	Fibrosis	0	0	-	0	-	-	-	-	0	0	-	0	1	0	-	1
	Cast, hyaline	0	0	-	0	-	-	-	-	0	1	-	1	1	0	-	1
	Cyst	0	0	-	0	-	-	-	-	0	1	-	1	0	0	-	0

Fate: A, animals that impregnated a female; B, animals that did not impregnate a female; C, animals that died during the study; T, total (A+B+C).

a: Values represent the number of animals that showed abnormal findings.

b: Statistical analyses were made between the control and 15000 ppm groups, except for the thyroid between the control and all treated groups, based on the total number of animals examined.

c: Organs/tissues examined were the liver, thymus, thyroids, spleen, adrenals, bone marrow (femur), mesenteric lymph node, Peyer's patch, testis, epididymis, seminal vesicles, coagulating glands, prostate, mammary gland and pituitary gland.

d: The number of animals examined on the thyroids was 22 due to autolysis.

-: Not applicable.

\*\* : Significantly different from the control at  $p \leq 0.01$  by Fisher's exact probability test.