

Table 17 Locomotor activity count in 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	Locomotor activity count							
			Determination time (minutes)							
			0-10	10-20	20-30	30-40	40-50	50-60	0-60	
F1	Control	10	Mean	196.9	77.6	40.4	13.0	5.4	0.8	334.1
			S.D.	75.8	50.0	44.7	30.9	14.2	1.9	174.2
	HBCD 150 ppm	10	Mean	194.1	70.7	52.1	15.4	2.3	1.3	335.9
			S.D.	112.7	64.3	62.3	42.0	7.3	3.5	213.2
	HBCD 1500 ppm	10	Mean	176.7	84.7	39.5	5.6	9.9	4.9	321.3
			S.D.	93.8	66.2	49.4	12.3	31.3	12.4	198.3
	HBCD 15000 ppm	10	Mean	172.6	35.2	17.7	15.8	3.6	5.0	249.9
			S.D.	101.9	31.8	31.2	22.0	11.4	11.2	130.4

Table 18 Data on learning tests in F1 parental male rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Generation	Group	Number of animals		Time for maze trials (sec)				Number of errors for maze trials			
				Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
F1	Control	10	Mean	8.3	48.7	38.9	27.5	0.1	9.6	6.0	2.0
			S.D.	2.5	19.1	14.8	12.3	0.1	5.0	3.4	1.3
	HBCD 150 ppm	10	Mean	8.0	43.5	27.8	30.4	0.0	8.4	3.1	3.1
			S.D.	1.1	18.4	8.8	12.3	0.0	3.9	1.5	2.5
	HBCD 1500 ppm	10	Mean	6.9	33.2	32.4 ^s	28.0	0.0	6.9	5.2	2.5
			S.D.	1.3	12.0	37.3	24.7	0.0	2.9	6.0	1.8
	HBCD 15000 ppm	10	Mean	8.3	40.8	18.4 ^{ss}	19.6	0.1	8.0	2.1 ^{ss}	2.0
			S.D.	2.5	17.4	4.9	5.2	0.1	4.1	1.2	1.9

Day 1 : Used a straight channel.

Days 2-4 : Used a multiple T-maze.

^s: Significantly different from the control at $p \leq 0.05$ by Mann-Whitney U-test.

^{ss}: Significantly different from the control at $p \leq 0.01$ by Mann-Whitney U-test.

Table 19 Data on learning tests in 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		Time for maze trials (sec)				Number of errors for maze trials			
				Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
F1	Control	10	Mean	12.2	49.1	42.1	28.3	0.4	8.6	5.5	2.7
			S.D.	4.7	18.2	32.6	8.1	0.4	2.8	4.1	1.7
	HBCD 150 ppm	10	Mean	10.8	43.4	35.1	31.6	0.2	7.7	5.3	3.8
			S.D.	4.0	17.1	15.8	19.6	0.2	3.4	3.1	4.4
	HBCD 1500 ppm	10	Mean	8.8	40.7	34.5	30.7	0.1	7.2	5.0	4.0
			S.D.	4.4	14.2	23.3	13.0	0.1	2.7	3.8	2.6
	HBCD 15000 ppm	10	Mean	10.5	39.2	31.5	25.4	0.3	8.3	5.3	4.0
			S.D.	2.3	12.2	19.4	10.1	0.3	2.7	2.7	2.1

Day 1 : Used a straight channel.
Days 2-4 : Used a multiple T-maze.

Table 20 Hematological 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	Group	Number of animals	WBC $10^2/\mu\text{L}$	Differential count of WBC %								
				Neutrophil		Eosino- phil	Baso- phil	Mono- cyte	Lympho- cyte	Others		
				Stab form	Seg- mented							
F0	Control	10	Mean	104	0.48	8.00	0.84	0.00	2.20	88.5	0.00	
			S.D.	26	0.73	5.24	1.12	0.00	0.78	6.5	0.00	
	HBCD 150 ppm	10	Mean	105	0.36	8.24	0.60	0.00	2.04	88.8	0.00	
			S.D.	34	0.30	1.98	0.54	0.00	0.87	2.4	0.00	
	HBCD 1500 ppm	10	Mean	109	0.64	7.68	0.52	0.00	2.32	88.8	0.00	
			S.D.	34	0.28	3.26	0.42	0.00	1.16	3.9	0.00	
	HBCD 15000 ppm	10	Mean	96	0.56	8.68	1.16	0.00	2.08	87.5	0.00	
			S.D.	28	0.51	4.61	0.79	0.00	0.86	4.6	0.00	
	F1	Control	10	Mean	108	0.68	8.64	0.64	0.04	1.84	88.2	0.00
				S.D.	24	0.46	3.57	0.39	0.13	0.66	4.4	0.00
		HBCD 150 ppm	10	Mean	104	0.36	6.92	0.52	0.00	1.28	90.9	0.00
				S.D.	24	0.40	2.68	0.46	0.00	0.70	2.7	0.00
HBCD 1500 ppm		10	Mean	130	0.48	9.76	0.52	0.00	1.52	87.7	0.00	
			S.D.	35	0.53	4.76	0.46	0.00	0.80	5.9	0.00	
HBCD 15000 ppm		10	Mean	112	0.68	9.80	1.00	0.00	1.24	87.3	0.00	
			S.D.	28	0.42	4.91	0.57	0.00	0.61	5.7	0.00	

Table 21 Hematological 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	Group	Number of animals	WBC 10 ³ /μL	Differential count of WBC %								
				Neutrophil		Eosino- phil	Baso- phil	Mono- cyte	Lympho- cyte	Others		
				Stab form	Seg- mented							
F0	Control	10	Mean	85	1.32	21.68	1.48	0.00	3.04	72.5	0.00	
			S.D.	30	0.57	8.08	1.05	0.00	0.63	8.7	0.00	
	HBCD 150 ppm	10	Mean	85	0.60 *	10.56 **	1.12	0.00	2.76	85.0 **	0.00	
			S.D.	23	0.39	4.19	0.67	0.00	1.15	5.0	0.00	
	HBCD 1500 ppm	10	Mean	76	0.84	16.84	1.24	0.04	2.60	78.4	0.00	
			S.D.	13	0.55	9.19	0.74	0.13	1.55	9.5	0.00	
	HBCD 15000 ppm	10	Mean	81	1.12	23.28	0.88	0.04	3.88	70.8	0.00	
			S.D.	21	0.70	8.13	0.75	0.13	1.36	9.0	0.00	
	F1	Control	10	Mean	111	0.80	12.72	0.60	0.00	2.32	83.6	0.00
				S.D.	40	0.57	8.21	0.66	0.00	0.49	9.4	0.00
		HBCD 150 ppm	10	Mean	108	1.12	18.88	0.60	0.00	3.24	76.2	0.00
				S.D.	25	0.49	9.19	0.47	0.00	1.56	9.6	0.00
HBCD 1500 ppm		10	Mean	88	0.80	12.88	1.00	0.00	1.72	83.6	0.00	
			S.D.	26	0.50	7.46	0.66	0.00	1.61	8.3	0.00	
HBCD 15000 ppm		10	Mean	92	1.24	22.44	0.64	0.00	2.68	73.0	0.00	
			S.D.	26	0.87	11.17	0.39	0.00	1.25	11.6	0.00	

*: 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 22 Blood chemical 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	Group	Number of animals		TP g/dL	Albumin g/dL	Globulin g/dL	
F0	Control	10	Mean	5.98	2.30	3.68	
			S.D.	0.22	0.12	0.21	
	HBCD 150 ppm	10	Mean	6.05	2.33	3.72	
			S.D.	0.30	0.09	0.25	
	HBCD 1500 ppm	10	Mean	6.30 **	2.28	4.02 **	
			S.D.	0.19	0.10	0.13	
	HBCD 15000 ppm	10	Mean	6.40 **	2.39	4.01 **	
			S.D.	0.17	0.07	0.19	
	F1	Control	10	Mean	5.95	2.25	3.70
				S.D.	0.08	0.10	0.12
		HBCD 150 ppm	10	Mean	5.87	2.22	3.65
				S.D.	0.29	0.14	0.25
HBCD 1500 ppm		10	Mean	6.04	2.23	3.81	
			S.D.	0.27	0.13	0.20	
HBCD 15000 ppm		10	Mean	6.27 ^{ss}	2.29	3.98 **	
			S.D.	0.26	0.14	0.21	

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

^{ss} : Significantly different from the control at $p \leq 0.01$ by Mann-Whitney U-test.

Table 23 Blood chemical 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)

Generation	Group	Number of animals		TP g/dL	Albumin g/dL	Globulin g/dL	
F0	Control	10	Mean	5.85	2.47	3.38	
			S.D.	0.39	0.18	0.28	
	HBCD 150 ppm	10	Mean	6.33 *	2.63	3.70 *	
			S.D.	0.26	0.14	0.19	
	HBCD 1500 ppm	10	Mean	6.19	2.59	3.60	
			S.D.	0.43	0.22	0.29	
	HBCD 15000 ppm	10	Mean	6.54 **	2.60	3.94 **	
			S.D.	0.48	0.18	0.33	
	F1	Control	10	Mean	6.05	2.47	3.58
				S.D.	0.25	0.14	0.19
		HBCD 150 ppm	10	Mean	6.25	2.52	3.73
				S.D.	0.37	0.19	0.23
HBCD 1500 ppm		10	Mean	5.97	2.48	3.49	
			S.D.	0.51	0.15	0.37	
HBCD 15000 ppm		10	Mean	6.36	2.53	3.83	
			S.D.	0.32	0.13	0.28	

*: 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 24 Serum hormone levels 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		Testosterone (ng/mL)	DHT (pg/mL)	LH ^a (ng/mL)	FSH (ng/mL)	T3 (ng/dL)	T4 (µg/dL)	TSH (ng/mL)	
F0	Control	8	Mean	0.76	70.7	(1) 0.81	8.90	143.6	4.04	16.15	
			S.D.	0.48	20.8	-	1.25	29.0	1.42	3.78	
	HBCD 150 ppm	8	Mean	1.18	68.8	(0) -	8.69	138.2	3.98	16.18	
			S.D.	0.63	27.0	-	3.32	21.6	0.89	8.61	
	HBCD 1500 ppm	8	Mean	0.90	48.7	(0) -	7.52 ^{ss}	121.6	2.97	19.14	
			S.D.	0.55	13.8	-	0.37	15.6	0.76	6.02	
	HBCD 15000 ppm	8	Mean	1.02	54.8	(1) 0.87	7.99	126.9	2.49 ^{**}	23.26	
			S.D.	0.50	14.6	-	1.03	16.3	0.59	10.90	
	F1	Control	8	Mean	0.79	59.1	1.56	11.14	122.1	3.54	11.93
				S.D.	0.42	19.9	0.50	1.80	9.9	0.29	4.62
		HBCD 150 ppm	8	Mean	0.55	75.8	(7) 1.35	9.68	123.0	3.44	11.50
				S.D.	0.17	25.7	0.36	1.36	13.7	0.86	2.94
HBCD 1500 ppm		8	Mean	0.76	96.6 *	(7) 1.28	9.76	123.6	3.32	15.78	
			S.D.	0.37	34.4	0.33	1.07	22.6	0.98	6.48	
HBCD 15000 ppm		8	Mean	0.71	83.3	1.24	10.62	122.3	3.18	15.54	
			S.D.	0.18	21.6	0.16	1.15	20.4	0.48	5.76	

a: Values in parentheses are the number of data available; the actual measurement of LH was below the lower limit of quantification (<0.80 ng/mL) in 7, 8, 8 and 7 animals in the control, 150, 1500 and 15000 ppm groups, respectively, in the F0 generation and 1 animal each in the 150 and 1500 ppm groups in the F1 generation.

-: Not applicable.

*: 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.

^{ss}: Significantly different from the control at $p \leq 0.01$ by Mann-Whitney U-test.

Table 25 Serum hormone levels 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)

Generation	Group	Number of animals		Estradiol (pg/mL)	Progesterone (ng/mL)	LH ^a (ng/mL)	FSH (ng/mL)	T3 (ng/dL)	T4 (µg/dL)	TSH (ng/mL)	
F0	Control	8	Mean	56.2	8.45	(2) 0.98	4.17	133.1	2.84	10.68	
			S.D.	13.3	2.56	0.06	0.51	15.9	0.61	1.35	
	HBCD 150 ppm	8	Mean	65.8	8.22	(0) -	4.84	140.9	3.14	14.83 ^{SS}	
			S.D.	10.2	7.43	-	0.63	16.3	0.48	2.47	
	HBCD 1500 ppm	8	Mean	57.8	7.51	(0) -	4.88	146.5	3.00	15.37 ^{SS}	
			S.D.	21.1	3.62	-	1.05	29.5	0.77	2.17	
	HBCD 15000 ppm	8	Mean	59.0	6.06	(1) 1.11	5.86 ^{**}	134.7	1.96 [*]	21.59 ^{SS}	
			S.D.	23.6	2.91	-	1.11	25.6	0.55	8.87	
	F1	Control	8	Mean	66.5	7.04	(7) 1.38	5.89	146.7	3.59	10.35
				S.D.	14.2	3.31	0.22	1.60	17.5	1.08	2.04
		HBCD 150 ppm	8	Mean	75.3	7.10	(7) 1.43	6.07	143.3	3.56	15.36
				S.D.	24.7	3.63	0.30	0.60	18.1	0.53	4.18
HBCD 1500 ppm		8	Mean	57.6	6.91	1.22	6.33	132.1	3.39	18.09 ^{**}	
			S.D.	32.4	3.77	0.27	0.82	26.2	1.21	5.23	
HBCD 15000 ppm		8	Mean	59.0	9.19	1.17	6.52	130.4	2.58	17.28 [*]	
			S.D.	9.1	5.30	0.16	0.95	17.8	0.37	5.58	

a: Values in parentheses are the number of data available; the actual measurement of LH was below the lower limit of quantification (<0.80 ng/mL) in 6, 8, 8 and 7 animals in the control, 150, 1500 and 15000 ppm groups, respectively, in the F0 generation and 1 animal each in the control and 150 ppm groups in the F1 generation.

-: Not applicable.

*: 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.

^{SS}: Significantly different from the control at $p \leq 0.01$ by Mann-Whitney U-test.

Table 26 Autopsy 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	1	24
	Number of animals with abnormal findings	2	-	-	2	2	1	-	3	4	1	-	5	3	1 ^b	1	5
	Findings ^a																
	Harderian gland: Yellowish green mass	0	-	-	0	0	0	-	0	0	0	-	0	1	0	0	1
	Incisor: Malocclusion/fracture	0	-	-	0	1	0	-	1	0	1	-	1	1	0	0	1
	Maxilla: Deformity/fracture	0	-	-	0	0	0	-	0	0	1	-	1	0	1 ^b	0	1
	Hard palate: Hemorrhage	0	-	-	0	0	0	-	0	0	0	-	0	0	1 ^b	0	1
	Nasal skin: Edema, subcutis	0	-	-	0	0	0	-	0	0	0	-	0	0	1 ^b	0	1
	Cervical adipose tissue: Edematous	0	-	-	0	0	0	-	0	0	0	-	0	0	0	1	1
	Cerebrum: Dilatation, ventricle	0	-	-	0	0	0	-	0	1	0	-	1	0	0	0	0
	Pituitary gland: Cyst	1	-	-	1	0	0	-	0	0	0	-	0	0	0	0	0
	Liver: Hypertrophy	0	-	-	0	0	0	-	0	0	0	-	0	0	0	1	1
	Dark red discoloration	0	-	-	0	0	0	-	0	0	0	-	0	0	0	1	1
	Yellowish white patch	0	-	-	0	0	0	-	0	1	0	-	1	0	0	0	0
	Thoracic cavity: Hydrothorax	0	-	-	0	0	0	-	0	0	0	-	0	0	0	1	1
	Abdominal cavity: Ascites	0	-	-	0	0	0	-	0	0	0	-	0	0	0	1	1
	Stomach: Dark red contents	0	-	-	0	0	0	-	0	0	0	-	0	0	1 ^b	0	1
	Ileum: Diverticulum	0	-	-	0	0	1	-	1	0	0	-	0	0	0	0	0
	Kidney: Dilatation, renal pelvis	0	-	-	0	1	0	-	1	2	0	-	2	1	0	0	1
	Fine white granule, renal pelvis	0	-	-	0	1	0	-	1	0	0	-	0	1	0	0	1
	Testis: Small size	1	-	-	1	0	1	-	1	0	0	-	0	0	0	0	0
	Epididymis: Small size	0	-	-	0	0	1	-	1	0	0	-	0	0	0	0	0
	Hypoplasia	1	-	-	1	0	0	-	0	0	0	-	0	0	0	0	0
	Seminal vesicle: Small size	1	-	-	1	0	0	-	0	0	0	-	0	0	0	0	0

(to be continued)

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

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: Euthanized in treatment week 13 because of fracture of the nasal bone due to an accident in the cage.

-: Not applicable.

Table 26 (continued) Autopsy 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
F1	Number of animals examined	23	1	0	24	23	1	0	24	19	3	2	24	21	3	0	24
	Number of animals with abnormal findings	4	1	-	5	2	0	-	2	8	2	2	12	12	3	-	15 **
	Findings ^a																
	Eyeball: Opacity	0	0	-	0	0	0	-	0	0	0	0	0	1	0	-	1
	Incisor: Malocclusion	0	0	-	0	2	0	-	2	2	0	1	3	0	0	-	0
	Nasal bone: Deformity	0	0	-	0	2	0	-	2	1	0	1	2	0	0	-	0
	Spleen: Atrophy	0	0	-	0	0	0	-	0	0	0	1	1	0	0	-	0
	Liver: Hypertrophy	0	0	-	0	0	0	-	0	0	0	1	1	0	0	-	0
	Yellowish white patch	0	0	-	0	0	0	-	0	0	0	0	0	0	1	-	1
	Digestive tract: Retention, gas	0	0	-	0	0	0	-	0	0	0	1	1	0	0	-	0
	Kidney: Dilatation, renal pelvis	2	1	-	3	0	0	-	0	5	2	0	7	10	1	-	11 *
	Fine white granule, renal pelvis	2	1	-	3	0	0	-	0	2	0	0	2	6	2	-	8
	Rough surface	0	0	-	0	0	0	-	0	0	0	0	0	1	0	-	1
	Testis: Atrophy	1	0	-	1	0	0	-	0	0	0	0	0	0	0	-	0
	Epididymis: Atrophy	1	0	-	1	0	0	-	0	0	0	0	0	0	0	-	0

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

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.

-: 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 27 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	D	T	A	B	C	D	T	A	B	C	D	T	A	B	C	D	T
F0	Number of animals examined	24	0	0	0	24	21	1	2	0	24	20	0	4	0	24	17	1	4	2	24
	Number of animals with abnormal findings	1	-	-	-	1	0	1	0	-	1	0	-	2	-	2	1	0	0	2	3
	Findings ^a																				
	Incisor: Malocclusion	0	-	-	-	0	0	0	0	-	0	0	-	1	-	1	0	0	0	0	0
	Pituitary gland: Hypertrophy	0	-	-	-	0	0	0	0	-	0	0	-	1	-	1	0	0	0	0	0
	Cyst	1	-	-	-	1	0	0	0	-	0	0	-	0	-	0	0	0	0	0	0
	Thoracic cavity: White mass	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Hydrothorax	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Thymus: Atrophy	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Lung: Dark red discoloration	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	2	2
	Spleen: Swelling	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Lymph node: Swelling (submandibular, axillary, pancreaticosplenic, mesenteric, renal, lumbar and inguinal lymph nodes)	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Ovary: Dark red cyst	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Uterine horn: Yellowish white mass	0	-	-	-	0	0	1	0	-	1	0	-	0	-	0	0	0	0	0	0
	Dark red mass	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	1	0	0	0	1

(to be continued)

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 unsuccessfully mated or were not pregnant; D, animals that were euthanized or died during the study; T, total (A+B+C+D).

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

-: Not applicable.