Table 31 Histopathological 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	Item	Control					HBCD (ppm) 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[d]
	Findings in organs/tissues examined[a,b,c]																				
	Liver: Microgranuloma	10	-	-	-	10	-	1	1	-	2	-	-	1	-	1	10	0	1	1	12
	Focal necrosis	1	-	-	-	1	-	0	0	-	0	-	-	0	-	0	0	0	0	0	0
	Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Thymus: Atrophy of cortex	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Thyroid: Small size, follicle	0	-	-	-	0	0	0	0	-	0	5	-	0	-	5 *	8	0	3	0	11 **
	Hypertrophy of follicular cell	0	-	-	-	0	0	0	0	-	0	2	-	0	-	2	0	0	0	0	0
	Infiltration of thymic lymphoma	0	-	-	-	0	0	0	0	-	0	0	-	0	-	0	0	0	0	1	1
	Spleen: Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Adrenal: Cystic degeneration	2	-	-	-	2	-	0	0	-	0	-	-	0	-	0	2	0	0	0	2
	Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Bone marrow: Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Mesenteric lymph node: Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Peyer's patch: Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Ovary: Atrophy	0	-	-	-	0	-	0	0	-	0	-	-	1	-	1	0	0	0	0	0
	Follicular cyst	0	-	-	-	0	-	0	0	-	0	-	-	1	-	1	2	0	0	0	2
	Parovarian cyst	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Uterine horn: Cyst	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	1	0	0	0	1
	Focal necrosis of endometrium	0	-	-	-	0	-	1	0	-	1	-	-	0	-	0	0	0	0	0	0
	Uterine cervix: Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Mammary gland: Dilatation of duct	1	-	-	-	1	-	0	0	-	0	-	-	0	-	0	0	0	0	0	0
	Infiltration of thymic lymphoma	0	-	-	-	0	-	0	0	-	0	-	-	0	-	0	0	0	0	1	1
	Pituitary gland: Cyst on pars intermedia	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0
	Infiltration of thymic lymphoma	0	-	-	-	0	-	-	-	-	-	-	-	-	-	-	0	0	0	1	1
	Findings in organs/tissues in which abnormal findings were grossly observed[a]																				
	Number of animals examined	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
	Lung: Congestion, thrombosis and edema	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1
	Infiltration of thymic lymphoma	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1
	Lymph node: Infiltration of thymic lymphoma (submandibular, axillary, pancreaticosplenic, renal, lumbar and inguinal lymph nodes)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1

(to be continued)

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.

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, ovaries, uterus, vagina, mammary gland and pituitary gland.

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

-: Not applicable.

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

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

Table 31 (continued) Histopathological 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	Item	Control				HBCD (ppm) 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
	Findings in organs/tissues examined[a,b,c]																
	Liver: Microgranuloma	9	1	1	11	0	0	1	1	1	1	2	4	10	4	3	17
	Thyroid: Small size, follicle	0	0	0	0	1	0	0	1	5	0	0	5 *	7	4	2	13 **
	Uterine horn: Cellular infiltration of inflammatory cell	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Vagina: Cellular infiltration of inflammatory cell	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Mammary gland: Cellular infiltration of inflammatory cell	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	Findings in organs/tissues in which abnormal findings were grossly observed[a]																
	Number of animals examined	1	0	0	1	2	0	0	2	2	0	0	2	0	0	1	1
	Glandular stomach: Erosion	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-
	Kidney: Dilatation of renal pelvis	1	-	-	1	1	-	-	1	1	-	-	1	-	-	0	0
	Calculus in renal pelvis	0	-	-	0	0	-	-	0	0	-	-	0	-	-	1	1
	Dilatation of tubule, fibrosis and cellular infiltration of inflammatory cell in cortex	0	-	-	0	0	-	-	0	1	-	-	1	-	-	0	0

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.

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, ovaries, uterus, vagina, mammary gland and pituitary gland.

-: Not applicable.

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

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

Table 32 Number of primordial follicles in 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		Number of primordial follicles[a]
F1	Control	10	Mean	316.3
			S.D.	119.5
	HBCD 150 ppm	10	Mean	294.2
			S.D.	66.3
	HBCD 1500 ppm	10	Mean	197.9 *
			S.D.	76.9
	HBCD 15000 ppm	10	Mean	203.4 *
			S.D.	79.5

a: Counted based on a 5% nonrandom sample (every twentieth serial section) from right ovary of each animal.
*: Significantly different from the control at $p \leqq 0.05$ by Dunnett's test.

Table 33 General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Generation	Item	Postnatal day 0			
			HBCD (ppm)		
		Control	150	1500	15000
F1	Number of litters examined	24	21	20	18
	Number of pups examined	164	132	113	139
	Number of pups with abnormal findings	0 (0.00)	3 (2.38)	2 (2.92)	1 (1.11)
	Findings[a]				
	Rudimentary tail	0 (0.00)	1 (0.60)	0 (0.00)	0 (0.00)
	Found dead	0 (0.00)	2 (1.79)	2 (2.92)	1 (1.11)
F2	Number of litters examined	23	22	20	21
	Number of pups examined	159	157	139[b]	134
	Number of pups with abnormal findings	2 (1.48)	1 (0.57)	6 (4.11)	4 (2.75)
	Findings[a]				
	Found dead	2 (1.48)	1 (0.57)	6 (4.11)	4 (2.75)

(to be continued)

Values in parentheses represent the means of incidences of pups with abnormal findings (%, the litter is the unit evaluated).

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

b: Including one animal that was not distinguished its sex because of maternal cannibalism.

Table 33 (continued-1) General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener-ation	Item	Postnatal days 1-4			
		HBCD (ppm)			
		Control	150	1500	15000
F1	Number of litters examined	24	21	20	18
	Number of pups examined	164	130	111	138
	Number of pups with abnormal findings	11 (5.34)	3 (2.15)	1 (0.56)	6 (3.33)
	Findings[a]				
	Rudimentary tail	0 (0.00)	1 (0.68)	0 (0.00)	0 (0.00)
	Found dead/lost	11 (5.34)	2 (1.47)	1 (0.56)	6 (3.33)
F2	Number of litters examined	23	22	20	21
	Number of pups examined	157	156	133	130
	Number of pups with abnormal findings	19 (11.83)	13 (8.54)	14 (11.42)	36 (29.16)
	Findings[a]				
	Found dead/lost	19 (11.83)	13 (8.54)	14 (11.42)	36 (29.16)

(to be continued)

Values in parentheses represent the means of incidences of pups with abnormal findings (%, the litter is the unit evaluated).
a: Values represent the number of pups that showed abnormal findings.

Table 33 (continued-2) General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Generation	Item	Postnatal days 5-21			
			HBCD (ppm)		
		Control	150	1500	15000
F1	Number of litters examined	24	21	20	18
	Number of pups examined	99	81	76	80
	Number of pups with abnormal findings	9 (9.38)	0 (0.00) *	2 (2.50)	5 (5.56)
	Findings[a]				
	Moribund condition	4 (4.17)	0 (0.00)	2 (2.50)	0 (0.00)
	Found dead/lost	9 (9.38)	0 (0.00) *	2 (2.50)	5 (5.56)
F2	Number of litters examined	22	22	20	19
	Number of pups examined	82	88	77	70
	Number of pups with abnormal findings	11 (12.27)	9 (10.00)	25 (35.50) *	33 (49.91) **
	Findings[a]				
	Enlargement of eyeball	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.32)
	Found dead/lost	11 (12.27)	9 (10.00)	25 (35.50) *	32 (48.60) **

(to be continued)

Values in parentheses represent the means of incidences of pups with abnormal findings (%, the litter is the unit evaluated).

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

*: Significantly different from the control at $p \leqq 0.05$ by Wilcoxon rank-sum test.

**: Significantly different from the control at $p \leqq 0.01$ by Wilcoxon rank-sum test.

Table 33 (continued-3) General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener-ation	Item	Postnatal days 22-26			
		HBCD (ppm)			
		Control	150	1500	15000
F1	Number of litters examined	23	21	20	17
	Number of weanlings examined	90	80	70	72
	Number of weanlings with abnormal findings	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
F2	Number of litters examined	22	22	18	13
	Number of weanlings examined	71	79	52	38
	Number of weanlings with abnormal findings	0 (0.00)	0 (0.00)	1 (1.39)	2 (4.49)
	Findings[a]				
	Enlargement of eyeball	0 (0.00)	0 (0.00)	1 (1.39)	1 (2.56)
	Opacity of eyeball	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.92)

Values in parentheses represent the means of incidences of weanlings with abnormal findings (%, the litter is the unit evaluated).
a: Values represent the number of weanlings that showed abnormal findings.

Table 34 General appearance in F1 and F2 female rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener-ation	Item	Postnatal day 0			
			HBCD (ppm)		
		Control	150	1500	15000
F1	Number of litters examined	23	21	20	18
	Number of pups examined	149	148	152	104
	Number of pups with abnormal findings	1 (0.87)	5 (3.07)	1 (0.71)	2 (1.73)
	Findings[a]				
	Kinked tail	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.62)
	Found dead	1 (0.87)	5 (3.07)	1 (0.71)	1 (1.11)
F2	Number of litters examined	23	23	20	21
	Number of pups examined	145	162	129	142
	Number of pups with abnormal findings	1 (1.09)	6 (3.97)	6 (3.33)	3 (1.87)
	Findings[a]				
	Black discoloration of tail	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.60)
	Found dead	1 (1.09)	6 (3.97)	6 (3.33)	2 (1.28)

(to be continued)

Values in parentheses represent the means of incidences of pups with abnormal findings (%, the litter is the unit evaluated).
a: Values represent the number of pups that showed abnormal findings.

Table 34 (continued-1) General appearance in F1 and F2 female rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener-ation	Item	Postnatal days 1-4			
		HBCD (ppm)			
		Control	150	1500	15000
F1	Number of litters examined	23	21	20	18
	Number of pups examined	148	143	151	103
	Number of pups with abnormal findings	5 (3.80)	2 (1.16)	3 (1.93)	5 (6.17)
	Findings[a]				
	Kinked tail	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.62)
	Found dead/lost	5 (3.80)	2 (1.16)	3 (1.93)	4 (5.56)
F2	Number of litters examined	23	23	20	21
	Number of pups examined	144	156	123	140
	Number of pups with abnormal findings	26 (15.20)	16 (13.45)	9 (6.87)	47 (32.12)
	Findings[a]				
	Black discoloration of tail	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.60)
	Found dead/lost	26 (15.20)	16 (13.45)	9 (6.87)	47 (32.12)

(to be continued)

Values in parentheses represent the means of incidences of pups with abnormal findings (%, the litter is the unit evaluated).
a: Values represent the number of pups that showed abnormal findings.

Table 34 (continued-2) General appearance in F1 and F2 female rat pups and weanlings during postnatal days 0-26 treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Generation	Item	Postnatal days 5-21			
		HBCD (ppm)			
		Control	150	1500	15000
F1	Number of litters examined	23	21	20	18
	Number of pups examined	92	87	81	62
	Number of pups with abnormal findings	4 (4.35)	1 (0.79)	1 (1.25)	4 (6.94)
	Findings[a]				
	Moribund condition	1 (1.09)	1 (0.79)	0 (0.00)	0 (0.00)
	Found dead/lost	4 (4.35)	1 (0.79)	1 (1.25)	4 (6.94)
F2	Number of litters examined	22	22	20	20
	Number of pups examined	84	87	83	66
	Number of pups with abnormal findings	15 (17.05)	9 (11.14)	21 (25.35)	30 (48.33)*
	Findings[a]				
	Found dead/lost	15 (17.05)	9 (11.14)	21 (25.35)	30 (48.33)*

(to be continued)

Values in parentheses represent the means of incidences of pups with abnormal findings (%, the litter is the unit evaluated).

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

*: Significantly different from the control at $p \leqq 0.05$ by Wilcoxon rank-sum test.