

Two-generation reproductive toxicity study in rats with 1,2,5,6,9,10-hexabromocyclododecane (SR04222)

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Table 1 General appearance 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	Pre-mating period				Breeding period			
		Control	HBCD (ppm)			Control	HBCD (ppm)		
			150	1500	15000		150	1500	15000
F0	Number of animals examined	24	24	24	24	24	24	24	23
	Number of animals with abnormal findings	0	0	1	2	1	1	3	3
	Findings ^a								
	Deformation of the face with malocclusion	0	0	1	0	0	1	3	0
	Malocclusion	0	0	0	0	0	1	0	1
	Crushing of upper incisors	0	0	0	0	1	0	1	0
	Soil of periocular fur/perinasal fur	0	0	0	0	0	1	2	0
	Subcutaneous mass	0	0	0	1	0	0	0	1
	Scab formation	0	0	0	1	0	0	0	1
	Hemorrhage from hard palate	0	0	0	0	0	0	0	1
	Moribund condition (euthanized)	0	0	0	0	0	0	0	1
	Found dead	0	0	0	1	0	0	0	0
F1	Number of animals examined	24	24	24	24	24	24	23	24
	Number of animals with abnormal findings	0	0	1	1	0	2	3	3
	Findings ^a								
	Enlargement of eyeball	0	0	0	1	0	0	0	0
	Trauma on cornea	0	0	0	1	0	0	0	0
	Opacity of eyeball	0	0	0	1	0	0	0	1
	Deformation of the face with malocclusion	0	0	0	0	0	2	2	0
	Malocclusion	0	0	0	0	0	0	1	0
	Soil of periocular fur/perinasal fur	0	0	0	0	0	2	2	0
	Mass	0	0	0	0	0	0	0	1
	Hematuria	0	0	0	0	0	0	0	1
	Found dead	0	0	1	0	0	0	1	0

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

Table 2 General appearance 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	Breeding period											
		Pre-mating period				Gestation period ^a				Lactation period ^b			
		Control	HBCD (ppm)			Control	HBCD (ppm)			Control	HBCD (ppm)		
			150	1500	15000		150	1500	15000		150	1500	15000
F0	Number of animals examined ^c	24	24	24	24	24	22 (2)	20 (4)	19 (4)	24	21 (3)	20 (4)	18 (4)
	Number of animals with abnormal findings ^c	0	0	2	1	0	0 (0)	1 (1)	2 (0)	0	0 (0)	1 (1)	1 (0)
	Findings ^{c,d}												
	Deformation of the face with malocclusion	0	0	1	0	0	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)
	Malocclusion	0	0	0	0	0	0 (0)	0 (1)	0 (0)	0	0 (0)	0 (1)	0 (0)
	Soil of periocular fur/perinasal fur	0	0	2	1	0	0 (0)	1 (0)	0 (0)	0	0 (0)	1 (0)	0 (0)
	Soil of perigenital fur	0	0	1	1	0	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)
	Nasal hemorrhage	0	0	1	0	0	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)
	Alopecia	0	0	0	0	0	0 (0)	0 (0)	1 (0)	0	0 (0)	0 (0)	1 (0)
	Moribund condition (euthanized)	0	0	0	1	0	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)
	Dystocia	0	0	0	0	0	0 (0)	0 (0)	1 (0)	0	0 (0)	0 (0)	0 (0)
	Found dead	0	0	0	0	0	0 (0)	0 (0)	1 (0)	0	0 (0)	0 (0)	0 (0)
F1	Number of animals examined ^c	24	24	24	24	23 (1)	23 (1)	21 (3)	21 (3)	23 (1)	23 (1)	20 (4)	21 (3)
	Number of animals with abnormal findings ^c	0	0	1	0	0 (0)	0 (0)	1 (0)	0 (1)	0 (0)	0 (0)	2 (0)	0 (1)
	Findings ^{c,d}												
	Deformation of the face with malocclusion	0	0	1	0	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)
	Soil of periocular fur/perinasal fur	0	0	1	0	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)
	Mass	0	0	0	0	0 (0)	0 (0)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)	0 (1)

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

a: Including the mating period and delivery.

b: Including the period from weaning to autopsy.

c: Values in parentheses represent the number of animals that unsuccessfully mated or were not pregnant in the gestation period; and animals that did not produce viable pups in the lactation period.

d: Values represent the number of animals that showed abnormal findings during each period.

Table 3 Body weights of 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		Pre-mating period										Breeding period				Autopsy day	
				Body weight (g) in treatment week															
				0	1	2	3	4	5	6	7	8	9	10	11	12	13		14
F0	Control	24	Mean	142.4	208.4	266.2	320.1	362.0	397.4	428.4	451.0	472.5	491.0	504.5	513.5	531.0	542.9	553.1	566.0
			S.D.	3.7	5.9	9.7	14.0	17.8	21.3	23.1	25.3	26.3	28.8	31.0	31.8	31.4	33.1	33.3	36.5
															(23)				
	HBCD 150 ppm	24	Mean	142.5	211.3	271.0	324.1	370.9	405.4	436.8	460.5	482.7	502.0	518.4	529.3	546.0	560.0	570.4	584.2
			S.D.	3.5	6.6	11.1	17.3	22.2	27.5	29.0	32.3	34.4	37.3	39.5	40.2	41.6	43.2	44.3	44.3
															(22)				
	HBCD 1500 ppm	24	Mean	142.3	213.2	276.3 **	331.8 ^s	379.2 *	417.9 ^{ss}	450.5 *	478.2 **	502.4 **	522.9 **	535.0 *	545.2 *	557.7	574.8 *	585.9 *	597.7 *
			S.D.	3.6	8.8	13.7	18.6	24.4	27.8	31.2	33.9	35.7	40.2	43.9	43.5	48.4	50.4	54.5	55.7
								(23)	(23)	(23)	(23)	(23)	(23)	(23)	(23)	(22)	(21)	(22)	
HBCD 15000 ppm	24	Mean	142.4	213.3	274.5 *	329.0 ^s	375.8	409.3 ^s	437.4	463.4	485.8	502.3	514.8	522.9	539.4	548.7	560.0	572.5	
		S.D.	3.6	6.9	8.3	9.2	14.1	15.8	21.6	24.6	28.0	32.2	38.3	39.5	39.7	41.5	42.1	43.6	
F1	Control	24	Mean	70.9	119.7	181.0	243.8	308.0	364.0	409.7	446.4	478.3	506.1	527.4	541.0	556.6	578.2	590.1	605.6
			S.D.	6.6	11.2	16.2	20.7	22.0	23.6	25.5	27.2	29.5	30.1	33.4	34.2	35.6	37.5	38.3	41.9
	HBCD 150 ppm	24	Mean	71.0	119.4	182.6	243.6	305.3	358.1	397.6	432.2	462.8	490.5	512.9	514.4	528.7	546.6	561.7	576.7
			S.D.	7.1	12.2	16.3	19.3	24.4	27.8	32.4	37.2	40.6	44.1	46.2	44.1	47.2	52.6	54.2	59.0
											(23)	(23)	(23)	(23)	(23)	(22)	(22)	(22)	(22)
	HBCD 1500 ppm	24	Mean	70.5	118.0	181.8	245.2	311.9	369.3	413.1	452.2	485.1	512.0	534.8	540.3	561.5	582.2	594.1	613.3
			S.D.	6.7	10.7	14.7	17.9	21.3	25.9	28.2	31.3	34.5	37.4	38.7	54.8	53.8	54.4	62.8	59.2
HBCD 15000 ppm	24	Mean	69.2	113.5	174.0	229.9 *	289.7 *	343.4 *	387.0 *	425.6	458.0	485.7	508.0	521.5	540.7	556.9	567.5	584.4	
		S.D.	7.3	13.2	17.9	19.5	24.3	25.0	28.3	30.4	33.6	34.4	38.1	38.8	44.0	46.3	49.6	54.9	

Values in parentheses are the number of animals examined.

*: 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.

^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 4 Body weights of 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		Pre-mating period										Breeding period										Autopsy day	
				Body weight (g)																					
				Treatment week										Gestation day				Lactation day							
				0	1	2	3	4	5	6	7	8	9	10	0	7	14	20	0	4	7	14	21		
F0	Control	24	Mean	118.8	160.3	183.7	207.0	223.8	236.0	251.0	263.6	275.3	276.5	281.4	283.5	317.7	350.8	416.4	322.5	331.6	339.8	348.4	325.6	310.5	
			S.D.	4.5	9.4	11.2	15.9	19.0	21.4	20.3	19.8	22.6	24.4	22.3	25.5	27.2	26.8	29.4	27.0	30.2	26.6	23.1	19.0	18.2	
	HBCD 150 ppm	24	Mean	119.1	160.5	183.7	205.3	224.9	239.7	253.7	262.0	275.3	278.8	284.3	283.9	320.3	350.6	415.6	320.6	339.1	344.3	346.6	323.0	309.3	
			S.D.	4.4	10.5	12.8	16.4	18.9	23.5	24.5	23.6	25.3	27.9	27.0	27.2	25.7	25.4	31.9	31.4	31.2	27.9	25.9	22.2	22.7	
	HBCD 1500 ppm	24	Mean	118.9	159.8	184.8	208.0	223.5	237.8	249.9	263.7	271.4	274.4	280.3	272.5	305.2	337.6	409.4	314.3	331.4	334.5	344.2	322.2	304.8	
			S.D.	4.5	9.1	15.1	18.1	22.1	25.8	28.9	30.5	31.8	34.2	39.5	28.6	29.8	29.8	30.3	28.7	29.0	25.0	27.1	23.6	25.8	
	HBCD 15000 ppm	24	Mean	118.8	164.7	192.3 *	214.6	231.0	244.3	258.0	268.3	277.8	278.7	283.0	287.6	318.2	345.9	414.1	320.5	331.4	339.5	347.5	330.7	313.4	
			S.D.	4.5	7.1	8.7	9.3	13.8	16.6	20.0	19.7	21.1	22.0	21.8	28.3	29.2	31.2	32.6	27.4	28.6	26.1	21.5	18.5	24.2	
	F1	Control	24	Mean	65.5	104.5	146.8	179.3	206.5	231.0	249.9	267.9	278.5	289.3	300.2	(23)	(23)	(23)	(23)	(23)	(23)	(22)	(22)	(22)	(22)
				S.D.	7.2	9.3	11.5	14.9	16.2	20.3	23.4	25.4	26.3	26.7	29.1	28.1	29.7	31.1	38.4	28.8	31.7	29.7	28.7	25.9	25.9
		HBCD 150 ppm	24	Mean	65.8	104.7	146.9	180.8	206.2	230.8	251.9	267.5	279.8	289.5	299.0	(23)	(23)	(23)	(23)	(23)	(22)	(22)	(22)	(22)	(22)
				S.D.	7.6	10.4	13.2	11.7	14.6	16.5	20.2	21.4	20.2	21.6	24.4	20.6	24.5	27.0	30.0	30.9	25.6	23.9	25.4	18.6	24.8
HBCD 1500 ppm		24	Mean	65.6	103.1	145.9	177.0	204.3	228.0	243.8	259.8	270.9	281.3	291.1	(21)	(21)	(21)	(21)	(20)	(20)	(20)	(20)	(20)	(20)	
			S.D.	6.0	8.2	9.0	10.9	12.4	14.9	16.3	20.5	20.1	20.9	18.8	19.6	17.4	17.1	30.7	20.7	18.2	18.7	23.1	23.8	20.2	
HBCD 15000 ppm		24	Mean	63.4	99.4	140.0	169.1 *	198.3	220.2	235.7 *	252.0 *	262.0 *	271.2 *	276.3 **	(21)	(21)	(21)	(21)	(21)	(21)	(19)	(14)	(13)	(13)	
			S.D.	7.5	12.0	12.3	13.6	17.1	17.7	20.2	22.4	22.4	25.8	23.0	22.2	29.2	31.7	35.1	30.0	28.7	30.5	32.5	32.9	30.5	

Values in parentheses are the number of animals examined.

*: 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.[§]: Significantly different from the control at $p \leq 0.05$ by Mann-Whitney U-test.

Table 5 Body weight gains of 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		Pre-mating period										Breeding period				0-Autopsy day
				Body weight gain (g) in treatment weeks														
				0-1	0-2	0-3	0-4	0-5	0-6	0-7	0-8	0-9	0-10	0-11	0-12	0-13	0-14	
F0	Control	24	Mean	66.0	123.8	177.7	219.6	255.0	286.0	308.6	330.1	348.6	362.1	371.1	388.6	400.5	410.7	423.6
			S.D.	5.2	9.0	13.3	16.9	20.4	22.4	24.3	25.3	27.9	30.3	30.8	30.6	32.1	32.3	35.4
														(23)				
	HBCD 150 ppm	24	Mean	68.8	128.5	181.5	228.4	262.8	294.3	318.0	340.1	359.5	375.8	386.7	403.4	417.4	427.9	441.7
			S.D.	5.0	10.5	17.1	22.4	28.0	29.6	32.8	34.8	37.7	40.0	40.7	42.0	43.6	44.8	44.5
	HBCD 1500 ppm	24	Mean	70.9 **	133.9 ^{ss}	189.4 ^{ss}	236.9 **	275.6 **	308.2 *	335.8 **	360.1 **	380.5 **	392.7 *	403.2 *	415.4	432.5 *	443.5 *	455.4 *
			S.D.	6.7	11.8	16.5	22.3	25.6	28.9	31.7	33.7	38.2	41.9	41.5	47.3	49.4	53.6	54.9
													(22)					
	HBCD 15000 ppm	24	Mean	70.9 **	132.1 ^{ss}	186.6 ^s	233.4 *	266.9	295.0	321.0	343.3	359.8	372.4	380.5	397.0	406.5	417.5	430.4
			S.D.	4.6	6.4	8.3	14.3	16.6	21.8	25.0	28.5	32.4	38.5	39.6	39.9	42.3	42.7	44.1
F1	Control	24	Mean	48.8	110.2	173.0	237.1	293.1	338.8	375.5	407.4	435.2	456.5	470.2	485.8	507.3	519.2	534.7
			S.D.	6.8	12.1	17.1	18.4	20.4	23.5	26.8	29.9	30.8	34.2	35.1	37.3	39.4	40.1	43.2
	HBCD 150 ppm	24	Mean	48.3	111.5	172.6	234.2	287.0	326.6	361.1	391.8	419.5	441.9	443.3	457.7	475.5	490.6	505.7
			S.D.	6.2	11.2	15.4	20.8	25.2	30.6	35.8	39.8	43.6	45.8	43.0	46.2	51.5	53.1	57.8
	HBCD 1500 ppm	24	Mean	47.5	111.4	174.8	241.4	298.8	342.7	(23)	(23)	(23)	(23)	(23)	(22)	(22)	(22)	(22)
			S.D.	5.4	9.3	12.8	16.2	21.4	24.0	27.4	30.8	34.1	35.2	53.3	51.4	51.9	60.4	56.4
	HBCD 15000 ppm	24	Mean	44.3 *	104.8	160.7 *	220.5 **	274.2 *	317.8 *	356.4	388.8	416.5	438.8	452.3	471.5	487.7	498.3	515.2
			S.D.	6.4	11.5	14.8	20.8	23.2	27.3	30.8	34.3	35.5	39.4	40.8	45.8	47.9	50.9	56.5

Values in parentheses are the number of animals examined.

*: 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.

^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 6 Body weight gains of 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		Pre-mating period										Breeding period								
				Body weight gain (g)										Gestation days			Lactation days				0-Autopsy day	
				Treatment weeks										0-7	0-14	0-20	0-4	0-7	0-14	0-21		
				0-1	0-2	0-3	0-4	0-5	0-6	0-7	0-8	0-9	0-10									
F0	Control	24	Mean	41.5	64.9	88.3	105.0	117.2	132.3	144.8	156.5	157.7	162.6	34.3	67.3	133.0	9.2	17.4	26.0	3.1	191.7	
			S.D.	7.2	9.8	13.8	17.0	19.3	18.2	17.9	20.7	22.5	20.2	6.5	8.5	14.0	13.1	12.3	15.4	15.0	17.3	
	HBCD 150 ppm	24	Mean	41.4	64.6	86.2	105.8	120.6	134.6	142.9	156.2	159.7	165.2	(22)	(22)	(22)	(21)	(21)	(21)	(21)	(21)	
			S.D.	8.7	10.7	13.6	16.9	21.6	22.8	21.2	23.7	26.3	25.4	8.1	11.7	21.8	11.2	15.7	18.3	18.3	21.5	
	HBCD 1500 ppm	24	Mean	40.9	66.0	89.2	104.7	118.9	131.0	144.8	152.5	155.5	161.4	(20)	(20)	(20)	(20)	(20)	(20)	(20)	(20)	
			S.D.	6.2	12.4	15.0	19.6	23.3	26.3	28.0	29.5	32.0	37.1	7.4	9.7	17.8	13.2	10.2	12.7	15.2	22.7	
	HBCD 15000 ppm	24	Mean	45.9 ^{ss}	73.4 *	95.8 ^s	112.1	125.5	139.1	149.5	158.9	159.8	164.2	(19)	(19)	(19)	(18)	(17)	(17)	(17)	(17)	
			S.D.	4.7	7.0	8.2	12.2	14.7	18.1	17.7	19.4	19.8	19.3	5.3	7.0	13.1	11.6	10.9	14.9	16.2	20.8	
	F1	Control	24	Mean	39.0	81.3	113.8	141.0	165.5	184.3	202.3	212.9	223.8	234.6	(23)	(23)	(23)	(23)	(22)	(22)	(22)	(22)
				S.D.	3.7	8.0	12.6	14.7	20.0	23.6	25.9	27.3	27.5	30.5	6.1	9.5	18.7	13.8	15.8	13.4	16.6	27.1
		HBCD 150 ppm	24	Mean	38.8	81.0	115.0	140.4	165.0	186.1	201.7	214.0	223.6	233.2	(23)	(23)	(23)	(22)	(22)	(22)	(22)	(22)
				S.D.	5.3	8.9	9.0	13.1	15.4	19.6	20.6	20.2	22.3	24.5	8.7	11.2	16.4	13.8	16.0	19.3	18.2	25.1
HBCD 1500 ppm		24	Mean	37.5	80.3	111.4	138.7	162.4	178.1	194.2	205.3	215.7	225.5	(21)	(21)	(21)	(20)	(20)	(20)	(20)	(20)	
			S.D.	4.9	8.0	11.3	13.5	17.0	17.7	21.6	21.6	22.5	20.7	7.3	9.4	24.8	11.3	9.7	15.1	16.0	22.0	
HBCD 15000 ppm		24	Mean	36.0	76.7	105.8 *	134.9	156.8	172.3	188.7	198.7	207.8	212.9 **	(21)	(21)	(21)	(21)	(19)	(14)	(13)	(13)	
			S.D.	5.4	6.7	9.9	14.2	15.8	18.4	20.7	21.2	24.1	21.6	9.0	11.6	17.9	8.2	8.2	11.2	20.4	30.0	

Values in parentheses are the number of animals examined.

*: 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.^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 7 Food consumption of 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	Group	Number of animals		Pre-mating period										Breeding period		
				Food consumption (g/day) in treatment week										12	13	14
				1	2	3	4	5	6	7	8	9	10			
F0	Control	24												(22)	(22)	
			Mean	21.3	25.0	26.4	27.1	27.6	27.5	27.2	26.9	26.8	26.5	28.0	26.7	26.4
			S.D.	1.2	1.8	2.0	2.6	2.9	2.9	2.9	2.8	3.0	2.9	2.9	2.1	2.1
	HBCD 150 ppm	24													(23)	
			Mean	22.0	26.4 *	28.0 *	28.4	28.7	28.8	28.0	28.3	27.9	27.9	29.3	28.0	27.4
			S.D.	1.0	1.4	2.1	2.3	2.6	2.6	2.6	2.4	2.7	2.9	2.4	2.8	2.6
	HBCD 1500 ppm	24												(22)	(22)	(22)
			Mean	22.1	26.9 **	28.2 **	29.0 *	29.2	29.3 *	29.3 *	29.5 **	28.6	28.0	29.6	28.5	27.4
			S.D.	1.6	1.9	2.2	2.3	2.3	2.2	2.4	3.0	2.9	3.3	2.9	2.9	3.6
	HBCD 15000 ppm	24						(23)	(23)	(23)	(23)	(23)	(23)	(20)	(20)	(20)
			Mean	22.2	26.7 **	27.9 *	28.5	28.3	28.2	28.0	28.2	27.6	27.1	28.7	27.5	27.0
			S.D.	1.3	1.9	1.7	1.6	1.9	2.3	2.4	2.7	2.9	3.3	2.6	2.4	2.4
F1	Control	24												(23)		
			Mean	14.4	20.6	24.6	27.7	29.6	30.7	31.5	30.7	30.2	30.4	29.6	30.2	29.0
			S.D.	1.2	1.8	2.0	2.0	1.9	2.2	2.3	2.2	1.9	2.3	2.1	2.6	2.1
	HBCD 150 ppm	24												(22)	(23)	
			Mean	14.2	21.0	24.5	27.1	29.2	29.5	29.8 *	30.2	29.9	30.0	29.7	28.8	28.1
			S.D.	1.0	1.7	2.1	2.4	2.6	2.5	2.7	3.3	3.3	3.2	3.0	2.9	2.9
	HBCD 1500 ppm	24								(23)	(23)	(23)	(23)	(19)	(21)	(22)
			Mean	13.8	20.7	25.3	28.5	31.1	31.6	31.4	31.1	31.1	31.1	31.1	30.3	28.4
			S.D.	1.4	1.8	1.6	2.1	2.7	2.5	2.3	2.3	2.3	2.1	2.4	3.4	5.2
	HBCD 15000 ppm	24														
			Mean	13.2 **	19.5	23.2 *	25.8 *	27.9	29.2	30.1	30.2	30.1	29.8	30.0	29.0	28.1
			S.D.	1.5	2.1	2.2	2.7	2.7	2.8	2.6	2.7	2.8	2.9	3.6	2.9	3.3

Values in parentheses are the number of animals examined.

*: 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 8 Food consumption of 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		Pre-mating period										Breeding period					
				Food consumption (g/day)										Gestation days			Lactation days		
				Treatment week															
				1	2	3	4	5	6	7	8	9	10	0-7	7-14	14-20	0-7	7-14	14-21
F0	Control	24	Mean	17.4	19.6	19.6	19.7	19.6	20.1	19.9	19.9	18.7	19.0	22.2	23.9	22.8	32.5	51.0	66.8
			S.D.	1.3	1.7	2.1	1.9	1.8	2.2	1.8	1.9	2.0	2.3	2.3	2.3	2.3	4.4	5.2	9.7
	HBCD 150 ppm	24	Mean	17.5	19.1	19.2	19.4	19.5	19.9	19.2	20.0	18.9	18.7	(22)	(22)	(22)	(21)	(21)	(21)
			S.D.	1.7	1.7	2.0	2.2	2.4	2.8	2.8	3.2	3.0	2.4	2.5	2.4	2.8	4.8	5.0	7.6
	HBCD 1500 ppm	24	Mean	17.5	19.8	19.6	19.6	19.5	19.6	19.3	19.4	18.1	18.3	(23)	(20)	(20)	(20)	(20)	(20)
			S.D.	1.3	2.0	2.2	2.2	2.4	2.3	2.2	2.6	3.4	2.6	2.2	2.7	2.2	4.0	4.7	6.8
	HBCD 15000 ppm	24	Mean	18.1	20.4	20.3	19.9	19.8	19.9	19.4	19.4	18.0	18.1	(19)	(19)	(19)	(17)	(17)	(17)
			S.D.	1.3	1.6	1.9	1.9	2.1	2.1	2.0	2.3	2.1	3.5	2.3	2.6	2.6	3.8	4.4	6.4
F1	Control	24	Mean	13.0	17.6	19.2	20.4	21.2	21.2	21.5	21.2	21.0	20.8	(23)	(23)	(23)	(22)	(22)	(22)
			S.D.	1.0	1.1	1.5	1.6	2.2	2.0	2.2	2.1	2.3	2.2	2.3	2.1	2.1	4.5	8.2	11.5
	HBCD 150 ppm	24	Mean	12.9	17.7	19.4	20.2	21.7	22.3	22.0	21.7	21.0	21.4	(23)	(23)	(23)	(22)	(22)	(22)
			S.D.	1.0	1.5	1.6	1.8	2.4	2.5	2.1	2.1	2.3	2.4	2.6	2.8	2.3	4.8	6.4	7.9
	HBCD 1500 ppm	24	Mean	12.4	17.0	19.1	20.1	20.4	20.7	20.8	20.8	20.5	20.6	(21)	(21)	(21)	(20)	(20)	(20)
			S.D.	1.4	1.4	1.3	1.6	1.7	1.8	3.1	1.8	2.0	1.5	1.8	1.6	1.9	4.1	10.6	13.3
	HBCD 15000 ppm	24	Mean	11.8 **	16.1 **	18.0 *	19.1 *	19.4 **	20.0	20.0	20.1	20.0	19.6	(21)	(21)	(21)	(19)	(14)	(13)
			S.D.	1.1	1.2	1.4	1.8	1.8	2.4	2.4	2.0	2.4	2.3	3.3	3.0	2.7	3.1	9.3	11.4

Values in parentheses are the number of animals examined.

*: 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 9 Test substance intake of 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	Pre-mating period										Breeding period			All the periods			
			Test substance intake (mg/kg/day) in treatment week										12	13	14	Min	-	Max	Mean
			1	2	3	4	5	6	7	8	9	10							
F0	HBCD 150 ppm	24	15.6	14.6	13.0	11.5	10.6	9.9	9.1	8.8	8.3	8.1	8.0	7.5	7.2	7.2	-	15.6	10.2
	HBCD 1500 ppm	24	155	146	127	115	105	98	92	88	82	79	80	74	70	70	-	155	101
	HBCD 15000 ppm	24	1561	1459	1272	1138	1037	967	906	871	824	790	798	752	723	723	-	1561	1008
F1	HBCD 150 ppm	24	17.8	17.3	15.1	13.3	12.2	11.1	10.3	9.8	9.1	8.8	8.4	7.9	7.5	7.5	-	17.8	11.4
	HBCD 1500 ppm	24	175	171	155	137	126	115	104	96	91	87	83	78	72	72	-	175	115
	HBCD 15000 ppm	24	1744	1681	1514	1336	1219	1132	1061	989	930	880	832	781	743	743	-	1744	1142

Table 10 Test substance intake of 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	Pre-mating period										Breeding period						All the periods			
			Test substance intake (mg/kg/day)																			
			Treatment week										Gestation days			Lactation days						
			1	2	3	4	5	6	7	8	9	10	0-7	7-14	14-20	0-7	7-14	14-21	Min	-	Max	Mean
F0	HBCD 150 ppm	24	16.4	15.6	14.0	12.9	12.2	11.8	11.0	10.9	10.2	9.9	10.4	10.1	8.3	14.9	22.7	32.6	8.3	-	32.6	14.0
	HBCD 1500 ppm	24	164	161	141	132	123	118	110	107	99	98	102	103	84	155	233	331	84	-	331	141
	HBCD 15000 ppm	24	1648	1591	1419	1292	1216	1157	1085	1048	969	959	999	997	826	1378	2206	3016	826	-	3016	1363
F1	HBCD 150 ppm	24	18.5	18.1	16.1	14.7	14.1	13.3	12.3	11.6	10.9	10.7	10.3	10.3	8.5	13.6	20.0	25.3	8.5	-	25.3	14.3
	HBCD 1500 ppm	24	180	175	162	148	134	127	120	115	109	106	107	105	87	133	177	227	87	-	227	138
	HBCD 15000 ppm	24	1781	1725	1597	1445	1322	1273	1190	1151	1106	1064	1051	1057	876	1249	1714	2209	876	-	2209	1363

Table 11 Vaginal estrous cycles 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	Estrous cyclicity		
			Normality Incidence (%) ^a	Length (days)	
F0	Control	24	22/24	Mean	4.24
			(91.7)	S.D.	0.83
	HBCD 150 ppm	24	23/24	Mean	4.17
			(95.8)	S.D.	0.62
	HBCD 1500 ppm	24	21/24	Mean	(22) 4.10
			(87.5)	S.D.	0.26
	HBCD 15000 ppm	23	20/23	Mean	4.58
			(87.0)	S.D.	1.17
F1	Control	24	23/24	Mean	4.11
			(95.8)	S.D.	0.25
	HBCD 150 ppm	24	22/24	Mean	4.35
			(91.7)	S.D.	0.88
	HBCD 1500 ppm	24	22/24	Mean	4.43
			(91.7)	S.D.	0.76
	HBCD 15000 ppm	24	22/24	Mean	4.22
			(91.7)	S.D.	0.64

Values in parentheses are the number of animals examined.

a: Incidence of females with the normal estrous cycle (%) = (number of females cycling normally/number of females examined) x 100.

The normal estrous cycle is defined as having a mean cycle length between 4.0 and 6.0 days.

Table 12 Reproductive findings in F0 and F1 parental rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Group	Copulation index		Fertility index		Gestation index (Inci- dence, %)	Pre- coital interval (days)	Gesta- tion length (days)	Number of implanta- tions	Delivery index (%) ^a	Number of pups delivered	Sex ratio	Viability index (%) ^b on postnatal day			
		(Inci- dence, %)	(Inci- dence, %)	(Inci- dence, %)	(Inci- dence, %)								0	4	21	
F0	Control	24/24	24/24	24/24	24/24	24/24	Mean	3.4	22.1	14.2	92.0	13.0	F1 pup data			
		(100)	(100)	(100)	(100)	(100)	S.D.	3.9	0.3	2.1	7.7	2.3	0.524	99.6	95.6	93.2
	HBCD 150 ppm	24/24	24/24	22/24	22/24	21/22	Mean	3.1	22.3	(22) 13.7	(22) 89.3	13.3	0.471	97.5	98.7	99.4
		(100)	(100)	(91.7)	(91.7)	(95.5)	S.D.	3.3	0.5	3.3	20.9	1.7		8.5	2.8	2.7
	HBCD 1500 ppm	22/24	22/24	20/22	20/22	20/20	Mean	2.7	22.6 ^{ss}	14.5	90.7	13.3	0.426 *	98.8	98.7	98.1
		(91.7)	(91.7)	(90.9)	(90.9)	(100)	S.D.	1.4	0.5	1.4	13.8	2.6		2.8	4.4	4.6
	HBCD 15000 ppm	21/23	22/23	18/21	19/22	18/19	Mean	3.5	22.2	(19) 14.5	93.6	13.5	0.572	99.2	95.8	93.8
		(91.3)	(95.7)	(85.7)	(86.4)	(94.7)	S.D.	4.3	0.4	2.7	7.3	2.8		2.5	10.3	23.6
													F2 pup data			
F1	Control	24/24	24/24	23/24	23/24	23/23	Mean	2.6	22.5	14.3	91.4	13.2	0.523	98.6	86.9	(22) 85.0
		(100)	(100)	(95.8)	(95.8)	(100)	S.D.	1.6	0.5	2.5	12.3	3.4		5.3	24.8	22.0
	HBCD 150 ppm	24/24	24/24	23/24	23/24	23/23	Mean	3.4	22.4	14.7	94.8	13.9	0.492	97.7	87.3	(22) 89.6
		(100)	(100)	(95.8)	(95.8)	(100)	S.D.	4.1	0.6	3.4	6.0	3.3		4.9	21.1	13.9
HBCD 1500 ppm	23/23	24/24	20/23	21/24	20/21	Mean	3.3	22.4	(21) 14.0	(21) 88.1	13.4	0.517	96.0	92.1	71.3	
	(100)	(100)	(87.0)	(87.5)	(95.2)	S.D.	3.7	0.5	3.2	22.7	2.4		9.5	12.8	26.9	
HBCD 15000 ppm	24/24	24/24	21/24	21/24	21/21	Mean	2.3	22.4	14.3	92.6	13.1	0.486	97.8	68.4 ^s	(20) 49.7 ^{ss}	
	(100)	(100)	(87.5)	(87.5)	(100)	S.D.	1.3	0.5	2.8	8.0	2.4		5.1	33.5	41.1	

Copulation index (%) = (number of animals with successful copulation/number of animals paired) x 100.

Fertility index (%) = (number of animals that impregnated a female or were pregnant/number of animals with successful copulation) x 100.

Gestation index (%) = (number of females that delivered live pups/number of pregnant females) x 100.

Delivery index (%) = (number of pups delivered/number of implantations) x 100.

Sex ratio = total number of male pups/total number of pups.

Viability index on postnatal day 0 (%) = (number of live pups on postnatal day 0/number of pups delivered) x 100.

Viability index on postnatal day 4 (%) = (number of live pups on postnatal day 4/number of live pups on postnatal day 0) x 100.

Viability index on postnatal day 21 (%) = (number of live pups on postnatal day 21/number of live pups selected for use on postnatal day 4) x 100.

a and b: The litter is the unit evaluated.

Values in parentheses are the number of animals examined.

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

^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 13 Sperm number and motility 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	Group	Number of animals		Number of testis sperms		Number of epididymal sperms		% Motile	% Progressive	Swimming speed			Swimming pattern			
				10 ⁶ /testis	10 ⁶ /g testis	10 ⁶ /cauda	10 ⁶ /g cauda			VAP	VSL	VCL	ALH	BCF	STR	LIN
F0	Control	24	Mean	164.0	104.2	276.3	873.2	88.9	57.0	140.3	83.7	309.6	20.3	26.5	59.2	26.8
			S.D.	23.0	14.9	56.0	133.6	5.7	15.7	11.8	14.1	34.2	0.8	2.1	6.4	2.3
	HBCD 150 ppm	24	Mean	168.5	104.0	225.9	738.9 *	83.7	51.7	132.8	77.8	289.6	19.3	25.7	55.6	25.6
			S.D.	48.5	26.1	82.9	212.9	20.8	21.8	32.4	23.3	73.9	4.3	6.1	13.3	5.9
	HBCD 1500 ppm	24	Mean	171.1	105.2	259.0	873.8	91.2	57.9	139.6	82.1	307.8	20.4	25.7	58.3	26.5
			S.D.	36.7	18.6	42.9	157.4	4.7	16.6	10.4	14.7	31.4	0.7	1.8	6.6	2.5
	HBCD 15000 ppm	22	Mean	163.5	106.4	254.2	860.4	89.6	52.4	140.4	78.8	304.6	20.9 ^s	26.5	55.5	25.4
			S.D.	37.5	19.8	51.3	162.5	6.4	16.2	12.4	14.5	33.1	1.0	2.5	6.0	2.4
F1	Control	24	Mean	200.2	118.4	274.0	857.9	87.3	64.1	149.8	97.2	344.4	20.3	27.6	64.4	28.1
			S.D.	29.6	20.7	49.8	98.0	6.5	12.8	12.6	13.2	31.3	0.9	1.7	4.8	1.9
	HBCD 150 ppm	24	Mean	187.0	114.3	273.5	876.7	86.2	64.7	152.2	100.1	347.6	20.7	26.7	65.6	28.8
			S.D.	28.0	15.9	75.4	213.0	8.4	11.9	12.8	13.6	34.5	1.3	1.6	5.3	2.3
	HBCD 1500 ppm	22	Mean	183.7	113.3	251.1	859.3	86.2	64.3	151.1	100.2	349.1	20.3	27.8	65.6	28.6
			S.D.	32.4	19.2	74.3	198.5	7.9	13.1	15.2	14.9	39.2	1.1	2.2	4.4	1.9
	HBCD 15000 ppm	24	Mean	191.1	119.3	257.6	836.7	87.5	64.9	150.0	97.4	347.0	20.1	27.2	64.5	27.9
			S.D.	38.2	20.0	61.5	170.3	7.7	16.0	12.2	16.6	32.9	0.9	2.6	7.1	2.9

VAP: Mean path velocity (µm/sec).

VSL: Straight line average velocity (µm/sec).

VCL: Mean curvilinear velocity (µm/sec).

ALH: Mean lateral head displacement (µm).

BCF: Mean beat cross frequency (Hz).

STR: Mean straightness (%) = VSL/VAP x 100.

LIN: Mean linearity (%) = VSL/VCL x 100.

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

Table 14 Abnormal sperm ratio 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	Abnormal sperm ratio (%)												
			Total	Tailless sperm	Head					Two heads	Neck and middle piece			Tail	
					Small sized	Banana shaped	Hooked shaped	Truncated shaped	Amorphous shaped		Flexion	Two necks	Enlarge- ment	Fragement	Two tails
F0	Control	24	Mean	1.6	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
			S.D.	1.1	1.0	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0
	HBCD 150 ppm	23	Mean	4.9	4.5	0.0	0.0	0.0	0.1	0.0	0.3	0.0	0.0	0.0	0.0
			S.D.	16.5	15.3	0.0	0.1	0.0	0.2	0.1	1.3	0.0	0.0	0.0	0.0
	HBCD 1500 ppm	24	Mean	1.6	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
			S.D.	0.9	0.9	0.0	0.1	0.0	0.1	0.2	0.1	0.0	0.0	0.0	0.0
	HBCD 15000 ppm	22	Mean	2.3	1.9	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0
			S.D.	1.8	1.7	0.0	0.3	0.0	0.2	0.2	0.3	0.0	0.0	0.0	0.0
F1	Control	24	Mean	1.1	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
			S.D.	0.7	0.7	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	HBCD 150 ppm	24	Mean	1.3	1.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
			S.D.	0.8	0.7	0.0	0.1	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0
	HBCD 1500 ppm	22	Mean	2.1	1.9	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
			S.D.	2.1	1.9	0.0	0.4	0.0	0.1	0.1	0.2	0.0	0.0	0.0	0.0
	HBCD 15000 ppm	24	Mean	1.7	1.4	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
			S.D.	1.1	1.1	0.1	0.3	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0

Table 15 Sexual development in F1 parental rats treated with 1,2,5,6,9,10-hexabromocyclododecane (HBCD) in the two-generation reproductive toxicity study (SR04222)

Gener- ation	Group	Male				Female			
		Number of animals		Age at preputial separation (days)	Body weight (g) on the day at preputial separation	Number of animals		Age at vaginal opening (days)	Body weight (g) on the day at vaginal opening
F1	Control	24	Mean	42.8	225.6	24	Mean	30.9	106.0
			S.D.	1.7	17.1		S.D.	2.0	13.8
	HBCD 150 ppm	24	Mean	41.7	219.6	24	Mean	30.3	102.9
			S.D.	1.8	20.0		S.D.	2.6	13.8
	HBCD 1500 ppm	24	Mean	42.8	235.0	24	Mean	30.1	106.0
			S.D.	2.2	20.8		S.D.	1.8	10.6
	HBCD 15000 ppm	24	Mean	43.7	226.5	24	Mean	30.8	100.7
			S.D.	1.5	16.2		S.D.	2.2	13.0

Table 16 Locomotor activity count 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		Locomotor activity count						
				Determination time (minutes)						
				0-10	10-20	20-30	30-40	40-50	50-60	0-60
F1	Control	10	Mean	141.9	86.1	39.9	15.6	13.8	4.8	302.1
			S.D.	63.5	59.3	49.4	19.1	21.5	15.2	170.7
	HBCD 150 ppm	10	Mean	240.9	116.8	58.2	29.5	5.7	0.8	451.9
			S.D.	116.7	86.3	66.8	45.0	18.0	2.5	276.1
	HBCD 1500 ppm	10	Mean	127.4	71.7	11.8	2.9	0.0	0.0	213.8
			S.D.	79.2	44.4	11.4	5.9	0.0	0.0	125.6
	HBCD 15000 ppm	10	Mean	162.4	53.3	8.8	7.1	1.0	5.7	238.3
			S.D.	124.9	53.7	13.9	11.9	2.5	18.0	186.5

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)

Generation	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