

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)

Gener- ation	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.

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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	15000	150	1500	15000	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)

Generation	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		
	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	(23) 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		
	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 *	(22) 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		
	HBCD 15000 ppm	24	Mean	142.4	213.3	274.5 *	329.0 ^s	375.8	(23) 409.3 ^s	(23) 437.4	(23) 463.4	(23) 485.8	(23) 502.3	(23) 514.8	(23) 522.9	(23) 539.4	(22) 548.7	(21) 560.0	(22) 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	
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	(23) 540.3	(23) 561.5	(22) 582.2	(22) 594.1	(22) 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												
			Body weight (g)										Gestation day				Lactation day			Autopsy day					
			Treatment week										0	7	14	20	0	4	7		14	21			
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	297.7	328.0	360.4	425.9	332.5	344.4	345.6	355.0	334.0	322.9
				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	299.3	331.2	363.0	436.4	338.1	349.7	349.8	358.9	336.6	327.0
				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	290.2	321.8	355.0	423.9	333.3	340.3	343.7	356.2	338.5	328.6	
			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 **	272.9 **	302.6 **	333.6 ⁵	399.2 *	305.6 **	315.9 **	319.4 **	329.9 *	316.5	307.8	
			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.

⁵: 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	
	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	(23)	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	
F0	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 *	(22)	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	
	HBCD 15000 ppm	24	Mean	70.9 **	132.1 ^{SS}	186.6 ^S	233.4 *	(23)	(23)	(23)	(23)	(23)	(23)	(23)	(23)	(23)	(22)	(21)	(22)
			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	
F1	HBCD 1500 ppm	24	Mean	47.5	111.4	174.8	241.4	298.8	342.7	382.1	415.0	441.9	464.7	470.2	491.9	512.5	524.5	543.6	
			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.