

Table 24 Serum hormone levels in F0 and F1 parental male rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Group	Number of animals		Testosterone (ng/mL)	DHT <sup>a</sup> (pg/mL)	LH <sup>b</sup> (ng/mL)	FSH (ng/mL)	
F0	Control	8	Mean	1.32	80.9	1.03	8.87	
			S.D.	0.90	41.4	0.10	1.61	
	DCBS 80 ppm	8	Mean	1.38	82.2	0.83	9.55	
			S.D.	0.97	32.0	0.72	2.16	
	DCBS 600 ppm	8	Mean	1.01	69.1	1.26	9.43	
			S.D.	0.29	28.3	0.38	1.40	
	DCBS 4500 ppm	8	Mean	1.07	56.4	1.08	9.31	
			S.D.	0.92	34.9	0.54	0.97	
	F1	Control	8	Mean	0.40	39.2	1.38	7.68
				S.D.	0.13	26.7	0.32	1.46
		DCBS 80 ppm	8	Mean	0.99 <sup>s</sup>	49.7	1.23	7.05
				S.D.	0.70	14.6	0.56	1.02
DCBS 600 ppm		8	Mean	0.89	48.1	1.72 <sup>s</sup>	6.92	
			S.D.	0.63	21.1	0.12	1.41	
DCBS 4500 ppm		8	Mean	0.72	41.9	1.58	7.84	
			S.D.	0.43	25.6	0.34	1.53	

a: The actual measurement of DHT was below the lower limit of quantification (<25.0 pg/mL) in one F1 animal each in the control and 4500 ppm groups.

b: The actual measurement of LH was below the lower limit of quantification (<0.80 ng/mL) in three F0 and one F1 animals in the 80 ppm group and one F0 animal in the 4500 ppm group.

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

Table 25 Serum hormone levels in F0 and F1 parental female rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Group	Number of animals		Estradiol (pg/mL)	Progesterone (ng/mL)	LH <sup>a</sup> (ng/mL)	FSH (ng/mL)	
F0	Control	8	Mean	80.5	5.17	1.30	5.75	
			S.D.	15.7	3.59	0.22	0.99	
	DCBS 80 ppm	8	Mean	66.7	8.49	1.13	6.29	
			S.D.	16.2	4.37	0.27	1.14	
	DCBS 600 ppm	8	Mean	68.7	8.08	1.35	5.99	
			S.D.	16.0	4.70	0.20	1.06	
	DCBS 4500 ppm	8	Mean	64.0	9.88	1.15	5.60	
			S.D.	12.3	4.20	0.49	0.86	
	F1	Control	8	Mean	73.8	6.42	1.45	3.12
				S.D.	25.3	2.84	0.26	0.28
		DCBS 80 ppm	8	Mean	61.9	8.95	1.34	3.63
				S.D.	17.2	3.55	0.59	1.38
DCBS 600 ppm		8	Mean	59.7	7.20	1.52	3.91	
			S.D.	21.5	4.66	0.24	1.32	
DCBS 4500 ppm		8	Mean	63.5	8.59	1.55	4.50	
			S.D.	26.7	5.85	0.42	1.50	

a: The actual measurement of LH was below the lower limit of quantification (<0.80 ng/mL) in one F1 animal in the 80 ppm group and one F0 animal in the 4500 ppm group.

Table 26 Autopsy findings in F0 and F1 parental male rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	DCBS (ppm)															
		Control				80				600				4500			
		A	B	C	T	A	B	C	T	A	B	C	T	A	B	C	T
F0	Number of animals examined	22	2	0	24	23	0	1	24	24	0	0	24	24	0	0	24
	Number of animals with abnormal findings	0	0	-	0	0	-	1	1	3	-	-	3	1	-	-	1
	Findings <sup>a</sup>																
	Incisor: Malocclusion	0	0	-	0	0	-	1	1	1	-	-	1	0	-	-	0
	Nasal bone: Fracture	0	0	-	0	0	-	1	1	0	-	-	0	0	-	-	0
	Stomach, duodenum, jejunum, ileum and cecum: Retention gas	0	0	-	0	0	-	1	1	0	-	-	0	0	-	-	0
	Ileum: White mass, serosa	0	0	-	0	0	-	0	0	1	-	-	1	0	-	-	0
	Thickening, mucosa	0	0	-	0	0	-	0	0	1	-	-	1	0	-	-	0
	Mesenteric lymph node: Swelling	0	0	-	0	0	-	0	0	1	-	-	1	0	-	-	0
	Testis: Atrophy	0	0	-	0	0	-	0	0	0	-	-	0	1	-	-	1
	Epididymis: Atrophy	0	0	-	0	0	-	0	0	0	-	-	0	1	-	-	1
F1	Number of animals examined	23	1	0	24	22	2	0	24	20	4	0	24	24	0	0	24
	Number of animals with abnormal findings	2	1	-	3	4	0	-	4	1	0	-	1	6	-	-	6
	Findings <sup>a</sup>																
	Incisor: Malocclusion	0	0	-	0	0	0	-	0	0	0	-	0	1	-	-	1
	Ileum: Diverticulum	0	0	-	0	0	0	-	0	0	0	-	0	2	-	-	2
	Kidney : Dilatation, renal pelvis	1	1	-	2	3	0	-	3	1	0	-	1	2	-	-	2
	Fine white granule, renal pelvis	0	0	-	0	1	0	-	1	0	0	-	0	0	-	-	0
	Seminal vesicle : Small size	0	0	-	0	1	0	-	1	0	0	-	0	1	-	-	1
	Testis: Atrophy	1	0	-	1	0	0	-	0	0	0	-	0	0	-	-	0
	Epididymis: Atrophy	1	0	-	1	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 unsuccessfully mated or did not impregnate a female; C, animals that were euthanized during the study; T, total (A+B+C).

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

-: Not applicable.

Table 27 Autopsy findings in F0 and F1 parental female rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	DCBS (ppm)															
		Control				80				600				4500			
		A	B	C	T	A	B	C	T	A	B	C	T	A	B	C	T
F0	Number of animals examined	22	2	0	24	24	0	0	24	24	0	0	24	24	0	0	24
	Number of animals with abnormal findings	4	2	-	6	0	-	-	0*	0	-	-	0*	1	-	-	1
	Findings <sup>a</sup>																
	Skin: Subcutaneous yellowish/grayish white mass	1	0	-	1	0	-	-	0	0	-	-	0	1	-	-	1
	Incisor: Malocclusion/fracture	3	0	-	3	0	-	-	0	0	-	-	0	0	-	-	0
	Nasal bone: Deformity	1	0	-	1	0	-	-	0	0	-	-	0	0	-	-	0
	Ileum: Diverticulum	0	1	-	1	0	-	-	0	0	-	-	0	0	-	-	0
	Uterine horn: Retention, yellowish white mucous fluid	0	1	-	1	0	-	-	0	0	-	-	0	0	-	-	0
	Vagina: Atresia	0	2	-	2	0	-	-	0	0	-	-	0	0	-	-	0
F1	Number of animals examined	22	1	1	24	22	2	0	24	21	3	0	24	23	1	0	24
	Number of animals with abnormal findings	0	0	0	0	0	0	-	0	1	0	-	1	4	1	-	5*
	Findings <sup>a</sup>																
	Incisor: Malocclusion	0	0	0	0	0	0	-	0	0	0	-	0	3	0	-	3
	Cerebrum: Dilatation, ventricle	0	0	0	0	0	0	-	0	0	0	-	0	0	1	-	1
	Thyroid: Aplasia	0	0	0	0	0	0	-	0	0	0	-	0	1	0	-	1
	Thymus: Atrophy	0	0	0	0	0	0	-	0	0	0	-	0	1	0	-	1
	Kidney: Dilatation, renal pelvis	0	0	0	0	0	0	-	0	1	0	-	1	0	0	-	0
	Ureter: Dilatation	0	0	0	0	0	0	-	0	1	0	-	1	0	0	-	0

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

Fate: A, animals that had weanlings; B, animals that were not pregnant and that did not produce viable pups or weanlings; 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.

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Table 28 Absolute and relative organ weights in F0 and F1 parental male rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Group	Number of animals		Body weight		Brain			Pituitary gland		Thyroid <sup>a</sup>		Thymus		Liver		Kidney <sup>a</sup>		Spleen	
				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	624.4	2.25	0.366	12.8	2.07	24.0	3.85	300	48.2	20.45	3.25	3.64	0.585	882	142		
			S.D.	76.0	0.08	0.041	1.3	0.22	4.0	0.60	73	11.3	4.34	0.33	0.42	0.043	158	20		
	DCBS 80 ppm	23	Mean	612.5	2.28	0.375	13.1	2.16	23.7	3.87	289	47.2	19.76	3.22	3.64	0.595	835	137		
			S.D.	61.0	0.10	0.034	1.4	0.22	4.3	0.59	55	8.2	2.94	0.25	0.41	0.044	143	20		
	DCBS 600 ppm	24	Mean	603.4	2.25	0.376	12.9	2.15	24.4	4.08	318	52.9	19.76	3.27	3.57	0.593	846	140		
			S.D.	51.2	0.07	0.031	1.3	0.21	4.1	0.81	67	11.1	2.09	0.18	0.29	0.035	167	24		
	DCBS 4500 ppm	24	Mean	575.4 <sup>§</sup>	2.25	0.392 <sup>*</sup>	12.4	2.15	26.6	4.63 <sup>**</sup>	272	47.2	19.96	3.47 <sup>§</sup>	3.69	0.641 <sup>**</sup>	748 <sup>**</sup>	131		
			S.D.	42.3	0.08	0.030	1.2	0.19	5.2	0.86	49	6.8	2.21	0.26	0.36	0.040	112	21		
	F1	Control	24	Mean	630.7	2.26	0.363	13.6	2.17	24.9	3.95	346	54.8	20.80	3.28	3.70	0.586	909	145	
				S.D.	74.7	0.10	0.038	1.4	0.23	4.9	0.66	116	17.0	3.73	0.29	0.52	0.041	129	16	
		DCBS 80 ppm	24	Mean	605.1	2.29	0.380	13.9	2.30	23.3	3.86	269 <sup>§</sup>	44.5 <sup>§</sup>	19.69	3.25	3.66	0.606	845	139	
				S.D.	47.7	0.06	0.028	1.3	0.25	4.7	0.78	54	8.9	2.32	0.19	0.23	0.042	141	18	
DCBS 600 ppm		24	Mean	614.2	2.26	0.370	13.9	2.27	23.8	3.88	331	53.9	21.19	3.46	3.69	0.602	847	138		
			S.D.	52.5	0.06	0.030	1.1	0.17	4.5	0.69	83	12.7	2.06	0.28	0.36	0.047	124	17		
DCBS 4500 ppm		24	Mean	622.6	2.21 <sup>§</sup>	0.356	14.0	2.26	24.6	3.95	316	50.9	22.82 <sup>§</sup>	3.65 <sup>**</sup>	3.91	0.629 <sup>**</sup>	869	139		
			S.D.	51.8	0.09	0.027	1.6	0.26	4.9	0.67	62	9.8	3.37	0.28	0.43	0.044	162	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.

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

Table 28 (continued) Absolute and relative organ weights in F0 and F1 parental male rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

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	58.0	9.3	3.54	0.576	1350	219	2.31	0.376	899	145	
			S.D.	9.5	1.3	0.24	0.083	105	26	0.25	0.062	189	32	
	DCBS 80 ppm	23	Mean	57.9	9.5	3.62	0.598	1379	228	2.28	0.376	910	149	
			S.D.	7.7	1.1	0.20	0.075	74	28	0.24	0.060	150	20	
	DCBS 600 ppm	24	Mean	57.7	9.6	3.57	0.594	1354	225	2.27	0.376	853	142	
			S.D.	7.4	1.2	0.24	0.048	113	17	0.29	0.041	234	37	
	DCBS 4500 ppm	24	Mean	51.0 **	8.9	3.65	0.637 **	1330	232	2.15	0.375	769	134	
			S.D.	6.1	1.0	0.31	0.068	115	21	0.21	0.034	165	26	
	F1	Control	24	Mean	60.5	9.6	3.60	0.575	1348	215	2.30	0.368	838	133
				S.D.	9.8	1.5	0.35	0.062	138	24	0.23	0.047	174	24
		DCBS 80 ppm	24	Mean	60.3	10.0	3.61	0.601	1342	223	2.19	0.364	812	134
				S.D.	7.1	1.0	0.27	0.073	67	21	0.28	0.054	181	28
DCBS 600 ppm		24	Mean	61.8	10.1	3.60	0.589	1327	217	2.21	0.362	822	134	
			S.D.	7.2	1.3	0.27	0.066	111	22	0.22	0.039	190	29	
DCBS 4500 ppm		24	Mean	61.3	9.8	3.78	0.610	1346	217	2.07 **	0.333 *	784	127	
			S.D.	13.1	2.0	0.32	0.062	118	19	0.26	0.045	168	31	

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 N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Group	Number of animals		Body weight	Brain			Pituitary gland		Thyroid <sup>a</sup>		Thymus		Liver		Kidney <sup>a</sup>		Spleen	
					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	22	Mean	305.9	2.04	0.670	13.8	4.51	18.8	6.19	237	77.0	13.73	4.48	2.13	0.696	632	207	
			S.D.	28.5	0.10	0.050	1.8	0.47	4.4	1.57	71	21.6	2.51	0.67	0.29	0.063	97	27	
	DCBS 80 ppm	24	Mean	311.6	2.12 **	0.681	15.2 *	4.87	17.7	5.67	209	67.2	13.83	4.43	2.20	0.707	582	187 *	
			S.D.	17.1	0.09	0.046	1.9	0.63	2.2	0.71	55	17.5	1.73	0.44	0.16	0.058	78	26	
	DCBS 600 ppm	24	Mean	313.7	2.12 **	0.676	14.7	4.70	16.9	5.40	242	77.7	13.86	4.41	2.29	0.731	583	186 *	
			S.D.	17.8	0.07	0.042	2.2	0.66	3.1	0.92	57	19.8	1.84	0.47	0.23	0.068	77	22	
	DCBS 4500 ppm	24	Mean	288.5 ‡	2.07	0.720 **	13.6	4.71	17.5	6.10	197	68.5	13.67	4.74	2.27	0.786 **	560 *	194	
			S.D.	16.2	0.07	0.045	1.8	0.60	2.2	0.86	59	20.8	1.48	0.44	0.19	0.057	79	27	
	F1	Control	22	Mean	331.9	2.08	0.632	15.9	4.83	19.0	5.72	251	75.3	14.55	4.39	2.37	0.713	632	191
				S.D.	32.5	0.08	0.056	2.0	0.73	3.9	0.98	69	18.4	1.66	0.28	0.30	0.046	73	18
		DCBS 80 ppm	22	Mean	331.2	2.17 **	0.658	16.1	4.90	18.2	5.51	212	64.1	14.18	4.28	2.39	0.723	599	181
				S.D.	28.5	0.08	0.056	2.4	0.79	2.7	0.70	47	14.2	2.14	0.49	0.22	0.040	63	15
DCBS 600 ppm		21	Mean	331.3	2.15 *	0.651	15.8	4.78	17.7	5.35	261	79.2	14.32	4.33	2.40	0.726	609	184	
			S.D.	23.1	0.08	0.043	1.8	0.52	3.5	1.08	65	20.2	1.49	0.41	0.21	0.063	80	19	
DCBS 4500 ppm		23	Mean	330.2	2.08	0.633	16.1	4.89	19.4	5.89	211	64.0	15.83	4.81 ††	2.53	0.771 ††	639	194	
			S.D.	30.8	0.08	0.060	1.9	0.66	4.1	1.15	63	18.7	2.11	0.59	0.26	0.080	115	37	

(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.

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

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

Table 29 (continued) Absolute and relative organ weights in F0 and F1 parental female rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

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	22	Mean	66.8	21.8	100.2	32.8	957	313
			S.D.	9.4	2.3	15.8	4.4	189	56
	DCBS 80 ppm	24	Mean	65.9	21.2	95.4	30.7	962	310
			S.D.	6.1	2.1	11.6	3.9	186	65
	DCBS 600 ppm	24	Mean	68.3	21.8	101.1	32.3	975	311
			S.D.	8.6	2.6	9.1	3.1	198	63
	DCBS 4500 ppm	24	Mean	69.6	24.1 **	91.6	31.8	1024	357
			S.D.	8.1	2.7	12.4	4.1	203	76
F1	Control	22	Mean	70.0	21.2	110.6	33.4	927	280
			S.D.	9.7	3.2	13.0	2.9	191	54
	DCBS 80 ppm	22	Mean	73.5	22.2	109.1	33.0	928	283
			S.D.	10.9	3.1	16.3	4.5	128	48
	DCBS 600 ppm	21	Mean	73.4	22.2	108.5	32.8	976	295
			S.D.	9.3	3.0	12.5	3.2	185	52
	DCBS 4500 ppm	23	Mean	77.5 *	23.6 *	108.2	32.8	949	288
			S.D.	8.9	3.2	13.4	3.3	192	52

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 30 Histopathological findings in F0 and F1 parental male rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	DCBS (ppm)												
		Control			80			600			4500			
		A	B	T	A	B	T	A	B	T	A	B	T	
F0	Number of animals examined	22	2	24	0	0	0	0	0	0	0	24	0	24
	Findings in organs/tissues examined <sup>a,b,c</sup>													
	Liver: Microgranuloma	4	2	6	-	-	-	-	-	-	-	5	-	5
	Kidney: Hyaline droplet, proximal tubular epithelium	12	2	14	-	-	-	-	-	-	-	20	-	20
	Eosinophilic body, proximal tubular epithelium	12	2	14	-	-	-	-	-	-	-	20	-	20
	Regeneration, tubular epithelium	5	0	5	-	-	-	-	-	-	-	1	-	1
	Cast, hyaline	2	0	2	-	-	-	-	-	-	-	2	-	2
	Cellular infiltration, inflammatory cell, renal pelvic mucosa	0	1	1	-	-	-	-	-	-	-	0	-	0
	Cyst	2	0	2	-	-	-	-	-	-	-	1	-	1
	Testis: Atrophy, seminiferous tubule	0	0	0	-	-	-	-	-	-	-	1	-	1
	Epididymis: Decrease, sperm	0	0	0	-	-	-	-	-	-	-	1	-	1
	Cell debris, lumen	0	0	0	-	-	-	-	-	-	-	1	-	1
	Prostate: Cellular infiltration, inflammatory cell	15	0	15	-	-	-	-	-	-	-	17	-	17
	Pituitary gland: Cyst, pars distalis	1	0	1	-	-	-	-	-	-	-	0	-	0
	Cyst, pars intermedia	1	0	1	-	-	-	-	-	-	-	0	-	0
	Tubular hyperplasia, pars intermedia	1	0	1	-	-	-	-	-	-	-	1	-	1
	Findings in organs/tissues in which abnormal findings were grossly observed <sup>a,d</sup>													
	Ileum: Cyst, squamous cell	-	-	-	-	-	-	1(2)	-	1(2)	-	-	-	-
	Cellular infiltration, inflammatory cell	-	-	-	-	-	-	1(2)	-	1(2)	-	-	-	-
	Mesenteric lymph node: Hyperplasia, lymphoid	-	-	-	-	-	-	1(1)	-	1(1)	-	-	-	-

(to be continued)

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

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

b: Organs/tissues examined were the liver, kidneys, 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.

c: Statistical analyses were made between the control and 4500 ppm groups based on the total number of animals examined.

d: Values in parentheses are the number of animals examined.

-: Not applicable.

Table 30 (continued) Histopathological findings in F0 and F1 parental male rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	DCBS (ppm)											
		Control			80			600			4500		
		A	B	T	A	B	T	A	B	T	A	B	T
F1	Number of animals examined	23	1	24	0	2	2	0	4	4	24	0	24
	Findings in organs/tissues examined <sup>a,b,c</sup>												
	Liver: Microgranuloma	8	0	8	-	1	1	-	3	3	7	-	7
	Kidney: Hyaline droplet, proximal tubular epithelium	20	0	20	-	1	1	-	2	2	24	-	24
	Eosinophilic body, proximal tubular epithelium	20	0	20	-	1	1	-	2	2	24	-	24
	Regeneration, tubular epithelium	6	1	7	-	0	0	-	1	1	8	-	8
	Cast, hyaline	4	0	4	-	0	0	-	0	0	5	-	5
	Mineralization, papilla	0	0	0	-	0	0	-	0	0	1	-	1
	Dilatation, renal pelvis	1	1	2	-	0	0	-	0	0	2	-	2
	Testis: Atrophy, seminiferous tubule	1	0	1	-	0	0	-	0	0	0	-	0
	Epididymis: Decrease, sperm	1	0	1	-	0	0	-	0	0	0	-	0
	Cell debris, lumen	1	0	1	-	0	0	-	0	0	0	-	0
	Prostate: Cellular infiltration, inflammatory cell	13	0	13	-	2	2	-	1	1	12	-	12
	Pituitary gland: Cyst, pars distalis	0	0	0	-	0	0	-	1	1	1	-	1
	Tubular hyperplasia, pars intermedia	0	0	0	-	0	0	-	0	0	1	-	1

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

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

b: Organs/tissues examined were the liver, kidneys, 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.

c: Statistical analyses were made between the control and 4500 ppm groups based on the total number of animals examined.

-: Not applicable.

Table 31 Histopathological findings in F0 and F1 parental female rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	DCBS (ppm)															
		Control				80				600				4500			
		A	B	C	T	A	B	C	T	A	B	C	T	A	B	C	T
F0	Number of animals examined	22	2	0	24	0	0	0	0	0	0	0	0	24	0	0	24
	Findings in organs/tissues examined <sup>a,b,c</sup>																
	Liver: Microgranuloma	5	0	-	5	-	-	-	-	-	-	-	-	7	-	-	7
	Kidney: Regeneration, tubular epithelium	1	0	-	1	-	-	-	-	-	-	-	-	1	-	-	1
	Cellular infiltration, inflammatory cell, renal pelvic mucosa	1	0	-	1	-	-	-	-	-	-	-	-	0	-	-	0
	Mineralization, renal pelvic mucosa	0	1	-	1	-	-	-	-	-	-	-	-	0	-	-	0
	Mineralization, cortex	0	0	-	0	-	-	-	-	-	-	-	-	1	-	-	1
	Uterine horn: Cellular infiltration, inflammatory cell	0	1	-	1	-	-	-	-	-	-	-	-	0	-	-	0
	Vagina: Atresia	0	2	-	2	-	-	-	-	-	-	-	-	0	-	-	0
	Pituitary gland: Cyst, pars intermedia	1	0	-	1	-	-	-	-	-	-	-	-	0	-	-	0
	Tubular hyperplasia, pars intermedia	1	0	-	1	-	-	-	-	-	-	-	-	1	-	-	1
	Mammary gland: Adenocarcinoma	1	0	-	1	-	-	-	-	-	-	-	-	1	-	-	1
F1	Number of animals examined	21	2	1	24 <sup>e</sup>	0	2	0	2	0	4	0	4	23	1	0	24
	Findings in organs/tissues examined <sup>a,b,c</sup>																
	Liver: Microgranuloma	11	1	0	12	-	1	-	1	-	3	-	3	11	1	-	12
	Kidney: Regeneration, tubular epithelium	1	0	-	1	-	0	-	0	-	1	-	1	0	0	-	0
	Dilatation, tubule	0	0	-	0	-	0	-	0	-	0	-	0	1	0	-	1
	Cellular infiltration, inflammatory cell, renal pelvic mucosa	1	0	-	1	-	0	-	0	-	0	-	0	0	0	-	0
	Cellular infiltration, inflammatory cell, cortex	0	0	-	0	-	0	-	0	-	0	-	0	1	0	-	1
	Mineralization, cortico-medullary junction	0	0	-	0	-	0	-	0	-	0	-	0	1	0	-	1
	Cast, hyaline	0	0	-	0	-	0	-	0	-	0	-	0	1	0	-	1
	Cyst	0	0	-	0	-	0	-	0	-	0	-	0	1	0	-	1
	Dilatation, renal pelvis	0	0	-	0	-	0	-	0	-	1	-	1	0	0	-	0
	Thymus: Atrophy, cortex	0	0	0	0	-	0	-	0	-	0	-	0	1	0	-	1
	Pituitary gland: Cyst, pars intermedia	1	0	0	1	-	0	-	0	-	1	-	1	0	0	-	0
	Tubular hyperplasia, pars intermedia	1	0	0	1	-	0	-	0	-	0	-	0	0	0	-	0
	Findings in organs/tissues in which abnormal findings were grossly observed <sup>a,d</sup>																
	Cerebrum: Dilatation, ventricle	-	-	-	-	-	-	-	-	-	-	-	-	-	1(1)	-	1(1)

Fate: A, animals that had weanlings; B, animals that were not pregnant, did not produce viable pups or weanlings, or showed abnormal estrous cyclicity; C, animals that died during the study; T, total (A+B+C).

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

b: Organs/tissues examined were the liver, kidneys, thymus, thyroids, spleen, adrenals, bone marrow (femur), mesenteric lymph node, Peyer's patch, ovaries, uterus, vagina, mammary gland and pituitary gland.

c: Statistical analyses were made between the control and 4500 ppm groups based on the total number of animals examined.

d: Values in parentheses are the number of animals examined.

e: The number of animals examined on the kidney was 23 because both sides of the kidneys in one dead animal showed autolysis.

-: Not applicable.

Table 32 Number of primordial follicles in F1 parental female rats treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Group	Number of animals		Number of primordial follicles <sup>a</sup>
F1	Control	10	Mean	323.1
			S.D.	56.6
	DCBS 4500 ppm	10	Mean	255.4
			S.D.	109.1

a: Counted based on a 5% nonrandom sample (every twentieth serial section) from right ovary of each animal.

Table 33 General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal day 0			
		Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of pups examined	149	175	167	158
	Number of pups with abnormal findings	2 ( 0.98 )	2 ( 1.46 )	1 ( 0.42 )	1 ( 1.39 )
	Findings <sup>a</sup>				
	Found dead	2 ( 0.98 )	2 ( 1.46 )	1 ( 0.42 )	1 ( 1.39 )
F2	Number of litters examined	23	22	21	24
	Number of pups examined	143	143	147	163
	Number of pups with abnormal findings	0 ( 0.00 )	1 ( 0.65 )	2 ( 1.55 )	8 ( 4.67 )*
	Findings <sup>a</sup>				
	Found dead	0 ( 0.00 )	1 ( 0.65 )	2 ( 1.55 )	8 ( 4.67 )*

(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  $p \leq 0.05$  by Wilcoxon rank-sum test.

Table 33 (continued-1) General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal days 1-4			
		Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of pups examined	147	173	166	157
	Number of pups with abnormal findings	1 ( 0.91 )	3 ( 1.40 )	8 ( 4.73 )	3 ( 1.74 )
	Findings <sup>a</sup>				
	Found dead/lost	1 ( 0.91 )	3 ( 1.40 )	8 ( 4.73 )	3 ( 1.74 )
F2	Number of litters examined	23	22	21	24
	Number of pups examined	143	142	145	155
	Number of pups with abnormal findings	6 ( 4.09 )	9 ( 4.55 )	11 ( 7.80 )	18 ( 12.56 )
	Findings <sup>a</sup>				
	Scab on auricle	0 ( 0.00 )	0 ( 0.00 )	1 ( 0.68 )	0 ( 0.00 )
	Found dead/lost	6 ( 4.09 )	9 ( 4.55 )	10 ( 7.12 )	18 ( 12.56 )

(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 N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal days 5-21			
		Control	DCBS (ppm)		
	80		600	4500	
F1	Number of litters examined	22	24	24	24
	Number of pups examined	86	98	95	97
	Number of pups with abnormal findings	0 ( 0.00 )	1 ( 1.04 )	1 ( 1.39 )	0 ( 0.00 )
	Findings <sup>a</sup>				
	Found dead/lost	0 ( 0.00 )	1 ( 1.04 )	1 ( 1.39 )	0 ( 0.00 )
F2	Number of litters examined	23	22	21	23
	Number of pups examined	87	81	81	92
	Number of pups with abnormal findings	0 ( 0.00 )	1 ( 1.14 )	2 ( 2.38 )	2 ( 2.17 )
	Findings <sup>a</sup>				
		Microphthalmia	0 ( 0.00 )	1 ( 1.14 )	0 ( 0.00 )
	Lost	0 ( 0.00 )	0 ( 0.00 )	2 ( 2.38 )	2 ( 2.17 )

(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-3) General appearance in F1 and F2 male rat pups and weanlings during postnatal days 0-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal days 22-26			
		Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of weanlings examined	86	97	94	97
	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	21	23
	Number of weanlings examined	83	81	79	90
	Number of weanlings with abnormal findings	0 ( 0.00 )	1 ( 1.14 )	0 ( 0.00 )	0 ( 0.00 )
	<i>Findings<sup>a</sup></i>				
	Microphthalmia	0 ( 0.00 )	1 ( 1.14 )	0 ( 0.00 )	0 ( 0.00 )

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 N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Item	Postnatal day 0			
		Control	80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of pups examined	133	141	163	143
	Number of pups with abnormal findings	1 ( 0.45 )	0 ( 0.00 )	0 ( 0.00 )	2 ( 1.22 )
	Findings <sup>a</sup>				
	Found dead	1 ( 0.45 )	0 ( 0.00 )	0 ( 0.00 )	2 ( 1.22 )
F2	Number of litters examined	23	22	20	24
	Number of pups examined	150	134	117	149
	Number of pups with abnormal findings	4 ( 2.42 )	0 ( 0.00 )*	2 ( 1.83 )	4 ( 2.43 )
	Findings <sup>a</sup>				
	Found dead	4 ( 2.42 )	0 ( 0.00 )*	2 ( 1.83 )	4 ( 2.43 )

(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  $p \leq 0.05$  by Wilcoxon rank-sum test.

Table 34 (continued-1) General appearance in F1 and F2 female rat pups and weanlings during postnatal days 0-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal days 1-4			
		Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of pups examined	132	141	163	141
	Number of pups with abnormal findings	4 ( 3.05 )	3 ( 1.81 )	3 ( 1.88 )	4 ( 2.22 )
	Findings <sup>a</sup>				
	Trauma and scab on forelimb	1 ( 0.76 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )
	Found dead/lost	3 ( 2.29 )	3 ( 1.81 )	3 ( 1.88 )	4 ( 2.22 )
F2	Number of litters examined	23	22	20	24
	Number of pups examined	146	134	115	145
	Number of pups with abnormal findings	8 ( 3.98 )	10 ( 7.05 )	5 ( 4.43 )	16 ( 10.68 )
	Findings <sup>a</sup>				
	Scab on hindlimb	0 ( 0.00 )	1 ( 0.76 )	0 ( 0.00 )	0 ( 0.00 )
	Found dead/lost	8 ( 3.98 )	9 ( 6.29 )	5 ( 4.43 )	16 ( 10.68 )

(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 N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal days 5-21			
		Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of pups examined	88	94	97	95
	Number of pups with abnormal findings	0 ( 0.00 )	1 ( 1.04 )	0 ( 0.00 )	1 ( 1.04 )
	Findings <sup>a</sup>				
	Found dead/lost	0 ( 0.00 )	1 ( 1.04 )	0 ( 0.00 )	1 ( 1.04 )
F2	Number of litters examined	23	22	20	23
	Number of pups examined	90	80	77	86
	Number of pups with abnormal findings	0 ( 0.00 )	0 ( 0.00 )	3 ( 4.17 )	2 ( 2.54 )
	Findings <sup>a</sup>				
	Found dead/lost	0 ( 0.00 )	0 ( 0.00 )	3 ( 4.17 )	2 ( 2.54 )

(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-3) General appearance in F1 and F2 female rat pups and weanlings during postnatal days 0-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Postnatal days 22-26			
		Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of weanlings examined	88	93	97	94
	Number of weanlings with abnormal findings	0 ( 0.00 )	2 ( 2.08 )	0 ( 0.00 )	0 ( 0.00 )
	Findings <sup>a</sup>				
	Found dead	0 ( 0.00 )	2 ( 2.08 )	0 ( 0.00 )	0 ( 0.00 )
F2	Number of litters examined	22	22	20	23
	Number of weanlings examined	86	80	74	84
	Number of weanlings with abnormal findings	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )

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 35 Body weights of F1 and F2 rat pups treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Group	Number of litters		Male					Female					
				Body weight (g) on postnatal day					Body weight (g) on postnatal day					
				0	4	7	14	21	0	4	7	14	21	
F1	Control	22	Mean	6.9	11.2	18.6	37.2	62.3	6.5	10.9	18.1	36.3	60.7	
			S.D.	0.5	1.1	1.8	3.6	5.6	0.5	1.3	1.9	3.5	5.2	
	DCBS 80 ppm	24	Mean	6.7	10.5	18.1	36.8	62.2	6.3	10.1	17.1	34.8	58.5	
			S.D.	0.6	1.2	1.7	2.4	3.7	0.5	1.4	2.3	3.6	6.0	
	DCBS 600 ppm	24	Mean	6.7	10.5	17.7	36.0	60.2	6.3	10.0	17.2	35.0	58.2	
			S.D.	0.6	1.4	2.5	4.0	6.3	0.5	1.2	2.3	4.0	6.5	
	DCBS 4500 ppm	24	Mean	6.6	10.3 *	16.7 **	33.6 <sup>SS</sup>	55.3 **	6.3	9.9 *	16.2 **	32.8 **	53.7 **	
			S.D.	0.7	1.0	1.6	2.5	4.8	0.6	1.0	1.4	2.6	4.5	
	F2	Control	23	Mean	6.8	11.0	18.5	37.1	62.5	6.5	10.5	17.6	35.9	59.6
				S.D.	0.9	2.3	2.7	4.0	7.0	1.0	2.3	2.9	4.1	6.6
		DCBS 80 ppm	22	Mean	6.7	11.1	18.4	37.8	63.4	6.3	10.5	17.7	36.6	60.7
				S.D.	0.8	2.6	3.8	6.3	9.4	0.7	2.5	3.8	5.7	8.5
DCBS 600 ppm		21	Mean	6.7	10.0	17.1	35.5	60.6	(20) 6.3	(20) 9.7	(20) 16.3	(20) 33.5	(20) 56.3	
			S.D.	0.5	2.1	2.8	3.8	5.6	0.4	2.0	2.8	4.9	7.0	
DCBS 4500 ppm		24	Mean	6.7	10.0	15.9 *	32.3 **	53.5 **	(23) 6.3	(23) 9.5	(23) 15.5	(23) 31.7 *	(23) 52.0 **	
			S.D.	0.6	1.4	2.3	4.1	5.9	0.7	1.5	2.2	3.9	5.7	

Values in parentheses are the number of litters 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.

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

Table 36 Anogenital distance of F1 and F2 rat pups on postnatal day 4 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Group	Number of litters		Male		Female	
				AGD (mm)	AGD/(BW) <sup>1/3</sup>	AGD (mm)	AGD/(BW) <sup>1/3</sup>
F1	Control	22	Mean	5.60	2.51	3.02	1.36
			S.D.	0.28	0.09	0.11	0.05
	DCBS 80 ppm	24	Mean	5.50	2.52	2.95	1.37
			S.D.	0.28	0.08	0.14	0.06
	DCBS 600 ppm	24	Mean	5.51	2.52	2.99	1.39
			S.D.	0.41	0.12	0.14	0.04
	DCBS 4500 ppm	24	Mean	5.54	2.55	2.96	1.38
			S.D.	0.28	0.09	0.14	0.04
F2	Control	23	Mean	5.54	2.50	2.93	1.34
			S.D.	0.51	0.12	0.19	0.04
	DCBS 80 ppm	22	Mean	5.60	2.53	2.91	1.34
			S.D.	0.55	0.14	0.22	0.06
	DCBS 600 ppm	21	Mean	5.39	2.51	(20) 2.88	(20) 1.35
			S.D.	0.56	0.12	0.19	0.03
	DCBS 4500 ppm	23	Mean	5.47	2.55	2.85	1.35
			S.D.	0.38	0.08	0.18	0.05

Values in parentheses are the number of litters examined.

AGD: Anogenital distance.

BW: Body weight.

Table 37 Physical development in F1 and F2 rat pups treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Group	Number of litters		Male						Female					
				Pinna detachment				Incisor eruption Age at compla- tion (days)	Eye opening Age at compla- tion (days)	Pinna detachment				Incisor eruption Age at compla- tion (days)	Eye opening Age at compla- tion (days)
				Completion rate (%) on postnatal day						Completion rate (%) on postnatal day					
1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
F1	Control	22	Mean	6.3	25.5	95.9	100.0	10.2	14.5	6.4	33.9	97.2	100.0	10.1	14.4
			S.D.	18.3	35.3	11.3	0.0	0.6	0.6	21.0	38.9	7.6	0.0	0.6	0.6
	DCBS 80 ppm	24	Mean	1.2	31.2	93.8	100.0	10.8 **	14.5	3.5	39.3	93.4	99.4	10.7 **	14.5
			S.D.	4.0	41.7	15.1	0.0	0.6	0.5	8.6	43.4	15.7	2.9	0.7	0.7
DCBS 600 ppm	24	Mean	0.0	15.2	94.4	100.0	10.3	14.7	0.0	20.0	93.3	100.0	10.2	14.4	
		S.D.	0.0	22.8	20.7	0.0	0.6	0.5	0.0	32.4	21.1	0.0	0.7	0.4	
DCBS 4500 ppm	24	Mean	5.0	23.6	99.3	100.0	10.5	14.6	4.2	27.1	99.5	100.0	10.2	14.5	
		S.D.	16.9	33.7	3.4	0.0	0.4	0.5	20.4	34.4	2.3	0.0	0.6	0.5	
F2	Control	23	Mean	13.8	30.0	87.2	100.0	(22) 9.7	(22) 14.4	10.3	30.2	88.0	99.1	(22) 9.8	(22) 14.3
			S.D.	32.0	44.2	29.1	0.0	0.7	0.7	28.4	40.0	29.2	4.2	0.7	0.6
	DCBS 80 ppm	22	Mean	9.1	28.6	91.5	100.0	10.6 **	14.6	7.6	30.8	91.7	97.7	10.4 *	14.4
			S.D.	29.4	41.1	23.1	0.0	0.9	0.8	25.1	43.8	22.4	10.7	0.8	0.8
DCBS 600 ppm	21	Mean	3.1	26.1	86.6	100.0	9.9	14.3	(20) 0.7	(20) 26.1	(20) 91.7	(20) 100.0	(20) 10.0	(20) 14.4	
		S.D.	11.2	40.5	23.2	0.0	0.6	0.7	3.2	37.8	15.0	0.0	0.6	0.5	
DCBS 4500 ppm	24	Mean	1.7	31.7	92.4	100.0	(23) 10.3 *	(23) 14.6			(23) 92.6	(23) 100.0	(23) 10.4 *	(23) 14.5	
		S.D.	8.2	38.8	18.0	0.0	0.8	0.6	15.4	40.0	18.3	0.0	0.9	0.7	

Values in parentheses are the number of litters 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.