

Table 38 Reflex response tests 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 animals		Male						Female				
				Surface righting reflex		Negative geotaxis reflex		Air righting reflex	Surface righting reflex		Negative geotaxis reflex		Air righting reflex	
				Success rate (%)	Response time (sec)	Completion ratio (%)	Response time (sec)	Success rate (%)	Success rate (%)	Response time (sec)	Completion ratio (%)	Response time (sec)	Success rate (%)	
F1	Control	22	Mean	100.0	2.1	22/22	14.5	100.0	100.0	2.8	22/22	15.3	100.0	
			S.D.	0.0	1.6	(100.0)	8.0	0.0	0.0	3.4	(100.0)	6.8	0.0	
	DCBS 80 ppm	24	Mean	100.0	1.5	24/24	15.4	100.0	100.0	1.6	24/24	14.1	100.0	
			S.D.	0.0	0.5	(100.0)	8.2	0.0	0.0	0.6	(100.0)	6.0	0.0	
F1	DCBS 600 ppm	24	Mean	100.0	2.4	24/24	13.8	100.0	100.0	1.9	24/24	15.4	100.0	
			S.D.	0.0	2.3	(100.0)	6.4	0.0	0.0	0.9	(100.0)	6.2	0.0	
	DCBS 4500 ppm	24	Mean	100.0	1.8	24/24	16.0	100.0	100.0	3.4	24/24	18.3	100.0	
			S.D.	0.0	1.2	(100.0)	7.5	0.0	0.0	3.9	(100.0)	7.6	0.0	
F2	Control	22	Mean	100.0	2.5	22/22	15.3	100.0	100.0	2.6	22/22	16.9	100.0	
			S.D.	0.0	1.6	(100.0)	6.3	0.0	0.0	1.8	(100.0)	7.2	0.0	
	DCBS 80 ppm	22	Mean	100.0	2.2	22/22	17.2	98.5	97.0	2.4	22/22	14.0	100.0	
			S.D.	0.0	1.8	(100.0)	7.4	7.1	14.2	2.0	(100.0)	6.5	0.0	
F2	DCBS 600 ppm	21	Mean	100.0	1.7	21/21	14.4	100.0	100.0	2.5	20/20	12.6	98.3	
			S.D.	0.0	0.5	(100.0)	5.7	0.0	0.0	1.7	(100.0)	8.1	7.4	
	DCBS 4500 ppm	23	Mean	100.0	2.1	23/23	16.1	100.0	100.0	3.2	22/23	16.0	100.0	
			S.D.	0.0	1.9	(100.0)	4.9	0.0	0.0	4.5	(95.7)	6.2	0.0	

Surface righting reflex, negative geotaxis reflex and air righting reflex were examined on postnatal day 5, 8 and 18, respectively.

Completion ratio (%) = (number of animals showing positive response/number of animals examined) x 100.

Values in parentheses are the number of animals examined.

Table 39 Autopsy findings in F1 and F2 male rat pups euthanized on postnatal day 4 or found dead on postnatal days 0-4 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	17	23	21	21
	Number of pups examined	62	77	67	61
	Number of pups with abnormal findings	0 ( 0.00 )	1 ( 1.09 )	0 ( 0.00 )	0 ( 0.00 )
	Findings <sup>a</sup>				
	Liver: Yellowish white discoloration	0 ( 0.00 )	1 ( 1.09 )	0 ( 0.00 )	0 ( 0.00 )
F2	Number of litters examined	17	17	15	19
	Number of pups examined	52	58	57	59
	Number of pups with abnormal findings	2 ( 1.96 )	1 ( 1.47 )	1 ( 2.22 )	1 ( 2.63 )
	Findings <sup>a</sup>				
	Auricle: Scab	0 ( 0.00 )	0 ( 0.00 )	1 ( 2.22 )	0 ( 0.00 )
Digestive tract: Retention, gas	2 ( 1.96 )	1 ( 1.47 )	0 ( 0.00 )	0 ( 0.00 )	
Kidney: Dilatation, renal pelvis	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	1 ( 2.63 )	

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 40 Autopsy findings in F1 and F2 female rat pups euthanized on postnatal day 4 or found dead on postnatal days 0-4 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Control	DCBS (ppm)			
			80	600	4500	
F1	Number of litters examined	17	18	21	17	
	Number of pups examined	44	46	64	46	
	Number of pups with abnormal findings	3 ( 7.06 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	
	Findings <sup>a</sup>					
	Liver: Yellowish white discoloration	1 ( 2.94 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	
	Kidney: Dilatation, renal pelvis	1 ( 1.18 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	
	Ureter: Dilatation	1 ( 1.18 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	
	Forelimb: Scab	1 ( 2.94 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	
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	F2	Number of litters examined	18	14	15	19
Number of pups examined		53	49	37	51	
Number of pups with abnormal findings		2 ( 11.11 )	1 ( 3.57 )	1 ( 3.33 )	1 ( 2.63 )	
Findings <sup>a</sup>						
Digestive tract: Retention, gas		1 ( 5.56 )	0 ( 0.00 )	0 ( 0.00 )	1 ( 2.63 )	
Digestive tract: Dark red contents		0 ( 0.00 )	0 ( 0.00 )	1 ( 3.33 )	0 ( 0.00 )	
Forelimb: Oligodactyly		1 ( 5.56 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	
Hindlimb: Scab		0 ( 0.00 )	1 ( 3.57 )	0 ( 0.00 )	0 ( 0.00 )	

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 41 Autopsy findings in F1 and F2 male rat weanlings euthanized on postnatal day 26 or animals found dead on postnatal days 5-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of animals examined	62	73	71	73
	Number of animals with abnormal findings	0 ( 0.00 )	1 ( 1.39 )	3 ( 4.17 )	1 ( 1.39 )
	Findings <sup>a</sup>				
	Ileum: Diverticulum	0 ( 0.00 )	1 ( 1.39 )	0 ( 0.00 )	0 ( 0.00 )
Kidney: Dilatation, renal pelvis	0 ( 0.00 )	0 ( 0.00 )	3 ( 4.17 )	1 ( 1.39 )	
F2	Number of litters examined	23	22	21	23
	Number of animals examined	87 <sup>b</sup>	81	79	90
	Number of animals with abnormal findings	2 ( 2.90 )	6 ( 6.59 )	6 ( 7.86 )	4 ( 4.35 )
	Findings <sup>a</sup>				
	Eyeball: Microphthalmia	0 ( 0.00 )	1 ( 1.14 )	0 ( 0.00 )	0 ( 0.00 )
	Kidney: Dilatation, renal pelvis	1 ( 1.45 )	5 ( 5.45 )	6 ( 7.86 )*	3 ( 3.26 )
Testis: Small size	1 ( 1.45 )	0 ( 0.00 )	0 ( 0.00 )	1 ( 1.09 )	
Epididymis: Small size	1 ( 1.45 )	0 ( 0.00 )	0 ( 0.00 )	1 ( 1.09 )	

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

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

b: Including pups that were euthanized on postnatal day 5 because of maternal death.

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

Table 42 Autopsy findings in F1 and F2 female rat weanlings euthanized on postnatal day 26 or animals found dead on postnatal days 5-26 treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Control	DCBS (ppm)		
			80	600	4500
F1	Number of litters examined	22	24	24	24
	Number of animals examined	64	70	73	70
	Number of animals with abnormal findings	5 ( 9.09 )	3 ( 4.51 )	0 ( 0.00 )	5 ( 7.64 )
	Findings <sup>a</sup>				
	Cerebrum: Dilatation, ventricle	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	1 ( 1.39 )
	Glandular stomach: Fine dark red patch, mucosa, multifocal	0 ( 0.00 )	1 ( 1.39 )	0 ( 0.00 )	0 ( 0.00 )
	Ileum: Diverticulum	1 ( 1.52 )	0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )
	Kidney: Dilatation, renal pelvis	4 ( 7.58 )	2 ( 3.13 )	0 ( 0.00 )	4 ( 6.25 )
	Urinary bladder: Dark red contents	0 ( 0.00 )	1 ( 1.39 )	0 ( 0.00 )	0 ( 0.00 )
	F2	Number of litters examined	23	22	20
Number of animals examined		90 <sup>b</sup>	80	74	85
Number of animals with abnormal findings		0 ( 0.00 )	1 ( 1.14 )	6 ( 7.50 )*	2 ( 2.32 )
Findings <sup>a</sup>					
Ileum: Diverticulum		0 ( 0.00 )	0 ( 0.00 )	2 ( 2.50 )	0 ( 0.00 )
Digestive tract: Retention, gas		0 ( 0.00 )	0 ( 0.00 )	0 ( 0.00 )	1 ( 1.45 )
Kidney: Dilatation, renal pelvis		0 ( 0.00 )	1 ( 1.14 )	4 ( 5.00 )	1 ( 0.87 )

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

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

b: Including pups that were euthanized on postnatal day 5 because of maternal death.

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

Table 43 Absolute and relative organ weights in F1 and F2 male rat weanlings 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		Thymus		Liver		Kidney <sup>a</sup>		Spleen	
				g	g	g	%	mg	10 <sup>-3</sup> %	g	%	g	%	mg	10 <sup>-3</sup> %
F1	Control	22	Mean	92.2	1.69	1.84	359	388	4.16	4.51	1.023	1.110	394	425	
			S.D.	8.0	0.07	0.13	68	52	0.49	0.26	0.111	0.073	68	52	
	DCBS 80 ppm	24	Mean	88.9	1.69	1.91	350	393	4.09	4.60	1.040	1.171 *	352	395	
			S.D.	6.2	0.05	0.13	53	50	0.37	0.25	0.079	0.064	68	63	
	DCBS 600 ppm	24	Mean	88.1	1.70	1.94	365	416	4.09	4.64 <sup>s</sup>	1.003	1.137	356	405	
			S.D.	9.1	0.08	0.15	52	61	0.44	0.15	0.135	0.079	61	59	
	DCBS 4500 ppm	24	Mean	78.2 **	1.63 **	2.09 **	278 <sup>ss</sup>	357	3.83 *	4.89 <sup>ss</sup>	0.894 <sup>ss</sup>	1.146	278 **	357 **	
			S.D.	7.2	0.07	0.17	37	48	0.51	0.28	0.069	0.073	41	48	
F2	Control	22	Mean	90.8	1.67	1.85	355	392	4.08	4.49	1.006	1.109	383	422	
			S.D.	8.7	0.08	0.14	56	58	0.47	0.23	0.102	0.037	61	49	
	DCBS 80 ppm	22	Mean	91.4	1.69	1.87	325	355	4.12	4.50	1.009	1.105	350 <sup>s</sup>	381 *	
			S.D.	13.1	0.09	0.22	64	47	0.66	0.26	0.147	0.066	83	53	
	DCBS 600 ppm	21	Mean	89.1	1.70	1.92	361	406	4.21	4.72 <sup>ss</sup>	1.022	1.146 <sup>s</sup>	356	400	
			S.D.	6.5	0.08	0.13	47	48	0.44	0.27	0.089	0.049	46	50	
	DCBS 4500 ppm	23	Mean	80.0 <sup>ss</sup>	1.63	2.05 **	283 **	354 *	3.74	4.66 <sup>ss</sup>	0.923	1.152 <sup>s</sup>	286 <sup>ss</sup>	357 **	
			S.D.	7.8	0.09	0.18	52	55	0.54	0.42	0.133	0.117	52	54	

(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.

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

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

Table 43 (continued) Absolute and relative organ weights in F1 and F2 male rat weanlings 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>		Prostate		
				mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	mg	10 <sup>-3</sup> %	
F1	Control	22	Mean	25.5	27.8	561	608	78.6	85.5	49.2	53.3	
			S.D.	2.6	2.9	77	61	9.4	9.8	9.8	9.1	
	DCBS 80 ppm	24	Mean	25.5	28.7	542	610	77.3	86.9	47.5	53.4	
			S.D.	3.3	3.0	64	55	9.5	8.4	7.8	7.8	
	DCBS 600 ppm	24	Mean	25.0	28.4	541	612	75.9	86.4	43.7	49.6	
			S.D.	3.3	3.1	88	58	11.6	11.3	10.1	10.7	
	DCBS 4500 ppm	24	Mean	22.4 **	28.8	529	677 <sup>SS</sup>	71.3 *	91.3	42.3 *	54.0	
			S.D.	2.9	4.0	88	95	10.2	11.7	8.9	9.5	
	F2	Control	22	Mean	25.5	28.1	548	602	79.5	87.6	50.9	55.6
				S.D.	2.8	2.8	106	89	12.5	10.6	16.6	15.0
		DCBS 80 ppm	22	Mean	24.1	26.5	516	563	72.9	80.4	44.6	48.9
				S.D.	3.4	2.6	103	69	12.3	12.6	10.4	9.9
DCBS 600 ppm		21	Mean	24.2	27.2	528	590	72.7	81.7	47.0	52.7	
			S.D.	3.8	4.3	82	65	10.0	10.6	10.3	10.1	
DCBS 4500 ppm		23	Mean	22.7 *	28.5	525	653	71.3	89.0	42.6	52.9	
			S.D.	3.4	4.2	98	91	11.2	10.0	12.2	13.1	

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.

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

Table 44 Absolute and relative organ weights in F1 and F2 female rat weanlings treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Generation	Group	Number of animals		Body weight		Brain			Thymus		Liver		Kidney <sup>a</sup>		Spleen	
				g	g	g	%	mg	10 <sup>-3</sup> %	g	%	g	%	mg	10 <sup>-3</sup> %	
F1	Control	22	Mean	85.9	1.62	1.90	361	418	3.72	4.33	0.954	1.110	338	392		
			S.D.	7.8	0.07	0.14	77	65	0.44	0.34	0.108	0.068	58	43		
	DCBS 80 ppm	24	Mean	82.5	1.65	2.01	327	398	3.52	4.27	0.967	1.173 **	323	392		
			S.D.	6.4	0.05	0.17	49	60	0.35	0.22	0.081	0.055	47	54		
	DCBS 600 ppm	24	Mean	82.8	1.64	2.00	350	423	3.65	4.41	0.940	1.133	316	382		
			S.D.	7.2	0.05	0.16	60	63	0.40	0.29	0.114	0.065	53	55		
	DCBS 4500 ppm	24	Mean	74.3 **	1.57 **	2.13 **	281 <sup>ss</sup>	379	3.43 *	4.62 **	0.850 **	1.148	249 <sup>ss</sup>	337 **		
			S.D.	6.7	0.05	0.16	43	56	0.40	0.31	0.082	0.088	32	49		
	F2	Control	22	Mean	83.6	1.62	1.96	364	439	3.71	4.44	0.915	1.096	340	407	
				S.D.	9.5	0.08	0.20	50	63	0.47	0.18	0.093	0.046	63	58	
		DCBS 80 ppm	22	Mean	87.2	1.66	1.92	326	373 **	3.87	4.44	0.983	1.129	331	380	
				S.D.	10.8	0.07	0.19	66	56	0.50	0.23	0.137	0.085	55	46	
DCBS 600 ppm		20	Mean	82.4	1.66	2.03	348	424	3.80	4.61 *	0.960	1.164 <sup>ss</sup>	320	389		
			S.D.	6.5	0.05	0.16	68	80	0.37	0.19	0.111	0.083	46	56		
DCBS 4500 ppm		23	Mean	74.6 **	1.57 *	2.11 *	283 **	379 **	3.57	4.78 **	0.885	1.187 <sup>ss</sup>	274 **	370		
			S.D.	7.9	0.07	0.18	56	63	0.46	0.26	0.101	0.061	40	52		

(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.

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



Table 44 (continued) Absolute and relative organ weights in F1 and F2 female rat wearlings 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> %	
F1	Control	22	Mean	23.8	27.8	23.2	27.1	58.2	67.9	
			S.D.	2.6	2.8	3.3	3.3	14.5	15.8	
	DCBS 80 ppm	24	Mean	24.5	29.8	22.2	27.0	55.8	67.9	
			S.D.	2.7	3.6	3.4	4.0	7.6	9.9	
	DCBS 600 ppm	24	Mean	23.1	27.9	20.5 *	24.8	62.1	75.2	
			S.D.	2.9	2.6	3.2	4.3	12.3	14.1	
	DCBS 4500 ppm	24	Mean	21.5 *	29.1	20.3 *	27.5	48.4 <sup>s</sup>	65.0	
			S.D.	2.4	3.6	3.2	4.7	11.8	14.1	
	F2	Control	22	Mean	23.6	28.4	22.0	26.6	61.8	73.3
				S.D.	2.9	3.3	3.9	5.2	18.9	17.2
		DCBS 80 ppm	22	Mean	23.3	26.7	22.5	26.0	58.1	67.0
				S.D.	4.0	3.3	2.8	3.0	11.9	13.5
DCBS 600 ppm		20	Mean	22.2	27.0	20.9	25.5	50.0 <sup>s</sup>	60.7 *	
			S.D.	3.3	4.0	3.1	4.4	10.0	11.5	
DCBS 4500 ppm		23	Mean	21.6	29.0	21.4	29.0	46.6 <sup>ss</sup>	62.3 *	
			S.D.	3.0	3.9	2.9	4.3	12.9	15.0	

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.

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

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

Table 45 Histopathological findings in F1 and F2 rat weanlings treated with N,N-Dicyclohexyl-2-benzothiazolesulfenamide (DCBS) in the two-generation reproductive toxicity study (SR05241)

Gener- ation	Item	Male		Female	
		Control	DCBS 4500 ppm	Control	DCBS 4500 ppm
F1	Number of weanlings examined <sup>a</sup>	22	24	22	24
	Number of weanlings with abnormal findings	0	0	0	0
F2	Number of weanlings examined <sup>a</sup>	22	23	22	23
	Number of weanlings with abnormal findings	0	0	0	0

a: Weanlings were examined on the liver, spleen and thymus in the control and DCBS 4500 ppm groups.