

Table 2-99 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Grip strength of female rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Fore limb g	Hind limb g
0	No.	5	5
	Mean	1054	791
	S.D.	157	85
1000	No.	5	5
	Mean	1110	704
	S.D.	217	164

No significant difference between treated group and control group.

Table 2-100 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Motor activity of male rats (Main group, Week 6 of administration)

Dose mg/kg		Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
	Mean	390	185	77	118	100	63	934
	S.D.	40	69	51	67	169	111	416
100	No.	5	5	5	5	5	5	5
	Mean	362	238	169	171	111	87	1135
	S.D.	56	111	139	89	87	88	294
300	No.	5	5	5	5	5	5	5
	Mean	327	256	110	83	58	44	878
	S.D.	114	101	91	52	44	47	247
1000	No.	5	5	5	5	5	5	5
	Mean	343	276	146	126	59	26	977
	S.D.	45	58	57	62	51	12	138

No significant difference in any treated groups from control group.

Table 2-101 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Motor activity of female rats (Main group, Day 4 of lactation)

Dose mg/kg		Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
	Mean	176	59	30	13	37	39	354
	S.D.	109	104	45	16	67	52	362
100	No.	5	5	5	5	5	5	5
	Mean	168	52	22	13	54	44	353
	S.D.	60	63	17	9	41	88	118
300	No.	5	5	5	5	5	5	5
	Mean	261	112	124*	103*	114	20	733
	S.D.	75	84	79D	61DT	56	11	267
1000	No.	5	5	5	5	5	5	5
	Mean	108	17	38	17	11	39	230
	S.D.	70	12	39	10	14	45	102

* : p<0.05 (Significant difference from control group)
D: Dunnett's test
DT: Dunnett-type rank test

Table 2-102 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Motor activity of male rats (Recovery group, Week 6 of administration)

Dose mg/kg		Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
	Mean	265	208	64	35	48	50	670
	S.D.	171	148	65	22	71	39	334
1000	No.	5	5	5	5	5	5	5
	Mean	386	254	93	26	75	34	867
	S.D.	42	93	74	27	100	27	149

No significant difference between treated group and control group.

Table 2-103

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Motor activity of female rats (Recovery group, Week 6 of administration)

Dose mg/kg		Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
	Mean	365	271	62	35	51	149	932
	S.D.	57	87	74	42	79	151	208
1000	No.	5	5	5	5	5	5	5
	Mean	363	273	222*	245*	227**	232	1562**
	S.D.	53	133	88T	127AT	71T	132	343T

* : p<0.05 ; ** : p<0.01 (Significant difference from control group)
T: Student's t-test
AT: Aspin-Welch t-test

Table 2-104

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Motor activity of male rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Interval (minutes)						Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60	
0	No.	5	5	5	5	5	5	5
	Mean	311	217	224	123	127	110	1112
	S.D.	87	96	88	92	99	87	223
1000	No.	5	5	5	5	5	5	5
	Mean	305	283	265	205	146	144	1349
	S.D.	89	78	98	170	162	141	639

No significant difference between treated group and control group.

Table 2-105

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone

Motor activity of female rats (Recovery group, Week 2 of recovery)

Dose mg/kg		Interval (minutes)							Total(0-60)
		0-10	10-20	20-30	30-40	40-50	50-60		
0	No.	5	5	5	5	5	5	5	
	Mean	265	228	168	163	126	107	1057	
	S.D.	91	117	128	123	122	129	513	
1000	No.	5	5	5	5	5	5	5	
	Mean	271	210	177	185	165	86	1092	
	S.D.	54	65	56	58	133	85	336	

No significant difference between treated group and control group.

Table 3-1

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone

Body weight of male rats (Main group)

Dose mg/kg		Pre-mating period					Mating period				Post-mating period				Gain 1-42
		1	4	8	11	15	18	22	25	29	32	36	39	42a)	
0	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	361.8	374.8	390.4	405.5	416.1	424.8	439.4	449.8	461.9	474.4	486.6	496.6	502.9	141.1
	S.D.	15.9	17.4	20.8	23.1	27.2	28.2	29.6	30.2	31.6	32.7	31.0	33.1	33.9	23.3
100	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	360.9	375.6	390.3	402.3	414.3	419.3	433.4	442.1	457.3	468.3	481.5	490.8	495.3	134.4
	S.D.	12.6	13.9	17.5	20.0	23.1	24.3	25.6	27.0	28.7	31.0	33.2	32.5	33.1	26.4
300	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	359.6	371.0	385.1	398.5	411.3	417.8	431.8	444.8	457.1	465.6	480.3	487.8	493.3	133.7
	S.D.	15.1	16.4	18.8	19.5	19.8	22.7	23.6	21.5	23.5	25.9	26.9	27.3	27.0	19.2
1000	No.	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Mean	360.8	382.4	371.0*	383.2*	389.3*	392.6*	406.8*	415.1**	424.7**	432.3**	441.5**	442.7**	447.5**	86.7**
	S.D.	14.8	17.3	20.0D	23.4D	26.0D	28.6D	28.3D	28.0D	29.0D	30.7D	33.4D	34.9D	35.0D	26.1D

Unit: g

No.: No. of animals

a): Day of administration

*: p<0.05; **: p<0.01 (Significant difference from control group)

D: Dunnett's test

Table 3-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone

Body weight of female rats during the pre-mating period (Main group)

Dose mg/kg		Administration					Gain 1-15
		1	4	8	11	15a)	
0	No.	12	12	12	12	12	12
	Mean	224.3	233.2	240.9	246.6	252.8	28.5
	S.D.	8.9	9.6	9.6	10.8	11.1	6.9
100	No.	12	12	12	12	12	12
	Mean	225.6	233.7	244.8	250.7	257.3	31.8
	S.D.	7.3	7.0	9.5	11.7	12.7	7.4
300	No.	12	12	12	12	12	12
	Mean	223.7	230.5	236.2	239.8	244.4	20.8
	S.D.	12.3	11.3	12.7	14.0	15.6	9.1
1000	No.	12	12	12	12	12	12
	Mean	223.8	224.1*	224.1**	223.7**	240.2	16.4**
	S.D.	9.8	7.6D	14.5D	17.5D	12.4	8.7D

Unit: g
 No.: No. of animals
 a): Day of administration
 *: p<0.05; **: p<0.01 (Significant difference from control group)
 D: Dunnett's test

Table 3-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone

Body weight of dams during the gestation period (Main group)

Dose mg/kg		Administration							Gain 0-20
		0	4	7	11	14	17	20a)	
0	No.	12	12	12	12	12	12	12	12
	Mean	254.8	277.9	290.8	314.3	329.0	360.8	407.3	152.5
	S.D.	10.9	13.8	17.6	20.1	24.0	23.0	24.8	19.8
100	No.	12	12	12	12	12	12	12	12
	Mean	259.3	276.7	291.2	313.7	329.8	361.0	408.2	148.9
	S.D.	13.8	14.2	15.3	17.2	17.3	19.1	22.3	16.2
300	No.	12	12	12	12	12	12	12	12
	Mean	251.7	273.2	281.1	304.0	318.4	348.8	396.6	144.9
	S.D.	18.2	16.3	18.7	18.0	19.5	23.0	26.3	11.0
1000	No.	11	11	11	11	11	11	11	11
	Mean	236.1*	254.2**	265.7**	280.8**	286.6**	317.8**	351.5**	115.4**
	S.D.	14.8D	20.7D	18.2D	21.1D	27.2D	29.3D	33.9D	23.5D

Unit: g
 No.: No. of dams
 a): Day of gestation
 *: p<0.05; **: p<0.01 (Significant difference from control group)
 D: Dunnett's test

Table 3-4 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Body weight of dams during the lactation period (Main group)

Dose mg/kg		Administration		Gain 0-4
		0	4a)	
0	No.	12	12	12
	Mean	309.9	328.8	18.8
	S.D.	31.8	26.0	19.3
100	No.	12	12	12
	Mean	316.4	325.3	8.9
	S.D.	21.3	20.9	13.1
300	No.	12	12	12
	Mean	300.2	299.8*	-0.4
	S.D.	27.6	28.1D	22.4
1000	No.	11	10 ^{b)}	10
	Mean	268.8**	274.4**	3.2
	S.D.	33.0D	35.3D	26.7

Unit: g
No.: No. of dams
a): Day of lactation
b): One dam died on day 0 of lactation.
*: p<0.05; **: p<0.01 (Significant difference from control group)
D: Dunnett's test

Table 3-5 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Body weight of male rats during the administration period (Recovery group)

Dose mg/kg		Day of administration												Gain 1-42	
		1	4	8	11	15	18	22	25	29	32	36	39		42
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	355.0	363.6	377.2	390.8	400.8	408.6	422.8	430.8	444.2	454.8	469.0	478.6	476.4	121.4
	S.D.	13.5	17.9	20.1	26.0	26.8	29.8	32.6	37.9	38.0	39.1	40.0	40.3	45.9	38.2
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	357.4	356.4	363.6	377.4	386.2	393.0	405.0	414.4	422.2	430.0	438.0	442.8	447.8	90.4
	S.D.	17.9	18.9	17.7	24.2	25.7	28.6	29.6	28.3	29.8	28.1	32.2	35.9	31.6	16.6

Unit: g
No.: No. of animals
No significant difference between treated group and control group.

Table 3-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Body weight of female rats during the administration period (Recovery group)

Dose mg/kg		Day of administration												Gain 1-42	
		1	4	8	11	15	18	22	25	29	32	36	39		42
0	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	218.8	230.6	239.2	241.8	248.0	248.4	250.2	259.0	263.6	266.8	272.0	274.4	270.4	51.6
	S.D.	8.3	9.0	10.4	13.5	19.0	20.1	18.9	25.6	23.4	18.3	21.7	22.0	21.1	17.9
1000	No.	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mean	224.6	226.2	229.8	231.8	234.6	240.4	246.0	249.8	253.8	253.4	259.2	257.4	258.2	33.6
	S.D.	11.4	15.7	14.4	16.9	17.7	12.8	17.9	19.6	16.2	24.1	20.8	19.7	21.8	12.7

Unit: g

No.: No. of animals

No significant difference between treated group and control group.

Table 3-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Body weight of male rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery					Gain 1-14
		1	4	8	11	14	
0	No.	5	5	5	5	5	5
	Mean	482.2	491.4	496.8	501.4	504.8	22.6
	S.D.	42.5	44.1	44.3	44.5	48.4	7.2
1000	No.	5	5	5	5	5	5
	Mean	450.0	456.4	471.8	486.0	486.6	36.6**
	S.D.	32.6	30.1	35.5	29.7	32.2	5.9T

Unit: g

No.: No. of animals

**: p<0.01 (Significant difference from control group)

T: Student's t-test

Table 3-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Body weight of female rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery					Gain 1-14
		1	4	8	11	14	
0	No.	5	5	5	5	5	5
	Mean	278.6	275.2	277.0	282.2	279.4	0.8
	S.D.	24.1	21.5	25.4	25.4	23.6	6.7
1000	No.	5	5	5	5	5	5
	Mean	259.4	261.0	268.2	275.8	272.4	13.0*
	S.D.	25.0	19.6	20.9	23.1	27.9	8.6T

Unit: g
No.: No. of animals
*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 4-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Food consumption of male rats (Main group)

Dose mg/kg		Pre-mating period					Post-mating period			
		1	4	8	11	15	32	36	39	42a)
0	No.	12	12	12	12	12	12	12	12	12
	Mean	26.8	24.9	25.0	21.5	24.1	23.9	23.6	22.7	25.3
	S.D.	2.8	1.9	2.9	2.5	2.7	2.2	1.7	2.8	2.0
100	No.	12	12	12	12	12	12	12	12	12
	Mean	25.3	24.2	22.5	21.2	23.6	22.5	22.2	22.4	22.9
	S.D.	2.1	2.7	2.8	2.7	2.4	4.1	2.0	2.4	2.6
300	No.	12	12	12	12	12	12	12	12	12
	Mean	25.7	22.3	23.8	20.8	25.1	23.2	23.9	21.9	25.4
	S.D.	4.1	2.7	2.6	2.7	2.5	4.5	3.7	3.7	2.2
1000	No.	12	12	12	12	12	12	12	12	12
	Mean	26.1	16.8**	24.1	21.6	26.5	24.7	23.7	22.1	26.6
	S.D.	3.2	5.4DT	3.7	2.8	4.3	4.5	4.3	4.1	4.4

Unit: g/rat/day
No.: No. of animals
a): Day of administration
**: p<0.01 (Significant difference from control group)
DT: Dunnett-type rank test

Table 4-2 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Food consumption of female rats during the pre-mating period (Main group)

Dose mg/kg		Administration				
		1	4	8	11	15a)
0	No.	12	12	12	12	12
	Mean	17.7	18.8	18.6	14.3	19.4
	S.D.	3.1	2.2	1.6	2.4	3.1
100	No.	12	12	12	12	12
	Mean	18.8	17.9	18.0	15.0	19.4
	S.D.	2.4	1.5	2.3	1.4	2.7
300	No.	12	12	12	12	12
	Mean	17.3	16.5*	18.5	14.7	18.8
	S.D.	2.1	1.8D	2.7	3.6	3.1
1000	No.	12	12	12	12	12
	Mean	18.5	10.8**	14.7	12.4	24.9*
	S.D.	3.1	3.0D	7.9	5.4	7.8DT

Unit: g/rat/day

No.: No. of animals

a): Day of administration

*: p<0.05; **: p<0.01 (Significant difference from control group)

D: Dunnett's test

DT: Dunnett-type rank test

Table 4-3 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Food consumption of dams during the gestation period (Main group)

Dose mg/kg		Administration						
		1	4	7	11	14	17	20a)
0	No.	12	12	12	12	12	12	12
	Mean	17.4	20.1	21.1	23.2	22.7	24.7	21.2
	S.D.	2.2	3.0	3.3	3.3	3.1	4.1	3.6
100	No.	12	12	12	12	12	12	12
	Mean	17.8	20.8	21.2	21.9	22.4	24.8	20.1
	S.D.	2.6	3.1	2.3	2.4	3.3	2.4	2.5
300	No.	12	12	12	12	12	12	12
	Mean	17.2	22.1	20.4	22.2	21.9	25.5	19.9
	S.D.	2.6	3.4	3.7	3.0	3.3	3.6	3.8
1000	No.	11	11	11	11	11	11	11
	Mean	18.2	22.1	20.5	18.8	19.0	23.8	14.0**
	S.D.	4.8	4.7	4.8	6.5	7.7	4.5	4.8D

Unit: g/rat/day

No.: No. of dams

a): Day of gestation

*: p<0.05; **: p<0.01 (Significant difference from control group)

D: Dunnett's test

Table 4-4

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone

Food consumption of dams during the lactation period (Main group)

Dose mg/kg		Administration	
		2	4a)
0	No.	12	12
	Mean	22.7	37.3
	S.D.	6.5	8.1
100	No.	12	12
	Mean	19.2	38.2
	S.D.	3.9	6.7
300	No.	12	12
	Mean	13.5**	35.0
	S.D.	6.2D	11.7
1000	No.	10 ^{b)}	10
	Mean	12.7**	31.4
	S.D.	8.8D	12.6

Unit: g/rat/day

No.: No. of dams

a): Day of lactation

b): One dam died on day 0 of lactation.

** : p<0.01 (Significant difference from control group)

D: Dunnett's test

Table 4-5

A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone

Food consumption of male rats during the administration period (Recovery group)

Dose mg/kg		Day of administration								
		1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5	5
	Mean	24.0	22.4	24.0	19.8	25.0	22.6	23.0	23.6	22.0
	S.D.	3.2	2.6	2.7	0.8	2.3	3.1	2.1	1.9	2.8
1000	No.	5	5	5	5	5	5	5	5	5
	Mean	25.6	14.0**	23.4	22.0	25.0	22.4	23.4	24.2	25.8*
	S.D.	4.6	3.7T	6.1	3.7	2.8	2.2	2.5	4.6	1.8T

Unit: g/rat/day

No.: No. of animals

*: p<0.05; **: p<0.01 (Significant difference from control group)

T: Student's t-test

Table 4-6 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Food consumption of female rats during the administration period (Recovery group)

Dose mg/kg		Day of administration								
		1	4	8	11	15	32	36	39	42
0	No.	5	5	5	5	5	5	5	5	5
	Mean	15.8	18.2	19.4	14.6	18.4	16.6	15.8	17.4	11.4
	S.D.	2.8	0.4	1.9	3.8	2.8	3.1	1.9	2.8	2.7
1000	No.	5	5	5	5	5	5	5	5	5
	Mean	19.0	12.0*	19.4	10.2	19.6	16.4	16.0	16.4	16.0
	S.D.	3.5	4.4AT	3.6	3.4	3.8	8.4	3.2	1.8	4.6

Unit: g/rat/day
No.: No. of animals
*: p<0.05 (Significant difference from control group)
AT: Aspin-Weich t-test

Table 4-7 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Food consumption of male rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery				
		1	4	8	11	14
0	No.	5	5	5	5	5
	Mean	22.6	27.0	25.6	27.6	28.4
	S.D.	2.1	2.8	1.9	1.9	3.4
1000	No.	5	5	5	5	5
	Mean	22.2	30.6	32.0*	33.0*	27.8
	S.D.	5.2	3.2	4.2T	3.1T	2.8

Unit: g/rat/day
No.: No. of animals
*: p<0.05 (Significant difference from control group)
T: Student's t-test

Table 4-8 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Food consumption of female rats during the recovery period (Recovery group)

Dose mg/kg		Day of recovery				
		1	4	8	11	14
0	No.	5	5	5	5	5
	Mean	15.4	14.4	18.2	21.0	17.6
	S.D.	2.7	1.3	2.4	2.1	0.9
1000	No.	5	5	5	5	5
	Mean	15.8	23.0**	19.8	23.2	18.8
	S.D.	4.0	3.1T	2.2	1.8	5.4

Unit: g/rat/day
No.: No. of animals
*: p<0.01 (Significant difference from control group)
T: Student's t-test

Table 5-1 A combined repeated-dose/reproductive-developmental toxicity study in rats treated orally with 2,3,4,4'-Tetrahydroxybenzophenone
Urinalysis of male rats (Week 6 of administration)

Dose mg/kg	No.	pH										1) Protein					2) Ketone body					3) Glucose						
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	-	+	++	+++	++++	-	+	++	+++	++++	-	+	++	+++	++++			
0	17	0	0	0	1	0	1	4	10	1	3	6	8	0	0	0	5	5	7	0	0	0	17	0	0	0	0	0
100	12	0	0	0	0	1	1	4	6	0	0	1	11	0	0	0	0	3	9	0	0	0	12	0	0	0	0	0
300	12	0	0	0	0	2	3	4	3	0	3	4	5	0	0	0	2	3	7	0	0	0	12	0	0	0	0	0
1000	17	0	0	0	3	5	7	2	0	0	4	9	4	0	0	0	3	7	7	0	0	0	17	0	0	0	0	0

1) -: <10 mg/dL +- : 10 - 25 mg/dL + : 26 - 85 mg/dL ++ : 86 - 250 mg/dL +++ : 251 - 600 mg/dL ++++ : >600 mg/dL
2) -: <5 mg/dL +- : 5 - 7.5 mg/dL + : 7.6 - 30 mg/dL ++ : 31 - 70 mg/dL +++ : 71 - 125 mg/dL ++++ : >125 mg/dL
3) -: <30 mg/dL +- : 30 - 60 mg/dL + : 61 - 125 mg/dL ++ : 126 - 250 mg/dL +++ : 251 - 750 mg/dL ++++ : >750 mg/dL