ADME NTP Study S0556 *p-tert*-Butylcatechol

The contract laboratory abbreviation for the test article is TBC.
Sex/Species: adult male F344 rats and B6C3F1 mice.
Vehicles: intravenous, 10% Emulphor in F344 rat plasma (rats), isotonic saline or 10% Emulphor in B6C3F1 plasma (mice); oral, water, 20% Emulphor in water or 80% Emulphor in water; dermal, acetone.

CASRN 98-29-3

Radiolabeled with carbon-14 in the methine carbon of the t-butyl group; p-tert-Butylcatechol, [methine-^{14}C]-

p-tert-Butylcatechol Studies Performed:

1. Single 3 mg/kg intravenous dose in rats with sacrifice 72 hours postdose.

2. Single 2 oral gavage dose in rats with sacrifice at 72 hours postdose (vehicle is water).

3. Single 200 mg/kg oral gavage dose in rats with sacrifice at 72 hours postdose (vehicle is 20% Emulphor in water).

4. Single 1000 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose (vehicle is 80% Emulphor in water).

5. Single 0.6, 6 and 63 mg/kg dermal doses in rats with dose site covered and sacrifice 72 hours postdose.

6. Single 3 mg/kg intravenous dose in mice with sacrifice 72 hours postdose (vehicle is isotonic saline).

7. Single 3 mg/kg intravenous dose in mice with sacrifice 72 hours postdose (vehicle is 10% Emulphor in B6C3F1 plasma).

8. Single 300 mg/kg oral gavage dose in mice with sacrifice 72 hours post dosing (vehicle is 20% Emulphor in water).

9. 0.04 and 4 mg/mouse dermal doses in mice with dose site covered and sacrifice 72 hours postdose.

10. Single 200 mg/kg oral gavage dose in rats with sacrifice 24 hours postdose and 20% Emulphor in water (toxicokinetics).

11. Single 63 mg/kg dermal dose in rat with dose site covered and sacrifice 24 hours postdose (toxicokinetics).

The 3 mg/kg intravenous dose study in mice was repeated because the tissue to blood ratio favored the lung over the liver by a factor of 10 in the first mouse study, but was about equal in the rat. This repeat study used 10% Emulphor in plasma as the vehicle matching the 10% Emulphor in rat plasma vehicle used for the rat 3 mg/kg intravenous study.

No parameters were calculated for the two 24 hour toxicokinetic studies.

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Table 1

Disposition of Radioactivity 72 h after an iv Dose of [^{14}C]TBC (3 mg/kg) to Male F-344 Rats[a]

Cumulative Excretion of Radioactivity

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
6 h	53.7 ± 1.77		53.7 ± 1.77
24 h	81.0 ± 2.43	4.45 ± 3.31	85.5 ± 3.64
48 h	86.3 ± 1.92	5.69 ± 3.02	91.9 ± 1.87
72 h	89.8 ± 1.90	5.97 ± 2.98	95.8 ± 1.50

Distribution in Tissues

Tissue	ng-eq TBC per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	2.90 ± 0.371	0.0748 ± 0.0245	0.00643 ± 0.000651
Adrenal Gland	26.9 ± 2.45	0.684 ± 0.172	0.000161± 0.0000253
Blood	40.9 ± 9.59	unity	0.0678 ± 0.0175
Brain	7.36 ± 0.908	0.190 ± 0.0585	0.00160 ± 0.000210
Kidney	61.7 ± 10.3	1.60 ± 0.578	0.0142 ± 0.00151
Liver	46.8 ± 5.13	1.20 ± 0.351	0.0580 ± 0.00340
Lung	63.0 ± 10.5	1.62 ± 0.514	0.0134 ± 0.00155
Muscle	2.88 ± 0.698	0.0759 ± 0.0312	0.0437 ± 0.00983
Prostate	5.60 ± 0.832	0.143 ± 0.0431	0.000163± 0.0000468
Seminal Vesicle	4.45 ± 1.06	0.116 ± 0.0510	0.000393± 0.0000721
Stomach[b]			0.00320 ± 0.000577
Small Intestine[b]			0.0292 ± 0.00437
Cecum[b]			0.0222 ± 0.0822
Large Intestine[b]			0.0152 ± 0.00601
Skin	13.5 ± 6.13	0.356 ± 0.227	0.0724 ± 0.0307
Spleen	49.9 ± 18.1	1.34 ± 0.730	0.00380 ± 0.00141
Testis	3.00 ± 0.353	0.0753 ± 0.0133	0.000992± 0.000145
		Total in tissues	0.283 ± 0.0230

a N=4
b Includes contents

Table 2

Excretion of Radioactivity following Oral Administration of [^{14}C]TBC to Male F-344 Rats

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
2 mg/kg Oral dose			
6 h	38.7 ± 11.3		38.7 ± 11.3
24 h	74.5 ± 10.6	3.77 ± 0.76	78.3 ± 10.6
48 h	83.5 ± 7.8	4.59 ± 0.70	88.1 ± 7.7
72 h	89.0 ± 4.5	4.90 ± 0.75	93.9 ± 4.1
200 mg/kg Oral Dose			
6 h	16.0 ± 11.4		16.0 ± 11.4
24 h	72.2 ± 2.0	4.35 ± 1.75	76.5 ± 1.1
48 h	87.0 ± 2.3	5.69 ± 1.59	92.7 ± 1.8
72 h	94.4 ± 4.0	6.45 ± 1.34	101 ± 3.4

Table 3

Distribution of Radioactivity in Tissues 72 h following Oral Administration of [^{14}C]TBC to Male F-344 Rats[a]

Tissue	ng-eq TBC per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
	2 mg/kg Oral Dose		
Adipose	0.381 ± 0.279	0.0205 ± 0.0227	0.00135 ± 0.000977
Adrenal Gland	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 10.00
Blood	25.1 ± 13.5	unity	0.0670 ± 0.0366
Brain	0.0564± 0.0639	0.00345± 0.00542	0.0000191 ± 0.0000224
Kidney	79.4 ± 25.8	3.47 ± 0.921	0.0305 ± 0.0114
Liver	27.3 ± 1.85	1.33 ± 0.625	0.0603 ± 0.00191
Lung	22.3 ± 9.95	0.982 ± 0.502	0.00782 ± 0.00412
Muscle	0.0377± 0.0260	0.00199± 0.00200	0.000919 ± 0.000629
Prostate	1.15 ± 1.13	0.0719 ± 0.102	0.0000585 ± 0.0000562
Seminal Vesicle	0.602 ± 0.595	0.0388 ± 0.0532	0.0000864 ± 0.0000581
Stomach[b]			0.125 ± 0.0376
Small Intestine[b]			0.0384 ± 0.00286
Cecum[b]			0.0221 ± 0.00753
Large Intestine[b]			0.0124 ± 0.000865
Skin	1.43 ± 0.843	0.0811 ± 0.0876	0.0123 ± 0.00697
Spleen	26.3 ± 8.95	1.13 ± 0.244	0.00344 ± 0.00120
Testis	0.184 ± 0.117	0.0107 ± 0.0120	0.000101 ± 0.0000695
		Total in tissues	0.18 ± 0.05
	200 mg/kg Oral Dose		
Adipose	69.8 ± 18.9	0.0580 ± 0.0182	0.00272 ± 0.000747
Adrenal Gland	105 ± 24.4	0.0871 ± 0.0214	0.0000118 ± 0.00000279
Blood	1220 ± 127	unity	0.0353 ± 0.00345
Brain	19.2 ± 6.59	0.0159 ± 0.00601	0.0000676 ± 0.0000199
Kidney	2860 ± 1060	2.39 ± 0.955	0.0105 ± 0.00367
Liver	2840 ± 137	2.34 ± 0.256	0.0638 ± 0.0119
Lung	1390 ± 219	1.14 ± 0.162	0.00489 ± 0.00123
Muscle	22.0 ± 6.15	0.0178 ± 0.00422	0.00586 ± 0.00160
Prostate	139 ± 78.2	0.119 ± 0.0787	0.0000773 ± 0.0000411
Seminal Vesicle	58.7 ± 29.5	0.0487 ± 0.0260	0.0000823 ± 0.0000393
Stomach[b]			0.0102 ± 0.00202
Small Intestine[b]			0.0468 ± 0.0106
Cecum[b]			0.0468 ± 0.0140
Large Intestine[b]			0.0216 ± 0.00698
Skin	368 ± 281	0.299 ± 0.223	0.0347 ± 0.0264
Spleen	3110 ± 2880	2.42 ± 2.03	0.00412 ± 0.00367
Testis	28.2 ± 10.3	0.0232 ± 0.00883	0.000167 ± 0.0000542
		Total in tissues	0.16 ± 0.05

a N=4
b Includes contents

Table 4

Cumulative Excretion of Radioactivity 72 h after an Oral Dose of [^{14}C]TBC (1000 mg/kg) to Male F-344 Rats[a]

End of Collection Period	Percent of Dose Recovered in:		
	Urine	Feces	Total
6 h	4.74 ± 1.45		4.74 ± 1.45
24 h	18.9 ± 2.3	1.80 ± 0.47	20.8 ± 2.2
48 h	40.0 ± 7.1	18.9 ± 9.8	58.9 ± 7.3
72 h	56.6 ± 7.9	24.7 ± 9.1	81.3 ± 1.8

Table 5

Excretion of Radioactivity following Dermal Administration of [^{14}C]TBC to Male F-344 Rats

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
0.6 mg/kg Dermal Dose			
6 h	1.45 ± 1.82		1.45 ± 1.82
24 h	16.3 ± 2.4	0.363± 0.135	16.7 ± 2.6
48 h	24.6 ± 5.3	1.11 ± 0.77	25.7 ± 5.6
72 h	31.7 ± 7.8	1.34 ± 0.88	33.1 ± 8.2
6 mg/kg Dermal Dose			
6 h	7.46 ± 2.16		7.46 ± 2.16
24 h	27.4 ± 5.7	0.641± 0.221	28.1 ± 5.9
48 h	38.9 ± 6.4	1.04 ± 0.30	39.9 ± 6.7
72 h	46.8 ± 6.8	1.69 ± 0.83	48.5 ± 6.8
63 mg/kg Dermal Dose			
6 h	12.2 ± 16.5		12.2 ± 16.5
24 h	64.3 ± 4.3	2.43 ± 0.67	66.7 ± 4.2
48 h	73.2 ± 5.0	3.37 ± 0.87	76.6 ± 4.6
72 h	79.5 ± 5.2	4.09 ± 1.41	83.6 ± 4.2

Table 6

Distribution of Radioactivity 72 h following Dermal Administration of [^{14}C]TBC to Male F-344 Rats

	Percent of Dose		
Dose	0.6 mg/kg	6 mg/kg	63 mg/kg
Absorbed			
Tissues	0.35 ± 0.11	0.52 ± 0.19	0.995± 0.444
Dose site	10.2 ± 4.3	8.24 ± 2.48	2.84 ± 0.17
Feces	1.34 ± 0.88	1.69 ± 0.83	4.09 ± 1.41
Urine	31.7 ± 7.75	46.8 ± 6.8	79.5 ± 5.2
Total	43.7 ± 9.75	57.2 ± 4.7	87.4 ± 4.31
Unabsorbed			
Appliance	26.6 ± 12.9	16.7 ± 3.1	1.67 ± 1.02
Skin Gauze	5.35 ± 1.93	11.5 ± 3.1	0.606± 0.532
Skin Wash	8.41 ± 4.04	0.73 ± 0.48	0.463± 0.131
Total	40.4 ± 9.83	28.9 ± 6.1	2.74 ± 0.76

Table 7

Disposition of Radioactivity 72 h following Intravenous Administration of [^{14}C]TBC (3 mg/kg, vehicle=isotonic saline) to Male B6C3F1 Mice[a]

Cumulative Excretion of Radioactivity

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
6 h	13.3 ± 9.65		13.3 ± 9.65
24 h	37.3 ± 17.6	16.4 ± 13.4	53.7 ± 21.7
48 h	43.2 ± 19.9	21.0 ± 15.5	64.3 ± 20.3
72 h	59.9 ± 22.3	28.1 ± 17.2	88.0 ± 8.27

Distribution in Tissues

Tissue	ng-eq TBC per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	2.51 ± 1.15	0.0482 ± 0.0278	0.00780 ± 0.00367
Adrenal Gland	9.66 ± 2.64	0.185 ± 0.0699	0.000111 ± 0.0000256
Blood	54.6 ± 12.8	unity	0.131 ± 0.0294
Brain	7.59 ± 1.17	0.141 ± 0.0156	0.00337 ± 0.000379
Kidney	25.2 ± 6.51	0.479 ± 0.172	0.0119 ± 0.00276
Liver	12.2 ± 1.91	0.235 ± 0.0711	0.0216 ± 0.0126
Lung	136 ± 37.4	2.68 ± 1.23	0.0270 ± 0.0113
Muscle	3.61 ± 2.35	0.0708 ± 0.0558	0.0519 ± 0.0348
Prostate	9.62 ± 9.83	0.176 ± 0.197	0.000134 ± 0.000146
Seminal Vesicl e	2.57 ± 1.02	0.0492 ± 0.0239	0.000417 ± 0.000168
Stomach[b]			0.0155 ± 0.00984
Small Intestine[b]			0.0104 ± 0.00421
Cecum[b]			0.00535 ± 0.00716
Large Intestine[b]			0.0215 ± 0.0405
Skin	10.8 ± 3.90	0.207 ± 0.0998	0.0497 ± 0.0189
Spleen	23.0 ± 4.40	0.430 ± 0.0924	0.00177 ± 0.00031
Testis	2.75 ± 1.38	0.0535 ± 0.0338	0.000662 ± 0.000368
		Total in tissues	0.36 ± 0.091

a N=4
b Includes contents

Table 8

Disposition of Radioactivity 72 h following Intravenous Administration of [^{14}C]TBC (3 mg/kg, vehicle=10% Emulphor in plasma) to Male B6C3F1 Mice[a]

Cumulative Excretion of Radioactivity

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
6 h	8.26 ± 7.74		8.26 ± 7.74
24 h	28.7 ± 14.5	13.1 ± 13.1	41.8 ± 27.7
48 h	37.6 ± 22.8	24.5 ± 0.8	62.1 ± 22.0
72 h	40.8 ± 21.2	25.7 ± 1.1	66.6 ± 20.0
Cage rinse	63.2 ± 7.78	25.7 ± 1.1	88.9 ± 6.7

Distribution in Tissues

Tissue	ng-eq TBC per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	16.7 ± 7.6	0.521 ± 0.137	0.0663 ± 0.0271
Adrenal Gland	27.5 ± 7.2	0.876 ± 0.052	0.000273 ± 0.000030
Blood	31.2 ± 6.4	unity	0.0971 ± 0.0148
Brain	7.06 ± 2.0	0.225 ± 0.017	0.00500 ± 0.00168
Kidney	31.7 ± 5.7	1.02 ± 0.03	0.0239 ± 0.0016
Liver	41.9 ± 7.4	1.35 ± 0.04	0.0765 ± 0.0067
Lung	73.0 ± 18.9	2.33 ± 0.13	0.0185 ± 0.0037
Muscle	9.64 ± 2.4	0.308 ± 0.015	0.177 ± 0.035
Prostate	22.5 ± 7.2	0.714 ± 0.086	0.00149 ± 0.00019
Seminal Vesicle	7.81 ± 4.5	0.241 ± 0.094	0.00153 ± 0.00030
Stomach[b]			0.0123 ± 0.0049
Small Intestine[b]			0.0787 ± 0.0470
Cecum[b]			0.0574 ± 0.0262
Large Intestine[b]			0.0299 ± 0.0177
Skin	26.0 ± 5.7	0.834 ± 0.013	0.154 ± 0.0259
Spleen	18.2 ± 3.9	0.583 ± 0.005	0.00178 ± 0.00001
Testis	8.55 ± 0.8	0.277 ± 0.030	0.00266 ± 0.00027
		Total in tissues	0.805 ± 0.214

a N=2
b Includes contents

Table 9

Disposition of Radioactivity 72 h following Oral Administration of [^{14}C]TBC (300 mg/kg) to Male B6C3F1 Mice[a]

Cumulative Excretion of Radioactivity

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
6 h	21.3 ± 15.5		21.3 ± 15.5
24 h	40.2 ± 18.1	14.2 ± 6.2	54.4 ± 15.4
48 h	47.6 ± 18.6	20.5 ± 6.2	68.1 ± 12.8
72 h	50.1 ± 18.1	25.6 ± 9.5	75.7 ± 10.3
Cage rinse	64.6 ± 11.1	25.6 ± 9.5	90.2 ± 1.6

Distribution in Tissues

Tissue	ng-eq TBC per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	373 ± 153	0.733 ± 0.090	0.0117 ± 0.0047
Adrenal Gland	577 ± 161	1.22 ± 0.39	0.000137 ± 0.000165
Blood	495 ± 146	unity	0.0117 ± 0.0034
Brain	169 ± 55	0.353 ± 0.12	0.00103 ± 0.00044
Kidney	1160 ± 184	2.43 ± 0.40	0.00657 ± 0.00086
Liver	2620 ± 332	5.53 ± 1.16	0.0412 ± 0.0048
Lung	920 ± 204	1.91 ± 0.35	0.00188 ± 0.00030
Muscle	206 ± 100	0.421 ± 0.228	0.0296 ± 0.0145
Prostate	398 ± 156	0.784 ± 0.177	0.000197 ± 0.000076
Seminal Vesicle	191 ± 70	0.380 ± 0.054	0.000317 ± 0.000096
Stomach[b]			0.0197 ± 0.0112
Small Intestine[b]			0.0536 ± 0.0296
Cecum[b]			0.0145 ± 0.0038
Large Intestine[b]			0.00771 ± 0.00522
Skin	691 ± 305	1.39 ± 0.56	0.0320 ± 0.0140
Spleen	196 ± 80	0.384 ± 0.070	0.000169 ± 0.000056
Testis	126 ± 40	0.253 ± 0.031	0.000298 ± 0.000081
		Total in tissues	0.234 ± 0.065

a N=4
b Includes contents

Table 10

Excretion of Radioactivity following Dermal Administration of [^{14}C]TBC to Male Mice

End of Collection Period	Percent of Dose Recovered in: Urine	Feces	Total
4 mg/mouse Dermal Dose			
6 h	11.9 ± 14.0		11.9 ± 14.0
24 h	54.3 ± 10.5	2.58 ± 1.30	56.9 ± 10.3
48 h	68.3 ± 3.9	3.48 ± 1.51	71.8 ± 3.0
72 h	71.4 ± 3.5	5.42 ± 2.55	76.8 ± 1.4
Cage rinse	73.7 ± 3.2	5.42 ± 2.55	79.1 ± 2.1
0.04mg/mouse Dermal Dose			
6 h	4.26 ± 5.2		4.26 ± 5.20
24 h	32.1 ± 9.6	7.45 ± 5.39	39.6 ± 13.6
48 h	47.1 ± 10.7	8.15 ± 5.31	55.2 ± 15.3
72 h	51.7 ± 8.9	12.4 ± 7.68	64.1 ± 15.7
Cage rinse	57.0 ± 7.5	12.4 ± 7.68	69.4 ± 13.4

Table 11

Distribution of Radioactivity 72 h following Dermal Administration of [^{14}C]TBC to Male Mice

	Percent of Dose	
Dose	4 mg/mouse	0.04 mg/mouse
Absorbed		
Tissues	0.76 ± 0.30	11.6 ± 8.3
Dose site	6.18 ± 0.52	1.51 ± 0.43
Feces	5.42 ± 2.6	12.4 ± 7.7
Urine	73.7 ± 3.2	57.0 ± 7.5
Total	86.0 ± 2.7	72.2 ± 14.2
Unabsorbed		
Skin Wash	2.25 ± 0.81	11.6 ± 8.3
Total recovery	88.3 ± 2.7	83.7 ± 11.3

Table 12

Concentration of TBC Equivalents in Plasma Following Oral Administration of [^{14}C]TBC (200 mg/kg) to Male Rats

	ng-eq/g plasma				
Timepoint (h)	Rat 1	Rat 2	Rat 3	Rat 4	mean ± SD
0.25	36700	32100	42200	34900	36500 ± 4290
0.5	64200	38600	44000	45700	48100 ±11100
1	52100	36200	30500	36400	38800 ± 9250
2	15400	26100	25800	28000	23800 ± 5680
4	29400	27200	26400	30400	28300 ± 1890
8	21400	16100	28700	26100	23100 ± 5550
24	2540	2370	2700	1710	2330 ± 436

Table 13

Concentration of TBC Equivalents in Plasma Following Dermal Administration of [^{14}C]TBC (63 mg/kg) to Male Rats

	ng-eq./g plasma				
Timepoint (h)	Rat 1	Rat 2	Rat 3	Rat 4	mean ± SD
0.25	15500[a]	15200	10000	10300	12700 ± 3010
0.5	25400	25000	21400	18500	22600 ± 3270
1	28700	29900	22200	28600	27300 ± 3490
2	20400	21000	23400	27600	23100 ± 3260
4	10000	10700	12500	8660	10500 ± 1620
8	5370	5180	19500	8900	9740 ± 6730
24	717	745	1010	628	776 ± 165