

ADME NTP Study S0214 Tri-o-cresyl phosphate

The contractor used the abbreviation of TOCP for the test article.

Sex/Species: male F344 rats.

Vehicle: intravenous, Emulphor EL-620:ethanol:water (1:3:6, v/v/v); oral, ethanol:Emulphor EL-620:water (4:3:3, v/v/v).

CASRN 78-30-8

Radiolabeled with carbon-14, position not specified; [¹⁴C]Tri-o-cresyl phosphate

Studies Performed:

- Single 20.0 mg/kg intravenous dose to rats with sacrifice at 0.5, 1, 2, 4, 8, 12, 24, 48, or 72 hours postdose. (n = 3 per time point)
- Single 2.0 or 20.0 mg/kg intravenous dose to bile duct cannulated rats for bile collection with sacrifice at 6 hours postdose. (n = 3 per group)
- Single 2.0, 20.0, or 200.0 mg/kg oral gavage dose to rats with sacrifice 9 days postdose. (n = 3)

Toxicokinetics:

Blood and tissue samples were analyzed for parent TOCP by HPLC. Pharmacokinetic parameters for percent dose in blood and tissue decay curves were modeled using the mono-exponential equation $C = C_0e^{-kt}$ for parent TOCP (except for adipose) or biexponential ($C = Ae^{-\alpha t} + Be^{-\beta t}$) equation for total ¹⁴C (and parent TOCP in adipose). Rate constants and half-lives were determined.

The potential absorptive phase for adipose and spinal cord could not be modeled properly with only two time points. The mean value of the 8-hour percent dose for parent TOCP was eliminated as an outlier from the modeling calculations for the liver elimination curve.

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Table 1

Percent Dose in Excreta after Oral Dose

| Dose (mg/kg) | Day | Percent Dose (\bar{x} + SEM, n=3) | |
|-----------------|-----|--------------------------------------|--------------|
| | | Urine | Feces |
| 2.0 | 1 | 69.17 ± 5.45 | 20.95 ± 1.8 |
| | 2 | 4.78 ± 0.21 | 4.18 ± 1.55 |
| | 3 | 2.02 ± 0.39 | 0.28 ± 0.03 |
| | 4 | 1.41 ± 0.33 | 0.26 ± 0.11 |
| | 5 | 0.64 ± 0.12 | 0.09 ± 0.01 |
| | 6 | 0.48 ± 0.10 | 0.09 ± 0.01 |
| | 7 | 0.43 ± 0.05 | 0.10 ± 0.05 |
| | 8 | 0.28 ± 0.04 | 0.04 ± 0.00 |
| | 9 | 0.18 ± 0.06 | 0.03 ± 0.00 |
| 20.0 | 1 | 63.19 ± 5.04 | 25.00 ± 2.22 |
| | 2 | 3.64 ± 0.39 | 5.12 ± 1.51 |
| | 3 | 1.43 ± 0.14 | 0.39 ± 0.07 |
| | 4 | 0.68 ± 0.09 | 0.17 ± 0.00 |
| | 5 | 0.39 ± 0.04 | 0.10 ± 0.02 |
| | 6 | 0.25 ± 0.03 | 0.05 ± 0.01 |
| | 7 | 0.21 ± 0.01 | 0.04 ± 0.00 |
| | 8 | 0.13 ± 0.02 | 0.03 ± 0.00 |
| | 9 | 0.07 ± 0.01 | 0.02 ± 0.00 |
| 200.0 | 1 | 44.61 ± 10.18 | 15.96 ± 2.39 |
| | 2 | 18.21 ± 2.90 | 14.67 ± 1.89 |
| | 3 | 1.78 ± 0.32 | 2.29 ± 0.71 |
| | 4 | 0.76 ± 0.06 | 0.22 ± 0.04 |
| | 5 | 0.37 ± 0.07 | 0.09 ± 0.01 |
| | 6 | 0.28 ± 0.05 | 0.06 ± 0.01 |
| | 7 | 0.16 ± 0.02 | 0.05 ± 0.02 |
| | 8 | 0.10 ± 0.01 | 0.04 ± 0.01 |
| | 9 | 0.06 ± 0.01 | 0.03 ± 0.00 |

Table 2
Cumulative Percent Dose in Excreta after Oral Dose

| Dose (mg/kg) | Day | Percent Dose (as Total ¹⁴ C) (n=3) | | |
|-----------------|-----|---|-------|--------|
| | | Urine | Feces | Total |
| 2.0 | 1 | 69.17 | 20.95 | 90.12 |
| | 2 | 73.93 | 25.13 | 99.06 |
| | 3 | 75.97 | 25.41 | 101.38 |
| | 4 | 77.38 | 25.67 | 103.05 |
| | 5 | 78.02 | 25.76 | 103.78 |
| | 6 | 78.51 | 25.85 | 104.36 |
| | 7 | 78.94 | 25.95 | 104.89 |
| | 8 | 79.22 | 25.99 | 105.21 |
| | 9 | 79.40 | 26.02 | 105.42 |
| 20.0 | 1 | 63.2 | 25.0 | 88.2 |
| | 2 | 66.8 | 30.2 | 97.0 |
| | 3 | 68.3 | 30.6 | 98.9 |
| | 4 | 69.0 | 30.8 | 99.8 |
| | 5 | 69.4 | 30.9 | 100.3 |
| | 6 | 69.6 | 30.9 | 100.6 |
| | 7 | 69.8 | 31.0 | 100.8 |
| | 8 | 70.0 | 31.0 | 101.0 |
| | 9 | 70.1 | 31.0 | 101.1 |
| 200.0 | 1 | 44.6 | 16.0 | 60.6 |
| | 2 | 62.8 | 30.7 | 93.5 |
| | 3 | 64.4 | 33.0 | 97.4 |
| | 4 | 65.2 | 33.2 | 98.4 |
| | 5 | 65.6 | 33.3 | 98.9 |
| | 6 | 65.9 | 33.4 | 99.3 |
| | 7 | 66.1 | 33.4 | 99.5 |
| | 8 | 66.2 | 33.5 | 99.7 |
| | 9 | 66.3 | 33.5 | 99.8 |

Table 3
 Percent Dose (as total ^{14}C) in Tissues and Excreta
 Nine Days after Each of Three Oral Dose Levels

| Tissue | Percent Dose ($\bar{x} \pm \text{SEM}$, n=3) | | |
|-----------------|--|-----------------|-----------------|
| | 2.0 mg/kg | 20.0 mg/kg | 200.0 mg/kg |
| Brain | 0.00 \pm 0.00 | 0.00 \pm 0.00 | 0.00 \pm 0.00 |
| Lung | 0.02 \pm 0.00 | 0.01 \pm 0.00 | 0.01 \pm 0.00 |
| Liver | 0.74 \pm 0.12 | 0.22 \pm 0.01 | 0.19 \pm 0.02 |
| Kidney | 0.03 \pm 0.00 | 0.03 \pm 0.00 | 0.02 \pm 0.00 |
| Spleen | 0.00 \pm 0.00 | 0.00 \pm 0.00 | 0.00 \pm 0.00 |
| Small Intestine | 0.03 \pm 0.00 | 0.02 \pm 0.00 | 0.02 \pm 0.00 |
| Testes | 0.01 \pm 0.00 | 0.01 \pm 0.00 | 0.06 \pm 0.01 |
| Adipose Tissue | 0.05 \pm 0.03 | 0.08 \pm 0.00 | 0.19 \pm 0.02 |
| Muscle | 0.10 \pm 0.05 | 0.16 \pm 0.02 | 0.00 \pm 0.00 |
| Skin | 0.11 \pm 0.01 | 0.05 \pm 0.02 | 0.10 \pm 0.01 |
| Blood | 0.58 \pm 0.06 | 0.63 \pm 0.01 | 0.77 \pm 0.03 |
| Plasma | 0.57 \pm 0.01 | 0.06 \pm 0.00 | 0.05 \pm 0.01 |
| Tissue Total | 1.61 | 1.27 | 1.40 |
| Urine | 79.40 | 84.63 | 77.14 |
| Feces | 26.02 | 37.36 | 38.84 |
| Total | 107.30 | 123.26 | 117.38 |

Table 4

Tissue/Blood Concentration Ratios Nine Days After
Each of Three Oral Doses

| Tissue | Con | | |
|---------------------------------------|-------------|-------------|--------------|
| | 2.0 mg/kg | 20.0 mg/kg | 200.0 mg/kg |
| Brain | 0.02 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.01 |
| Lungs | 0.57 ± 0.04 | 0.27 ± 0.05 | 0.21 ± 0.01 |
| Liver | 2.77 ± 0.59 | 0.69 ± 0.04 | 0.47 ± 0.05 |
| Kidneys | 0.52 ± 0.02 | 0.47 ± 0.02 | 0.30 ± 0.01 |
| Spleen | 0.22 ± 0.03 | 0.31 ± 0.03 | 0.22 ± 0.02 |
| Small Intestine | 0.18 ± 0.00 | 0.12 ± 0.01 | 0.09 ± 0.01 |
| Testes | 0.08 ± 0.02 | 0.10 ± 0.01 | 0.03 ± 0.00 |
| Adipose Tissue | 0.11 ± 0.06 | 0.15 ± 0.01 | 0.10 ± 0.01 |
| Muscle | 0.31 ± 0.02 | 0.05 ± 0.00 | 0.04 ± 0.00 |
| Skin | 0.01 ± 0.01 | 0.04 ± 0.02 | 0.08 ± 0.00 |
| Blood Concentration (nmoles/gm) | 0.28 ± 0.03 | 2.17 ± 0.04 | 35.21 ± 2.94 |

Table 5

Cumulative Percent Dose (as Total ^{14}C) in Excreta
After Intravenous Administration of 20 mg/kg TOCP

| Time | Percent Dose ($\bar{x} \pm \text{SEM}, n=3$) | | Total |
|--------|--|------------------|-------------------|
| | Urine | Feces * | |
| 30 min | 8.51 \pm 3.39 | 23.32 \pm 5.82 | 31.92 \pm 8.07 |
| 1 hr | 20.00 \pm 3.37 | 25.25 \pm 3.6 | 45.26 \pm 1.82 |
| 2 hr | 29.36 \pm 4.01 | 34.58 \pm 4.58 | 63.94 \pm 6.15 |
| 4 hr | 35.49 \pm 6.12 | 30.39 \pm 1.11 | 65.88 \pm 5.64 |
| 8 hr | 40.59 \pm 8.53 | 20.38 \pm 1.22 | 60.97 \pm 8.99 |
| 12 hr | 61.36 \pm 1.46 | 28.06 \pm 0.55 | 89.42 \pm 1.68 |
| 24 hr | 56.37 \pm 1.16 | 22.41 \pm 1.80 | 78.78 \pm 1.10 |
| 48 hr | 79.05 \pm 4.42 | 25.22 \pm 0.37 | 108.33 \pm 3.53 |
| 72 hr | 75.49 \pm 1.62 | 28.66 \pm 2.40 | 104.15 \pm 1.82 |

* Includes feces plus intestinal contents.

Table 6
Biliary Excretion of Percent Dose (as total ^{14}C) after
Intravenous Dose of 2.0 mg/kg TOCP

| Time (Hr) | Percent of Dose | | | | | Cumulative % of Dose | | | | |
|--------------|-----------------|-------|-------|-----------|------|----------------------|-------|-------|-----------|------|
| | 1 | 2 | 3 | \bar{x} | SD | 1 | 2 | 3 | \bar{x} | SD |
| 0.5 | 23.72 | 15.98 | 25.14 | 21.61 | 4.93 | 23.72 | 15.98 | 25.14 | 21.61 | 4.93 |
| 1.0 | 6.44 | 11.54 | 6.73 | 8.24 | 2.86 | 30.16 | 27.52 | 31.87 | 29.85 | 2.19 |
| 1.5 | 3.21 | 5.00 | 3.40 | 3.87 | 0.98 | 33.37 | 32.52 | 35.27 | 33.72 | 1.41 |
| 2.0 | 2.15 | 2.62 | 1.76 | 2.18 | 0.43 | 35.52 | 35.15 | 37.03 | 35.90 | 1.00 |
| 2.5 | 1.43 | 1.41 | 1.12 | 1.32 | 0.17 | 36.92 | 36.55 | 38.15 | 37.21 | 0.84 |
| 3.0 | 0.89 | 0.96 | 0.90 | 0.92 | 0.05 | 37.81 | 37.51 | 39.05 | 38.12 | 0.82 |
| 3.5 | 0.70 | 0.60 | 0.75 | 0.68 | 0.08 | 38.51 | 38.11 | 39.08 | 38.57 | 0.49 |
| 4.0 | 0.46 | 0.40 | 0.58 | 0.48 | 0.09 | 38.97 | 38.51 | 40.38 | 39.29 | 0.97 |
| 4.5 | 0.33 | 0.38 | 0.45 | 0.39 | 0.06 | 39.30 | 38.89 | 40.83 | 39.67 | 1.02 |
| 5.0 | 0.29 | 0.30 | 0.29 | 0.29 | 0.01 | 39.59 | 39.19 | 41.12 | 39.97 | 1.02 |
| 5.5 | 0.28 | 0.24 | 0.22 | 0.25 | 0.03 | 39.87 | 39.43 | 41.34 | 40.21 | 1.00 |
| 6.0 | 0.31 | | 0.21 | 0.26 | 0.07 | 40.18 | | 41.55 | 40.86 | 0.97 |

Table 7

Biliary Excretion of Percent Dose (as total ^{14}C) after
Intravenous Dose of 20.0 mg/kg TOCP

| Time | Percent of Dose | | | | | Cumulative % of Dose | | | | |
|------|-----------------|-------|-------|-----------|------|----------------------|-------|-------|-----------|------|
| | 1 | 2 | 3 | \bar{x} | SD | 1 | 2 | 3 | \bar{x} | SD |
| 0.5 | 23.93 | 21.76 | 14.06 | 19.92 | 5.19 | 23.93 | 21.76 | 14.06 | 19.92 | 5.19 |
| 1.0 | 6.18 | 6.90 | 10.16 | 7.75 | 2.12 | 30.11 | 28.66 | 24.22 | 27.66 | 3.07 |
| 1.5 | 3.42 | 3.56 | 4.30 | 3.76 | 0.47 | 34.53 | 32.22 | 28.52 | 31.76 | 3.03 |
| 2.0 | 2.34 | 2.11 | 2.53 | 2.33 | 0.21 | 36.87 | 34.33 | 31.05 | 34.08 | 2.92 |
| 2.5 | 1.57 | 1.20 | 1.72 | 1.50 | 0.27 | 38.44 | 35.53 | 32.77 | 35.58 | 2.84 |
| 3.0 | 1.14 | 1.07 | 1.32 | 1.18 | 0.13 | 39.58 | 36.60 | 34.09 | 36.76 | 2.75 |
| 3.5 | 0.82 | 0.77 | 1.07 | 0.89 | 0.16 | 40.40 | 37.37 | 35.16 | 37.64 | 2.63 |
| 4.0 | 0.62 | 0.52 | 0.78 | 0.64 | 0.13 | 41.02 | 37.89 | 35.94 | 38.28 | 2.56 |
| 4.5 | 0.50 | 0.45 | 0.44 | 0.46 | 0.03 | 41.52 | 38.34 | 36.38 | 38.75 | 2.59 |
| 5.0 | 0.49 | 0.42 | 0.39 | 0.43 | 0.05 | 42.01 | 38.76 | 36.77 | 39.18 | 2.65 |
| 5.5 | 0.39 | 0.38 | 0.43 | 0.40 | 0.03 | 42.40 | 39.14 | 37.20 | 39.58 | 2.63 |
| 6.0 | 0.36 | 0.35 | 0.28 | 0.33 | 0.04 | 42.76 | 39.49 | 37.48 | 39.91 | 2.66 |

Table 8

Percent Dose in Selected Tissues vs. Time after Intravenous Administration of TOCP

| | 30 min. | 1 hr. | 2 hr. | 4 hr. | 8 hr. | 12 hr. | 24 hr. | 48 hr. | 72 hr. |
|-----------------|---------------------------|---------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Brain | 0.3628 <u>+0.0214</u> | 0.2419 <u>+0.0263</u> | 0.0793 <u>+0.0027</u> | 0.0341 <u>+0.0019</u> | 0.0168 <u>+0.0004</u> | 0.0112 <u>+0.0009</u> | 0.0123 <u>+0.0014</u> | 0.0188 <u>+0.0043</u> | 0.117 <u>+0.0012</u> |
| Lung | 0.3792 <u>+0.0150</u> | 0.3040 <u>+0.0033</u> | 0.2531 <u>+0.0564</u> | 0.1168 <u>+0.0105</u> | 0.0565 <u>+0.0015</u> | 0.0541 <u>+0.0015</u> | 0.0452 <u>+0.0039</u> | 0.0420 <u>+0.0048</u> | 0.0376 <u>+0.0092</u> |
| Liver | 6.2613 <u>+0.1924</u> | 4.4401 <u>+0.4470</u> | 4.1372 <u>+0.5368</u> | 2.5505 <u>+0.0087</u> | 1.8781 <u>+0.1728</u> | 1.6158 <u>+0.1510</u> | 1.4481 <u>+0.0450</u> | 1.1846 <u>+0.1058</u> | 1.1489 <u>+0.2198</u> |
| Kidney | 1.6505 <u>+0.0529</u> | 1.0924 <u>+0.0179</u> | 0.8061 <u>+0.0580</u> | 0.4863 <u>+0.0165</u> | 0.2814 <u>+0.0329</u> | 0.2532 <u>+0.0219</u> | 0.1888 <u>+0.0163</u> | 0.1455 <u>+0.0045</u> | 0.1033 <u>+0.0041</u> |
| Spleen | 0.0671 <u>+0.0093</u> | 0.0643 <u>+0.0030</u> | 0.0427 <u>+0.0038</u> | 0.0287 <u>+0.0030</u> | 0.0215 <u>+0.0019</u> | 0.0153 <u>+0.0016</u> | 0.0106 <u>+0.0005</u> | 0.0136 <u>+0.0015</u> | 0.0078 <u>+0.0004</u> |
| Small Intestine | 5.8242 <u>+1.7909</u> | 7.6103 <u>+1.9226</u> | 10.1328 <u>+3.9614</u> | 1.8685 <u>+0.7660</u> | 0.5796 <u>+0.1586</u> | 0.6313 <u>+0.1742</u> | 0.4367 <u>+0.0018</u> | 0.2032 <u>+0.0317</u> | 0.1081 <u>+0.0151</u> |
| Testes | 0.4954 <u>+0.0168</u> | 0.4425 <u>+0.0381</u> | 0.2977 <u>+0.0196</u> | 0.2006 <u>+0.0126</u> | 0.0847 <u>+0.0085</u> | 0.0792 <u>+0.0048</u> | 0.0796 <u>+0.0018</u> | 0.0553 <u>+0.0102</u> | 0.0632 <u>+0.0139</u> |
| Adipose | 5.6145 <u>+1.2888</u> | 7.3295 <u>+1.5628</u> | 5.7342 <u>+1.8279</u> | 5.8460 <u>+1.4570</u> | 5.2028 <u>+1.1485</u> | 5.5388 <u>+1.8652</u> | 4.8086 <u>+1.3692</u> | 3.7255 <u>+1.477</u> | 2.5111 <u>+1.1174</u> |
| Muscle | 18.2708 <u>+1.8224</u> | 13.7172 <u>+2.2289</u> | 8.0923 <u>+1.2699</u> | 3.9091 <u>+0.3793</u> | 1.9774 <u>+0.5129</u> | 2.0010 <u>+0.2737</u> | 1.6948 <u>+0.3199</u> | 1.5667 <u>+0.3367</u> | 0.9573 <u>+0.1048</u> |
| Skin | 9.9698 <u>+1.6738</u> | 9.8032 <u>+1.6379</u> | 8.7239 <u>+1.6039</u> | 7.8871 <u>+1.9627</u> | 3.5909 <u>+1.7321</u> | 2.4112 <u>+1.4299</u> | 1.6581 <u>+1.2270</u> | .7591 <u>+1.1024</u> | .5986 <u>+1.0710</u> |
| Spinal Cord | 0.0621 <u>+0.0041</u> | 0.1026 <u>+0.0144</u> | 0.0514 <u>+0.0082</u> | 0.0183 <u>+0.0011</u> | 0.0073 <u>+0.0014</u> | 0.0039 <u>+0.0006</u> | 0.0094 <u>+0.0032</u> | 0.0066 <u>+0.0008</u> | 0.0036 <u>+0.0006</u> |

Table 8 (continued)

| | | | | | | | | | |
|---------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Sciatic Nerve | 0.0265 <u>+0.0033</u> | 0.0216 <u>+0.0044</u> | 0.0219 <u>+0.0076</u> | 0.0234 <u>+0.0058</u> | 0.0153 <u>+0.0015</u> | 0.0074 <u>+0.0029</u> | 0.0063 <u>+0.0020</u> | 0.0071 <u>+0.0017</u> | 0.0046 <u>+0.0006</u> |
| Blood | 5.0877 <u>+0.3139</u> | 4.1485 <u>+0.4654</u> | 3.5864 <u>+0.2504</u> | 2.6564 <u>+0.0648</u> | 1.6275 <u>+0.0404</u> | 1.5236 <u>+0.0587</u> | 1.2741 <u>+0.1131</u> | 1.0006 <u>+0.0468</u> | 0.8770 <u>+0.0070</u> |
| Plasma | 3.3469 <u>+0.2326</u> | 5.3502 <u>+0.5550</u> | 2.2010 <u>+0.1098</u> | 1.4450 <u>+0.0769</u> | 0.8289 <u>+0.0241</u> | 0.6846 <u>+0.0160</u> | 0.4762 <u>+0.0501</u> | 0.3239 <u>+0.0141</u> | 0.2497 <u>+0.0080</u> |

Table 9

Percent of Dose ($\bar{x} \pm \text{SEM}$) as Unchanged Parent (P), Metabolite (M), and Unextracted Fraction (U) in Selected Tissues after Intravenous Administration of 20.0 mg/kg TOCP

| Time | | 30 min | 1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 1 day | 2 days | 3 days |
|---------------|-----|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| <u>Tissue</u> | | | | | | | | | | |
| Blood | (P) | 0.38 ± 0.04 | 0.23 ± 0.02 | 0.08 ± 0.01 | 0.02 ± 0.00 | | | | | |
| | (M) | 2.30 ± 0.15 | 1.98 ± 0.16 | 1.14 ± 0.08 | 0.63 ± 0.02 | | | | | |
| | (U) | 2.60 ± 0.03 | 2.17 ± 0.12 | 2.44 ± 0.06 | 2.04 ± 0.02 | | | | | |
| Liver | (P) | 0.38 ± 0.04 | 0.11 ± 0.01 | 0.05 ± 0.01 | 0.02 ± 0.00 | 0.06 ± 0.01 | | | | |
| | (M) | 2.15 ± 0.10 | 1.19 ± 0.06 | 0.82 ± 0.05 | 0.32 ± 0.01 | 0.10 ± 0.00 | | | | |
| | (U) | 3.73 ± 0.02 | 3.14 ± 0.20 | 3.28 ± 0.24 | 2.21 ± 0.01 | 1.72 ± 0.10 | | | | |
| Adipose | (P) | 3.42 ± 0.28 | 5.70 ± 0.56 | 4.93 ± 0.41 | 4.86 ± 0.41 | 2.92 ± 0.18 | 3.09 ± 0.35 | 2.05 ± 0.53 | 2.26 ± 0.37 | 1.38 ± 0.22 |
| | (M) | 1.45 ± 0.86 | 0.54 ± 0.08 | 0.38 ± 0.03 | 0.30 ± 0.04 | 1.20 ± 0.34 | 1.31 ± 0.44 | 0.55 ± 0.09 | 0.25 ± 0.06 | 0.25 ± 0.04 |
| | (U) | 0.74 ± 0.58 | 1.09 ± 0.43 | 0.43 ± 0.41 | 0.68 ± 0.39 | 1.09 ± 0.18 | 1.15 ± 0.33 | 2.20 ± 0.66 | 1.22 ± 0.52 | 0.89 ± 0.34 |

Table 9 (continued)

| Time | | 30 min | 1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 1 day | 2 days | 3 days |
|------------------------|-----|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|--------|--------|
| <u>Tissue</u> | | | | | | | | | | |
| Muscle | (P) | 10.41 <u>+1.38</u> | 7.08 <u>+2.22</u> | 4.29 <u>+4.43</u> | 1.81 <u>+2.25</u> | 1.50 <u>+3.34</u> | 0.42 <u>+1.18</u> | | | |
| | (M) | 1.98 <u>+2.22</u> | 3.84 <u>+1.43</u> | 1.18 <u>+1.11</u> | 1.19 <u>+1.17</u> | 0.48 <u>+1.12</u> | 0.17 <u>+0.03</u> | | | |
| | (U) | 5.88 <u>+2.54</u> | 2.80 <u>+2.20</u> | 2.62 <u>+2.27</u> | 1.04 <u>+3.38</u> | 0.00 <u>+0.00</u> | 1.40 <u>+2.29</u> | | | |
| Small Intestine | (P) | 0.44 <u>+0.06</u> | 0.37 <u>+0.02</u> | 0.24 <u>+0.03</u> | 0.10 <u>+0.04</u> | 0.09 <u>+0.02</u> | 0.10 <u>+0.00</u> | | | |
| | (M) | 3.08 <u>+0.60</u> | 2.75 <u>+0.35</u> | 2.30 <u>+0.44</u> | 0.32 <u>+0.11</u> | 0.15 <u>+0.04</u> | 0.11 <u>+0.01</u> | | | |
| | (U) | 2.30 <u>+0.42</u> | 4.55 <u>+0.96</u> | 7.59 <u>+2.33</u> | 0.39 <u>+0.17</u> | 0.34 <u>+0.03</u> | 0.33 <u>+0.08</u> | | | |
| Skin | (P) | 5.04 <u>+0.65</u> | 4.85 <u>+1.03</u> | 5.92 <u>+2.29</u> | 3.07 <u>+0.71</u> | 1.93 <u>+0.66</u> | 0.90 <u>+0.17</u> | 0.70 <u>+0.14</u> | | |
| | (M) | 1.28 <u>+0.04</u> | 1.82 <u>+0.47</u> | 1.28 <u>+0.15</u> | 1.28 <u>+0.31</u> | 0.65 <u>+0.40</u> | 0.30 <u>+0.03</u> | 0.19 <u>+0.02</u> | | |
| | (U) | 3.65 <u>+0.91</u> | 3.14 <u>+0.57</u> | 1.53 <u>+0.88</u> | 3.53 <u>+1.21</u> | 1.02 <u>+0.70</u> | 1.21 <u>+0.49</u> | 0.46 <u>+0.34</u> | | |

Table 9 (continued)

| Time | | 30 min | 1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 1 day | 2 days | 3 days |
|---------------|-----|---------------------|---------------------|---------------------|---------------------|------|-------|-------|--------|--------|
| <u>Tissue</u> | | | | | | | | | | |
| Spinal Cord | (P) | 0.026 \pm .007 | 0.073 \pm .005 | 0.016 \pm .005 | 0.004 \pm .000 | | | | | |
| | (M) | 0.005 \pm .001 | 0.013 \pm .001 | 0.009 \pm .001 | 0.002 \pm .001 | | | | | |
| | (U) | 0.030 \pm .009 | 0.017 \pm .003 | 0.026 \pm .006 | 0.013 \pm .001 | | | | | |

Table 10

Pharmacokinetic Parameters for
Percent Dose of TOCP as Total ^{14}C

| Tissue | A % | α hr^{-1} | B % | β hr^{-1} | α $t_{1/2}$ hr | β $t_{1/2}$ hr | CORR. |
|---------|--------|------------------------------|--------|-----------------------------|-----------------------------|----------------------------|-------|
| Blood | 4.03 | 0.33 | 1.52 | 0.008 | 2.09 | 87.02 | 0.998 |
| Plasma | 3.65 | 0.37 | 0.71 | 0.015 | 1.85 | 45.52 | 0.911 |
| Liver | 4.09 | 0.40 | 1.68 | 0.006 | 1.74 | 117.55 | 0.987 |
| Kidney | 1.51 | 0.50 | 0.28 | 0.014 | 1.38 | 49.35 | 0.990 |
| Muscle | 22.15 | 0.65 | 2.20 | 0.010 | 1.07 | 65.83 | 1.000 |
| Skin | 10.96 | 0.31 | 2.95 | 0.024 | 2.24 | 28.88 | 0.953 |
| Adipose | 6.88 | 0.04 | 6.59 | 0.013 | 18.30 | 53.5 | 0.988 |
| Lung | 0.42 | 0.46 | 0.05 | 0.004 | 1.52 | 160.0 | 0.995 |
| Testes | 0.53 | 0.40 | 0.08 | 0.004 | 1.71 | 200.0 | 0.997 |
| Brain | 0.51 | 0.91 | 0.14 | 0.161 | 0.76 | 431.0 | 0.997 |
| Spinal | 0.18 | 0.65 | 0.005 | 0.001 | 1.07 | 486.0 | 0.998 |

Table 11

Pharmacokinetic Parameters for Percent Dose
as Parent TOCP in Selected Tissues

| | A | α | t1/2 | F | β | t1/2 | CORR. |
|-------------|------|------------------|------|-------|------------------|------|-------|
| Tissue | % | hr ⁻¹ | hr | % | hr ⁻¹ | hr | |
| Blood | -- | -- | -- | 0.68 | 1.12 | 0.62 | 0.999 |
| Liver | -- | -- | -- | 0.39 | 1.16 | 0.60 | 0.953 |
| Kidney | -- | -- | -- | 0.16 | 0.20 | 3.46 | 0.924 |
| Muscle | -- | -- | -- | 12.73 | 0.50 | 1.38 | 0.972 |
| Skin | -- | -- | -- | 4.93 | 0.09 | 7.83 | 0.861 |
| Adipose | 4.98 | 0.05 | 3.87 | 3.21 | 0.01 | 71.9 | 0.816 |
| Spinal Cord | -- | -- | -- | 0.07 | 0.81 | 0.86 | 0.534 |