

ADME NTP Study S0036 tris(2,3-Dibromopropyl) phosphate

The contractor used the abbreviation Tris-BP for the test article.

Sex/Species: male and female Sprague-Dawley rats.

Vehicle: intravenous, aqueous Emulphor 719 (25% v/v).

CASRN 126-72-7

Radiolabeled with carbon-14 at carbon 1 of the propyl moiety; tris(2,3-Dibromopropyl) phosphate, [propyl-1-¹⁴C]

Studies Performed:

- Single 8.4* umol/kg intravenous dose to male rats with sacrifice at 120 hours postdose. (n = 4)
- Single 8.4* umol/kg intravenous dose to male rats with sacrifice at 5 minutes, and 0.5, 8, and 24 hours postdose. (n = 2 per time point)
- Single 8.4* umol/kg intravenous dose to male rats with sacrifice at 24 hours postdose. (bile collection; n = 3)
- Single 8.4* umol/kg intravenous dose to male and female rats with sacrifice at 72 hours postdose. (n = 3 for each group)

*The dose is estimated based on information in the report (estimated range of 8.125-8.69 umol/kg).

For the distribution study, rats from the first two groups listed above were used for tissue collection (those sacrificed at 120 hour and those sacrificed at 5 minutes to 24 hours postdose). Table 1 has interval and Table 3, cumulative, excretion. Bis-BP is the Tris-BP metabolite bis(2,3-dibromopropyl)phosphate.

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TABLE 1
EXCRETION OF RADIOLABEL FOLLOWING I.V. ADMINISTRATION OF ^{14}C -TRIS-BP

	24 hr	48 hr	72 hr	96 hr	120 hr	TOTAL
Urine	39.10(4.17)	9.59(4.12)	4.22(0.35)	3.16(0.55)	2.00(0.23)	58.07(7.07)
$^{14}\text{CO}_2$	14.69(4.06)	2.45(0.83)	0.81(0.16)	0.59(0.25)	0.31(0.13)	18.85(3.50)
Feces	4.40(3.26)	3.03(1.52)	0.79(0.54)	0.52(0.40)	0.28(0.14)	9.02(0.28)
Total	58.19(7.77)	15.07(5.84)	5.82(0.87)	4.27(1.06)	2.59(0.24)	85.94(4.64)
Carcass	-	-	-	-	9.11(1.12)	95.05(4.71)

The quantity of radiolabel excreted in urine, feces, and expired $^{14}\text{CO}_2$ was determined at 24 hr intervals for 120 hr in four rats after administration of ^{14}C -Tris-BP. Numbers in the table represent the percentage of administered radiolabel recovered. Numbers in parentheses represent standard deviations.

TABLE 2

DISTRIBUTION OF TOTAL RADIOLABEL, TRIS-BP AND BIS-BP AFTER I.V. ADMINISTRATION OF ¹⁴C TRIS-BP

		% Dose per Tissue ^a	% Dose per g	Tris-BP nmoles/g ^b	Bis-BP nmoles/g ^b		% Dose per Tissue ^a	% Dose per g	Tris-BP nmoles/g ^b	Bis-BP nmoles/g ^b
MUSCLE ^c	5 min	30.66	0.20	3.91(78)	0.32(4)	STOMACH ^d	0.64	0.30	5.27(70)	0.30(3)
	30 min	16.38	0.11	1.47(53)	0.80(19)		0.32	0.17	1.61(38)	0.17(3)
	8 hr	9.93	0.07	-	1.18(45)		0.19	0.11	-	0.11(3)
	24 hr	7.76	0.05	-	0.81(43)		0.19	0.09	-	0.09(3)
	120 hr	2.09(0.51)	0.01(0.003)	e	e		0.04(0.01)	0.02(0.007)	e	e
LIVER	5 min	18.68	1.83	0.07(0.2)	8.44(12)	SPLEEN	0.19	0.31	1.73(22)	1.12(10)
	30 min	8.98	0.87	-	7.15(22)		0.15	0.20	0.29(6)	2.79(37)
	8 hr	3.06	0.31	-	1.35(12)		0.08	0.10	-	1.10(29)
	24 hr	2.19	0.28	-	1.59(15)		0.05	0.07	-	0.74(28)
	120 hr	1.12(0.17)	0.12(0.014)	e	e		0.05(0.04)	0.06(0.037)	e	e
BLOOD ^c	5 min	12.83	0.48	4.70(39)	7.10(39)	HEART	0.50	0.47	6.79(57)	2.32(13)
	30 min	19.58	0.72	1.22(7)	23.59(87)		0.33	0.33	0.66(8)	7.10(57)
	8 hr	13.93	0.52	-	18.61(95)		0.36	0.22	-	5.38(65)
	24 hr	9.97	0.37	-	8.95(64)		0.18	0.13	-	-
	120 hr	2.34(0.56)	0.09(.020)	e	e		0.04(0.01)	0.04(0.009)	e	e
FAT ^c	5 min	7.68	0.37	4.62(50)	1.56(11)	TESTES	0.60	0.18	-	1.39(20)
	30 min	13.78	0.66	10.44(63)	3.82(15)		0.71	0.22	-	2.06(25)
	8 hr	2.15	0.10	-	1.81(48)		0.42	0.14	-	1.05(20)
	24 hr	1.91	0.09	-	1.93(57)		0.43	0.12	-	0.92(20)
	120 hr	0.37(0.08)	0.02(0.004)	e	e		0.09(0.02)	0.03(0.008)	e	e

Table 2 (Continued)

DISTRIBUTION OF TOTAL RADIOLABEL, TRIS-BP AND BIS-BP AFTER I.V. ADMINISTRATION OF ¹⁴C TRIS-BP

SMALL INTESTINE	5 min	4.72	0.50	5.55(44)	2.76(15)	BRAIN	0.60	0.38	2.34(24)	3.80(27)
	30 min	10.88	0.86	2.29(11)	7.93(24)		0.13	0.16	0.54(13)	1.04(17)
	8 hr	2.06	0.30	-	1.86(16)		0.07	0.04	-	0.32(21)
	24 hr	0.53	0.11	-	0.85(20)		0.03	0.02	e	e
	120 hr	0.17(0.08)	0.03(0.012)	e	e		0.02(0.01)	0.01(0.005)	e	e
KIDNEY	5 min	2.30	1.00	2.79(11)	4.05(11)	CARCASS ^g	61.25	0.26	4.28(65)	0.51(5)
	30 min	1.62	0.72	1.01(6)	3.94(15)		61.00	0.26	3.18(49)	1.78(18)
	8 hr	1.39	0.59	-	3.24(15)		54.14	0.27	-	2.61(26)
	24 hr	0.70	0.33	-	1.74(14)		22.66	0.09	-	1.37(40)
	120 hr	0.72(0.05)	0.34(0.034) ^f	e	0.27(2) ^f		5.79(0.98)	0.02(0.004)	e	e
L	5 min	1.66	1.10	1.62(6)	14.58(35)	LARGE INTESTINE ^d	1.32	0.31	4.88(62)	0.80(7)
	30 min	1.51	1.01	0.19(0.7)	21.08(55)		0.64	0.25	2.00(32)	1.84(20)
	8 hr	1.10	0.53	-	14.60(73)		1.32	0.27	-	2.00(20)
	24 hr	0.50	0.29	-	4.62(42)		0.71	0.18	-	1.39(20)
	120 hr	0.19(0.14)	0.09(0.043)	e	e		0.09(0.03)	0.02(0.009)	e	e

^aPercent administered radiolabel recovered in tissue. Mean of two determinations except for 120 hr which represents mean of four determinations. Numbers in parentheses are standard deviations.

^bDetermined by HPLC-LSC. A dash indicates concentration too low for accurate determination. Numbers in parentheses represent Tris-BP or Bis-BP as the percentage of the total radiolabel in the tissue.

^cPercent dose per tissue calculated using estimated total tissue mass.

^dIncluding contents.

^eNot analyzed by HPLC-LSC.

^fFigures 3 and 4 in original report show identification of peaks as metabolite Bis-BP.

^gRemainder of animal after removal of tissues and samples of muscle, blood and fat.

TABLE 3
EXCRETION OF RADIOLABEL 72 HR AFTER IV ADMINISTRATION OF

¹⁴C-TRIS-BP: MALE VS. FEMALE^a

	URINE	FECES	CO ₂	CARCASS	TOTAL
FEMALE	54.95(6.32)	16.76(7.96)	11.44(3.24)	4.68(1.28)	87.83
MALE	52.91(4.31) ^b	8.22(3.55) ^b	17.95(4.15) ^b	11.19(1.34)	90.27

^a The quantity of radiolabel excreted in urine, feces, and expired ¹⁴CO₂ was determined at 24 hr intervals for 72 hr in 3 male and 3 female rats after iv administration of ¹⁴C-Tris-BP. Numbers in the table represent the percentage of administered radiolabel recovered. Numbers in parentheses represent standard deviations.

^b Taken from animals in Table 1.

Table 4 Radiolabel Excretion in Bile Following Intravenous Administration of [¹⁴C] tris(2,3-Dibromopropyl) phosphate^a

Time (hours)	% Dose
0-1	20.44 ± 1.85
1-2	5.81 ± 0.90
2-4	3.40 ± 0.49
4-8	1.95 ± 0.24
8-12	0.77 ± 0.32
12-16	0.68 ± 0.29
16-24	0.87 ± 0.55
Total	33.92 ± 3.45^b

^aMean ± standard deviation, n=3

^bBis-BP accounted for 21.5 ± 1.8% (Mean ± standard deviation, n=3) of the total radiolabel in the composite (0-24 hours) bile samples. The remaining radiolabel consisted of numerous unidentified metabolites.