

ADME NTP Study S0440 tris(1,3-Dichloro-2-propyl) phosphate

The contract laboratory used the synonym Fryol-FR2 and the abbreviation Fryol for the test article.

Sex/Strain: not specified; Animals used were rats.

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

CASRN 13674-87-8

Radiolabeled with carbon-14 in the 1- and 3-position carbons of the 2-propyl moiety; tris(1,3-Dichloro-(2-propyl-[1,3-¹⁴C])) phosphate

Studies Performed:

- Single intravenous administration of 803.2 nmole Fryol/rat with sacrifice 5 days postdose (n=4).
- Single intravenous administration of 803.2 nmole Fryol/rat with sacrifice 24 hours postdose (n = 2, bile excretion study).
- Single intravenous administration of 803.2 nmole Fryol/rat with sacrifice at 5 minutes, 30 minutes, 8 hours, and 24 hours postdose (n=2 per timepoint).

The minimum detectable quantity of Fryol was 0.01% dose/g tissue. Metabolism to bis(1,3-dichloro-2-propyl)phosphate (BDCP) was the major route of elimination of Fryol.

Toxicokinetics:

Fryol disappeared rapidly from plasma (half-life of < 5 minutes) accompanied by a rapid rise in BDCP. After 2 hours, the concentration of BDCP declined with a half-life of approximately 4 hours. The log concentration-time curve was plotted (figure not shown) but no modeling was performed.

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TABLE 1

CUMULATIVE EXCRETION OF RADIOLABEL AFTER IV
ADMINISTRATION OF ^{14}C -Fyrol^a

HOUR	URINE	FECES	$^{14}\text{CO}_2$	CARCASS	TOTAL
24	45.73(4.79)	9.97(7.09)	18.73(1.33)	-	74.43(10.48)
48	51.60(3.81)	15.39(3.95)	20.75(1.47)	-	87.74(4.01)
72	53.46(3.13)	16.02(3.43)	21.50(1.58)	-	90.98(1.58)
96	53.83(3.15)	16.36(3.15)	21.94(1.66)	-	92.13(1.06)
120	53.99(3.14)	16.44(3.11)	22.20(1.68)	3.75(0.13)	96.38(1.07)

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

TABLE 2
 EXCRETION OF RADIOLABEL IN CONTROL AND BILE-EXTERIORIZED ANIMALS
 24 HR AFTER IV ADMINISTRATION OF ^{14}C -FYROL

	CONTROL ^a	BILE-EXTERIORIZED ^b		
		Exp. #1	Exp. #2	Mean ^c
URINE	45.73 (4.79)	37.69	43.84	40.77
FECES	9.97 (7.09)	0.42	1.08	0.75
$^{14}\text{CO}_2$	18.73 (1.33)	10.46	11.43	10.95
BILE	-	31.61	28.16	29.89

^aPercentage of administered radiolabel. Mean of four rats.
 Standard deviation in parentheses.

^bTwo rats (Experiments 1 and 2) with exteriorized bile flow were studied.

^cMean of experiments 1 and 2.

TABLE 3
DISTRIBUTION OF FYROL AND ITS MAJOR METABOLITE, BDCP, AFTER IV ADMINISTRATION OF ¹⁴C-FYROL

Time	Tissue	Fyrol ^a nmol/g	BDCP ^a nmol/g	Tissue	Fyrol ^a nmol/g	BDCP ^a nmol/g	Tissue	Fyrol ^a nmol/g	BDCP ^a nmol/g
5 min	MUSCLE	1.32	0.09	HEART	1.53	0.56	LRG INT	1.66	0.13
30 min		0.42	0.31		0.19	1.07		0.35	0.33
8 hr		-	0.20		-	0.98		-	1.48
24 hr		-	0.03		-	0.14		-	0.08
120 hr		-	-		-	-		-	-
5 min	LIVER	2.75	4.79	BRAIN	2.38	- ^c	LRG INT ^b CONTENTS	- ^c	- ^c
30 min		0.13	3.44		0.23	0.16 ^c		-	5.5
8 hr		-	2.28		-	-		-	60.27
24 hr		-	0.22		-	0.01		-	4.38
120 hr		-	-		-	-		-	-
5 min	BLOOD	1.84	5.34	TESTES	0.43	0.46	STOMACH	1.47	0.17
30 min		0.06	2.62		0.17	0.56		0.28	0.38
8 hr		-	3.24		-	0.81		-	0.37
24 hr		-	0.61		-	0.21		-	0.04
120 hr		-	-		-	-		-	-
5 min	FAT	1.33	0.10	SPLEEN	1.32	0.21	URINE	- ^c	- ^c
30 min		3.43	1.51		0.07	0.41		- ^c	- ^c
8 hr		0.18	0.40		-	0.31		0.63	229.44 ^d
24 hr		-	0.15		-	0.03		-	380.55 ^d
120 hr		-	-		-	-		-	405.24 ^d (60.58)
5 min	SML INT	1.98	0.40	LUNG	0.29	12.19	FECES	- ^c	- ^c
30 min		0.44	0.89		0.12	9.05		- ^c	- ^c
8 hr		-	0.29		-	4.27		-	3.34 ^d
24 hr		-	0.05		-	0.28		-	66.76 ^d
120 hr		-	-		-	-		-	99.93 ^d (20.13)
5 min	SML INT ^b	- ^c	- ^c	KIDNEY	6.75	1.17	CARCASS	1.475	0.138
30 min	Contents	-	23.3		1.23	2.32		0.568	0.447
8 hr	-	-	7.35		-	1.54		-	0.376
24 hr	-	-	-		-	0.31		-	0.072
120 hr	-	-	-		-	-		-	-

^aDetermined by HPLC-LSC. A dash indicates concentration too low for accurate determination.

^bTotal nmoles present in contents; not concentration.

^cNo HPLC-LSC analysis performed.

^dCumulative BDCP in 0-x hr.

TABLE 4

CONCENTRATION OF TOTAL RADIOLABEL IN TISSUES AFTER IV ADMINISTRATION OF ^{14}C -FYROL

TIME ^a	TISSUE	% dose/gram	TISSUE	% dose/gram	TISSUE	% dose/gram
5 min	MUSCLE	.218	HEART	.351	LRG INT	.289
30 min		.162		.244		.161
8 hr		.045		.135		.362
24 hr		.024		.046		.058
120 hr		.010 (.004)		.013 (.003)		.009 (.002)
5 min	LIVER	1.42	BRAIN	.375	CARCASS	.258
30 min		1.11		.086		.234
8 hr		.474		.027		.098
24 hr		.172		.020		.047
120 hr		.055 (.010)		.010 (.004)		.010 (.011)
5 min	SKIN	.218	TESTES	.154	STOMACH	.355
30 min		.171		.152		.152
8 hr		.107		.119		.076
24 hr		.056		.050		.039
120 hr		.009 (.010)		.011 (.003)		.012 (.001)
5 min	BLOOD	.416	SPLEEN	.272		
30 min		.337		.125		
8 hr		.322		.078		
24 hr		.102		.048		
120 hr		.017 (.003)		.017 (.003)		
5 min	FAT	.421	LUNG	2.74		
30 min		.419		1.47		
8 hr		.087		.525		
24 hr		.030		.122		
120 hr		.008 (.001)		.035 (.013)		
5 min	SML INT	.460	KIDNEY	1.25		
30 min		.489		.889		
8 hr		.140		.443		
24 hr		.061		.271		
120 hr		.010 (.002)		.084 (.012)		

TABLE 5
DISTRIBUTION OF TOTAL RADIOLABEL AFTER IV ADMINISTRATION OF ¹⁴C-FYROL

TIME	TISSUE	% dose ^a	TISSUE	% dose ^a	TISSUE	% dose ^a
5 min 30 min 8 hr 24 hr 120 hr	MUSCLE ^b	32.7 24.3 6.75 3.60 1.57 (0.57)	HEART	0.332 0.219 0.077 0.042 0.014 (.004)	LRG INT	0.798 0.669 1.07 0.264 0.020 (.002)
5 min 30 min 8 hr 24 hr 120 hr	LIVER	16.0 13.4 4.55 1.67 0.520 (.041)	BRAIN	0.572 0.143 0.037 0.027 0.015 (.007)	LRG INT CONTENTS	0.253 1.25 10.4 0.885 0.024 (.010)
5 min 30 min 8 hr 24 hr 120 hr	SKIN ^b	10.5 8.21 5.14 2.69 0.444 (.045)	TESTES	0.480 0.533 0.369 0.158 0.036 (.011)	STOMACH	0.523 0.240 0.116 0.058 0.017 (.002)
5 min 30 min 8 hr 24 hr 120 hr	BLOOD ^b	11.2 9.10 8.69 2.75 0.452 (.077)	CO ₂ ^c	- 1.14 15.1 19.4 22.2 (1.62)	STOMACH CONTENTS	0.158 0.158 0.048 0.026 -
5 min 30 min 8 hr 24 hr 120 hr	FAT ^b	8.84 8.73 1.83 0.630 0.162 (.026)	URINE ^c	- 4.30 34.5 49.4 54.0 (3.14)	SPLEEN	0.216 0.086 0.059 0.032 0.013 (.001)
5 min 30 min 8 hr 24 hr 120 hr	SML INT	2.88 3.50 0.968 0.365 0.058 (.014)	FECES ^c	- - 0.61 13.5 16.4 (3.11)	LUNG	4.06 2.68 0.791 0.185 0.057 (.006)
5 min 30 min 8 hr 24 hr 120 hr	SML INT CONTENTS	1.10 6.76 1.85 0.311 0.032 (.006)	CARCASS	59.8 54.0 20.8 9.87 2.34 (.277)	KIDNEY	3.01 2.10 1.01 0.645 0.175 (.013)

^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.

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

^cCumulative recovery of radiolabel.

TABLE 6
RECOVERY OF FYROL AND BDCP AFTER IV ADMINISTRATION OF ¹⁴C-FYROL

The dose of Fyrol was 803.2 nanomoles. At each time interval after dosing the total Fyrol or BDCP was determined by adding the quantities found in individual tissues, carcass, and excreta.

TIME	Fyrol nanomoles	BDCP nanomoles
5 min	430.9	128.1
30 min	145.1	216.7
8 hr	4.4	447.1
24 hr	- ^a	473.8
120 hr	- ^a	505.2 ± (78.8) ^b

^aQuantity below detectable limits of assay

^bMean ± SD, n = 4

TABLE 7

PLASMA CONCENTRATIONS (PICOMOLES/ML PLASMA) OF FYROL AND ITS
MAJOR METABOLITE FOLLOWING IV ADMINISTRATION OF ^{14}C -FYROL^a

TIME	F18	F19	F20	F21	Mean \pm SD
<u>Major Metabolite, BDCP</u>					
2 min	1978	884	1412	1412	1421 \pm 447
10 min	7887	7060	6456	5730	6783 \pm 915
20 min	7930	7528	7104	5978	7135 \pm 842
30 min	7707	7252	6544	5204	6677 \pm 1092
40 min	7261	6846	6575	4928	6402 \pm 1023
60 min	6603	6044	6428	4399	5868 \pm 1007
1.5 hr	5890	5503	6167	3742	5325 \pm 1090
2 hr	5792	6311	5676	3352	5282 \pm 1316
4 hr	4783	4123	5220	2534	4165 \pm 1177
6 hr	3673	3377	4151	1538	3184 \pm 1143
8 hr	2808	2849	2899	1038	2398 \pm 908
10 hr	2245	1465	2248	698	1664 \pm 742
12 hr	720	902	1572	440	908 \pm 481
18 hr	384	352	522	91	312 \pm 178
24 hr	123	132	148	—	134 \pm 13
<u>Fyrol</u>					
2 min	1869	<u>b</u>	4776	6329	4324 \pm 2263
10 min	549	1021	1280	1367	1054 \pm 367
20 min	110	437	357	565	367 \pm 192
30 min	133	262	355	327	269 \pm 99
40 min	75	171	206	229	170 \pm 68
60 min	28	79	199	138	111 \pm 74
1.5 hr	<u>c</u>	44	126	93	
2 hr	<u>c</u>	30	82	54	
4 hr	<u>c</u>	<u>c</u>	33	<u>c</u>	

^aAnimals were dosed intravenously and serial blood samples removed through a jugular vein catheter. The concentrations of Fyrol and its major metabolite, BDCP, were determined by HPLC-LSC. See Fig. 10 for graphical presentation.

^bNot determined.

^cConcentration too low for accurate determination.