

投与後 1 時間における組成比 (% in analysis sample) はそれぞれ 80.2%及び 77.4% (それぞれ 196.3 及び 191.3 ng eq./mL) であり, 各回投与後 24 時間における組成比はそれぞれ 58.5%及び 61.1% (それぞれ 81.8 及び 101.6 ng eq./mL) であった.

7.5.2.2 大脳

単回投与後 28 日及び 4 回投与後 168 時間の脳試料中において, いずれも 2 種 (mCM-1 及び mCM-2) の放射性ピークが検出された. これらのピークのうち, mCM-2 (P092) が最も大きく, 単回投与後 28 日における組成比は 53.9% (62.5 ng eq./g) であり, 4 回投与後 168 時間における組成比は 59.7% (276.6 ng eq./g) であった.

なお, P092 濃度を mol 単位に換算 (フリー体分子量: 502.70) すると, 単回投与後 28 日及び 4 回投与後 168 時間の脳中 P092 濃度はそれぞれ 0.124 及び 0.550 nmol/g となる.

血液及び大脳から抽出した放射能を HPLC にて分析した結果, ラジオクロマトグラム上, P092 がほぼ単一ピークとして検出され, 血液及び大脳中の放射能の主要成分は P092 未変化体であることが示唆された.

8. 参考資料

- [1] R. J. Lutz, et. al., Drug Metab. Disp., 12, 529 (1984)

9. 特記事項

9.1 予見することができなかつた試験の信頼性に影響を及ぼす疑いのある事態なし.

Table 1 Radioactivity concentrations and pharmacokinetic parameters in blood and plasma after 1st, 2nd, 3rd, and 4th intravenous administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg/week as free base

Time/Parameter	Radioactivity concentration (ng eq./mL)							
	1st administration		2nd administration		3rd administration		4th administration	
	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
5 min	558.1	119.8	579.8	153.1	738.3	214.3	632.7	182.1
15 min	228.5	64.6	307.6	99.6	372.0	132.0	407.9	135.2
1 h	133.5	39.4	193.6	75.5	244.8	107.1	247.2	113.7
4 h	91.7	38.7	152.9	78.7	182.7	106.3	199.3	109.6
8 h	75.2	37.5	157.2	80.3	171.5	105.2	193.7	110.3
24 h	71.4	47.9	100.1	73.6	139.8	107.9	166.3	120.7
96 h	53.4	48.9	107.5	78.4	80.6	81.2	127.6	87.3
168 h	42.5	36.6	70.3	62.3	88.6	70.6	98.7	78.4
C ₀ (ng eq./mL)	869.9	162.8	794.5	189.6	1038.0	272.7	787.0	211.1
t _{1/2} (h) ^{a)}	191.4	371.0	145.7	580.2	147.1	261.8	191.3	292.5
AUC _{0-t} (ng eq.·h/mL)	9991	7555	17251	12393	18043	14804	23334	16140
AUC _{0-inf} (ng eq.·h/mL)	21726	27143	32030	64538	36845	41469	50576	49221
CL _{total} (mL/h/kg)	46	37	31	15	27	24	20	20
Vd _{ss} (mL/kg)	12590	19537	6720	12825	6217	9125	5403	8570
MRT _{0-inf} (h)	273.5	530.3	215.2	827.7	229.1	378.4	273.2	421.8

a) The t_{1/2} was automatically calculated by WinNonlin.

Table 2 Radioactivity concentrations in tissues 168 h after 4th intravenous administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg/week as free base

Tissue	Radioactivity concentration (ng eq./mL or g)	
Blood	98.7	(1.26)
Plasma	78.4	(1.00)
Cerebrum	463.4	(5.91)
Cerebellum	275.6	(3.52)
Medulla oblongata	416.6	(5.31)
Cerebrospinal fluid	ND	(NC)
Spinal cord	296.0	(3.78)
Pituitary	13146.0	(167.68)
Eyeball	453.2	(5.78)
Submaxillary gland	13010.0	(165.94)
Mesenteric lymph nodes	34848.9	(444.50)
Heart	4671.6	(59.59)
Lung	24565.6	(313.34)
Liver	14109.5	(179.97)
Adrenal	25016.2	(319.08)
Kidney	11566.4	(147.53)
Spleen	57370.8	(731.77)
Pancreas	13986.2	(178.40)
Testis	2879.4	(36.73)
Skin	1644.8	(20.98)
Skeletal muscle	801.0	(10.22)
Bone	50.2	(0.64)
White adipose tissue	1113.9	(14.21)
Brown adipose tissue	14916.2	(190.26)
Bile	12191.1	(155.50)

Values in parentheses are expressed as the ratio of tissue concentration to plasma concentration (K_p).

ND: Not detected

NC: Not calculated

Table 3 Radioactivity distribution in tissues 168 h after 4th intravenous administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg/week as free base

Tissue	Radioactivity distribution (% of dose)
Blood ^{a)}	0.14
Cerebrum	0.13
Cerebellum	0.01
Medulla oblongata	0.00
Pituitary	0.01
Eyeball	0.01
Submaxillary gland	0.22
Heart	0.34
Lung	2.14
Liver	5.09
Adrenal	0.07
Kidney	1.05
Spleen	0.94
Pancreas	0.54
Testis	0.20
Skin ^{a)}	3.75
Skeletal muscle ^{a)}	8.04
White adipose tissue ^{a)}	2.11
Bile	0.11
Total	24.90

a) The whole weights of the blood, skin, skeletal muscle, and white adipose tissue were assumed as 6.0%, 9.4%, 41.4%, and 7.8% of body weight, respectively.

Table 4 Radioactivity concentrations in tissues 672 h after single intravenous administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./mL or g)	
Blood	15.2	(0.98)
Plasma	15.5	(1.00)
Cerebrum	115.9	(7.48)
Cerebellum	49.0	(3.16)
Medulla oblongata	120.1	(7.75)
Cerebrospinal fluid	ND	(NC)
Spinal cord	95.1	(6.14)
Pituitary	1628.6	(105.07)
Eyeball	250.6	(16.17)
Submaxillary gland	1274.4	(82.22)
Mesenteric lymph nodes	6078.2	(392.14)
Heart	843.4	(54.41)
Lung	2585.8	(166.83)
Liver	1484.1	(95.75)
Adrenal	3784.6	(244.17)
Kidney	1122.2	(72.40)
Spleen	3030.6	(195.52)
Pancreas	2446.3	(157.83)
Testis	921.0	(59.42)
Skin	192.1	(12.39)
Skeletal muscle	80.3	(5.18)
Bone	15.4	(0.99)
White adipose tissue	136.2	(8.79)
Brown adipose tissue	1314.3	(84.79)
Bile	1552.6	(100.17)

Values in parentheses are expressed as the ratio of tissue concentration to plasma concentration (K_p).

ND: Not detected

NC: Not calculated

Table 5 Radioactivity distribution in tissues 672 h after single intravenous administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg as free base

Tissue	Radioactivity distribution (% of dose)
Blood ^{a)}	0.09
Cerebrum	0.12
Cerebellum	0.00
Medulla oblongata	0.00
Pituitary	0.00
Eyeball	0.03
Submaxillary gland	0.14
Heart	0.18
Lung	0.95
Liver	1.97
Adrenal	0.03
Kidney	0.33
Spleen	0.28
Pancreas	0.31
Testis	0.39
Skin ^{a)}	1.80
Skeletal muscle ^{a)}	3.31
White adipose tissue ^{a)}	1.06
Bile	0.06
Total	11.05

a) The whole weights of the blood, skin, skeletal muscle, and white adipose tissue were assumed as 6.0%, 9.4%, 41.4%, and 7.8% of body weight, respectively.

Table 6 Recovery of radioactivity in sample pretreatment and radio-HPLC measurement

Analysis sample	Number of dose	Time (h)	Recovery of radioactivity (%)		
			Extract ^{*1}	HPLC sample ^{*2}	HPLC column ^{*3}
Blood	3rd	1	96.3	93.7	97.8
		24	90.1	89.8	107.3
	4th	1	96.1	90.5	99.1
		24	100.1	93.3	98.5
Cerebrum	Single	672	76.1	61.2	100.0
	4th	168	84.4	66.0	98.9

*1: Recovery of radioactivity from analysis sample to extract

*2: Recovery of radioactivity from analysis sample to HPLC sample

*3: Recovery of radioactivity from HPLC column

Table 7 **Composition ratios and concentrations of radioactivity, P092, and its metabolites in blood 1 and 24 h after 3rd and 4th intravenous administration of [¹⁴C]P092 maleate to a male monkey at 1 mg/kg/week as free base**

Analysis sample	Metabolite No.	Composition	% peaks [% in analysis sample] (ng eq./mL)			
			3rd administration		4th administration	
			1 h	24 h	1 h	24 h
Blood	mBM-1	Unknown	0.9	4.9	1.4	3.5
			[0.8]	[4.4]	[1.3]	[3.3]
			(2.0)	(6.2)	(3.2)	(5.5)
	mBM-2	Unknown	2.7	11.5	4.7	11.7
			[2.5]	[10.3]	[4.3]	[10.9]
			(6.1)	(14.4)	(10.6)	(18.1)
	mBM-3	P092	85.6	65.2	85.5	65.5
[80.2]			[58.5]	[77.4]	[61.1]	
		(196.3)	(81.8)	(191.3)	(101.6)	
Others	--	10.8	18.4	8.4	19.3	
		[10.1]	[16.5]	[7.6]	[18.0]	
		(24.7)	(23.1)	(18.8)	(29.9)	
Unextracted	--	--	--	--	--	
		[6.3]	[10.2]	[9.5]	[6.7]	
		(15.4)	(14.3)	(23.5)	(11.1)	
	Recovery (%)	93.7	89.8	90.5	93.3	
	Total radioactivity	(244.8)	(139.8)	(247.2)	(166.3)	

Table 8 **Composition ratios and concentrations of radioactivity, P092, and its metabolites in cerebrum after single or 4th intravenous administration of [¹⁴C]P092 maleate to male monkeys at 1 mg/kg/week as free base**

Analysis sample	Metabolite No.	Composition	% peaks [% in analysis sample] (ng eq./g)	
			Single administration	4th administration
			672 h	168 h
Cerebrum	mCM-1	Unknown	4.4	3.5
			[2.7]	[2.3]
			(3.1)	(10.7)
	mCM-2	P092	88.0	90.4
			[53.9]	[59.7]
			(62.5)	(276.6)
	Others	--	7.6	6.1
[4.7]			[4.0]	
		(5.4)	(18.5)	
Unextracted	--	--	--	
		[38.8]	[34.0]	
		(45.0)	(157.6)	
Recovery (%)			61.2	66.0
Total radioactivity			(115.9)	(463.4)

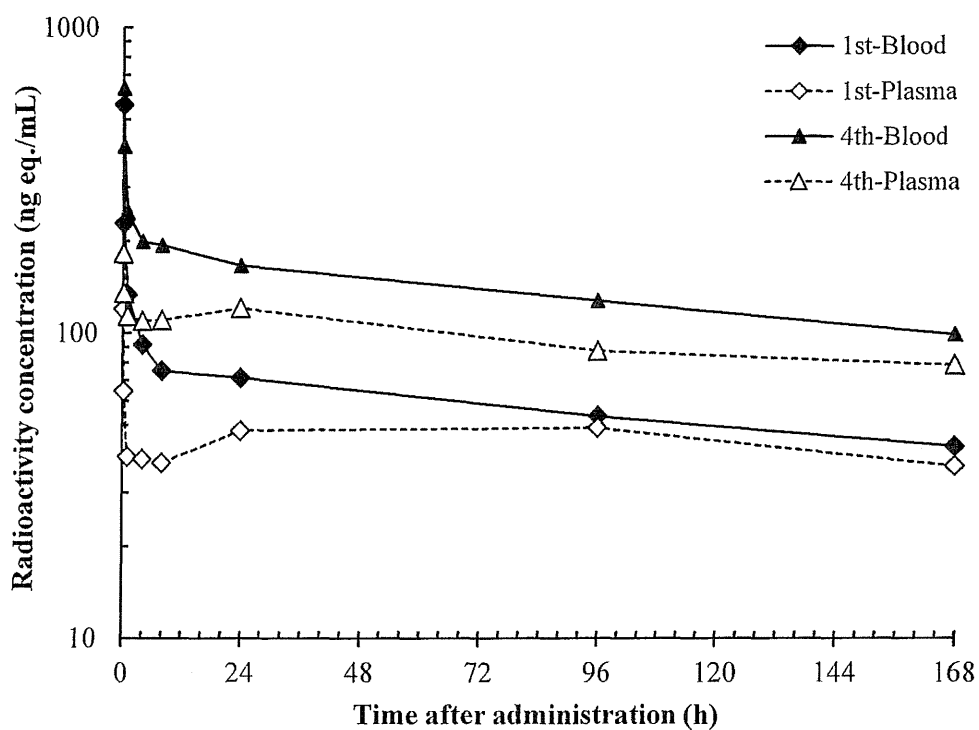


Figure 1 Radioactivity concentrations in blood and plasma after 1st and 4th intravenous administration of [^{14}C]P092 maleate to a male monkey at 1 mg/kg/week as free base

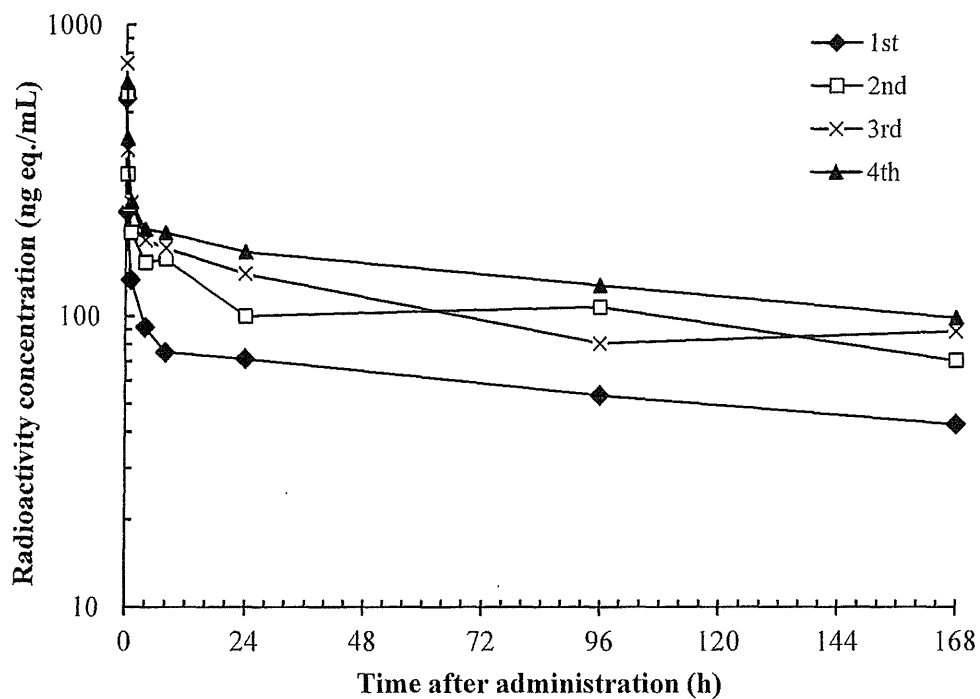


Figure 2 Radioactivity concentrations in blood after 1st, 2nd, 3rd, and 4th intravenous administration of [^{14}C]P092 maleate to a male monkey at 1 mg/kg/week as free base

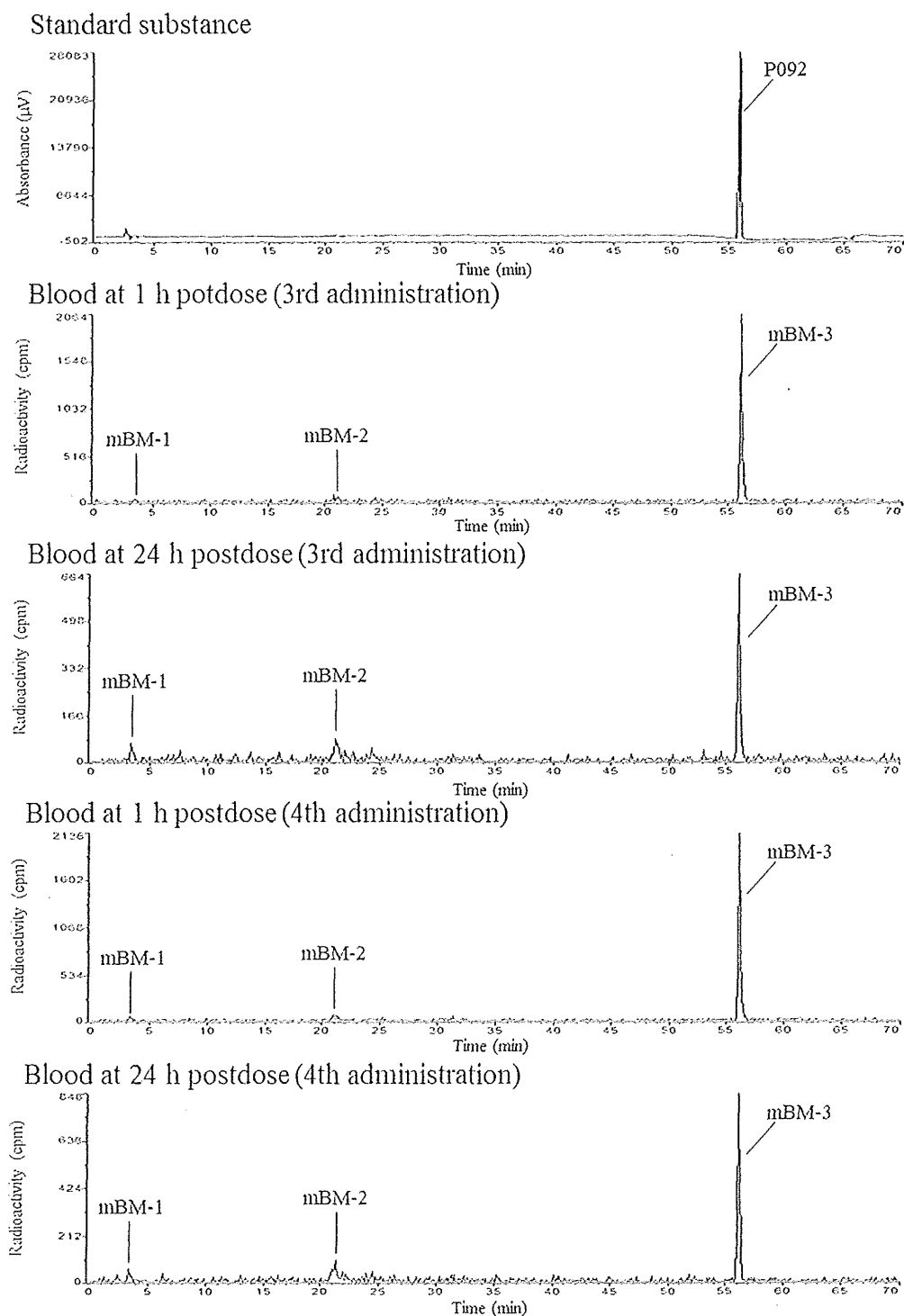


Figure 3 UV chromatogram of P092 maleate standard substance and radiochromatograms of blood after 3rd, and 4th intravenous administration of [^{14}C]P092 maleate to a male monkey at 1 mg/kg/week as free base

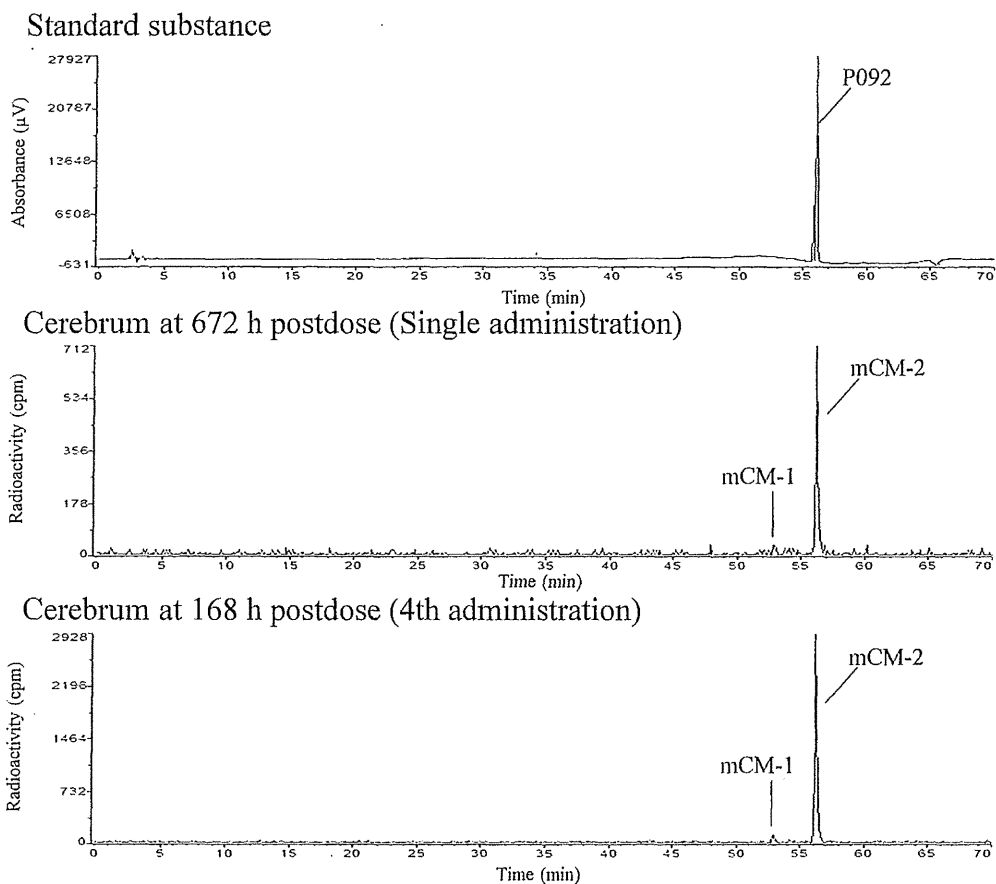


Figure 4 UV chromatogram of P092 maleate standard substance and radiochromatograms of cerebrum after single and 4th intravenous administration of [^{14}C]P092 maleate to male monkeys at 1 mg/kg/week as free base

Appendix 1 Radioactivity concentrations of [¹⁴C]P092 maleate in dosing formulations

Nominal concentration	Date of measurement (After administration)	Radioactivity concentration			% of nominal concentration
		Individual value (MBq/mL)	Mean ± SD (MBq/mL)	CV (%)	
2 mg/4.288 MBq/mL	January 23, 2015 (1st lot)	4.354	4.366 ± 0.026	0.6	101.8
		4.395			
		4.348			
	January 30, 2015 (2nd lot)	4.207	4.388 ± 0.177	4.0	102.3
		4.396			
		4.560			
	February 6, 2015 (3rd lot)	4.123	4.178 ± 0.056	1.3	97.4
		4.176			
		4.235			
	February 13, 2015 (4th lot)	4.178	4.285 ± 0.129	3.0	99.9
		4.250			
		4.428			

Appendix 2 Radiochemical purity of [¹⁴C]P092 maleate in dosing formulation

Date of analysis (Day of preparation)	Sample	Detection ^{a)}	Retention time (min)	Radiochemical purity (%)	Recovery ^{b)} (%)
February 13, 2015 (4th lot)	Non-labeled standard solution	UV	14.6	--	--
	Dosing formulation	RI	14.8	99.0	101.9

a) UV: Absorbance (254 nm), RI: Radioactivity

b) Radioactivity recovery from HPLC system

--: Not applicable

【参考データ】¹⁴C]P092・マレイン酸塩1mg/kg iv サル組織中放射能濃度(2試験の結果のまとめ)

Tissue	放射能濃度 (ng eq./mL or g)				PKパラメータ(参考データ)			
	24 h ^{*1}	168 h ^{*1}	336 h ^{*1}	672 h ^{*2}	t _{1/2} (h)	AUC _{0-t}	AUC _{0-inf}	T/P (AUC _{0-inf})
Blood	73.9	35.6	22.9	15.2	427	20,586	29,959	1.1
Plasma	44.8	38.4	21.2	15.5	403	18,048	27,055	1.0
Cerebrum	101.2	147.6	148.8	115.9	1,340	89,480	313,473	11.6
Cerebellum	98.1	108.9	80.8	49.0	441	54,439	85,633	3.2
Medulla oblongata	66.2	106.8	163.6	120.1				
Spinal cord	32.2	73.1	70.8	95.1				
Pituitary	4195.4	4157.5	3261.7	1628.6				
Eyeball	256.5	308.2	792.4	250.6				
Submaxillary gland	2225.1	3960.7	3967.2	1274.4				
Mesenteric lymph nodes	2703.7	6308.9	7248.4	6078.2				
Heart	5284.5	2499.7	1692.1	843.4				
Lung	15664.4	10419.4	4958.7	2585.8	249	4,701,483	5,618,651	207.7
Liver	8098.3	3910.6	2661.2	1484.1	366	2,257,606	3,040,341	112.4
Adrenal	10985.2	7429.8	8575.9	3784.6	457	4,891,869	7,387,963	273.1
Kidney	8359.0	3962.3	2617.8	1122.2	277	2,257,606	2,647,829	97.9
Spleen	13960.8	11204.3	7560.8	3030.6	265	5,367,126	6,527,208	241.3
Pancreas	5288.7	4480.1	3018.2	2446.3				
Testis	356.5	497.2	741.7	921.0				
Skin	264.9	359.5	311.9	192.1				
Skeletal muscle	1220.9	472.2	219.6	80.3				
Bone	62.9	23.9	18.7	15.4				
White adipose tissue	569.0	465.3	317.8	136.2				
Brown adipose tissue	4737.8	2595.0	1586.1	1314.3				
Bile	10938.4	6720.8	3165.8	1552.6				

*1(24, 168, 336 h): 試験番号B130899から引用(n=3の平均値)

*2(672 h): 試験番号B141136から引用(n=1)

AUC: ng eq·h/mL or g

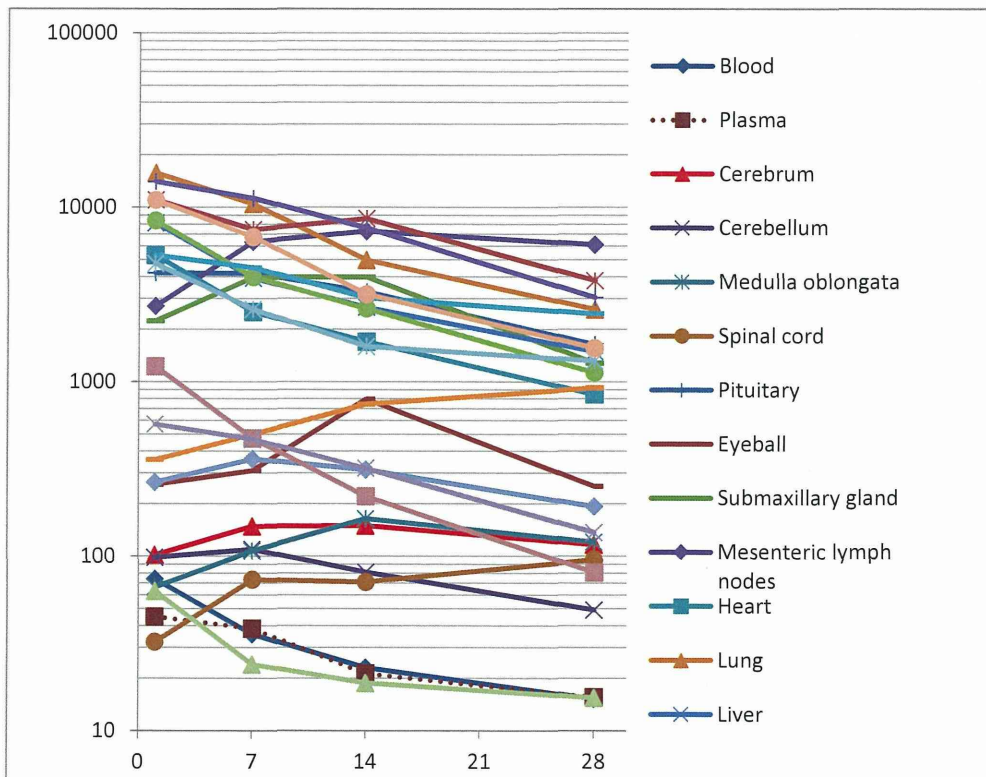
T/P: AUC_{0-inf} of tissue/AUC_{0-inf} of plasma

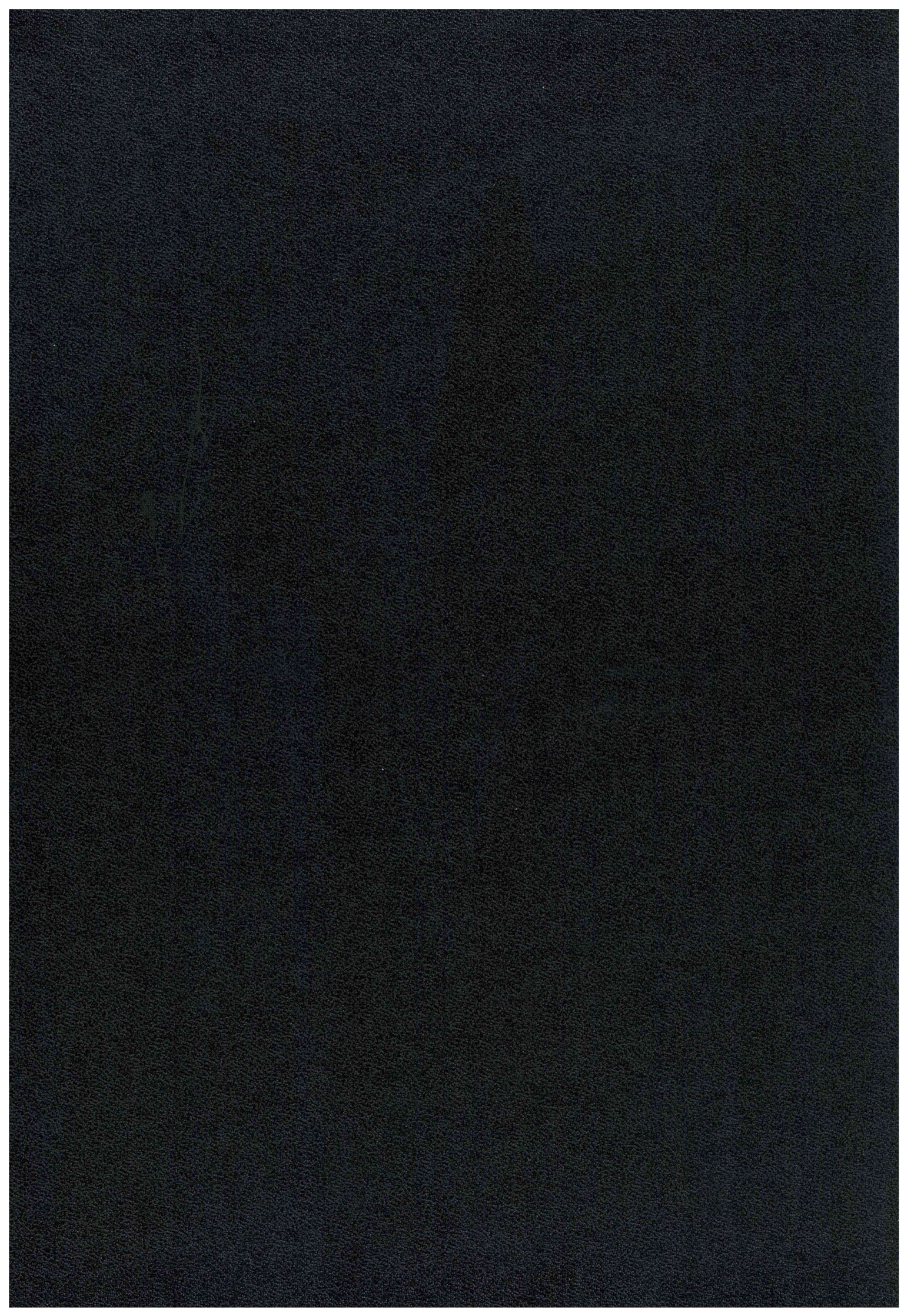
【参考データ】 ^{14}C P092・マレイン酸塩1mg/kg iv サル組織中放射能濃度(2試験の結果のまとめ)

Tissue	放射能濃度 (ng eq./mL or g)			
	1	7	14	28
Blood	73.9	35.6	22.9	15.2
Plasma	44.8	38.4	21.2	15.5
Cerebrum	101.2	147.6	148.8	115.9
Cerebellum	98.1	108.9	80.8	49.0
Medulla oblongata	66.2	106.8	163.6	120.1
Spinal cord	32.2	73.1	70.8	95.1
Pituitary	4195.4	4157.5	3261.7	1628.6
Eyeball	256.5	308.2	792.4	250.6
Submaxillary gland	2225.1	3960.7	3967.2	1274.4
Mesenteric lymph nodes	2703.7	6308.9	7248.4	6078.2
Heart	5284.5	2499.7	1692.1	843.4
Lung	15664.4	10419.4	4958.7	2585.8
Liver	8098.3	3910.6	2661.2	1484.1
Adrenal	10985.2	7429.8	8575.9	3784.6
Kidney	8359.0	3962.3	2617.8	1122.2
Spleen	13960.8	11204.3	7560.8	3030.6
Pancreas	5288.7	4480.1	3018.2	2446.3
Testis	356.5	497.2	741.7	921.0
Skin	264.9	359.5	311.9	192.1
Skeletal muscle	1220.9	472.2	219.6	80.3
Bone	62.9	23.9	18.7	15.4
White adipose tissue	569.0	465.3	317.8	136.2
Brown adipose tissue	4737.8	2595.0	1586.1	1314.3
Bile	10938.4	6720.8	3165.8	1552.6

*1(24, 168, 336 h): 試験番号B130899から引用 (n=3の平均値)

*2(672 h): 試験番号B141136から引用 (n=1)





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