Appendix 4 Cumulative radioactivity excretions in urine, feces, and expired air after single intravenous administration of [^{14}C]P092 maleate to male rats at 1 mg/kg as free base

Measurement -item	Animal No.	Cumulative radioactivity excretion (% of dose)								
		0-24 h	-48 h	-72 h	-96 h	-120 h	-144 h	-168 h	-240 h	-336 h
Urine	02104	3.0	5.5	7.6	9.3	10.4	11.4	12.2	13.6	14.3
	02105	3.1	5.5	7.5	9.0	10.2	11.3	12.1	13.4	14.2
	02106	1.5	3.0	4.3	5.3	6.1	6.7	7.3	8.2	8.5
	Mean	2.5	4.7	6.5	7.9	8.9	9.8	10.5	11.7	12.3
	SD	0.9	1.4	1.9	2.2	2.4	2.7	2.8	3.1	3.3
Feces	02104	10.5	32.2	47.2	57.0	63.3	68.7	73.0	80.7	86.6
	02105	16.1	33.2	46.8	56.4	63.1	68.1	71.9	80.1	85.6
	02106	8.0	24.1	35.5	44.9	52.1	58.3	62.9	74.5	83.5
	Mean	11.5	29.8	43.2	52.8	59.5	65.0	69.3	78.4	85.2
	SD	4.1	5.0	6.6	6.8	6.4	5.8	5.5	3.4	1.6
Expired air	02104	--	--	--	ND	--	--	ND	--	--
	02105	--	--	--	ND	--	--	ND	--	--
	02106	--	--	--	ND	--	--	ND	--	--
	Mean	--	--	--	ND	--	--	ND	--	--
	SD									
Cage washing	02104	0.3	0.6	0.7	0.8	0.9	1.0	1.0	1.2	1.6
	02105	0.2	0.6	0.8	1.0	1.1	1.1	1.2	1.4	1.7
	02106	0.2	0.6	0.8	1.0	1.1	1.3	1.4	1.7	2.8
	Mean	0.2	0.6	0.8	0.9	1.0	1.1	1.2	1.4	2.0
	SD	0.1	0.0	0.1	0.1	0.1	0.2	0.2	0.3	0.7
Total	02104	13.8	38.3	55.5	67.1	74.6	81.1	86.2	95.5	102.5
	02105	19.4	39.3	55.1	66.4	74.4	80.5	85.2	94.9	101.5
	02106	9.7	27.7	40.6	51.2	59.3	66.3	71.6	84.4	94.8
	Mean	14.3	35.1	50.4	61.6	69.4	76.0	81.0	91.6	99.6
	SD	4.9	6.4	8.5	9.0	8.8	8.4	8.2	6.2	4.2
Carcass	02104	--	--	--	--	--	--	--	--	12.8
	02105	--	--	--	--	--	--	--	--	13.4
	02106	--	--	--	--	--	--	--	--	20.6
	Mean	--	--	--	--	--	--	--	--	15.6
	SD									4.3
Total recovery	02104	13.8	38.3	55.5	67.1	74.6	81.1	86.2	95.5	115.3
	02105	19.4	39.3	55.1	66.4	74.4	80.5	85.2	94.9	114.9
	02106	9.7	27.7	40.6	51.2	59.3	66.3	71.6	84.4	115.4
	Mean	14.3	35.1	50.4	61.6	69.4	76.0	81.0	91.6	115.2
	SD	4.9	6.4	8.5	9.0	8.8	8.4	8.2	6.2	0.3

ND: Not detected

--: Not determined

Appendix 5 Correlation coefficient of calibration curve used for quantitative whole-body autoradiography

Time	Animal No.	Section	r
1 h	03111	Left axis aspect-1	0.99951
		Left axis aspect-2	0.99921
		Left axis aspect-3	0.99944
		Central axis aspect	0.99934
24 h	04123	Left axis aspect-1	0.99889
		Left axis aspect-2	0.99925
		Central axis aspect	0.99930
168 h	05125	Left axis aspect-1	0.99923
		Left axis aspect-2	0.99984
		Left axis aspect-3	0.99949
		Central axis aspect	0.99925
336 h	06127	Left axis aspect-1	0.99944
		Left axis aspect-2	0.99932
		Central axis aspect	0.99950

r: Correlation coefficient of calibration curve

Appendix 6 Accuracy and precision of back-calculated radioactivity concentrations in calibration blood samples of thin sections

Time	Animal No.	Section	Radioactivity concentration of calibration blood sample determined by back calculation (ng eq./g)			
			7.5	39.0	399.0	3928.2
1 h	03111	Left axis aspect-1	9.2	32.8	366.9	3960.6
		Left axis aspect-2	9.5	32.5	355.2	3969.7
		Left axis aspect-3	9.1	34.1	361.2	3964.4
		Central axis aspect	9.4	32.6	360.0	3966.0
24 h	04123	Left axis aspect-1	9.8	32.0	345.7	3976.6
		Left axis aspect-2	9.6	31.9	358.0	3967.8
		Central axis aspect	9.4	32.9	357.7	3967.7
168 h	05125	Left axis aspect-1	9.6	31.5	357.7	3968.1
		Left axis aspect-2	8.6	34.9	382.6	3946.3
		Left axis aspect-3	9.1	33.9	363.7	3962.6
		Central axis aspect	9.4	33.1	355.3	3969.3
336 h	06127	Left axis aspect-1	9.3	32.8	363.3	3963.3
		Left axis aspect-2	9.5	31.7	360.8	3965.7
		Central axis aspect	9.4	31.5	369.4	3959.0
Mean			9.4	32.7	361.3	3964.8
SD			0.3	1.0	8.4	6.9
RE (%)			25.3	-16.2	-9.4	0.9
CV (%)			3.2	3.1	2.3	0.2

RE: Relative error (%), CV: Coefficient of variation (%)

Appendix 7 Radioactivity concentrations in tissues 1 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./g)				
	Left axis aspect-1	Left axis aspect-2	Left axis aspect-3	Central axis aspect	Mean
Blood	NA	242.0	199.9	160.3	200.7
Cerebrum	NA	NA	NA	17.0	17.0
Cerebellum	NA	NA	NA	15.2	15.2
Pituitary	NA	NA	NA	2050.7	2050.7
Spinal cord	NA	NA	NA	20.6	20.6
Eyeball	NA	NA	81.3	NA	81.3
Harderian gland	NA	NA	486.6	NA	486.6
Submaxillary gland	NA	NA	NA	1374.1	1374.1
Thyroid	NA	NA	NA	AUQ	AUQ
Thymus	NA	677.5	680.8	646.4	668.2
Heart	NA	AUQ	AUQ	AUQ	AUQ
Lung	NA	AUQ	AUQ	AUQ	AUQ
Liver	2310.5	2229.5	2239.3	2263.2	2260.6
Kidney	3363.6	3048.3	NA	NA	3206.0
Adrenal	NA	3716.2	3482.0	NA	3599.1
Spleen	AUQ	NA	NA	NA	AUQ
Pancreas	1781.7	NA	NA	NA	1781.7
Prostate	NA	NA	548.8	486.6	517.7
Testis	NA	20.9	20.4	19.3	20.2
Epididymis	NA	96.3	91.3	160.0	115.9
Seminal vesicle	NA	11.5	10.1	9.7	10.4
Skin	182.0	218.2	116.7	199.8	179.2
Skeletal muscle	1993.4	NA	NA	NA	1993.4
Bone (femur)	150.8	NA	NA	NA	150.8
Bone marrow (femur)	1454.3	NA	NA	NA	1454.3
White adipose tissue	86.5	NA	NA	NA	86.5
Brown adipose tissue	NA	NA	NA	288.7	288.7
Bladder	NA	NA	NA	207.0	207.0
Mesenteric lymph node	NA	NA	NA	3133.3	3133.3
Stomach	1089.8	1323.1	1336.9	885.2	1158.8
Small intestine	NA	NA	790.4	636.8	713.6
Large intestine	NA	NA	NA	578.3	578.3

The tissue radioactivity concentrations were calculated from the tissue radioactivity concentration ([PSL-BG]/mm^2) and the calibration curve.

NA: Not applicable

AUQ: Above the upper limit of quantification (> 3928.2 ng eq./g)

Appendix 8 Radioactivity concentrations in tissues 24 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./g)			
	Left axis aspect-1	Left axis aspect-2	Central axis aspect	Mean
Blood	NA	67.3	49.1	58.2
Cerebrum	NA	NA	13.4	13.4
Cerebellum	NA	NA	12.7	12.7
Pituitary	NA	NA	2675.5	2675.5
Spinal cord	NA	NA	17.5	17.5
Eyeball	NA	115.6	NA	115.6
Harderian gland	NA	632.0	NA	632.0
Submaxillary gland	NA	NA	2541.2	2541.2
Thyroid	NA	NA	3236.4	3236.4
Thymus	NA	1167.6	1131.9	1149.8
Heart	NA	981.0	955.0	968.0
Lung	NA	3319.7	2590.6	2955.2
Liver	1926.4	2030.3	1985.1	1980.6
Kidney	AUQ	NA	NA	AUQ
Adrenal	NA	AUQ	NA	AUQ
Spleen	AUQ	NA	NA	AUQ
Pancreas	2022.7	NA	NA	2022.7
Prostate	NA	795.1	970.3	882.7
Testis	NA	30.9	31.8	31.4
Epididymis	NA	76.9	173.1	125.0
Seminal vesicle	NA	26.4	31.0	28.7
Skin	204.4	292.4	289.3	262.0
Skeletal muscle	554.4	NA	NA	554.4
Bone (femur)	112.1	NA	NA	112.1
Bone marrow (femur)	2268.9	NA	NA	2268.9
White adipose tissue	90.5	NA	NA	90.5
Brown adipose tissue	NA	NA	1257.4	1257.4
Bladder	NA	NA	424.5	424.5
Mesenteric lymph node	NA	3302.5	NA	3302.5
Stomach	1039.3	1006.5	NA	1022.9
Small intestine	1229.7	1919.2	1615.6	1588.2
Large intestine	NA	NA	996.0	996.0

The tissue radioactivity concentrations were calculated from the tissue radioactivity concentration ([PSL-BG]/mm^2) and the calibration curve.

NA: Not applicable

AUQ: Above the upper limit of quantification (> 3928.2 ng eq./g)

Appendix 9 Radioactivity concentrations in tissues 168 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./g)				
	Left axis aspect-1	Left axis aspect-2	Left axis aspect-3	Central axis aspect	Mean
Blood	NA	14.7	14.2	15.8	14.9
Cerebrum	NA	NA	NA	18.3	18.3
Cerebellum	NA	NA	NA	10.0	10.0
Pituitary	NA	NA	NA	3405.2	3405.2
Spinal cord	NA	NA	NA	15.0	15.0
Eyeball	NA	38.5	NA	NA	38.5
Harderian gland	NA	1102.9	950.1	NA	1026.5
Submaxillary gland	NA	NA	NA	1060.4	1060.4
Thyroid	NA	NA	NA	875.6	875.6
Thymus	NA	NA	1595.8	1486.6	1541.2
Heart	NA	128.0	131.1	162.3	140.5
Lung	NA	726.5	741.0	683.3	716.9
Liver	407.2	388.2	370.9	381.9	387.1
Kidney	850.1	670.9	653.3	NA	724.8
Adrenal	NA	NA	3352.6	NA	3352.6
Spleen	AUQ	NA	NA	NA	AUQ
Pancreas	273.8	282.8	NA	NA	278.3
Prostate	NA	NA	462.0	462.1	462.1
Testis	NA	29.6	27.8	33.1	30.2
Epididymis	NA	NA	NA	65.5	65.5
Seminal vesicle	NA	NA	20.2	31.2	25.7
Skin	238.0	214.3	217.4	199.1	217.2
Skeletal muscle	67.5	NA	NA	NA	67.5
Bone (femur)	17.8	NA	NA	NA	17.8
Bone marrow (femur)	1377.5	NA	NA	NA	1377.5
White adipose tissue	20.1	NA	NA	NA	20.1
Brown adipose tissue	NA	NA	NA	243.9	243.9
Bladder	NA	NA	138.0	NA	138.0
Mesenteric lymph node	NA	NA	NA	2342.1	2342.1
Stomach	193.2	165.7	183.7	191.2	183.5
Small intestine	NA	NA	507.5	112.0	309.8
Large intestine	NA	NA	214.7	231.7	223.2

The tissue radioactivity concentrations were calculated from the tissue radioactivity concentration ([PSL-BG]/mm^2) and the calibration curve.

NA: Not applicable

AUQ: Above the upper limit of quantification (> 3928.2 ng eq./g)

Appendix 10 Radioactivity concentrations in tissues 336 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./g)			
	Left axis aspect-1	Left axis aspect-2	Central axis aspect	Mean
Blood	NA	10.9	9.1	10.0
Cerebrum	NA	NA	21.0	21.0
Cerebellum	NA	NA	BLQ	BLQ
Pituitary	NA	NA	1646.0	1646.0
Spinal cord	NA	NA	17.3	17.3
Eyeball	NA	26.3	NA	26.3
Harderian gland	NA	1375.9	NA	1375.9
Submaxillary gland	NA	NA	791.6	791.6
Thyroid	NA	NA	646.9	646.9
Thymus	NA	1571.0	1692.0	1631.5
Heart	NA	82.4	82.4	82.4
Lung	NA	395.9	456.0	426.0
Liver	245.8	252.1	253.6	250.5
Kidney	435.8	NA	NA	435.8
Adrenal	NA	2257.4	NA	2257.4
Spleen	3122.5	NA	NA	3122.5
Pancreas	151.3	NA	NA	151.3
Prostate	NA	NA	391.8	391.8
Testis	NA	30.8	NA	30.8
Epididymis	NA	66.9	NA	66.9
Seminal vesicle	NA	11.6	12.9	12.3
Skin	135.9	199.9	149.2	161.7
Skeletal muscle	41.8	NA	NA	41.8
Bone (femur)	32.2	NA	NA	32.2
Bone marrow (femur)	1387.8	NA	NA	1387.8
White adipose tissue	10.4	NA	NA	10.4
Brown adipose tissue	NA	NA	80.1	80.1
Bladder	NA	NA	50.3	50.3
Mesenteric lymph node	NA	NA	1132.5	1132.5
Stomach	118.4	115.9	NA	117.2
Small intestine	125.9	193.0	194.8	171.2
Large intestine	NA	NA	84.7	84.7

The tissue radioactivity concentrations were calculated from the tissue radioactivity concentration ([PSL-BG]/mm^2) and the calibration curve.

NA: Not applicable

BLQ: Below the lower limit of quantification (< 7.5 ng eq./g)

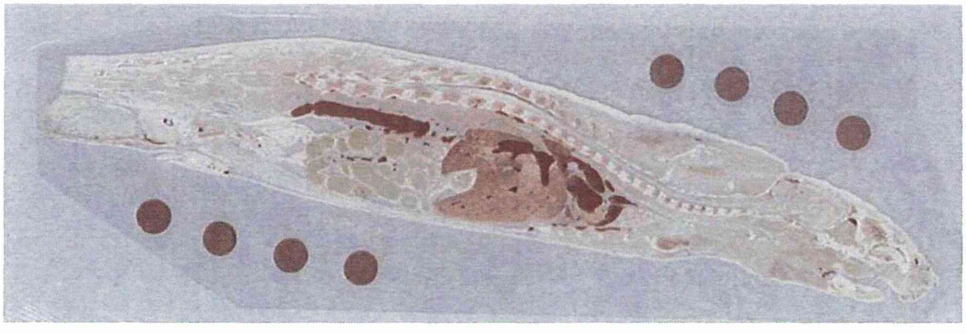
Appendix 11 Pictures 1 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Left axis aspect-1

Left axis aspect-2

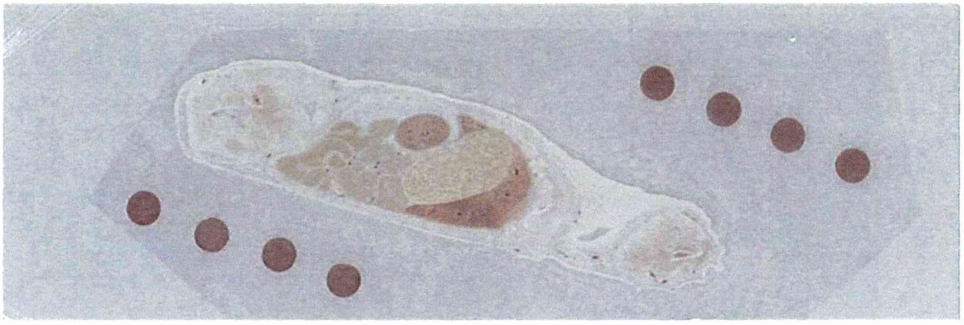
Left axis aspect-3

Central axis aspect

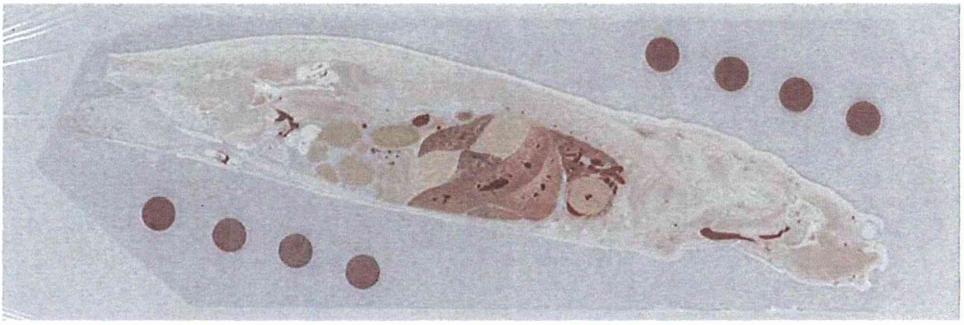


Appendix 12 Pictures 24 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

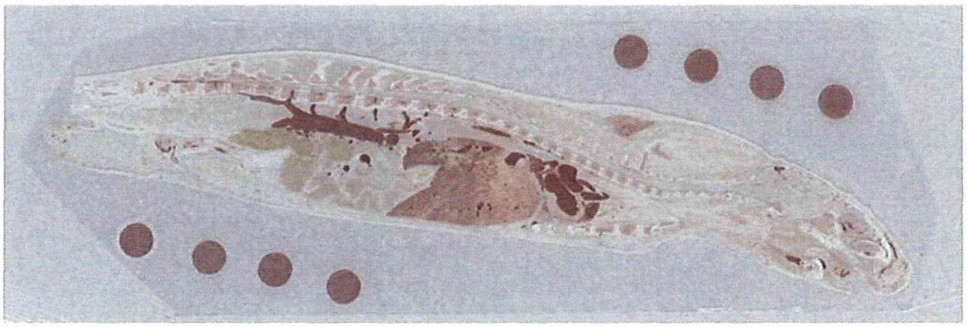
Left axis aspect-1



Left axis aspect-2

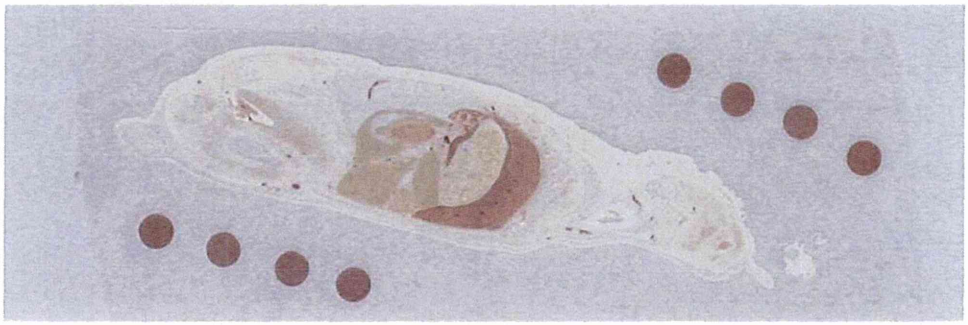


Central axis aspect



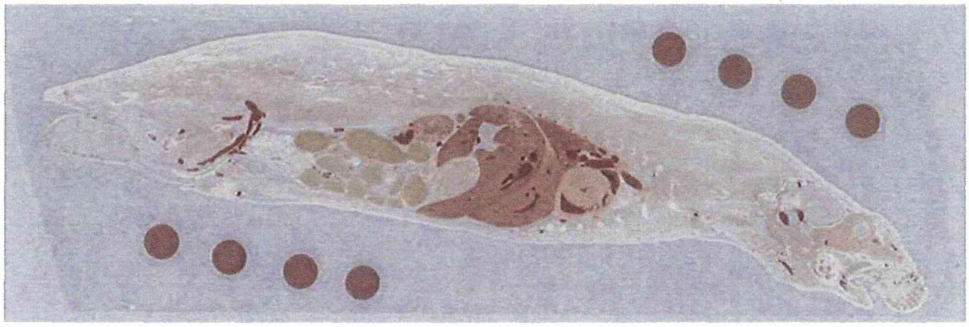
Appendix 13 Pictures 168 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Left axis aspect-1



Left axis aspect-2

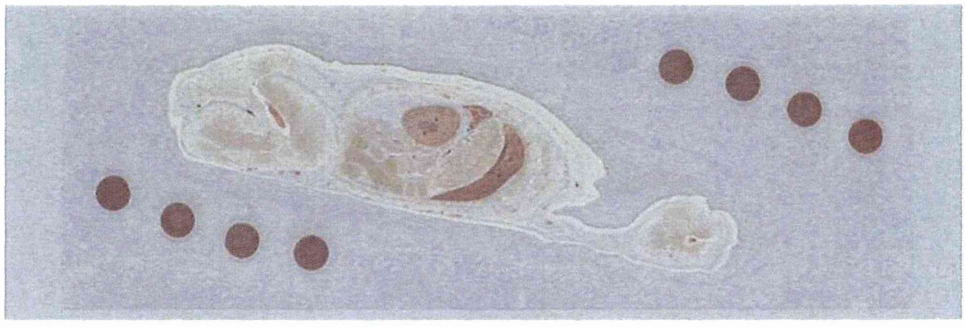
Left axis aspect-3



Central axis aspect

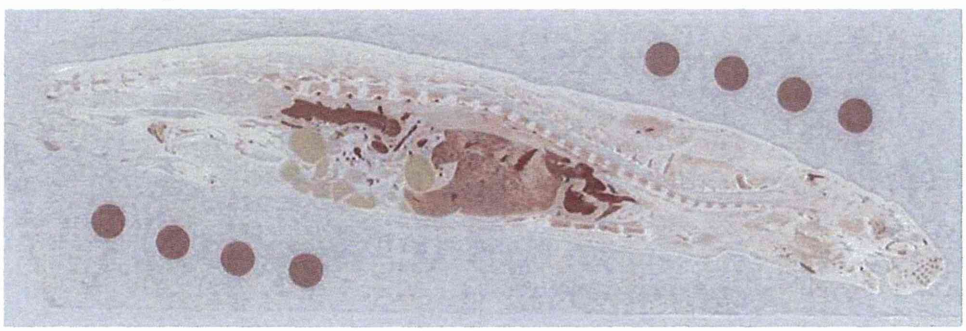
Appendix 14 Pictures 336 h after single intravenous administration of [^{14}C]P092 maleate to a male rat at 1 mg/kg as free base

Left axis aspect-1



Left axis aspect-2

Central axis aspect



Appendix 15 Radioactivity concentrations in blood, plasma, brain, and cerebrospinal fluid 1 h after single intravenous administration of [^{14}C]P092 maleate to male rats at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./mL or g)			
	Animal No. 07131	Animal No. 07132	Animal No. 07133	Mean ± SD
Blood	88.4	59.1	75.1	74.2 ± 14.7
Plasma	7.5	7.1	6.8	7.1 ± 0.4
Brain	26.6	22.2	22.8	23.9 ± 2.4
Cerebrospinal fluid	ND	ND	ND	ND

ND: Not detected

Appendix 16 Radioactivity concentrations in blood, plasma, brain, and cerebrospinal fluid 24 h after single intravenous administration of [^{14}C]P092 maleate to male rats at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./mL or g)			
	Animal No. 08136	Animal No. 08137	Animal No. 08138	Mean ± SD
Blood	24.8	31.8	35.6	30.7 ± 5.5
Plasma	3.4	4.5	3.0	3.6 ± 0.8
Brain	34.3	31.4	33.6	33.1 ± 1.5
Cerebrospinal fluid	ND	ND	ND	ND

ND: Not detected

Appendix 17 Radioactivity concentrations in blood, plasma, brain, and cerebrospinal fluid 168 h after single intravenous administration of [^{14}C]P092 maleate to male rats at 1 mg/kg as free base

Tissue	Radioactivity concentration (ng eq./mL or g)			
	Animal No. 09141	Animal No. 09142	Animal No. 09143	Mean ± SD
Blood	11.9	8.6	12.6	11.0 ± 2.1
Plasma	1.2	ND	ND	ND
Brain	36.3	35.7	39.7	37.2 ± 2.2
Cerebrospinal fluid	ND	ND	ND	ND

ND: Not detected

信 頼 性 保 証 証 明 書

試験委託者　：　国立大学法人岐阜大学

表　　題　：　[^{14}C]P092・マレイン酸塩をラットに単回静脈内投与したときの放射能の血中濃度，排泄及び分布

試 験 番 号　：　B130898

本試験は下記の基準に従って実施され，本最終報告書は，試験の方法，結果が正確に記載されていることを保証する．調査の内容，調査日および報告日を以下に示す．

申請資料の信頼性の基準

医薬品，医療機器等の品質，有効性及び安全性の確保等に関する法律施行規則　第43条

調 査 内 容	調査日	報告日	
		試験責任者	運営管理者
試験計画書			
試験計画書	2015年01月19日	2015年01月19日	2015年01月19日
（再調査）	2015年01月19日	2015年01月19日	2015年01月19日
試験計画書変更書 (1)	2015年01月21日	2015年01月21日	2015年01月21日
試験資料・最終報告書			
試験資料・最終報告書草案	2015年03月06日 ～2015年03月10日	2015年03月10日	2015年03月10日
（再調査）	2015年03月12日	2015年03月12日	2015年03月12日
試験資料・最終報告書	2015年03月18日	2015年03月18日	2015年03月18日

2015年 3月 18日

信頼性保証部門責任者　東川国男

東川 国男
株式会社ＬＳＩメディエンス
鹿島研究所

18. [^{14}C]P092 マレイン酸塩をカニクイザルに単回静脈内投与したときの放射能の血中濃度、排泄及び分布

最終報告書

[^{14}C]P092・マレイン酸塩をカニクイザルに単回静脈内投与したときの
放射能の血中濃度，排泄及び分布

（試験番号：B130899）

株式会社ＬＳＩメディエンス

1. 陳述書

表題： [^{14}C]P092・マレイン酸塩をカニクイザルに単回静脈内投与したときの放射能の血中濃度，排泄及び分布

試験番号：B130899

本試験は下記の基準に従い実施したものである．

「申請資料の信頼性の基準」
（医薬品，医療機器等の品質，有効性及び安全性の確保等に関する法律施行規則　第 43 条）

試験責任者：

2015 年 3 月 18 日　中井弘司

中井　弘司
株式会社ＬＳＩメディエンス
創薬支援事業本部　試験研究センター
分析代謝研究部

2. 目次

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