

## 7.5 尿及び糞中放射能排泄

[<sup>14</sup>C]P092・マレイン酸塩を雄性サルに 1 mg/kg (フリー体換算) の用量で単回静脈内投与したときの放射能の尿及び糞中累積排泄率を Table 2 に示し、これらの個体別値を Appendix 6 に示す。

投与後 24 時間までの尿及び糞中にはそれぞれ投与放射能の 1.7%及び 0.6%が排泄された。投与後 336 時間までの尿及び糞中にはそれぞれ投与放射能の 17.2%及び 44.6%が排泄され、ケージ洗浄液を含めた放射能の総排泄率は 64.6%であった。

静脈内投与された放射能の大部分は糞中に排泄され、サルにおける [<sup>14</sup>C]P092・マレイン酸塩の主排泄経路は糞中排泄であることが示唆された。さらに、組織中放射能濃度の結果において、胆嚢中の胆汁に比較的高い濃度の放射能が認められたことから、糞中への放射能の排泄経路として胆汁を介した排泄の寄与が考えられた。

## 7.6 組織中放射能濃度

[<sup>14</sup>C]P092・マレイン酸塩を雄性サルに 1 mg/kg (フリー体換算) の用量で単回静脈内投与したときの投与後 24, 168 及び 336 時間における組織中放射能濃度及び組織中放射能分布率をそれぞれ Table 3 及び Table 4 に示し、これらの個体別値を Appendix 7~Appendix 12 に示す。各組織中放射能濃度の最高値は、小脳、脊髄及び皮膚においては投与後 168 時間、大脳、延髄、眼球、顎下腺、腸間膜リンパ及び精巣においては投与後 336 時間、その他の組織においては投与後 24 時間に認められた。脳脊髄液中の放射能はいずれの測定時点においても検出限界未満 (ND) であった。

投与後 24 時間においては、肺に最も高い放射能濃度 (15664.4 ng eq./g) が認められ、 $K_p$  値は 349.65 であった。次いで、脾臓 (13960.8 ng eq./g,  $K_p$  値 311.63), 副腎 (10985.2 ng eq./g,  $K_p$  値 245.21), 胆汁 (10938.4 ng eq./g,  $K_p$  値 244.16), 腎臓 (8359.0 ng eq./g,  $K_p$  値 186.58) 及び肝臓 (8098.3 ng eq./g,  $K_p$  値 180.77) で高い放射能濃度が認められた。大脳中放射能濃度は 101.2 ng eq./g ( $K_p$  値 2.26) であり、小脳、延髄及び脊髄における  $K_p$  値は 0.72~2.19 であった。最も高い放射能分布率を示した組織は骨格筋 (52.00%) であり、次いで、肝臓 (15.66%), 肺 (7.71%) 及び白色脂肪 (4.63%) であった。

投与後 168 時間においては、脾臓に最も高い放射能濃度 (11204.3 ng eq./g) が認められ、 $K_p$  値は 291.78 であった。次いで、肺 (10419.4 ng eq./g,  $K_p$  値 271.34), 副腎 (7429.8 ng eq./g,  $K_p$  値 193.48), 胆汁 (6720.8 ng eq./g,  $K_p$  値 175.02) 及び腸間膜リンパ (6308.9 ng eq./g,  $K_p$  値 164.29) で高い放射能濃度が認められた。大脳中放射能濃度は 147.6 ng eq./g ( $K_p$  値 3.84) であり、小脳、延髄及び脊髄における  $K_p$  値は 1.90~2.84 であった。最も高い放射能分布率を示した組織は骨格筋 (20.20%) であり、次いで、肝臓 (6.90%), 肺 (4.80%) 及び白色脂肪 (3.75%) であった。

投与後 336 時間においては、副腎に最も高い放射能濃度 (8575.9 ng eq./g) が認められ、 $K_p$  値は 404.52 であった。次いで、脾臓 (7560.8 ng eq./g,  $K_p$  値 356.64), 腸間膜リンパ (7248.4 ng eq./g,  $K_p$  値 341.91), 肺 (4958.7 ng eq./g,  $K_p$  値 233.90) 及び顎下腺 (3967.2 ng eq./g,  $K_p$  値 187.13) で高い放射能濃度が認められた。大脳中放射能濃度は 148.8 ng eq./g ( $K_p$  値 7.02) であり、小脳、延髄及び脊髄における  $K_p$  値は 3.34~7.72 であった。最も高い放射能分布率を示した組織

は骨格筋 (9.12%) であり、次いで、肝臓 (4.42%)、皮膚 (2.93%) 及び白色脂肪 (2.52%) であった。

組織中放射能濃度は大部分の組織において血漿よりも高く、特に、肺、副腎、脾臓及び顎下腺では顕著に高い濃度の放射能が認められ、 $[^{14}\text{C}]\text{P092}$  及び/又はその代謝物は組織移行性が高いことが示唆された。また、投与後 168 又は 336 時間に放射能濃度の最高値を示す組織も存在し、 $[^{14}\text{C}]\text{P092}$  及び/又はその代謝物組織への移行は比較的緩徐であることが示唆された。一方、投与後 336 時間までの総排泄率は 64.6%に留まり、組織中放射能分布率の合計が投与放射能の 25.11%であったことから、 $[^{14}\text{C}]\text{P092}$  及び/又はその代謝物には組織残留性があり、体外への排泄は緩徐であると考えられた。

**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った試験の信頼性に影響を及ぼす疑いのある事態なし。

### 9.2 試験計画書に従わなかったこと

- (1) 6.6.1 項 (試験計画書 2.6.1 項) において、飼育室は「5132 又は 5133 室のいずれか」と設定したが、実際には 5132 及び 5133 室を使用していた。動物使用数が 9 匹であり、一部屋では収容できないため、二部屋を使用した。

動物 9 匹を収容するための措置であり、使用した飼育室はいずれも試験計画書で規定した飼育室であることから、本件は試験の信頼性に影響を与えないと判断した。

- (2) 動物番号 01102 について、採血が試験計画書で設定した時間よりも 2 分早く実施されていた。原因は採血のワークシートへの投与時刻の誤記載 (薬物動態システム表示時刻の転記ミス) であり、9 時 46 分と記載するところを誤って 9 時 44 分と記載したため、その後の採血予定時刻を 2 分早く記載し、これに従い採血していた。SOP で許容されている採血時間は、「投与後 10 分未満の時点では±1 分以内とし、±10%時間が 30 分を越える時点の許容範囲では±30 分以内とする」であり、投与後 5 分の採血が SOP からの逸脱となった。

その対応としては、SOP での許容範囲も考慮して、採血時間のズレの影響が懸念される投与後初期時点 (投与後 1 時間まで) は実際の採血時点 (3 分, 28 分, 58 分をそれぞれ 0.05, 0.47, 0.97 時間として) を用いて、動物番号 01102 の血液及び血漿中放射能濃度推移の薬物動態パラメータを再解析した。そして、薬物動態パラメータに採血時間のズレによる大きな変動が認められなかったことから、各測定時点の血液及び血漿中放射能濃度については、動物番号 01102 の 2 分ズレでの測定値を試験計画書で規定した測定時点の結果として、3 例で Mean ± SD を算出し、評価した。

動物番号 01102 については、血液及び血漿中放射能濃度の薬物動態パラメータの再解析値を評価に採用することで、本件は試験の信頼性に大きな影響を与えないと判断した。

**Table 1** Radioactivity concentrations and pharmacokinetic parameters in blood and plasma after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base

| Time/Parameter                     | Radioactivity concentration<br>(ng eq./mL) |               |
|------------------------------------|--|---------------|
|                                    | Blood                                      | Plasma        |
|                                    | Mean ± SD                                  | Mean ± SD     |
| 5 min                              | 511.2 ± 116.7                              | 131.5 ± 24.0  |
| 30 min                             | 171.9 ± 54.4                               | 56.8 ± 11.1   |
| 1 h                                | 121.3 ± 32.8                               | 47.6 ± 10.3   |
| 2 h                                | 104.9 ± 34.6                               | 46.1 ± 7.8    |
| 4 h                                | 87.7 ± 29.6                                | 46.9 ± 9.5    |
| 8 h                                | 82.6 ± 25.8                                | 48.2 ± 11.2   |
| 24 h                               | 64.8 ± 21.5                                | 46.9 ± 9.3    |
| 48 h                               | 65.1 ± 11.1                                | 55.3 ± 9.8    |
| 96 h                               | 48.8 ± 11.7                                | 43.7 ± 9.4    |
| 168 h                              | 40.0 ± 8.5                                 | 33.7 ± 6.8    |
| 240 h                              | 28.3 ± 5.9                                 | 27.3 ± 3.4    |
| 336 h                              | 22.9 ± 6.9                                 | 21.2 ± 3.1    |
| C <sub>0</sub> (ng eq./mL)         | 622.5 ± 153.2                              | 151.7 ± 23.1  |
| t <sub>1/2</sub> (h) <sup>a)</sup> | 186.3 ± 20.2                               | 290.2 ± 137.4 |
| AUC <sub>0-t</sub> (ng eq.·h/mL)   | 14405 ± 3379                               | 12024 ± 1910  |
| AUC <sub>0-inf</sub> (ng eq.·h/mL) | 20679 ± 5611                               | 21142 ± 4887  |
| CL <sub>total</sub> (mL/h/kg)      | 51 ± 16                                    | 49 ± 11       |
| V <sub>dss</sub> (mL/kg)           | 13702 ± 3078                               | 19108 ± 5168  |
| MRT <sub>0-inf</sub> (h)           | 272.1 ± 30.1                               | 413.1 ± 190.2 |

Data are expressed as the mean ± SD of three animals.

a) The t<sub>1/2</sub> was automatically calculated by WinNonlin.

**Table 2** Cumulative radioactivity excretions in urine and feces after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base

| Time (h) | Cumulative radioactivity excretion (% of dose) |            |              |            |
|----------|--|------------|--------------|------------|
|          | Urine  | Feces      | Cage washing | Total      |
| 0-24     | 1.7 ± 0.4                                      | 0.6 ± 0.7  | 0.4 ± 0.1    | 2.6 ± 1.0  |
| -48      | 4.3 ± 0.6                                      | 3.8 ± 1.8  | 0.8 ± 0.3    | 8.9 ± 2.3  |
| -72      | 5.9 ± 0.7                                      | 9.8 ± 3.3  | 1.0 ± 0.3    | 16.7 ± 3.8 |
| -96      | 7.7 ± 0.6                                      | 15.7 ± 4.9 | 1.5 ± 0.8    | 24.9 ± 4.9 |
| -120     | 9.1 ± 0.6                                      | 20.1 ± 7.2 | 1.9 ± 1.2    | 31.0 ± 7.0 |
| -168     | 11.6 ± 0.6                                     | 26.7 ± 8.8 | 2.2 ± 1.2    | 40.4 ± 8.4 |
| -240     | 14.3 ± 0.6                                     | 36.9 ± 6.6 | 2.5 ± 1.2    | 53.7 ± 6.3 |
| -336     | 17.2 ± 0.7                                     | 44.6 ± 6.0 | 2.8 ± 1.1    | 64.6 ± 5.4 |

Data are expressed as the mean ± SD of three animals.

**Table 3** Radioactivity concentrations in tissues after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base

| Tissue                 | Radioactivity concentration, ng eq./mL or g (K <sub>p</sub> ) |            |                  |            |                 |            |
|------------------------|---|------------|------------------|------------|-----------------|------------|
|                        | 24 h  |            | 168 h            |            | 336 h           |            |
| Blood                  | 73.9 ± 16.5   | ( 1.65 )   | 35.6 ± 9.6       | ( 0.93 )   | 22.9 ± 6.9      | ( 1.08 )   |
| Plasma                 | 44.8 ± 18.3   | ( 1.00 )   | 38.4 ± 15.5      | ( 1.00 )   | 21.2 ± 3.1      | ( 1.00 )   |
| Cerebrum               | 101.2 ± 52.9  | ( 2.26 )   | 147.6 ± 22.8     | ( 3.84 )   | 148.8 ± 59.9    | ( 7.02 )   |
| Cerebellum             | 98.1 ± 37.2   | ( 2.19 )   | 108.9 ± 14.4     | ( 2.84 )   | 80.8 ± 31.7     | ( 3.81 )   |
| Medulla oblongata      | 66.2 ± 20.2   | ( 1.48 )   | 106.8 ± 6.7      | ( 2.78 )   | 163.6 ± 93.9    | ( 7.72 )   |
| Cerebrospinal fluid    | ND  | ( NC )     | ND               | ( NC )     | ND              | ( NC )     |
| Spinal cord            | 32.2 ± 9.5  | ( 0.72 )   | 73.1 ± 6.8       | ( 1.90 )   | 70.8 ± 33.5     | ( 3.34 )   |
| Pituitary              | 4195.4 ± 1019.0   | ( 93.65 )  | 4157.5 ± 683.2   | ( 108.27 ) | 3261.7 ± 529.6  | ( 153.85 ) |
| Eyeball                | 256.5 ± 251.5   | ( 5.73 )   | 308.2 ± 42.9     | ( 8.03 )   | 792.4 ± 167.9   | ( 37.38 )  |
| Submaxillary gland     | 2225.1 ± 856.5  | ( 49.67 )  | 3960.7 ± 1067.7  | ( 103.14 ) | 3967.2 ± 1003.8 | ( 187.13 ) |
| Mesenteric lymph nodes | 2703.7 ± 829.8  | ( 60.35 )  | 6308.9 ± 1643.7  | ( 164.29 ) | 7248.4 ± 1116.8 | ( 341.91 ) |
| Heart                  | 5284.5 ± 1680.6   | ( 117.96 ) | 2499.7 ± 359.7   | ( 65.10 )  | 1692.1 ± 265.4  | ( 79.82 )  |
| Lung                   | 15664.4 ± 1199.3  | ( 349.65 ) | 10419.4 ± 1568.3 | ( 271.34 ) | 4958.7 ± 2851.4 | ( 233.90 ) |
| Liver                  | 8098.3 ± 1599.7   | ( 180.77 ) | 3910.6 ± 552.0   | ( 101.84 ) | 2661.2 ± 550.1  | ( 125.53 ) |
| Adrenal                | 10985.2 ± 2331.8  | ( 245.21 ) | 7429.8 ± 1018.8  | ( 193.48 ) | 8575.9 ± 1592.2 | ( 404.52 ) |
| Kidney                 | 8359.0 ± 1330.9   | ( 186.58 ) | 3962.3 ± 390.6   | ( 103.18 ) | 2617.8 ± 737.4  | ( 123.48 ) |
| Spleen                 | 13960.8 ± 1454.7  | ( 311.63 ) | 11204.3 ± 1859.7 | ( 291.78 ) | 7560.8 ± 682.4  | ( 356.64 ) |
| Pancreas               | 5288.7 ± 622.4  | ( 118.05 ) | 4480.1 ± 2711.7  | ( 116.67 ) | 3018.2 ± 945.5  | ( 142.37 ) |
| Testis                 | 356.5 ± 198.6   | ( 7.96 )   | 497.2 ± 29.7     | ( 12.95 )  | 741.7 ± 60.3    | ( 34.99 )  |
| Skin                   | 264.9 ± 63.9  | ( 5.91 )   | 359.5 ± 38.2     | ( 9.36 )   | 311.9 ± 114.4   | ( 14.71 )  |
| Skeletal muscle        | 1220.9 ± 279.8  | ( 27.25 )  | 472.2 ± 94.7     | ( 12.30 )  | 219.6 ± 85.2    | ( 10.36 )  |
| Bone                   | 62.9 ± 10.1   | ( 1.40 )   | 23.9 ± 2.1       | ( 0.62 )   | 18.7 ± 2.5      | ( 0.88 )   |
| White adipose tissue   | 569.0 ± 58.1  | ( 12.70 )  | 465.3 ± 48.4     | ( 12.12 )  | 317.8 ± 79.8    | ( 14.99 )  |
| Brown adipose tissue   | 4737.8 ± 2604.3   | ( 105.75 ) | 2595.0 ± 705.7   | ( 67.58 )  | 1586.1 ± 220.1  | ( 74.82 )  |
| Bile                   | 10938.4 ± 8358.7  | ( 244.16 ) | 6720.8 ± 3127.3  | ( 175.02 ) | 3165.8 ± 587.4  | ( 149.33 ) |

Data are expressed as the mean ± SD of three animals.

Values in parentheses are expressed as the ratio of tissue concentration to plasma concentration (K<sub>p</sub>).

ND: Not detected

NC: Not calculated

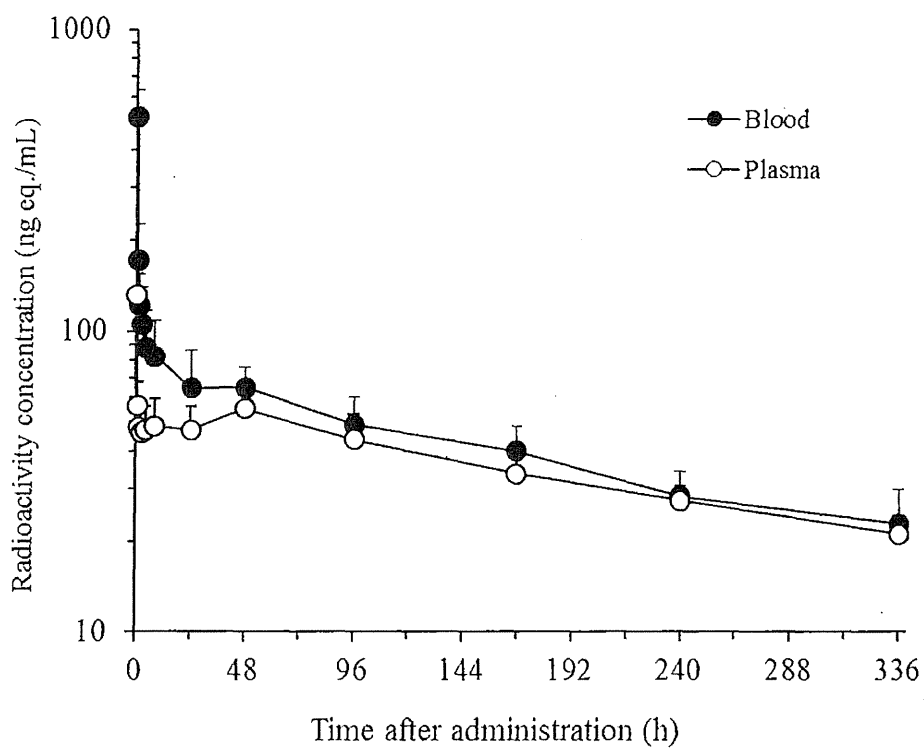
**Table 4 Radioactivity distribution in tissues after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                             | Radioactivity distribution (% of dose) |              |             |
|------------------------------------|--|--------------|-------------|
|                                    | 24 h                                   | 168 h        | 336 h       |
| Blood <sup>a)</sup>                | 0.46 ± 0.08                            | 0.22 ± 0.06  | 0.14 ± 0.04 |
| Cerebrum                           | 0.15 ± 0.07                            | 0.24 ± 0.01  | 0.23 ± 0.05 |
| Cerebellum                         | 0.01 ± 0.01                            | 0.02 ± 0.00  | 0.01 ± 0.01 |
| Medulla oblongata                  | 0.00 ± 0.00                            | 0.00 ± 0.00  | 0.00 ± 0.01 |
| Pituitary                          | 0.01 ± 0.00                            | 0.01 ± 0.01  | 0.00 ± 0.01 |
| Eyeball                            | 0.05 ± 0.05                            | 0.05 ± 0.01  | 0.14 ± 0.02 |
| Submaxillary gland                 | 0.12 ± 0.05                            | 0.32 ± 0.16  | 0.24 ± 0.03 |
| Heart                              | 1.66 ± 0.35                            | 0.79 ± 0.15  | 0.57 ± 0.05 |
| Lung                               | 7.71 ± 1.82                            | 4.80 ± 1.22  | 2.26 ± 1.01 |
| Liver                              | 15.66 ± 4.56                           | 6.90 ± 2.10  | 4.42 ± 0.23 |
| Adrenal                            | 0.16 ± 0.03                            | 0.13 ± 0.01  | 0.12 ± 0.04 |
| Kidney                             | 2.94 ± 0.28                            | 1.36 ± 0.26  | 0.94 ± 0.24 |
| Spleen                             | 1.75 ± 0.71                            | 0.85 ± 0.08  | 0.62 ± 0.15 |
| Pancreas                           | 0.79 ± 0.13                            | 0.72 ± 0.33  | 0.48 ± 0.19 |
| Testis                             | 0.11 ± 0.02                            | 0.34 ± 0.11  | 0.24 ± 0.10 |
| Skin <sup>a)</sup>                 | 2.58 ± 0.56                            | 3.49 ± 0.35  | 2.93 ± 0.89 |
| Skeletal muscle <sup>a)</sup>      | 52.00 ± 8.79                           | 20.20 ± 4.09 | 9.12 ± 3.28 |
| White adipose tissue <sup>a)</sup> | 4.63 ± 0.73                            | 3.75 ± 0.39  | 2.52 ± 0.75 |
| Bile                               | 0.52 ± 0.38                            | 0.23 ± 0.07  | 0.13 ± 0.04 |
| Total                              | 91.31                                  | 44.42        | 25.11       |

Data are expressed as the mean ± SD of three animals.

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





**Figure 1** Radioactivity concentrations in blood and plasma after single intravenous administration of [ $^{14}\text{C}$ ]P092 maleate to male monkeys at 1 mg/kg as free base

Data are expressed as the mean + SD of three animals.

### Appendix 1 Radiochemical purity of [<sup>14</sup>C]P092 maleate

| Date of analysis                 | Sample                         | Detection <sup>a)</sup> | Retention time (min) | Radiochemical purity (%) | Recovery <sup>b)</sup> (%) |
|----------------------------------|--------------------------------|-------------------------|----------------------|--------------------------|----------------------------|
| Before use<br>(January 21, 2015) | Non-labeled standard solution  | UV                      | 13.8                 | --                       | --                         |
|                                  | [ <sup>14</sup> C]P092 maleate | RI                      | 14.0                 | 99.0                     | 95.8                       |
| After use<br>(February 24, 2015) | Non-labeled standard solution  | UV                      | 14.8                 | --                       | --                         |
|                                  | [ <sup>14</sup> C]P092 maleate | RI                      | 15.1                 | 99.1                     | 103.9                      |

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

b) Radioactivity recovery from HPLC system

--: Not applicable

## Appendix 2 Radioactivity concentrations of [<sup>14</sup>C]P092 maleate in dosing formulation

| Nominal concentration | Date of measurement                      | Radioactivity concentration |                    |        | % of nominal concentration |
|-----------------------|--|-----------------------------|--------------------|--------|----------------------------|
|                       |  | Individual value (MBq/mL)   | Mean ± SD (MBq/mL) | CV (%) |                            |
| 2 mg/4.288 MBq/mL     | Before administration (January 22, 2015) | 4.376                       | 4.356 ± 0.058      | 1.3    | 101.6                      |
|                       |  | 4.291                       |                    |        |                            |
|                       |  | 4.402                       |                    |        |                            |
|                       | After administration (January 22, 2015)  | 4.372                       | 4.361 ± 0.016      | 0.4    | 101.7                      |
|                       |  | 4.368                       |                    |        |                            |
|                       |  | 4.343                       |                    |        |                            |

## Appendix 3 Radiochemical purity of [<sup>14</sup>C]P092 maleate in dosing formulation

| Date of analysis                         | Sample                        | Detection <sup>a)</sup> | Retention time (min) | Radiochemical purity (%) | Recovery <sup>b)</sup> (%) |
|--|-------------------------------|-------------------------|----------------------|--------------------------|----------------------------|
| Before administration (January 22, 2015) | Non-labeled standard solution | UV                      | 13.7                 | --                       | --                         |
|  | Dosing formulation            | RI                      | 13.9                 | 99.2                     | 98.7                       |
| After administration (January 22, 2015)  | Non-labeled standard solution | UV                      | 13.7                 | --                       | --                         |
|  | Dosing formulation            | RI                      | 13.8                 | 99.1                     | 98.3                       |

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

b) Radioactivity recovery from HPLC system

--: Not applicable

**Appendix 4 Radioactivity concentrations and pharmacokinetic parameters in blood after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Time/Parameter                     | Radioactivity concentration (ng eq./mL) |                     |                     |               |
|------------------------------------|---|---------------------|---------------------|---------------|
|                                    | Animal No.<br>01101                     | Animal No.<br>01102 | Animal No.<br>01103 | Mean ± SD     |
| 5 min <sup>a)</sup>                | 445.6                                   | 442.1               | 646.0               | 511.2 ± 116.7 |
| 30 min <sup>b)</sup>               | 122.1                                   | 163.6               | 230.0               | 171.9 ± 54.4  |
| 1 h <sup>c)</sup>                  | 88.0                                    | 122.4               | 153.6               | 121.3 ± 32.8  |
| 2 h                                | 69.1                                    | 107.5               | 138.2               | 104.9 ± 34.6  |
| 4 h                                | 54.8                                    | 95.8                | 112.4               | 87.7 ± 29.6   |
| 8 h                                | 55.6                                    | 85.0                | 107.1               | 82.6 ± 25.8   |
| 24 h                               | 44.4                                    | 62.9                | 87.2                | 64.8 ± 21.5   |
| 48 h                               | 53.1                                    | 67.1                | 75.1                | 65.1 ± 11.1   |
| 96 h                               | 35.4                                    | 54.9                | 56.2                | 48.8 ± 11.7   |
| 168 h                              | 30.3                                    | 43.7                | 46.0                | 40.0 ± 8.5    |
| 240 h                              | 21.6                                    | 30.4                | 32.9                | 28.3 ± 5.9    |
| 336 h                              | 15.0                                    | 26.5                | 27.3                | 22.9 ± 6.9    |
| C <sub>0</sub> (ng eq./mL)         | 576.6                                   | 497.6               | 793.4               | 622.5 ± 153.2 |
| t <sub>1/2</sub> (h) <sup>d)</sup> | 166.5                                   | 206.8               | 185.6               | 186.3 ± 20.2  |
| AUC <sub>0-t</sub> (ng eq.·h/mL)   | 10628                                   | 15447               | 17141               | 14405 ± 3379  |
| AUC <sub>0-inf</sub> (ng eq.·h/mL) | 14231                                   | 23353               | 24453               | 20679 ± 5611  |
| CL <sub>total</sub> (mL/h/kg)      | 70                                      | 43                  | 41                  | 51 ± 16       |
| Vd <sub>ss</sub> (mL/kg)           | 17077                                   | 12978               | 11051               | 13702 ± 3078  |
| MRT <sub>0-inf</sub> (h)           | 243.0                                   | 303.1               | 270.2               | 272.1 ± 30.1  |

a) 3 min in animal No.01102

b) 28 min in animal No.01102

c) 58 min in animal No.01102

d) The t<sub>1/2</sub> was automatically calculated by WinNonlin.

Animal No. 01101: Half-life, from 168 h to 336 h

Animal No. 01102: Half-life, from 48 h to 336 h

Animal No. 01103: Half-life, from 24 h to 336 h

**Appendix 5 Radioactivity concentrations and pharmacokinetic parameters in plasma after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Time/Parameter                     | Radioactivity concentration (ng eq./mL) |                     |                     | Mean ± SD     |
|------------------------------------|---|---------------------|---------------------|---------------|
|                                    | Animal No.<br>01101                     | Animal No.<br>01102 | Animal No.<br>01103 |               |
| 5 min <sup>a)</sup>                | 106.3                                   | 154.0               | 134.3               | 131.5 ± 24.0  |
| 30 min <sup>b)</sup>               | 46.0                                    | 68.1                | 56.3                | 56.8 ± 11.1   |
| 1 h <sup>c)</sup>                  | 38.9                                    | 58.9                | 45.0                | 47.6 ± 10.3   |
| 2 h                                | 40.7                                    | 55.0                | 42.6                | 46.1 ± 7.8    |
| 4 h                                | 39.7                                    | 57.7                | 43.3                | 46.9 ± 9.5    |
| 8 h                                | 42.4                                    | 61.1                | 41.0                | 48.2 ± 11.2   |
| 24 h                               | 43.5                                    | 57.5                | 39.8                | 46.9 ± 9.3    |
| 48 h                               | 56.9                                    | 64.1                | 44.8                | 55.3 ± 9.8    |
| 96 h                               | 37.7                                    | 54.5                | 38.8                | 43.7 ± 9.4    |
| 168 h                              | 28.7                                    | 41.5                | 31.0                | 33.7 ± 6.8    |
| 240 h                              | 23.6                                    | 30.2                | 28.2                | 27.3 ± 3.4    |
| 336 h                              | 17.8                                    | 21.9                | 23.9                | 21.2 ± 3.1    |
| C <sub>0</sub> (ng eq./mL)         | 125.6                                   | 169.7               | 159.7               | 151.7 ± 23.1  |
| t <sub>1/2</sub> (h) <sup>d)</sup> | 243.3                                   | 182.4               | 445.0               | 290.2 ± 137.4 |
| AUC <sub>0-t</sub> (ng eq.·h/mL)   | 10695                                   | 14213               | 11163               | 12024 ± 1910  |
| AUC <sub>0-inf</sub> (ng eq.·h/mL) | 16944                                   | 19975               | 26506               | 21142 ± 4887  |
| CL <sub>total</sub> (mL/h/kg)      | 59                                      | 50                  | 38                  | 49 ± 11       |
| Vd <sub>ss</sub> (mL/kg)           | 20067                                   | 13527               | 23729               | 19108 ± 5168  |
| MRT <sub>0-inf</sub> (h)           | 340.0                                   | 270.2               | 629.0               | 413.1 ± 190.2 |

a) 3 min in animal No.01102

b) 28 min in animal No.01102

c) 58 min in animal No.01102

d) The t<sub>1/2</sub> was automatically calculated by WinNonlin.

Animal No. 01101: Half-life, from 168 h to 336 h

Animal No. 01102: Half-life, from 48 h to 336 h

Animal No. 01103: Half-life, from 168 h to 336 h

**Appendix 6 Cumulative radioactivity excretions in urine and feces after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Measurement<br>-item | Animal<br>No. | Cumulative radioactivity excretion (% of dose) |       |       |       |        |        |        |        |
|----------------------|---------------|--|-------|-------|-------|--------|--------|--------|--------|
|                      |               | 0-24 h   | -48 h | -72 h | -96 h | -120 h | -168 h | -240 h | -336 h |
| Urine                | 01101         | 2.1  | 4.9   | 6.7   | 8.3   | 9.8    | 12.2   | 14.7   | 17.4   |
|                      | 01102         | 1.3  | 4.3   | 5.5   | 7.7   | 8.8    | 11.6   | 14.6   | 17.8   |
|                      | 01103         | 1.6  | 3.7   | 5.5   | 7.1   | 8.6    | 11.0   | 13.7   | 16.4   |
|                      | Mean          | 1.7  | 4.3   | 5.9   | 7.7   | 9.1    | 11.6   | 14.3   | 17.2   |
|                      | SD            | 0.4  | 0.6   | 0.7   | 0.6   | 0.6    | 0.6    | 0.6    | 0.7    |
| Feces                | 01101         | 1.3  | 5.9   | 13.2  | 20.9  | 27.6   | 35.7   | 44.3   | 51.3   |
|                      | 01102         | 0.0  | 2.8   | 6.7   | 11.2  | 13.3   | 18.1   | 31.6   | 39.6   |
|                      | 01103         | 0.4  | 2.8   | 9.4   | 14.9  | 19.3   | 26.2   | 34.8   | 43.0   |
|                      | Mean          | 0.6  | 3.8   | 9.8   | 15.7  | 20.1   | 26.7   | 36.9   | 44.6   |
|                      | SD            | 0.7  | 1.8   | 3.3   | 4.9   | 7.2    | 8.8    | 6.6    | 6.0    |
| Cage<br>washing      | 01101         | 0.4  | 0.7   | 1.0   | 1.2   | 1.4    | 1.7    | 2.0    | 2.2    |
|                      | 01102         | 0.5  | 1.1   | 1.3   | 2.4   | 3.3    | 3.5    | 3.8    | 4.1    |
|                      | 01103         | 0.3  | 0.6   | 0.7   | 0.9   | 1.0    | 1.3    | 1.6    | 2.1    |
|                      | Mean          | 0.4  | 0.8   | 1.0   | 1.5   | 1.9    | 2.2    | 2.5    | 2.8    |
|                      | SD            | 0.1  | 0.3   | 0.3   | 0.8   | 1.2    | 1.2    | 1.2    | 1.1    |
| Total                | 01101         | 3.8  | 11.5  | 20.9  | 30.4  | 38.8   | 49.6   | 61.0   | 70.9   |
|                      | 01102         | 1.8  | 8.2   | 13.5  | 21.3  | 25.4   | 33.2   | 50.0   | 61.5   |
|                      | 01103         | 2.3  | 7.1   | 15.6  | 22.9  | 28.9   | 38.5   | 50.1   | 61.5   |
|                      | Mean          | 2.6  | 8.9   | 16.7  | 24.9  | 31.0   | 40.4   | 53.7   | 64.6   |
|                      | SD            | 1.0  | 2.3   | 3.8   | 4.9   | 7.0    | 8.4    | 6.3    | 5.4    |

**Appendix 7 Radioactivity concentrations in tissues 24 h after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                 | Radioactivity concentration (ng eq./mL or g) |                     |                     | Mean ± SD        |
|------------------------|--|---------------------|---------------------|------------------|
|                        | Animal No.<br>02106                          | Animal No.<br>02107 | Animal No.<br>02108 |                  |
| Blood                  | 87.5   | 78.6                | 55.5                | 73.9 ± 16.5      |
| Plasma                 | 63.8   | 43.2                | 27.4                | 44.8 ± 18.3      |
| Cerebrum               | 79.4   | 161.6               | 62.7                | 101.2 ± 52.9     |
| Cerebellum             | 86.4   | 139.8               | 68.2                | 98.1 ± 37.2      |
| Medulla oblongata      | 57.7   | 89.2                | 51.6                | 66.2 ± 20.2      |
| Cerebrospinal fluid    | ND   | ND                  | ND                  | ND               |
| Spinal cord            | 33.6   | 40.9                | 22.1                | 32.2 ± 9.5       |
| Pituitary              | 3894.9                                       | 5330.9              | 3360.4              | 4195.4 ± 1019.0  |
| Eyeball                | 179.3  | 537.6               | 52.6                | 256.5 ± 251.5    |
| Submaxillary gland     | 2308.3                                       | 3037.0              | 1330.1              | 2225.1 ± 856.5   |
| Mesenteric lymph nodes | 3290.6                                       | 3066.3              | 1754.3              | 2703.7 ± 829.8   |
| Heart                  | 3881.2                                       | 7146.9              | 4825.4              | 5284.5 ± 1680.6  |
| Lung                   | 14297.6                                      | 16154.7             | 16540.8             | 15664.4 ± 1199.3 |
| Liver                  | 7519.6                                       | 6868.5              | 9906.8              | 8098.3 ± 1599.7  |
| Adrenal                | 9130.1                                       | 13602.8             | 10222.8             | 10985.2 ± 2331.8 |
| Kidney                 | 7679.9                                       | 9892.5              | 7504.6              | 8359.0 ± 1330.9  |
| Spleen                 | 14861.5                                      | 14738.4             | 12282.6             | 13960.8 ± 1454.7 |
| Pancreas               | 5551.7                                       | 5736.4              | 4578.0              | 5288.7 ± 622.4   |
| Testis                 | 277.5  | 582.4               | 209.5               | 356.5 ± 198.6    |
| Skin                   | 234.8  | 338.2               | 221.6               | 264.9 ± 63.9     |
| Skeletal muscle        | 1386.9                                       | 1377.9              | 897.8               | 1220.9 ± 279.8   |
| Bone                   | 59.4   | 74.3                | 55.0                | 62.9 ± 10.1      |
| White adipose tissue   | 585.4  | 504.5               | 617.1               | 569.0 ± 58.1     |
| Brown adipose tissue   | 7167.4                                       | 5057.7              | 1988.4              | 4737.8 ± 2604.3  |
| Bile                   | 20126.0                                      | 8905.9              | 3783.4              | 10938.4 ± 8358.7 |

ND: Not detected

**Appendix 8 Radioactivity concentrations in tissues 168 h after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                 | Radioactivity concentration (ng eq./mL or g) |                     |                     | Mean ± SD        |
|------------------------|--|---------------------|---------------------|------------------|
|                        | Animal No.<br>03111                          | Animal No.<br>03112 | Animal No.<br>03113 |                  |
| Blood                  | 30.1   | 30.1                | 46.7                | 35.6 ± 9.6       |
| Plasma                 | 31.1   | 27.8                | 56.2                | 38.4 ± 15.5      |
| Cerebrum               | 132.9  | 136.1               | 173.9               | 147.6 ± 22.8     |
| Cerebellum             | 125.2  | 103.4               | 98.0                | 108.9 ± 14.4     |
| Medulla oblongata      | 112.9  | 99.7                | 107.8               | 106.8 ± 6.7      |
| Cerebrospinal fluid    | ND   | ND                  | ND                  | ND               |
| Spinal cord            | 70.3   | 68.1                | 80.8                | 73.1 ± 6.8       |
| Pituitary              | 4214.9                                       | 3447.4              | 4810.1              | 4157.5 ± 683.2   |
| Eyeball                | 357.8  | 284.1               | 282.8               | 308.2 ± 42.9     |
| Submaxillary gland     | 5035.7                                       | 2900.5              | 3946.0              | 3960.7 ± 1067.7  |
| Mesenteric lymph nodes | 8154.6                                       | 5769.2              | 5002.8              | 6308.9 ± 1643.7  |
| Heart                  | 2304.4                                       | 2279.8              | 2914.8              | 2499.7 ± 359.7   |
| Lung                   | 10105.3                                      | 9032.0              | 12121.0             | 10419.4 ± 1568.3 |
| Liver                  | 4547.5                                       | 3571.5              | 3612.8              | 3910.6 ± 552.0   |
| Adrenal                | 7403.9                                       | 8461.4              | 6424.2              | 7429.8 ± 1018.8  |
| Kidney                 | 4319.2                                       | 3545.1              | 4022.7              | 3962.3 ± 390.6   |
| Spleen                 | 9813.7                                       | 10482.4             | 13316.7             | 11204.3 ± 1859.7 |
| Pancreas               | 7559.5                                       | 3431.2              | 2449.5              | 4480.1 ± 2711.7  |
| Testis                 | 518.6  | 509.7               | 463.3               | 497.2 ± 29.7     |
| Skin                   | 315.5  | 378.7               | 384.3               | 359.5 ± 38.2     |
| Skeletal muscle        | 397.3  | 578.6               | 440.6               | 472.2 ± 94.7     |
| Bone                   | 23.2   | 26.2                | 22.2                | 23.9 ± 2.1       |
| White adipose tissue   | 505.2  | 411.5               | 479.3               | 465.3 ± 48.4     |
| Brown adipose tissue   | 1943.8                                       | 2496.4              | 3344.8              | 2595.0 ± 705.7   |
| Bile                   | 3202.7                                       | 9185.2              | 7774.5              | 6720.8 ± 3127.3  |

ND: Not detected



**Appendix 9 Radioactivity concentrations in tissues 336 h after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                 | Radioactivity concentration (ng eq./mL or g) |                     |                     | Mean ± SD       |
|------------------------|--|---------------------|---------------------|-----------------|
|                        | Animal No.<br>01101                          | Animal No.<br>01102 | Animal No.<br>01103 |                 |
| Blood                  | 15.0   | 26.5                | 27.3                | 22.9 ± 6.9      |
| Plasma                 | 17.8   | 21.9                | 23.9                | 21.2 ± 3.1      |
| Cerebrum               | 95.4   | 137.5               | 213.6               | 148.8 ± 59.9    |
| Cerebellum             | 57.5   | 68.0                | 116.9               | 80.8 ± 31.7     |
| Medulla oblongata      | 73.8   | 155.8               | 261.1               | 163.6 ± 93.9    |
| Cerebrospinal fluid    | ND   | ND                  | ND                  | ND              |
| Spinal cord            | 37.6   | 70.3                | 104.5               | 70.8 ± 33.5     |
| Pituitary              | 2663.3                                       | 3451.8              | 3670.0              | 3261.7 ± 529.6  |
| Eyeball                | 745.9  | 652.7               | 978.7               | 792.4 ± 167.9   |
| Submaxillary gland     | 3098.3                                       | 3737.2              | 5066.0              | 3967.2 ± 1003.8 |
| Mesenteric lymph nodes | 6213.7                                       | 7099.2              | 8432.3              | 7248.4 ± 1116.8 |
| Heart                  | 1399.3                                       | 1916.7              | 1760.3              | 1692.1 ± 265.4  |
| Lung                   | 8187.5                                       | 3902.6              | 2786.1              | 4958.7 ± 2851.4 |
| Liver                  | 2049.2                                       | 2819.9              | 3114.5              | 2661.2 ± 550.1  |
| Adrenal                | 7458.2                                       | 7870.6              | 10398.9             | 8575.9 ± 1592.2 |
| Kidney                 | 2489.8                                       | 1952.8              | 3410.8              | 2617.8 ± 737.4  |
| Spleen                 | 8080.3                                       | 7814.2              | 6787.9              | 7560.8 ± 682.4  |
| Pancreas               | 2089.4                                       | 2985.6              | 3979.6              | 3018.2 ± 945.5  |
| Testis                 | 700.0  | 714.3               | 810.9               | 741.7 ± 60.3    |
| Skin                   | 250.0  | 241.9               | 443.9               | 311.9 ± 114.4   |
| Skeletal muscle        | 127.3  | 236.2               | 295.2               | 219.6 ± 85.2    |
| Bone                   | 20.4   | 15.9                | 19.9                | 18.7 ± 2.5      |
| White adipose tissue   | 254.6  | 407.5               | 291.3               | 317.8 ± 79.8    |
| Brown adipose tissue   | 1606.5                                       | 1356.5              | 1795.3              | 1586.1 ± 220.1  |
| Bile                   | 3442.2                                       | 2491.1              | 3564.0              | 3165.8 ± 587.4  |

ND: Not detected

**Appendix 10 Radioactivity distribution in tissues 24 h after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                             | Radioactivity distribution (% of dose) |                     |                     |              |
|------------------------------------|--|---------------------|---------------------|--------------|
|                                    | Animal No.<br>02106                    | Animal No.<br>02107 | Animal No.<br>02108 | Mean ± SD    |
| Blood <sup>a)</sup>                | 0.52                                   | 0.48                | 0.37                | 0.46 ± 0.08  |
| Cerebrum                           | 0.12                                   | 0.23                | 0.11                | 0.15 ± 0.07  |
| Cerebellum                         | 0.01                                   | 0.02                | 0.01                | 0.01 ± 0.01  |
| Medulla oblongata                  | 0.00                                   | 0.00                | 0.00                | 0.00 ± 0.00  |
| Pituitary                          | 0.01                                   | 0.01                | 0.01                | 0.01 ± 0.00  |
| Eyeball                            | 0.03                                   | 0.11                | 0.01                | 0.05 ± 0.05  |
| Submaxillary gland                 | 0.10                                   | 0.17                | 0.08                | 0.12 ± 0.05  |
| Heart                              | 1.32                                   | 2.01                | 1.64                | 1.66 ± 0.35  |
| Lung                               | 6.95                                   | 6.39                | 9.79                | 7.71 ± 1.82  |
| Liver                              | 15.10                                  | 11.40               | 20.47               | 15.66 ± 4.56 |
| Adrenal                            | 0.20                                   | 0.14                | 0.15                | 0.16 ± 0.03  |
| Kidney                             | 2.64                                   | 3.19                | 2.99                | 2.94 ± 0.28  |
| Spleen                             | 2.57                                   | 1.31                | 1.36                | 1.75 ± 0.71  |
| Pancreas                           | 0.82                                   | 0.90                | 0.65                | 0.79 ± 0.13  |
| Testis                             | 0.13                                   | 0.10                | 0.09                | 0.11 ± 0.02  |
| Skin <sup>a)</sup>                 | 2.17                                   | 3.21                | 2.35                | 2.58 ± 0.56  |
| Skeletal muscle <sup>a)</sup>      | 56.49                                  | 57.65               | 41.87               | 52.00 ± 8.79 |
| White adipose tissue <sup>a)</sup> | 4.49                                   | 3.98                | 5.42                | 4.63 ± 0.73  |
| Bile                               | 0.94                                   | 0.41                | 0.21                | 0.52 ± 0.38  |

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

**Appendix 11 Radioactivity distribution in tissues 168 h after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                             | Radioactivity distribution (% of dose) |                     |                     |              |
|------------------------------------|--|---------------------|---------------------|--------------|
|                                    | Animal No.<br>03111                    | Animal No.<br>03112 | Animal No.<br>03113 | Mean ± SD    |
| Blood <sup>a)</sup>                | 0.19                                   | 0.19                | 0.29                | 0.22 ± 0.06  |
| Cerebrum                           | 0.23                                   | 0.25                | 0.23                | 0.24 ± 0.01  |
| Cerebellum                         | 0.02                                   | 0.02                | 0.02                | 0.02 ± 0.00  |
| Medulla oblongata                  | 0.00                                   | 0.00                | 0.00                | 0.00 ± 0.00  |
| Pituitary                          | 0.00                                   | 0.01                | 0.01                | 0.01 ± 0.01  |
| Eyeball                            | 0.06                                   | 0.05                | 0.05                | 0.05 ± 0.01  |
| Submaxillary gland                 | 0.51                                   | 0.21                | 0.25                | 0.32 ± 0.16  |
| Heart                              | 0.72                                   | 0.68                | 0.96                | 0.79 ± 0.15  |
| Lung                               | 5.75                                   | 3.42                | 5.22                | 4.80 ± 1.22  |
| Liver                              | 9.30                                   | 5.98                | 5.42                | 6.90 ± 2.10  |
| Adrenal                            | 0.14                                   | 0.13                | 0.13                | 0.13 ± 0.01  |
| Kidney                             | 1.66                                   | 1.18                | 1.25                | 1.36 ± 0.26  |
| Spleen                             | 0.76                                   | 0.88                | 0.92                | 0.85 ± 0.08  |
| Pancreas                           | 1.10                                   | 0.54                | 0.51                | 0.72 ± 0.33  |
| Testis                             | 0.30                                   | 0.46                | 0.26                | 0.34 ± 0.11  |
| Skin <sup>a)</sup>                 | 3.09                                   | 3.69                | 3.69                | 3.49 ± 0.35  |
| Skeletal muscle <sup>a)</sup>      | 17.14                                  | 24.84               | 18.61               | 20.20 ± 4.09 |
| White adipose tissue <sup>a)</sup> | 4.11                                   | 3.33                | 3.81                | 3.75 ± 0.39  |
| Bile                               | 0.20                                   | 0.31                | 0.19                | 0.23 ± 0.07  |

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

**Appendix 12 Radioactivity distribution in tissues 336 h after single intravenous administration of [<sup>14</sup>C]P092 maleate to male monkeys at 1 mg/kg as free base**

| Tissue                             | Radioactivity distribution (% of dose) |                     |                     |             |
|------------------------------------|--|---------------------|---------------------|-------------|
|                                    | Animal No.<br>01101                    | Animal No.<br>01102 | Animal No.<br>01103 | Mean ± SD   |
| Blood <sup>a)</sup>                | 0.09                                   | 0.17                | 0.16                | 0.14 ± 0.04 |
| Cerebrum                           | 0.17                                   | 0.25                | 0.27                | 0.23 ± 0.05 |
| Cerebellum                         | 0.01                                   | 0.01                | 0.02                | 0.01 ± 0.01 |
| Medulla oblongata                  | 0.00                                   | 0.00                | 0.01                | 0.00 ± 0.01 |
| Pituitary                          | 0.00                                   | 0.00                | 0.01                | 0.00 ± 0.01 |
| Eyeball                            | 0.14                                   | 0.13                | 0.16                | 0.14 ± 0.02 |
| Submaxillary gland                 | 0.24                                   | 0.22                | 0.27                | 0.24 ± 0.03 |
| Heart                              | 0.56                                   | 0.62                | 0.53                | 0.57 ± 0.05 |
| Lung                               | 3.28                                   | 2.24                | 1.27                | 2.26 ± 1.01 |
| Liver                              | 4.20                                   | 4.65                | 4.40                | 4.42 ± 0.23 |
| Adrenal                            | 0.16                                   | 0.08                | 0.12                | 0.12 ± 0.04 |
| Kidney                             | 1.08                                   | 0.66                | 1.08                | 0.94 ± 0.24 |
| Spleen                             | 0.45                                   | 0.74                | 0.66                | 0.62 ± 0.15 |
| Pancreas                           | 0.26                                   | 0.56                | 0.61                | 0.48 ± 0.19 |
| Testis                             | 0.29                                   | 0.13                | 0.30                | 0.24 ± 0.10 |
| Skin <sup>a)</sup>                 | 2.41                                   | 2.42                | 3.96                | 2.93 ± 0.89 |
| Skeletal muscle <sup>a)</sup>      | 5.40                                   | 10.39               | 11.58               | 9.12 ± 3.28 |
| White adipose tissue <sup>a)</sup> | 2.03                                   | 3.38                | 2.15                | 2.52 ± 0.75 |
| Bile                               | 0.15                                   | 0.08                | 0.15                | 0.13 ± 0.04 |

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