Whole-body Biodistribution and Radiation Dosimetry Estimates for The Cannabinoid Type 1 (CB$_1$) Receptor Radioligand [^{11}C]SD5024 in Nonhuman Primates

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The cannabinoid type 1 (CB_1) receptor is one of the most abundant G protein-coupled receptors in the brain. It is found on glutamatergic, dopaminergic, and gamma aminobutyric acid (GABA)-ergic synaptic terminals and mediates the effects of endocannabinoids (ECs), which suppresses the release of neurotransmitters. The CB_1 receptor is a target for drug therapy, including the use of a CB_1 receptor antagonist as an appetite suppressant. Our laboratory recently developed a promising positron emission tomography (PET) ligand for the CB_1 receptor: [^{11}C]SD5024 (Donohue 2008).

The following report presents measurements of whole-body biodistribution over time of [^{11}C]SD5024 and estimation of resulting radiation exposure to organs of the body. Absorbed doses were estimated following administration of [^{11}C]SD5024 and calculated from rhesus monkey biodistribution data.

Radioactivity distribution

Two male rhesus monkeys (14.0 and 11.3 kg) underwent whole-body PET scans after intravenous injection of 8.2 and 8.4 mCi of [^{11}C]SD5024, respectively. 2D dynamic scans were acquired on the GE Advance tomography (GE Medical Systems, WI) in 5 or 4 segments of the body (head to upper thigh) in frames of increasing duration (15 s to 4 min) for a total scan time of up to 114 minutes.

Image analysis was done placing regions of interest on the dynamic 3D tomographic images. Regions were drawn in source organs that could be identified: brain, heart, lungs, liver, spleen, kidneys, and lumbar vertebrae. Large regions were placed to assure that all accumulated radioactivity in each organ was encompassed. Some of the source organs were not confined to a single bed position. In these cases, we used the time points of the bed position in which the organ was primarily included. Image analysis was done using PMOD 3.16.

Since the images did not include the body below mid-thigh, organ uptake was corrected for this recovery. The mean recovery of activity in the body above the thigh measured by PET was 87.6% of the injected activity measured by a dose calibrator. Total activity in the body measured by PET was used as injected activity for each scan.

Calculating Residence Times

At each time point, non-decay-corrected data of identified organs were converted to the fraction of the injected dose by dividing the organ activities by the recovered injected activity. Time-activity curves for the source organs are shown in Figures 1 to 3 (curves are decay-corrected for time of injection). The area under the curve of each organ was calculated by the trapezoidal method up to the termination of acquisition (up to 114 min). The area under the curve after the acquisition of the last image, i.e., to infinity, was

calculated by assuming that the decline in radioactivity after this time point occurred by only physical decay, without any further biological clearance. The area under the curve of the fraction of measured injected activity from time zero to infinity is equivalent to the residence time.

The residence time of all red marrow in the body was estimated from that of lumbar vertebrae. Small portion of radioactivity in lumbar vertebrae may have come from bone but not from red marrow. To estimate radiation-absorbed doses in a conservative way, we assigned all radioactivity of lumbar vertebrae to red marrow. Because the mass of red marrow in lumbar vertebrae is 17% of the mass of all red marrow in the body (Taketa 1970), residence time of red marrow in the entire body was calculated by multiplying that of lumbar vertebrae by 100/17.

The residence times from the monkeys were converted into corresponding human values by multiplication with a factor to scale organ and body weights: $(b_m/o_m) \times (o_h/b_h)$, where b_m and b_h are the body weights of monkey and human, respectively; and o_m and o_h are the organ weights of monkey and human, respectively (Appendix D). For total red marrow, the scaling factor of reminder of the body was used because its organ weight has not been found in publications.

The residence times for all of the source organs were summed and subtracted from the fixed theoretical value of $T_{1/2} / \ln 2 = 0.49$ to calculate the residence time of remainder of in the body. Table 1 lists the individual and mean residence times estimated for humans for each of the source organs and remainder in the body, as collected from the three monkeys.

Estimation of human absorbed radiation dose

The radiation absorbed doses were calculated by entering the mean residence times for each source organ into OLINDA 1.1 computer program using the model for a 70-kg adult male (Appendix A).

Results

Intravenous injection of [¹¹C]SD5024 caused no significant changes in ECG, heart, or respiration rates from baseline values. [¹¹C]SD5024 appears to be excreted mainly through bile in monkey, as we could not detect activity in the urinary bladder at the last time frame.

The brain, heart, lungs, liver, spleen, kidneys, and lumbar vertebrae were identified on the images (Appendix B). The liver had the highest uptake of [¹¹C]SD5024 with 49 and39% injected activity at about 7 and 10 min post-injection, respectively. The

brain, lungs, and spleen also exhibited relatively high uptake of radioactivity with respective peak values of about 5, 4, and 4% injected activity, respectively, while the heart, kidney and lumbar vertebrae had relatively low uptakes of radioactivity except for in blood flow phase. On the other hand, urinary bladder and small intestine did not show significant radioactivity uptake throughout the length of the scan (Figures 1-7).

The residence times for the two animals are shown in Table 1. Radiation absorbed dose estimates were calculated from mean residence times using OLINDA computer program (Appendix C). Radiation absorbed doses (μSv/MBq) calculated by the MIRD scheme were highest in spleen (62.4), liver (33.2), and kidneys (19.3). The effective dose was 5.9 μSv/MBq (Table 2).

References

Donohue SR, Pike VW, Finnema SJ, et al. Discovery and labeling of high-affinity 3,4-diarylpyrazolines as candidate radioligands for in vivo imaging of cannabinoid subtype-1 (CB1) receptors. *J Med Chem.* 2008;51:5608-5616.

Taketa ST, AL Carsten, SH Cohn, HL Atkins and VP Bond. Active bone marrow distribution in the monkey. *Life Sci*. 1970;9:169-174.

Table 1. Estimated human residence times for [^{11}C]SD5024 extrapolated from two rhesus monkeys calculated from whole-body images.

Organs	Residence time (h)		
	Monkey 1	Monkey 2	AVERAGE ± SD
Brain	0.0334	0.0293	0.031 ± 0.003
Lung	0.0481	0.0382	0.044 ± 0.007
Heart	0.0143	0.0273	0.021 ± 0.007
Liver	0.1738	0.2141	0.194 ± 0.028
Spleen	0.0385	0.0448	0.042 ± 0.004
Kidney	0.0210	0.0167	0.019 ± 0.003
Total red marrow	0.0240	0.0186	0.021 ± 0.004
Reminder of the body	0.1372	0.1011	0.119 ± 0.026

Table 2. Radiation dosimetry estimates for [^{11}C]SD5024 in human extrapolated from the mean of the two monkeys

Target Organ	Radiation dose	
	(μSv/MBq)	(mrem/mCi)
Adrenals	3.9	14.5
Brain	7.3	26.9
Breasts	1.2	4.5
Gallbladder wall	5.1	18.8
Lower large intestine wall	0.7	2.5
Small Intestine	1.3	4.9
Stomach wall	2.3	8.5
Upper large intestine wall	1.6	6.1
Heart wall	8.9	32.9
Kidneys	19.3	71.3
Liver	33.2	122.5
Lungs	12.6	46.4
Muscle	1.1	4.1
Ovaries	0.8	3.0
Pancreas	4.3	15.8
Red marrow	3.5	12.9
Osteogenic cells	2.5	9.4
Skin	0.7	2.6
Spleen	62.4	230.5
Testes	0.4	1.3
Thymus	1.6	5.7
Thyroid	0.7	2.6
Urinary bladder wall	0.5	2.0
Uterus	0.7	2.7
Total body	2.6	9.5
Effective dose	5.9	21.9
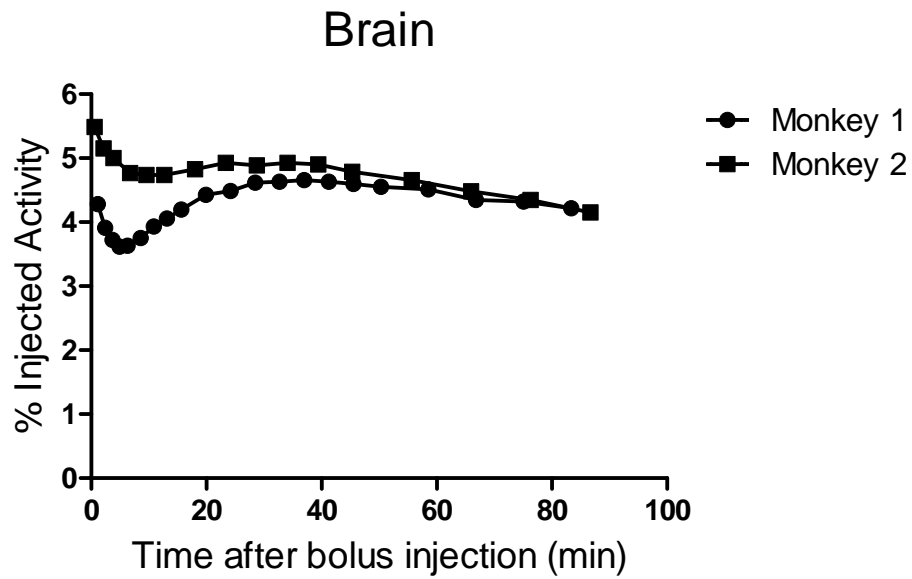
Brain

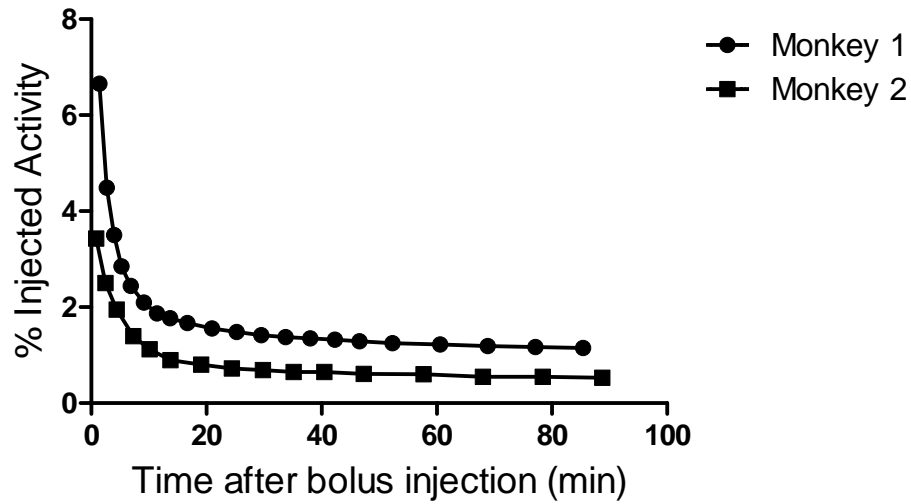

Figure 1. Time-activities curve for [^{11}C]SD5024 as determined by PET imaging of the brain. Data are corrected for radioactive decay.

Lungs
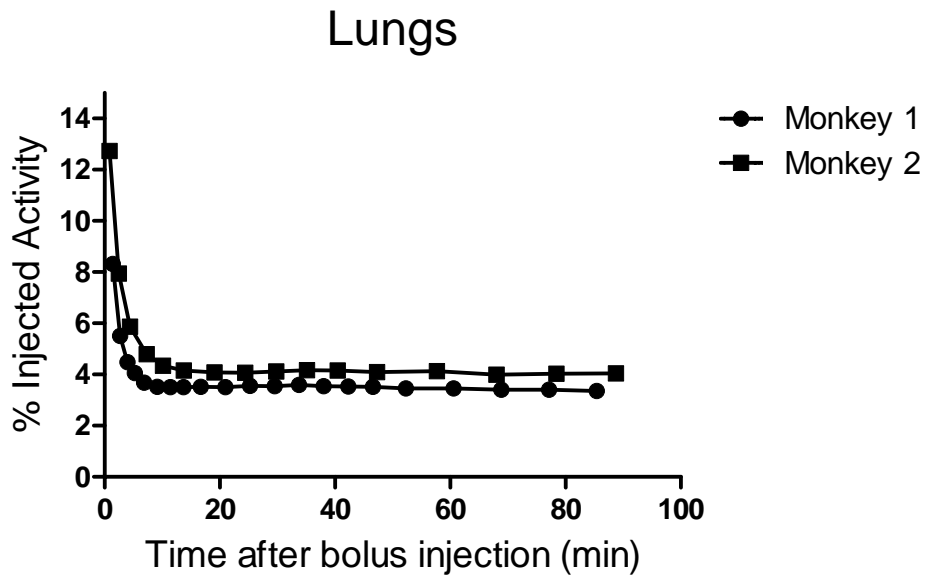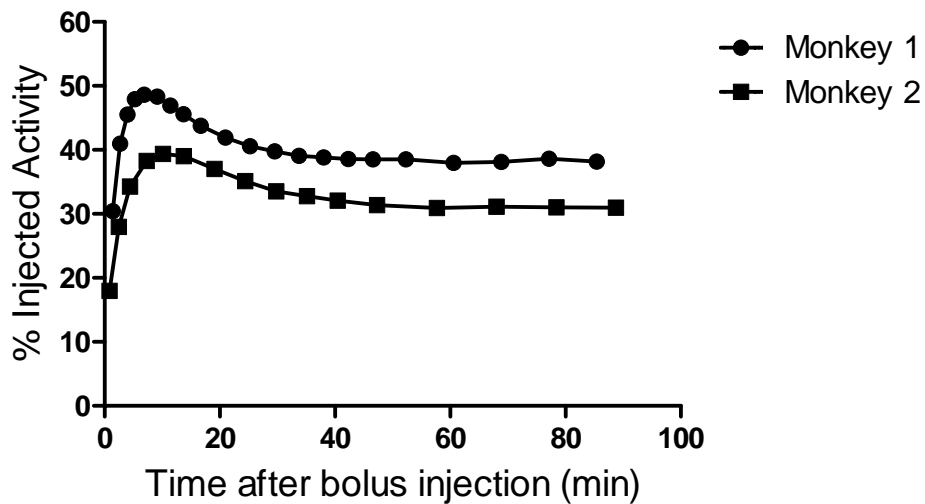

Figure 2. Time-activities curve for [^{11}C]SD5024 as determined by PET imaging of the lung. Data are corrected for radioactive decay.
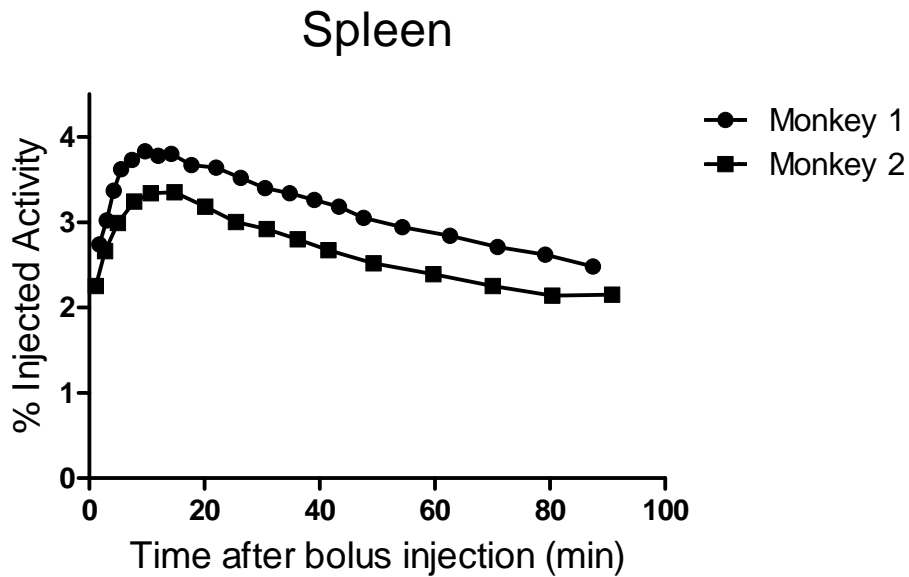
Heart

Figure 3. Time-activities curve for $[^{11}C]SD5024$ as determined by PET imaging of the heart. Data are corrected for radioactive decay.

Liver
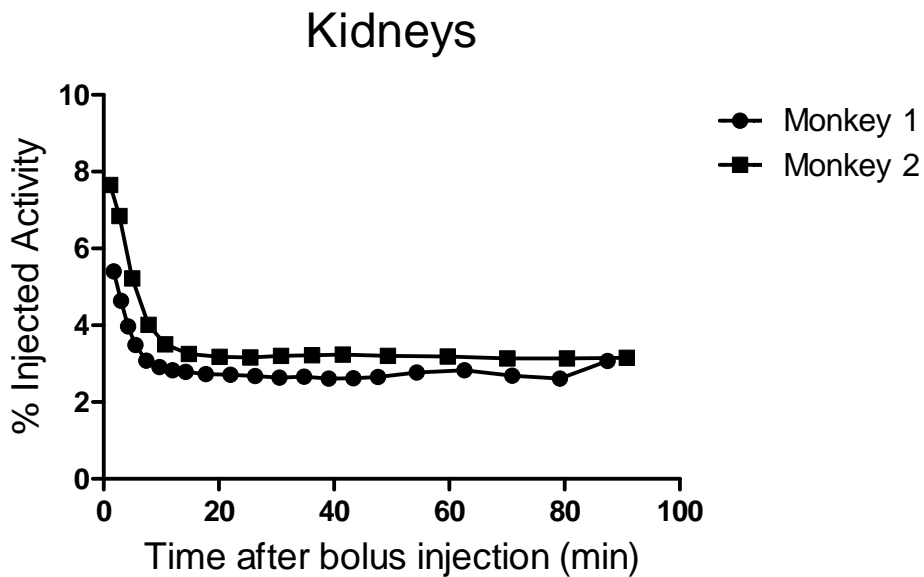

Figure 4. Time-activities curve for $[^{11}C]SD5024$ as determined by PET imaging of the liver. Data are corrected for radioactive decay.
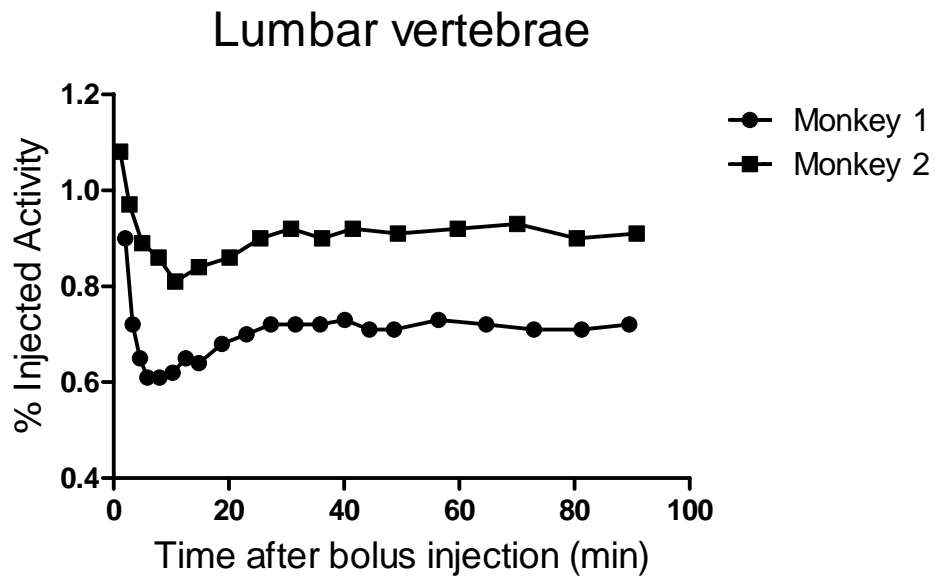
Figure 5. Time-activities curve for [^{11}C]SD5024 as determined by PET imaging of the spleen. Data are corrected for radioactive decay.

Figure 6. Time-activities curve for [^{11}C]SD5024 as determined by PET imaging of the kidneys. Data are corrected for radioactive decay.

Figure 7. Time-activities curve for [^{11}C]SD5024 as determined by PET imaging of the lumbar vertebrae. Data are corrected for radioactive decay.

Appendix A

Entry of residence times into OLINDA.

Appendix B

Whole-body images demonstrating biodistribution of $[^{11}C]SD5024$ in monkey 2 at 3, 20, and 90 min after radioligand injection.

3min	**20min**	**90min**
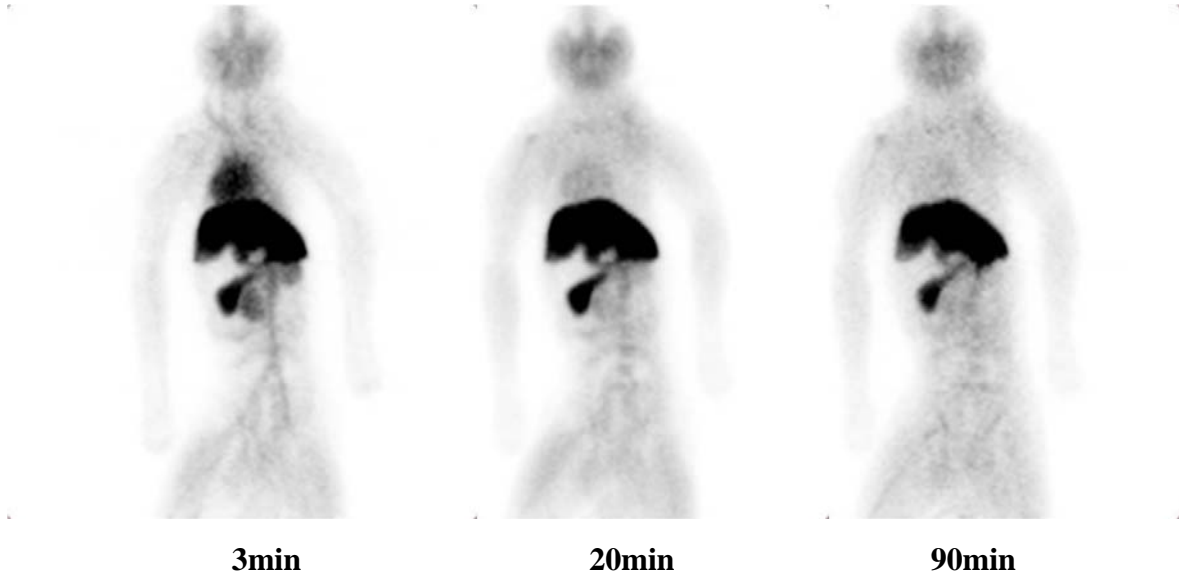
Appendix C

OLINDA - Organ Level INternal Dose Assessment Code (Version 1.1, copyright Vanderbilt University, 2007)

NOTE: This code gives doses for stylized models of average individuals -

results should be applied with caution to specific human subjects.

NOTE: Users should always carefully check input data (shown below) and

critically review the reported results.

Organ Doses (mSv/MBq), Nuclide: C-11 (1.22E03 sec), Adult Male

Calculated: 03.24.2011 at 04:10:05 EDT

Target Organ	Alpha	Beta	Photon	Total	EDE Cont.	ED Cont.
Adrenals	0.00E+00	3.04E-04	4.12E-03	4.42E-03	0.00E+00	1.11E-05
Brain	0.00E+00	4.58E-03	2.26E-03	6.84E-03	4.10E-04	1.71E-05
Breasts	0.00E+00	3.04E-04	1.23E-03	1.54E-03	2.31E-04	7.69E-05
Gallbladder Wall	0.00E+00	3.04E-04	5.53E-03	5.83E-03	0.00E+00	0.00E+00
LLI Wall	0.00E+00	3.04E-04	7.15E-04	1.02E-03	0.00E+00	1.22E-04
Small Intestine	0.00E+00	3.04E-04	1.42E-03	1.72E-03	0.00E+00	4.31E-06
Stomach Wall	0.00E+00	3.04E-04	2.47E-03	2.77E-03	0.00E+00	3.32E-04
ULI Wall	0.00E+00	3.04E-04	1.76E-03	2.07E-03	0.00E+00	5.17E-06
Heart Wall	0.00E+00	6.97E-03	4.34E-03	1.13E-02	6.79E-04	0.00E+00
Kidneys	0.00E+00	1.23E-02	5.36E-03	1.77E-02	1.06E-03	4.42E-05
Liver	0.00E+00	2.49E-02	1.18E-02	3.66E-02	2.20E-03	1.83E-03
Lungs	0.00E+00	8.47E-03	3.11E-03	1.16E-02	1.39E-03	1.39E-03
Muscle	0.00E+00	3.04E-04	1.15E-03	1.46E-03	0.00E+00	3.64E-06
Ovaries	0.00E+00	3.04E-04	8.77E-04	1.18E-03	2.95E-04	2.36E-04
Pancreas	0.00E+00	3.04E-04	4.56E-03	4.86E-03	0.00E+00	1.22E-05
Red Marrow	0.00E+00	1.91E-03	1.60E-03	3.51E-03	4.22E-04	4.22E-04
Osteogenic Cells	0.00E+00	1.58E-03	1.25E-03	2.83E-03	8.49E-05	2.83E-05
Skin	0.00E+00	3.04E-04	6.76E-04	9.80E-04	0.00E+00	9.80E-06
Spleen	0.00E+00	5.40E-02	1.31E-02	6.71E-02	4.03E-03	1.68E-03
Testes	0.00E+00	3.04E-04	3.67E-04	6.71E-04	0.00E+00	0.00E+00
Thymus	0.00E+00	3.04E-04	1.68E-03	1.99E-03	0.00E+00	4.96E-06
Thyroid	0.00E+00	3.04E-04	7.09E-04	1.01E-03	3.04E-05	5.06E-05
Urinary Bladder Wall	0.00E+00	3.04E-04	6.02E-04	9.06E-04	0.00E+00	4.53E-05
Uterus	0.00E+00	3.04E-04	8.09E-04	1.11E-03	0.00E+00	2.78E-06
Total Body	0.00E+00	1.42E-03	1.52E-03	2.94E-03	0.00E+00	0.00E+00

Effective Dose Equivalent (mSv/MBq)	1.08E-02
Effective Dose (mSv/MBq)	6.33E-03

Organ Doses (rem/mCi), Nuclide: C-11 (1.22E03 sec), Adult Male

Calculated: 03.24.2011 at 04:10:05 EDT

Target Organ	Alpha	Beta	Photon	Total	EDE Cont.	ED Cont.
Adrenals	0.00E+00	1.13E-03	1.52E-02	1.64E-02	0.00E+00	4.09E-05
Brain	0.00E+00	1.69E-02	8.36E-03	2.53E-02	1.52E-03	6.32E-05
Breasts	0.00E+00	1.13E-03	4.56E-03	5.69E-03	8.53E-04	2.84E-04
Gallbladder Wall	0.00E+00	1.13E-03	2.05E-02	2.16E-02	0.00E+00	0.00E+00
LLI Wall	0.00E+00	1.13E-03	2.64E-03	3.77E-03	0.00E+00	4.53E-04
Small Intestine	0.00E+00	1.13E-03	5.25E-03	6.38E-03	0.00E+00	1.59E-05
Stomach Wall	0.00E+00	1.13E-03	9.12E-03	1.02E-02	0.00E+00	1.23E-03
ULI Wall	0.00E+00	1.13E-03	6.53E-03	7.65E-03	0.00E+00	1.91E-05
Heart Wall	0.00E+00	2.58E-02	1.61E-02	4.19E-02	2.51E-03	0.00E+00
Kidneys	0.00E+00	4.56E-02	1.98E-02	6.55E-02	3.93E-03	1.64E-04
Liver	0.00E+00	9.20E-02	4.35E-02	1.35E-01	8.13E-03	6.77E-03
Lungs	0.00E+00	3.14E-02	1.15E-02	4.29E-02	5.15E-03	5.15E-03
Muscle	0.00E+00	1.13E-03	4.26E-03	5.38E-03	0.00E+00	1.35E-05
Ovaries	0.00E+00	1.13E-03	3.25E-03	4.37E-03	1.09E-03	8.74E-04
Pancreas	0.00E+00	1.13E-03	1.69E-02	1.80E-02	0.00E+00	4.50E-05
Red Marrow	0.00E+00	7.07E-03	5.94E-03	1.30E-02	1.56E-03	1.56E-03
Osteogenic Cells	0.00E+00	5.84E-03	4.64E-03	1.05E-02	3.14E-04	1.05E-04
Skin	0.00E+00	1.13E-03	2.50E-03	3.63E-03	0.00E+00	3.63E-05
Spleen	0.00E+00	2.00E-01	4.86E-02	2.48E-01	1.49E-02	6.21E-03
Testes	0.00E+00	1.13E-03	1.36E-03	2.48E-03	0.00E+00	0.00E+00
Thymus	0.00E+00	1.13E-03	6.22E-03	7.35E-03	0.00E+00	1.84E-05
Thyroid	0.00E+00	1.13E-03	2.62E-03	3.75E-03	1.12E-04	1.87E-04
Urinary Bladder Wall	0.00E+00	1.13E-03	2.23E-03	3.35E-03	0.00E+00	1.68E-04
Uterus	0.00E+00	1.13E-03	2.99E-03	4.12E-03	0.00E+00	1.03E-05
Total Body	0.00E+00	5.26E-03	5.62E-03	1.09E-02	0.00E+00	0.00E+00

Effective Dose Equivalent (rem/mCi)	4.01E-02
Effective Dose (rem/mCi)	2.34E-02

Number of Disintegrations in Source Organs:

Adrenals	0.00E+00	MBq-h/MBq or uCi-h/uCi
Brain	2.93E-02	MBq-h/MBq or uCi-h/uCi
Breasts	0.00E+00	MBq-h/MBq or uCi-h/uCi
Gallbladder Contents	0.00E+00	MBq-h/MBq or uCi-h/uCi
LLI	0.00E+00	MBq-h/MBq or uCi-h/uCi
Small Intestine	0.00E+00	MBq-h/MBq or uCi-h/uCi

Stomach	0.00E+00	MBq-h/MBq or uCi-h/uCi
ULI	0.00E+00	MBq-h/MBq or uCi-h/uCi
Heart Contents	2.73E-02	MBq-h/MBq or uCi-h/uCi
Heart Wall	0.00E+00	MBq-h/MBq or uCi-h/uCi
Kidneys	1.67E-02	MBq-h/MBq or uCi-h/uCi
Liver	2.14E-01	MBq-h/MBq or uCi-h/uCi
Lungs	3.82E-02	MBq-h/MBq or uCi-h/uCi
Muscle	0.00E+00	MBq-h/MBq or uCi-h/uCi
Ovaries	0.00E+00	MBq-h/MBq or uCi-h/uCi
Pancreas	0.00E+00	MBq-h/MBq or uCi-h/uCi
Red Marrow	1.86E-02	MBq-h/MBq or uCi-h/uCi
Cortical Bone	0.00E+00	MBq-h/MBq or uCi-h/uCi
Trabecular Bone	0.00E+00	MBq-h/MBq or uCi-h/uCi
Spleen	4.48E-02	MBq-h/MBq or uCi-h/uCi
Testes	0.00E+00	MBq-h/MBq or uCi-h/uCi
Thymus	0.00E+00	MBq-h/MBq or uCi-h/uCi
Thyroid	0.00E+00	MBq-h/MBq or uCi-h/uCi
Urinary Bladder Contents	0.00E+00	MBq-h/MBq or uCi-h/uCi
Uterus/Uterine Wall	0.00E+00	MBq-h/MBq or uCi-h/uCi
Remainder	1.01E-01	MBq-h/MBq or uCi-h/uCi

Target Organ Masses:

Adrenals	1.63E001 g
Brain	1.42E003 g
Breasts	3.51E002 g
Gallbladder Wall	1.05E001 g
LLI Wall	1.67E002 g
Small Intestine	6.77E002 g
Stomach Wall	1.58E002 g
ULI Wall	2.20E002 g
Heart Wall	3.16E002 g
Kidneys	2.99E002 g
Liver	1.91E003 g
Lungs	1.00E003 g
Muscle	2.80E004 g
Ovaries	8.71E000 g
Pancreas	9.43E001 g
Red Marrow	1.12E003 g
Osteogenic Cells	1.20E002 g
Skin	3.01E003 g
Spleen	1.83E002 g
Testes	3.91E001 g
Thymus	2.09E001 g

Thyroid	2.07E001 g
Urinary Bladder Wall	4.76E001 g
Uterus	7.90E001 g
Total Body	7.37E004 g

* Mass modified by user

Radiation Weighting Factors:

Alpha:	5.00E+00
Beta:	1.00E+00
Photon:	1.00E+00

** Weighting factor modified by user

Appendix D

Percentage of body weight for organs and their associated scaling factors

Organ	% of Total Body Weight		Scaling Factor
	Monkey	**Human**[3]	$(b_m/o_m) \times (o_h/b_h)$
Brain[1]	1.4%	2.0%	1.410
Heart Wall (with blood)[1]	0.4%	1.2%	2.596
Lung (with blood)[1]	0.8%	1.6%	1.961
Liver[1]	2.3%	2.5%	1.053
Gallbladder[*]	< 0.1%	< 0.1%	0.979
Spleen[1]	0.1%	0.2%	2.751
Kidney[1]	0.4%	0.4%	1.088
Cortical Bone[2]	2.9%	6.0%	2.067
Trabecular Bone[2]	1.0%	1.5%	1.485
Small Intestine[1,†]	2.3%	0.9%	0.390
Upper Large Instestine[1,†]	0.5%	0.2%	0.390
Lower Large Intestine[1,†]	0.5%	0.2%	0.390
Urinary Bladder[‡]	0.1%	0.1%	1.000
Remainder of body	84.9%	78.2%	0.921

[*]Gallbladder estimated from proportion of gallbladder/(liver plus gallbladder) in human, as gallbladder weight was recorded together with liver in monkey

[†]Proportions for small intestine, upper large intestine, and lower large intestine taken from human, since only total intestine weight was reported for monkey

[‡]Urinary bladder is not available for monkey; equal proportion was assumed

1. Bourne GH (1975) The Rhesus Monkey. Academic Press, Academic Press.

2. Gong, JK (1971) Volumetric Composition of the Monkey Skeleton. Anatomical Record, *172:* 543-550.

3. International Commission on Radiological Protection (ICRP), Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values, ICRP Publication 89, Ann. ICRP, 32(3-4) 2002.