Animal Biodistribution and Dosimetry

Human radiation dosimetry estimates were calculated by standard MIRD methodology from animal biodistribution data obtained by standard organ dissection methods. Animal biodistribution data were obtained using male and female C57 Balb/c (40 males, 40 females) mice injected with 9 μCi/100 μL of ^{131}I-PGN650 divided in 8 groups of 5 animals each. The average mouse weight was 20.4 g and the average age was 6-7 weeks. Animals were euthanized and organs were harvested in groups of five at the following time points: 1, 4, 12, 24, 48, 72, 96 and 120 hr post injection. The female animals were dissected at 1, 4, 12, and 24 hr to extract the female reproductive organs. Those data were combined with the male biodistribution data. The following organs were harvested, weighed and counted for radioactivity in a gamma well counter: blood, lungs, liver, spleen, kidneys, bladder, muscle, heart, brain, bones, red marrow, testes, adrenals, thyroid, pancreas, uterus, ovaries, stomach, small intestine, upper and lower large intestines. A separate group of animals were maintained in metabolic cages; there urine and feces were collected, weighed and counted for radioactivity. The biodistribution data are presented in Tables 1 and 2 for male and female Balb/c mice, respectively.

Based on these animal biodistribution data, the residence times (in hr) for each harvested organ were calculated by numerical integration of the time activity data expressed in percent injected dose per gram of tissue. It was assumed that no biological excretion occur beyond the last measured time point and that radioactivity only decreased thereafter as a result of physical decay. The animal organ residence times were then scaled to human organ weight by the "relative organ mass scaling" method. Organ residence times are presented in Table 3.

Except for the blood, the largest residence times were observed in muscle, bone and fat. The internal organ showing the largest accumulation is the liver. The residence time in the blood is high at 13 hr (10 hr in females) reflecting the relatively slow clearance of the activity from the blood. The blood clearance half-life was measured at 13.3 hr while the whole-body clearance (biological, established from a mono-exponential fit on the sum of all percent injected dose per organ plotted over time) half-life was measured at 15.1 hr using mono-exponential models (see Figure 1). This corresponds to an effective whole-body clearance half-life of 13.1 hr when accounting for physical decay.

The cumulative activities in urine and feces (in percent injected dose) were plotted as a function of time, and an uptake function was fitted to the data [$F(t) = A_0 (1-\exp(-A_1 t))$], see Figure 2. Analytical integration of excreted feces data, accounting for radioactive decay, yielded an excreted residence time of 1.67 ± 0.10 hr in the feces. Analytical integration of the excreted urine data resulted in a urine residence time of 95.8 hr. The urinary bladder filling fraction of 79% and the filling half-life of 19.25 hr ($=\ln(2)/0.036 hr^{-1}$) was used in the MIRD voiding model along with a voiding interval of 2 hr to yield a bladder residence time of 0.67 hr, and a modeled amount of activity excreted in urine of 95.1 hr. The residence time of excreted activity is therefore equal to 96.8 hr or 67% in terms of total-activity residence time.

Table 1. Male Balb/C mice biodistribution data for ^{131}I-131 PGN650

	1 hr	6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr
Blood	45.99 ± 3.78	34.68 ± 4.10	27.65 ± 2.78	11.34 ± 0.58	3.62 ± 0.86	0.58 ± 0.11	0.22 ± 0.09	0.18 ± 0.05
Lung	12.78 ± 1.48	8.34 ± 1.50	9.06 ± 1.29	4.09 ± 0.34	1.51 ± 0.44	0.22 ± 0.05	0.11 ± 0.04	0.17 ± 0.20
Liver	7.84 ± 0.99	7.80 ± 0.94	5.72 ± 0.71	2.06 ± 0.08	0.85 ± 0.18	0.12 ± 0.02	0.06 ± 0.02	0.14 ± 0.17
Spleen	6.59 ± 0.70	6.13 ± 1.51	5.74 ± 0.79	2.42 ± 0.12	0.90 ± 0.27	0.15 ± 0.04	0.07 ± 0.02	0.08 ± 0.01
Kidney	10.90 ± 0.87	9.33 ± 1.54	7.04 ± 0.86	3.35 ± 0.18	1.20 ± 0.29	0.25 ± 0.04	0.12 ± 0.04	0.12 ± 0.03
Bladder	4.10 ± 2.61	9.84 ± 7.53	31.91 ± 11.90	4.42 ± 2.39	1.34 ± 0.41	0.60 ± 0.35	0.29 ± 0.26	0.13 ± 0.05
Muscle	1.25 ± 0.12	1.64 ± 0.08	1.44 ± 0.24	0.84 ± 0.08	0.36 ± 0.17	0.07 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Heart	2.66 ± 1.40	1.83 ± 0.19	1.86 ± 0.17	0.94 ± 0.12	0.31 ± 0.10	0.10 ± 0.02	0.04 ± 0.01	0.03 ± 0.02
Brain	11.82 ± 6.08	9.28 ± 5.47	7.28 ± 1.69	3.16 ± 0.26	0.99 ± 0.28	0.16 ± 0.04	0.08 ± 0.03	0.06 ± 0.02
Bone	1.66 ± 0.49	1.15 ± 0.19	0.89 ± 0.34	0.51 ± 0.20	0.13 ± 0.05	0.02 ± 0.01	0.01 ± 0.00	0.01 ± 0.00
Marrow	5.06 ± 0.46	3.78 ± 1.10	3.18 ± 0.35	1.47 ± 0.15	0.55 ± 0.08	0.09 ± 0.02	0.05 ± 0.02	0.06 ± 0.02
Testes	7.03 ± 1.84	4.62 ± 1.43	4.33 ± 0.95	2.04 ± 0.62	0.63 ± 0.19	0.08 ± 0.18	0.07 ± 0.06	0.75 ± 3.14
Adrenals	1.88 ± 0.29	3.05 ± 0.42	2.59 ± 0.47	1.13 ± 0.12	0.45 ± 0.18	0.06 ± 0.02	0.03 ± 0.01	0.03 ± 0.01
Thyroid	1.70 ± 0.77	2.75 ± 1.23	3.75 ± 1.75	1.46 ± 0.34	0.57 ± 0.15	0.16 ± 0.06	0.04 ± 0.05	0.06 ± 0.03
Pancreas	10.10 ± 2.13	7.33 ± 2.56	5.66 ± 0.96	2.34 ± 0.48	0.99 ± 0.38	0.12 ± 0.06	0.06 ± 0.04	0.05 ± 0.02
Thymus	9.26 ± 4.36	7.75 ± 2.04	7.37 ± 2.70	3.33 ± 0.80	2.65 ± 2.61	0.47 ± 0.14	0.18 ± 0.07	3.89 ± 4.33
Stomach	2.46 ± 0.51	2.61 ± 0.97	2.50 ± 0.30	1.31 ± 0.12	0.46 ± 0.08	0.07 ± 0.02	0.03 ± 0.01	0.04 ± 0.02
Small intestine	2.30 ± 0.42	5.17 ± 2.54	3.33 ± 0.67	1.54 ± 0.32	1.28 ± 0.52	0.12 ± 0.04	0.04 ± 0.03	0.10 ± 0.03
Upper large intestine	2.72 ± 0.32	3.05 ± 0.82	2.29 ± 0.41	1.09 ± 0.12	0.52 ± 0.11	0.07 ± 0.01	0.02 ± 0.01	0.04 ± 0.01
Lower large intestine	2.24 ± 0.46	2.95 ± 0.59	2.07 ± 0.34	0.93 ± 0.07	0.47 ± 0.04	0.06 ± 0.01	0.02 ± 0.01	0.04 ± 0.01

Table 2. Biodistribution of ^{131}I-131 PGN650 in C57 female mice expressed in percent injected dose per gram of tissue (%ID/g) for the uterus and ovaries.

Organ	1 hr	4 hr	12 hr	24 hr
Uterus	4.32 ± 2.24	6.38 ± 1.62	5.54 ± 1.13	2.15 ± 0.37
Ovaries	4.60 ± 0.67	5.14 ± 0.76	3.76 ± 0.59	1.92 ± 0.41

Figure 1. Whole-body and blood activity retention from the decay-corrected percent of injected activity per organ in all measured organs and in the blood. Curves represent a fit from a mono-exponential function from which the biological half-life was extracted.

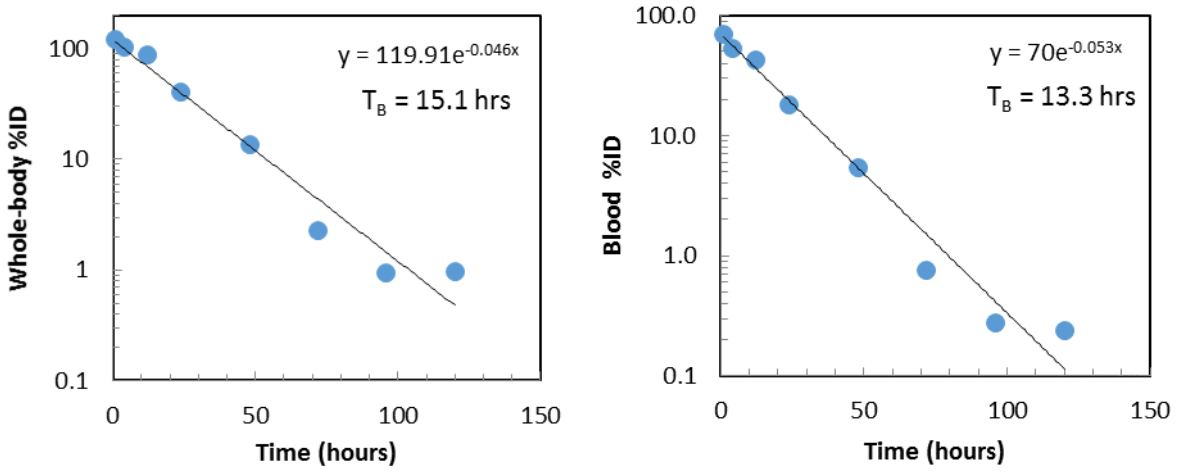

Figure 2. Cumulative time activity curves in the excreted urine and feces.

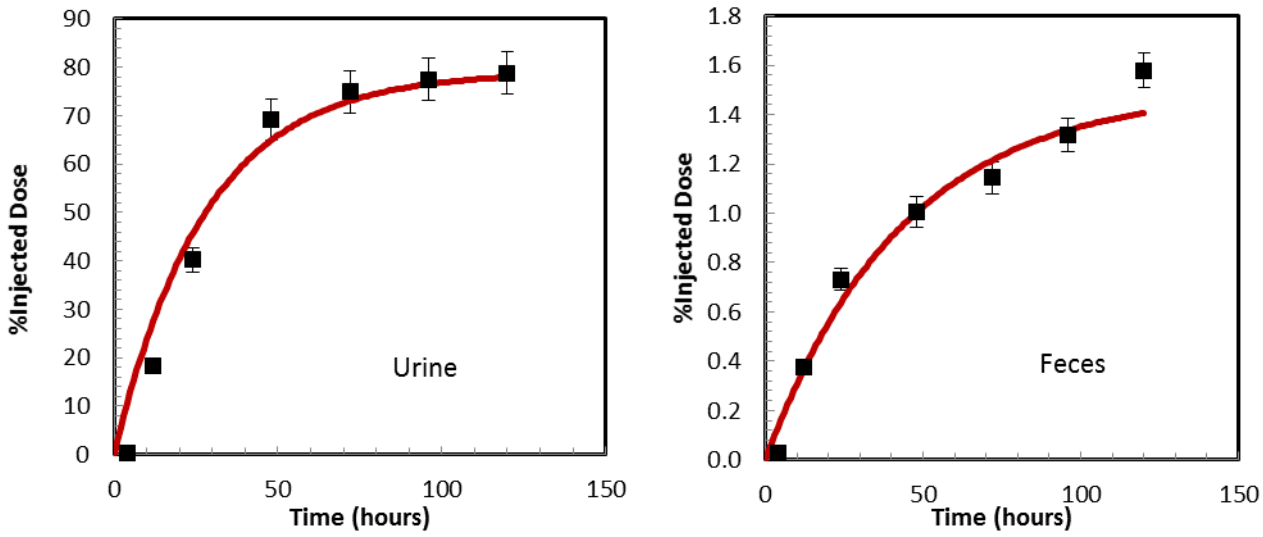

Table 3. Organ residence times extrapolated to human organs expressed in hours.

Organ	Residence Time (hr) in human males	Residence Time (hr) in human females
Blood	13.3 ± 1.8	10.3 ± 1.4
Lung	0.72 ± 0.17	0.58 ± 0.14
Liver(all)	0.89 ± 0.19	0.66 ± 0.14
Spleen	0.08 ± 0.02	0.07 ± 0.01
Kidney	0.18 ± 0.03	0.17 ± 0.03
Bladder	0.06 ± 0.03	0.05 ± 0.02
Muscle	3.60 ± 0.88	2.19 ± 0.54
Fat	1.13 ± 0.28	0.88 ± 0.22
Heart	0.19 ± 0.07	0.14 ± 0.05
Brain	0.11 ± 0.04	0.10 ± 0.04
Bone	3.03 ± 0.59	2.34 ± 0.46
Marrow	0.54 ± 0.79	0.62 ± 0.92
Testes	0.008 ± 0.002	
Prostate	0.009 ± 0.004	
Adrenals	0.008 ± 0.002	0.007 ± 0.002
Thyroid	0.029 ± 0.025	0.023 ± 0.020
Pancreas	0.019 ± 0.004	0.017 ± 0.004
Stomach	0.05 ± 0.02	0.005 ± 0.02
Small intestine	0.14 ± 0.03	0.12 ± 0.03
Upper large intestine	0.004 ± 0.008	0.036 ± 0.007
Lower large intestine	0.022 ± 0.005	0.021 ± 0.005
Uterus		0.035 ± 0.018
Ovaries		0.004 ± 0.002
Remainder of the body	33.4	16.6

Radiation Dosimetry

Radiation doses were calculated with the program OLINDA/EXM (Version 1.1) for ^{124}I using the residence times in Table 3 and the standard MIRD adult male and female models. The following additional assumptions were made: 5% of the blood residence time was assigned to the left ventricle; the bone activity was assigned in equal part to the cortical and trabecular bone source organs. Organ radiation dose estimates for the adult male and female models are presented in Table 4. The error bars on the dose estimates were assumed to be in proportion to the organ residence time uncertainties.

Table 4. Extrapolated human radiation dose estimates for ^{124}I-PGN650 per unit of administered activity. Radiation doses can be converted to the units of rad/mCi or rem/mCi by multiplying by 3.7.

Organ	**Dose (mGy/MBq)**	
	Males	**Females**
Adrenals	0.21	0.25
Brain	0.073	0.095
Breasts		0.23
Gallbladder wall	0.23	0.26
Lower large intestine wall	0.24	0.31
Small Intestine wall	0.27	0.28
Stomach wall	0.22	0.28
Upper large intestine wall	0.24	0.30
Heart muscle	0.37	0.37
Kidneys	0.22	0.52
Liver	0.19	0.22
Lungs	0.22	0.25
Muscle	0.15	0.18
Ovaries		0.25
Pancreas	0.18	0.21
Red marrow	0.25	0.28
Bones (osteogenic cells)	0.40	0.50
Skin	0.14	0.19
Spleen	0.19	0.22
Testes	0.20	
Thymus	0.21	0.28
Thyroid	0.31	0.32
Urinary bladder wall	0.49	0.59
Uterus		0.26
Total body	0.20	0.26
Effective Dose (mSv/MBq)	0.25	0.27
Effective Dose Equivalent (mSv/MBq)	0.29	0.27

The radiation doses above include contribution from beta and gamma rays emitted from ^{124}I, and include contribution from activity within one organ to itself, from neighboring organs and the remainder of the body. Because of the nature and energy of the beta particles, the self-organ dose contribution from the beta particles dominates the dose contributions. The largest radiation dose is observed in the heart wall with values of 0.37 mGy/MBq injected for males or females and urinary bladder wall at approximately 0.55 mSv/MBq. The effective dose is calculated at 0.29 mSv/MBq in males and 0.27 mSv/MBq in females.

Figure 3. Comparative radiation dosimetry between animal and humans. The radiation doses reported are in mSv/MBq, units of rem/mCi is obtained by multiplying the values by 3.7