

Michael G. Stabin

## Contents

3.1 Introduction .....	65
3.2 Radiation Dose Calculations .....	66
3.3 Biokinetic Analyses .....	66
3.4 Example Dose Calculations .....	71
3.5 The Pregnant or Lactating Patient .....	74
Conclusions .....	75
References .....	75

---

## Abstract

The basics of internal dosimetry in nuclear medicine are reviewed. The design and execution of medical imaging studies are explained, for animal and human studies. Animal data extrapolation and data analysis for human imaging data are given by example. Dose quantities are explained and, again, given by example. Standardized doses, for general cases and for the pregnant or lactating female, are given.

---

## 3.1 Introduction

The majority of PET pharmaceuticals are used in diagnostic imaging. Radiation dosimetry is generally not evaluated on a daily basis for individual patients, unless a misadministration occurs or if a pregnant or potentially pregnant patient is imaged (in which case the dose to the embryo/fetus may be of concern). In order to get any radiopharmaceutical approved, however, a complete treatment of dosimetry is an essential part of the approval process. Systems of radiation dose calculations have been standardized for many years and now are greatly facilitated by standardized computer resources. The difficult task in establishing the dosimetry of a new PET agent lies in gathering the biokinetic data to use

---

M.G. Stabin, PhD, CHP  
Department of Radiology and Radiological Sciences,  
Vanderbilt University, 1161 21st Avenue South,  
Nashville, TN 37232-2675, USA  
e-mail: [michael.g.stabin@vanderbilt.edu](mailto:michael.g.stabin@vanderbilt.edu)

in the dose calculations. Once these data are correctly gathered, the dose calculations may be performed in a matter of minutes using established computing resources. In this chapter, methods for designing and executing such studies will be outlined, some sample dose calculations will be shown, and dosimetry for a handful of PET agents will be provided.

### 3.2 Radiation Dose Calculations

The basic equation for calculating the radiation dose from one organ to another (or any organ to itself) is given as [1]

$$D_T = \frac{k \tilde{A}_s \sum_i n_i E_i \phi_i(T \leftarrow S)}{m_T}$$

where  $D_T$  = absorbed dose (Gy) in target organ  $T$   
 $\tilde{A}_s$  = the number of nuclear transitions in a source organ  $S$ , sometimes referred to as the “cumulated activity” (MBq-s)

$n_i$  = number of radiations with energy  $E_i$  emitted per nuclear transition

$E_i$  = energy per radiation (MeV)

$\phi_i f(T \leftarrow S)$  = fraction of energy emitted that is absorbed in target organ  $T$  from source organ  $S$  for radiation  $i$

$m_T$  = mass of target region (kg)

$k$  = a proportionality constant (e.g., Gy-kg/MBq-s-MeV)

The term  $\tilde{A}$  is the integral of the time-activity curve for a “source” organ, i.e., an organ that exhibits a significant uptake of the administered activity. As becquerel is the number of disintegrations per second that occur at a given time, the integral over time is Bq-s (MBq s was used above), which is the total number of disintegrations that occurred in the organ over the period of integration (almost always to infinite time). The activity at any given time is determined in the biokinetic analysis; data are obtained in animals or human subjects at specified times after administration of the radiopharmaceutical, and then these data are integrated over time to give  $\tilde{A}$ .

First, a review of how to obtain the biokinetic data will be provided, and later we will return to show some actual sample dose calculations.

### 3.3 Biokinetic Analyses

#### (i) Study design

Time-activity curves for most organs are usually characterized by one or more exponential terms, i.e.,  $A(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + \dots$ . The rate constants  $\lambda_1$  and  $\lambda_2$  describe the kinetics of removal of activity components  $A_1$  and  $A_2$ ; we can define half-times  $T_1$  and  $T_2$ , by  $\lambda = 0.693/T$ ; the half-time is the time needed for half of that component of activity to be removed from an organ. Each exponential term has two unknown variables; therefore, the time-activity curve has to have two data points for each phase of clearance for which we wish to define an exponential term. So, if a given time-activity curve is best characterized by two exponentials, an absolute minimum of four data points is needed to define the curve, with two points during each phase (i.e., not one during the first phase and three during the second). The starting point in a kinetic analysis is thus deciding on when to obtain samples, whether they are from a study involving animals or human subjects. For a completely new agent, this can obviously be a challenge, as the biokinetics are not yet known. An absolute limitation is the physical half-life of the radionuclide employed; F-18 has a half-life of 1.83 h, so data may be gathered over several hours after administration, but C-11 has a half-life of only 20 min, so data must be gathered much more quickly. Then, the biological clearance of the agent must be considered. The equation above with the exponential terms was not explicit, but the complete removal of activity from an organ or the body is due to both radioactive decay and biological clearance; this is characterized by a rate constant  $\lambda_c$ , an “effective rate constant,” which is the sum of the biological rate constant ( $\lambda_b$ ) and the physical rate

constant ( $\lambda_p$ ). Some agents are cleared very quickly, others more slowly. So the study must be planned to get the needed number of data points taking into account both physical and biological clearance. Often experience with other similar agents can be helpful, or the data points can be spaced out over the range of times possible over several physical half-lives of the radionuclide, with several early time points and several later time points. There is not an exact formula for guiding the selection process of sampling times; care must be taken to provide enough data before spending the time and money on gathering the data so that the data collection process will be successful and the experiments will not have to be repeated. In addition to activity levels in organs and the body, an essential element of a biokinetic analysis is evaluation of the excretion of activity from the body (via the urinary or intestinal pathway). It is not uncommon for excretory organs to receive the highest doses of any other organ in the body, as often 100% of the activity eventually passes through these organs (urinary bladder or intestines). For PET radiopharmaceuticals, excretion may be more limited than for other agents, due to their short physical half-lives. For C-11 compounds, for example, it is common to assume that there is no time for appreciable excretion from the body to occur, although activity might accumulate in the urinary bladder and decay there. So for studies using imaging data, if activity is seen in the urinary bladder, the activity levels may be quantified, and the activity may be integrated to get the number of disintegrations in the urinary bladder; collecting urine data is unlikely to provide any useful information. For F-18, it is common for there to be urinary excretion during the duration of the study, and the use of image data or urine collection may be helpful.

(ii) *Animal data*

Preclinical studies are required for any New Drug Application (NDA) to the US Food and Drug Administration (FDA). Most

research is done with some rodent species, but any animal species in theory is acceptable. Some have an inclination to use primate species, with the idea that they may produce results more similar to humans. Extrapolation of animal data to humans has produced misleading information in many cases, in most any animal species [2]. So, this is a necessary step in the process of evaluating the dosimetry of a new radiopharmaceutical, but one should bear in mind that the real dosimetry will not be known until well-designed and executed studies using human subjects are performed. Time-activity curves for radiopharmaceuticals using animals may be established by administering the radiopharmaceutical and either sacrificing the animals, extracting tissue samples, and performing a radioassay or by small animal imaging studies.

(a) *Tissue extraction* – using a minimum of three animals per time point, individual samples of organs and tissues may be extracted from the animals after sacrificed and counted in any radiation detector system (e.g., sodium iodide scintillation, liquid scintillation). Collection of urine and/or fecal samples via the use of “metabolic cages” may characterize the excretion of the agent. Extrapolating the organ/tissue data to humans is not an exact science. One may assume that the percent of the administered activity seen in any organ at a given time will likely be the same concentration seen in humans; one may say that this is a “direct extrapolation.” One may assume that the percent of administered activity per gram in an organ will be the same in humans; due to the normally considerable differences in body and organ masses, this is likely to produce erroneous results. Many have evaluated various extrapolation methods proposed in the literature. One method of extrapolating animal data

that has been applied by many is the % kg/g method [3]. In this method, the animal organ data need to be reported as % of injected activity per gram of

tissue, and this information plus knowledge of the animal whole body weight is employed in the following extrapolation:

$$\left( \frac{\%}{\text{organ}} \right)_{\text{human}} = \left[ \left( \frac{\%}{\text{g}_{\text{organ}}} \right)_{\text{animal}} \times (\text{kg}_{\text{TB weight}})_{\text{animal}} \right] \times \left( \frac{\text{g}_{\text{organ}}}{\text{kg}_{\text{TB weight}}} \right)_{\text{human}}$$

The percent uptake per gram of tissue is multiplied by the animal whole body weight in kg; the percent in any organ in humans is obtained by applying the corresponding organ and body masses of a reference adult human. A numerical example using this method was provided by Stabin [2] (Table 3.1):

The animal whole body weight was 20 g (0.02 kg), and the source organ chosen had a mass of around 299 g. The human total body weight for the standard adult male of 70 kg was then applied in the transformation. For example:

$$\frac{38.1 \%}{\text{g}} (\text{animal}) \times 0.020 \text{ kg} \times \frac{299 \text{ g}}{70 \text{ kg}} = \frac{3.26 \%}{\text{organ}} (\text{human})$$

The idea of this method is that the percent in an organ is weighted for the fraction of total body mass that the organ comprises. As noted above, this is not a “gold standard” method by any means; it is an attempt to perform a reasonable extrapolation that avoids some pitfalls in other methods. Some also suggest adding a scaling in time, to account for the different metabolic rates of species of different size:

$$t_h = t_a \left[ \frac{m_h}{m_a} \right]^{0.25}$$

where  $t_a$  is the time at which a measurement was made in an animal system,  $t_h$  is the

corresponding time assumed for the human data, and  $m_a$  and  $m_h$  are the total body masses of the animal species and of the human. Again from Stabin [2], Table 3.2 shows an example case with data extrapolated from an animal species to the human using this time scaling approach:

Here, a human body mass of 70 kg was used, and the animal whole body mass was assumed to be 200 g. Sparks and Aydogan [4] studied the success of animal data extrapolation for several radiopharmaceuticals, using direct extrapolation, and mass and/or time extrapolation. They found that no particular method was superior to any other and that, in many cases, extrapolated animal data significantly underestimated observed uptakes in human organs. So, in conclusion, choice of an animal species and extrapolation method are areas of freedom in designing an animal study, and results obtained from animal studies must be recognized as only preliminary estimates of the dosimetry for any radiopharmaceutical.

#### (b) Small animal imaging

Small animal imaging techniques have greatly improved the science of drug

**Table 3.1** Animal data extrapolation example (mass extrapolation)

Animal	Source organ				
	1 h	3 h	6 h	16 h	24 h
%ID/organ	3.79	3.55	2.82	1.02	0.585
(%ID/g)	38.1	36.6	30.8	11.3	5.70
Human					
%ID/organ	3.26	3.12	2.63	0.962	0.486

**Table 3.2** Animal data extrapolation example (time extrapolation)

Animal time scale	5 min	15 min	30 min	60 min	1.5 h
Extrapolated human time scale	22 min	1.1 h	2.2 h	4.3 h	6.5 h

development. It has also allowed the characterization of radiopharmaceutical dosimetry in living animals, eliminating the need to sacrifice them. A drawback, however, is that the animals generally need to be anesthetized for the imaging session. Anesthetics may alter the distribution of the radiopharmaceutical, leading to inaccurate evaluation of organ uptakes and subsequent dosimetric analyses. Quantitative analyses of organ uptake at any imaging time are the same as those from human imaging studies. PET images are inherently quantitative; counts in a given voxel are easily related to absolute values of activity. Drawing volumes of interest (VOIs) over recognized organ regions provides values of activity in the organ that can be related to percentages or fractions of the administered activity, which is always known. Thus time-activity curves can be readily (but not easily!) developed from the image data and integrated to obtain the time-activity integrals needed for development of dose estimates. Organ and whole body biokinetics, combined with analyses of excretion, will allow development of a complete dosimetric analysis.

(c) *Small animal dosimetry*

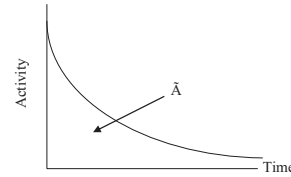
Some researchers have expressed interest in calculating dose to animal organs. As with the development of human dosimetry phantoms, to be discussed below, early efforts involved animal dosimetry phantoms comprised of geometric shapes to describe organs and progressed to more realistic, image-based voxel phantoms. Yoriyaz and Stabin [5] constructed a geometric model of the mouse and generated dose factors (DFs) for a selected number of

source and target pairs for  $^{213}\text{Bi}$  and  $^{90}\text{Y}$ . Muthuswamy et al. [6] developed a dosimetric model of mouse marrow and provided DFs for  $^{131}\text{I}$ ,  $^{186}\text{Re}$ , and  $^{90}\text{Y}$ . Konijnenberg et al. [7] developed a stylized representation of Wistar rats and performed Monte Carlo calculations to develop DFs for several radionuclides. With the advent of small animal imaging technologies, it became possible to move away from the use of stylized, equation-based body models and develop representations that more realistically define organ size, shape, and proximity. Kolbert et al. [8] used MR images of a female athymic mouse to develop realistic models of several organs and estimated self-dose and cross-dose values for these organs. Hindorf et al. [9] developed a model of a mouse using geometric shapes to define ten organs and then converted the model to a voxel format. Stabin et al. [10] segmented micro-CT images of a mouse and rat and developed specific absorbed fractions (SAFs) for photon and electron sources within the animal organs and DFs for several source and target regions. Keenan et al. [11] developed three mouse and five rat dosimetric models, using the MOBY and ROBY models developed by Segars and Tsui [12] and provided photon and electron absorbed fractions and dose factors for several radionuclides. These animal models have been incorporated into the OLINDA/EXM dosimetry code [13], thus facilitating dose calculations for these eight small animal types.

(iii) *Human data*

Imaging studies with either patients or healthy volunteers, required by the FDA

for new drug approval (strict dose limits for new drugs do not exist, but dosimetry must be presented and is usually compared to other similar agents), need to be done according to the same requirements for number and spacing of time points as described above. The two basic imaging methods are planar imaging and tomographic imaging. For PET radiopharmaceuticals, tomographic methods are by far the most common approach, so an extensive description of planar methods will not be presented here. Briefly, anterior and posterior images are taken, regions of interest (ROIs) are drawn over recognized organs, and corrections for attenuation and scatter should be made [2]. Relating counts in an ROI to absolute values of activity is usually not straightforward, unless calibration factors have been developed from phantom image analysis, which is not common. Usually counts in the total body at the earliest imaging time, corrected for radioactive decay, are used to define 100% of the administered activity, and counts in the body and organs at later times are related to this value. In tomographic images, as for animal studies, counts in voxels associated with an organ may be related to absolute values of activity via a calibration factor, and time-activity curves may be developed from this information. PET images are inherently quantitative, as PET analyses evaluate absolute levels of activity in organs and tumors (standardized uptake values, SUVs). In contrast, few centers practice quantitative analyses with single-photon emission computed tomography (SPECT); Dewaraja et al. [14] outlined the many steps required to obtain quantitative SPECT data for therapy dosimetry calculations, including choice of collimator, choice of energy windows, reconstruction methods, attenuation and scatter correction, dead time corrections, compensation for other image-degrading effects, choice of target regions, corrections for dose nonuniformities, and other aspects to be considered to obtain quanti-



**Fig. 3.1** Hypothetical time-Time abscissa curve

tative information in individual voxels used to define source and target regions.

(iv) *Kinetic analyses*

The result of the biokinetic analyses described above is a series of values of percent or fraction of administered activity over time (Fig. 3.1). Values of doses for individual organs rely on the integration of these values over time. The most common method for performing this integration is to fit a function comprised of one or more exponential terms to the data. One may also integrate the data “directly,” i.e., by a “trapezoidal” integration, simply directly calculating the area under the curve between any two time points and adding up the values. A drawback of this approach is that estimating the area under the curve after the last data point is complicated; various approaches include assuming only radioactive decay after the last point, using a straight line defined by the last two or three data points, and other approaches. When an exponential function is fit to the data, the time-activity integral is easily calculated. If the function is  $A(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$ , and the values of  $\lambda$  are effective rate constants (including both radioactive decay and biological removal), the integral of this function to infinite time is just  $A_1/\lambda_1 + A_2/\lambda_2$ . If values of  $A$  are in MBq and values of  $\lambda$  have units of  $s^{-1}$ , then the integral has units of MBq-s or millions of disintegrations. These integrals are often normalized to the amount of activity administered (MBq), so that doses are developed per unit administered activity. The units of this normalized integral are thus MBq-s/MBq. It is tempting to think of this as having units of time (here s), but this is not any measure of time.

### 3.4 Example Dose Calculations

#### (a) Organ doses

Data from a kinetic study yield the following parameters for a new compound tagged to  $^{18}\text{F}$  (the values of  $f$  are the fraction of administered activity observed with the noted half-times):

Liver	$f_1=0.35$	$T_{c1}=0.9\text{ h}$
	$f_2=0.15$	$T_{c2}=1.2\text{ h}$

Assuming a 1 MBq administration, the number of disintegrations would be

$$N = \frac{0.35\text{ MBq} \times 3600\text{ s h}^{-1}}{0.9\text{ h}^{-1}} + \frac{0.15\text{ MBq} \times 3600\text{ s h}^{-1}}{1.2\text{ h}^{-1}}$$

$$N = 1799\text{ MBq-s} = 1.8 \times 10^9\text{ disintegrations}$$

The dose factor from the liver to the liver for F-18 is  $3.4\text{E-}05\text{ mGy/MBq-s}$ ; the dose factor from the liver to the spleen is  $5.54\text{E-}7\text{ mGy/MBq-s}$ . So given this input data, the dose to the liver and the spleen would be  $1799\text{ MBq-s} \times 3.4\text{E-}05\text{ mGy/MBq-s} = 0.061\text{ mGy}$  and  $1799\text{ MBq-s} \times 5.54\text{E-}07\text{ mGy/MBq-s} = 0.001\text{ mGy}$ , respectively. There would be many more source and target organs to consider in a real problem, of course. The OLINDA/EXM software code [13] facilitated and standardized the calculation of radiation doses from radiopharmaceuticals. Available dose factors have been based for years on “stylized” anthropomorphic phantoms for adults, children, and pregnant women (e.g., [15, 16]), but are now replaced with realistic, image-based voxelized models [17]. Monte Carlo studies establish absorbed fractions for electrons and photons for defined organ pairs; dose factors are developed using decay data and defined organ masses, as described above.

#### (b) Effective dose

The International Commission on Radiological Protection [18], in the context

**Table 3.3** Weighting factors recommended by the ICRP for calculation of effective dose

Organ	ICRP 30 (1979)	ICRP 60 (1991)	ICRP 103 (2007)
Gonads	0.25	0.20	0.08
Red marrow	0.12	0.12	0.12
Colon		0.12	0.12
Lungs	0.12	0.12	0.12
Stomach		0.12	0.12
Bladder		0.05	0.04
Breasts	0.15	0.05	0.12
Liver		0.05	0.04
Esophagus		0.05	0.04
Thyroid	0.03	0.05	0.04
Skin		0.01	0.01
Bone surfaces	0.03	0.01	0.01
Brain			0.01
Salivary glands			0.01
Remainder	0.30	0.05	0.12

of radiation protection quantities and limits for radiation workers, defined a new dosimetry quantity, the “effective dose equivalent.” The ICRP subsequently renamed this quantity “effective dose” in 1991 [19], and new weighting factors were given again in ICRP Publication 103 [20]. Certain organs or organ systems were assigned dimensionless weighting factors (Table 3.3), which are assumed to relate to their differing radiosensitivity for expressing fatal cancers or genetic defects.

The assumed radiosensitivities were derived from the observed rates of expression of these effects in various populations exposed to radiation. Multiplying an organ’s dose equivalent by its assigned weighting factor gives a “weighted dose equivalent.” The sum of weighted dose equivalents for a given exposure to radiation is the effective dose:

$$E = \sum_T H_T \times w_T$$

An example calculation of the effective dose using the tissue weighting factors from ICRP

60 and assumed individual organ equivalent doses is shown here:

Organ	Weighting Factor	Equivalent Dose (mSv)	Weighted dose Equivalent (mSv)
Liver	0.05	0.59	0.0295
Kidneys	0.005	0.33	0.00165
Ovaries	0.20	0.25	0.050
Red marrow	0.12	0.42	0.0504
Bone surfaces	0.01	0.55	0.0055
Thyroid	0.05	0.15	0.0075
Total (effective dose)			0.145

The effective dose is meant to represent the equivalent dose that, if received uniformly by the whole body, would result in the same total risk as that actually incurred by a given actual nonuniform irradiation.

(c) *Standardized dose tables*

Dose tables for many PET radiopharmaceuticals have been generated by the OLINDA/EXM code [13]. Example tables are shown here (Tables 3.4 and 3.5):

(d) *Patient-individualized dosimetry in radiopharmaceutical therapy*

An extensive debate is ongoing regarding the role of patient-individualized dosimetry in therapeutic applications of radiopharmaceuticals. Stabin [21] addressed many of the objections raised by physicians and others to the use of dosimetry in radionuclide therapy, which is of course routine in external beam radiotherapy. Brans et al. [22] discussed the “quest for the ‘Holy Gray,’” strengths and weaknesses of current models, and methods related to the development of clinical radiopharmaceutical dosimetry for individual subjects and concluded that “...only prospective, randomised trials with adequate methodology can provide the evidence that applied clinical dosimetry results in better patient outcome than is achieved with fixed activity dosing methods.” Flux et al. [23] responded that “it is now time for a fundamental change in the way that radionuclide therapies are conducted. Individual treatment planning

**Table 3.4** Sample dose estimates for selected PET radiopharmaceuticals in adults (mSv/MBq administered)

Target organ	F-18 FDG <sup>a</sup>	F-18L-DOPA <sup>b</sup>	C-11 acetate
Adrenals	1.16E-02	9.36E-03	3.27E-03
Brain	3.68E-02	6.79E-03	9.61E-04
Breasts	8.26E-03	6.40E-03	1.21E-03
Gallbladder wall	1.25E-02	1.00E-02	3.47E-03
LLI wall	1.34E-02	1.71E-02	1.33E-03
Small intestine	1.17E-02	1.23E-02	1.78E-03
Stomach wall	1.07E-02	9.10E-03	2.01E-03
ULI wall	1.14E-02	1.14E-02	1.88E-03
Heart wall	6.74E-02	8.56E-03	1.26E-02
Kidneys	1.03E-02	2.42E-02	5.33E-02
Liver	2.05E-02	8.73E-03	1.35E-02
Lungs	1.93E-02	7.61E-03	1.67E-03
Muscle	9.73E-03	9.53E-03	1.38E-03
Ovaries	1.35E-02	1.67E-02	1.44E-03
Pancreas	1.12E-02	9.73E-03	1.14E-02
Red marrow	9.59E-03	8.55E-03	1.47E-03
Osteogenic cells	1.45E-02	1.26E-02	1.82E-03
Skin	7.36E-03	6.71E-03	1.04E-03
Spleen	1.00E-02	8.96E-03	2.46E-03
Testes	1.05E-02	1.29E-02	1.05E-03
Thymus	1.10E-02	7.86E-03	1.48E-03
Thyroid	9.60E-03	7.81E-03	1.13E-03
Urinary bladder wall	1.32E-01	2.91E-01	1.27E-03
Uterus	1.79E-02	2.69E-02	1.43E-03
Total body	1.12E-02	9.43E-03	1.97E-03
Effective dose	1.79E-02	2.17E-02	2.75E-03

<sup>a</sup>Fluorodeoxyglucose

<sup>b</sup>L-3,4-dihydroxyphenylalanine

and assessment, based on accurate absorbed dose estimates, will prevent unnecessary therapies from being carried out, will significantly improve treatment efficacy and will provide the foundation for significant advances in radionuclide therapy.” The discussion continues with considerable passion on both sides of the argument. In Europe, there is some movement toward advancing dosimetry into the nuclear medicine clinical environment, which will hopefully be reflected in other countries soon. Planning of individual therapies requires an evaluation of the biodistribution and biokinetics expected of the agent during the therapeutic regime.



**Table 3.5** Sample dose estimates for  $^{18}\text{F}$ FDG in adults and children (mSv/MBq administered)

	Adults	15-year-olds	10-year-olds	5-year-olds	1-year-olds
Adrenals	1.16E-02	1.46E-02	2.24E-02	3.54E-02	6.41E-02
Brain	3.68E-02	3.73E-02	3.92E-02	4.41E-02	6.09E-02
Breasts	8.26E-03	1.05E-02	1.66E-02	2.63E-02	5.00E-02
Gallbladder wall	1.25E-02	1.50E-02	2.29E-02	3.45E-02	6.30E-02
LLI wall	1.34E-02	1.60E-02	2.54E-02	3.81E-02	6.31E-02
Small intestine	1.17E-02	1.49E-02	2.36E-02	3.68E-02	6.65E-02
Stomach wall	1.07E-02	1.33E-02	2.05E-02	3.27E-02	6.03E-02
ULI wall	1.14E-02	1.40E-02	2.21E-02	3.53E-02	6.29E-02
Heart wall	6.74E-02	8.74E-02	1.35E-01	2.13E-01	3.78E-01
Kidneys	1.03E-02	1.29E-02	2.00E-02	3.26E-02	5.92E-02
Liver	2.05E-02	2.70E-02	4.00E-02	5.99E-02	1.10E-01
Lungs	1.93E-02	2.78E-02	3.93E-02	5.97E-02	1.15E-01
Muscle	9.73E-03	1.21E-02	1.90E-02	3.00E-02	5.55E-02
Ovaries	1.35E-02	1.71E-02	2.60E-02	3.98E-02	6.91E-02
Pancreas	1.12E-02	1.42E-02	2.22E-02	3.52E-02	6.49E-02
Red marrow	9.59E-03	1.20E-02	1.79E-02	2.76E-02	6.22E-02
Osteogenic cells	1.45E-02	1.87E-02	2.66E-02	4.06E-02	8.36E-02
Skin	7.36E-03	9.01E-03	1.43E-02	2.32E-02	4.40E-02
Spleen	1.00E-02	1.28E-02	1.97E-02	3.23E-02	5.96E-02
Testes	1.05E-02	1.37E-02	2.24E-02	3.41E-02	6.01E-02
Thymus	1.10E-02	1.38E-02	2.09E-02	3.24E-02	6.02E-02
Thyroid	9.60E-03	1.21E-02	1.91E-02	3.12E-02	5.85E-02
Urinary bladder wall	1.32E-01	1.68E-01	2.51E-01	3.45E-01	4.62E-01
Uterus	1.79E-02	2.18E-02	3.46E-02	5.14E-02	8.24E-02
Total body	1.12E-02	1.39E-02	2.20E-02	3.45E-02	6.39E-02
Effective dose	1.79E-02	2.30E-02	3.46E-02	5.17E-02	8.90E-02

Usually a small amount of the same radiopharmaceutical is administered, and subjects are imaged over several times, and the therapeutic administration may be monitored to confirm the behavior of the compound. Kobe et al. [24] significantly improved the first treatment efficacy of  $^{131}\text{I}$ NaI in treating hyperthyroidism with this approach. Flux et al. [25] stressed the importance of internal dose calculations for individual patients (many who are pediatric subjects) for the therapeutic use of  $^{131}\text{I}$ -mIBG. Appropriate PET radiopharmaceuticals would be highly desirable for therapy planning, due to their superior resolution and inherent quantitative nature. “Surrogate” radiopharmaceuticals can be problematic to prove congruence (e.g., use of  $^{111}\text{In}$  Zevalin to plan  $^{90}\text{Y}$  Zevalin therapy for

non-Hodgkin’s lymphoma); the ideal situation is to use a positron emitting isotope of the same element, e.g.,  $^{124}\text{I}$  to plan  $^{131}\text{I}$  therapies and  $^{86}\text{Y}$  to plan  $^{90}\text{Y}$  therapies. Blaickner and Baum [26] noted that “Individual organ dosimetry is also essential for critical organs in order to prevent radiotoxicities” and reviewed the clinical utility of using  $^{86}\text{Y}$ -DOTATOC to plan  $^{90}\text{Y}$ -DOTATOC therapy for neuroendocrine tumors, noting the advantages of spatial resolution and quantification and noting the drawback of the prompt gamma emissions and the short physical half-life. There are also issues of the availability of  $^{86}\text{Y}$  in the marketplace.  $^{90}\text{Y}$  has a very small positron component (0.003%), but if therapeutic levels are administered, very nice PET images can be obtained for

selective internal radiotherapy (SIRT) (e.g., [27]). Ga-68-labeled DOTA-peptides are useful in imaging and planning therapies for neuroendocrine tumors [28], but the short half-life (68 min) does not allow for characterization of some of the possible long-term retention components.

Because of the reluctance of physicians to gather data for dosimetry calculations, the database of information at present is sparse. Everyone agrees that a large clinical trial with and without a dosimetry component would settle the discussion about the relevance of dosimetry to radiopharmaceutical therapy, but no one seems willing to fund this effort. Many centers have established that clinical dosimetry can be done with good accuracy, with prediction of biological response. Still the resistance of most of the nuclear medicine community remains strong against realizing this component. PET radiopharmaceuticals will certainly have a role to play in this process, should it someday become routine.

---

### 3.5 The Pregnant or Lactating Patient

Dose to the embryo/fetus in the pregnant or potentially pregnant patient is an area of significant concern, due to the radiosensitivity of the unborn child. The distribution of the radiopharmaceutical in the pregnant patient is generally assumed to be the same as in the nonpregnant subject. Dose to the embryo/fetus is due to photon radiation coming from organs in the mother and photon and electron radiation from activity that may cross the placenta and enter the body of the embryo/fetus. There are some animal data regarding placental crossover of radiopharmaceuticals and sparse human data [29]. The pregnant female models of Stabin et al. [16], implemented in the OLINDA/EXM computer code [13], permit calculation of radiation dose to the embryo/fetus, including from the fetus itself, and activity in the placenta for the 6- and 9-month

models. Again, data are difficult to obtain, but are available for some compounds. Particularly for  $^{18}\text{F}$ FDG, data have been obtained in both animal and human subjects. Russell et al. [30] reported dose estimates for  $^{18}\text{F}$ -FDG with no consideration of placental crossover. Later, Stabin [31] revised the fetal doses throughout gestation using measured  $^{18}\text{F}$ FDG placental crossover in primates. Takalkar et al. [32] reported  $^{18}\text{F}$ FDG fetal uptakes in five pregnant subjects, using nuclear medicine imaging to quantify the uptakes. Their measured time-activity integrals and estimated doses were reasonably consistent with those of Stabin for different stages of gestation, but generally lower (0.007–0.02 mGy/MBq vs. 0.017–0.02 mGy/MBq reported by Stabin). Zanotti-Fregonara et al. [33] evaluated fetal uptake and dose in a 21-week pregnant subject. Their estimate of fetal dose was 0.0197 mGy/MBq administered to the mother.

Many radiopharmaceuticals are excreted in breast milk. Stabin and Breitz [34] discussed some of the many compounds and nutrients that are expressed in breast milk. Measuring activity in a milk sample is easier than quantitative imaging of the fetus in a pregnant subject, so a number of authors have presented data on measured concentrations at various times after radiopharmaceutical administration to a lactating mother. There are difficulties in assigning doses to the nursing infant, as most radiopharmaceutical dose estimates are based on injected, not ingested compounds. The measurements typically do not account for the chemical form that was in the breast milk. Calculated dose estimates generally assume that the ingested radioactivity quickly enters the infant's bloodstream and then is distributed and cleared from the body in the same manner as an injection to an adult subject, as this is probably a conservative way to treat the data and there are simply no data to support any other approach. A recent ICRP publication [35] reviewed the available data on breast milk excretion of radiopharmaceuticals using a dose criterion of 1 mSv effective dose to the infant to estimate recommended breast milk interruption times; they recommended that no breast feeding

interruption is warranted for any PET compound that they evaluated.

### Conclusions

Calculation of dose estimates for PET radiopharmaceuticals relies mostly on the gathering of high-quality biokinetic data. Data from animal studies are a necessary part, but are not highly reliable in predicting human dosimetry. Trials with human subjects are always the key step in understanding the dosimetry of a new agent. Once adequate biokinetic data are available, standardized dosimetry codes (i.e., OLINDA/EXM) can provide excellent tables of doses to organs and effective doses.

### References

1. Stabin MG, Xu XG. Basic principles in the radiation dosimetry of nuclear medicine. *Semin Nucl Med.* 2014;44:162–71.
2. Stabin MG. *Fundamentals of nuclear medicine dosimetry.* New York: Springer; 2008.
3. Kirschner A, Ice R, Beierwaltes W. Radiation dosimetry of <sup>131</sup>I-19-iodocholesterol: the pitfalls of using tissue concentration data, the author's reply. *J Nucl Med.* 1975;16(3):248–9.
4. Sparks R, Aydogan B. Comparison of the effectiveness of some common animal data scaling techniques in estimating human radiation dose. In: *Proceedings of the sixth international radiopharmaceutical dosimetry symposium.* Oak Ridge Institute for Science and Education; 1999, p. 705–16.
5. Yoriyaz H, Stabin M. Electron and photon transport in a model of a 30 g mouse. *J Nucl Med.* 1997;38(Suppl):228P.
6. Muthuswamy MS, Roberson PL, Buchsbaum DJ. A mouse bone marrow dosimetry model. *J Nucl Med.* 1998;39:1243–7.
7. Konijnenberg MW, Bijster M, Krenning EP, de Jong M. A stylized computational model of the rat for organ dosimetry in support of preclinical evaluations of peptide receptor radionuclide therapy with <sup>90</sup>Y, <sup>111</sup>In, or <sup>177</sup>Lu. *J Nucl Med.* 2004;45:1260–9.
8. Kolbert KS, Watson T, Matei C, Xu S, Koutcher JA, Sgouros G. Murine S factors for liver, spleen and kidney. *J Nucl Med.* 2003;44:784–91.
9. Hindorf C, Ljungberg M, Strand S-E. Evaluation of parameters influencing S values in mouse dosimetry. *J Nucl Med.* 2004;45:1960–5.
10. Stabin MG, Peterson TE, Holburn GE, Emmons MA. Voxel-based mouse and rat models for internal dose calculations. *J Nucl Med.* 2006;47:655–9.
11. Keenan MA, Stabin MG, Segars WP, Fernald MJ. RADAR realistic animal model series for dose assessment. *J Nucl Med.* 2010;51(3):471–6.
12. Segars W, Tsui B. 4D MOBY and NCAT phantoms for medical imaging simulation of mice and men. *J Nucl Med.* 2007;48(Supplement 2):203P.
13. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med.* 2005;46:1023–7.
14. Dewaraja YK, Frey EC, Sgouros G, Brill AB, Roberson P, Zanzonico PB, Ljungberg M. MIRD pamphlet no. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. *J Nucl Med.* 2012;53(8):1310–25.
15. Cristy M, Eckerman K. Specific absorbed fractions of energy at various ages from internal photons sources. ORNL/TM-8381 V1-V7. Oak Ridge: Oak Ridge National Laboratory; 1987.
16. Stabin M, Watson E, Cristy M, Ryman J, Eckerman K, Davis J, Marshall D, Gehlen K. Mathematical models and specific absorbed fractions of photon energy in the nonpregnant adult female and at the end of each trimester of pregnancy. ORNL report ORNL/TM-12907; 1995.
17. Stabin MG, Xu XG, Emmons MA, Segars WP, Shi C, Fernald MJ. RADAR reference adult, pediatric, and pregnant female phantom series for internal and external dosimetry. *J Nucl Med.* 2012;53:1807–13.
18. International Commission on Radiological Protection. *Limits for Intakes of Radionuclides by Workers.* ICRP Publication 30. New York: Pergamon Press; 1979.
19. International Commission on Radiological Protection. *1990 Recommendations of the International Commission on Radiological Protection.* ICRP Publication 60. New York: Pergamon Press; 1991.
20. International Commission on Radiological Protection. *Recommendations of the ICRP.* ICRP Publication 103. *Ann ICRP.* 2007;37(2–3).
21. Stabin MG. The case for patient-specific dosimetry in radionuclide therapy. *Cancer Biother Radiopharm.* 2008;23(3):273–84.
22. Brans B, Bodei L, Giammarile F, Linden O, Luster M, Oyen WJG, Tennvall J. Clinical radionuclide therapy dosimetry: the quest for the “Holy Gray”. *Eur J Nucl Med Mol Imaging.* 2007;34:772–86.
23. Flux G, Bardies M, Chiesa C, Monsieurs M, Savolainen S, Strand SE, Lassmann M. Letter to the editor, clinical radionuclide therapy dosimetry: the quest for the “Holy Gray”. *Eur J Nucl Med Mol Imaging.* 2007;34:1699–700.
24. Kobe C, Eschner W, Sudbrock F, et al. Graves' disease and radioiodine therapy: is success of ablation dependent on the achieved dose above 200 Gy? *Nuklearmedizin.* 2007;47:13.
25. Flux GD, Chittenden SJ, Saran F, Gaze MN. Clinical applications of dosimetry for mIBG therapy. *Q J Nucl Med Mol Imaging.* 2011;55:116–25.
26. Blaickner M, Baum R. Relevance of PET for pretherapeutic prediction of doses in peptide receptor radionuclide therapy. *PET Clin.* 2014;9:99–112.

27. Werner MK, Brechtel K, Beyer T, et al. PET/CT for the assessment and quantification of (90)Y biodistribution after selective internal radiotherapy (SIRT) of liver metastases. *Eur J Nucl Med Mol Imaging*. 2010;37(2):407–8.
28. Breeman WA, de Blois E, Sze Chan H, et al. Ga-labeled DOTA-peptides and (68)Ga-labeled radiopharmaceuticals for positron emission tomography: current status of research, clinical applications, and future perspectives. *Semin Nucl Med*. 2011;41(4):314–21.
29. Russell J, Stabin M, Sparks R. Placental transfer of radiopharmaceuticals and dosimetry in pregnancy. *Health Phys*. 1997;73(5):747–55.
30. Russell JR, Stabin MG, Sparks RB, Watson EE. Radiation absorbed dose to the embryo/fetus from radiopharmaceuticals. *Health Phys*. 1997;73(5):756–69.
31. Stabin M. Proposed addendum to previously published fetal dose estimate tables for 18F-FDG. *J Nucl Med*. 2004;45(4):634–5.
32. Takalkar AM, Khandelwal A, Lokitz S, Lilien DL, Stabin MG. 18F-FDG PET in pregnancy and fetal radiation dose estimates. *J Nucl Med*. 2011;52:1035–40.
33. Zanotti-Fregonara P, Koroscil TM, Mantil J, Satter M. Radiation dose to the fetus from [18F]-FDG administration during the second trimester of pregnancy. *Health Phys*. 2012;102(2):217–9.
34. Stabin M, Breitz H. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. *Continuing Medical Education Article*. *J Nucl Med*. 2000;41(5):863–73.
35. International Commission on Radiological Protection. ICRP Publication 106. Radiation Dose to Patients from Radiopharmaceuticals – Addendum 3 to ICRP Publication 53 ICRP Publication 106. *Ann ICRP*. 2008;38(1–2).