

RADAR Guide: Standard Methods for Calculating Radiation Doses for Radiopharmaceuticals

Part 2. Data Analysis and Dosimetry

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Abstract

This paper presents standardized methods for performing dose calculations for radiopharmaceuticals. Various steps in the process are outlined, with some specific examples given. Special models for calculating time-activity integrals (urinary bladder, intestines) are also reviewed. This document can be used as a template for designing and executing kinetic studies for calculating radiation dose estimates, from animal or human data.

Introduction

Currently, there is renewed interest in performing radiation dosimetry for radiopharmaceuticals, particularly in therapy applications. To have any new radiopharmaceutical approved by the US Food and Drug Administration (FDA), whether for diagnostic or therapeutic applications, human radiation doses must be estimated. In 1999, Siegel et al. (1) published a guide for obtaining quantitative data for use in radiopharmaceutical dosimetry. This document, and the companion document to it (2), updates that information with practical guidance and worked examples.

Methods for Biokinetic Data Analysis

Whether the investigator has a series of data extrapolated from animals, or a series of data from patient images, either planar or tomographic, one must integrate the human time-activity curve for each source region, to get the area under the curve for all sources, which in each case is the number of disintegrations that occurred in that region. A kinetic model must be derived that can be used to estimate the number of disintegrations occurring in each significant source region in the body. In general, there are three levels of complexity that analysis can take:

1. Direct integration - One can directly integrate under the actual measured values by a number of methods. This does not give very much information about the biokinetic system, but it does allow calculation of the number of disintegrations rather easily. The most common method used is the Trapezoidal Method, which uses linear interpolation between the measured data points and approximates the area under the time-activity curve as a series of trapezoids. An important concern with this method is the calculation of the integrated area under the curve after the last datum. If activity is clearing slowly near the end of the

data set, a significant portion of the total decays may occur after the last time point and be represented by the area under the curve after that point. Several approaches may be used to estimate this area. The most conservative is to assume that activity is removed only by physical decay after the last point; another approach is to calculate the slope of the line using the last two or three points, and assume that this slope continues until the retention curve crosses the time axis. No single approach is necessarily right or wrong – a number of approaches may be acceptable under different circumstances. It is generally preferable to overestimate the cumulated activity rather than to underestimate it, as long as the overestimation is not too severe. The important point is to calculate this area by an appropriate method and to clearly document what was done.

2. Least Squares Analysis - An alternative to simple, direct integration of a data set is to attempt to fit mathematical functions to the data; these functions than can be analytically integrated. The most common approach is to characterize a set of data by a series of exponential terms, as many biological processes are well represented by this form, and exponential terms are easy to integrate. In general, the approach is to minimize the sum of the squared distance of the data points from the fitted curve. The curve will have the form:

$$A(t) = a_1 e^{-b_1 t} + a_2 e^{-b_2 t} + \dots \quad (1)$$

The fitting minimizes the sum of the squared differences between each point and the solution of the fitted curve at that point, taking the partial derivative of this expression with

respect to each of the unknowns a_i and b_i and setting it equal to zero. Once the ideal estimates of a_i and b_i are obtained, the integral of $A(t)$ from zero to infinity is simply:

$$\int_0^{\infty} A(t)dt = \frac{a_1}{b_1} + \frac{a_2}{b_2} + \dots \quad (2)$$

If the coefficients a_i are in units of activity, this integral represents cumulated activity (the units of the b_i are time^{-1}). If the coefficients give fractions of the administered activity, then the area represents the normalized cumulated activity (e.g. Bq-h/Bq).

Consider the following data set. We will integrate it by the trapezoidal and least-squares methods Error! Bookmark not defined.

Table 1. Theoretical data set.

Time (hr)	Activity (Bq)
0	100
0.5	72
1	35
2	24
4	20
6	15
10	12

Trapezoidal method. Each interval is treated separately, and the parts are added:

Table 2. Trapezoidal integration

$A1 = (100 + 72) \cdot 0.5/2 =$	43 Bq-hr
$A2 = (72 + 35) \cdot 0.5/2 =$	26.75 Bq -hr
$A3 = (35 + 24) \cdot 1.0/2 =$	29.5 Bq -hr
$A4 = (24 + 20) \cdot 2.0/2 =$	44 Bq -hr
$A5 = (20 + 15) \cdot 2.0/2 =$	35 Bq -hr
$A6 = (15 + 12) \cdot 4.0/2 =$	54 Bq -hr
Total =	232 Bq -hr

Least-squares analysis. A computer fit of the data yielded the following fit (Figure 1):

$$A(t) = 18.6 \exp(-0.039t) + 81.4 \exp(-1.23t)$$

The cumulated activity for this system, integrating from zero to infinity, then is:

$$\tilde{A} = 18.6/0.039 + 81.4/1.23 = 477 + 66 = 543 \text{ Bq-hr}$$

This does not agree well with the estimate from the trapezoidal method. The reason is that in that calculation, we did not make an estimate of the area under the curve beyond 10 hours. If we integrate the analytical expression only to 10 hours, the answer is

$$\begin{aligned} \tilde{A} &= 18.6/0.039 \cdot [1 - \exp(-0.039 \cdot 10)] \\ &+ (81.4/1.23 \cdot [1 - \exp(-1.23 \cdot 10)]) \\ &= 220 \text{ Bq -hr} \end{aligned}$$

This does agree well with the trapezoidal estimate. The appropriate calculation to apply to the trapezoidal case is that beyond the last data point, activity decreases either with the radioactive half-time or, if it can be estimated reliably, the half-time for the last phase of clearance. In this case, the second phase has a half time of

$$0.693/0.039 = 17.8 \text{ hours}$$

The area under the curve beyond 10 hours, assuming that this rate continues, is

$$1.443 \cdot 12 \text{ Bq} \cdot 17.8 \text{ hours} = 308 \text{ Bq -hr}$$

Adding this value to the previous estimate for the trapezoidal method yields 540 Bq -hr, in excellent agreement with the estimate obtained by the least-squares method. Of course, the second half-time was obtained by the least-squares method. If these data were for, say, ^{131}I , and if one did not feel that there was a good estimate of this (effective) half-time, the remaining area would have to be estimated as:

$$1.443 \cdot 12 \text{ Bq} \cdot 8.04 \text{ d} \cdot 24 \text{ hr/d} = 3,340 \text{ Bq -hr}$$

This estimate is an order of magnitude higher than the previous estimates and may be overly conservative. Many people, because of the possibility that another, slower clearance phase might exist, will use this assumption even if a least-squares method has been used to fit the existing data. In this case, this highly conservative assumption may unrealistically increase the estimate of the normalized cumulated activity (\tilde{A}/A_0) and thus the estimated dose to this and other organs. But if a slower component did exist, the assumption that the 17.8-hour clearance rate continued beyond 10 hours could have resulted in a considerable underestimation of the number of disintegrations.

3. Compartmental Models. The situation may arise that either quite a bit about the biological system under investigation is available or more about how this system is working is desired to be known. In this case, one may describe the system as a group of compartments linked through transfer rate coefficients. Solving for \tilde{A} of the various compartments involves solving a system of coupled differential equations describing transfers of the tracer between compartments and elimination from the system. The solution to the time-activity curve for each compartment will usually be a sum of

exponentials that are obtained not by least squares fitting of each compartment separately, but rather by varying the transfer rate coefficients between compartments until the data are well fit by the model. Computer programs such as SAAM II (3), Stella (4), PMod (5), Simple (6), and others have been used for these purposes.

Dosimetric Methods

Basic dose calculations

A 'generic' equation for the absorbed dose rate in an organ or tumor in which radioactivity is uniformly distributed is given by:

$$\dot{D}_T = \frac{k \sum_S A_S \sum_i n_i E_i \phi_i(T \leftarrow S)}{m_T} \quad (3)$$

where \dot{D}_T = absorbed dose rate in the target region T (rad/hr or Gy/sec)

A_S = activity (μ Ci or MBq) in source region S

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

E_i = energy for the i th radiation emitted by the nuclide (MeV)

$\phi_i(T \leftarrow S)$ = fraction of energy emitted that is absorbed in the target region T originating in source region S

m_T = mass of target region T (g or kg)

k = proportionality constant (rad-g/ μ Ci-hr-MeV or Gy-kg/MBq-sec-MeV)

It is essential that the proportionality constant be properly calculated and applied for the unit system of choice. One may also apply *radiation weighting factors* (once called "quality factors") to the result of this equation to calculate the *equivalent dose rate*. For many years, this was not an important issue as nuclear medicine involved only beta and gamma emitters; the more recent

introduction of some alpha emitters makes this an important consideration. The value recommended by the International Commission on Radiological Protection (ICRP) for the radiation weighting factor for alpha emitters is 20, but this is believed to be too high for use in calculating doses from nuclear medicine therapy agents (7). Some radiobiological evidence indicates that this value may be as low as 5 (8), or even 1 (9).

We are usually interested in an estimate of the total absorbed dose from an administration, rather than an initial dose rate. In equation 3, the quantity activity (nuclear transitions per unit time) causes the outcome of the equation to have a time dependence. To calculate cumulative dose, the time integral of the dose equation must be calculated. In most cases, the only term that has time dependence is activity, so the integral is just the product of all of the factors in the above equation except for activity multiplied by the integral of the time-activity curve.

Regardless of the shape of the time-activity curve, its integral, however obtained, *will have units of the number of total nuclear transitions* (i.e., activity, which is transitions per unit time, multiplied by time). Therefore, the equation for cumulative dose would be given by:

$$D_T = \frac{k \sum_S N_S \sum_i n_i E_i \phi_i(T \leftarrow S)}{m_T} \quad (4)$$

where D_T is the absorbed dose in target region T (rad or Gy) and N_S is the number of disintegrations (cumulated activity) in source region S ($\mu\text{Ci}\cdot\text{hr}$ or $\text{MBq}\cdot\text{sec}$). N_S is the total area under the time-activity curve, which may be due to contributions of one or more exponential terms, with different effective half-times.

Anthropomorphic Phantoms

The factors ϕ and m_T in the equation above are determined using models of the human body referred to as 'phantoms'. A very simple, and not very anthropomorphic, phantom is the ICRU reference sphere (10). For many decades, there was only one set of phantoms available for use in internal dosimetry: the Oak Ridge phantom series (11,12). These have now been replaced with image-derived, realistic phantoms (13), that are based on reference masses defined by the ICRP (14) (Figure 2).

Special Cases

The Dynamic Urinary Bladder

Developing the AUC for most organs requires the acquisition of a number of data points over the time of uptake and elimination of the radiopharmaceutical. In the case of the urinary bladder, however, except for very short lived-nuclides for which no emptying of the bladder may occur during the decay of the nuclide, obtaining enough data points to characterize the complex filling and voiding pattern is not possible (Figure 3).

An ingenious solution to the integration of this complicated curve was developed by Cloutier et al. (15), and is implemented in the OLINDA/EXM computer code (16):

$$N = A_0 \sum_i f_i \left[\frac{1 - e^{-\lambda_i T}}{\lambda_i} - \frac{1 - e^{-(\lambda_i + \lambda_p)T}}{\lambda_i + \lambda_p} \right] \left[\frac{1}{1 - e^{-(\lambda_i + \lambda_p)T}} \right] \quad (11)$$

Here, the number of disintegrations, N, is given knowing the rate constants for clearance from the body, λ , and the (assumed regular) bladder voiding interval T. It should be noted, however, that empirical evidence suggests that, in reality, people urinate when their urinary bladders have filled to a particular volume that varies among individuals (17) and not at constant time intervals.

The Gastrointestinal Tract

Quantification of activity in the stomach and intestines is also more difficult than in most body organs, because of the continuous movement of material through the system. The International Commission on Radiological Protection (ICRP) has developed two models (Figure 4) that facilitate calculation of the activity in the stomach and intestines, given an input of the fraction of administered activity that enters either at the stomach or the small intestine (18,19). These models have also been implemented in the OLINDA/EXM software code (27) (Figure 5).

Remainder of body

The remainder of body is a special source organ that contains all of the cumulated activity that is not assigned to any other source organ. It depends on which organs are not included in it. The challenge is that we do not have an dose factor (MIRD called these 'S-values') for each of the numerous possibilities for the remainder of the body. Instead, we modify the total body S-factor to compute the S-factor for the remainder of the body (20) (Equation 12 and Figure 6).

$$S(r_k \leftarrow RB) = S(r_k \leftarrow TB) \left(\frac{m_{TB}}{m_{RB}} \right) - \sum_h S(r_k \leftarrow r_h) \left(\frac{m_h}{m_{RB}} \right)$$

(12)

where r_h denotes the source organ with index h , r_k denotes the target organ with index k and RB and TB denote the remainder of the body and the total body source organs, respectively. Recall that the S-value is the mean absorbed dose in the target organ per disintegration in the source organ.

Blood data and the archaic quantity ‘dose to blood’

Blood data are relatively easy to gather and analyze, but generally are difficult to employ in internal dose calculations. Activity clears from the blood and is distributed into various organs. Later, some re-enters the blood and is excreted. We are usually interested only in the dose to organs in the body; the dose to the blood itself is not of direct interest biologically. However, an early publication (21) suggested the use of ‘dose to blood’ as a surrogate for the dose to the bone marrow in the safe administration of ^{131}I in therapy. ‘Blood’ is not a defined source or target region in any anthropomorphic phantom. Akabani (22) attempted to develop absorbed fractions for different sized blood vessels, but this has not been implemented in any practical way. As ‘dose to blood’ is physiologically not meaningful, it should be abandoned in practical internal dose calculations. Very well-developed models for the dose to the bone marrow are available (e.g. 23) and are implemented in the OLINDA/EXM computer code.

Patient-individualized target organ mass corrections

It is common in cancer patients to encounter organs whose masses are notably different than those in the standard models, due to the disease or complications thereof. The reported dose using a standard model may be adjusted for mass, scaling the electron and photon dose contributions separately. For electrons, the scaling is:

$$DF_2 = DF_1 \frac{m_1}{m_2}$$

Here DF_1 and DF_2 are the dose factors appropriate for use with organ masses m_1 and m_2 . For photons, the scaling is:

$$\phi_2 = \phi_1 \left(\frac{m_2}{m_1} \right)^{1/3} \quad \Phi_2 = \Phi_1 \left(\frac{m_1}{m_2} \right)^{2/3}$$

where ϕ (ϕ) is the absorbed fraction and Φ (Φ) is the specific absorbed fraction.

To perform this calculation, one must isolate the emissions and frequencies for penetrating and non-penetrating emissions, multiply them by these new absorbed fractions, and then recalculate the total dose by adding the two components together. The OLINDA/EXM code (16) performs this calculation automatically for the user, given entry of the new mass of the organ of interest. Note that the correction for electrons assumes that all electron energy is absorbed in the source region, which is an approximation that is generally used in internal dose calculations. Newer absorbed fractions for electrons include explicit electron transport and possible losses at source region surfaces.

Total body dose and effective dose

Although complete dose tables give doses to all of the defined target organs in the reference anthropomorphic phantoms, the two doses of the greatest interest have traditionally been those to the ‘critical organ’ (i.e., the organ receiving the highest absorbed dose) and the total body. For most radiopharmaceuticals, however, the dose to the ‘total body’, which is the energy deposited in all target regions divided by the mass of the whole body, is of no biological relevance. If one receives a uniform dose to all tissues of the body, this can predict biological response, but for most radiopharmaceuticals, this is not a useful quantity because the actual dose distribution is highly nonuniform by design and intention. Imagine, for example, an administration of ^{131}I sodium iodide, for which a large amount of beta energy is deposited in a 20 g thyroid gland. Dividing this same energy into 70,000 g of body tissue gives a vastly smaller dose number that has no clinical meaning. Instead of the uniform whole-body dose, the ICRP developed a quantity called ‘effective dose’, which gives a risk-based weighted average dose for diagnostic radiopharmaceuticals.

Assume for a given compound that the liver receives 0.53 mGy, the kidneys receive 0.37 mGy, the ovaries receive 0.19 mGy, the testes receive 0.07 mGy, the red marrow receives 0.42 mGy, the endosteal cells on bone surfaces receive 0.55 mGy, and the thyroid receives 0.05 mGy. Because all of the radiation weighting factors are 1.0, these absorbed doses can be directly converted to equivalent dose, i.e., the radiation absorbed dose in Gy times the radiation weighting factor (w_R):

Table 3. Theoretical organ doses

<u>Organ</u>	<u>Dose Equivalent (mSv)</u>
Liver	0.53
Kidneys	0.37
Ovaries	0.19
Testes	0.07
Red Marrow	0.42
Bone Surfaces	0.55
Thyroid	0.05

Strictly speaking, radiation weighting factors are dimensionless. Gy is 1 J/kg, $1 \text{ Gy} \times w_R = 1 \text{ Sv}$, so w_R may be thought of as having units of Sv/Bq. The tissue weighting factor (w_T) for the gonads may be applied to the higher of the values for the ovaries or testes. There is a little confusion on this point; ICRP 30 (24) used the higher of the two while ICRP 53 (25) used the average of the two. To use the remainder weighting factor in the ICRP 30 system, one chooses the five organs that are not assigned an explicit weighting factor and which have the highest dose equivalents and assign them each a weighting factor of 0.06 (although a different scheme was applied to the remainder organs in the ICRP 60 system). In our example, we have only two to consider. Assign each a factor of 0.06, and ignore the remaining weight of 0.18 (out of 0.30). The doses delivered to breast and lung and the other organs could be calculated and summed, but they will probably be of limited importance. To calculate the H_e , add up the weighted dose equivalents:

Table 4. Effective dose calculation

<u>Organ</u>	<u>Weighting Factor</u>	<u>Dose Equivalent (mSv)</u>	<u>Weighted Dose Equivalent (mSv)</u>
Liver	0.06	0.53	0.0318
Kidneys	0.06	0.37	0.0222
Ovaries	0.25	0.19	0.0475
Red Marrow	0.12	0.42	0.0504
Bone Surfaces	0.03	0.55	0.0165
Thyroid	0.03	0.05	0.0015
TOTAL (Effective Dose Equivalent)			0.1699

So we would conclude that the H_e for this compound is 0.17 mSv (0.017 rem or 17 mrem). This suggests that if the whole body were uniformly irradiated to receive 0.17 mSv, the individual would incur the same additional risk (of fatal cancer or genetic defects) as from the combination of 0.53 mSv to the liver, 0.37 mSv to the kidneys, etc.

The same calculation can be performed using the tissue weighting factors from ICRP 60 (26):

Table 5. Another effective dose calculation

<u>Organ</u>	<u>Weighting Factor</u>	<u>Dose Equivalent (mSv)</u>	<u>Weighted Dose Equivalent (mSv)</u>
Liver	0.05	0.53	0.0265
Kidneys	0.005	0.37	0.00185
Ovaries	0.20	0.19	0.038
Red Marrow	0.12	0.42	0.0504
Bone Surfaces	0.01	0.55	0.0055
Thyroid	0.05	0.05	0.0025
TOTAL (Effective Dose)			0.1248

Note: The ICRP, who defined the quantity ‘effective dose’, explicitly note that in any given calculation, all weighting factors may not be used, and the sum of the weighting factors does not always equal 1.0.

It is very important to emphasize that the quantity ‘effective dose’:

- Must NOT BE USED to evaluate the short term effects in situations involving radionuclide therapy. The quantity is based on *stochastic* effects of radiation whereas as the intended effect of a therapeutic administration is deterministic.
- Must NOT BE APPLIED to specific individuals. The tissue weighting factors are defined for *populations, not individuals*.
- Should NOT BE USED to develop numerical estimates of risks to populations in the low dose ranges, e.g diagnostic radiology or nuclear medicine procedures, as noted by the Health Physics Society in 2012 (27).

The Need for Patient-Individualized Dosimetry for Therapeutic Uses of Radiopharmaceuticals

In 2008, Stabin (28) addressed all of the main objections that physicians and others cite for not performing patient-individualized dosimetry for radiopharmaceutical therapy administration, as is done for each and every cancer patient receiving external beam radiation, every day. The reasons addressed were:

- Performing such calculations is difficult and expensive, requiring too much effort.
- There are no standardized methods for performing individualized dose calculations, and methods vary significantly among different institutions.
- Dose calculations performed to date have had poor success in predicting tissue response.
- With the level of difficulty involved, there must be some objective evidence that the use of radiation dose calculations provides positive benefit that justifies extra effort and cost.

This document thoroughly addresses the second point; all other points will not be reargued here.

But the conclusion remains that:

“Treating all nuclear medicine patients with a single, uniform method of activity administration amounts to consciously choosing that these patients be treated with a lower standard of care than patients who receive radiation externally for cancer treatments.”

Patient-individualized medicine is being practiced in almost all disciplines in the radiation sciences today EXCEPT radiopharmaceutical therapy. In the 2008 article, Stabin argued that “The time has come for this reasonable paradigm shift in the practice of nuclear medicine.” It was true then, and it is still true now.

Conclusions

Standardized methods for the quantification of animal data or human image data to provide numerical estimates of radiation dose from the use of radiopharmaceuticals are very well established. They are outlined, with many examples, in this document. Imaging methods are improving and will continue to improve. The methods outlined above are adequate to provide guidance on the design and execution of preclinical or clinical studies to establish the radiation dosimetry of any radiopharmaceutical for diagnostic or therapeutic use with almost any technology. As noted above, the medical professionals have been reluctant to perform patient-individualized dose calculations for nuclear medicine therapy patients, with one of the arguments being that no standardized methods are available and reliable for dose calculations. This document provides all of the current methods and models needed for standardized dose calculations. More advanced methods are also currently in some commercial software programs, using image fusion methods to provide three-dimensional distributions of dose at the individual voxel level and dose-volume histograms. Patient-individualized dosimetry for nuclear medicine therapy patients should become standard practice. The only people in modern medicine that don't receive patient-individualized dosimetry are nuclear medicine therapy patients. We generate dose estimates for adults and children receiving CT scans, airline crews, nuclear workers, nuclear medicine doctors and technologists, just not for nuclear medicine therapy patients. Not only is this resulting in suboptimal therapy for the patients, but when patients may need other therapies in the future, knowledge of previous therapy doses is essential to planning those treatments. It is time to change the historical practice of 'one dose fits all' approach to nuclear medicine therapy.

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Figure 1. Sample biokinetic data set, showing two-exponential fit.

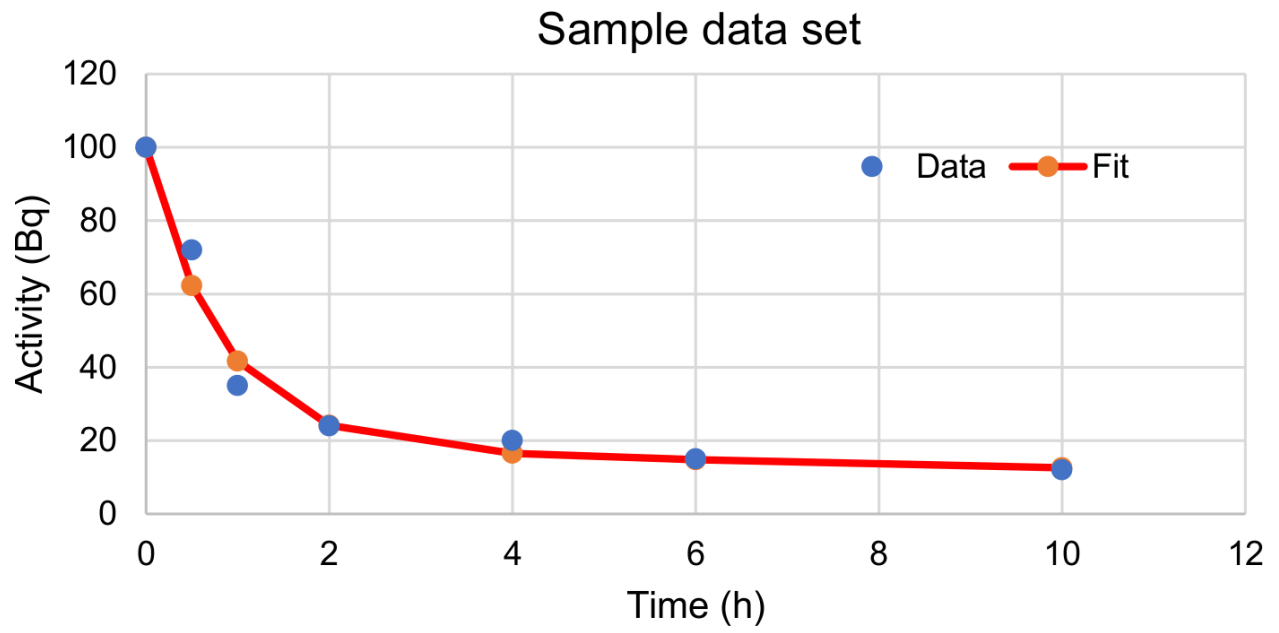


Figure 2. A. Cristy-Eckerman ‘stylized’ computational phantoms (11) and B. RADAR ‘NURBS’ realistic, voxel-based phantoms.

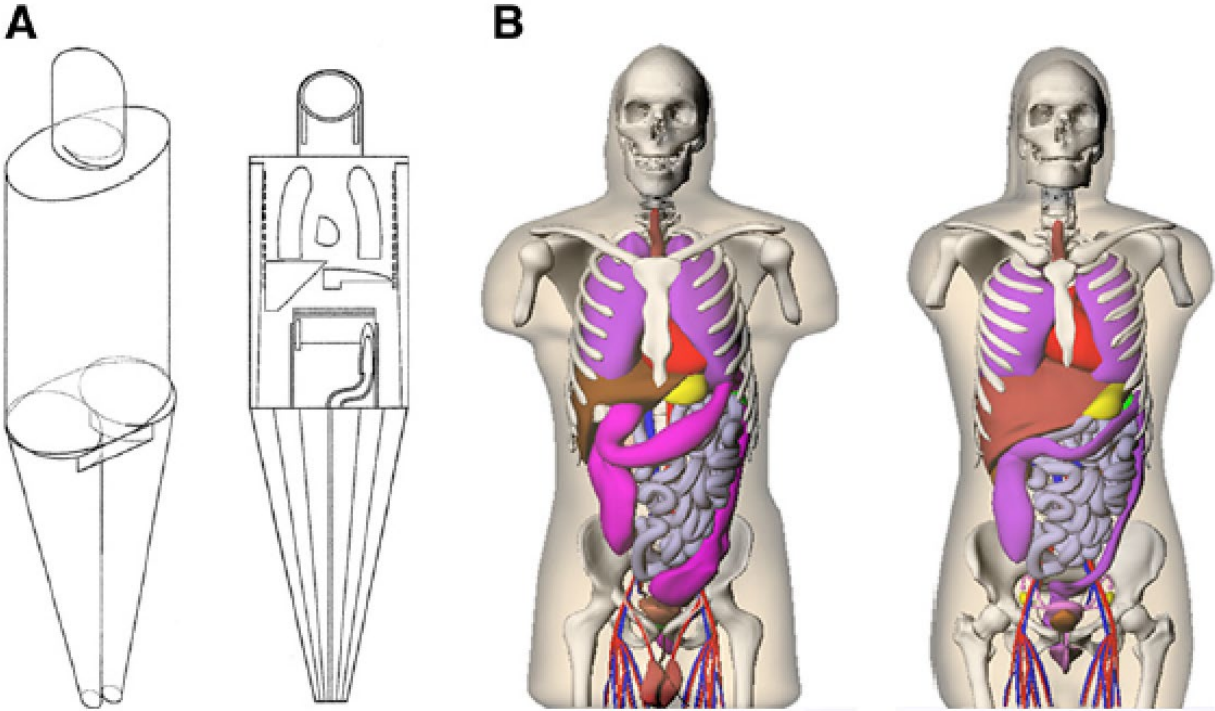


Figure 3. Hypothetical urinary bladder time-activity curve, with and without periodic voiding.

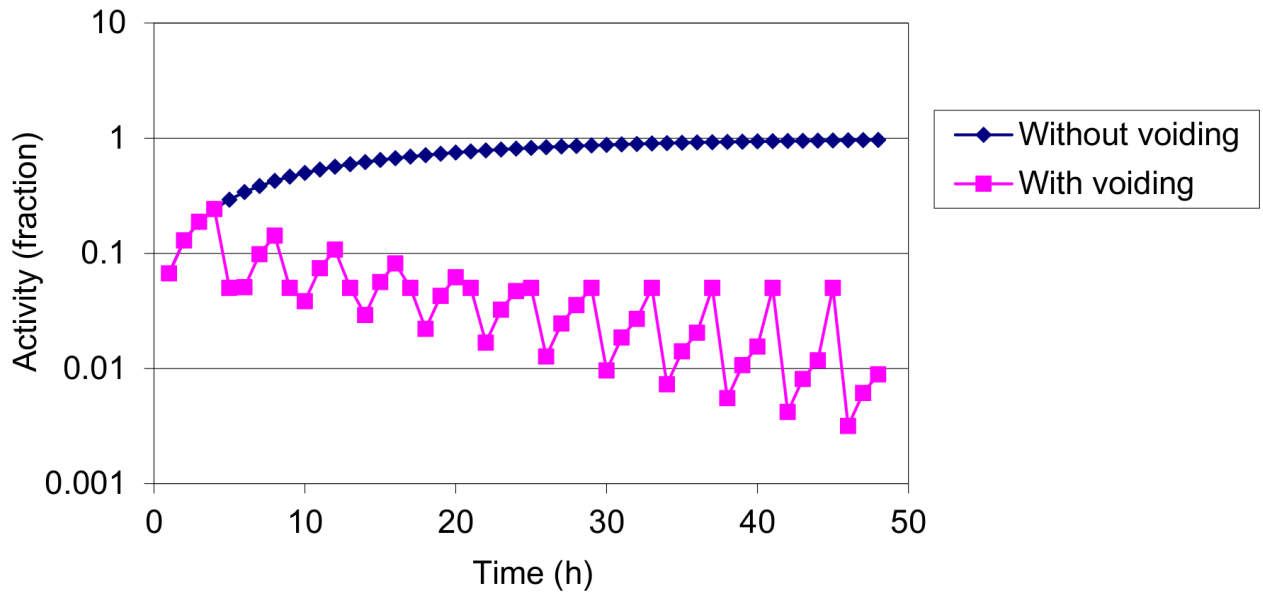


Figure 4. ICRP 30 and ICRP 100 gastrointestinal tract models.

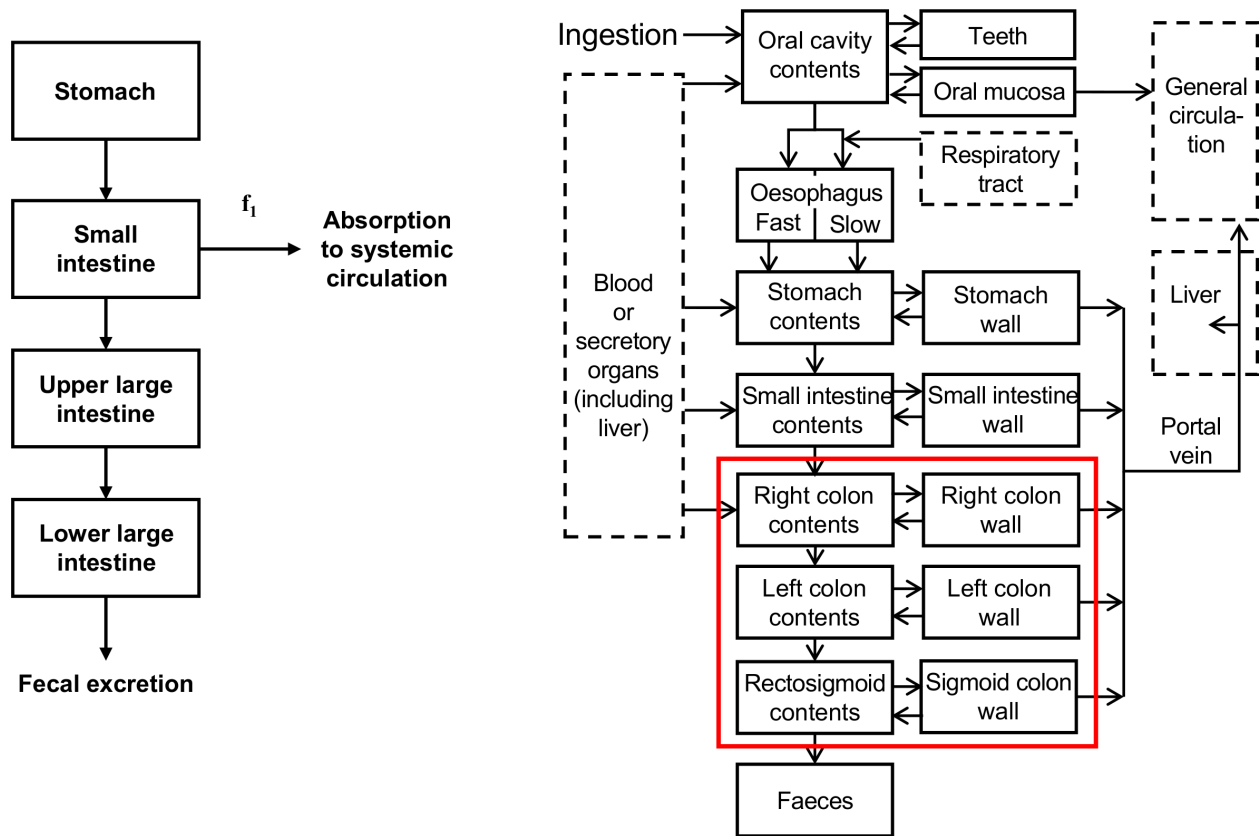


Figure 5. OLINDA/EXM data entry form for the dynamic bladder and gastrointestinal models.

Help

Voiding Bladder Model	ICRP 30 GI Model	ICRP HAT Model
Fraction 1: <input type="text"/> Half-life 1 (h): <input type="text"/>	<input checked="" type="radio"/> Activity enters stomach	<input checked="" type="radio"/> Total Diet
Fraction 2: <input type="text"/> Half-life 2 (h): <input type="text"/>	<input type="radio"/> Activity enters small intestine	<input type="radio"/> Solids
Fraction 3: <input type="text"/> Half-life 3 (h): <input type="text"/>	Fraction entering: <input type="text"/>	<input checked="" type="radio"/> Activity enters esophagus
Fraction 4: <input type="text"/> Half-life 4 (h): <input type="text"/>	Fraction absorbed from small intestine: <input type="text"/>	<input type="radio"/> Activity enters small intestine
Bladder voiding interval (h): <input type="text"/>		<input type="radio"/> Caloric Liquids
		<input type="radio"/> Non-Caloric Liquids
		Fraction entering: <input type="text"/>
		Fraction absorbed from stomach: <input type="text"/>
		Fraction absorbed from small intestine: <input type="text"/>
		Fraction absorbed from right colon: <input type="text"/>
		Fraction absorbed from left colon: <input type="text"/>

Current Model:

Figure 6. Remainder of Body method. Since the remainder of the body depends upon which source organs are identified, the dose conversion factor must be computed for each situation. The fundamental concept is to apportion the cumulated activity in each source organ into two parts. One has the same cumulated activity density as the remainder of the body, which yields a total body with a uniform cumulated activity, and a second part of the source organ that has the remaining cumulated activity.

