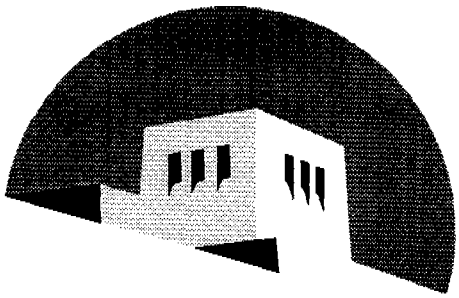

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Internal Radiation Dosimetry: Principles, Applications, and Resources

by:

Michael G. Stabin, PhD

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Internal Radiation Dosimetry: Principles, Applications, and Resources

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INTERNAL RADIATION DOSIMETRY: PRINCIPLES, APPLICATIONS, AND RESOURCES

STATEMENT OF OBJECTIVES

The purpose of this lesson is to provide a general introduction to internal dose calculations in nuclear medicine. Methods for extrapolating animal data to humans and for integrating time-activity curves are briefly discussed. The general theory and basic equations in the MIRD calculational methodology are introduced, and some example calculations are shown. Literature and software resources for assisting the user in calculation of dose estimates are also discussed.

Upon successful completion of this material, the reader should be able to:

1. Use and explain the basic quantities and units involved in radiation dose calculations.

2. Identify the symbols and definitions used in the MIRD internal dose calculational schema.

3. Assess time-activity data gathered in animals or humans and use it to calculate areas under the time-activity curves (cumulated activities or residence times) for application in dose calculations.

4. Combine cumulated activities or residence times with S values to obtain absorbed doses to organs in the body or to the embryo/fetus.

5. Relate the sources of uncertainty in radiation dose estimates.

6. Discuss some of the important literature and software resources available for calculation of radiation dose estimates.

Editor's note: ***Due to the complexity of the material contained in this lesson and to assure the author's material is unaltered, the text of this lesson will not be produced in column format.***

COURSE OUTLINE

I. INTRODUCTION

II. BASIC CONCEPTS

- A. The Importance and Application of Internal Dose Calculations
- B. Quantities and Units
- C. General Equation

III. MIRD EQUATION

IV. EXAMPLES

- A. Calculation of Human Time-Activity Data from Animal Data
- B. Integration of Time-Activity Data to Obtain Ã
- C. Combining Cumulated Activities and S Values to Get Doses
- D. Dose Estimates for The Pregnant Patient

V. UNCERTAINTIES IN RADIATION DOSE ESTIMATES

VI. RESOURCES FOR CALCULATING RADIATION DOSE ESTIMATES

INTERNAL RADIATION DOSIMETRY: PRINCIPLES, APPLICATIONS, AND RESOURCES

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INTRODUCTION

The calculation of radiation dose is essential to the evaluation of the safe use of a radioactive drug. Certainly in the therapeutic use of internally administered radionuclides, it is important to have estimates of the radiation doses to many organs, particularly those of high radiosensitivity such as the active (red) marrow. Even when a diagnostic drug is employed, and the radiation doses are expected to be relatively low [for example, between 10 μGy (1 mrem) and 50 mGy (5 rem)], the best estimate of the radiation dose to many organs of the body must be obtained. Physicians and regulators require the best information possible for 1) evaluating the safe use of the drug, 2) evaluating the drug's comparative safety with other similar agents or procedures (e.g., those that use radiology, ultrasound or MRI for diagnosis or brachytherapy or external beam radiation for therapy), 3) providing the patient with reasonably accurate guidance on the risks of the drug's use, and 4) possible later use in other arenas (e.g., population dose studies, epidemiology, litigation). While there is considerable uncertainty in the final numbers calculated, the best available methods and models should be used to estimate these values. A well calculated dose estimate will give the best available information for understanding the dose and risk to an organ of interest. As methods for gathering data for use in dose calculations and dose calculational methods improve, an understanding of the real situation will improve and confidence in predicting and influencing radiation effects will grow.

BASIC CONCEPTS

The importance and application of internal dose calculations

First, internal dose calculations are of basic scientific interest. Scientists and clinicians want to know, with the best accuracy afforded by available models, what the doses will be to different organs of the body from the administration of a radiopharmaceutical. Such knowledge is of general interest to the scientific and medical communites when a new drug is employed. This information is useful, among other things, for demonstrating energy deposition patterns and dose distributions in different tissues. It may also have longer term scientific interest such as in the area of developing information trends within the nuclear medicine population, and in other studies.

Second, dosimetry is of interest from a safety and regulatory standpoint. Medical practitioners want to know where the highest radiation doses may occur for a given agent, in order to make decisions about patient safety. This information is necessary in making appropriate choices about which radiopharmaceuticals should be used, whether a radiopharmaceutical or other approach (a modality which may or may not involve ionizing radiation) should be used, and how much of the compound should be given to optimize the amount of information gained while ensuring the safety of the subject. When considering approval of a new or modified radiopharmaceutical, regulators must take into account the radiation dose profiles that occur from its use in humans. There are also situations involving misadministrations of radiopharmaceuticals in which the dosimetry must be characterized in order to demonstrate compliance with existing regulations. Universities and other organizations may also have

committees (e.g., Radioactive Drug Research Committees) that have oversight of activities involving radioactive materials; these committees need to know the radiation doses that will result from radiopharmaceuticals in use at their facilities.

Third, information on the internal doses received by patients or others is of historical interest. The doses received should be well documented, and records should be retained in a retrievable system for many years. Often, such information is desired at times long after the doses have been received, for epidemiologic purposes, for use in population dose studies, for litigation purposes, or simply for general historical interest. The recent investigations by the federal government into the uses of human subjects in studies involving ionizing radiation as much as 50 years ago[1] demonstrate the need for all facilities to have good documentation and record keeping practices.

What doses should be calculated for a given compound? Some investigators have concentrated only on a "critical organ" (the organ receiving the highest dose) and the "total body" dose (which is calculated as the total energy absorbed by all tissues of the body, divided by the total mass of the body). This latter value is probably not very useful for risk estimation in situations involving nonuniform localization of radionuclides in the body, such as are common in nuclear medicine; it is also different than the "effective dose equivalent," discussed later in this lesson. In the case of a photon emitter, the dose to other organs is of interest, especially when these organs are biologically significant, particularly the red marrow, gonads, and uterus (the latter due to interest in the dose to the embryo/fetus). With the wide availability of the free software MIRDOSE,[2] which automatically calculates and reports dose to all organs in the body, it is reasonable to report the dose to all of these organs for any radiopharmaceutical, along with some calculated value of effective whole body dose equivalent.

Another commonly asked question is, "For which individuals can internal dose estimates be made?" The usual practice over the years has been to calculate the dose to a standard reference adult, whose total body mass is 70 kg. This model was originally developed to represent the adult male, although it has both male and female organs. Recently, models for children of various ages[3] and for the adult female[4] (both nonpregnant and at several stages of pregnancy) have been made available. Their use is also facilitated through the MIRDOSE software.[2] Dose calculations are usually developed during the drug approval process for the standard adult. When dose estimates are needed for a particular individual in a clinical situation, the use of a more appropriate model may be considered. Adjustments for individual differences from the standard models both in terms of kinetic behavior and of physical differences may be required. For example, if it is known that the subject in a nuclear medicine renal study has only one kidney, or that one of the kidneys is obstructed, the dose to the kidney may be considerably higher than the standard number given for the renal imaging agent. Similarly, if a person has a greatly enlarged spleen or thyroid, the dose to these organs may be much lower than that predicted by the standard model, and should be adjusted accordingly.

In all cases, one should remember that the ultimate goal of these calculations is the **protection of the patient**. It is often easy to become preoccupied with equations and numbers, regulatory pressure, or other factors when a dose calculation is needed. The focus should be on the welfare of the patient, and the justification for pursuing a certain level of accuracy in the calculations should always come back to this focus.

Quantities and units

To define the task of calculating internal doses, the quantities we wish to estimate must first be defined. The principal quantity of interest in internal dosimetry is the *absorbed dose*, or the *dose equivalent*. Absorbed dose (D) is defined[5] as:

$$D = \frac{d\epsilon}{dm} \qquad (1)$$

where dε is the mean energy imparted by ionizing radiation to matter of mass dm. The units of absorbed dose are typically erg/g or J/kg. The special units are the rad (1 rad = 100 erg/g) or the gray (Gy) (1 Gy = 1 J/kg = 100 rad = 10^4 erg/g). The dose equivalent (H) is the absorbed dose multiplied by a "quality factor" (Q), the latter accounting for the effectiveness of different types of radiation in causing biological effects:

$$H = D\,Q \qquad \textbf{(2)}$$

Because the quality factor is in principle dimensionless, the pure units of this quantity are the same as absorbed dose (i.e., erg/g or J/kg). However, the special units for dose equivalent have unique names, specifically, the rem and the sievert (Sv). Values for the quality factor have changed as new information about radiation effectiveness has become available. Current values for radiation types encountered in nuclear medicine, recommended by the International Commission on Radiological Protection (ICRP),[6] are given in Table 1.

TABLE 1

Quality Factors Recommended in ICRP 30

Alpha particles	20
Beta particles (+/-)	1
Gamma rays	1
X-rays	1

The quantity dose equivalent was originally derived for use in radiation protection programs. The development of the effective dose equivalent (EDE) by the ICRP in 1979,[6] and the effective dose (ED) in 1991,[7] however, allowed nonuniform internal doses to be expressed as a single value, representing an equivalent whole body dose. Thus, dose equivalents are now often calculated in nuclear medicine for use in determining the EDE and ED, as these quantities are thought to be more meaningful than "total body dose" and they facilitate comparisons of the dose from different nuclear medicine procedures or other procedures.

General equation

In order to estimate absorbed dose for all significant tissues, one must determine for each tissue the quantity of energy absorbed per unit mass. Once the energy per unit mass is calculated, it need only be expressed in the units desired (e.g., rad or Gy). What quantities are then needed to calculate the two key parameters, energy and mass? To facilitate this analysis, imagine an object that is uniformly contaminated with radioactive material (Figure 1).

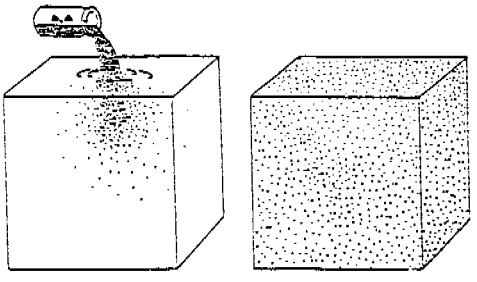

Figure 1

Depending upon the identity of the radionuclide, particles or rays of characteristic energy and abundance will be given off at a rate dependent upon the amount of activity present. The object must have some mass. Already we have almost all of the quantities needed for our equation: energy per decay (and number per decay), activity, and mass of the target region. One other factor needed is the *fraction of emitted energy* that is absorbed within the target. This quantity is most often called the "absorbed fraction" and is represented by the symbol ϕ. For photons (gamma rays and X-rays), some of the emitted energy will escape objects of the size and composition of interest to internal dosimetry (mostly soft tissue organs with diameters of the order of centimeters). For electrons and beta particles, most energy is usually considered to be absorbed, so the absorbed fraction is usually set at 1.0. Electrons, beta particles, and the like are usually grouped into a class of radiations referred to as *nonpenetrating* emissions while X- and γ-rays are called *penetrating* radiations. A generic equation for the absorbed dose rate in our object can be given as:

$$\dot{D} = \frac{kA\sum_i n_i E_i \phi_i}{m} \qquad \textbf{(3)}$$

where:

$\dot{D}$ = absorbed dose rate (rad/hr or Gy/sec)
A = activity (μCi or MBq)
n = fraction of radiations with energy E emitted per nuclear transition
E = energy per radiation (MeV)
ϕ = fraction of energy absorbed in the target
m = mass of target region (g or kg)
k = proportionality constant (rad-g/μCi-hr-MeV
or Gy-kg/MBq-sec-MeV)

It is *extremely important* that the proportionality constant be properly calculated and applied. The results of the calculation will be useless unless the units within are consistent and they correctly express the quantity desired. The application of quality factors to this equation to calculate the dose equivalent rate is a trivial matter; for most of this lesson, absorbed doses will be considered for discussion purposes.

The investigator is usually interested not only in the absorbed dose rate, but more likely also desires an estimate of total absorbed dose from an administration. In equation 3, the quantity activity (nuclear transitions per unit time) causes the outcome of the equation to have a time dependence. In order to calculate cumulative dose, the time integral of the activity must be calculated. Regardless of the shape of the time-activity curve, its integral, however obtained, will have units of transitions (activity, which is transitions per unit time, multiplied by time). Therefore, the equation for cumulative dose is:

$$D = \frac{k\tilde{A}\sum_i n_i E_i \phi_i}{m} \qquad \textbf{(4)}$$

where:

D = absorbed dose (rad or Gy)
$\tilde{A}$ = cumulated activity (μCi-hr or Mbq-sec)

The quantity cumulated activity (Ã) gives the area under a time-activity curve (Figure 2):

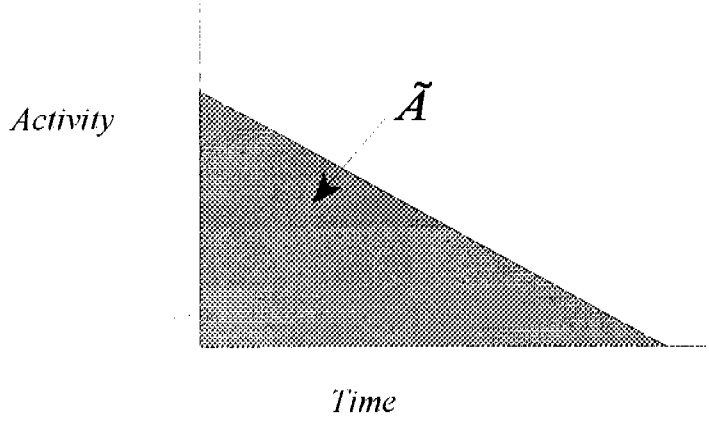

Figure 2

If activity is in units of Bq and time is in units of seconds, Ã will have units of Bq-sec. This is a measure of the number of disintegrations that have occurred in a source region over time; Bq is a number of disintegrations per second, thus Ã has units of disintegrations. If activity is in units of μCi and time is in hours, the principle is the same; 1 μCi-hr is equivalent to 1.33×10^8 disintegrations.

Now consider that we have two objects that are contaminated with radioactive material, and are able to irradiate themselves, each other, and possibly some other objects in the system (Figure 3):

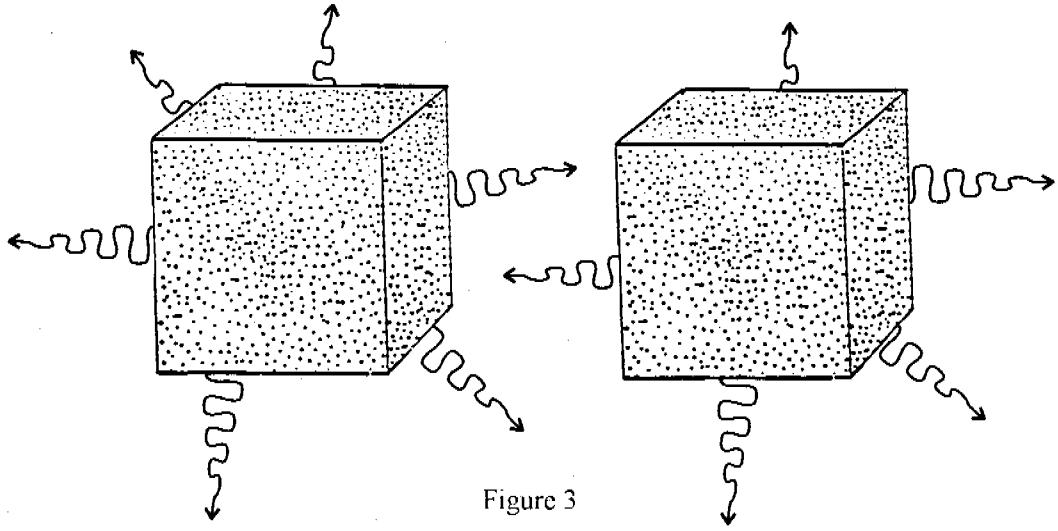

Figure 3

To obtain the total dose to any object in the system[a], absorbed fractions for one object irradiating another must be defined. Absorbed fractions may be determined for an object irradiating itself (as in our first definition of this term, above) - $\phi(1-1)$ - and then absorbed fractions for the other source and target pairs - $\phi(1-2)$, $\phi(2-2)$, $\phi(2-1)$, $\phi(3-1)$, etc. Then, to calculate the total dose to an object from all sources, the individual contributions are added:

$$D_1 = \frac{k\tilde{A}_1 \sum_i n_i E_i \phi_i(1-1)}{m_1} + \frac{k\tilde{A}_2 \sum_i n_i E_i \phi_i(1-2)}{m_1} + \ldots \qquad \textbf{(5)}$$

Adding up numerous contributions is something that computers are designed to do well, so it is natural to employ them in performing these calculations, once the problem has been defined and assuming that all of the factors in our equation have been calculated.

[a] In the human body, the "objects in the system," referred to above, are various organs. The source organ contains the radioactivity that is irradiating the target organ. The target organ is the organ for which the dose estimate is being calculated. With most radiopharmaceuticals, it is common to have multiple source organs and to estimate radiation dose for multiple target organs.

MIRD EQUATION

The most commonly used method for calculating dose in nuclear medicine is that proposed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine. The MIRD equation that performs the calculation shown in equation 5 is:[8]

$$D_{r_k} = \sum_h \tilde{A}_h \, S(r_k \leftarrow r_h) \qquad \textbf{(6)}$$

In this equation, r_k represents a target region and r_h represents a source region. The factor S includes all of the terms in equation 5 other than $\tilde{A}$:

$$S(r_k \leftarrow r_h) = \frac{k \sum_i n_i E_i \phi_i(r_k \leftarrow r_h)}{m_{r_k}} \qquad \textbf{(7)}$$

In the MIRD equation, the factor k is 2.13, which gives doses in rad, from activity in microcuries, mass in grams, and energy in MeV. Sometimes the three factors k, n, and E are combined into a single factor called Δ:

$$\Delta_i = k\, n_i\, E_i \qquad \textbf{(8)}$$

Much of the detail in these equations has been shown to aid the understanding of dose calculation. In an actual dose calculation problem, one needs only to calculate the values of Ã (these should be calculated for all important source regions), and multiply it by the appropriate S values, as these are readily available in tabulated form or from computer programs. In the following section, a few simple problems will be presented to illustrate the main principles involved in these calculations. Some of the uncertainties involved in applying these values to individual patients will be discussed along with some of the appropriate adjustments that may be made to make the values more subject-specific. The final section of this lesson will focus on some of the resources available in the literature, via computer programs and on the internet, that are helpful in solving real life problems.

EXAMPLES

Calculation of human time-activity data from animal data

Often, the only available kinetic data for a problem come from measurements made in animals. This occurs in the preclinical phase of the drug approval process and at times when a compound is used that may have not been subject to human trials, but for which dose estimates are desired. Extrapolation of animal data to humans is not an exact science, nor is there any standard method for this calculation. In this example, one approach will be illustrated, but others are available from which to choose. Consider the following data, gathered from the livers of mice (body mass = 20 g):

Time (h)	Mouse Organ Activity Concentration (%/g)[#]
1	4.5
5	2.5
10	1.0
24	0.8

[#] %/g refers to percent of injected activity per gram of liver tissue

To obtain estimates of Ã in the human, these values must be expressed as % of injected activity in the liver at the various times listed. As stated above, many approaches exist for extrapolating these data. It could be assumed that the % in the animal whole organ was equal to the % in the human organ, that the %/g in the animal organ was equal to the %/g in the human organ, etc. One approach, described by Kirschner et al.,[9] involves extrapolating on the basis of the %/g, normalized to the total body weight of each organism (i.e., mouse or human). Thus, each value of %/g in the animal is multiplied by the animal whole body weight (here 0.02 kg), then this result (which has units of %-kg/g) is multiplied by the human organ weight (the human liver is approximately 1900 g) and divided by the human whole body weight (70 kg):

Time (h)	Mouse Organ Activity Concentration (%/g)	Mouse Normalized Activity Concentration (%-kg/g)	Human Organ Activity (%)
1	4.5	0.09	2.44
5	2.5	0.05	1.36
10	1.0	0.02	0.54
24	0.8	0.016	0.43

Another extrapolation method that may be applied is to scale the times (when data is collected and recorded) to account for the different metabolic rates of the two species. This is often done by scaling each time point by a ratio of the species' total body masses raised to some power.[10] Sparks and Aydogen[10] use the scaling factor of 0.25, so that $t_{human} = t_{animal} \times (\text{body mass}_{human}/\text{body mass}_{animal})^{0.25}$ as follows:

Actual Time (h)	Scaled Time (h)
1	7.7
5	38
10	77
24	185

Thus, the scaled times for the humans may be combined with the scaled organ activities to obtain a set of human time-activity data that may be integrated, as in the following example. Again, however, it must be stressed that the choice of extrapolation methods is an area of freedom for the investigator; the two techniques presented here are not the only acceptable methods.

Integration of time-activity data to obtain Ã

Once a set of time-activity data is available, whether extrapolated from animal data or directly measured in humans, one needs to obtain the area under the time-activity curve (Ã). There are a number of ways to obtain this information. Two common methods will be illustrated and then the results of these two methods will be compared. First, one may *directly integrate* the data using the so-called "trapezoidal method." In this method, the area under the curve between any two points is estimated by connecting the points with straight lines and calculating the area of the resulting trapezoid. At time zero, in the liver, it would be assumed that there was zero activity; after the last time point, it might be assumed that removal is only by radioactive decay. For this example, the radionuclide is I-131 at an administered dose of 100 μCi. The area under the curve can be calculated by adding the areas from the various trapezoids:

Time (h)	Human Organ Activity (μCi)	Time Difference from Previous Time Point (h)
0	0.0	--
7.7	2.44	7.7
38	1.36	30.3
77	0.54	39
185	0.43	108

(* = multiplication symbol)

$A_1 = (0 + 2.44) * 7.7/2 =$	9.39 μCi-hr
$A_2 = (2.44 + 1.36) * 30.3/2 =$	57.6 μCi-hr
$A_3 = (1.36 + 0.54) * 39/2 =$	37.1 μCi-hr
$A_4 = (0.54 + 0.43) * 108/2 =$	52.4 μCi-hr
$A_5 = 0.43$ μCi * 1.443 * 8.04 d * 24 hr/d =	120 μCi-hr[b]
Total	276 μCi-hr

[b] The area under the A_5 trapezoid is obtained by assuming that the remaining activity (0.43 μCi) is removed only by physical decay (8.04 days). It can be shown that this area is given by 1.443 * the remaining activity * the physical half-life.

A second method for obtaining the area under the curve would be to fit a function, usually a sum of exponentials, through the data. For this data set, an attempt was made to fit a two exponential function to the data. The resultant fit, obtained using the SAAM II software[11] is shown here as Figure 4.

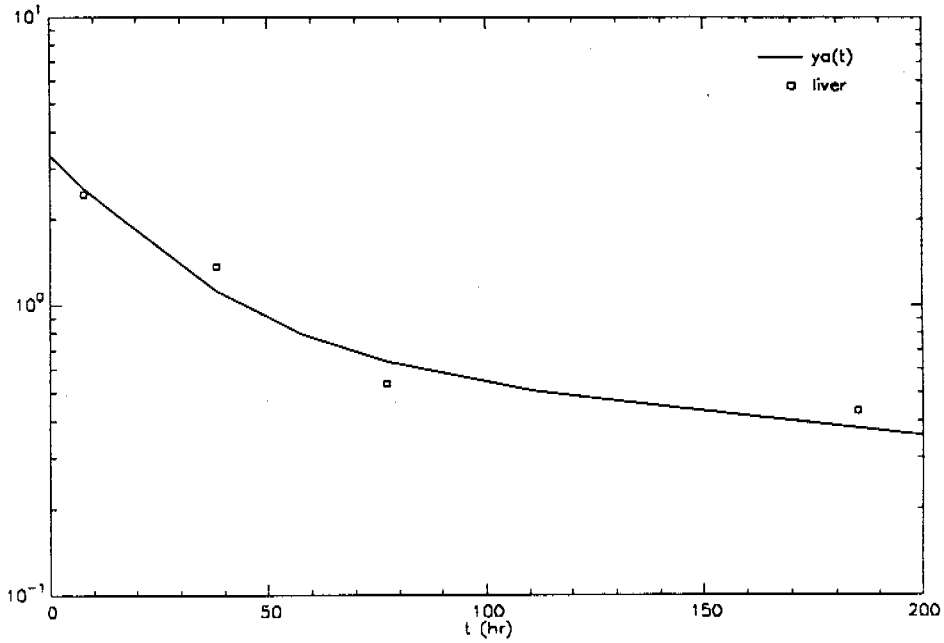

Figure 4

The fitted function is:

$A(t) = 2.6 * \exp(-0.044\ t) + 0.73 * \exp(-0.00359\ t)$.

The integral of this expression, from time zero to infinity is very easily calculated as:

$\tilde{A} = 2.6/0.044 + 0.73/0.00359 = 262\ \mu Ci\text{-hr}$

Note that in the fitted function the curve was not forced to go through zero at time zero. This probably resulted in a slight overestimation of the area under the curve between time zero and the first data point. As shown in the calculation using the trapezoidal method, most of the area under this curve exists from time 38 hours and beyond, so this slight overestimation is probably not important. In other cases, however, this correction might be important, and a function employing this rise from zero to the first time point might be considered.

Combining cumulated activities and S values to get doses

Once reliable estimates of the cumulated activities ($\tilde{A}$) have been determined, they are easily combined with appropriate S values to obtain radiation dose estimates. The S value for liver (as source organ) to liver (as target organ) for I-131 is given by the MIRDOSE code[2] as 2.82×10^{-4} rad/μCi-hr. Continuing with the same example, the dose to the liver would be:

$D_{liver} = \tilde{A}_{liver} * S(liver \leftarrow liver) = 262\ \mu Ci\text{-hr} * 2.82 \times 10^{-4}\ rad/\mu Ci\text{-hr} = 0.074\ rad.$

What if values of Ã for several other organs were also available? In this case, it would be necessary to add up the contributions to the liver's total dose that each organ comprised, as follows:

$\tilde{A}_{kidneys}$ = 200 μCi-hr S(liver←kidneys) = 1.08 x 10^{-5} rad/μCi-hr
$\tilde{A}_{spleen}$ = 100 μCi-hr S(liver←spleen) = 2.86 x 10^{-6} rad/μCi-hr

D(liver←kidneys) = 200 μCi-hr * 1.08 x 10^{-5} rad/μCi-hr = 0.00216 rad
D(liver←spleen) = 100 μCi-hr * 2.86 x 10^{-6} rad/μCi-hr = 0.00029 rad

Therefore, taking into account the contributions of the liver, kidneys, and spleen as source organs, the total dose to the liver is:

D_{liver} = 0.074 + 0.00216 + 0.00029 = 0.076 rad/100 μCi (0.76 rad/mCi)

Another approach to these calculations is to substitute the quantity *residence time*[8] for cumulated activity. The relationship between the two is:

$$\tau_h = \frac{\tilde{A}_h}{A_0} \qquad \textbf{(9)}$$

where τ_h is the residence time of radioactivity in the source organ and A_0 is the total administered activity. The units on τ here are hr (Ã has units of μCi-hr, and A_0 has units of μCi); however, a "residence time" is not a measure of time at all, it is simply the area under the time-activity curve, normalized to the amount of activity administered. If, in the problem above, remembering that the administered activity (A_0) was 100 μCi, the residence times would be:

τ_{liver} = 2.62 hr
$\tau_{kidneys}$ = 2.0 hr
τ_{spleen} = 1.0 hr

To calculate dose using residence times instead of cumulated activities, the following formula is used:

$$D_{r_k} = A_0 \sum_h \tau_h \, S(r_k \leftarrow r_h) \qquad \textbf{(10)}$$

The software program MIRDOSE[2] (discussed in the final section of this lesson) asks the user to enter residence times instead of cumulated activities. If the residence times shown here are entered into the MIRDOSE code and, to make the problem slightly more realistic, if a residence time of 0.15 hr for bladder is included (to simulate urinary excretion) along with a residence time of 5.0 hr for remainder of body (to account for disintigrations that occurred in blood and other nonspecified tissues), the following estimates for the doses to all organs are obtained:

TARGET ORGAN	TOTAL DOSE mGy/MBq	rad/mCi	TARGET ORGAN	TOTAL DOSE mGy/MBq	rad/mCi
Adrenals	4.44E-02	1.64E-01	Pancreas	4.71E-02	1.74E-01
Brain	1.24E-02	4.60E-02	Red Marrow	2.09E-02	7.72E-02
Breasts	1.47E-02	5.42E-02	Bone Surfaces	1.99E-02	7.38E-02
Gallbladder Wall	4.51E-02	1.67E-01	Skin	1.37E-02	5.06E-02
LLI Wall	1.79E-02	6.63E-02	Spleen	7.15E-01	2.64E-00
Small Intestine	2.37E-02	8.77E-02	Testes	1.39E-02	5.13E-02
Stomach	3.04E-02	1.13E-01	Thymus	1.61E-02	5.95E-02
ULI Wall	2.50E-02	9.23E-02	Thyroid	1.42E-02	5.25E-02
Heart Wall	2.33E-02	8.61E-02	Urin Bladder Wall	5.84E-02	2.16E-01
Kidneys	8.58E-01	3.18E-00	Uterus	1.98E-02	7.32E-02
Liver	2.11E-01	7.79E-01	Total Body	2.83E-02	1.05E-01
Lungs	2.12E-02	7.84E-02	EFF DOSE EQUIV	1.26E-01	4.68E-01
Muscle	1.83E-02	6.78E-02	EFF DOSE	5.72E-02	2.12E-01
Ovaries	1.91E-02	7.06E-02	Units on EDE and ED: mSv/MBq or rem/mCi		

The liver dose is slightly higher than that calculated using cumulated activity, mainly due to contributions from the remainder of body.

Note that the software automatically calculates the effective dose equivalent[6] and effective dose.[7] In the calculation of these quantities, certain organs are assigned explicit risk weighting factors, and other organs are chosen for assignment to the "remainder." In the ICRP 30 system, the five highest organs (other than those for which explicit factors are assigned - gonads, breasts, liver, marrow, thyroid and bone surfaces) are given a weighting factor of 0.06. In the ICRP 60 system, some additional organs are given explicit weighting factors, and for the remainder, ten organs (adrenals, brain, ULI, small intestine, kidneys, muscle, pancreas, spleen, thymus and uterus) are assigned weighting factors of 0.005 (total weight 0.05 for the ten organs). However, in cases in which one remainder organ receives a dose that is much higher than the others, that organ is assigned half of the 0.05 weight, and the remaining 9 organs share the rest (0.025/9 = 0.0028). The following table shows how these quantities are derived from the individual organ doses.

Target Organ	Dose (mGy/MBq)	ICRP 30 Weighting Factor	Eff. Dose Equiv Contribution
Ovaries	0.0706	0.25	0.01765
Breasts	0.0542	0.15	0.00813
Lungs	0.0784	0.12	0.00941
Marrow	0.0772	0.12	0.00926
Thyroid	0.0525	0.03	0.00158
Bone Surfaces	0.0738	0.03	0.00221
Kidneys	3.18	0.06	0.191
Spleen	2.64	0.06	0.158
Liver	0.779	0.06	0.047
Bladder	0.216	0.06	0.0130
Pancreas	0.174	0.06	0.0104
TOTAL:			0.468 mSv/MBq

The calculation of effective dose is more complicated, due to more complex rules for handling the remainder organs, but the principle is basically the same.

Dose estimates for the pregnant patient

The accidental or intentional administration of a radiopharmaceutical to a pregnant patient is a topic that deserves some consideration, particularly in regard to the radiation dose received by the embryo/fetus in these situations. Significant improvements in the amount of available information in this area have been made, with the release of the pregnant female phantom series,[4] its implementation in the MIRDOSE software[2], and the release of two publications that apply these results to administration of radiopharmaceuticals. These two publications include the summary of fetal doses for radiopharmaceuticals by Russell et al.[12] and of the workbook by Stabin[13] that summarizes available models for fetal dosimetry. The following example calculations are taken from the fetal dose workbook.[13] Since the tables of Russell et al. address the majority of available radiopharmaceuticals, most dose calculations are just a matter of lookup and perhaps interpolation. Given the uncertainties in the numbers, careful interpolation may not be needed. In most cases, one can look at the dose on either side of the actual time of gestation, and simply use what is believed to be the most appropriate, most conservative estimate. During the first three to six weeks of gestation, the dose to the nongravid uterus (the "early pregnancy" dose) is probably a good estimate of the dose to the fetus.

Example - A woman receives 1000 MBq of Tc-99m sestamibi for a cardiac stress test. Later it is found out that she was one week pregnant at the time of the scan. Here, using data from Russell et al.,[12] the fetal dose estimate is 1000 MBq * 0.012 mGy/MBq = 12 mGy.

Example - A woman receives 200 MBq of Tc-99m MAA for a lung scan at approximately seven months gestation. This situation is not unusual; some women have a tendency to form blood clots in later pregnancy, and lung scans are often performed on patients known to be pregnant. The fetal dose estimate at six months is 200 MBq * 0.005 mGy/MBq = 1 mGy, and the estimate at nine months is 200 MBq * 0.004 mGy/MBq = 0.8 mGy. Since Russell et al. only give dose estimates at three, six, and nine months, some interpolation is required. Given the uncertainty in fetal dose estimates in general, as well as the proximity in time to six months, the most reasonable dose to use might be 1 mGy.

Example: 750 MBq Tc-99m DTPA is administered to a woman in early pregnancy, but due to an obstruction in the collecting system of the kidney, the kidney residence time is thought to be much higher than in the standard model, i.e., there is an increase in kidney residence time to approximately 2.5 hours. No estimates are made of the bladder or remainder of the body residence times. The standard dose estimate (without obstruction of the renal collecting system) as given in the tables provided by Russell et al.[12] is:

$$D_{fetus} = A_0 * [\tau_{kidneys} * S(uterus \leftarrow kidneys) + \tau_{bladder} * S(uterus \leftarrow bladder) + \tau_{remainder} * S(uterus \leftarrow remainder)]$$

$$D_{fetus} = 750 MBq * [0.092 hr * 3600 \,\text{sec}/hr * 8.42 x 10^{-8} mGy/MBq\text{-}s + 1.84 hr * 3600 \,\text{sec}/hr * 1.48 x 10^{-6} mGy/MBq\text{-}s + 2.84 hr * 3600 \,\text{sec}/hr * 2.17 x 10^{-7} mGy/MBq\text{-}s]$$

$$D_{fetus} = 9.0 \; mGy$$

The new dose, modified for this subject is:

$$D_{fetus} = 750MBq*[2.5hr * 3600\,\text{sec}/hr * 8.42x10^{-8}mGy/MBq-s + 1.84hr$$

$$* 3600\,\text{sec}/hr * 1.48x10^{-6}mGy/MBq-s + 2.84hr * 3600\,\text{sec}/hr * 2.17x10^{-7}mGy/MBq-s]$$

$$D_{fetus} = 9.6\ mGy$$

This is a very small change in the dose estimate, which is not surprising, given the small magnitude of the kidney to uterus S value. Consider the situation in which the same woman was encouraged to void her bladder more frequently than in the standard dose estimate for Tc-99m DTPA, and her bladder residence time decreased to 0.9 hr:

$$D_{fetus} = 750MBq*[2.5hr * 3600\,\text{sec}/hr * 8.42x10^{-8}mGy/MBq-s + 0.9hr$$

$$* 3600\,\text{sec}/hr * 1.48x10^{-6}mGy/MBq-s + 2.84hr * 3600\,\text{sec}/hr * 2.17x10^{-7}mGy/MBq-s]$$

$$D_{fetus} = 5.8\ mGy$$

UNCERTAINTIES IN RADIATION DOSE ESTIMATES

The dose estimates calculated above have many uncertainties associated with them. There are uncertainties in the measured values (the animal organ concentrations, human organ activities, etc.). Moreover, extrapolating animal data to humans obviously introduces indeterminate uncertainties into the calculations. The doses are calculated based on a standard individual (70 kg) whose organs are of standard size. Often, the kinetics measured in a test population (e.g., in clinical trials) are applied to obtain a set of radiation dose estimates that are used for all patients. Real patients vary in size and shape from the standard model, and their kinetics also vary from the averages obtained in previous trials. Thus, it must be realized that dose estimates taken from a table of standard numbers have very large uncertainties in application to any patient.

The magnitude of these uncertainties has not been quantitated in any systematic way to date; a 95% confidence interval built around a dose estimate could conceivably include values within a factor of 2 or more of the dose estimate in either direction. And in cases in which the subject's kinetics or organ sizes are known to be aberrant (e.g., obstructed kidneys or biliary duct, enlarged organ, drug-radiopharmaceutical interaactions, etc.), the doses may vary tremendously from the standard values, and some patient-specific calculations may be appropriate.

Such adjustments, however, are not always easy to make. Generally, an organ's self-dose will vary inversely with its mass for electrons and beta particles and inversely to the 2/3 power for photons.[14] Thus, for a pure beta emitter, a person whose spleen is twice the standard mass (180 g) would have a beta self-dose one half the standard value; its photon dose would be $(1/2)^{2/3} = 0.63$ times as large. For cross-irradiation, it is usually safe to assume that the doses will not vary much with organ size.

RESOURCES FOR CALCULATING RADIATION DOSE ESTIMATES

To become adept at these calculations, it is necessary to know as much about available resources as about the actual equations. There are many very useful documents in the literature, and more recently, some resources have become available through electronic means. The MIRD Committee has been publishing many useful documents for over 20 years. The two most common forms of these documents are the MIRD Pamphlets (which give both instruction and tables of useful numerical values for calculating dose estimates) and the MIRD Dose Estimate Reports (which give kinetic models and dose estimates for popular radiopharmaceuticals). Some of these MIRD publications can still be obtained from the Society of Nuclear Medicine. In addition, a number of other documents have been published, including a primer on radiation dose estimates[8] and a compendium of radionuclide decay data.[15] Many other useful papers have been published in a series of Proceedings of the International Radiopharmaceutical Dosimetry Symposia by the Radiation Internal Dose Information Center (RIDIC) in Oak Ridge, TN. Naturally, the open literature also contains various papers of interest, which are too numerous to mention here. RIDIC is a request center that provides information about internal dose to anyone who needs it; it also provides training and calculational services. The telephone number to contact RIDIC is (423)576-3478. RIDIC also makes available at no charge the MIRDOSE personal computer program and maintains an internet web site at which several useful compendia of dose estimates (for adults, children and pregnant women for many radiopharmaceuticals), guidelines on the breast milk excretion of radiopharmaceuticals, and other information are available. The web page address is http://www.orau.gov/ehsd/ridic.htm. Of course, the amount and nature of information on the internet changes rapidly, and also varies in reliability. The reader of this lesson should consider availing him/herself of this information, but should also be wary of material that is not tied to material published in some form in the peer reviewed literature. However, the various publications of the MIRD Committee, especially the MIRD Pamphlets and Dose Estimate Reports, are almost necessary to have if one is to be actively involved in these calculations with any regularity.

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QUESTIONS

1. Calculation of good radiation dose estimates is important:

   a. to satisfy regulators that doses calculated in misadministrations have negligible uncertainty.
   b. to ensure that material published in the scientific literature on radiation dosimetry will be used by the MIRD Committee.
   c. to ensure the safety of the patient and to provide physicians, regulators, and others with the best available information on radiation doses.
   d. to do all of the above.

2. The important dose estimate(s) to calculate for a radiopharmaceutical are:

   a. the critical organ dose and the dose to the organ nearest the critical organ.
   b. the total body dose.
   c. the effective dose equivalent.
   d. doses to most organs, plus some measure of effective whole body dose.

3. Absorbed dose, as defined by the ICRU, is

   a. the mean energy imparted by ionizing radiation to some mass.
   b. the total energy imparted by ionizing radiation due to complete decay of a radionuclide in a defined tissue of interest.
   c. the mean energy imparted by ionizing radiation to some mass, modified by an appropriate quality factor.
   d. the mean energy imparted by ionizing radiation to the mass of the total body, modified appropriately by risk weighting factors for individual organs.

4. Possible units for absorbed dose are:

   a. erg/g
   b. J/kg
   c. Gy
   d. any of the above.

5. Dose equivalent, as defined by the ICRU, is

   a. the mean energy imparted by ionizing radiation to some mass.
   b. the total energy imparted by ionizing radiation due to complete decay of a radionuclide in a defined tissue of interest.
   c. the mean energy imparted by ionizing radiation to some mass, modified by an appropriate quality factor.
   d. the mean energy imparted by ionizing radiation to the mass of the total body, modified appropriately by risk weighting factors for individual organs.

6. Possible units for dose equivalent are:

   a. erg
   b. rad
   c. Sv
   d. Gy

7. The effective dose equivalent (EDE) and the effective dose (ED):

   a. are numerically equal to the "total body" dose in most cases.
   b. are numerically equal to each other in most cases.
   c. are calculated by multiplying calculated absorbed doses by "quality factors", which are in principle dimensionless.
   d. allow nonuniform internal doses to be expressed as a single value, representing an equivalent whole body dose.

8. In our generic form of the absorbed dose rate equation, absorbed dose rate is *directly* proportional to:

   a. the organ mass.
   b. the energy emitted per decay of the nuclide.
   c. the radiation quality factor.
   d. the radionuclide half-life.

9. In our generic form of the absorbed dose rate equation, absorbed dose rate is *inversely* proportional to:

   a. the organ mass.
   b. the energy emitted per decay of the nuclide.
   c. the radiation quality factor.
   d. the radionuclide half-life.

10. In our generic form of the absorbed dose rate equation, in most circumstances, the only term which varies with time, and therefore is subject to integration when we calculate the cumulative absorbed dose equation, is:

   a. the absorbed fraction.
   b. the activity in the organ.
   c. the yield of a particular radionuclide emission.
   d. the organ mass.

11. The cumulated activity, $\tilde{A}$, is:

   a. a measure of the cumulative risk of the organ from its exposure to ionizing radiation.
   b. a measure of the number of disintegrations that have occurred in a source region over time.
   c. a measure of the amount of energy deposited in a target region over time.
   d. a measure of the amount of activity remaining in a source region after several half-lives of the radionuclide have passed.

12. Extrapolation of animal data to humans:

   a. probably introduces some error into the dose estimate calculation.
   b. is not an exact science, and several different methods are available and acceptable.
   c. may be made specific to the animal species involved.
   d. all of the above.

13. Using the extrapolation methods described in the text, a concentration of 0.1%/g in the lungs of a rat, whole body mass 0.2 kg, would compute to what uptake in the lungs of a human (lung mass 1000 g, total body mass 70 kg)?

a. 100%.
b. 0.0014%.
c. 0.286%.
d. 0.02%.

14. The time extrapolation method described in the text is meant to adjust for:

a. the length of the data gathering experiment being shorter than 10 half-lives of the radionuclide.
b. the whole body mass of the species used relative to that of humans.
c. the large differences in activity levels expected in the organ early in time relative to later times.
d. the difference in metabolic rates of the species employed relative to that in humans.

15. One method of *directly* integrating time-activity curves is the:

a. trapezoidal method.
b. successive approximations method.
c. method of least squares.
d. partial derivative method.

16. The integral of the equation $a_1 * \exp(-b_1 t)$ from time zero to infinity may be easily calculated as:

a. $a_1 * \exp(-b_1)$.
b. $a_1 / \exp(-b_1)$.
c. $a_1 * b_1$.
d. a_1 / b_1.

17. In a problem in which $\tilde{A}_{thyroid} = 400$ μCi-hr and S(thyroid ← thyroid) = 2×10^{-4} rad/μCi-hr, what is the dose to the thyroid, assuming no other significant contributions?

a. 0.08 mrad.
b. 0.008 rad.
c. 0.08 rad.
d. 0.8 mrad.

18. The relationship between cumulated activity, $\tilde{A}$, and residence time, τ, is:

a. $\tau = \tilde{A}/A_0$.
b. $\tau = \tilde{A} * A_0$.
c. $\tau / \tilde{A} = A_0$.
d. $A_0 / \tau = \tilde{A}$.

19. In a given situation, the administered activity (A_0) was 10 mCi. The residence times in liver and kidneys were 1.5 hr and 0.9 hr. The S values for these organs irradiating the ovaries are 2.1×10^{-6} rad/μCi-hr and 3.9×10^{-6} rad/μCi-hr. What is the total dose to the ovaries?

a. 67 mrad.
b. 6.7 mrad.
c. 67 rad.
d. 6.7 rad.

20. Uncertainties in radiation dose estimates may arise from:

a. uncertainties in the measured time-activity data.
b. differences between the actual subject and the standard models used to calculate the dose.
c. uncertainties in the masses assumed for the standard individuals.
d. all of the above.

21. The total uncertainty in a calculated radiation dose estimate may be perhaps:

a. around 0.1%.
b. around 1%.
c. around 10%.
d. around 100%.

22. If a patient's thyroid is 3 times the size of the one assumed in a standard phantom, the *electron or beta* self-dose would be:

a. 3 times as large.
b. 1/3 as large.
c. $3^{2/3}$ as large.
d. $(1/3)^{2/3}$ as large.

23. If a patient's thyroid is 3 times the size of the one assumed in a standard phantom, the *photon* self-dose would be:

a. 3 times as large.
b. 1/3 as large.
c. $3^{2/3}$ as large.
d. $(1/3)^{2/3}$ as large.

24. Two indispensable references for anyone working in internal dosimetry in nuclear medicine are:

a. open literature references and symposium proceedings.
b. the MIRD Pamphlets and the MIRD Dose Estimate Reports.
c. the MIRD Pamphlets and symposium proceedings.
d. open literature references and MIRD Dose Estimate Reports.

25. An important information center which provides internal dose information to requestors is:

a. RIDIC.
b. RSIC.
c. NRC.
d. FDA.