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Internal Dose Assessment in Nuclear Medicine

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

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INTERNAL DOSE ASSESSMENT IN NUCLEAR MEDICINE

STATEMENT OF LEARNING OBJECTIVES:

Upon completion of this course, participants will understand the current state of the art in internal dose models and methods and be able to perform basic internal dose calculations for diagnostic and therapeutic radiopharmaceuticals, including some patient-specific modifications.

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INTERNAL DOSE ASSESSMENT IN NUCLEAR MEDICINE

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RADIATION DOSE ASSESSMENT: INPUT DATA, METHODS AND MODELS

In any use of ionizing radiation, an analysis of the risks and benefits is needed to justify and optimize the procedures involved. When radiopharmaceuticals are administered to patients to diagnose and evaluate disease or for therapeutic purposes, estimates of radiation dose to major organs and tissues of the body are required. Internal dose estimates are performed via calculations and the use of theoretical models, as it is not possible to make direct measurements of the radiation doses received. Standardized models of the human body and standardized models of radiopharmaceutical behavior in the body may be used to characterize the radiation doses received by various tissues in the body. The use of standardized models and methods will result in calculations that are both traceable and reproducible. One must always bear in mind, however, that calculated dose estimates are applicable only given the assumptions employed in these standardized models and also are only as good as the input data employed in the calculations. In diagnostic applications, the broad generalization of doses to the nuclear medicine population for a particular patient group (e.g. adults, children, pregnant women) is usually acceptable. All input data have some associated uncertainty, and the calculated results will include the inherent uncertainty from the input data as well as those related to the application of standardized models of the body to a population of patients who may vary substantially in size, age, and other physical characteristics. In therapeutic applications, however, more attention to accuracy and precision is needed, as with the higher doses likely to be encountered, we may approach some organ thresholds for radiation damage, and we should employ more patient-individualized data and models, as possible.

Dose Quantities and Units

The principal quantity of interest to our calculations is 'Absorbed Dose' (D), which is defined as the energy absorbed per unit mass of any material (i.e. not only human tissue):

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

where dε is the mean energy imparted by ionizing radiation to matter in a volume element of mass dm. The units of absorbed dose are energy per unit mass, e.g. erg/g, J/kg, or others. Special units in common use include the rad (equal to 100 erg/g) and the gray (Gy) (1 J/kg). The rad is being replaced by the SI unit value, the gray (Gy), which is numerically equal to 100 rad (i.e., 1 Gy = 100 rad). The multiple of the Gy most applicable to the exposures encountered in diagnostic applications of radiopharmaceuticals is the milligray (mGy), which is equal to 0.001 Gy. In therapeutic applications in nuclear medicine, doses in Gy may be more commonly discussed. Note, as an aside, that doses in 'rad' or 'gray' never need to be given with a plural form; one may speak of 0.5 Gy or 3 Gy, the latter said as "three gray", not "three grays".

The quantity 'Activity' is defined as the number of nuclear transformations per unit time occurring in a given sample of radioactive material. The units are nuclear transformations/unit time. Special units include:

curie (Ci) = 3.7×10^{10} transformations/sec
becquerel (Bq) = 1 transformation/sec

Note: transformations/sec are commonly referred to as dps, standing for disintegrations per second or decays per second.

The radioactive decay constant (λ) is the rate constant for radioactive atoms undergoing spontaneous nuclear transformation. It is a first-order rate constant (i.e., the fraction of radioactive atoms undergoing nuclear transformation per time). Its units are inverse time, (e.g. h^{-1}). The radioactive half-life is the time needed for one half of the atoms in a sample of radioactive material to undergo transformation. Mathematically the half-life is $\ln(2)/\lambda = 0.693/\lambda$, with units of time (hours (h), for

example). A radioactive material with initial activity A_0 will decrease its activity with time according to the expression:

$$A(t) = A_0 e^{-\lambda t} \qquad (2)$$

Plots of the activity of a radioactive substance as a function of time may be made on linear or logarithmic graphs, as in Figure 1.

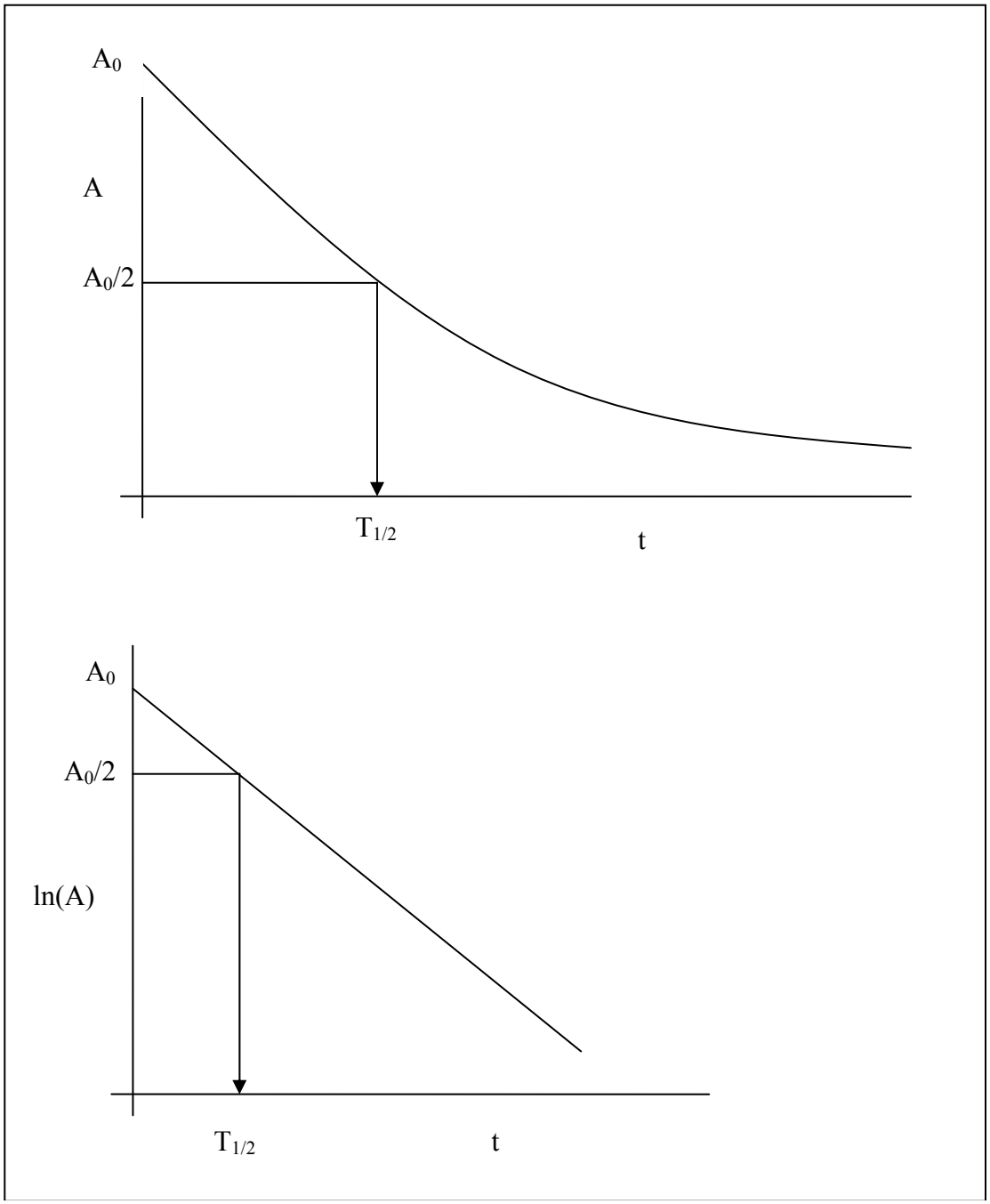


Figure 1. Linear and semi-logarithmic plots of the activity of a radioactive substance as a function of time, showing the radionuclide 'half-life'.

Doses from radiopharmaceuticals are often given as absorbed dose per unit administered activity. This is convenient, in that different studies or different institutions may employ different quantities of activity for various studies using the same radiopharmaceutical. The principal units given most commonly are mGy/MBq, although sometimes traditional units of rad/mCi are provided as well (when one performs all unit conversions, one can show that there are 3.7 rad/mCi or 1 mGy/MBq). Table 1 shows example dose calculations for administration of ^{18}FDG to an adult[1].

Table 1

RADIATION DOSE ESTIMATES FOR ^{18}FDG		
	Estimated Absorbed Dose	
Target Organ	**mGy/MBq**	**rad/mCi**
Adrenals	0.012	0.044
Bladder	0.130	0.481
Bone surfaces	0.011	0.041
Brain	0.038	0.141
Breasts	0.009	0.033
Gall bladder	0.013	0.048
GI-tract:		
Stomach	0.011	0.041
Small Intestine	0.012	0.044
Colon	0.013	0.048
Upper Large Intestine	0.012	0.044
Lower Large Intestine	0.014	0.041
Heart	0.067	0.248
Kidneys	0.017	0.063
Liver	0.021	0.078
Lungs	0.020	0.074
Muscles	0.010	0.041
Esophagus	0.012	0.044
Ovaries	0.014	0.052
Pancreas	0.013	0.048
Red marrow	0.011	0.041
Skin	0.008	0.041
Spleen	0.011	0.041
Testes	0.011	0.041
Thymus	0.012	0.044
Thyroid	0.010	0.037
Uterus	0.018	0.067
Remaining organs	0.012	0.041

Relating Absorbed Doses to Biological Effects - Equivalent Dose

It is often observed that all types of radiation do not produce the same effects at a given dose level (mGy). If a dose D' of a given radiation type produces the same biological endpoint in a given experiment as a dose D of a defined 'reference radiation' (perhaps X-rays of a given kVp), we can define a quantity called the Relative Biological Effectiveness (RBE)[2]:

$$RBE = \frac{D}{D'} \tag{4}$$

So, for example, if a dose of 1 Gy of a reference radiation produces a particular cell survival level, but only 0.1 Gy of another radiation produces the same level of cell killing, the RBE for this experiment would be given as 10. RBE is closely related to the Linear Energy Transfer (LET) radiation (energy imparted to a medium per unit pathlength of the radiation track). High LET radiations generally have higher RBEs (250 kVp X-rays are generally considered to be low LET radiation). The relationship of the two variables is not directly linear, but there is a positive correlation between RBE and LET, until very high LET values are reached, where "overkill" of cells causes the RBE to increase less quickly.

The quantity equivalent dose ($H_{T,R}$) has been defined to account for differences in the effectiveness of different types of radiation in producing biological damage:

$$H_{T,R} = w_R \, D_{T,R} \tag{5}$$

where $D_{T,R}$ is the dose delivered by radiation type R averaged over a tissue or organ T and w_R is the radiation weighting factor for radiation type R. The weighting factor w_R is dimensionless, so fundamentally, the units of equivalent dose are the same as absorbed dose (energy/mass). Operationally, however, we distinguish this using the special units of the rem (which is the D(rad) x w_R) and sievert (Sv) (equal to the D(Gy) x w_R). As 1 Gy = 100 rad, 1 Sv = 100 rem. Like the units for absorbed dose, the rem and sievert (Sv) are collective terms; one need not speak of "rems" and "sieverts", although this may be heard in common speech and even observed in publications.

Values of w_R are very closely tied to RBE values, however, they are NOT exactly equal. Generally, conservative values of RBE were used to set the values assigned for w_R values (also formerly called "quality factors", some readers may recall). RBE values are highly dependent on the experimental conditions (cell type, radiation type, radiation dose rate) and the biological endpoint defined for study

in which they were defined. Radiation weighting factors, on the other hand, are *operational quantities* to be applied to a type of radiation in all situations.

Equivalent dose is defined for ANY kind of radiation, but ONLY in human tissue. The recommended values of the radiation weighting factor have varied somewhat over the years, as evidence from biological experiments has been given and interpreted. The current values recommended by the International Commission on Radiological Protection[3] are (note that values for neutrons are not given, as they are not often of interest in internal dose assessment):

Table 2

RADIATION WEIGHTING FACTORS CURRENTLY RECOMMENDED BY THE ICRP	
Type of radiation	**w_R**
Photons, all energies	1
Electrons and muons	1
Protons and charged pions	2
Alpha particles, fission fragments, heavy ions	20

The weighting factor of 20 for alpha particles is reasonable for radiation protection purposes, but some radiobiological evidence indicates that this value may be too conservative for use in radiopharmaceutical therapy, and may be as low as five[4] or even one[5]. The contrary argument applies to the use of Auger emitters, for which literature values indicate a range of potential RBEs greater than 1, particularly if the emitters are closely associated with cellular DNA[6]. Clearly more investigation and guidance from regulatory and international advisory bodies is needed for the application of these values to therapy with internal emitters.

Relating Absorbed Doses to Biological Effects - Effective Dose

The International Commission on Radiological Protection (ICRP), in its 1979 description of radiation protection quantities and limits for radiation workers[7], defined a new dosimetry quantity, the *effective dose* equivalent (H_e or EDE). The ICRP subsequently renamed this quantity *effective dose* (E) in 1991[8], and new weighting factors were given in ICRP Publication 103[3]. Certain organs or organ systems were assigned dimensionless weighting factors (Table 3), which are assumed to relate to their differing radiosensitivity for expressing fatal cancers or genetic defects.

Table 3

WEIGHTING FACTORS RECOMMENDED BY THE ICRP FOR CALCULATION OF THE 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

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:

$$E = \sum_T H_T \times w_T \qquad (6)$$

Here is an example calculation of the effective dose using the tissue weighting factors from ICRP 60 and given individual organ equivalent doses (note that all weighting factors are not used, and thus do not sum to 1.0):

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. It is *entirely different* from the equivalent dose that one might calculate for the 'whole body', using dose conversion factors for the total body. 'Whole body' doses are not useful in nuclear medicine applications, as all energy from the radiation deposited in the body (usually quite nonuniformly) is averaged over the mass of the whole body (70 kg). Thus, if a radiopharmaceutical concentrates heavily in a few organs, all of the energy absorbed by these (and other) organs is divided by the mass of the whole body to obtain the 'whole body' dose. This quantity is not meaningful in internal dose assessment, unless the radionuclide distribution is nearly uniform, as, for example, for intakes of $^{3}H_2O$, or ^{137}Cs. The goal of nuclear medicine is to administer compounds that selectively concentrate in particular organs or regions of the body for diagnostic or therapeutic purposes, so 'whole body' dose is not a descriptive or useful quantity to calculate. The following table summarizes some of the dose quantities of interest in nuclear medicine dosimetry:

Table 4

SUMMARY OF NUCLEAR MEDICINE DOSE QUANTITIES		
Quantity	**Units**	**Comments**
Individual organ dose (absorbed dose or equivalent dose)	Gy or Sv	Doses to all available organs and tissues in the standardized phantoms should be routinely reported.
Maximum dose organ (absorbed dose or equivalent dose)	Gy or Sv	The individual organ that receives the highest dose per unit activity administered or per study should be considered in study design and execution.
Whole body dose (absorbed dose or equivalent dose)	Gy or Sv	Useful only if all organs and tissues in the body receive an approximately uniform dose. Rarely of value for radiopharmaceuticals. Most useful in external dose assessment.
Effective Dose	Sv	Risk weighted effective whole body dose. Gives the equivalent dose uniform to the whole body that theoretically has the same risk as the actual, nonuniform dose pattern received.

The use of the effective dose in nuclear medicine has been controversial. The MIRD Committee of the Society of Nuclear Medicine has objected to the use of the effective dose quantity in nuclear medicine, due to the uncertainties involved and the fact that the quantity was derived for use with a radiation worker population[9]. Its use, however, is supported by the ICRP and routinely provided for radiopharmaceutical doses[1]. Also, NRC regulations for radiation dose limits to workers are specified in

terms of effective dose equivalent (i.e., 5 rem/yr effective dose equivalent) [reference: 10 CFR 20.1201). For the doses in Table 1, the ICRP gives the effective dose as 0.019 mSv/MBq (0.070 rem/mCi). One should recognize the limitations on the use of the 'effective dose':

- The quantity should never be used in situations involving radiation therapy, as it is related to the evaluation of stochastic risks from exposures involving low doses and dose rates.

- It should not be used to evaluate the risk to a given individual; its application is to populations that receive doses at these levels.

If one accepts the quantity, with all of its inherent assumptions and uncertainties, however, it provides some useful features:

- As just noted, it allows direct comparison of different radiopharmaceuticals that may have completely different radiation dose patterns. For example, compare the use of ^{201}Tl chloride with ^{99m}Tc Sestamibi for use in myocardial perfusion imaging studies. There are many variables that enter into a discussion of which agent is preferable for these studies, and we will not review all of them here. But just from a radiation dose standpoint, if one uses for example 74 MBq (2 mCi) of ^{201}Tl chloride, the two highest dose organs are the thyroid, which may receive about 40 mGy (4 rad) and the kidneys, which may receive about 30 mSv (3 rem)[10]. One might instead use 740 MBq (20 mCi) of ^{99m}Tc Sestamibi, in which case the two highest dose organs are the gallbladder, which may receive about 29 mSv (2.9 rem) and the kidneys, which may receive about 27 mSv (2.7 rem) (rest patients)[11]. The dose to the kidneys is similar, but is 40 mGy to the thyroid more acceptable than 29 mGy to the gallbladder? The effective doses for ^{201}Tl chloride is 11.5 mSv (1.15 rem) and for ^{99m}Tc Sestamibi is 6.7 mSv (0.67 rem). So strictly from a dose standpoint, the use of ^{99m}Tc Sestamibi appears more desirable, although this was not immediately obvious by looking at the highest dose organs.

- Effective doses from radiopharmaceuticals may be added to those received from other procedures outside of nuclear medicine. For example, if a typical value of an effective dose for a lumbar spine x-ray is 2.1 mSv (0.21 rem), and a subject has had two such exams recently and then receives a ^{99m}Tc Sestamibi heart scan, the total effective dose is estimated as 6.7 + (2 x 2.1) = 11 mSv (1.1 rem).

- A popular way to explain radiation risks in a simple way that many members of the public can understand is to express the dose in terms of equivalent years of exposure to background radiation[12]. Estimates of background radiation dose rates vary, but if one chooses 3 mSv/year (300 mrem/year) as an example, then the ^{99m}Tc Sestamibi study discussed above may be thought of as equivalent in total risk to slightly more than 2 years of exposure to natural background radiation. Also, radiation risk can be compared to the annual allowable radiation dose to a radiation worker (i.e., 5 rem effective dose equivalent). The 99mTc Sestamibi study discussed above may also be thought of as equivalent in total risk to 13 % of the annual exposure allowed for a radiation worker.

Kinetic Parameters – Effective half-time

As discussed above, radioactive materials decay according to exponential processes:

$$A(t) = A_0\ e^{-\lambda t} \tag{7}$$

Many materials are also cleared from the body or certain organs in the same way. We can thus develop an equation in these cases for the reduction in the amount of a *nonradioactive* substance:

$$X(t) = X_0\ e^{-\lambda_b t} \tag{8}$$

where X(t) = the amount of the *nonradioactive* substance at time t
X_0 = the initial amount of substance X
λ_b = the *biological* disappearance constant = $0.693/T_b$
T_b = the *biological* half-time for removal.

A biological half-time for removal is exactly analogous to a radioactive (or physical) half-life; i.e., it is the time in which half of the remaining material is removed, but in this case only by biological processes. If we now consider a certain amount of *radioactive* material in the body that is being cleared from the body by an exponential process, two exponential processes will be involved in removing the activity from the body - radioactive decay and biological disappearance. Because these decay constants are essentially probabilities of removal per unit time, the disappearance constants for the two processes can be added to give an "effective disappearance constant":

$$\lambda_e = \lambda_b + \lambda_p \tag{9}$$

where λ_e = effective disappearance constant
λ_p = radioactive (physical) decay constant
λ_b = biological disappearance constant

We can also define an "effective half-time" equal to $0.693/\lambda_e$, which is the time for half of the activity to be removed from the body or organ, by both physical decay and biological removal. It can be easily shown that the effective half-time is related to the other biological and physical half-times by the following relationship:

$$T_e = \frac{T_b \times T_p}{T_b + T_p} \tag{10}$$

Note that the effective half-time for a compound will always be *less than or equal to the shorter of either the biological or radiological half-time*. As two processes are contributing to the removal of the element, the action of the two together must act faster than either acting alone. Note also that to solve the equation for effective half-time, the units for the biological and physical half-times must be the same. Here are some examples.

$T_b = 7$ days $T_p = 20$ days $\qquad T_{eff} = \frac{20 \times 7}{20 + 7} = 5.19\ days$

$T_b = 7$ days $T_p = 7$ days $\qquad T_{eff} = \frac{7 \times 7}{7 + 7} = 3.5\ days$

(note – this is not a coincidence. Every time that the biological and physical half-times are the same, the effective half-time is exactly half of either value, because the value is $(x \cdot x)/2x = x/2$)

$T_b = 7$ days $T_p = 100$ days $\qquad T_{eff} = \frac{100 \times 7}{100 + 7} = 6.54\ days$

$T_b = 7$ days $T_p = 10^9$ days $\qquad T_{eff} = \frac{10^9 \times 7}{10^9 + 7} \approx 7.00\ days$

So, as one half-time gets very long relative to the other, the effective half-time approaches the *shorter of the two*.

Kinetic Parameters – Cumulated Activity

Total dose over some period of integration (usually from the time of administration to infinity) requires calculation of the time integral of the time-activity curve for all important organs. This quantity is sometimes seen with the symbol Ã, as in Figure 2.

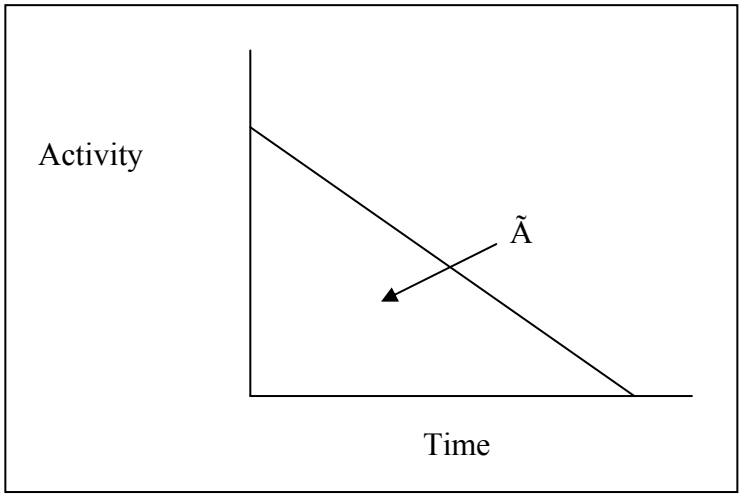


Figure 2. Generalized time-activity curve for an organ in the body with uptake of a radiopharmaceutical.

Regardless of the shape of the time-activity curve, its integral, however obtained, *will have units of the number of total nuclear transitions* (activity, which is transitions per unit time, multiplied by time). Common units for activity are Bq or MBq, and time may be given in seconds or hours. One Bq-s is numerically equal to one transformation (disintegration). For materials that cleared from the body or an organ by exponential processes, the integral of the time-activity curve may be easily evaluated:

$$\widetilde{A} = \int_0^\infty A(t)\,dt = \int_0^\infty A_0\, e^{-\lambda_e t}\,dt = \frac{A_0}{\lambda_e} = 1.443\ A_0 T_e \qquad (11)$$

where A_0 is the initial activity in a given region. Effective half-time is a critical parameter in the determination of cumulated activity and cumulative dose.

Dose Calculations

To estimate absorbed dose in a given organ of the body, one must determine the amount of energy deposited per unit mass of the organ. This yields the quantity absorbed dose, when expressed in proper units, and can be extended to calculation of equivalent and effective dose if desired. We can develop a generic equation for the absorbed dose rate in an organ by assigning numerical values to all quantities needed to establish the energy deposited and the mass of the organ. Once we cite the radionuclide involved, we know the characteristic energies and abundances of the nuclide's emissions. We must know the amount of activity in the organ, and one other factor that we will need is the *fraction of energy released in the organ* that is absorbed within the organ. This quantity is most often called the absorbed fraction and is often 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 having diameters on the order of centimeters). For alpha emissions, electrons and beta particles, most of the energy considered to be absorbed, so we usually assume that the absorbed fraction is 1.0. Alphas, electrons, beta particles, and the like are usually grouped into a class of radiations referred to as 'nonpenetrating emissions', while X and gamma rays are called 'penetrating radiations'. This is simply an *operational definition* used in internal dosimetry. Certainly many beta particles may penetrate materials like paper and Mylar and even penetrate the outer layers of the skin and give a radiation dose to sensitive cells in the body. Using all of these terms, we can develop the proportionality:

$$\dot{D} = \frac{k\ A \sum_i n_i\ E_i\ \phi_i}{m} \qquad (12)$$

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

It is *essential* that the proportionality constant be properly calculated and applied. The results of our calculation will be incorrect (perhaps dangerously so!) unless the units within are consistent and they correctly express the quantity desired. We are not usually interested only in the absorbed dose rate; more likely an estimate of total absorbed dose from an administration is desired. In the above equation the quantity activity (nuclear transformations per unit time) causes the outcome of the equation to have time dependence. To calculate the *cumulative* dose, the time integral of the dose equation must be calculated. In most cases, the only term that has a time dependence is activity, so the integral is just the product of all of the factors in the above equation and the integral of the time-activity curve Ã, developed above. As noted above, the integral of the curve will have units of the number of nuclear transitions (activity, which is transitions per unit time, multiplied by time), Therefore, the equation for cumulative dose would be:

$$D = \frac{k\ \tilde{A} \sum_i n_i\ E_i\ \phi_i}{m} \qquad (13)$$

where D is the absorbed dose (Gy or rad) and Ã is the number of nuclear transitions, or 'cumulated activity' (perhaps given as MBq-sec or μCi-h). The numerical value of k reflects the units chosen for the other terms in the equation. In most problems, of course, we have more than one object (i.e., organ or tissue) containing radioactivity, and we need to add up contributions from all organs or regions with activity to all organs that we want to know the dose to. If we have two objects, 1 and 2, each of which has a calculated value of Ã, $\tilde{A}_1$ and $\tilde{A}_2$, we can calculate the dose to each object as:

$$D_1 = \frac{k\tilde{A}_1 \sum_i n_i E_i \phi_i (1 \leftarrow 1)}{m_1} + \frac{k\tilde{A}_2 \sum_i n_i E_i \phi_i (1 \leftarrow 2)}{m_1}$$

$$D_2 = \frac{k\tilde{A}_1 \sum_i n_i E_i \phi_i (2 \leftarrow 1)}{m_2} + \frac{k\tilde{A}_2 \sum_i n_i E_i \phi_i (2 \leftarrow 2)}{m_2} \quad (14)$$

Here we have now defined values of $\phi(1\leftarrow1)$ (the same as ϕ in equations 12 and 13 above), as well as $\phi(1\leftarrow2)$, $\phi(2\leftarrow1)$, and $\phi(2\leftarrow2)$. For electrons or alpha particles, these absorbed fractions are *generally* set to 1.0 for self irradiation ($\phi(1\leftarrow1)$ and $\phi(2\leftarrow2)$) and zero for cross irradiation ($\phi(1\leftarrow2)$ and $\phi(2\leftarrow1)$); there are some special exceptions. For photons, all absorbed fractions are between 0 and 1, and are determined by Monte Carlo studies, to be discussed below. This equation can obviously be extended to any number of source and target organs, one simply needs all of the input data (values of Ã, ϕ, and m).

Dosimetry systems

The dose equations derived above are generic. Different authors and groups have developed systems to calculate internal dose in different situations. Often some of the factors in the equations are grouped together to simplify calculations, particularly when dealing with radionuclides with complex emission spectra. Different physical quantities (for example absorbed fraction and mass) may be combined into single values. However these quantities may be grouped, hidden, or otherwise moved around in different systems, all of them incorporate the concepts from these equations, and all are based on the same basic concepts and principles. Given the same input data and assumptions, one will obtain identical results.

MIRD System

The equation for absorbed dose given in the MIRD system[13] is:

$$D_{r_k} = \sum_h \tilde{A}_h \; S(r_k \leftarrow r_h) \qquad (15)$$

In this equation, r_k represents a target region and r_h represents a source region. The use of the subscripts "h" and "k" for "source" and "target" is unusual. One might ask, why not "s" and "t", as in the ICRP system? The reason for this is a bit amusing – FORTRAN programmers did the early work done with this system. In the old FORTRAN, integers, which were used as looping indices, began in the alphabet with the letter "i". The letters "i" and "j" had already been used for other variables, so "h" and "k" were used here (with "h" assigned to be an integer)! The cumulated activity is as defined above; all other terms were lumped in the factor "S":

$$S(r_k \leftarrow r_h) = \frac{k \sum_i n_i \; E_i \; \phi_i(r_k \leftarrow r_h)}{m_{r_k}} \qquad (16)$$

In the MIRD equations, the factor k is 2.13, which gives doses in rad, from activity in microcuries, mass in grams, and energy in MeV.

RADAR System

The RAdiation Dose Assessment Resource is both a task group of the Society of Nuclear Medicine and an established electronic resource (www.doseinfo-radar.com) made available on the internet to provide rapid, worldwide dissemination of important dose quantities and data along with a number of publications on the data and methods used in the system as provided in the open literature. The RADAR system[14] has perhaps the simplest representation of the cumulative dose equation:

$$D = N \times DF \qquad (17)$$

where N is the number of disintegrations that occur in a source organ, and DF is:

$$DF = \frac{k \sum_i n_i E_i \phi_i}{m} \qquad (18)$$

The DF is conceptually similar to the 'S value' defined in the MIRD system. The number of disintegrations is the integral of a time-activity curve for a source region, like Ã. RADAR members produced compendia of decay data, dose conversion factors, and catalogued standardized dose models for radiation workers and nuclear medicine patients, among other resources. They also produced the widely used OLINDA/EXM[15] personal computer software code, which used the equations shown here and the input data from the RADAR site. This code was basically a revised version of the MIRDOSE[16] software, which implemented the MIRD method for internal dose calculations (but was not in any way associated with the MIRD Committee itself). The RADAR site and OLINDA/EXM software implement all of the most current and widely accepted models and methods for internal dose calculations (as are described in the next chapter), and are constantly updated to reflect changes that occur in the science of internal dose assessment.

Absorbed Fractions and Dose Conversion Factors

Absorbed fractions for photons at discrete energies were published for standardized phantoms, which contained approximately 25 source and target regions. Tables of S values were never published, but ultimately were made available in the MIRDOSE computer software[16]. Stabin et al. developed a series of phantoms for the adult female, both nonpregnant, and at 3 stages of pregnancy[17]. These phantoms modeled the changes to the uterus, intestines, bladder, and other organs that occur during pregnancy, and included specific models for the fetus, fetal soft tissue, fetal skeleton, and placenta. S values for these phantoms were also made available through the MIRDOSE software[16]. A number of authors have developed more realistic phantoms using image-based methods to replace the stylized models of the 1970's with voxel-based[18,19,20] or mathematical methods like non-uniform rational B-splines (NURBS)[21]. An example of modeling efforts involved with more realistic whole body and organ models, shown in Figure 3.

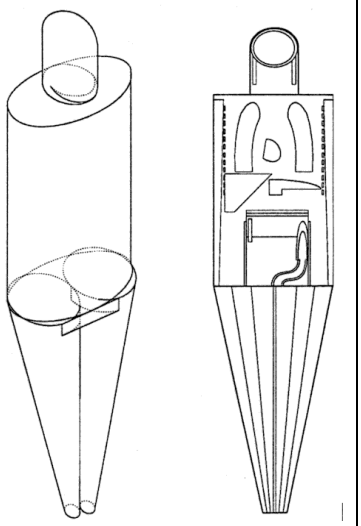
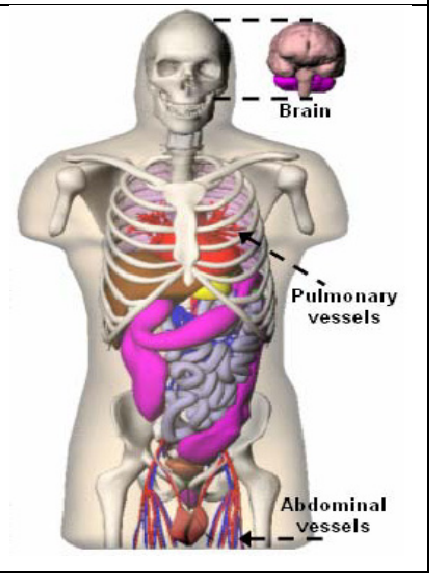
MIRD 5 Phantom[22]	NURBS-based adult male model[21]
	

Figure 3.

Spiers et al. at the University of Leeds[23] first established electron absorbed fractions (AFs) for bone and marrow in a healthy adult male, which were used in the dose factors (DFs), or S values, in MIRD Pamphlet No. 11[24]. Eckerman re-evaluated this work and extended the results to derive DFs for fifteen skeletal regions in six models representing individuals of various ages[25]. The results were used in the MIRDOSE 3 software[16] to provide mean marrow dose, regional marrow dose, and dose-volume histograms for different individuals. This model was updated and improved employing more realistic assumptions of energy absorption at low electron energies[26].

For many years, the only source of dose factors for use in practical calculations were found in MIRD Pamphlet 11[24], in which factors were given for about 25 organs, but only in the adult male phantom, for 117 radionuclides. The MIRDOSE code provided dose factors for over 240 radionuclides, for about 25 organs as well, but in the entire Cristy-Eckerman and Stabin et al. pediatric, adult, and pregnant female phantoms series (10 phantoms). Stabin and Siegel[14] then calculated dose factors for over 800 radionuclides for:

1) All source and target regions in the six models in the Cristy-Eckerman phantom series[27] (see Figure 3),
2) All source and target regions in the four models in the Stabin et al. pregnant female phantoms series[17],
3) All target regions in the Watson and Stabin peritoneal cavity model[28],
4) All target regions in the Stabin prostate gland model[29],
5) All source and target regions in the six models of the MIRD head and brain model[30],

6) All source and target regions in the MIRD regional kidney model[31], and
7) The unit density sphere models of Stabin and Konijnenberg[32].

These dose factors were based on decay data from the Brookhaven National Laboratory resource (http://www.nndc.bnl.gov/)[33], and are useful for implementation in the dose equations described above. The same dose factors are available in the OLINDA/EXM[15] code for use in practical calculations. These dose conversion factors use the child, adult, and pregnant woman phantoms and bone and marrow models described above, and included standard modeling assumptions, as were described in that paper. Examples of absorbed fractions and dose factors are given in the Stabin and Siegel document[14], and on the RADAR internet web site (www.doseinfo-radar.com).

Input Data for Internal Dose Calculations

Input data for radiopharmaceutical dosimetry generally comes from preclinical studies (using animal species) or clinical studies (using human volunteers or patients). In either type of study, one must take care to take enough samples to characterize both the *distribution* and *retention* of the radiopharmaceutical in the body over time. One must gather enough data to study early and late intake and washout phases. In general one should collect data over at least three effective half times of the radiopharmaceutical, and it is essential to collect *at least two time points* per phase of uptake or clearance[34]. One must of course account for 100% of the activity at all times, and account for all major paths of excretion (urine, feces, exhalation, etc.). To design either a preclinical or clinical study, one must have some knowledge of the expected kinetics of the pharmaceutical before data collection begins. For example, the spacing of the measurements and the time of the initial measurement will be greatly different if we are studying a ^{99m}Tc labeled renal agent which is 95% cleared from the body in 180 minutes or an ^{131}I labeled antibody which clears about 80% in the first day and the remaining 20% over the next two weeks. Collecting samples to characterize excretion is sometimes overlooked, but is very important. Often the excretory organs receive the highest doses from a radiopharmaceutical administration. If excretion is not quantified, the modeler must make the assumption that the compound is retained in the body and removed only by radioactive decay. For very short-lived radionuclides, this may not be a problem and in fact may be quite accurate. For moderately long-lived nuclides, this can cause an overestimate of the dose to most body organs and an underestimate of the dose to the excretory organs, perhaps significantly.

Preclinical Studies

Performance of preclinical studies is generally seen to be a necessary step in the development of dose calculations for a new radiopharmaceutical. Obtaining such data involves administration of the radiopharmaceutical to a number of animals for which organ, whole body, and excretion data may be collected. Animal data must be somehow extrapolated to obtain dose estimates for humans. The extrapolation of animal data to humans is not an exact science. Crawford and Richmond[35] and Wegst[36] studied some of the strengths and weaknesses of various extrapolation methods proposed in the literature. One method of extrapolating animal data is the % kg/g method[37]. This method assumes that the concentration in an animal organ will be equal to that in a human organ, after being scaled for the whole body masses of the animal species relative to humans. In this method, the animal organ data need to be reported as % of injected activity per gram of tissue, and the animal whole body weight must be known. The extrapolation to humans then uses the human organ and whole body weight, as follows:

$$\left[\left(\frac{\%}{g_{organ}}\right)_{animal} x(kg_{TB\ weight})_{animal}\right] x\left(\frac{g_{organ}}{kg_{TB\ weight}}\right)_{human} = \left(\frac{\%}{organ}\right)_{human} \qquad (19)$$

More recently, with the advent of imaging systems for small animals, instead of harvesting and counting organs, the animals may be imaged, and the uptake in the various organs of the body quantified as we do in humans, which will be described now.

Clinical Studies

In clinical studies, data are collected with a nuclear medicine gamma camera. Quantification of data gathered with these cameras may be achieved in a number of ways. One method is the use of developed and processed anterior and posterior projection images of the patient which (the 'Conjugate View' method). As this is a projection image, the actual depth of objects containing activity within the patient is not known. Regions of Interest (ROIs) are drawn around objects that are recognizable as internal organs or structures; the number of counts in a ROI, however, cannot be used directly to calculate how much activity is in the organ. Some corrections are needed to the observed number of counts to obtain a reliable estimate of activity in this object. In this method, images are taken in front of and behind the patient, and a geometric mean of the two values is taken. This geometric mean, when corrected for attenuation, is theoretically independent of depth for most radionuclides of interest, and

thus this quantity is thought to be the most reliable for use in quantification. Corrections for the presence of scattered radiations within the photopeak channel can be addressed by using an appropriate scatter correction technique; one popular approach is the Double or Triple Energy Window method[38]. After scatter correction has been applied, the activity of the source within the ROI is thus given by:

$$A_{ROI} = \sqrt{\frac{I_A I_P}{e^{-\mu_e t}}} \frac{f_j}{C} \qquad (20)$$

where I_A and I_P are the Anterior and Posterior counts in the region, μ_e is the effective attenuation coefficient, t is the average patient thickness over the ROI, f_j is the source self-attenuation coefficient (given as $[(\mu_e t/2)/\sinh(\mu_e t/2)]$, but which is rarely of much impact in the calculation and so is usually neglected), and C is a source calibration factor (cts/s per Bq), obtained by counting a source of known activity in air. Thus, activity in identifiable regions of the body, like liver, spleen, kidneys, etc. may be determined at individual times. ROIs may be drawn over the entire body, to track the retention and excretion of the compound in the body. Excreta samples may also be taken to study excretion pathways. If only a single excretion pathway is important, knowledge of whole body clearance may be used to explain excretion. Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) methods may also be used to obtain quantitative data for dosimetry studies. This takes considerably more effort, both in data gathering and analysis, and is employed by fewer investigators.

Data Analysis

Once a suitable set of kinetic data is gathered, we wish to obtain an estimate of the area under the time-activity curve for each of the source regions to obtain the numbers of disintegrations (N or Ã). In general, there are three levels of complexity that our analysis can take:

Direct integration

One can directly integrate under the actual measured values by a number of methods. This does not give very much information about your system, but it does allow you to calculate the area under the time-activity curve rather easily. The most common method used is the Trapezoidal Method, simply approximating the area by a series of trapezoids.

Least Squares Analysis

In this application, one attempts to fit curves of a given shape to the data. The curves are represented by mathematical expressions that can be directly integrated. The most common approach is to attempt to characterize a set of data by a series of exponential terms, as many systems 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:

$$A(t) = a_1 e^{-b_1 t} + a_2 e^{-b_2 t} + \cdots \qquad (21)$$

The method evaluates the squared difference between each point and the solution of the fitted curve at that point, and minimizes this quantity by 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:

$$\int_0^\infty A(t)\,dt = \frac{a_1}{b_1} + \frac{a_2}{b_2} + \ldots \qquad (22)$$

If the coefficients a_i are in units of activity, this integral represents cumulated activity (the units of the b_i are time^{-1}).

Compartmental analysis

Another approach is to describe the system as a group of compartments linked through transfer rate coefficients. Solving for Ã of the various compartments involves solving a system of coupled differential equations describing transfer 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, but not obtained by least squares fitting each compartment separately, but by varying the transfer rate coefficients between compartments until the data are well fit by the model. [39]

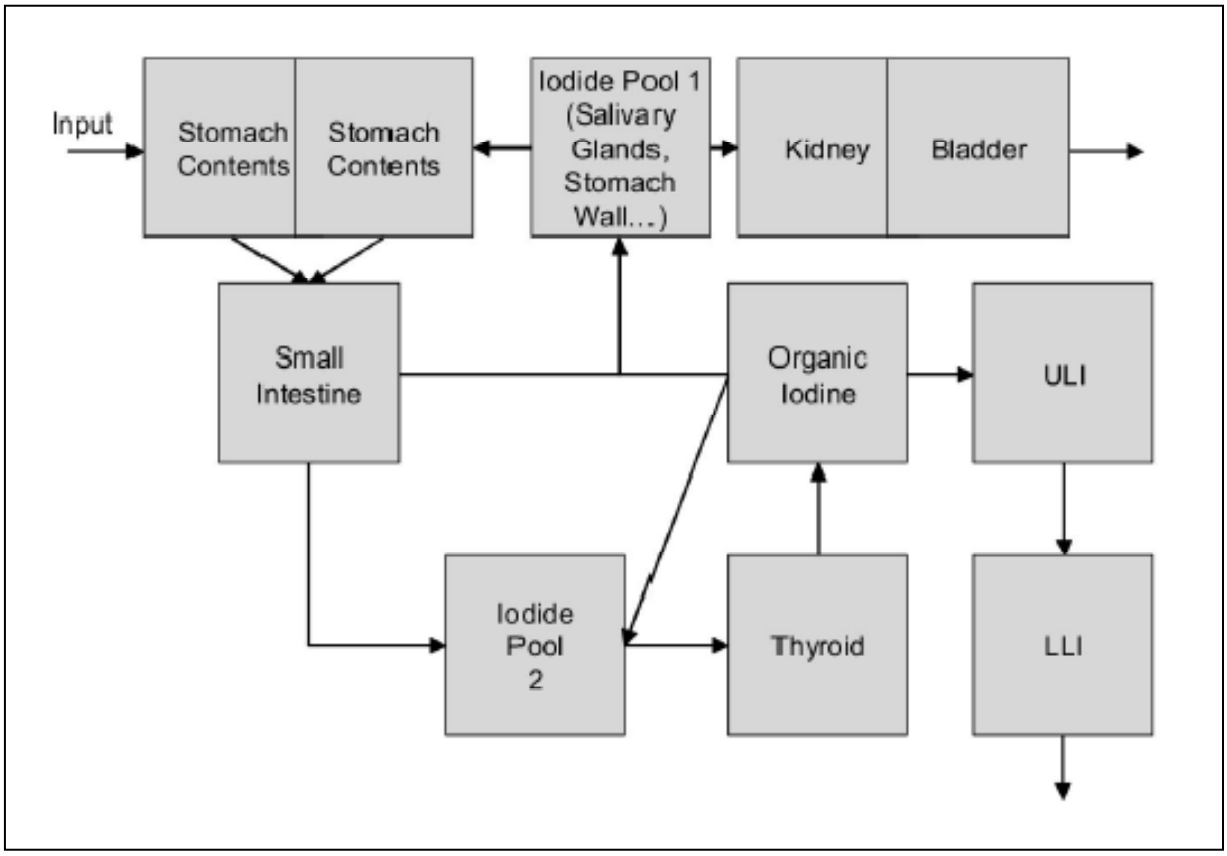


Figure 4. Compartmental model for oral intake of iodide, from Vicini et al.

Examples

Animal Data Extrapolation

We will now work some numerical examples, to clarify the use of all data and variables in a typical dose study. Consider the following set of data collected in an animal weighing 20g. The data include the radioactive decay of the radionuclide (^{123}I).

Table 5

ANIMAL DATA EXTRAPOLATION EXAMPLE					
	Activity in Source Organ at Indicated Time After Administration				
ANIMAL	**1 hr**	**3 hr**	**6 hr**	**16 hr**	**24 hr**
%ID/organ	**2.65**	**2.49**	**1.97**	**0.714**	**0.410**
(%ID/g)	**26.7**	**25.6**	**21.6**	**7.91**	**3.99**
HUMAN					
%ID/organ	**14.6**	**14.0**	**11.8**	**4.32**	**2.18**

The animal whole body weight was 20 g (0.02 kg), and the source organ was the liver, with a (human) mass of 1910 g. The human total body weight for the standard adult male of 70 kg was used in the calculations. For example:

$$\frac{26.7\ \%}{g}\ (animal) \times 0.020\ kg \times \frac{1910\ g}{70\ kg} = \frac{14.6\ \%}{organ}\ (human)$$

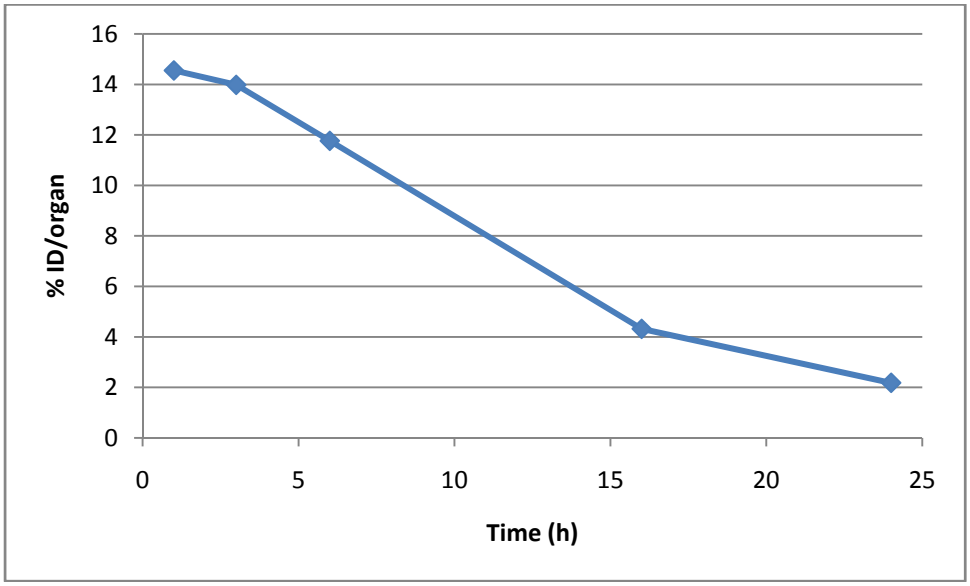


Figure 5. Time-Activity Curve for the Liver from the Extrapolated Animal Data

Numerical Integration of Extrapolated Animal Time-Activity Data Curve

We may assume that the activity in the liver was 0 at time 0, thus the area under the curve from 0 to 1 hour is simply (0.146 Bq/Bq administered) x 0.5 x 1 hr = 0.0728 Bq-h/Bq administered. For the next four segments of the curve, the area is that of a trapezoid connecting the points and the time axis. The second segment is (0.146 + 0.140 Bq/Bq administered) x 0.5 x (3-1) hr = 0.285 Bq-h/Bq administered. The next three segments are:

(0.140 + 0.118 Bq/Bq administered) x 0.5 x (6-3) hr = 0.386 Bq-h/Bq administered
(0.118 + 0.0432 Bq/Bq administered) x 0.5 x (16-6) hr = 0.804 Bq-h/Bq administered
(0.0432 + 0.0218 Bq/Bq administered) x 0.5 x (24-16) hr = 0.26 Bq-h/Bq administered

The sum of all of the areas calculated is 1.81 Bq-h/Bq administered. The activity is low, but still significant at the last time. Thus, we may wish to assume that after the last time point, there is removal only by radioactive decay, and add an area from 24 hours to infinity as:

1.443 x 0.0218 Bq/Bq administered x 13.2 h = 0.415 Bq-h/Bq administered, for a total of 2.22 Bq-h/Bq administered (also equal to 2.22 MBq-h/MBq administered). The dose from the liver to the liver (human), assuming a dose factor of 5.52×10^{-6} mGy/MBq-s (from the RADAR site or OLINDA/EXM code) would be:

$$2.22 \text{ MBq-h/MBq} \times 5.52 \times 10^{-6} \text{ mGy/MBq-s} \times 3600 \text{ s/h} = \underline{0.044 \text{ mGy}}$$

Clinical Data Set

The following data (for an ^{131}I labeled compound) were obtained with a ROI drawn around a region representing the liver on anterior and posterior planar whole body images of a subject:

Time (h)	View	organ # pixels	organ cts/pixel	bkgd # pixels	bkgd cts/pixel	Net cts/pixel	Net cts
2	Anterior	3500	27.87	290	8.80	19.07	66744
2	Posterior	3500	23.54	290	7.18	16.36	57250
4	Anterior	3500	25.20	290	9.35	15.85	55486
4	Posterior	3500	20.69	290	7.38	13.31	46577
24	Anterior	3500	10.09	290	5.03	5.07	17733
24	Posterior	3500	7.16	290	3.97	3.19	11173
48	Anterior	3500	3.96	290	2.16	1.80	6314
48	Posterior	3500	3.19	290	1.79	1.39	4874
72	Anterior	3500	1.59	290	0.94	0.66	2302
72	Posterior	3500	1.38	290	0.75	0.63	2218

The time at which the images were taken is in the first column, the number of pixels in the organ region and the counts per pixel in the third and fourth. The next two columns show the number of pixels and the counts per pixel in a background region associated with the ROI. The last two columns then give the net number of counts per pixel (source ROI counts/pixel minus the background ROI counts/pixel) and the last column gives the net counts established for the ROI (net counts per pixel times the number of pixels in the organ ROI). Adding a correction for attenuation, we obtain the following table:

Time (h)	Geometric Mean Counts	Attenuation Factor	Activity (counts)	Fraction of Administered Activity
2	61815	0.367	168294	0.0871
4	50837	0.367	138407	0.0749
24	14076	0.367	38322	0.0250
48	5547	0.367	15104	0.0103
72	2260	0.367	6152	0.0043

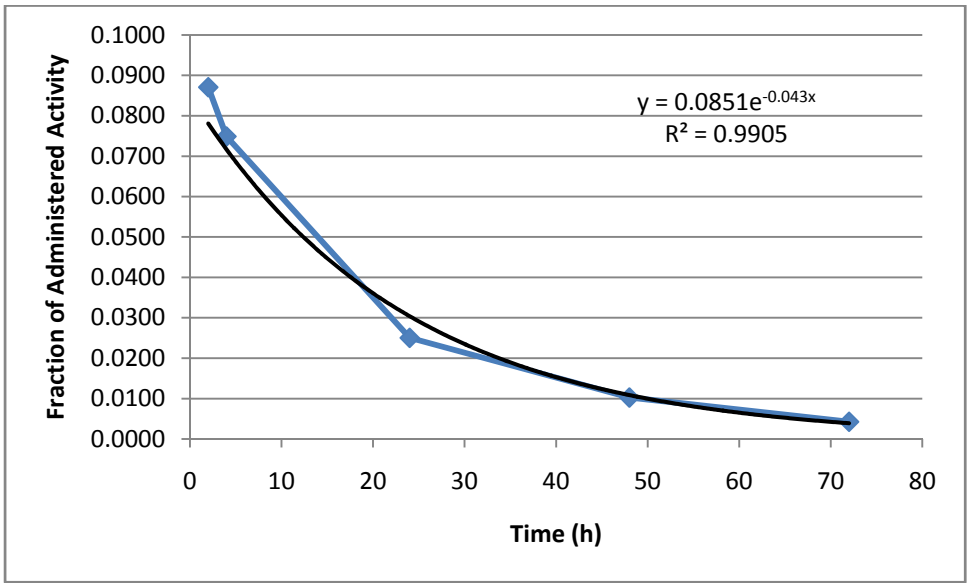


Figure 6. Time-Activity Curve for the Liver from the Clinical Data Set, Showing a Single Exponential Fit to the Data

Figure 6 shows a plot of the data, with a best fit single exponential trend line as well. As these data also include the radioactive decay of the nuclide (in this case ^{131}I), we can calculate the number of disintegrations easily:

$A_{liver}(t) = 0.0851 \times e^{-0.043xt}$

$\tilde{A}_{liver}$ = (0.0851 MBq/MBq administered)/0.043 h^{-1} = 1.98 MBq-h/MBq administered

Let's assume that we followed the same procedure for the spleen and obtained a value of $\tilde{A}_{spleen}$ = 0.45 MBq-h/MBq administered. We may obtain dose factors from the OLINDA/EXM code:

DF(liver←liver) = 2.15×10^{-5} mGy/MBq-s = 7.74×10^{-2} mGy/MBq-h

DF(spleen←liver) = 2.16×10^{-7} mGy/MBq-s = 7.78×10^{-4} mGy/MBq-h

DF(liver←spleen) = 2.16×10^{-7} mGy/MBq-s = 7.78×10^{-4} mGy/MBq-h

DF(spleen←spleen) = 1.96×10^{-4} mGy/MBq-s = 7.06×10^{-1} mGy/MBq-h

Thus we can calculate dose to liver and spleen, if these are the only two significant source regions in the problem:

D_{liver} = 1.98 MBq-h/MBq x 7.74×10^{-2} mGy/MBq-h + 0.45 MBq-h/MBq x 7.78×10^{-4} mGy/MBq-h

D_{liver} = 0.154 mGy/MBq

D_{spleen} = 1.98 MBq-h/MBq x 7.78×10^{-4} mGy/MBq-h + 0.45 MBq-h/MBq x 7.06×10^{-1} mGy/MBq-h

D_{spleen} = 0.319 mGy/MBq

CONCLUSION AND SUMMARY

Estimation of radiation doses is an important component in the overall safety evaluation of the use of any radiopharmaceutical, diagnostic or therapeutic. In the use of either preclinical or clinical data, a series of steps is needed to acquire and analyze sufficient data to perform a dosimetric assessment. Careful attention to data gathering methods and to numbers, quantities, and units in the analysis is essential to a successful outcome. At present, our analyses are based on standardized, reference individuals, which generally represent the median individual of a given population (e.g. adult males or females, children, etc.). Individual patients vary considerably, and a number of simple modifications can be made to standardized dose estimates (e.g. scaling of organ masses). For more details see the RADAR textbook on nuclear medicine fundamentals[40]. In addition, current research is ongoing to develop image-based, truly patient-individualized methods for therapy subjects[40]. For the present, however, for diagnostic pharmaceuticals, the use of the standardized methods and models given in this lesson are well accepted as adequate for most situations, and the use of these methods with some patient-specific adjustments is usually accepted for use with therapeutic agents as well.

ASSESSMENT QUESTIONS

1. Internal dose calculations:

    a. Are based on standardized models developed by expert groups, and thus are reported with very low uncertainties.
    b. Are developed for different patient groups (e.g. adults, children, pregnant women) and then averaged to apply to the entire population.
    c. Must be based on calculations, as one cannot generally measure absorbed doses within the body.
    d. Are not of interest for diagnostic radiopharmaceuticals, only those used in therapeutic applications.

2. The principal quantity of interest to internal dose calculations is the:

    a. Absorbed dose
    b. Equivalent dose
    c. Effective dose
    d. Population dose

3. One gray (Gy) is numerically equal to:

    a. 10 rad
    b. 1 rad
    c. 0.1 rad
    d. 100 rad

4. The radioactive half-life, $T_{1/2}$, is:

    a. The time required for half of the energy emitted by a radionuclide to be released within the body.
    b. The time required for half of the remaining activity in a radioactive sample to be removed.
    c. The time required for half of the atoms in a molecule to undergo reactions with a radioactive label.
    d. The time required for half of the activity in a radiopharmaceutical to be taken up in some organ or tissue.

5. The effective half-life, T_e, is:

    a. The time required for half of the remaining activity in an organ or the body to be removed, by both physical and biological processes.
    b. The time required for half of the remaining activity in an organ or the body to be removed, by physical processes only.
    c. The time required for half of the remaining activity in an organ or the body to be removed, by biological processes only.
    d. The time required for half of the remaining activity in an organ or the body to be removed, by a combination of physical, chemical, and biological processes.

6. Typical dose estimates for a radiopharmaceutical may be given in units of:

    a. mGy/mSv of equivalent dose expected to a population.
    b. mGy/MeV of emitted photon or electron energy.
    c. mGy/mGy to a standardized individual
    d. mGy/MBq of administered radiopharmaceutical.

7. The Relative Biological Effectiveness is:

    a. The dose needed to obtain some predefined radiation effect under a specified set of experimental conditions.
    b. The effectiveness of radiation in causing alterations in a living system, such that biological elimination is noticeably affected.
    c. The ratio of the dose needed to cause a biological effect in one individual over that needed to produce an effect in a reference individual.
    d. The ratio of the dose needed to obtain a biological effect from a reference radiation over that from the radiation in question.

8. Radiation weighting factors, w_R, are:

    a. Numerically equal to RBE values from which they were derived.
    b. Unrelated to RBE values; this is a common source of confusion.
    c. Closely tied to RBE values, but not numerically equal in all cases.
    d. Equal to the ratio of two RBE values, chosen to weight the absorbed dose in the context of a given biological experiment.

9. The quantity effective dose, E, is:

    a. The sum of the individual organ dose equivalents from individual organs in the body, which gives a total dose equivalent to that individual.
    b. The sum of equilibrium doses to a population, weighted according to age group and cancer risk statistics.
    c. The sum of weighted dose equivalents from individual organs in the body, in theory equal to a uniform whole body dose equivalent that would result in the same overall risk.
    d. The sum of absorbed doses to individual organs, with a weighting factor applied to the sum such that the equivalent dose is equal to the average absorbed dose in the whole body.

10. The quantity effective dose:

    a. Should always be used in evaluating the effects of the therapeutic applications of radiopharmaceuticals.
    b. Should never be used in evaluating the effects of the therapeutic applications of radiopharmaceuticals.
    c. Should be used cautiously in evaluating the effects of radiation on the developing embryo or fetus.
    d. Should be used by the physician in evaluating the amount of activity of a particular radiopharmaceutical to be applied to a given patient.

11. The ‘cumulated activity’, the area under the time-activity curve for an organ or region, is:

    a. The time-averaged disintegration rate for the organ or region, that gives the mean dose rate to that organ or region over time.
    b. The activity that an organ or region takes up, as a fraction of that administered to the subject.
    c. The total number of disintegrations that occurred in that organ or region, integrated over time.
    d. The cumulative effect of radiation damage to that organ or region, from all disintegrations that occurred over some specified time interval.

12. An absorbed fraction of unity (1.0) is usually assigned:

    a. For alpha, electron and beta emissions when the source of radiation is different than the target.
    b. For alpha, electron and beta emissions when the source of radiation is also the target.
    c. For photon emissions when the source of radiation is also the target.
    d. For photon emissions when the source of radiation is different than the target.

13. The various dosimetry systems developed by different authors or groups:

    a. Apply the same concepts and will give the same results, given the same input data.
    b. Were meant to be applied in different situations (nuclear medicine patients, radiation workers), and thus give different results as different dose limits are applicable.
    c. Are strictly only applicable to the group for which they were defined, for example nuclear medicine patients or radiation workers.
    d. Are based on different unit systems (SI or non-SI), and the results from different systems will be necessarily different.

14. The MIRDOSE and OLINDA/EXM personal computer software for internal dose calculations in nuclear medicine were developed by:

    a. The Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine.
    b. The International Commission on Radiological Protection (ICRP).
    c. The National Council on Radiological Protection and Measurements (NCRP).
    d. The RAdiation Dose Assessment Resource (RADAR) task group of the Society of Nuclear Medicine.

15. The number of time points per phase of radiopharmaceutical uptake or clearance needed to adequately characterize the kinetics of a given organ or region is:

    a. Two.
    b. One.
    c. Three.
    d. Four.

16. The two sources of input data for radiopharmaceutical dose estimates are usually:

    a. Preclinical (animal) studies and open literature articles.
    b. Open literature articles and clinical studies.
    c. Preclinical (animal) and clinical studies.
    d. Clinical studies and Monte Carlo studies.

17. The most common method for estimating activity from gamma camera images is:

    a. The Triple Energy Window method.
    b. The % kg/g method.
    c. The Conjugate View method.
    d. The least squares method.

18. One example of a ‘direct integration’ method for estimating the area under a time-activity curve is:

    a. The least squares method.
    b. The trapezoidal method.
    c. The conjugate view method.
    d. The compartmental modeling method.

19. One important issue with ‘direct integration’ methods is that:

    a. One must assume that the same geometric shape can represent all areas under the curve.
    b. One must have equally spaced data points to apply a direct integration method.
    c. One must calculate the area under the curve using strongly conservative assumptions, which may result in an overestimate of the dose.
    d. One must make an assumption about how to calculate the area under the time-activity curve after the last data point.

20. The most common type of curve used in regression analysis of radiopharmaceutical kinetic data is:

    a. A trapezoid or sum of trapezoids.
    b. A polynomial or sum of polynomials.
    c. A power function or sum of power functions.
    d. An exponential or sum of exponentials.

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