Radiation Dosimetry: Definitions and Basic Quantities

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7.1 Introduction

The discovery of X-rays by Roentgen in 1895 began a new era in medicine. The first uses of ionizing radiation permitted the noninvasive visualization of internal structures of the body, which was quite revolutionary. Later in 1924, de Hevesy and colleagues performed studies of the kinetics of lead-210 (^{210}Pb) and bismuth-210 (^{210}Bi) in animals, introducing the idea of the use of radioactive substances to investigate dynamic processes in the body and study physiological, as opposed to only anatomical, information [1].

This science grew steadily for many years, and the Society of Nuclear Medicine was organized 30 years later, to facilitate the exchange of information by professionals in this field. Most applications of the science of nuclear medicine are *diagnostic*, i.e., evaluating body structures and internal processes to diagnose diseases and guide medical response to potential human health issues. Radiopharmaceuticals used in nuclear medicine have also been applied for many decades in *therapeutics*, i.e., exploiting the ability of ionizing radiation to destroy potentially harmful tissues in the body (e.g., cancer or inflamed joints). A radiation dose analysis is a necessary element of the safety analysis to permit the use of either diagnostic or therapeutic radiopharmaceuticals. For diagnostic compounds, the US Food and Drug Administration (FDA) evaluates a number of safety parameters during the approval process for new pharmaceuticals; internal dose assessment (or "dosimetry") is one of the key areas of evaluation. During the various phases of the drug approval process, radiation dose estimates are generated, and average values will be included with the product information package that accompanies radioactive drugs that are brought successfully to market. These dose estimates are not often used directly in day-to-day practice in the clinic, but are often referred to when comparing advantages and disadvantages of possible competing drug products, by radioactive drug research committees (RDRCs) in evaluating safety concerns in research protocols, and other situations.

7.1.1 Practice of Internal Dosimetry

In therapeutic applications, physicians *should* perform a patient-specific evaluation of radiation doses to tumors and normal tissues in order to design a

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treatment protocol that maximizes the dose to malignant tissues while maintaining doses to healthy tissues at acceptable levels (i.e., below thresholds for direct deleterious effects). This is done routinely in external radiation therapy treatment planning, but unfortunately, dose assessment is not routinely practiced in most clinics at present in the administration of radiopharmaceuticals for therapy. All patients are generally treated with the same or similar amounts of activity, without regard to their specific biokinetic characteristics. Many investigators have called for dose assessment to become a routine part of the practice of radiopharmaceutical therapy [2–6]' in the interests of improving patient care.

7.1.2 Responsibilities

The patient/physician relationship involves trust, the weighing and balancing of a number of risks and benefits of possible procedures, discussion of personal information, and other delicate issues such as personal, ethical, and religious standards. Physicists provide information that the physician must understand and convey to his/her patients, and thus play a peripheral, but still important, part of the process of the delivery of medical care involving radioactive substances. In diagnostic applications, the physicist is rather removed from the process, having previously provided dose calculations to regulatory and other bodies for their evaluations of the use of radiopharmaceuticals in clinical practice and research. In radiopharmaceutical therapy, however, the physicist should be more involved in the future, as is true for external beam therapy, and much useful experience can be gained that will ultimately result in better and more durable patient outcomes [6].

7.2 Basic Quantities and Units

Accurate quantification of the various terms involved in our theoretical calculations is important to obtaining an acceptable outcome. Many of the conversions that occur in the use of quantities in the atomic world have very large or very small exponents (e.g., there are 1.6×10^{-13} J in 1 MeV). Thus, when unit conversions are performed, involving multiplication and/or division, small errors in values of a conversion constant may result in *enormous* errors in our final calculation. Common sense must be applied in the choice of the number of significant figures shown in presented dose estimates; the final value should also be rounded to a *sensible* number of significant figures. Roger Cloutier once quipped that "I only use one significant digit in reporting internal dose values because you can't use any fewer!" [7] In internal dose assessments, a number of modeling assumptions and simplifications are usually applied to solve a problem. Numerous uncertainties exist in the input values as well as the applicability of the values and the models used. Providing organ dose or effective dose values to ten significant figures is simply unreasonable. Final answers for any radiopharmaceutical dose estimate should be given to two or three significant figures, no more.

7.2.1 Administered Activity

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/s

Becquerel (Bq) = 1 transformation/s

Two other quantities are also defined: The radioactive decay constant (λ) is the rate constant for radioactive atoms undergoing spontaneous nuclear transformation. Its units are inverse time, (s^{-1}, for example). 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 $\ln(2)/\lambda = 0.693/\lambda$. Its units are time (seconds, for example).

7.2.2 Absorbed Dose

Absorbed Dose is the energy absorbed per unit mass of any material (i.e., not only human tissue). Absorbed dose (D) is defined as:

$$D = \frac{d\varepsilon}{dm}$$

where $d\varepsilon$ 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 include the rad (equal to 100 erg/g), the gray (Gy) (1 J/kg). 1 Gy = 100 rad. The word "rad" was originally an acronym meaning "radiation absorbed dose." The rad is being replaced by the SI unit value, the gray (Gy), which is equal to 100 rad. Note that "rad" and "gray" are collective quantities; one does not need to place an "s" after them to indicate more than one.

Closely related to absorbed dose is the quantity kerma, which is actually an acronym meaning "kinetic energy released in matter." Kerma is given as

$$K = \frac{dE_{\mathrm{Tr}}}{dm}$$

dE_{Tr} is the sum of the initial kinetic energies of all the charged ionizing particles liberated by uncharged ionizing particles in a material of mass dm. Kerma has the same units and special units as absorbed dose, but is a measure of energy *liberated*, rather than energy *absorbed*. The two will be equal under conditions of charged particle equilibrium, and assuming negligible losses by bremsstrahlung radiation.

7.2.3 Linear Energy Transfer

The quantity Linear Energy Transfer (LET) is given as:

$$\mathrm{LET} = \frac{dE_{\mathrm{L}}}{dl}$$

where dE_{L} is the average energy locally imparted to a given medium by a charged particle passing through a length of medium dl. The units of LET are often given as keV/μm, although any units may be used. LET is an important parameter used in characterizing energy deposition in radiation detectors and in biological media in which we wish to study the effects of different types of radiation.

7.2.4 Relative Biological Effectiveness (RBE)

When the effects of other radiations on the same cell population to produce the same endpoint are studied, it is often observed that all radiation does not produce the same effects at the same dose levels as this "reference" radiation. If a dose D' of a given radiation type produces the same biological endpoint in a given experiment as a dose D of our reference radiation, we can define a quantity called the Relative Biological Effectiveness (RBE) [8] as:

$$\mathrm{RBE} = \frac{D}{D'}$$

So, for example, if a dose of 1 Gy of the reference radiation produces a particular cell survival level, but only 0.05 Gy of alpha radiation produces the same level of cell killing, the RBE for alpha particles in this experiment is given as 20.

RBE is closely related to radiation LET. High LET radiations generally have high 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 clearly a positively correlated relationship of RBE with LET, until very high LET values are reached, where "overkill" of cells causes the RBE not to increase so quickly.

The reader may have noted that in the numerical example chosen above, the RBE for alpha particles is exactly equal to the currently recommended value of w_{R}, the radiation weighting factor used in radiation protection. This was done intentionally. 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"). 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 chosen operational quantities to be applied to a type of radiation in all situations.

7.2.5 Radiation Weighting Factor and Equivalent Dose

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:

$$H_{T,R}=w_R D_{T,R}$$

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 really dimensionless, so fundamentally, the units are the same as absorbed dose (energy/mass). Operationally, however, we distinguish using the special units of the rem (which is the D(rad) × w_R) and sievert (Sv) (equal to the D(Gy) × w_R). As 1 Gy = 100 rad, 1 Sv = 100 rem.

Note that like rad and gray, the rem and sievert are collective terms; one need not speak of "rems" and "sieverts", although this may be heard in common speech and even observed in publications. Also note that units that incorporate a person's name (Roentgen, Gray, Sievert) are given in lower case when spelled out completely, but with the first letter capitalized when given as the unit abbreviation (e.g., "sievert" and "Sv").

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 [9] are shown in Table 7.1 (note that values for neutrons are not given, as they are not often of interest in internal dosimetry).

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 [10] or even one [11] 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 [12] Clearly, more investigation and guidance from regulatory and international advisory bodies are needed for the application of these values to internal dosimetry therapy.

Table 7.1 Radiation weighting factors recommended by the ICRP [9]

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

7.2.6 Tissue Weighting Factor and Effective Dose

The International Commission on Radiological Protection (ICRP), in its 1979 description of radiation protection quantities and limits for radiation workers [13] defined a new dosimetry quantity, the *effective dose equivalent* (H_e or EDE). The ICRP subsequently renamed this quantity *effective dose* (E) in 1991 [14] and the weighting factors were again updated in ICRP Publication 103 [9]. Certain organs or organ

Table 7.2 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

systems were assigned dimensionless weighting factors (Table 7.2) which are a function of their assumed relative radiosensitivity for expressing fatal cancers or genetic defects.

Here is an example calculation using the tissue weighting factors from ICRP 60 and some assumed individual organ equivalent doses:

Organ	Weighting Factor	Equivalent Dose (mSv)	Weighted dose Equivalent (mSv)
Liver	0.05	0.53	0.0265
Kidneys	0.005	0.37	0.00185
Ovaries	0.20	0.19	0.038
Red marrow	0.12	0.42	0.0504
Bone surfaces	0.01	0.55	0.0055
Thyroid	0.05	0.05	0.0025
Total (effective dose)			0.125

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:

$$E = \sum_{T} H_T \times w_T$$

The effective dose is meant to represent the equivalent dose which, 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 dose equivalent to the "whole body" that is calculated using dose conversion factors for the total body. "Whole body" doses are basically meaningless in nuclear medicine applications, as nonuniform and localized energy deposition is simply 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. Table 7.3 summarizes some of the dose quantities of interest in nuclear medicine dosimetry.

Some have 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 [15] The ICRP itself, however, as well as many other international organizations, has affirmed that the quantity is useful for nuclear medicine applications, the associated uncertainties notwithstanding. It is clearly more useful in evaluating and comparing doses between radiopharmaceuticals with different distribution and retention patterns in the body. It is very important, however, to recognize the *limitations* on its use:

Table 7.3 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 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 which 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 which may have completely different radiation dose patterns. For example, compare the use of ^{201}Tl chloride with ^{99m}Tc Sestamibi for use in myocardial 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) [16] 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) [17] The kidney doses are similar, but is 40 mGy to the thyroid more acceptable than 29 mGy to the gallbladder? The effective dose 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 $6.7 + (2 \times 2.1) = 11$ 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 [18] 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.

7.2.7 Specific Energy

It is a generally accepted axiom that the cell nucleus is the critical target for either cell death or transformation (some arguments about dose to other cell structures, such as the mitochondria, being important have been raised, but are controversial). As the target size that we estimate the dose to becomes small, and as the dose becomes low, variations in dose may become very large, and average values become less meaningful. Thus, in many cases, it becomes more meaningful to express the absorbed dose as a *stochastic* quantity instead of as a single average value. The *stochastic quantity* that is the corollary to the average absorbed dose in macrodosimetry (the subject addressed previously in this chapter) is called the *specific energy* (z). It is defined as the quotient of e over m, where e is the energy imparted by ionizing radiation to matter of mass m:

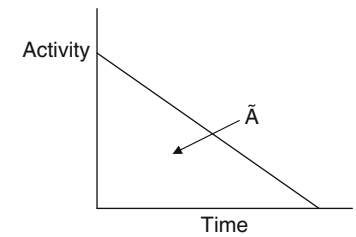
$$z = \frac{e}{m}$$

The mean absorbed dose in a specified volume, D, is the mean value of z over all possible values:

$$D = \overline{z}$$

7.2.8 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. Time–activity curves may have many forms; a very general function is shown here:



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. A Bq-s is numerically equal to one disintegration.

7.2.9 Radiation Dosimeters

Some interest has been shown using thermoluminescent dosimeters (TLD) to measure internal doses. These devices generally have a wide relatively flat response independent of energy, and a wide linear sensitivity to dose. These have been used mostly in inanimate phantoms, but have been used in animal studies, and have been proposed for some human applications. These are integrating devices and read out the dose absorbed between the time implanted and the time when retrieved from the subject. Small thermoluminescent dosimeters (TLDs) have been very useful in anthropomorphic phantoms in calibration of diagnostic and therapeutic external radiation sources, and attempts were made to place them into small animals, principally in tumors to measure accumulated radiation doses over time [19–21] Glass-encapsulated MOSFET detectors have been successfully used for radiation dosimetry with IMRT, and RIT [22, 23] and are under continued development. This kind of device may be of value in the validation of absorbed dose estimates from external beam and from internal emitter therapy, such as with ^{90}Y spheres currently being used in nuclear medicine therapy.

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