Update on Medical Internal Radiation Dosimetry:

2009 MIRD Committee Recommendations for Unifying MIRD and ICRP Formulas, Quantities, and Units

HPS Continuing Education Lecture

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Introduction: different purposes, but functionally the same math

- The ICRP and MIRD systems for internal dosimetry were developed at about the same time, using similar models and definitions

- The scientific foundations underlying the MIRD schema for medical internal radiation dosimetry, and the general ICRP framework for occupational internal dosimetry, are fundamentally the same

- The two systems differ more in notation, application, and end-purpose than in substance

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Application

- ICRP is concerned with overall risks of cancer and hereditary effects, risk coefficients

- MIRD is concerned with dose-related biological endpoints associated with radiopharmaceutical diagnostics or radionuclide therapy

- In ICRP dosimetry, intakes and times of intakes are usually not well known and must be determined, often indirectly, by radiobioassay, using assumed model parameters

- In MIRD dosimetry, the administered activities are usually well known; direct measurements show individual variations in radionuclide behavior

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Overview

- Both ICRP and MIRD use the concepts of absorbed fraction, specific absorbed fraction, source and target tissue regions, reference computational phantoms, and compartment models describing biokinetic distributions

- The MIRD schema borrows biokinetic models from ICRP publications (GI tract), but has developed some unique models (bladder voiding) apart from ICRP

- MIRD has developed other highly detailed anatomical models of the brain, kidneys, and bone marrow

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Recognizing the differences

ICRP Formalism

- Radiation protection in occupational, environmental, and medical applications
- Risk assessment for radiation exposure limits, regulatory practices
- Population doses
- Dosimetric constructs of risk or detriment

MIRD Schema

- Radiopharmaceutical dosimetry, package insert
- Patient-specific dose assessment and treatment planning
- Absorbed doses to target tissues

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Dosimetry: two approaches

1. **Dynamic Modeling**: Requires an appropriate pharmacokinetic or biokinetic model with known parameter values for the model compartments and transfer rates

   Example: Biokinetic models established by the International Commission on Radiological Protection (ICRP)

   Implemented using modeling software (SAAM II, STELLA)

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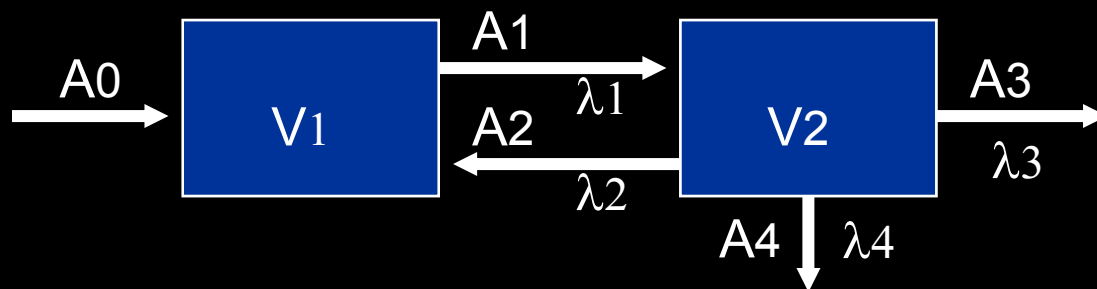
Dynamic modeling: typical data input

- Intake estimates (inhalation, ingestion, skin)
- Whole body counts
- Chest counts
- Urine sample measurements
- Fecal sample measurements
- Wound counts
- Biokinetic reference data
- Air sample data
- Other environmental measurements
- Animal data assumed applicable to man

Implementation software: (CINDY, GENMOD, IMBA Expert, IMBA Professional)
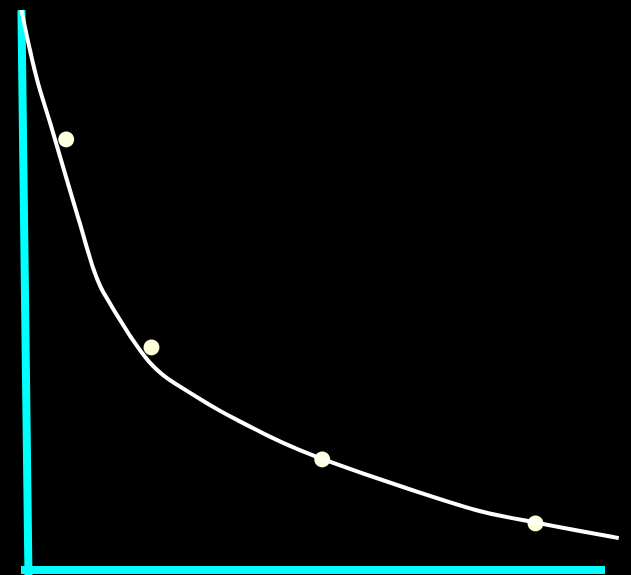
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Two approaches (continued)

2. Direct Measurements: Planar imaging, quantitative SPECT in medical internal radiation dosimetry

- Patient positioning, anterior/posterior geometric means
- Determining the regions of interest for the major organs, tumor, whole body
- Translation from counts to activity
- Calibration against a radionuclide standard
- Background subtraction, attenuation correction
- Marrow and tumor biopsy specimens
- Organ volumetrics by CT scans
- Activity-time curve-fitting
- Area-under-curve analysis
- Dosimetry calculations using the MIRD schema (implemented using software (such as OLINDA-EXM)

Imaging-based time-activity curve
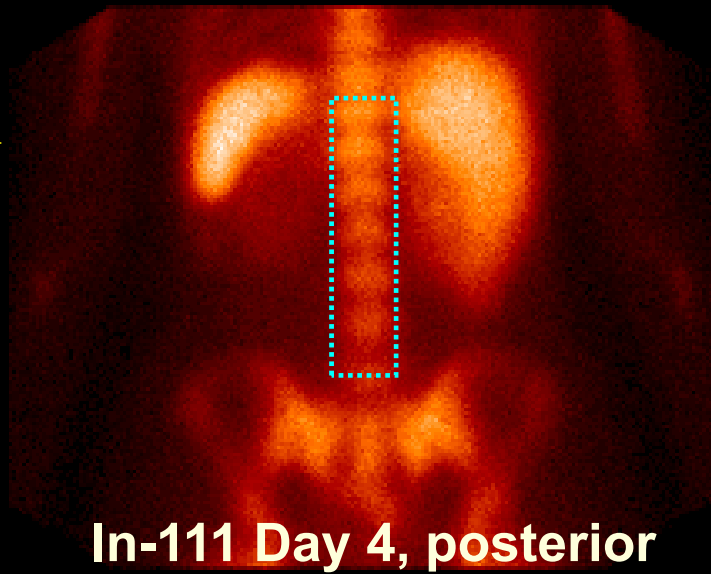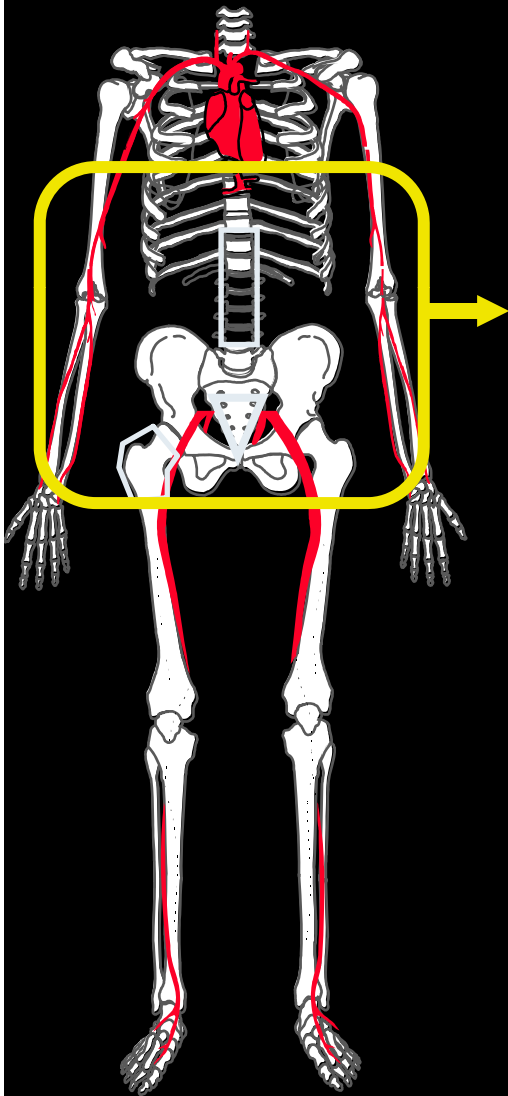
In-111 Day 4, posterior

activity

Time, hr

MIRD schema

- Medical intakes are usually known with relatively high accuracy
- The MIRD schema simplifies dose assessment without compromising on essential details
  - Is evolving to meet 21st century needs
  - Extends from the whole-organ to the cellular and multicellular levels
  - May be applied to uniform or non-uniform radionuclide distributions
- Patient-specific methods are preferred over use of generic model assumptions

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Relevant dosimetric quantity

- For radiation protection planning in diagnostic nuclear medicine, the relevant dosimetric unit is J kg^{-1} and the special name is the sievert (Sv)

- In the ICRP terminology, *effective dose* is defined only for stochastic effects (cancer induction)

  * Not for individual dosimetry

  * Does not apply to immediate deterministic effects

Relevant dosimetric quantity

- For radionuclide therapy, the relevant dosimetric quantity is the <u>absorbed dose</u> in J kg^{-1}, and the special name is the gray (Gy)
  - For individual patient dosimetry and treatment planning
  - Relevant to organ and tumor *deterministic* effects
- Not the "effective dose" (Sv)

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"Absorbed dose is probably the most important quantity in radiological physics."

-- Harald H. Rossi (1917-2000)

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Absorbed dose in biological systems

General equation

Gy (J kg^{-1})

where k is a unit conversion constant
A is the activity in the organ (Bq)
E is the total energy emitted (J)
f is the fraction of energy that is absorbed
m is the mass of target tissue (g)
$B(t)$ is the biological retention with time t

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Absorbed dose

Rearranged

MIRD
Formula

$$D(r_k \leftarrow r_h) = \tilde{A}_h \ \Sigma_i \ \Delta_i \ \varphi_i(r_k \leftarrow r_h) / m_k$$

where $\tilde{A}_h$ is the cumulated activity, Δ_i is the mean energy emitted per unit cumulated activity, and $\varphi (r_k \leftarrow r_h)$ is the absorbed fraction of energy imparted by a source organ

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Absorbed dose
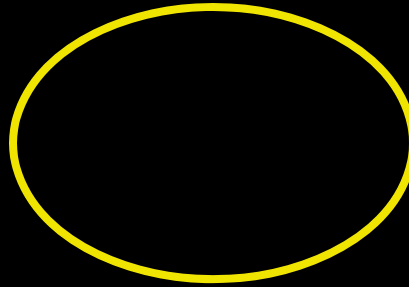
Rearranged

MIRD
Formula

$$D(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \Delta_i \varphi_i(r_k \leftarrow r_h) / m_k$$

Total number of transformations

Absorbed dose

Rearranged
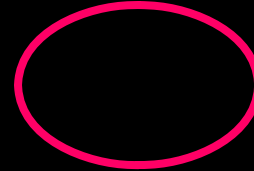
MIRD
Formula

$$D(r_k \leftarrow r_h) = \tilde{A}_h \left(\sum_i \Delta_i \, \varphi_i(r_k \leftarrow r_h) \right) / m_k$$

Energy imparted

Absorbed dose

Rearranged

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Formula

$$D(r_k \leftarrow r_h) = \tilde{A}_h \; \Sigma_i \; \Delta_i \; \varphi_i(r_k \leftarrow r_h) \, / m_k$$

Organ mass

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ICRP dosimetry formalism (ICRP-26)

Dose equivalent rate in a target organ or tissue:

$$\dot{H}_T = 1.6 \times 10^{-10}\ SEE_{(T \leftarrow S)}\ A_S$$

where $SEE_{(T \leftarrow S)}$ is the specific effective energy deposited in the target organ or tissue per radionuclide transformation in source organ S (MeV g^{-1}),

A_S is the radioactivity present in the source organ or tissue (bequerel), and

the factor 1.6×10^{-10} is a unit conversion constant.

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ICRP dosimetry formalism

Integrating over time, the dose equivalent H_T is

$$H_T \ = \ 1.6 \times 10^{-10} \ \text{SEE}_{(T \leftarrow S)} \ As \int_o R(t)dt$$

where H_T is the dose equivalent in sievert (Sv),

and $R(t)$ is a retention function, and where $As \int_o R(t)dt$ represents the total number of radioactive transformations in the source organ over time

ICRP dosimetry formalism

The committed dose equivalent to an organ or tissue ($H_{T,50}$), a measure of long-term organ dose equivalent, was first defined in ICRP-26/30 as the dose equivalent that would be received from an intake of radioactive material by an individual during the 50-year period following the intake

Numerically, this quantity was defined as

$$H_{50,T} = 1.6 \times 10^{-10} \sum A_s \, SEE_{(T \leftarrow S)}$$

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ICRP dosimetry formalism

The committed effective dose equivalent ($H_{E,50}$), a measure of total risk or detriment to the individual (sievert), was defined as the sum of the products of the weighting factors applicable to each of the body organs or tissues irradiated and the committed dose equivalent to those organs; thus

$$H_{E,50} = \sum W_T \, H_{T,50}$$

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Evolution of ICRP quantities and units

From dose equivalent to equivalent dose!
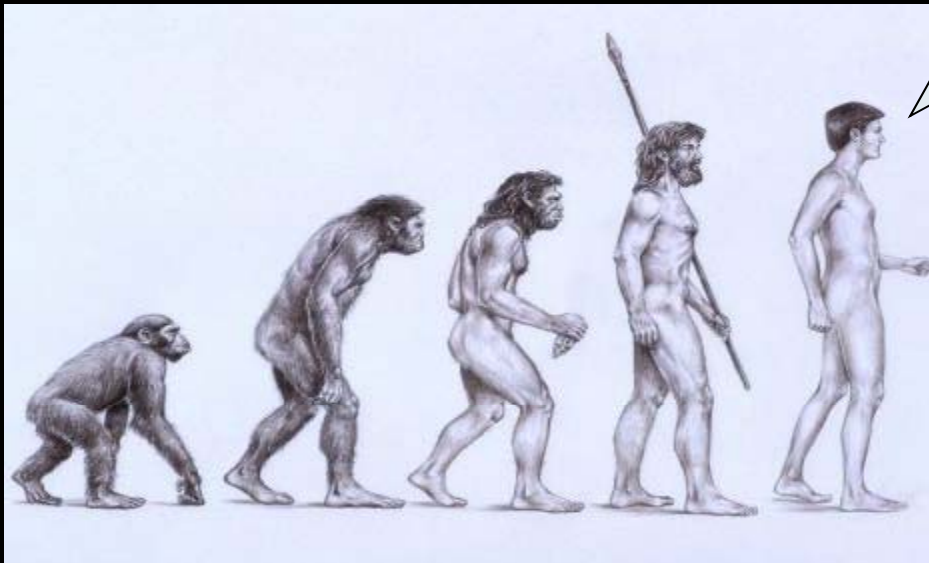
ICRP dosimetry formalism (ICRP-60)

Equivalent dose, H_T

$$H_T = \sum w_R D_{T,R}$$

where $D_{T,R}$ is the absorbed dose (averaged over a tissue or organ T) due to radiations of type R, and w_R is the radiation weighting factor. $D_{T,R}$ can not be measured experimentally. The weighting factor is introduced to weight the absorbed dose for biological effectiveness

Unit: J kg^{-1}

Special name for the unit of equivalent dose is sievert (Sv)

ICRP dosimetry formalism

Effective dose, E

$$E = \sum w_T H_T = \sum w_T \sum w_R D_{T,R}$$

where $D_{T,R}$ is as above and w_T is a tissue weighting factor which reflects the total detriment to health. This is a doubly-weighted surrogate of risk based on physical quantities imparted (i.e., not a physical dose quantity)

Unit: J kg^{-1}
Special name for the unit of effective dose equivalent is sievert (Sv).

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Toward consistency

- In 2009, the MIRD Committee recommended a revised framework for unifying the ICRP and MIRD equations, models, and terminology

→ The result is a general schema for internal dosimetry, consistent for both nuclear medicine and radiation protection.

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MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature

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MIRD Pamphlet No. 21

Purpose:

- Provides standardized formulas, nomenclature, quantities, and units
- Clarifies the use of *equivalent dose* and *effective dose* for applications in nuclear medicine
- Presents the case for a new dosimetric quantity, based on absorbed dose, for deterministic effects associated with radionuclide therapy

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Revised nomenclature, symbols

- Comparison of MIRD (old), MIRD (21, revised), and the ICRP quantities, parameters, symbols, and units

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MIRD Pamphlet No. 21 – Quantities and symbols

TABLE 1. Quantities, Parameters, Symbols, and Units Used in the MIRD and ICRP Dosimetry Schema (Listed in Order of Appearance in Equations 1–17)

Quantity or parameter	MIRD Pamphlet 21	MIRD Primer (1991) (4)	ICRP publications (7,8,18)	Units or special name
Source region (or tissue)	r_S	r_h	S	
Target region (or tissue)	r_T	r_k	T	
Absorbed dose rate to target region	$\dot{D}(r_T,t)$	$\dot{\bar{D}}(r_k)$ or $\dot{\bar{D}}_k$	$\dot{D}_{T,R}$	Gy s^{-1}
Activity in source region	$A(r_S,t)$	$A_h(t)$	$q_S(t)$	Bq
Absorbed dose rate per unit activity	$S(r_T \leftarrow r_S,t)$	$S(r_k \leftarrow r_h)$	Not defined	Gy (Bq s)$^{-1}$
Dose-integration period	T_D	Assumed to be ∞	τ	s
Absorbed dose to target	$D(r_T,T_D)$	$\bar{D}(r_k)$ or $\bar{D}_k$	$D_{T,R}$	Gy
Administered activity	A_0	A_0	q_0	Bq
Fraction of administered activity in the source region	$a(r_S,t) = A(r_S,t)/A_0$	$f_h(t)$	Not defined	Unitless
Absorbed dose coefficient	$d(r_T,T_D)$	Not defined	$d_T(\tau)$	Gy Bq^{-1}
Mean energy of the ith transition	E_i	E_i	E_i	J or MeV
Number of ith transitions per nuclear transformation	Y_i	n_i	Y_i	(Bq s)$^{-1}$
Mean energy of the i^{it} transition per nuclear transformation	Δ_i	Δ_i	Δ_i	J (Bq s)$^{-1}$ or MeV (Bq s)$^{-1}$

TABLE 1. Quantities, Parameters, Symbols, and Units Used in the MIRD and ICRP Dosimetry Schema (Listed in Order of Appearance in Equations 1–17)

Quantity or parameter	MIRD Pamphlet 21	MIRD Primer (1991) (4)	ICRP publications (7,8,18)	Units or special name
Absorbed fraction	$\phi(r_T \leftarrow r_S, E_i, t)$	$\phi(r_k \leftarrow r_h)$	$AF(T \leftarrow S, E_i)$	Unitless
Mass of target region	$M(r_T, t)$	m_k	m_T	kg
Specific absorbed fraction	$\Phi(r_T \leftarrow r_S, E_i, t)$	$\Phi(r_k \leftarrow r_h)$	$SAF(T \leftarrow S, E_i)$	kg^{-1}
Time-integrated activity in source region*	$\tilde{A}(r_S, T_D)$	$\tilde{A}_h$	U_S	Bq s
Time-integrated activity coefficient†	$\tilde{a}(r_S, T_D)$	τ	Not defined	s
Equivalent dose to target	$H(r_T, T_D)$	Not defined	H_T	Sv
Radiation weighting factor	w_R	Not defined	w_R	Unitless
Absorbed dose to target by radiation type R	$D_R(r_T, T_D)$	Not defined	$D_{T,R}$	Gy
Radiation-weighted S	$S_w(r_T \leftarrow r_S, t)$	Not defined	$SEE(T \leftarrow S)$	Sv (Bq s)$^{-1}$
Equivalent dose coefficient	$h(r_T, T_D)$	Not defined	$h_T(\tau)$	Sv Bq^{-1}
Effective dose	E	Not defined	E	Sv

*This quantity was termed *cumulated activity* in 1991 MIRD Primer.

†This quantity was termed *residence time* in 1991 MIRD Primer.

Absorbed dose - time dependent equations

Mean absorbed dose rate at time t

$$\dot{D}(r_T,t) = \sum_{r_S} A(r_S,t)\ S(r_T \leftarrow r_S,t)$$

Eq. 1

Mean absorbed dose

$$D(r_T,T_D) = \int_0^{T_D} \dot{D}(r_T,t)\,dt$$

$$= \sum_{r_S} \int_0^{T_D} A(r_S,t)\,S(r_T \leftarrow r_S,t)\,dt$$

Eq. 2

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Absorbed dose - time <u>dependent</u> equations

Mean absorbed dose rate at time t

Activity at time t

$$\dot{D}(r_T,t) = \sum_{r_S} A(r_S,t)\ S(r_T \leftarrow r_S,t)$$

Eq. 1

S value by radionuclide, target tissue, at time t

Mean absorbed dose

Dose-integration or dose commitment time period

$$D(r_T,T_D) = \int_0^{T_D} \dot{D}(r_T,t)\, dt$$

Eq. 2

$$= \sum_{r_S} \int_0^{T_D} A(r_S,t)\ S(r_T \leftarrow r_S,t)\, dt$$

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Absorbed dose - time <u>dependent</u> equations

Mean absorbed dose   (Gy, J kg^{-1})

$$D(r_T, T_D) = \int_0^{T_D} \dot{D}(r_T, t)\, dt$$

$$= \sum_{r_S} \int_0^{T_D} A(r_S, t)\, S(r_T \leftarrow r_S, t)\, dt$$

Eq. 2

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Absorbed dose - time dependent equations

Absorbed dose coefficient

Fraction of administered activity

Eq. 3

$$d(r_T, T_D) = \sum_{r_S} \int_0^{T_D} a(r_S, t)\, S(r_T \leftarrow r_S, t)\, dt$$

Determined by direct measurements or compartment modeling

"S" - Absorbed dose to target per unit activity in source

$$S(r_T \leftarrow r_S, t) = \frac{1}{M(r_T, t)} \sum_i E_i\, Y_i\, \phi(r_T \leftarrow r_S, E_i, t)$$

Eq. 4

$$= \frac{1}{M(r_T, t)} \sum_i \Delta_i\, \phi(r_T \leftarrow r_S, E_i, t)$$

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Absorbed dose - time dependent equations

Absorbed dose coefficient

$$d\left(r_T, T_D\right) = \sum_{r_S} \int_0^{T_D} a\left(r_S, t\right) S\left(r_T \leftarrow r_S, t\right) dt$$

"S" - Absorbed dose to target per unit activity in source

$$S\left(r_T \leftarrow r_S, t\right) = \frac{1}{M\left(r_T, t\right)} \sum_i E_i\, Y_i\, \phi\left(r_T \leftarrow r_S, E_i, t\right)$$

$$= \frac{1}{M\left(r_T, t\right)} \sum_i \Delta_i\, \phi\left(r_T \leftarrow r_S, E_i, t\right)$$

Time-dependent mass

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Absorbed fraction

Absorbed fraction and specific absorbed fraction

$$\Phi\left(r_T \leftarrow r_S, E_i, t\right) = \frac{\phi\left(r_T \leftarrow r_S, E_i, t\right)}{M\left(r_T, t\right)}$$

Eq. 5

"S" - Absorbed dose to target per unit activity in source

$$S\left(r_T \leftarrow r_S, t\right) = \sum_i \Delta_i\, \Phi\left(r_T \leftarrow r_S, E_i, t\right)$$

Eq. 6

Restated in terms of a specific absorbed fraction

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Absorbed dose - time <u>independent</u> equations

Mean absorbed dose

Neglecting the time-dependence of S for lifetime doses, long-lived radionuclides

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D)\, S(r_T \leftarrow r_S)$$

Eq. 7

Total nuclear transformations

where

$$\tilde{A}(r_S, T_D) = \int_0^{T_D} A(r_S, t)\, dt$$

Proposed quantity name: time-integrated activity

Previous quantity name: cumulated activity

Absorbed dose - time <u>independent</u> equations

Absorbed dose coefficient

$$d\left(r_T, T_D\right) = \sum_{r_S} \tilde{a}\left(r_S, T_D\right) S\left(r_T \leftarrow r_S\right)$$

Eq. 8

where

$$\tilde{a}\left(r_S, T_D\right) = \int_0^{T_D} a\left(r_S, t\right) dt = \frac{1}{A_0} \int_0^{T_D} A\left(r_S, t\right) dt$$

Eq. 9

Proposed quantity name: time-integrated activity coefficient

Previous quantity name: residence time τ

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Equivalent dose

Equivalent dose

$$H(r_T, T_D) = \sum_R w_R \, D_R(r_T, T_D)$$

Eq. 10

where w_R is the radiation-weighting factor for radiation type R, and $D_R(r_T, T_D)$ is the contribution of radiation type R to the mean absorbed dose in target tissue r_T.

$w_R = 1$ for photons, electrons, positrons, and beta-particles; and = 20 for alpha particles

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Equivalent dose

Equivalent dose

$$H(r_T, T_D) = \sum_R w_R \, D_R(r_T, T_D)$$

Eq. 10

where w_R is the radiation-weighting factor for radiation type R, and $D_R(r_T, T_D)$ is the contribution of radiation type R to the mean absorbed dose in target tissue r_T.

!! Applicable to a defined population, not the individual

w_R = 1 for photons, electrons, positrons, and beta-particles; and = 20 for alpha particles

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Equivalent dose

Equivalent dose

$$H(r_T, T_D) = \sum_R w_R \, D_R(r_T, T_D)$$

Eq. 10

Units of J kg-1, with special name sievert (Sv)

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Radiation-weighted S

Rewritten: Radiation-weighted S

$$S_w \left(r_T \leftarrow r_S , t \right) = \sum_R w_R \sum_i E_{R,i} \, Y_{R,i} \, \Phi \left(r_T \leftarrow r_S , E_{R,i} , t \right)$$

$$= \sum_R w_R \sum_i \Delta_{R,i} \, \Phi \left(r_T \leftarrow r_S , E_{R,i} , t \right)$$

Eq. 11

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Equivalent dose and dose rate

Equivalent dose rate

$$\dot{H}(r_T,t) = \sum_{r_S} A(r_S,t)\, S_w(r_T \leftarrow r_S,t)$$

Eq. 12

Equivalent dose

$$H(r_T,T_D) = \int_0^{T_D} \dot{H}(r_T,t)\, dt$$

$$= \sum_{r_S} \int_0^{T_D} A(r_S,t)\, S_w(r_T \leftarrow r_S,t)\, dt$$

Eq. 13

$$H(r_T,T_D) = \sum_{r_S} \tilde{A}(r_S,T_D)\, S_w(r_T \leftarrow r_S)$$

Eq. 14

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Equivalent dose

Equivalent dose coefficient – time <u>dependent</u>

$$h\left(r_T, T_D\right) = \sum_{r_S} \int_0^{T_D} a\left(r_S, t\right) S_w \left(r_T \leftarrow r_S, t\right) dt$$

Eq. 15

Equivalent dose coefficient – time <u>independent</u>

$$h\left(r_T, T_D\right) = \sum_{r_S} \tilde{a}\left(r_S, T_D\right) S_w \left(r_T \leftarrow r_S\right)$$

Eq. 16

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Equivalent dose in medical internal dosimetry

• Since the radiation-weighting factors are developed by committee (ICRP) for stochastic effects (cancer), they are not applicable to deterministic biological effects represented by the concept of relative biological effectiveness (RBE)

• W_R values should not be used to predict deterministic effects

- Not for evaluating toxicity or for treatment planning

- Not for individual patients

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Effective dose: an ICRP construct of risk

Effective dose

A hybrid reference (50th percentile) person

$$E = \sum_T w_T \left[\frac{H(r_T, T_D)^{Male} + H(r_T, T_D)^{Female}}{2} \right]$$

Eq. 17

A radiation protection quantity for establishing annual limits to workers and members of the general public

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Effective dose

- In radiation protection, used for comparing patient exposures that might result from different procedures, and for conveying a measure of future risk

- Appropriate for use by institutional review boards and radiation safety committees

- But this quantity is not patient-specific

- And it should not be used as a measure of individual risk or for expressing deterministic effects

- Not an organ or tissue dose

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Quantities relevant to deterministic effects

MIRD Pamphlet No. 21 concludes with a discussion of deterministic effects

- RBE-weighted absorbed dose – D

- Biologically effective dose – BED

- Equivalent uniform dose – EUD

- Isoeffective dose – D_{IsoE}

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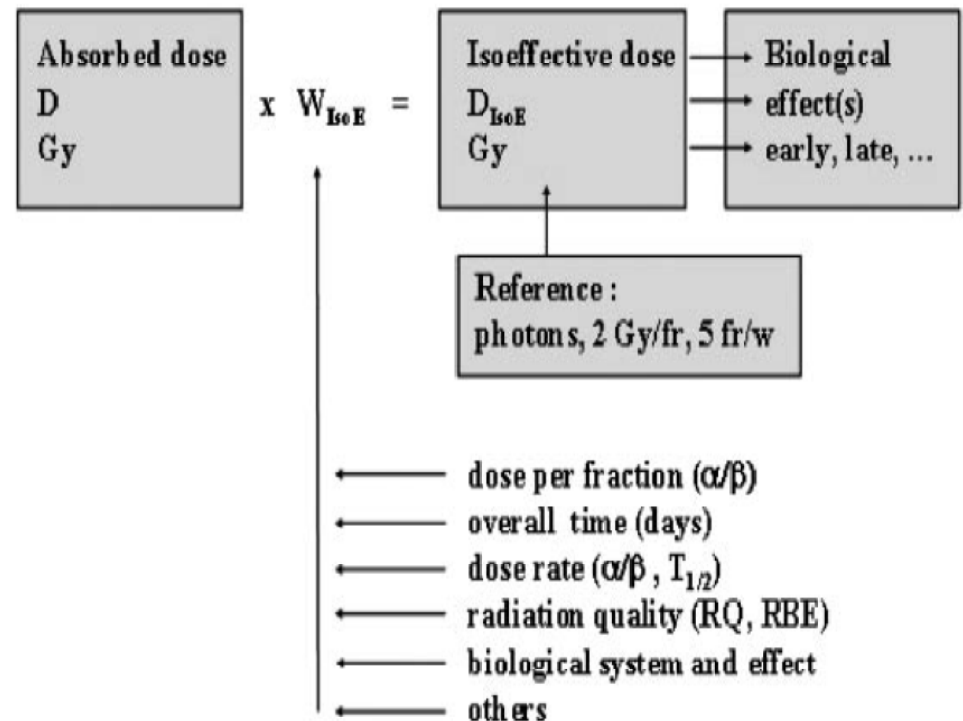# How do we deal with high absorbed doses in radionuclide therapy?

- For deterministic effects, ICRP recommends using an RBE-weighted absorbed dose to the organ or tissue
  - Relative to a specific tissue and endpoint
  - Measured under well-defined conditions

- Failure to recognize this difference between radiation-weighting factors for stochastic effects and RBE values for deterministic effects has led to confusion regarding which value is appropriate

> For alphas, the RBE is usually observed to be 3-6 for cell killing, not 20

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Quantities relevant to deterministic effects

The ICRU has already described a weighted absorbed dose quantity: the equivalent absorbed dose of low-LET radiation that, would produce the same clinical effects as the high-LET radiation, all other conditions being equal

$$\text{Absorbed dose } D\ \text{Gy} \quad \times\ W_{IsoE}\ =\ \text{Isoeffective dose } D_{IsoE}\ \text{Gy} \longrightarrow \text{Biological effect(s), early, late, ...}$$

Reference: photons, 2 Gy/fr, 5 fr/w

- dose per fraction (α/β)
- overall time (days)
- dose rate (α/β, $T_{1/2}$)
- radiation quality (RQ, RBE)
- biological system and effect
- others

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New MIRD recommendation

The MIRD Committee proposes* that the barendsen (Bd) be defined as the special named unit for the product of deterministic RBE and absorbed dose.

The resulting quantity is "isoeffective dose" (D_{isoE}). In addition to relative biological effectiveness, the term D_{isoE} also accounts for dose rate and other modifying effects.

$$D_{isoE}(r_T, T_D) = RBE_\alpha \cdot D_\alpha(r_T T_D) \qquad \text{J kg}^{-1}$$

*Sgouros G, Howell RW, Bolch WE, Fisher DR. MIRD Commentary: Proposed Name for a Dosimetry Unit Applicable to Deterministic Biological Effects—The Barendsen (Bd). *J Nucl Med.* 2009; 50(3):485-487.

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Summary

- The MIRD Committee of the Society of Nuclear Medicine has developed standardized nomenclature for harmonizing the ICRP and MIRD systems,

- ....has clarified the use of equivalent dose and effective dose in radiopharmaceutical dosimetry,

- ....and has proposed a new quantity (the barendsen, Bd) for describing the RBE-weighted absorbed dose for applications in high-LET radionuclide therapy

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