



RBE and radiation weighting factors as applied in the context of protection of the environment from ionising radiation

Kathryn Higley, PhD, CHP

Professor and Head

Nuclear Engineering & Radiation Health Physics

D.C. Kocher, A.G. Real, D.B. Chambers, ICRP Committee 5

Presented at the 13th Annual Congress of the International Radiation Protection Association

Living with Radiation – Engaging with Society

Why Is This Work Needed?

- Well recognized in human radiation protection that different radiation types vary in the degree of biological impact for the same absorbed dose
- Can this insight be used developing dose factors for plants and animals?
 - Yes and no.....
- This presentation provides an overview of ICRP C5 TG effort on analysis of available RBE studies in the context of impact to animals and plants

Overview

- RBE measurement and calculations
- Stochastic effects
- Deterministic effects
- Summary of data
- Challenges

RBE defined

The Relative Biological Effectiveness of radiation **A** with respect to the *reference radiation R* is defined as the ratio of an absorbed dose **D**, in a tissue to the dose **DA** that causes a quantitatively and qualitatively equal effect.

$$\text{RBE} = \text{D/DA}$$

Each RBE value derived from a set of observations for tissue cultures or for responses of tissues, in animals or in man, refers to a *defined end-point*, produced under a specified set of exposure conditions.

Reference Radiation

- Gamma rays
 - from ^{137}Cs or
 - ^{60}Co and
- 250 kVp x-rays are common reference radiation
- Overall, RBE for 250 kVp x-rays relative to ^{137}Cs or ^{60}Co ~ 2
- Reference radiation is important

Experimental determination

- RBE values mostly derived for large doses and high dose rates,
- Need to extrapolate to low doses and low dose rates for environmental protection purposes.
- Estimation of RBE for two conditions:
 - RBE_M for stochastic effects, and
 - RBE_m for deterministic effects
- Which are determined by radiation quality and end-points

Biological Endpoints

- Stochastic:
 - Chromosomal aberrations, induction of DNA double strand breaks (DSB), mutation and chromosome breaks
- Deterministic
 - Survival, acute skin injury, cell death and tissue impairment

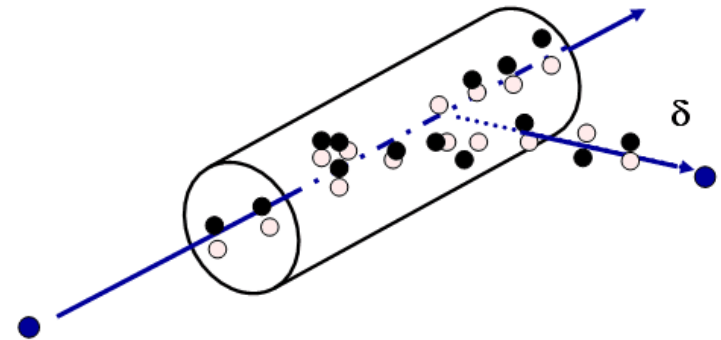
Factors Influencing RBE

RBE depends on / confounded by many factors:

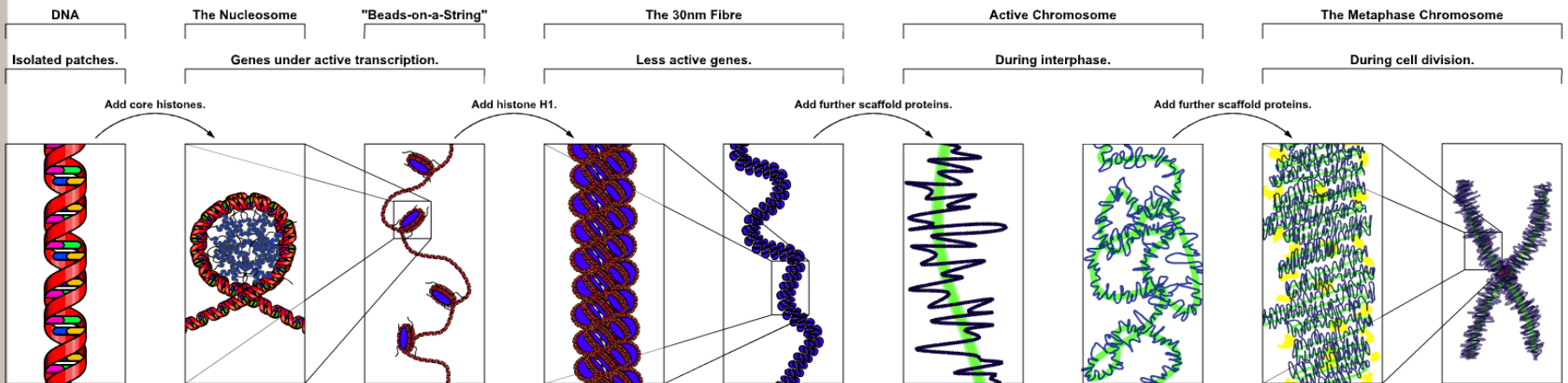
- Linear energy transfer (LET)
- Dose and dose rate
- Micro-dosimetry,
 - non-uniform distribution of radionuclide in tissues/organisms
- Cell or tissue under consideration
- Endpoint
- Repair capability
- ... etc.

Linear Energy Transfer (LET)

- The amount of energy absorbed by the target tissue per unit of path length;
 - Usually $\text{keV}/\mu\text{m}$ travelled in water
- Alpha particles
 - $\sim 4\text{-}6 \text{ MeV}$
 - LETs $\sim 100 \text{ keV}/\mu\text{m}$
- Low LET radiations
 - X-rays, gamma rays or electrons
 - LET $\sim 3.5 \text{ keV}/\mu\text{m}$ or less

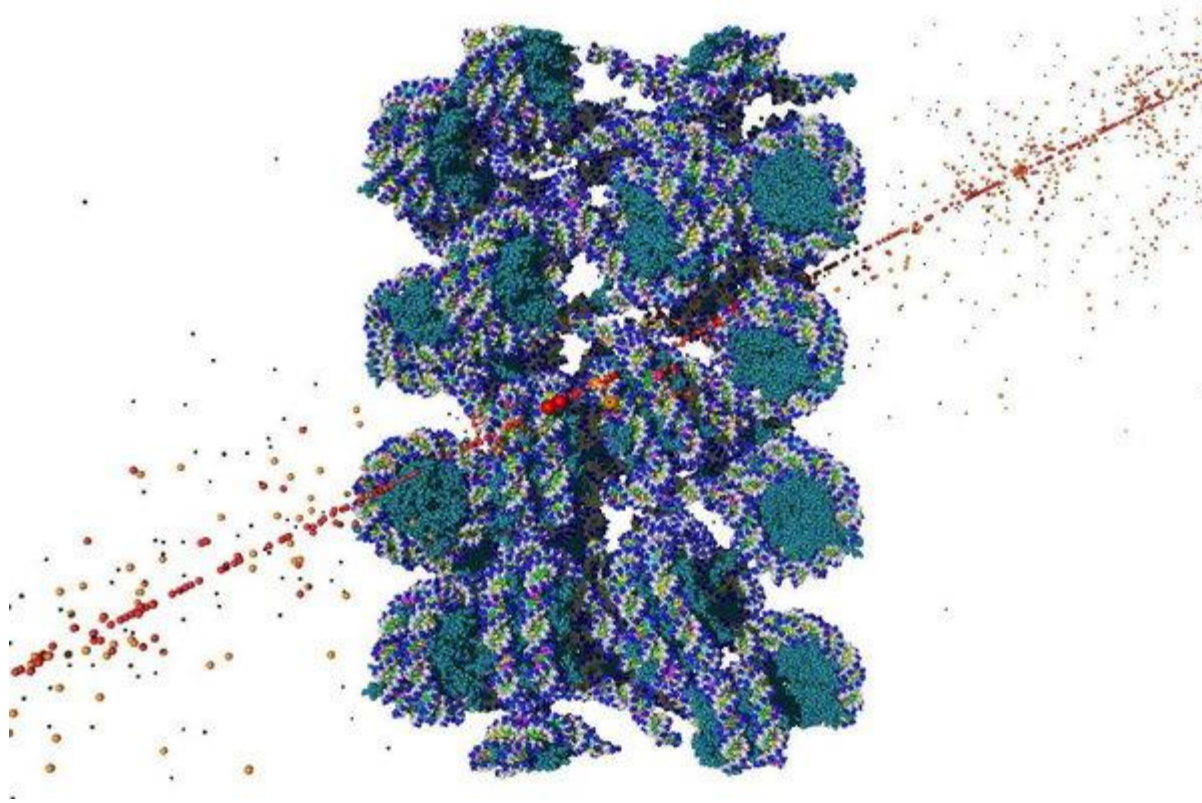


DNA Structure



http://commons.wikimedia.org/wiki/File:Chromatin_Structures.png

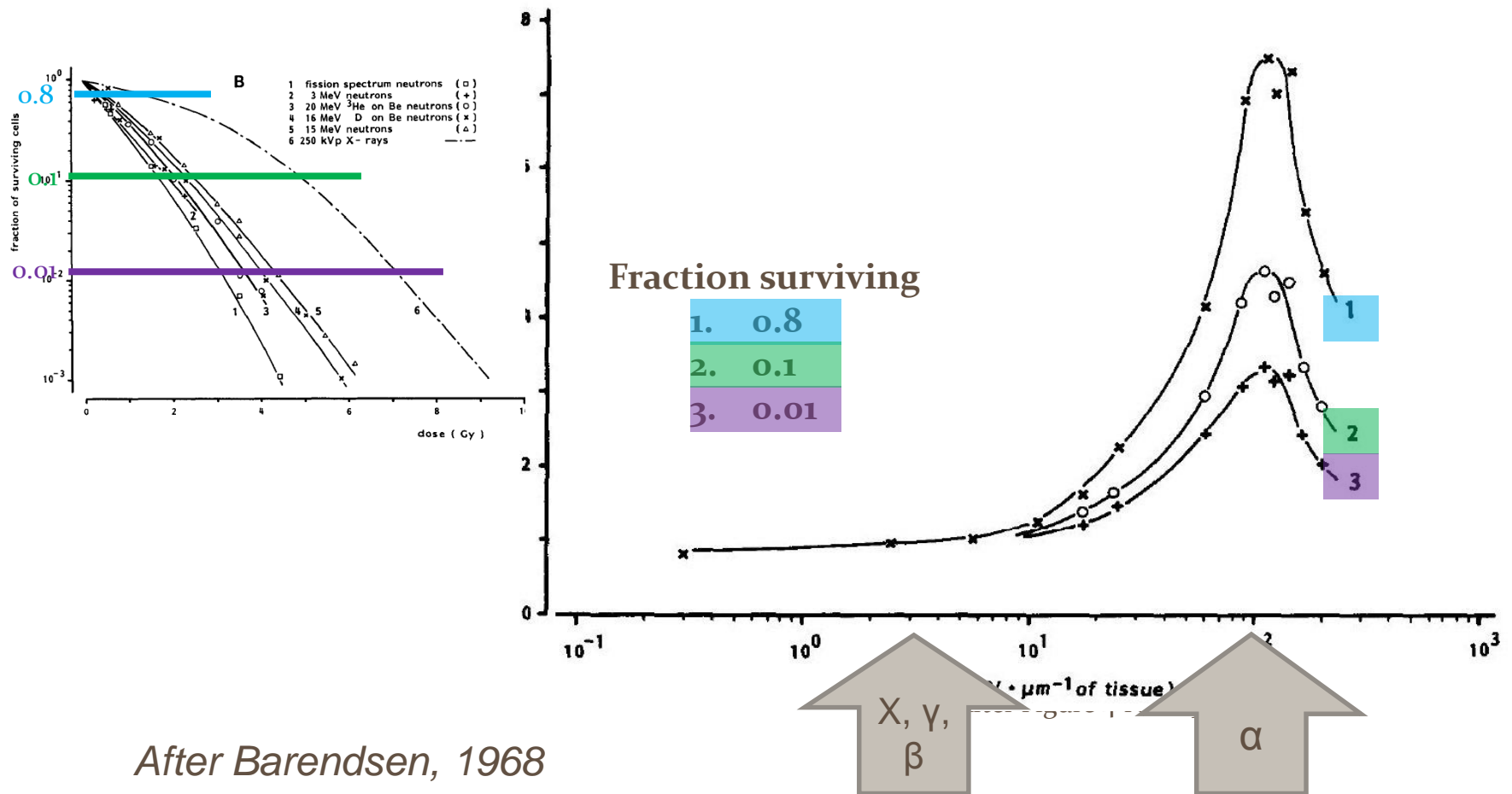
Visualization of a 10 MeV α -particle crossing a chromatin fiber



<http://www.helmholtz-muenchen.de/en/iss/radiation-risk/research-topics/biophysical-models/index.html>

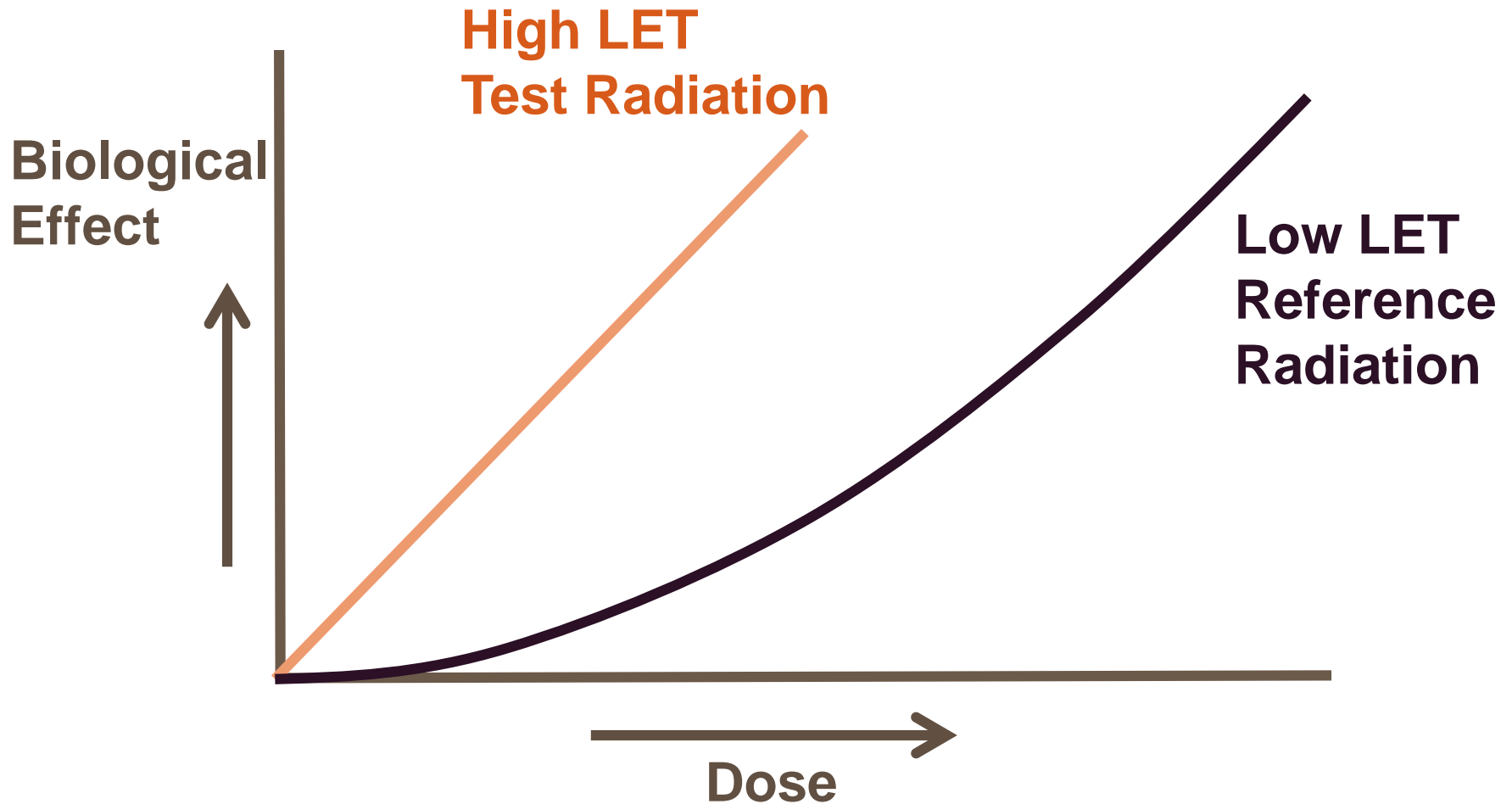
Dose Dependence of RBE vs LET

RBE vs. LET and Dose for Proliferative Capacity of Cultured Human Cells

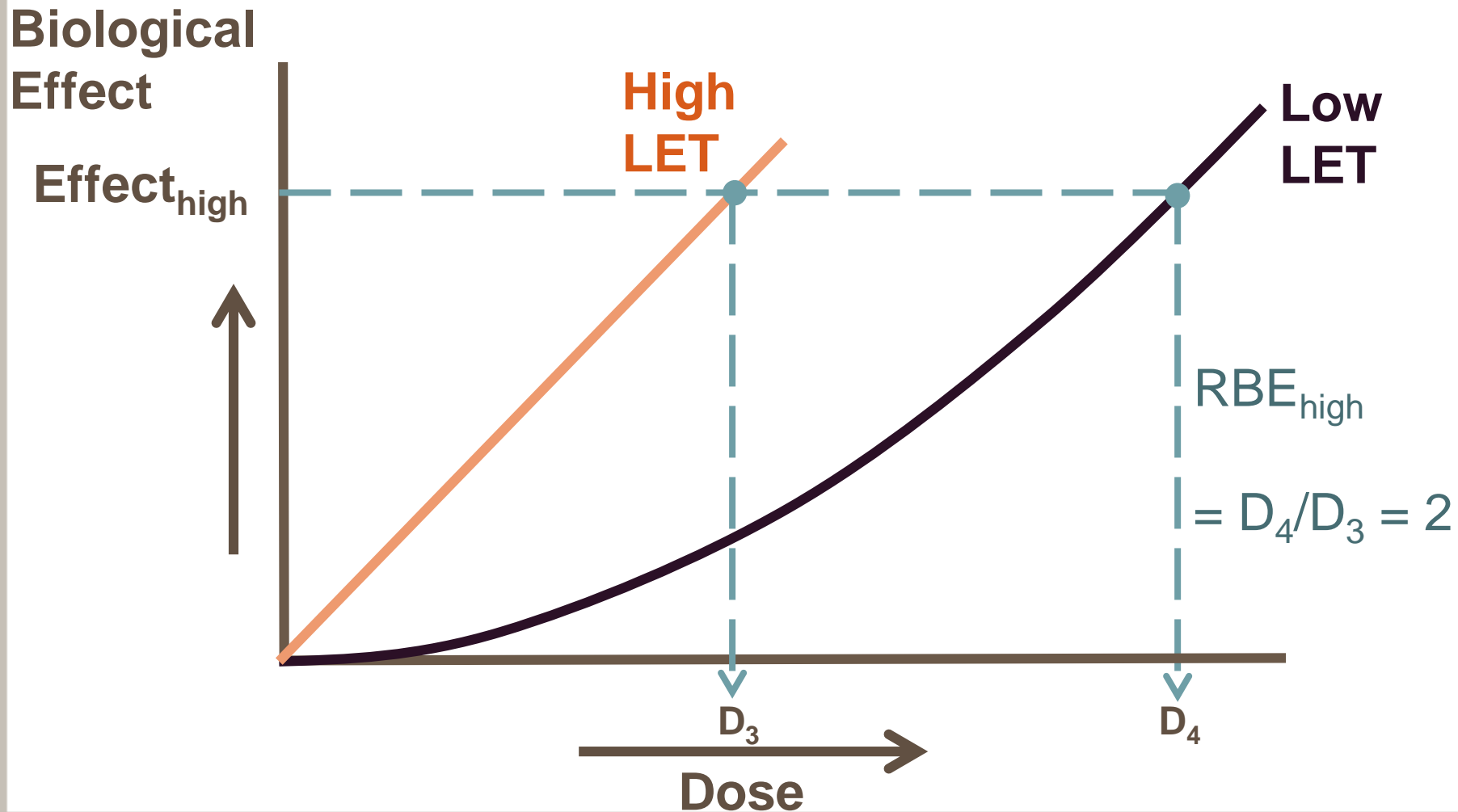


After Barendsen, 1968

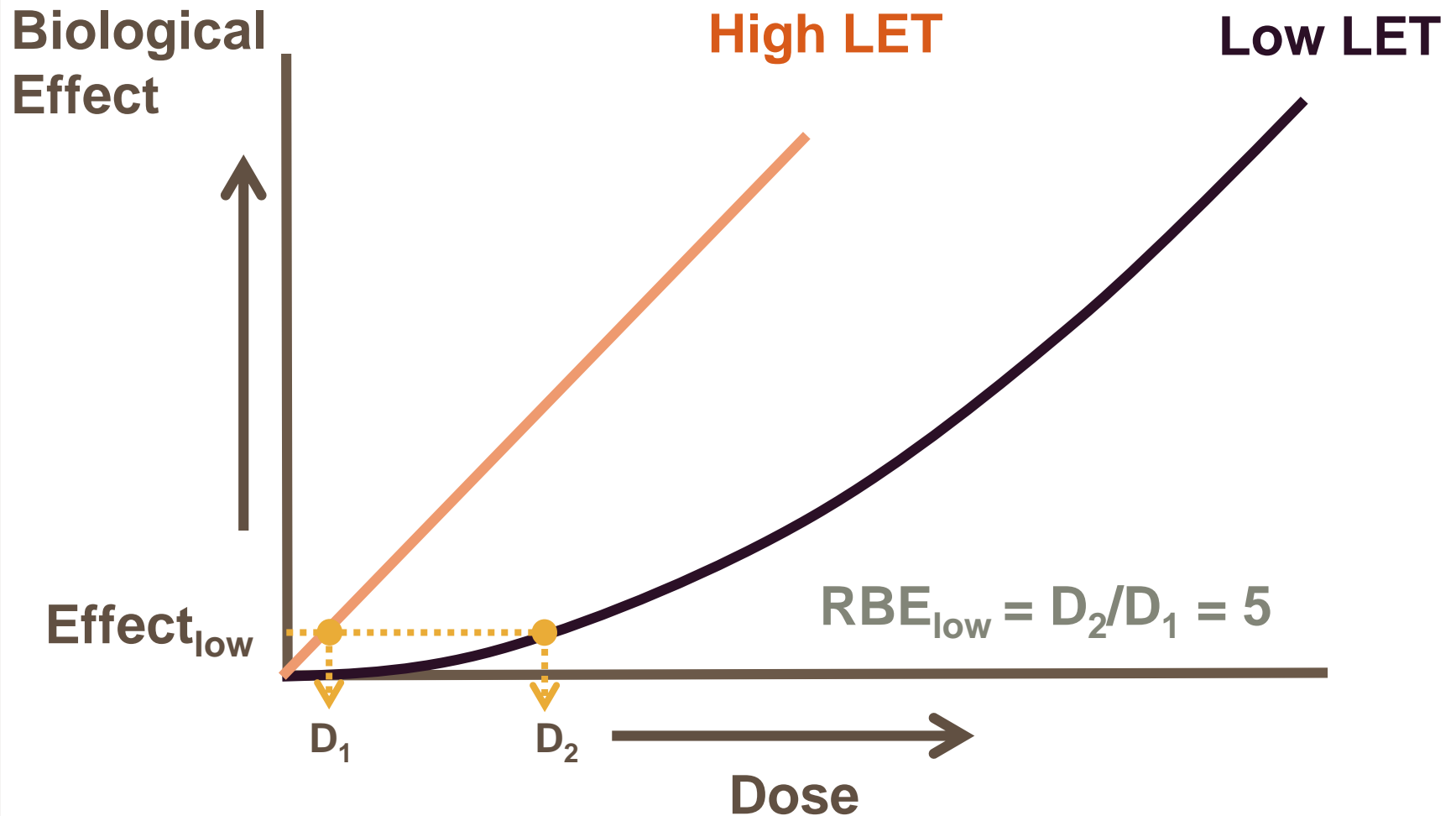
RBE Calculation for High LET radiation



RBE Calculation for High LET radiation at High Dose

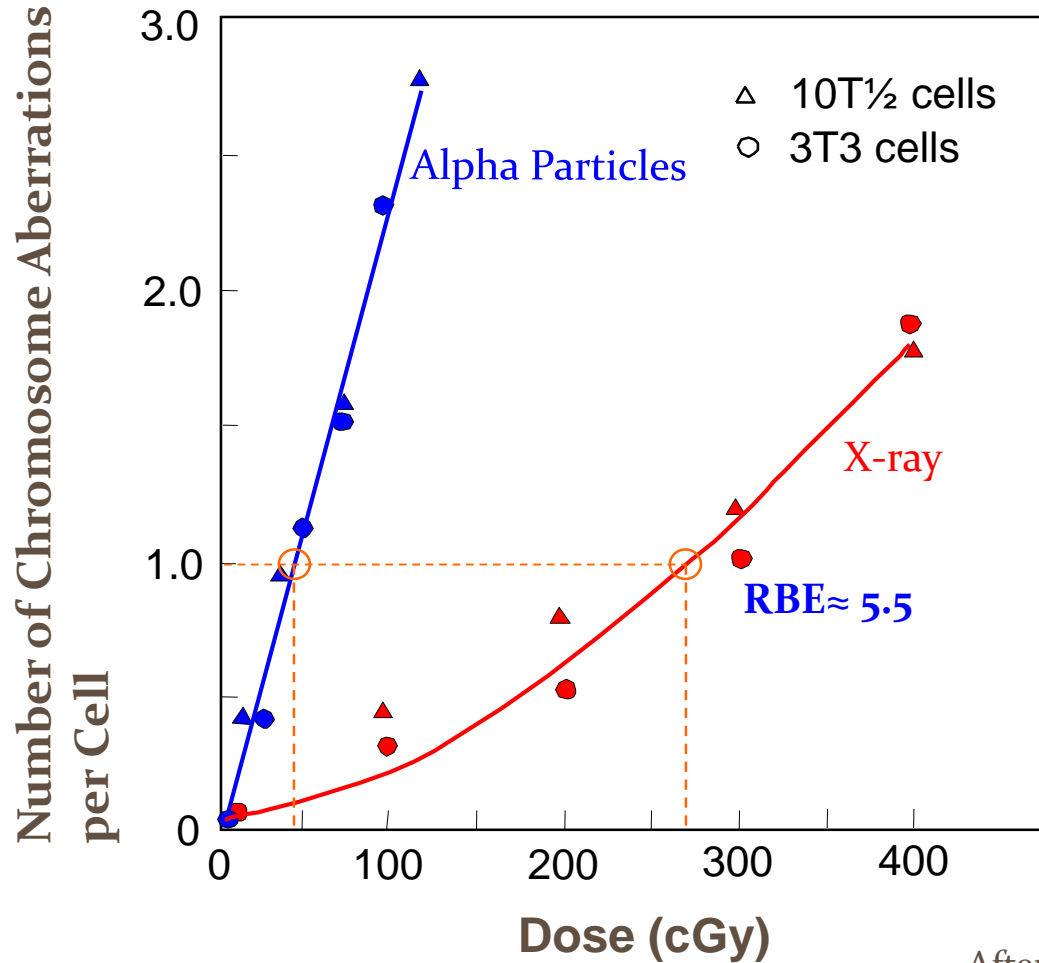


RBE Calculation for High LET radiation at Low dose



Dose Response and RBE

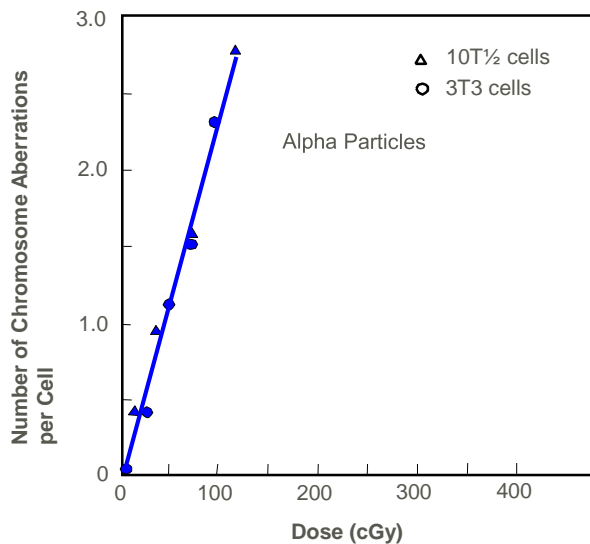
- Example



After Nagasawa et al., 1990

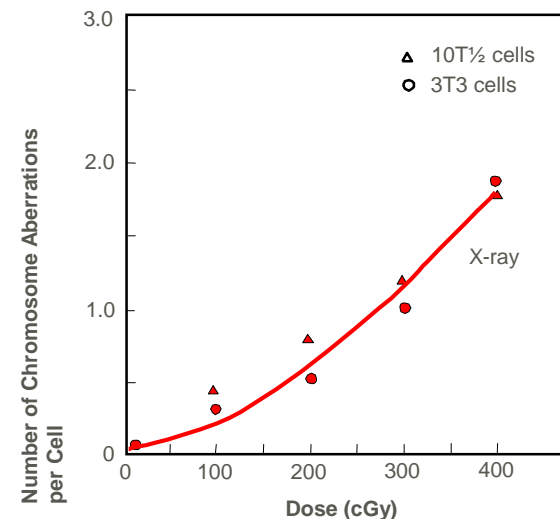
Finding RBE at Low Doses (RBE_m)

For high LET (α), dose response is linear; i.e.,



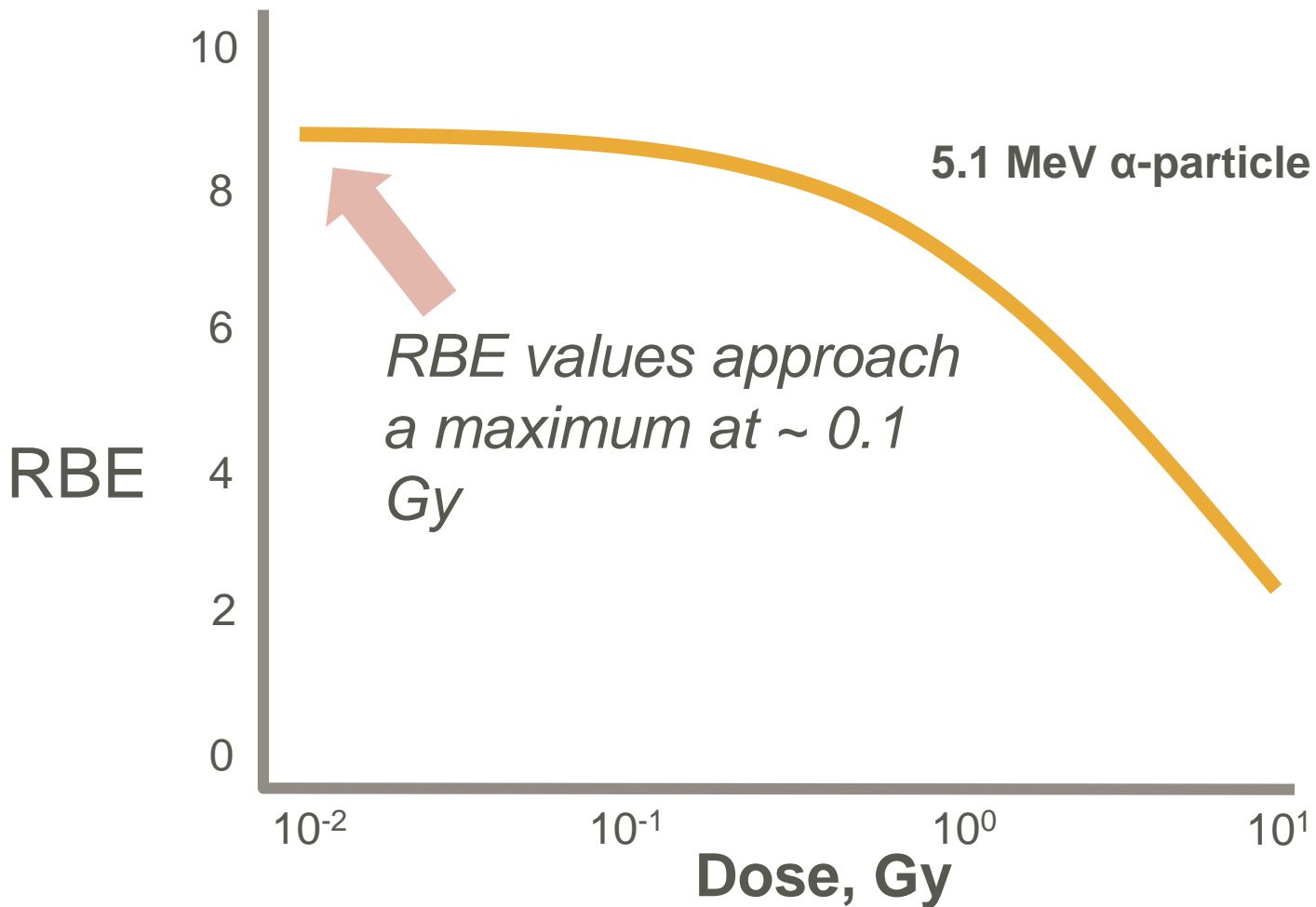
$$E_H = a_H D_H$$

For Low LET (b , x rays), dose response is linear quadratic; i.e.,



$$E_L = a_L D_L + b_L D_L^2$$

“Issue”: RBE varies as a function of dose*



*Example of RBE for 15 MeV alpha particles derived from cell survival data

after ICRP 58 and 92

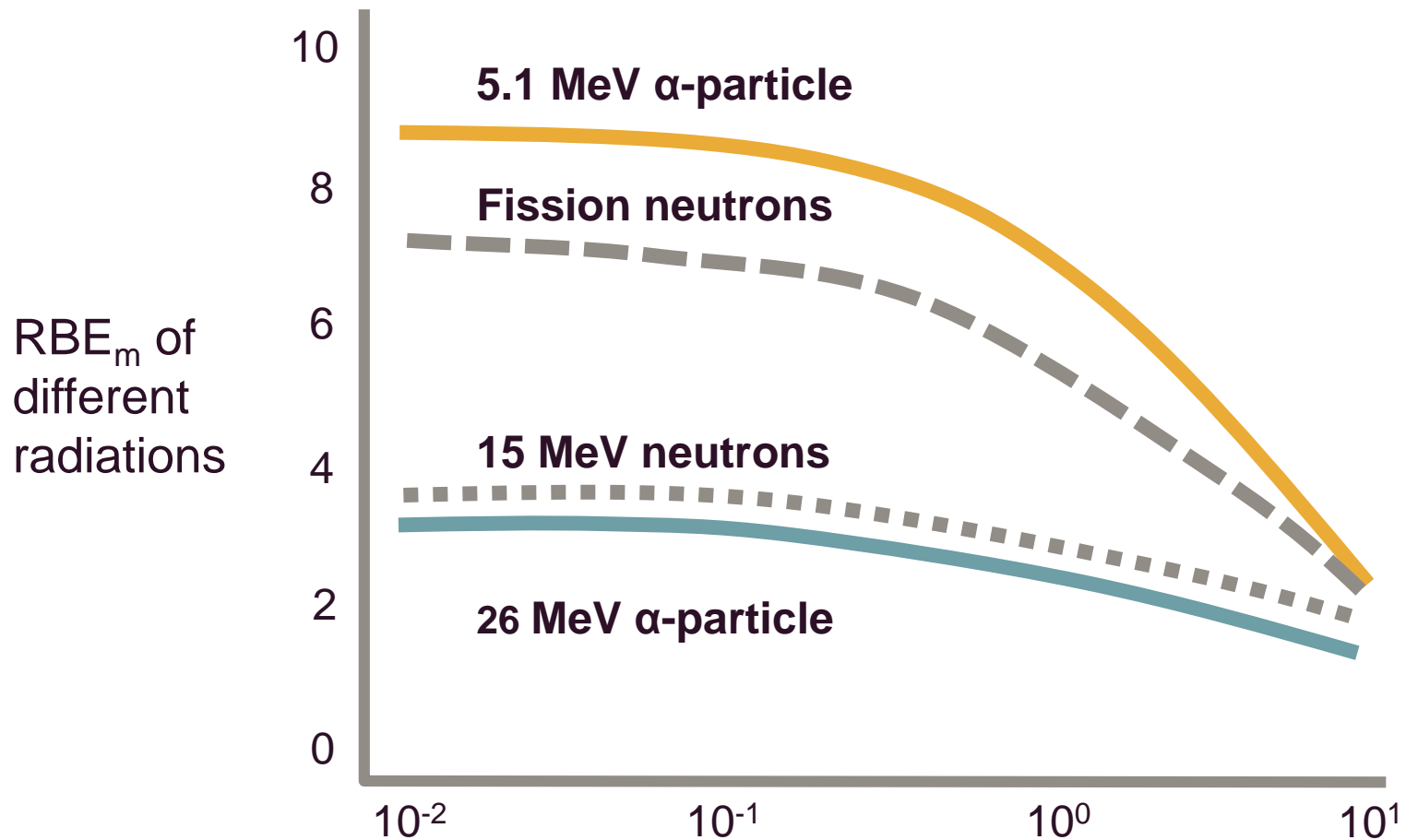
Solution: Measure or Calculate RBE_m

$$a_L D_L + b_L D_L^2 = a_H D_H$$

$$\text{RBE}_m = \frac{\alpha_H}{\alpha_L} \approx \text{RBE}(D_H) \cdot \left\langle 1 + \frac{D_L}{\left(\frac{\alpha_L}{\beta_L}\right)} \right\rangle$$

After ICRP 58 and 92

RBE_m for Deterministic Effects



RBE values approach RBE_m at doses 10^{-1} Gy of x-rays; derived from survival curves, after ICRP 58

Deterministic Effects

- Distinguishing characteristics
 - Incidence and severity increase as a function of dose above a threshold
- Other names
 - Normal tissue effects (clinicians)
 - Non cancer mortality (RERF)
 - Non-stochastic effects
- Categorization
 - Early
 - Late effects
- Major mode is cell killing
 - Death at mitosis (not necessarily first mitosis)
 - Also possibly interphase death (minor component)

Purpose of Task Group

- Review scientific literature on RBE
 - Stochastic effects
 - Deterministic effects
- Exclude data on “exotic” particles and energies – unless LET similar to alpha or beta
- Considered:
 - Alphas, fission neutrons, tritium
- Recommend dose-modifying value(s)
 - Relevant for non-human biota

Overview

- Hundreds of papers identified
- Many rejected
 - Dosimetry concerns
 - Radiation type not relevant
 - Not possible to calculate RBE_m or RBE_M
- Ultimately, would have liked more

Summary of Alpha Papers on Non-Human Biota (Deterministic and Stochastic Endpoints)

	Endpoints	N° Papers	Test Models
In-Vitro Studies	Cell Survival	30	C3H10T1/2 mouse cells V79-379A Chinese Hamster Cells, Fischer F344 rats and Swiss Webster mice.
	DNA Damage and DNA Double Strand Breaks	17	Ehrlich Ascites Tumor Cells, C3H10T1/2 mouse cells, V79-379A Chinese Hamster Cells, and Swiss Webster mice.
	Chromosomal Aberrations	12	C3H10T1/2 mouse cells, Chinese Hamster Cells
	Cell Transformations	9	Fischer F344 rats, C3H10T1/2 mouse cells, and Golden Syrian Hamster
In-Vivo / Ex Vivo Studies	Effect on haemopoietic tissue	3	Mice (C57B16 and C57B1)
	Tumor Induction	4	Beagles, Mice and Wistar Rats
	Organ/Tissue Effects	3	Rats and Zebrafish

Summary of Alpha RBE Papers (Deterministic & Stochastic Endpoints)

RBE Range	Classification of Endpoints		N°	Test Models
	In-Vitro	In-Vivo /Ex-Vivo		
0 - 4	Cell Survival, DNA Damage and Double Strand Breaks, Chromosomal Aberrations and Cell Transformations	Tumor Induction, Organ/Tissue Effects	33	C3H10T1/2 mouse cells, V79-379A Chinese Hamster Cells, Fischer F344 rats and Swiss Webster mice; Beagles, Mice, Wistar Rats and Zebrafish
5 - 10	Cell Survival, DNA Damage and Double Strand Breaks, Chromosomal Aberrations and Cell Transformations	Tumor Induction, Organ/Tissue Effects	24	Ehrlich Ascites Tumor Cells, C3H10T1/2 mouse cells, V79-379A Chinese Hamster Cells, and Swiss Webster mice, Beagles, Mice and Wistar Rats
11 - 20	DNA Double Strand Breaks, and Chromosomal Aberrations	Tumor Induction	4	C3H10T1/2 mouse cells, Chinese Hamster Cells Beagles, Mice and Wistar Rats
≤25 (+/-8)	Chromosomal Aberrations	Effect on haemopoietic tissue and Tumor Induction	7	Fischer F344 rats, C3H10T1/2 mouse cells, and Golden Syrian Hamster, Beagles, Mice and Wistar Rats

Alpha RBE Papers with Population Relevant, Deterministic Endpoints

RBE Range	Population Relevant Deterministic Endpoints		LET Range (Kev / μ m)	N ^o	Test Models
	In-Vitro	In-Vivo/Ex-Vivo			
0 - 4	Embryonic cell, survival/mortality, Ovary cell survival	Reproductive performance (eg. size of litter, post-natal survival and amount of time it takes female to become sterile), Oocyte Survival, Sperm survival	77-200 100-130*	7	Golden Hamster, Mouse, Male Swiss Webster mice, Chinese Hamster Embryo cells, Mouse Embryo cells, Chinese Hamster.
5 - 10	Testicular Abnormalities, Embryonic Cell survival /mortality, sperm abnormality.	Testis mass reduction, Oocyte Survival, Sperm Survival	90-142 50-135*	6	Mice (B6CF1), Swiss Webster mice, Golden Syrian Hamster, C3H 10T1/2 mouse embryo.
≤ 25 (+/-8)	Sperm abnormality	Reproductive effects (Egg production reduction)	130	5	Mice (B6CF1), Zebrafish (Danio rerio), Harvard Swiss Wistar mice

Summary of Tritium RBE for Deterministic ENDPOINTS (HTO)

RBE Range	Population Relevant Deterministic Endpoints		Nº of RBE values	Test Models
	In-Vitro	In-Vivo/Ex-Vivo		
1.0 - 1.9	Mortality (Embryos, haemato-poietic progenitors, germ cells)	Mortality (mice, fry, beans); Reproductive capacity (fertility and fecundity endpoints); Tissue cell death (spleen, intestinal crypts, thymus)	25 (18 in vivo, 7 in vitro)	Aquatic invertebrate (Ophryotrocha diadema); Plant (Vicia faba); Fish (Medaka); Mouse (Swiss-Webster, CBA/H, ICR, CF1, C57Bl/6, RFM/Nrs); Embryos (Mouse BC3F1, Golden hamster embryos); Cell lines (Murine L5178Y; murine C3H 10T1/2); Human cells (bone marrow)
2.0 - 2.9	Mortality (Germ cells, haemato-poietic progenitors)	Reproductive capacity (germ cells survival); Tissue cell death (Bone marrow, intestinal crypts)	11 (10 in vivo, 1 in vitro)	Mouse (C57Bl/6, RFM/Nrs, Swiss-Webster, DBA2); Fish (medaka); Human cells (bone marrow)
≥ 3.0		Reproductive capacity	1 (in vivo)	Fish (medaka)

Issues in the analysis of RBE Data

- Range of derived RBE values depends on:
 - Endpoint, cell-line, in vivo/in vitro, dose and dose rate.
 - Variability/variation with strains of model mammals (rats, mice etc. (in vivo studies)).
 - Variability of cell lines (in vitro studies).
 - Modifications – genetic or otherwise in
 - Cell lines (in vitro),
 - Rats/mice (in vivo),
 - (e.g. genes added or removed to enhance radioresistance or radiosensitivity)

Issues, continued

- Variations / inconsistencies within experimental setups.
- Choice of reference radiation
- High doses/dose rates studies.
- Extrapolating from cells to real populations.
- Linking experimental endpoints to measurement endpoints in the field.

Summary

- Critical evaluation of α and β RBE data have been conducted;
- Current data suggestive of a nominal dose modifying factor
 - ~ 10 for α emitters
 - Tritium still under discussion
 - Nominal HTO values ~ 2 to 3
 - OBT data insufficient to recommend a value
- Data are limited by end point and species and therefore judgment is required in extrapolating to whole organism