The Relevance of Dose for Low-Energy Beta Emitters

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EU Scientific Seminar
Emerging Issues on Tritium and Low Energy Beta Emitters

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OUTLINE

Introductory comments on dose, radiation quality and RBE

ICRP system

Some issues for this symposium

Beta-decay of radionuclides
- **Low-energy beta emitters**

Unusual features of low-energy beta emitters

A few additional comments

Conclusions and recommendations

Introductory comments on ‘Dose’ (and radiation quality)

Absorbed Dose

- **Physical quantity, precisely defined, no changeable parameters**
- **Absorbed dose is the quotient of de by dm, where de is the mean energy imparted to matter of mass dm.**
- **Absorbed dose = Deposited Energy ÷ Mass**
- **Units: joule per kilogram = gray (Gy)**

$$D = \mathrm{d}e/\mathrm{d}m$$

- **Independent of type (quality) of ionizing radiation**
- **Approximately proportional to the average density of ionizations in the mass (volume) of interest**

BUT biological effectiveness of a given absorbed dose depends on many additional factors, including:

- **Type of radiation (i.e. radiation quality)**
- **Dose rate, dose fractionation**
- **Particular biological system, effect and level of interest**

This symposium is particularly concerned with radiation quality

- **of tritium (^{3}H)and other low-energy beta emitters,**
  that is, with low energy electrons;

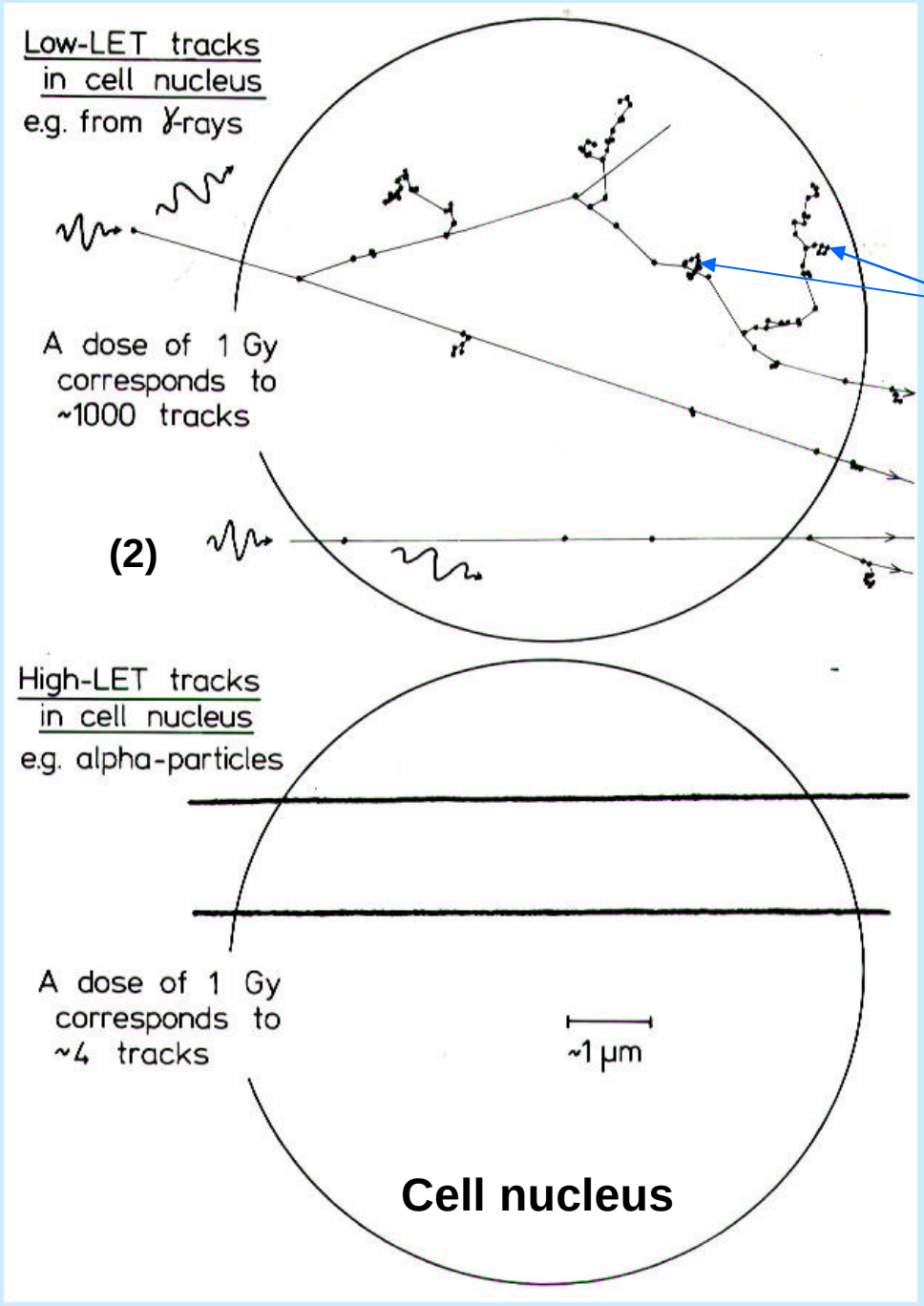
- **and comparison with reference radiations,**
  that is, mixed high- and low-energy electrons from gamma-rays or orthovoltage X-rays;

Also some additional special features of these beta emitters.

Radiation quality

Determined by the track structure of the radiation

- **Microscopic features of the individual tracks**
- **Relationship between separate tracks, in time and space.**



Low-LET reference radiation:

Sparsely ionizing on average, but ~ 1/4 of energy deposited via denser clusters of ionizations from low-energy secondary electrons (on scale of nanometres)
(Magnified in diagram)

Very low dose from a single track
(ave ~ 0.001 Gy to cell nucleus)

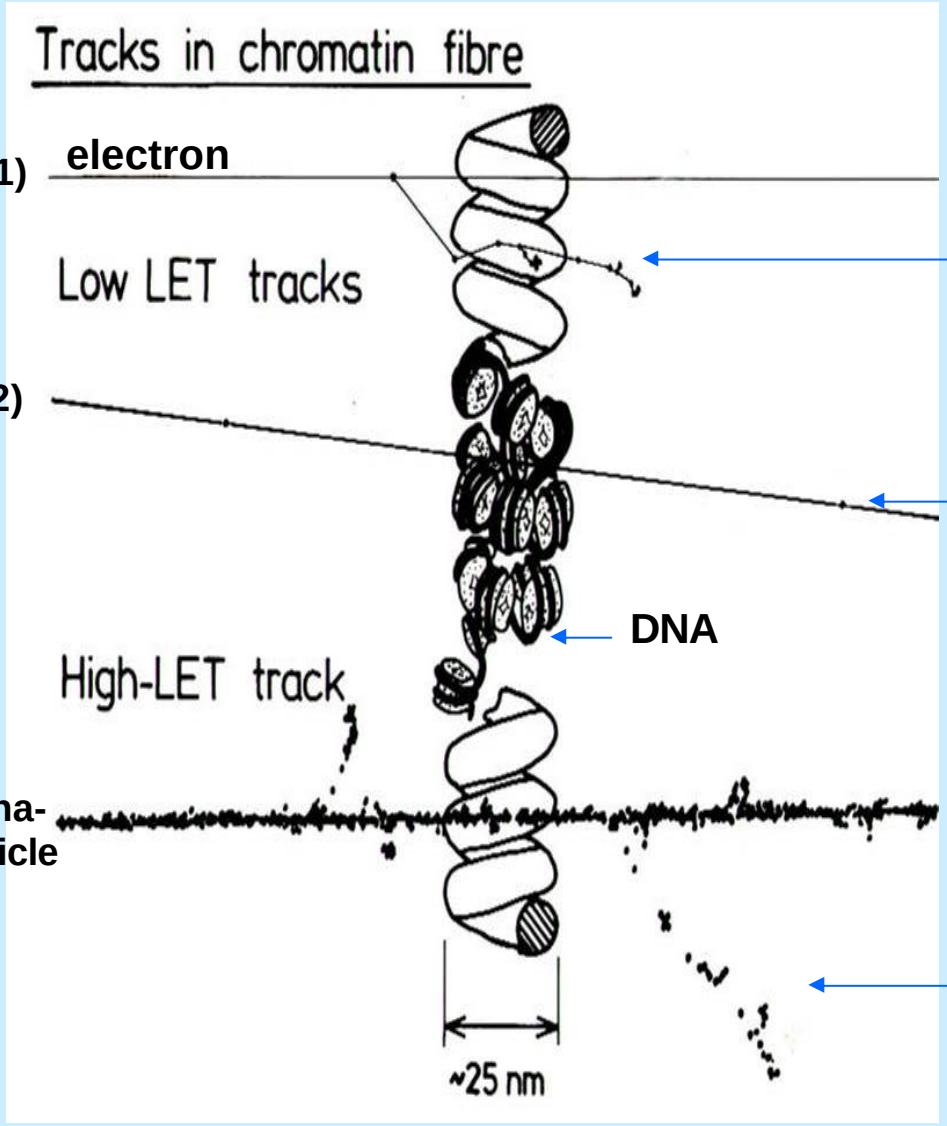
High-LET radiation:

Densely ionizing on average
(especially for low-velocity ions, natural alpha-particles, etc)

High dose from a single track
(~ 0.2 - 0.5 Gy from single a-track)

LET = Linear Energy Transfer

All radiation tracks are highly structured on the scale of DNA



Clustered ionizations from low-energy electron

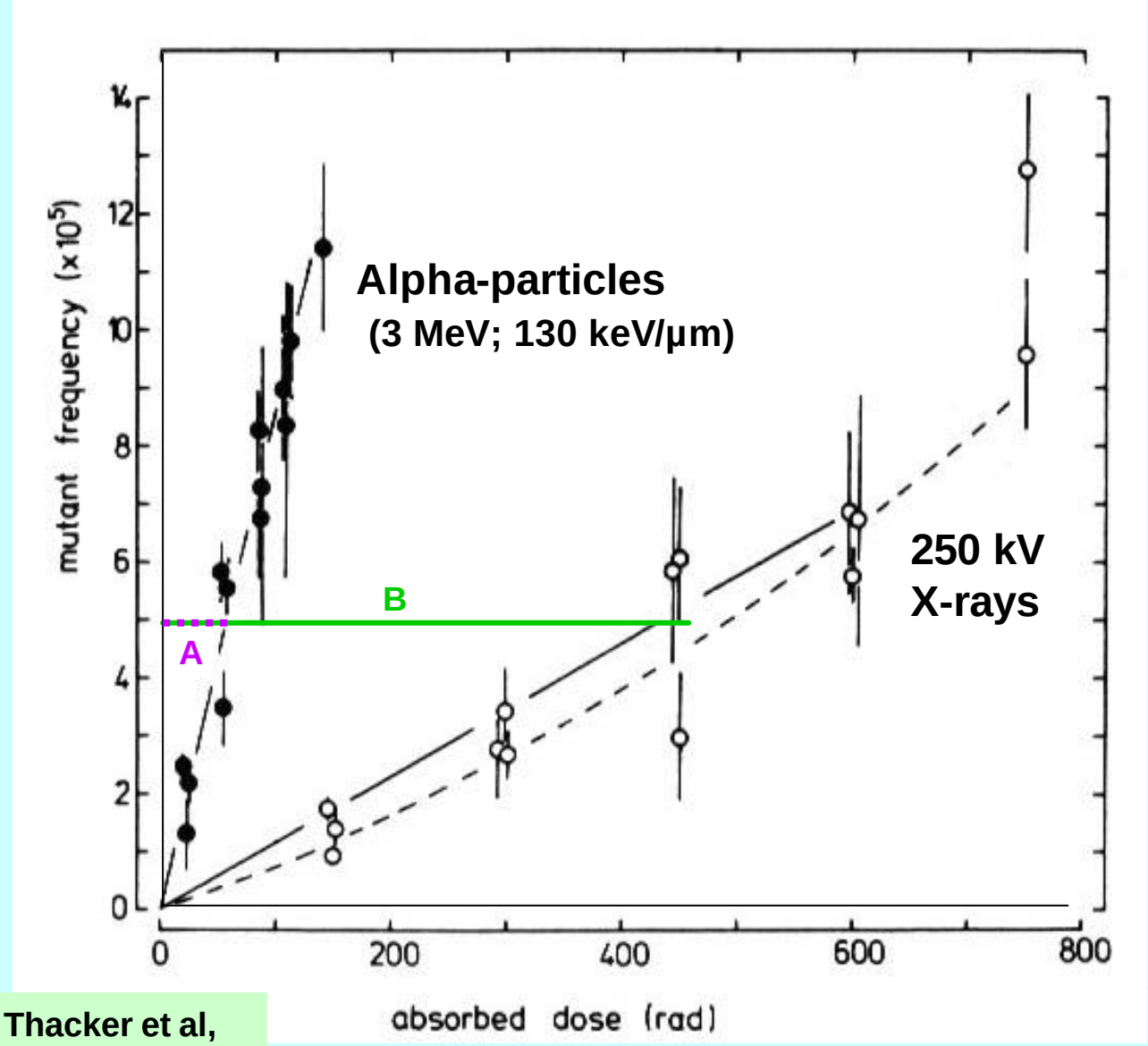
Single ionization

Opposing trends: Alpha-particle has
-- low probability of hitting DNA (few tracks per Gy)
-- high probability of damage when it does hit.

Delta-ray electron

Example:

hprt mutation-induction by alpha-particles compared to X-rays in V79 cells



Thacker et al,
Radiat Res 92,
343-352 (1982)

[100 rad = 1 Gy]

In general, biological effectiveness depends on:

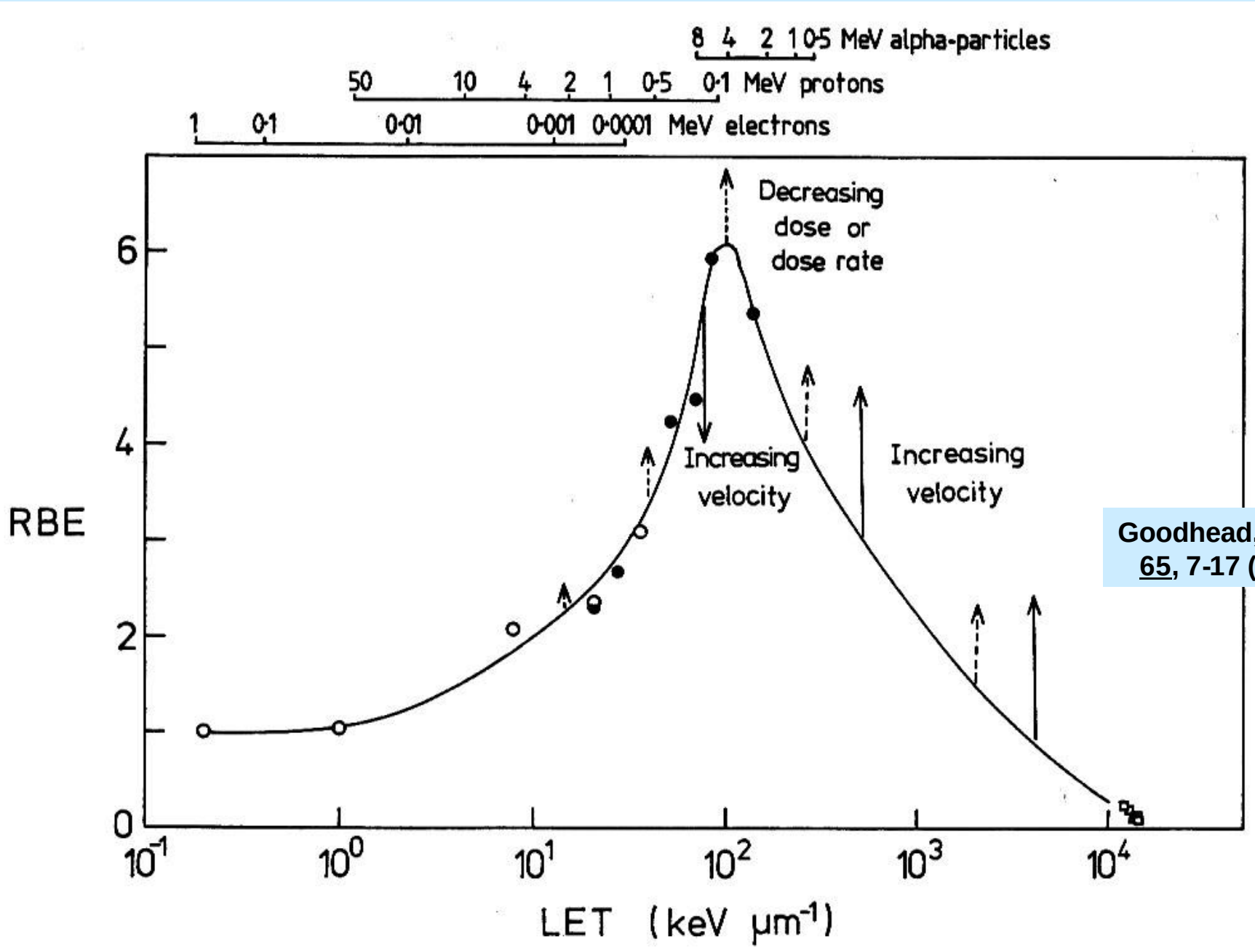
- --- radiation quality
- --- dose
- --- dose-rate
- --- biological system

Here:

Relative Biological Effectiveness (RBE) of alpha-particles in this system is

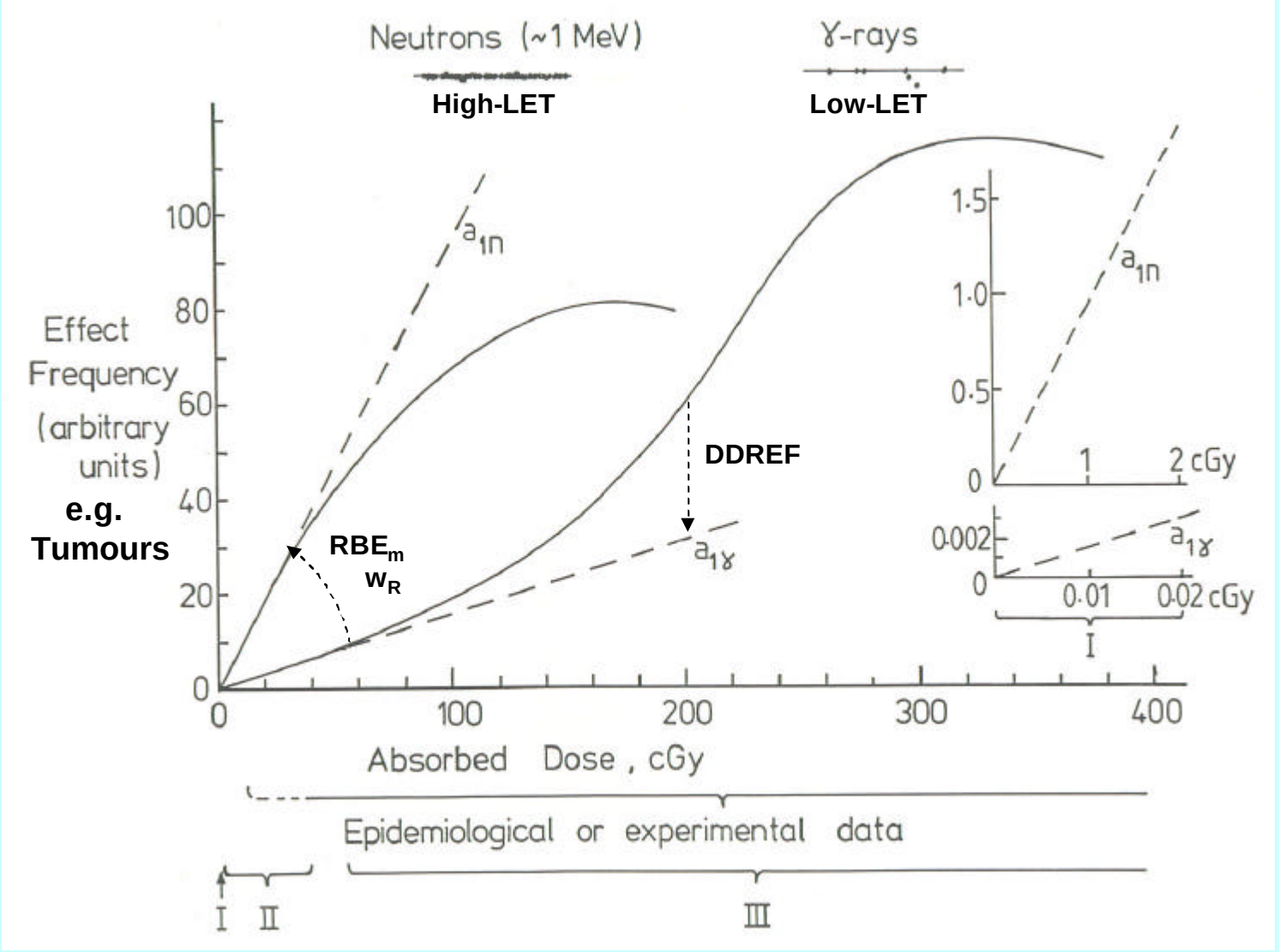
$$\frac{\text{Dose B}}{\text{Dose A}} \sim 8$$

Relative Biological Effectiveness for Cell Inactivation by Ionizing Radiations



Goodhead, IJRB 65, 7-17 (1994)

Schematic dose responses for radiation risks



LET = Linear Energy Transfer
RBE_m = Relative Biological Effectiveness (maximum)
w_R = Radiation weighting factor
DDREF = Dose and Dose-Rate effectiveness Factor

Mod from Goodhead, Adv Radiat Biol 16, 7 (1992)

ICRP system developed for radiation protection

Dosimetry/risk system based on

- **Absorbed dose (D_T) to each tissue or organ (ie physical dose)** — **Units: gray (Gy) = J/kg**

- **but with 'subjective' prescribed weighting factors for approximate dependence of human risks:**

(1) weighting for radiation quality:

Equivalent dose to a tissue,

$$H_T = S_R\,(w_R.D_{T,R})$$

Units: sievert (Sv) = J/kg

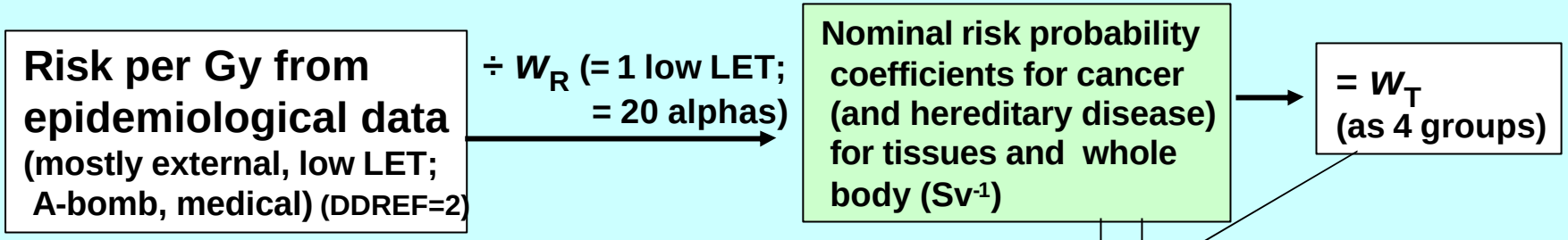
(2) weighting also for tissue sensitivity:

Effective dose to whole body,

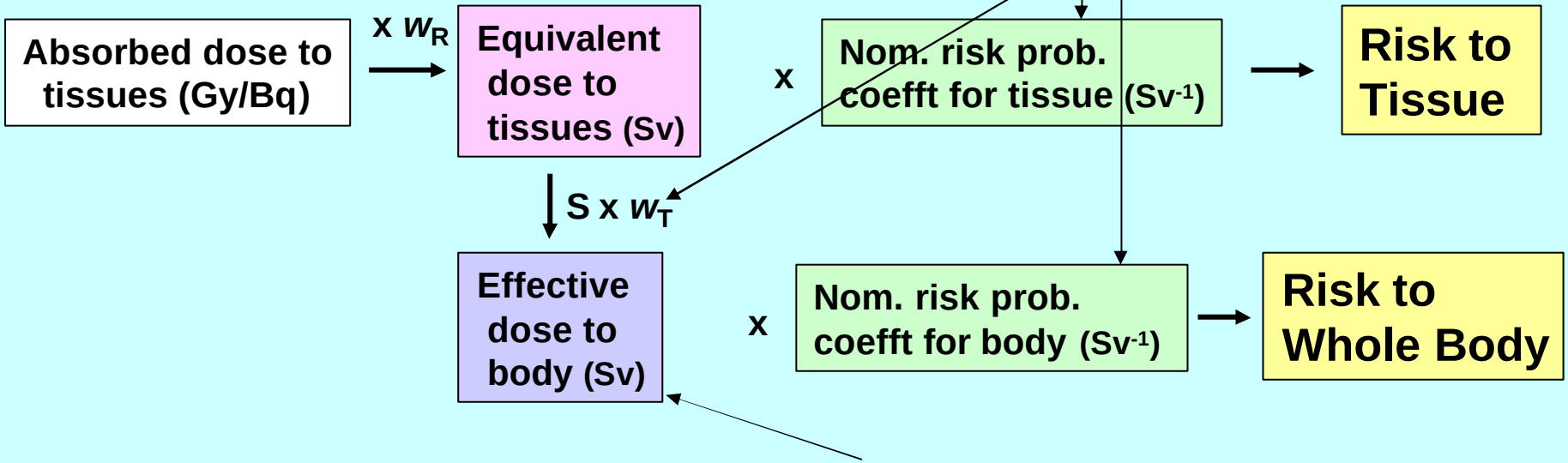
$$E = S_T\,(w_T.H_T)$$
$$= S_{T,R}\,(w_T.w_R.D_{T,R})$$

Units: sievert (Sv) = J/kg

1. Primary ICRP risk estimates:



2. Hence, Estimated Risk for external radiation exposures:



For radiation protection, limits are set in terms of effective dose (or equivalent dose) as surrogates for whole-body risk (or tissue risk).

Comment: Complex, yet crude, system to achieve additivity of risk from all exposures; Convenient for rough planning purposes in radiological protection.

1. Primary ICRP risk estimates:

Epi data
(mostly external, low LET; A-bomb, medical)

→ x w_R (=1 low LET; = 20 alphas)

Nominal risk probability coefficients for cancer (and hereditary) (Sv^{-1})

→ = w_T (as 4 groups)

2. ICRP Dose Coefficients for internal radionuclides:

(i.e.Dose per unit intake)

Biokinetic models (intake ? tissues)
+
Dosimetric models (decays ? absorbed dose)

→ Absorbed dose to tissues (Gy/Bq)

→ x w_R → Equivalent dose to tissues (Sv/Bq)

→ S x w_T → Effective dose to body (Sv/Bq)

3. Hence, Estimated Risk from internal radionuclide exposure:

Estimated intake (Bq) (ingestion, inhalation, absorption)

x Tissue dose coefft (Sv/Bq) x Nom. risk prob. coefft for tissue (Sv^{-1}) → **Risk to Tissue**

x Body dose coefft (Sv/Bq) x Nom. risk prob. coefft for body (Sv^{-1}) → **Risk to Whole Body**

For radiation protection, limits are set in terms of effective dose (or equivalent dose) as surrogates for whole-body risk (or tissue risk)

Comment: Complex, yet crude, system to achieve additivity of risk from all exposures; Convenient for rough planning purposes in radiological protection.

Hence, effective dose is used

- **as primary quantity for dose-limits in radiation protection**
  --- for prospective dose assessment, optimization and for demonstrating compliance

- **as surrogate for risk (within the broad approximations of the ICRP system)**

- **for simple additivity of doses (and implied risks) from low-dose exposure scenarios, including**
  - **non-uniform irradiation of body or tissues**
  - **mixed radiation qualities**
  - **internal and external radiation sources**
  - **any temporal distributions of dose (i.e. dose-rate and dose fractionations)**

Effective dose is not suitable for

- **more accurate retrospective assessments of individual doses and risks**

- **use in epidemiological studies**

- **probability of causation in exposed individuals**

[ICRP draft recommendations, Jan 2007]

Issues for this symposium could include:

- Appropriateness of ICRP specification of $w_R = 1$ for ALL photon and electron irradiations, including for low-energy beta emitters

- Under what circumstances should this value be used?
  (e.g. prospective planning and routine records in radiation protection when doses are well below dose limits, ….)

- What values of RBE should be used for particular low-energy beta-emitters when more accurate dose or risk assessments are required?
  (e.g. retrospective dose/risk assessments, prospective assessments/planning if approaching dose limits, epidemiology, compensation, litigation, …)

- What other factors, in addition to radiation quality, may require consideration for particular low-energy beta-emitters?
  (e.g. non-uniformity of absorbed dose to target cells within a tissue, to critical sub-cellular components, …)

- Appropriateness of ICRP w_T values for ALL radiations, including low-energy beta emitters?

ICRP-prescribed values of radiation weighting factor

Radiation type and energy range	Prescribed w_R ICRP(1991)	Prescribed w_R (ICRP2007 draft)
Photons, all energies	1 ☆	1 ☆
Electrons and muons, all energies	1 ☆	1 ☆
Neutrons, energy < 10 keV	5	Continuous fnc of energy, min 2.5, max 21
10 keV to 100 keV	10	
>100 keV to 2 MeV	20	
>2 MeV to 20 MeV	10	
>20 MeV	5	
Protons, other than recoil protons, >2 MeV	5	2
alpha particles, fission fragments, heavy nuclei	20	20

☆ Implies equal risk per unit effective dose to body
per unit equivalent dose to a tissue
per unit absorbed dose to a tissue

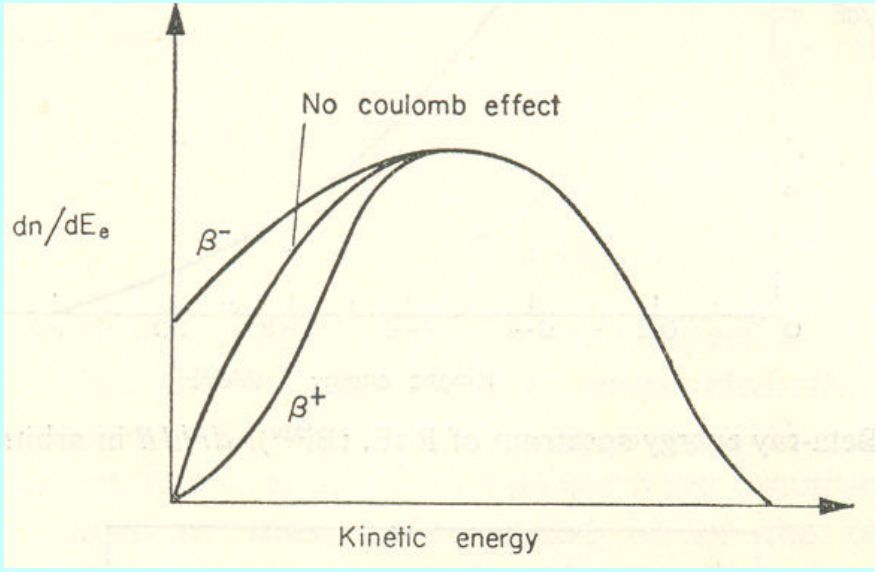
} For <u>ALL</u> photon and electron irradiations

ICRP treats: absorbed dose from low-energy beta emitters (few keV)
<u>exactly as if</u> from orthovoltage X-rays (~100 keV)
or from high-energy gamma-rays (~ 1 MeV).

Beta decay of radionuclides:

Electron emission (ß$^-$ decay):

$$ {}^{A}_{Z}X \longrightarrow {}^{A}_{Z+1}Y + {}^{0}_{-1}e + {}^{0}_{0}\bar{nu} $$



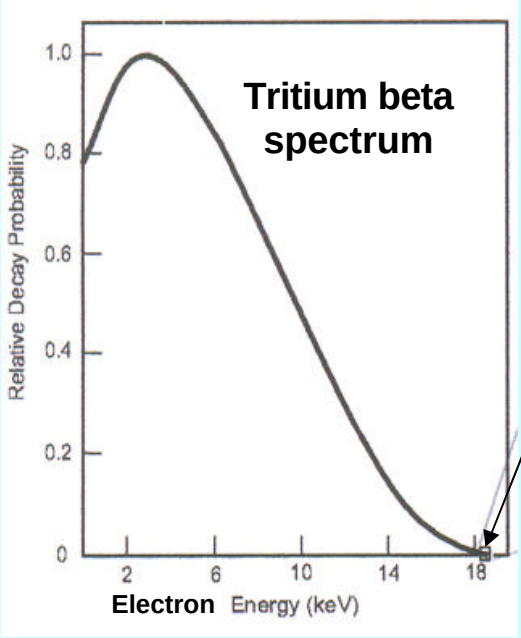
Positron emission (ß$^+$ decay):

$$ {}^{A}_{Z}X \longrightarrow {}^{A}_{Z-1}Y + {}^{0}_{+1}e + {}^{0}_{0}nu $$

[where nu is neutrino]

Tritium ß$^-$ decay:

$$ {}^{3}_{1}H \rightarrow {}^{3}_{2}He + e^{-} + \bar{nu} $$



E_{max} = 18.6 keV

E_{ave} = 5.7 keV

Some relevant low-energy beta$^-$ -emitting radionuclides:

ß$^-$ -decay	Electron energy (keV) Max	Electron energy (keV) Average	Electron range (µm) Max	Electron range (µm) Average	Half-life
$^{3}_{1}H \rightarrow {}^{3}_{2}He$	18.6	5.7	~7	~0.56	12.3 y
$^{14}_{6}C \rightarrow {}^{14}_{7}N$	157		~290		5730 y
$^{35}_{16}S \rightarrow {}^{35}_{17}Cl$	167		~320		87 d
$^{106}_{44}Ru \rightarrow {}^{106}_{45}Rh$	39.4		~28		574 d
$^{210}_{82}Pb \rightarrow {}^{210}_{83}Bi \rightarrow$ (ß,a)	63.5		~64		22 y
Compare:					
$^{90}_{38}Sr \rightarrow {}^{90}_{39}Y \rightarrow$ (ß)	546		~1950		29 y
$^{131}_{53}I \rightarrow {}^{131}_{54}Xe$ (+gamma)	971		~4200		8 d
$^{137}_{55}Cs \rightarrow {}^{137}_{56}Ba$ (+gamma)	1176		~5200		30 y

Unusual features of low-energy beta-emitters:

1) Increased average ionization density (LET)

2) Short electron tracks

3) Non-uniformity of dose

4) Cell (or nucleus) hit frequencies per unit dose (numbers of tracks)

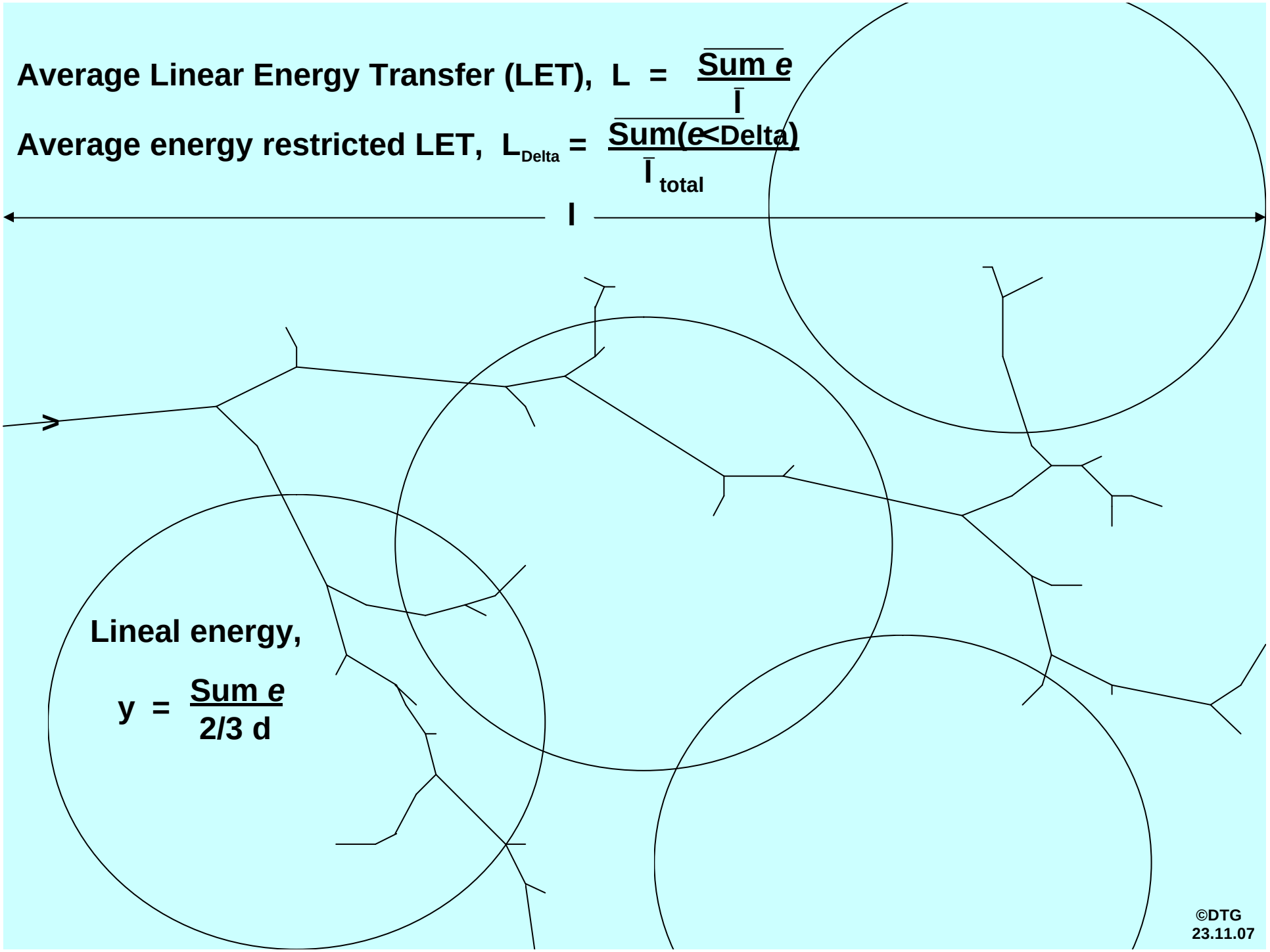
5) Nuclear transmutations

6) Isotopic mass differences

7) Molecular forms

[8) Positron annihilation for $ß^+$-emitters]

Most of these features are not incorporated into conventional radiation protection dosimetry.


Average Linear Energy Transfer (LET), L = $\frac{\overline{\text{Sum } e}}{\bar{l}}$
Average energy restricted LET, L_{Delta} = $\frac{\overline{\text{Sum}(e<\text{Delta})}}{\bar{l}_{total}}$
l
Lineal energy,
y = $\frac{\text{Sum } e}{2/3\ d}$
©DTG
23.11.07

Unusual features:

1) Increased average ionization density on subcellular scale (by whatever measure)

		Tritium ß	X-rays 50kV	X-rays 250kV	^{60}Co gamma
LET (Linear Energy Transfer) (keV/µm)					
Track-average LET ($\bar{L}_{100,T}$) [$L_{8,T}$]		4.7 [~12]	6.3	1.7	0.22
Dose-average LET ($\bar{L}_{100,D}$) [$\bar{L}_{Inf,D}$]		11.5	13.1	9.4	6.9 [0.31]
Lineal energy (keV/µm)					
			65kV	200kV	
Site diameter d = 5 µm	Frequency-mean ($\bar{y}_F$)	1.4	~1.7	1.0	0.28
	Dose-mean ($\bar{y}_D$)	2.1	~2.6	2.1	0.62
d = 1 µm	Frequency-mean ($\bar{y}_F$)	3.1	2.2	1.2	0.37
	Dose-mean ($\bar{y}_D$)	5.2	5.0	3.7	1.6
d = 0.5 µm	Frequency-mean ($\bar{y}_F$)	4.1	2.6	1.4	0.52
	Dose-mean ($\bar{y}_D$)	7.3	5.4	4.7	2.3
			40kV	250 kV	
d = 0.1 nm	Frequency-mean ($\bar{y}_F$)	4.0	-	-	-
	Dose-mean ($\bar{y}_D$)	9.2	-	8.1	4.3
d = 0.01 nm	Frequency-mean ($\bar{y}_F$)	7.8	6.9	6.1	-
	Dose-mean ($\bar{y}_D$)	18.0	17.7	17.0	12.6

Unusual features:

1) Increased average ionization density on subcellular scale
(by whatever measure)

<u>LET (Linear Energy Transfer)</u>

	Tritium ß	X-rays 50kV	X-rays 250kV	^{60}Co gamma
Track-average LET ($\bar{L}_{100,T}$) (keV/µm)	4.7	6.3	1.7	0.22
Dose-average LET ($\bar{L}_{100,D}$) (keV/µm)	11.5	13.1	9.4	6.9
($\bar{L}_{Inf,D}$) (keV/µm)				0.31

Compare with protons of similar LET:

~ 10 MeV protons have LET (L_T) = 4.7 keV/µm

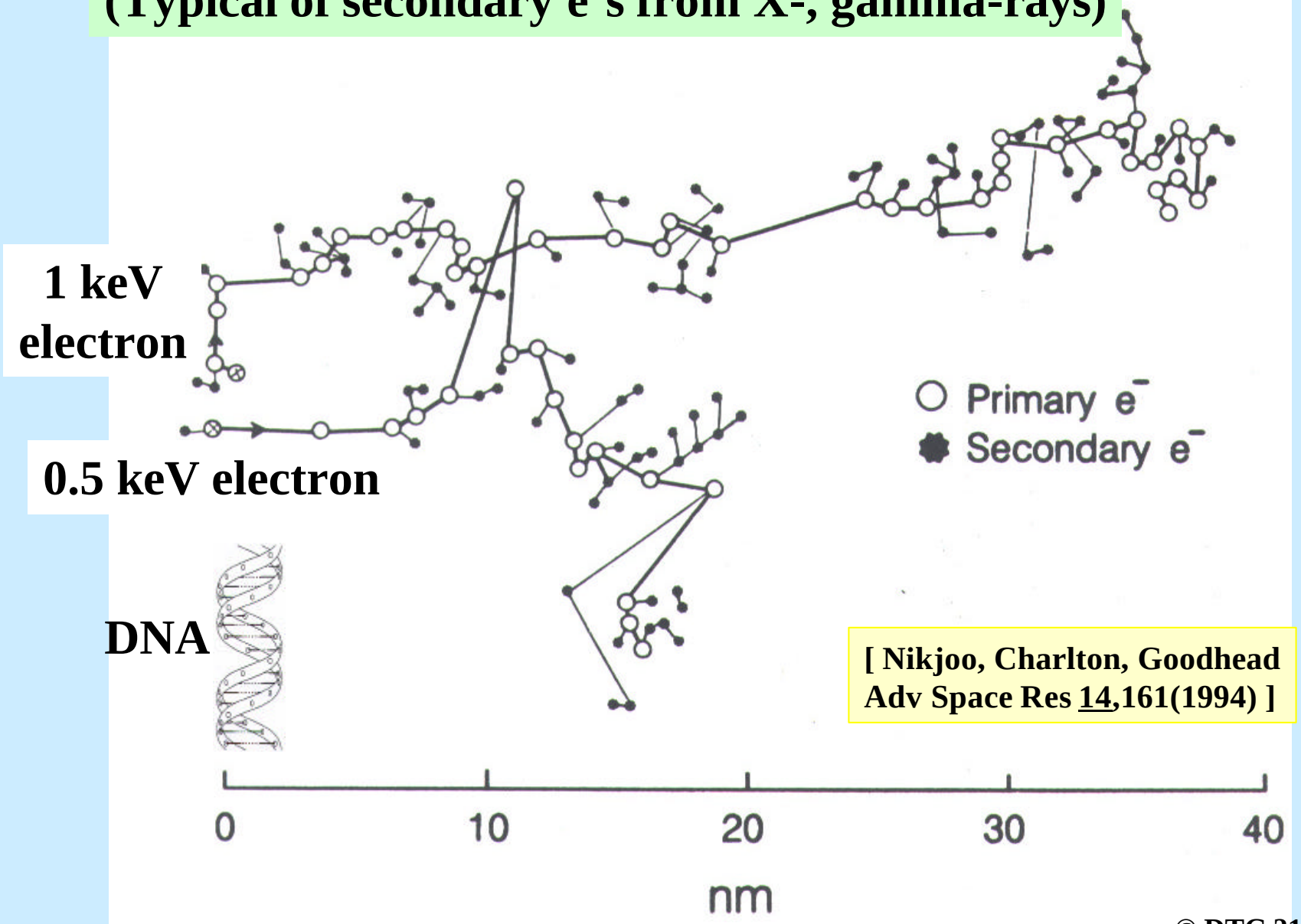
For protons ICRP prescribes w_R = 5 (ICRP60, 1991)

= 2 (ICRP draft recs, Jan 07)

(reduced partly on the basis of low penetration of <u>external</u> protons)

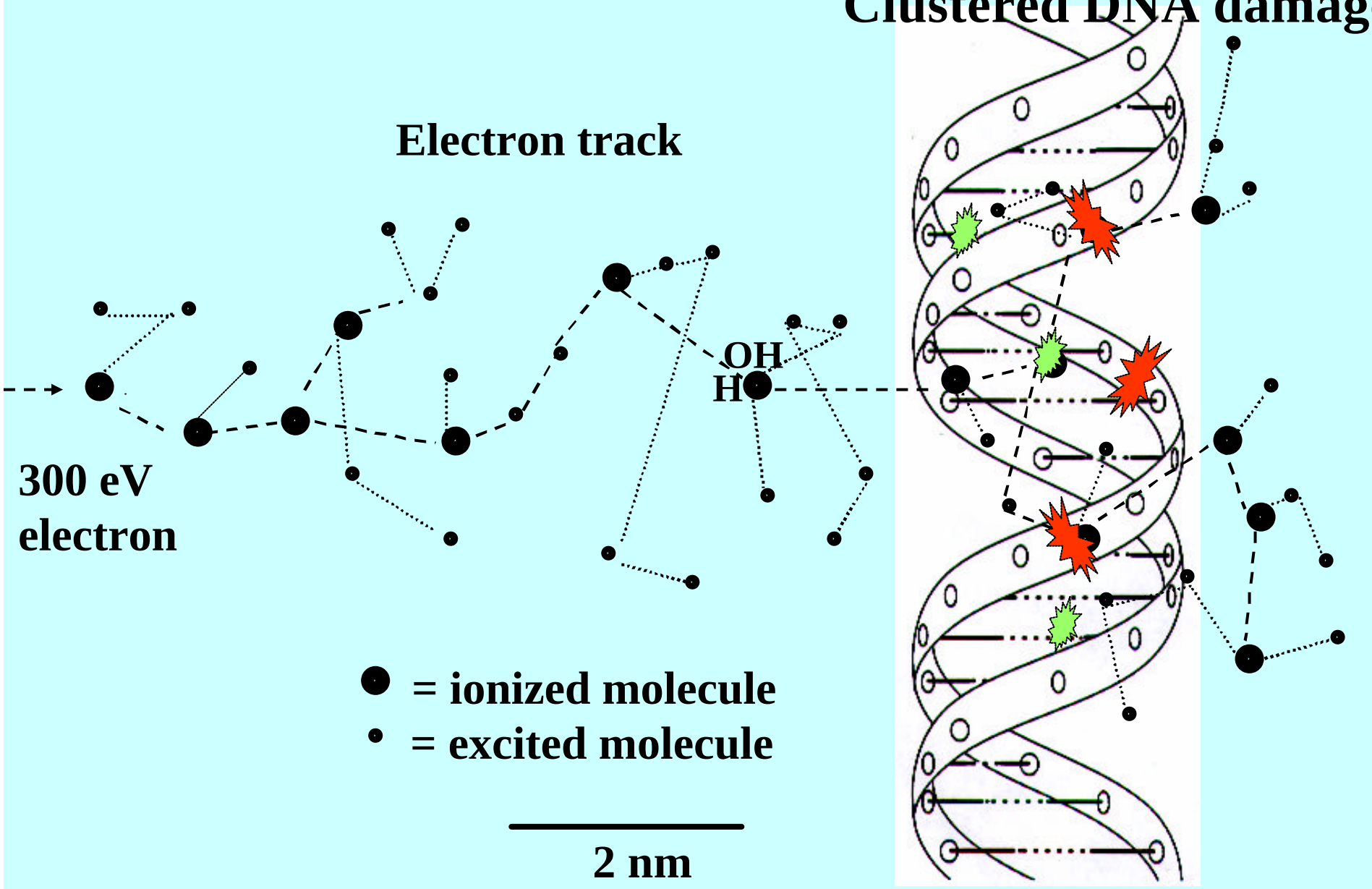
Two low-energy-electron tracks

(Typical of secondary e's from X-, gamma-rays)



[Nikjoo, Charlton, Goodhead Adv Space Res 14,161(1994)]

Clustered DNA damage



Unusual features:

2) Short ranges of electrons (beta-particles)

Ranges of tritium beta-particles:

Average	0.56 µm
Maximum	~ 7 µm

Compare with:

Typical cell diameters	~ 7 µm to 30µm
Typical cell nucleus diameters	~ 6 µm to 15 µm
Chromatin fibre diameter	~ 0.030 µm
DNA diameter	~ 0.0024 µm

Hence:

Short range

- **does not mask increased LET of these electrons on scale of DNA and chromatin;**
- **limits ability of single track to damage two distant targets on cellular scale;**
- **can lead to <u>non-uniformity of dose</u> when emitters are inhogeneously distributed.**

Unusual features:

3) Non-uniformity of absorbed dose

Occurs when ß-emitters are non-uniformly distributed on scales of:

- tissue compartments (all low-energy ß-emitters)
- individual cells (some low-energy ß-emitters)
- cell compartments, eg nucleus vs cytoplasm (a few low-energy ß-emitters)
- chromosomes or DNA (notably tritium)

Examples: Tritiated DNA precursors;
OBT in adipose tissue;
.....
etc

NOTE: Also, mean <u>ionization density</u> may be increased in targets with bound tritium compared to uniform HTO. [Chen (2006): $\overline{y}_D$ ratio ~ 1.7]
Additional to enhancement of absorbed dose.

Unusual features:

4) Cell (or nucleus) hit frequencies per unit dose

- Larger mean energy deposition by single ^{3}H ß than from single track from Co gamma;

- Hence, fewer hits from tritium than from Co gamma-rays (for equal average absorbed dose to tissue);

- i.e. Fewer cells (or nuclei) are hit by ^{3}H, but they are hit harder.

- Any consequences? (Thresholds, Dose rate)

		^{3}H	Co gamma
For sphere d = 7 µm	$\bar{z}_F$ (mGy)	4.6	1.1
	Hit frequency $=1/\bar{z}_F$ (mGy^{-1})	0.2	0.9
For sphere d = 12 µm	$\bar{z}_F$	1.3	0.4
	Hit frequency $=1/\bar{z}_F$ (mGy^{-1})	0.8	2.5

where $\bar{z}_F$ = mean specific energy

Unusual features:

5) Nuclear transmutation

- Molecular changes result from transmutation of ß-emitting radionuclide
- Conversion of ^{3}H to ^{3}He loses its chemical binding in molecule
  (e.g. deprotonation in a DNA base, potentially mutagenic?
  disruption of hydrogen bonding in DNA)
- Conversion of ^{14}C to ^{14}N in DNA base (potentially mutagenic?)
- Conversion of ^{35}S to ^{35}Cl alters the biomolecule

Unusual features:

6) Isotopic mass difference ratio compared to stable isotope

- **Affects physico-chemical properties**

- **Mass difference is very large for ^{3}H compared to normal ^{1}H, by ratio of 3**
  (e.g. affect chemical reaction rates for uptake and clearance;
  differential diffusion;
  'buried tritium':
  differential binding of water in hydration shell of DNA – enrichment factor 2?
  differential binding in proteins, other macromolecules -- " " 1.4?

- **Ratios are very small for most other ß-emitters**

Unusual features:

7) Molecular forms

- Different molecular compounds of ß-emitters can influence uptake ratios, retention times and other biokinetic parameters

- Notable forms for ^{3}H include:
  - -- tritiated water
  - -- organically bound tritium (OBT) – exchangable
  - -- non-exchangable
  - -- DNA precursors

Unusual features:

8) Positron annihilation (ß$^+$ emitters)

$$e^+ + e^- \longrightarrow 2\ \text{gamma}$$ **(High energies, >0.5 MeV each)**

- **Delocalizes energy of ß$^+$ -emitters**

Unusual features of low-energy beta-emitters:

1) Increased average ionization density (LET)

2) Short electron tracks

3) Non-uniformity of dose

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5) Nuclear transmutations

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[8) Positron annihilation for $ß^+$-emitters]

- Most of these features are not incorporated into conventional radiation protection dosimetry.

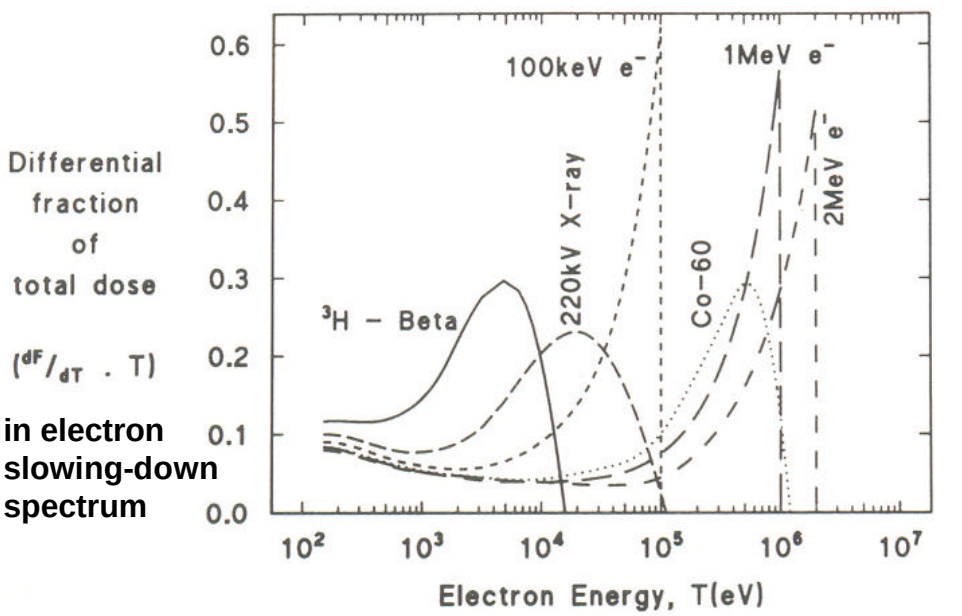
- They may be incorporated in various ways into experimental measurements of RBE

A few additional comments

Comment

Low-energy electrons are an important component for dose deposition by all low-LET radiations (X, gamma, e);

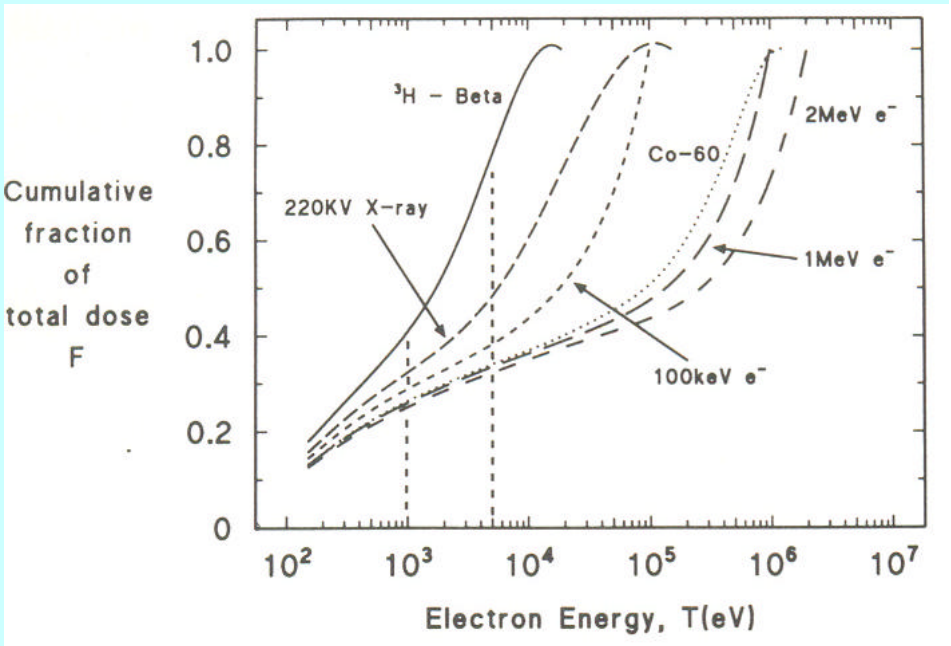
But <u>especially</u> so for tritium ß-decay.



COMPARE:

Dose fraction deposited by electrons of energies 0.1 to 5 keV from:

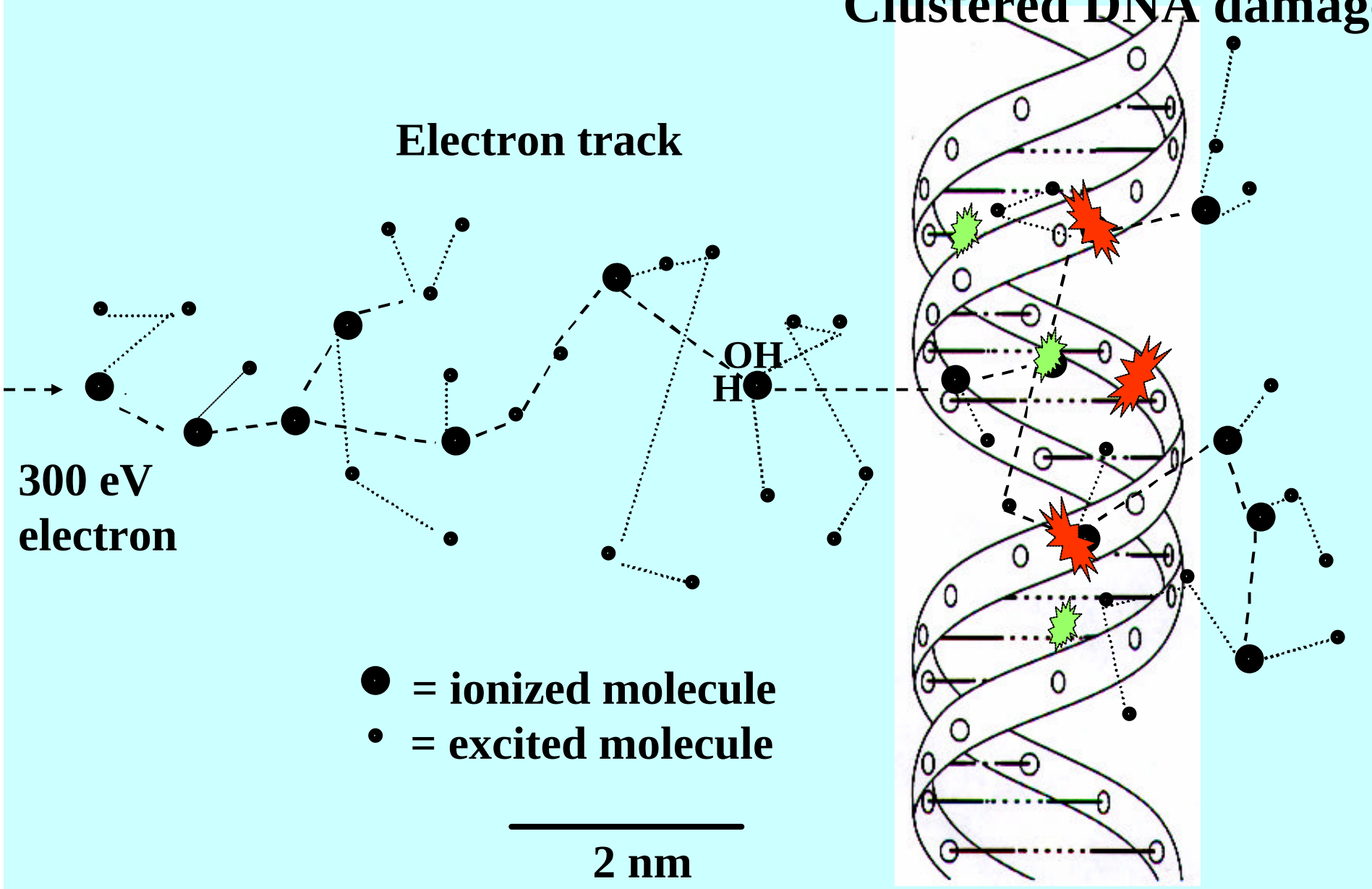
Tritium ß	**77 %**
220 kV X-rays	**38 %**
Co gamma rays	**34 %**



NOTE: Low energy electrons are more efficient at:

- **producing DNA double-strand breaks (DSB)**
- **producing a higher proportion of complex DSB (and other clustered damage)**

Clustered DNA damage



Complexity of DNA Strand Breaks

	Energy **keV**	% No Break	SSB %	SSB+ %	2SSB %	DSB %	DSB+ %	DSB++ %	SSB Complex Total	**DSB Compl. Total**	**SS DS**
ELECTRONS	0.1	73.9	22.4	1.86	0.09	1.39	0.27	0.015	8.0%	17%	17
	0.3	66.4	26.6	3.29	0.43	2.38	0.85	0.092	12.3%	28%	11
	0.5	68.7	25.4	2.78	0.47	1.86	0.79	0.070	11.3%	29%	13
	1.0	68.9	25.2	2.75	0.50	1.81	0.71	0.081	11.4%	**32%**	**13**
	1.5	70.5	24.3	2.39	0.40	1.68	0.63	0.074	10.3%	29%	14
	4.5	80.6	17.6	0.90	0.18	0.52	0.17	0.013	5.8%	26%	26
	10	81.1	17.4	0.78	0.13	0.47	0.13	0.014	5.0%	23%	30
	20	81.3	17.2	0.75	0.12	0.46	0.13	0.012	4.8%	23%	30
	50	81.8	16.9	0.70	0.12	0.44	0.12	0.009	4.6%	22%	31
	100	81.8	16.9	0.60	0.11	0.47	0.11	0.008	4.1%	**20%**	**30**
a	**MeV**										
	4.0	58.1	25.0	6.1	1.28	3.76	3.86	1.90	23 %	61%	3
	2.0	53.3	23.1	6.8	1.90	4.01	6.14	4.81	27 %	**73%**	**2**

Nikjoo/Goodhead/O'Neill/Terrissol/Wilson/Bolton/Watanabe: IJRB **71**,467('97); Rad Res **148**,485('97) & **156**,577('02); Rad Prot Dosim **99**,77('02)

Comment

Table commonly referred to as justification for claim of RBE = 2 of orthovoltage X-rays compared to ^{60}Co gamma rays!! (eg ICRP60)

Table D-3--- Low Dose RBE studies of Low-Let Radiation[a] (Bond et al 1978)

System	Radiation	RBE = alpha ratio
Tradescantia stamen hair mutation	X gamma	2.1
Lymphocyte chromosome aberrations	X e	3.2
Mouse oocyte killing	^{3}H gamma	2.9-4.2

[a]Effect = alpha.D + ß.D^2, RBE is equivalent to RBE_M

(Table copied from ICRU40, 1986)

- **Very poor justification!!**

Lymphocyte dicentric aberrations remain the mainstay of such claims, with heavy reliance on simple curve-fitting extrapolations.

Conclusions

- General expectation that low-energy beta emitters will have greater biological effectiveness than standard reference radiations
  - Supported from many directions, experimental and theoretical.
- The magnitude and practical implications need consideration.
- Some special features of low-energy beta emitters may be overlooked in routine RBE experiments
- There may be issues with use of standard tissue weighting factors for all low-energy beta emitters
  - e.g. access to target cells, or excesses therein (radiation quality differences)

Some recommendations

- Use available information (experimental and theoretical) to establish the likely effectiveness of low-energy beta emitters for human risk relative to reference radiations
- Consider special cases of potential practical relevance
  e.g. extreme inhogeneity
- Determine yields and complexity of DNA damage from tritium beta-emitters, including when bound to cellular DNA, in comparison with a reference radiation
- Seek agreement on a standard reference radiation of practical convenience and relevance to established human risks

THE END