Biological/health effects of ionizing radiation

RBPA course **(PHYS-450)**

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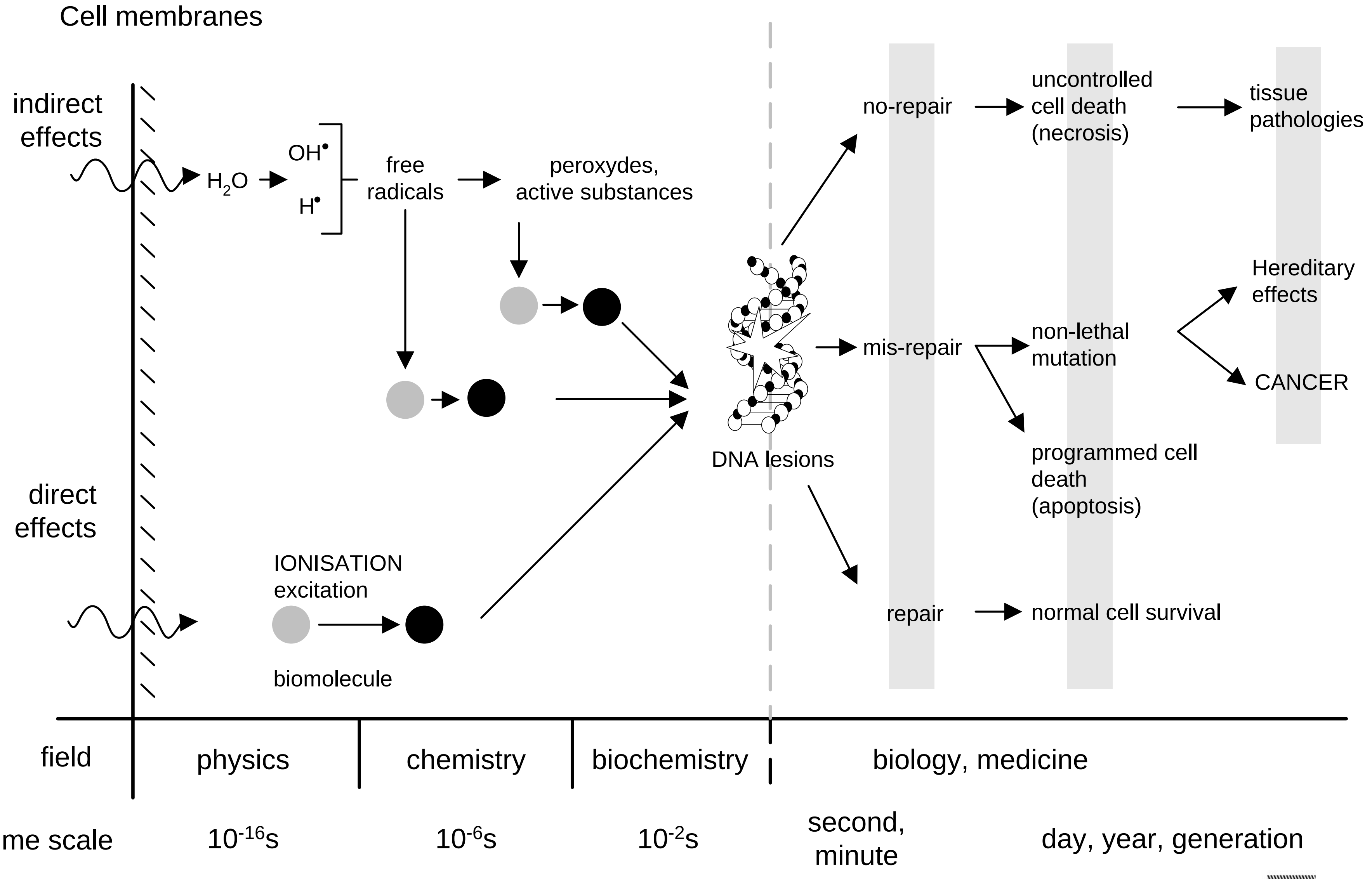
Questions to think about before we start with lecture:

- Why is ionizing radiation dangerous for our health?
- What are some possible outcomes of exposure to ionizing radiation?
- What do biological/health effects of ionizing radiation depend on?

Overview of Lecture 2



HEALTH EFFECTS OF IONIZING RADIATION

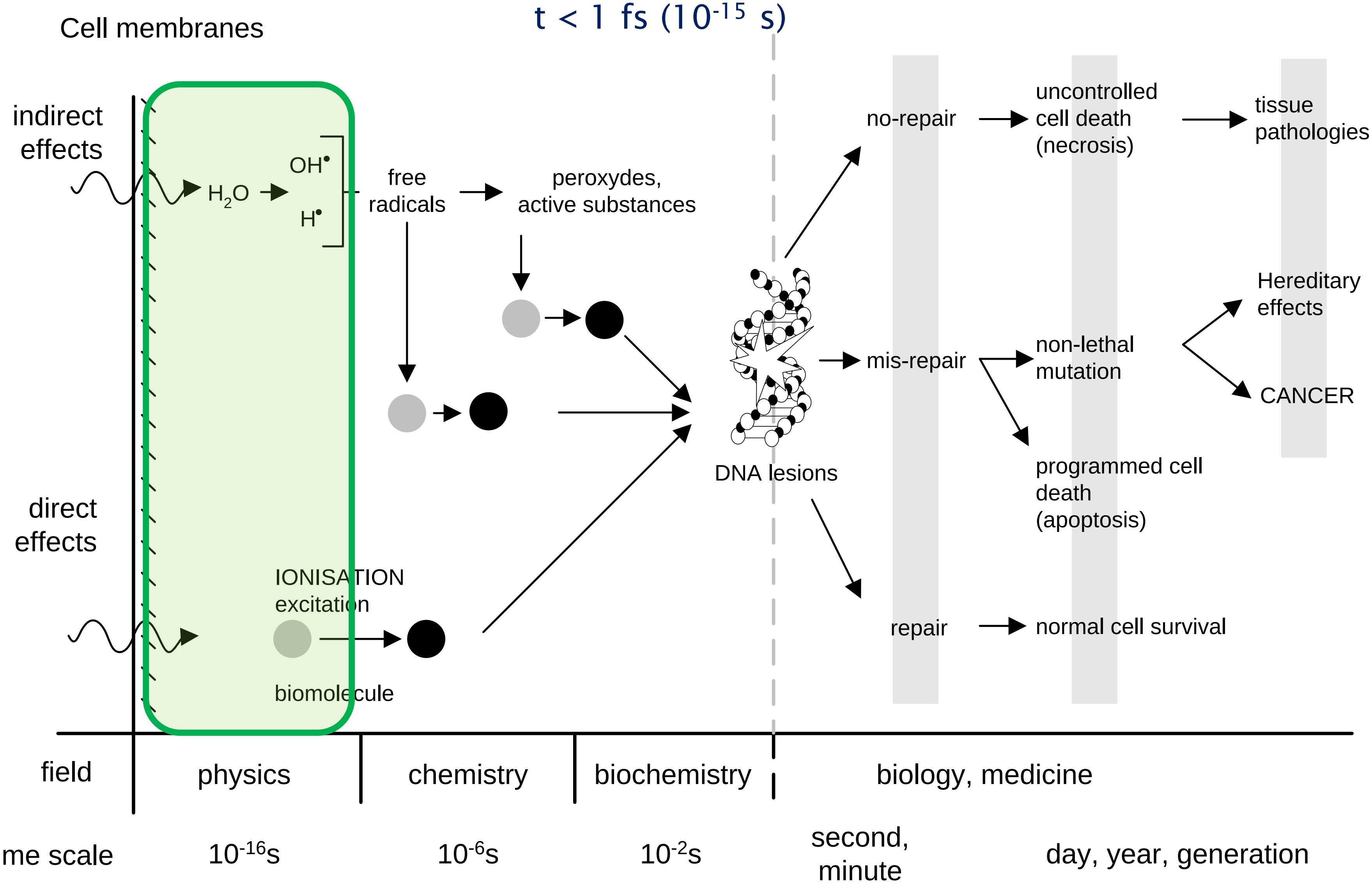
Lecture objectives

At the end of the lecture you should be able to :

- Describe the sequence of radiation effects on organic matter
- Understand the difference between deterministic and stohastic effects
- Evaluate the health effects that are expected after exposure to given dose

Physical stage

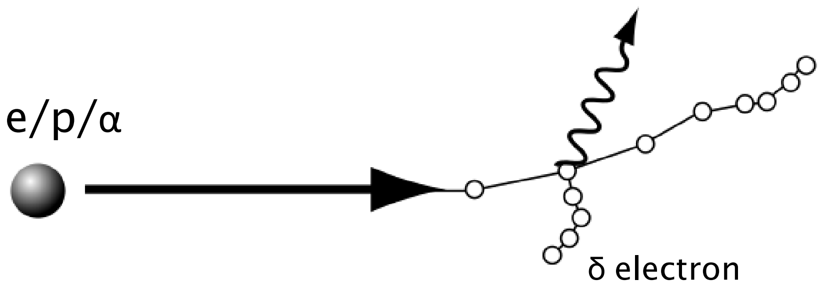
t < 1 fs (10^{-15} s)



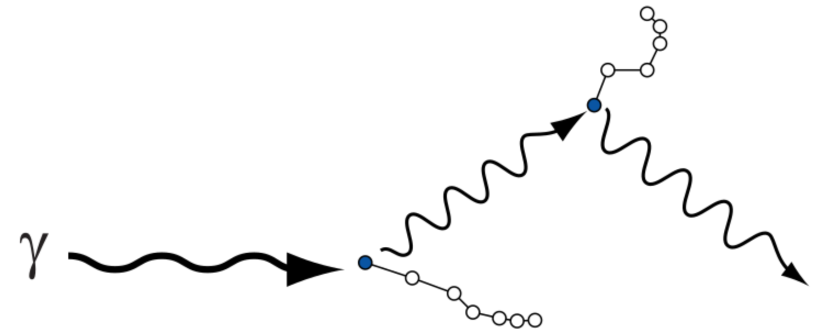
Energy deposition by charged particles

- Interactions of ionizing radiation with medium:

Directly ionizing (charged particles)



Indirectly ionizing (uncharged particles)



- Uncharged radiation will eventually get converted into charged particles
- Charged particles deposit energy by:
  1) Ionization of atoms in the medium } electronic
  2) Excitation of atoms in the medium } electronic
  3) Bremsstrahlung (important only for electrons) - radiative
  4) Nuclear interactions (important at the end of range) - nuclear

(1–4: **Stopping power**)

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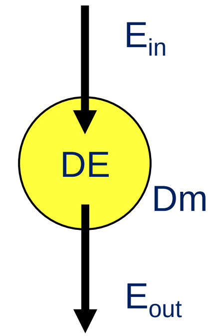
Absorbed dose and LET

- Absorbed dose (D) = energy deposited in the medium per unit mass:

$$D = \frac{\Delta E}{\Delta m} \qquad [J/kg] = [Gy]$$

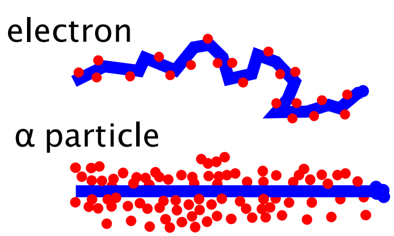


  - macroscopic quantity

- How to measure the absorbed dose? ⇨ Lecture 3

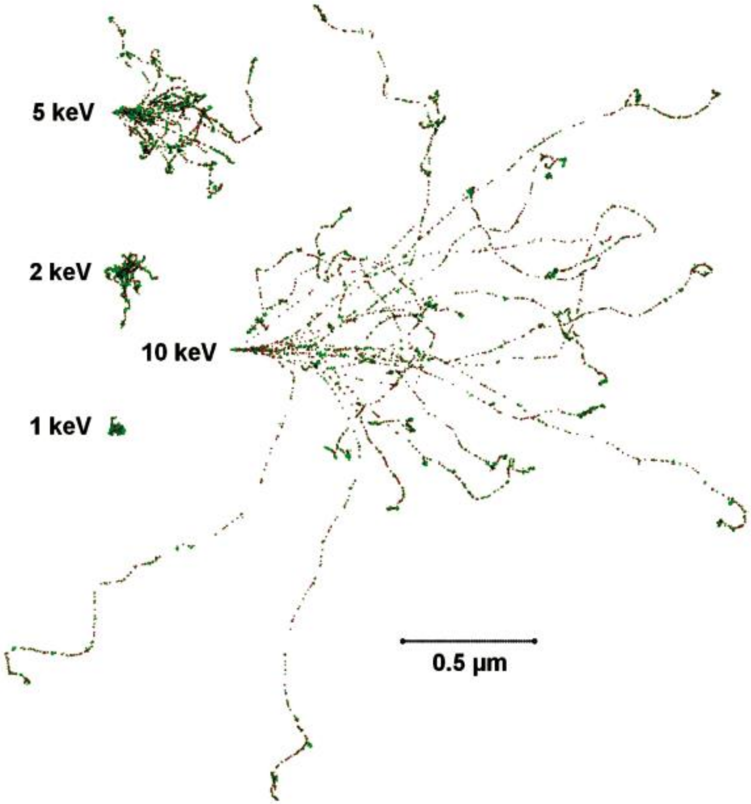
- Linear energy transfer (LET) = energy given to medium per unit distance

$$LET = \frac{\Delta E}{\Delta x} \qquad [eV / \mu m]$$



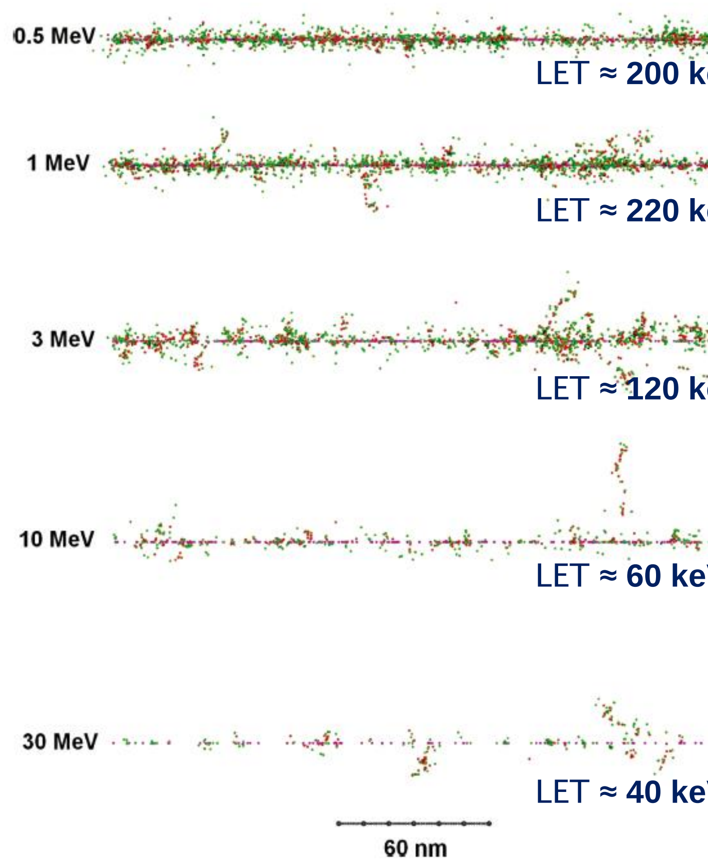
LET of different radiation

Electrons



LET ≈ **0.2 keV/µm**, independent on energy

Alphas

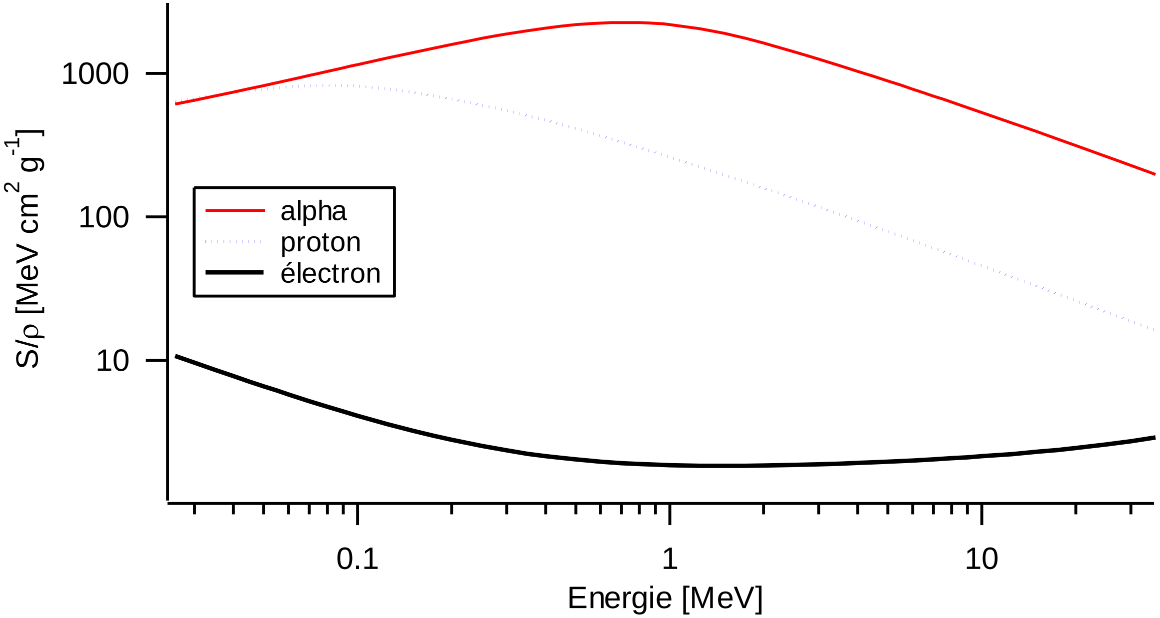


- 0.5 MeV: LET ≈ **200 keV/µm**
- 1 MeV: LET ≈ **220 keV/µm**
- 3 MeV: LET ≈ **120 keV/µm**
- 10 MeV: LET ≈ **60 keV/µm**
- 30 MeV: LET ≈ **40 keV/µm**

➢ The same dose of 1 Gy to the nucleus is deliverd by:
- 2-4 trajectories of α-particles
- ≈ 1000 trajectories of e

LET vs stopping power

- LET is closely related to electronic stopping power



Stopping power includes:

1) Ionization of atoms in the medium
2) Excitation of atoms in the medium

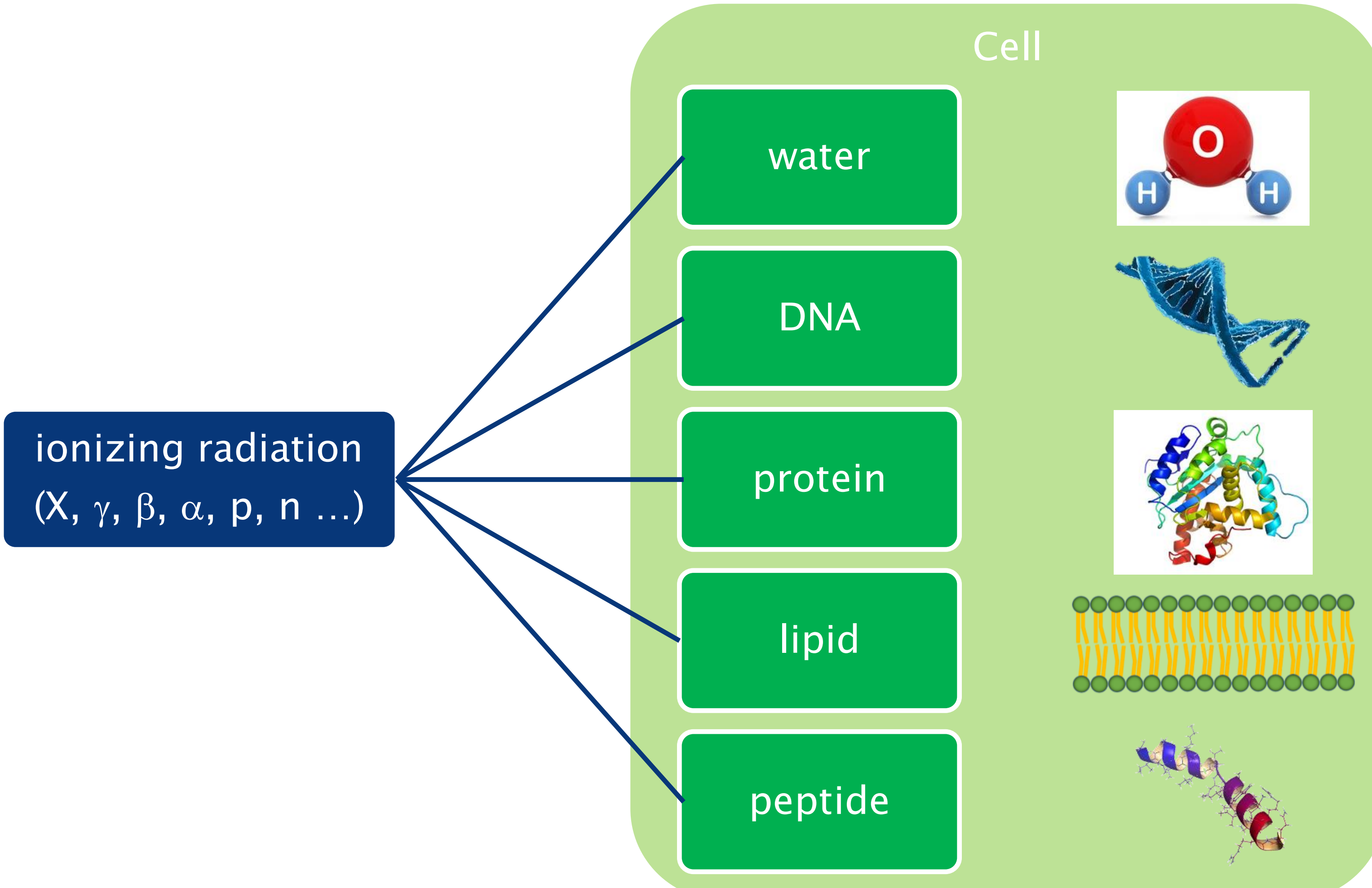
} **Contribute to LET**

3) Bremsstrahlung (important only for electrons)
4) Nuclear interactions (important at the end of range)

} **Do not contribute to LET**

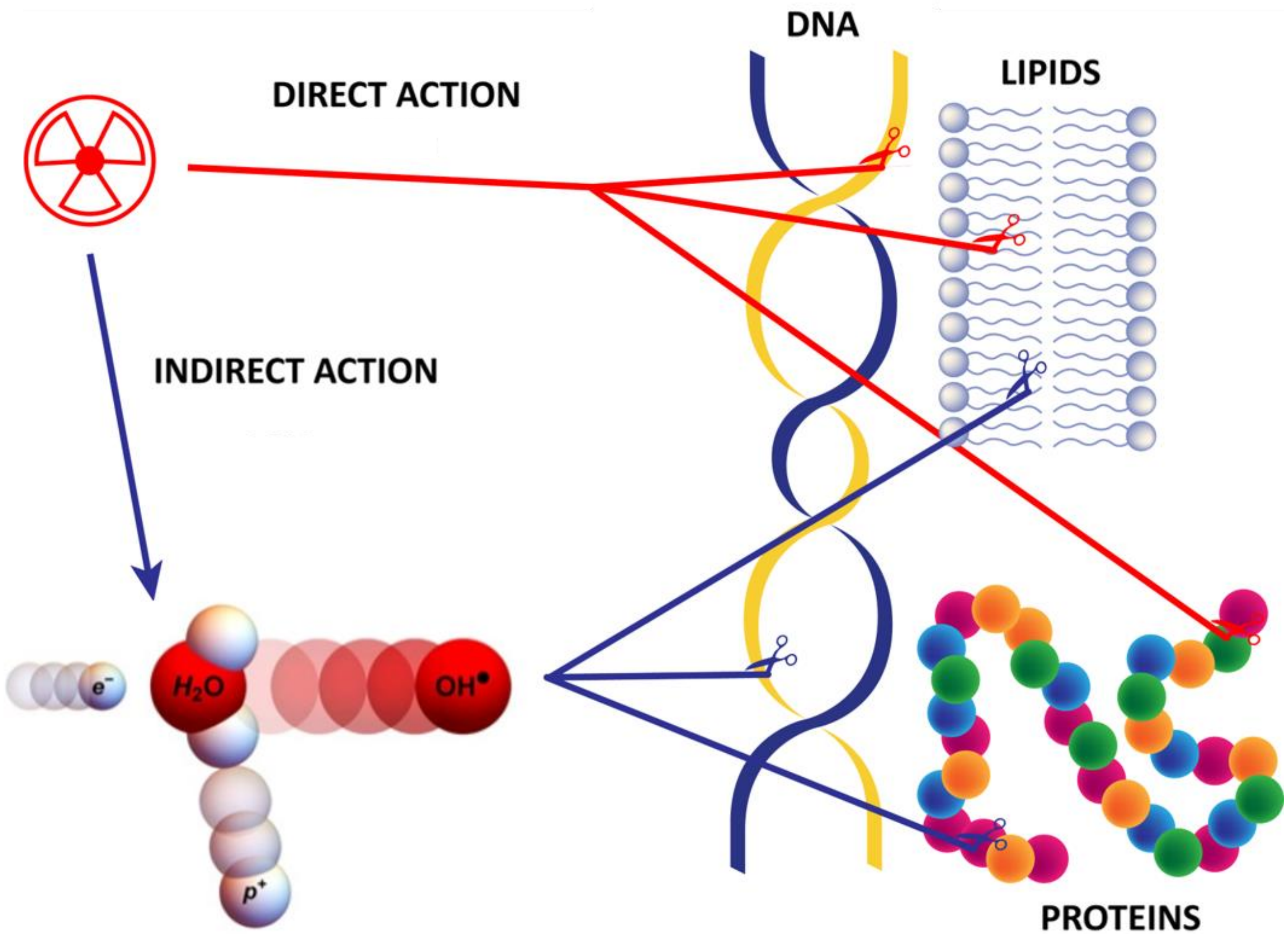
The medium of interest in radiobiology

- Radiobiology studies the interaction of radiation with living matter
  - Target is living cell containing various biomolecules



Direct and indirect action of radiation

- Charged particles deposit energy directly on biomolecules or water which leads to formation of free radicals (indirect action)



1. Physical effect of ionising radiation

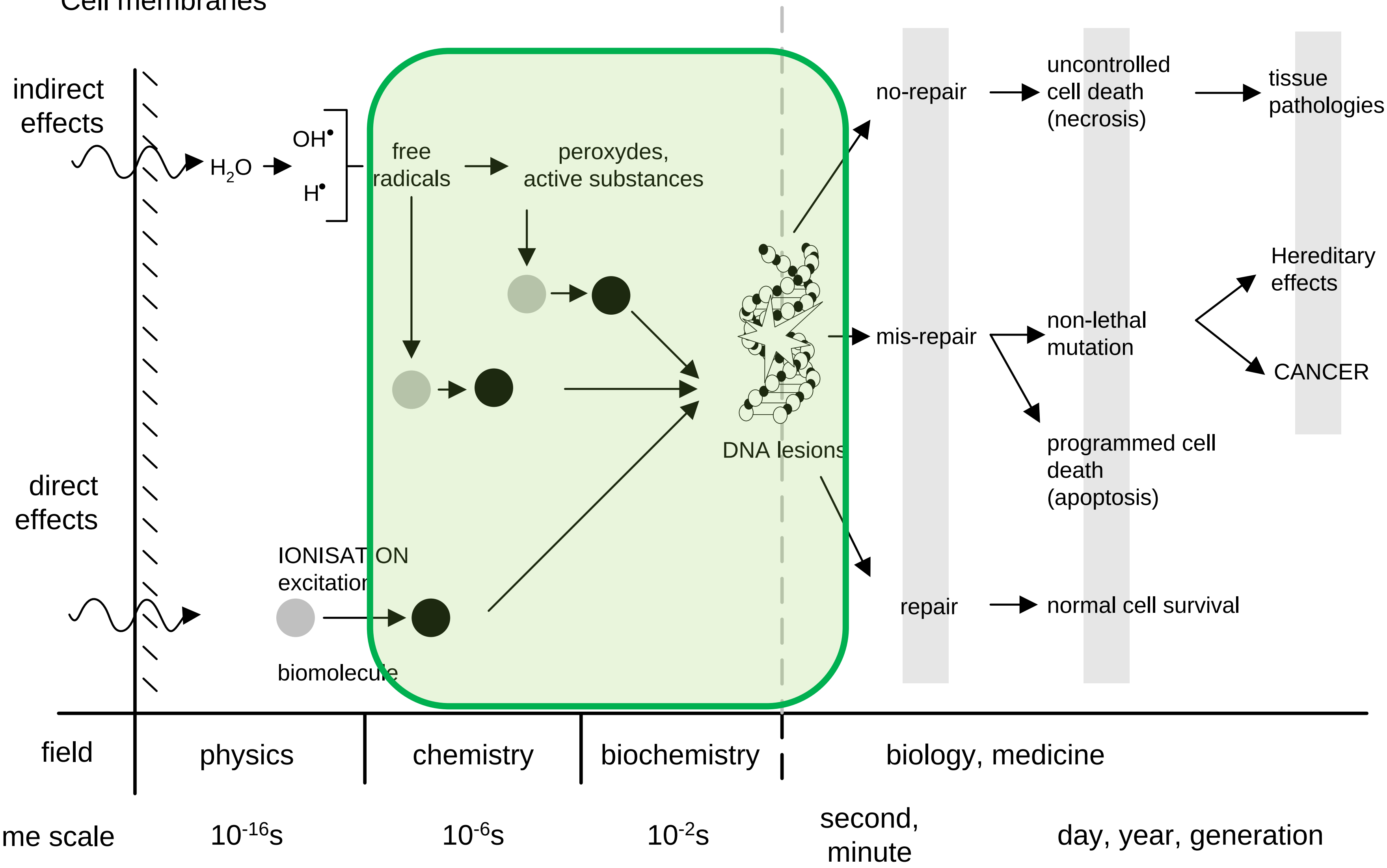
The new PhD student in your lab is accidently irradiated by a Co-60 source. The whole body absorbed dose is 15 Gy.

1. Compute the energy deposited in the body (70 kg).

2. Derive the temperature increase in the body and judge which biological effects it may cause (c_{water}=4.81 kJ/kg/K)?

Chemical stage

1 fs < t < 1 s



Chemical alteration of biomolecules (DNA)

- Direct effect:

$$RH + e^- \rightarrow R^\bullet + H^+$$

R - organic molecule

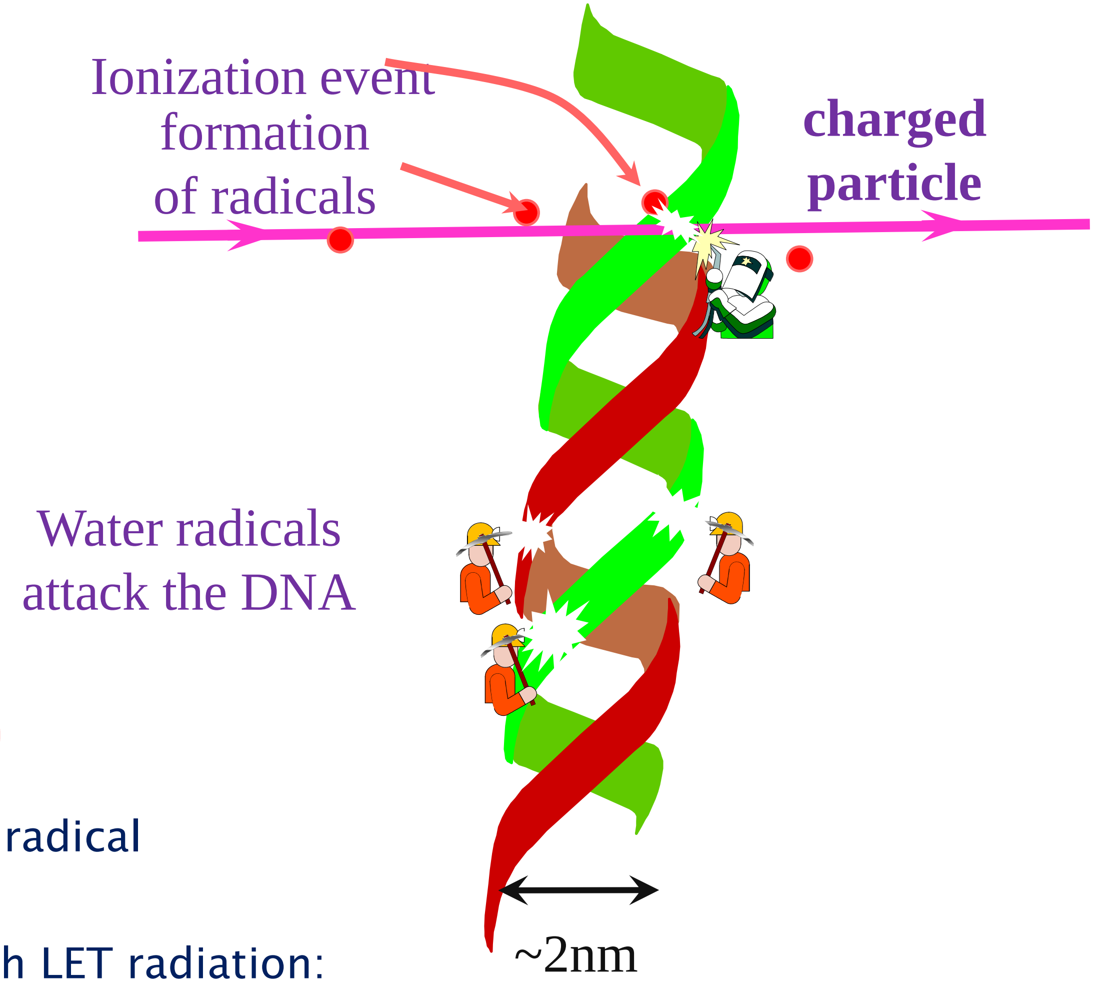
- Indirect effect:

$$H_2O \rightarrow H_2O^+ + e^-$$

$$H_2O^+ \rightarrow H^+ + OH^\bullet$$

$$RH + OH^\bullet \rightarrow R^\bullet + H_2O$$

$OH^\bullet$ - hydroxyl radical



Low LET radiation:

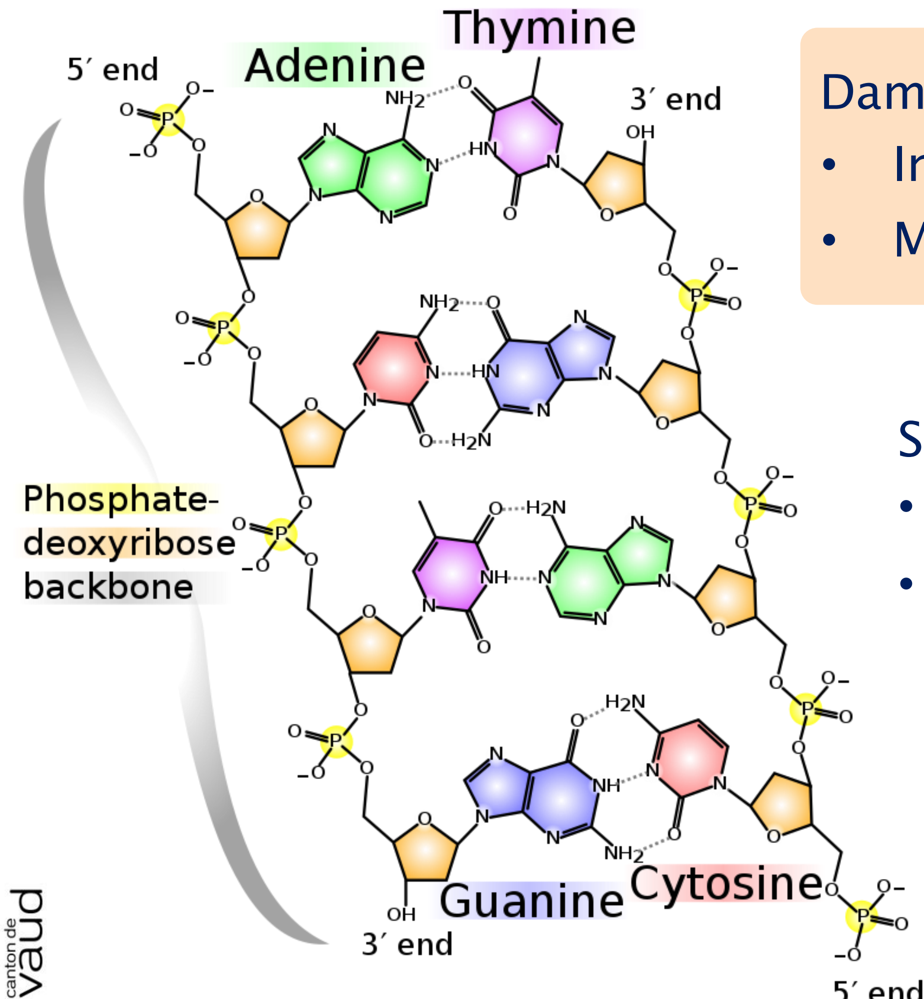
- Direct: 35% of lesions
- Indirect: 65% of lesions

High LET radiation:

- Increased direct action
- Complex lesions

DNA

- DNA contains all genetic information



Damage to DNA can lead to:

- Inability to reproduce → cell death
- Mutation → genomic instability, cancer

Structure:

- Sugar-phosphate backbone
- Nucleobases: Adenine (A)
  Thymine (T)
  Guanine (G)
  Cytosine (C)

Image credit: Wikipedia

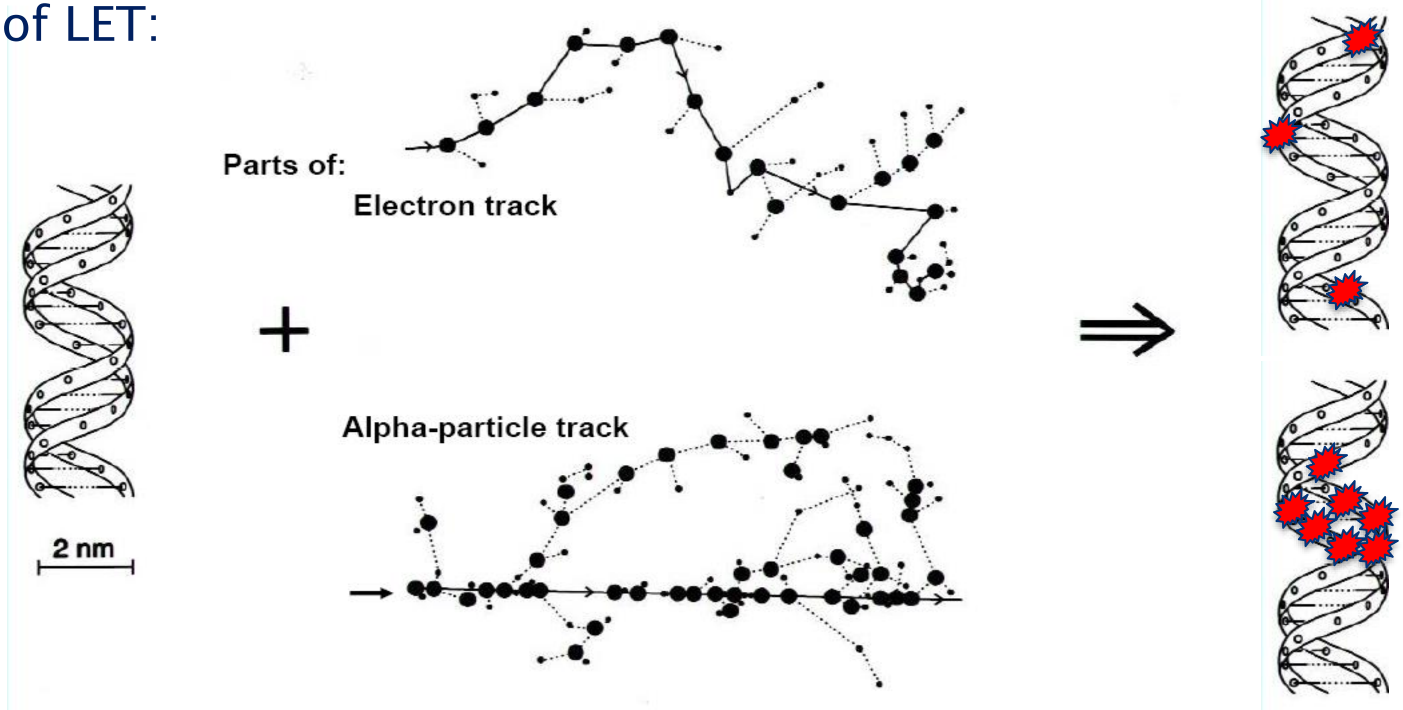
Radiation induced DNA lesions

- Type of damage caused by radiation:
  - damage to a DNA base ~80%
  - single-strand break (SSB) ~20%
  - double-strand break (DSB) ~1%
  - locally multiplied damaged site (LMDS): ~0.3%

1 Gy of low LET radiation
- 1000 SSB per cell
- 40 DSB per cell

Naturally occurring every day
- > 50000 SSB per cell
- < 10 DSB per cell

- Effects of LET:



Repair of DNA damage

- Living cells posses a complex machinery to repair damaged DNA
- Existence of **repair genes** that code for **repair proteins**
- Sequence od DNA damage repair:
  damage recognition → cell cycle arrest → recruitment of repair proteins
- Severity of DNA lesions:
  - Base damage and SSB easy to repair
  - DSB hard to repair
  - LMDS very hard to repair
- DNA repair proteins can be visualized:
  - Example of fluorescently labeled γ-H2AX → marker of DSB

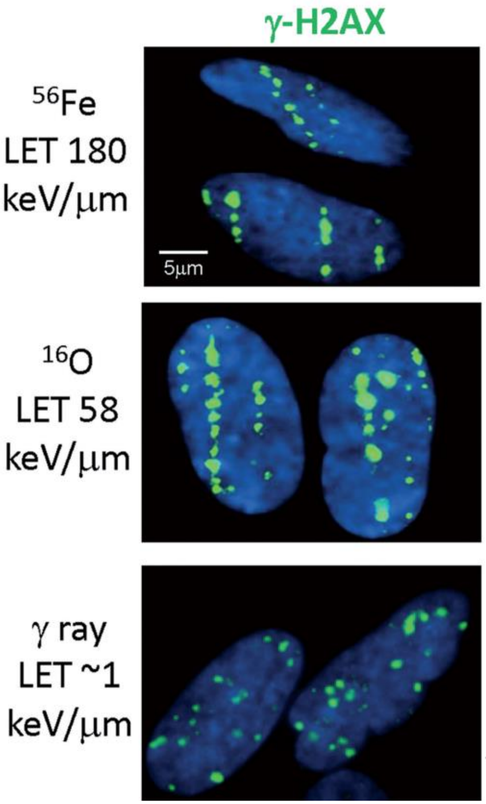


Image credit: Wang M. et al. Nucl. Acids Res. 2013, doi:10.1093/nar/gks1038

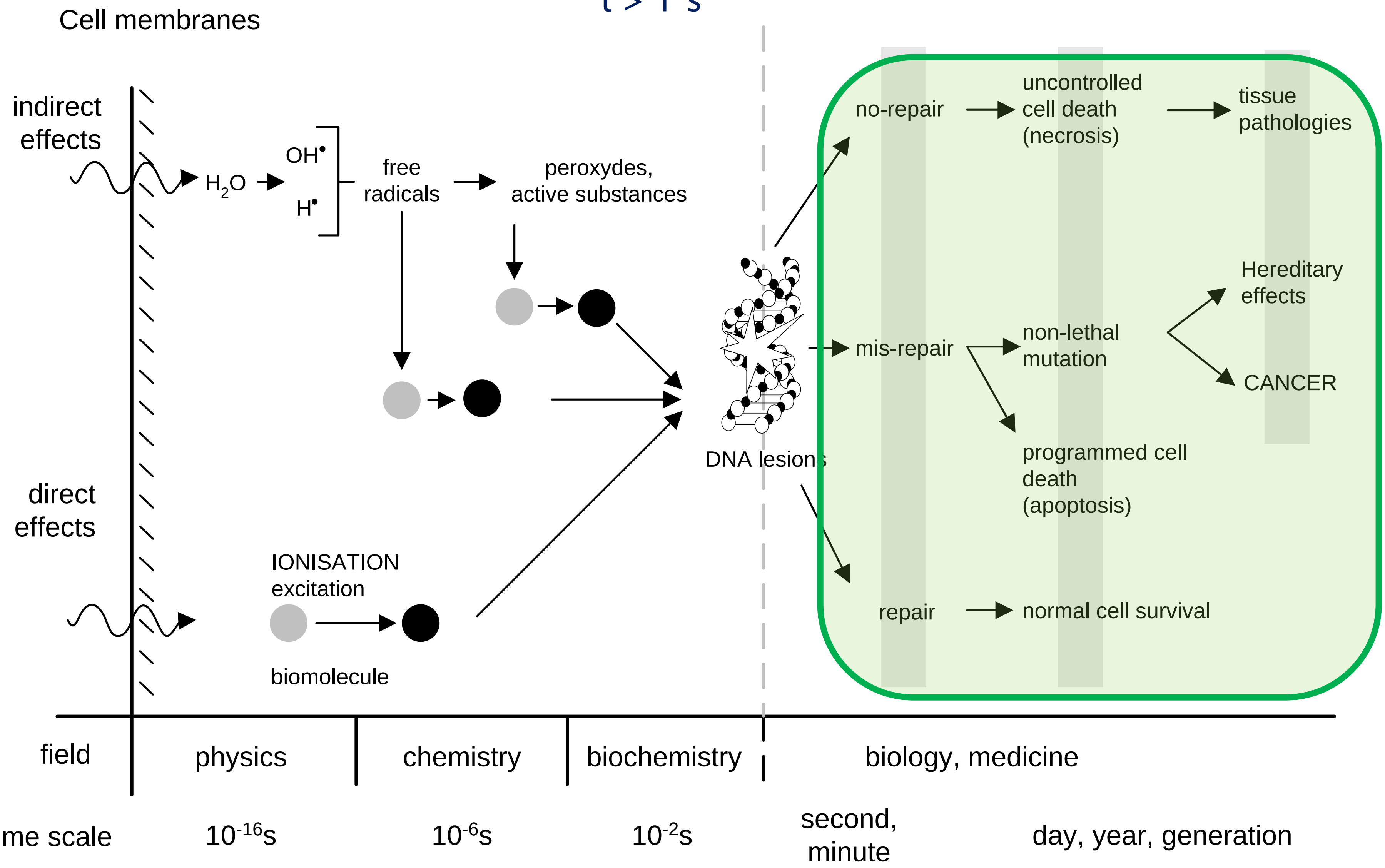
2. DNA damage

The hardest DNA lesions to repair are:

1) SBB
2) DSB
3) Locally multiplied damaged sites (LMDS)
4) Nucleobase damage

Biological stage

t > 1 s



Biological stage

Level of biological organization	Effects of radiation
molecular	Damage to macromolecules: enzymes, RNA, DNA
subcellular	Damage to the cell membrane, the nucleus, chromosomes
cellular	Inhibition of cell division, cell death, alterations / mutations
tissue, organ	Loss of functionality, induction of cancer
animal	Death of the individual
population	Genetic modification

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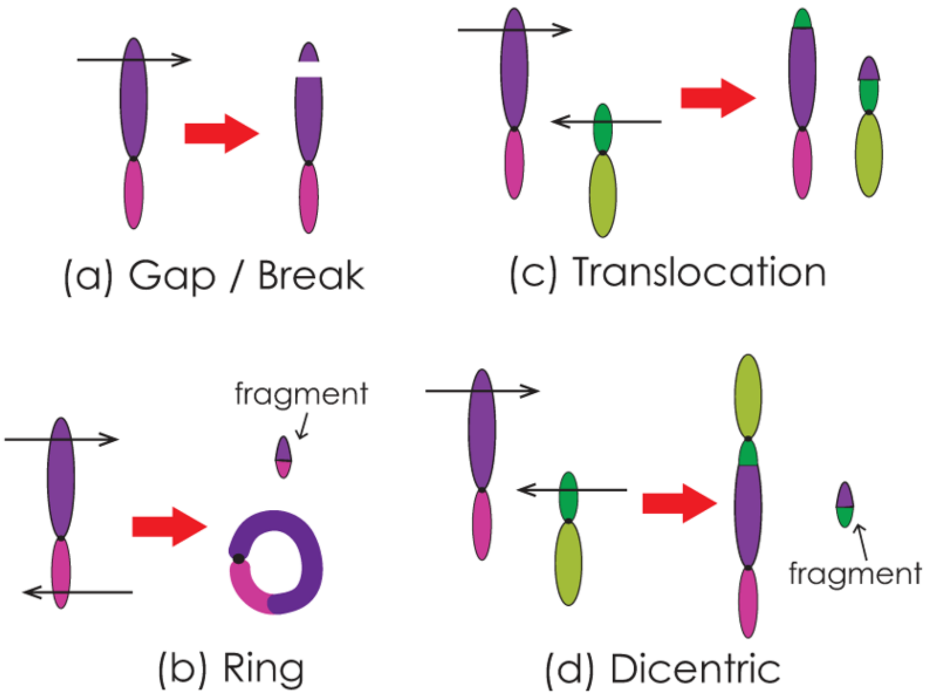
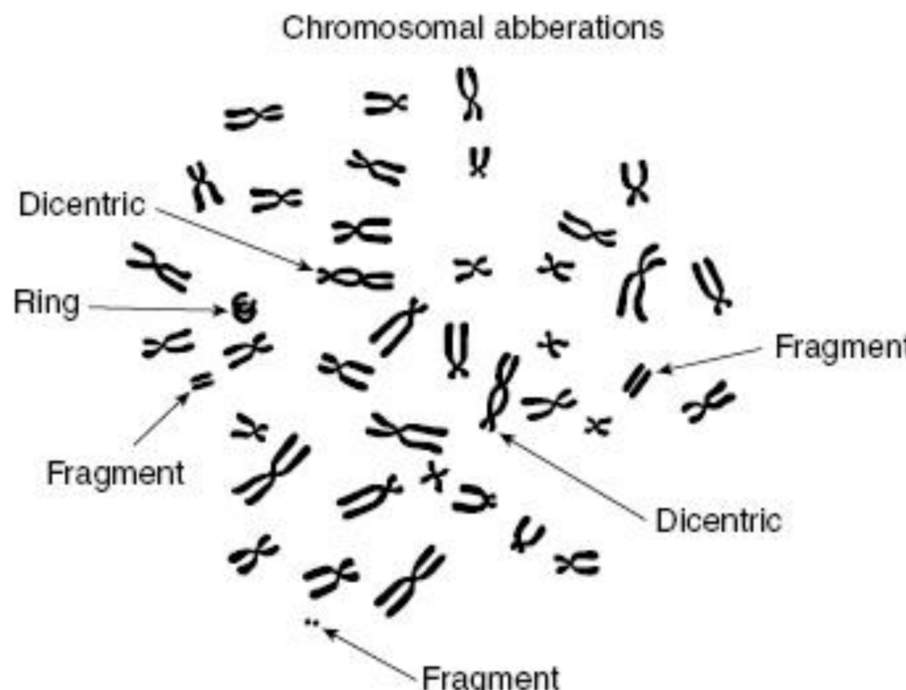
Effects on sub-cellular targets

Example of chromosomal aberrations



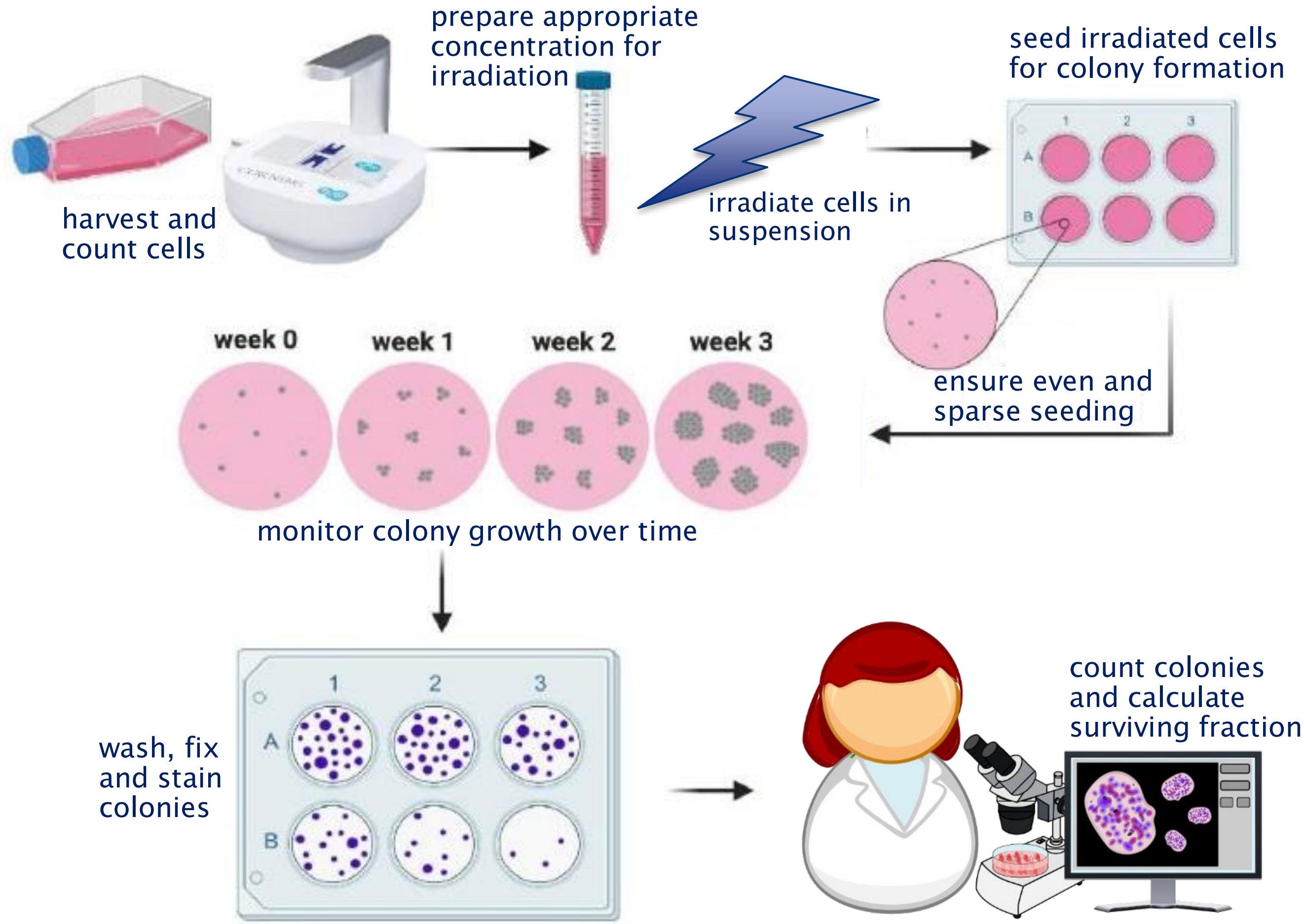
Different types of aberrations

Aberrations observed in metaphase

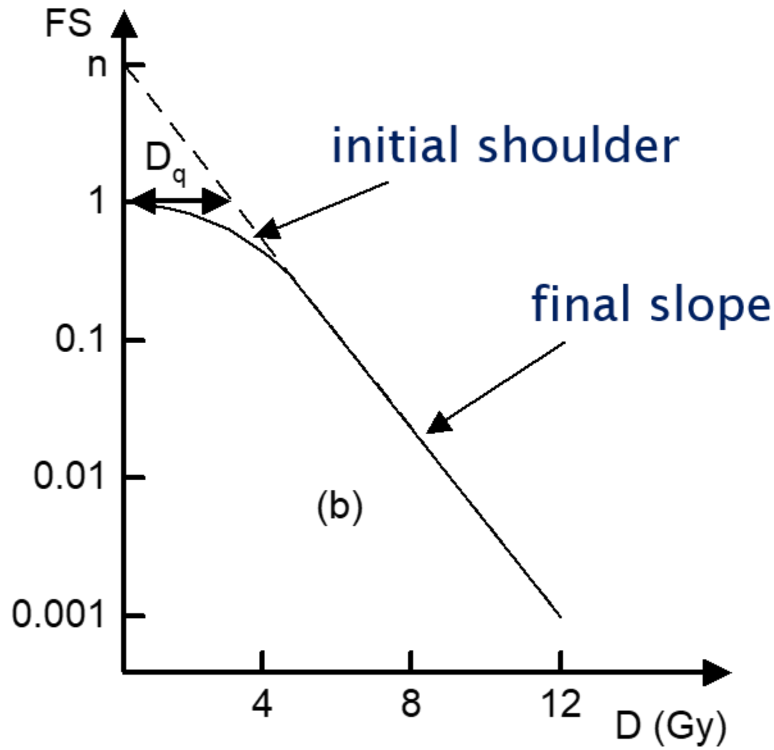


Effects on cells

- Studies of radiation effects on cells provide basis for understanding the mechanisms of radiation interaction with living matter
- Clonogenic survival assay – golden standard in radiobiology:



Cell survival curves



$$SF = e^{-\alpha D - \beta D^2}$$

Shoulder - Repair mechanism at low doses

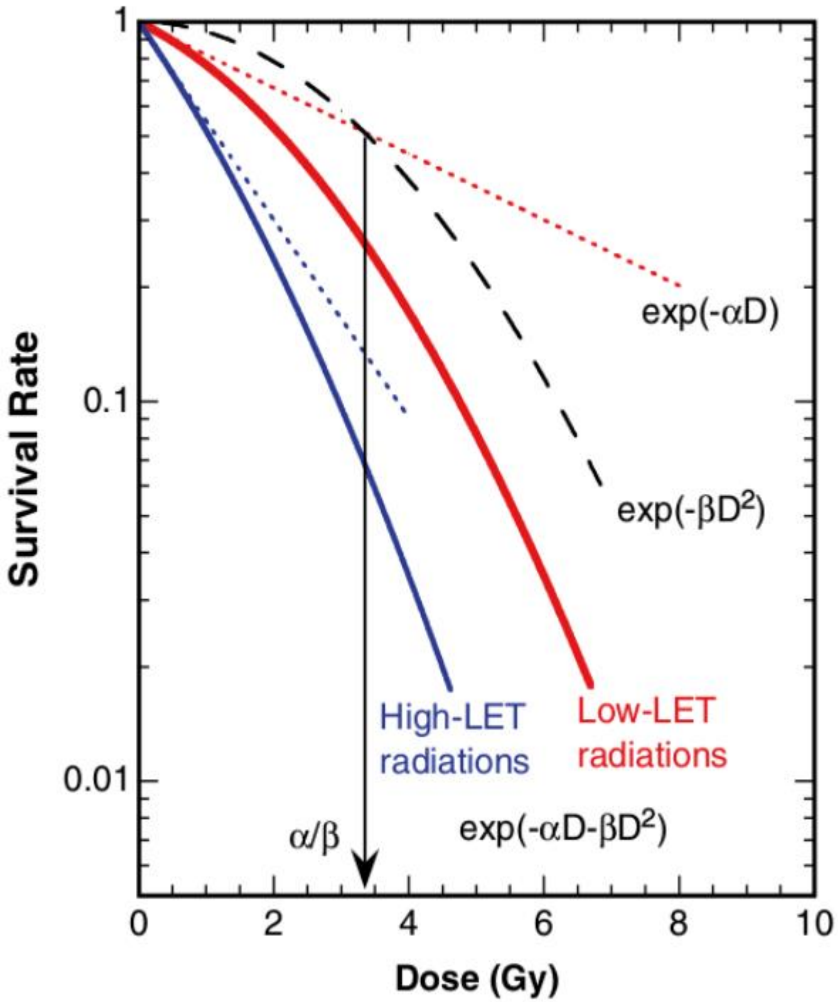
Linear-quadratic (LQ) model

The shoulder is characterized by α/β :

- α : **low dose** tissue response
- β : **high dose** tissue response
- High α/β : high cell kill at low dose
- Low α/β : radioresistance at low dose

α and β depend on LET:

- Low LET: α and β important
- High LET: α important, β less important

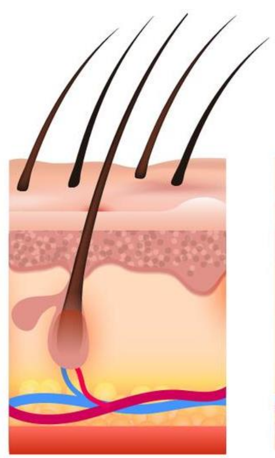


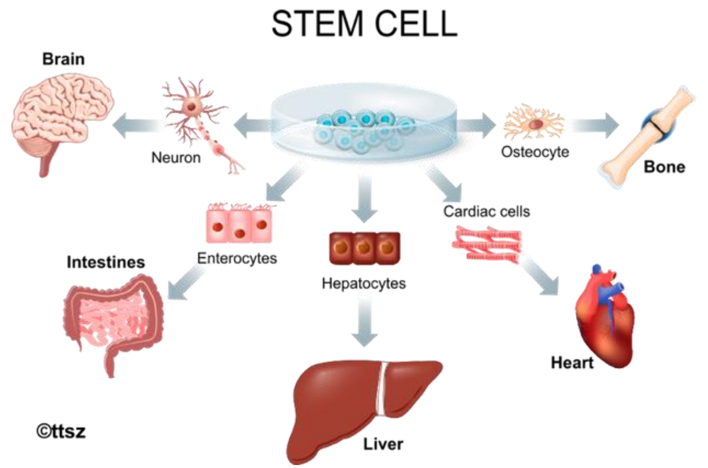
Radiosensitivity of cells

- Bergonié and Tribondeau law:

  Radiosensitivity of cells is directly proportional to mitotic activity and inversly proportional to the degree of differentiation

- **Most radiosensitive cells are:**
  - rapidly dividing cells (hematopoietic tissue, basal layer of the epidermis, intestinal epithelium, hair follicles)
  - young cells, i.e. with a long dividing future
  - less differentiated cells (tissue of the embryo, stem cells)





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Factors affecting radiosensitivity

Physical factors:

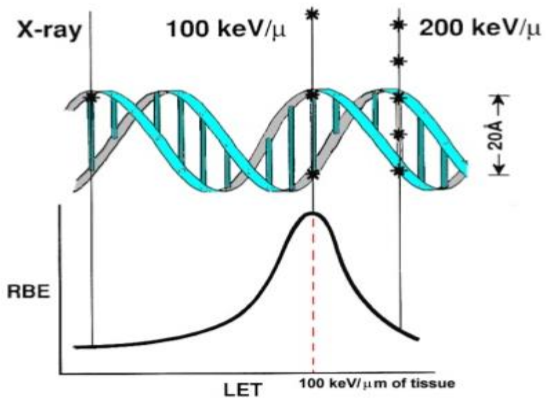
- LET
- Dose rate

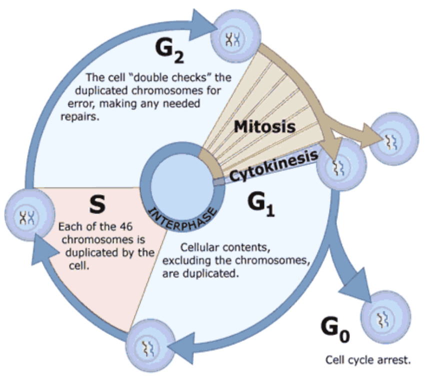
Chemical factors:

- Oxygen – increases radiosensitivity
- Antioxidants – decrease radiosensitivity

Biological factors:

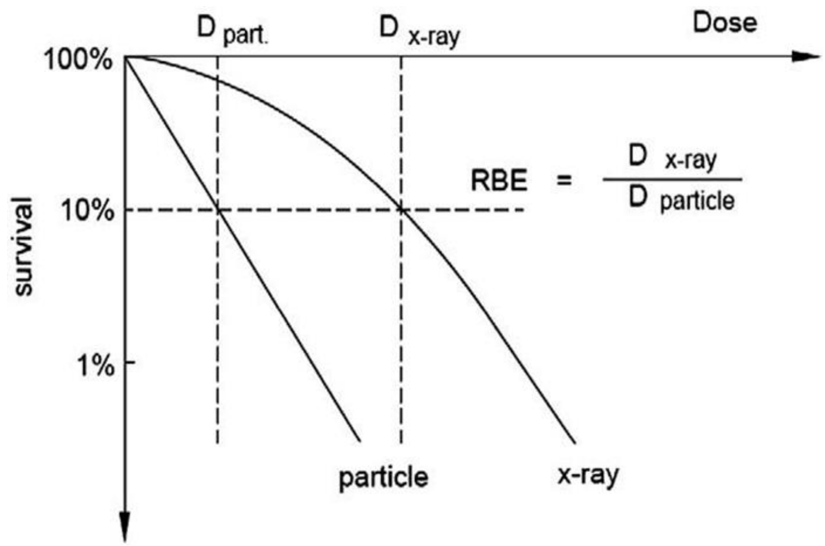
- Cell cycle phase
- Repair of sub-lethal damage

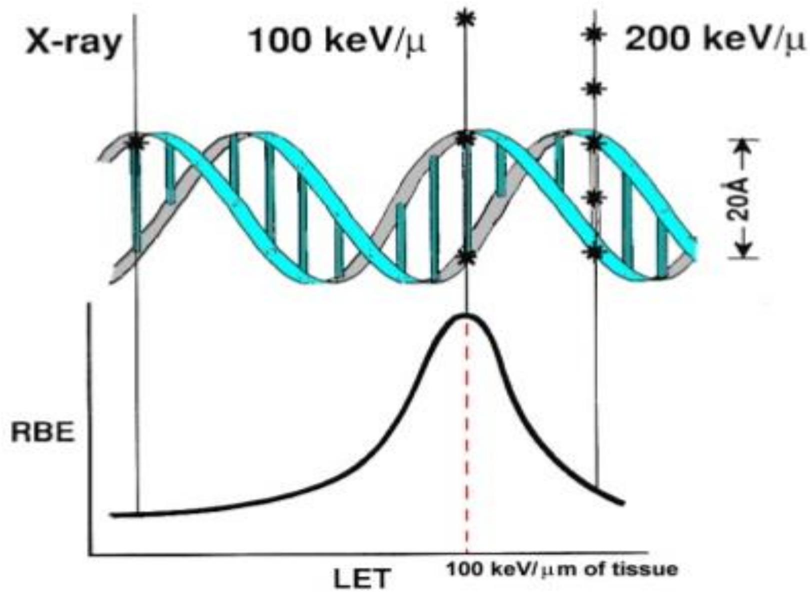




Impact of radiation type on radiosensitivity

- Densely ionizing radiation is more effective at killing cells





RBE vs LET

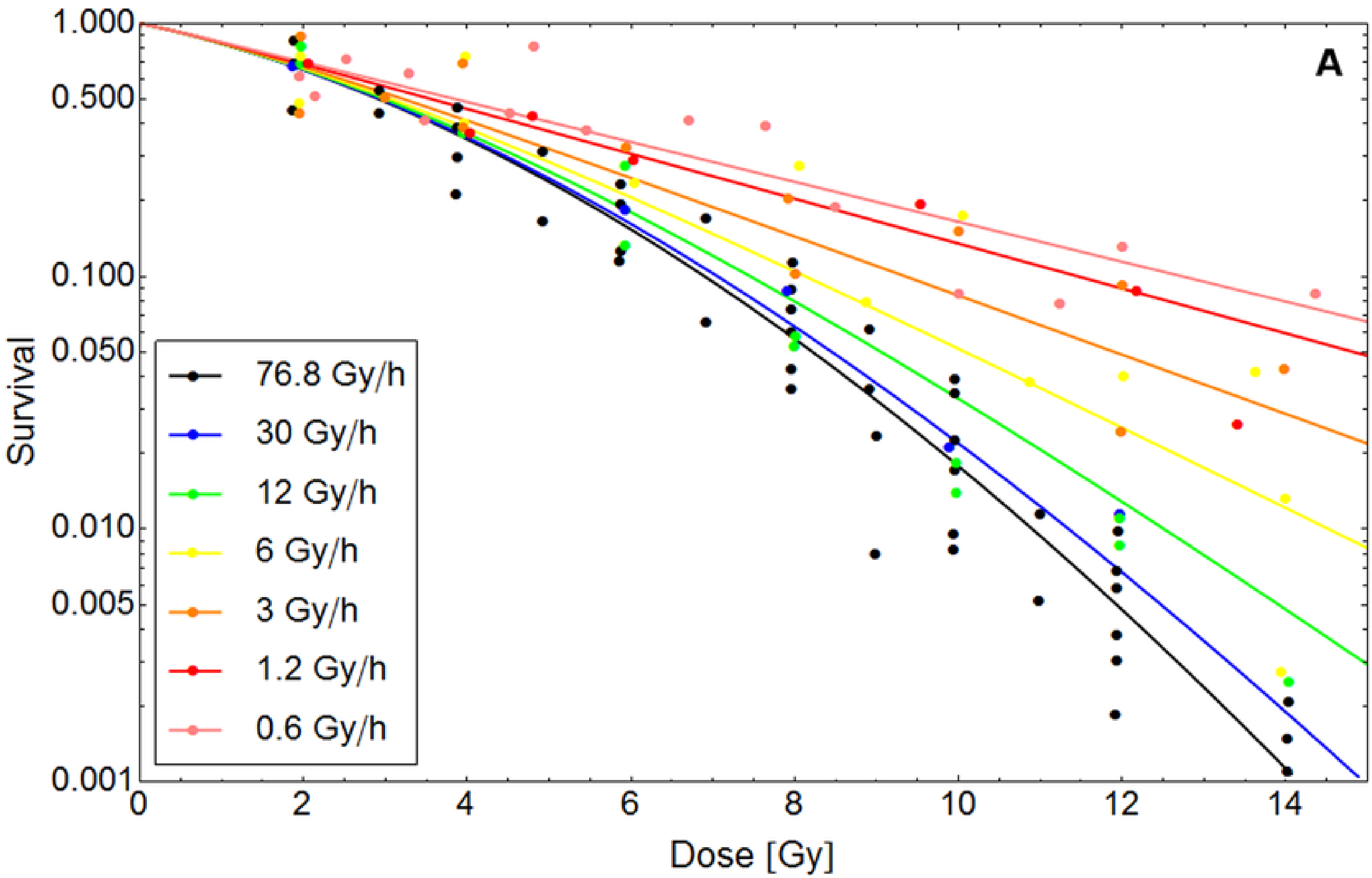
Relative biological effectiveness (RBE)

$$RBE = \left. \frac{\text{Dose of reference radiation}}{\text{Dose of applied radiation}} \right|_{\text{Same biological effect}}$$

- RBE is used to compare biological effects of different radiation types

Impact of dose rate on radiosensitivity

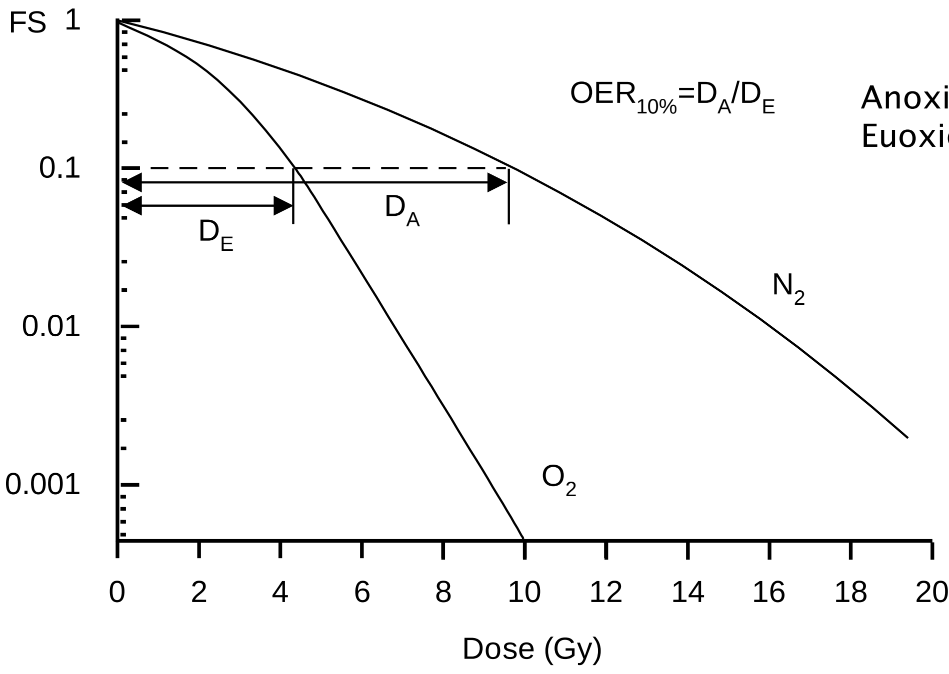
- At lower dose rates the repair of sub-lethal damage is increased, leading to higher survival of cells



Herr et al. A Model of Photon Cell Killing Based on the Spatio-Temporal Clustering of DNA Damage in Higher Order Chromatin Structures, PLoS ONE 2013

Impact of oxygen on radiosensitivity

- Oxygen acts as a radiosensitizer:
  well oxygenated cells are more sensitive to radiation



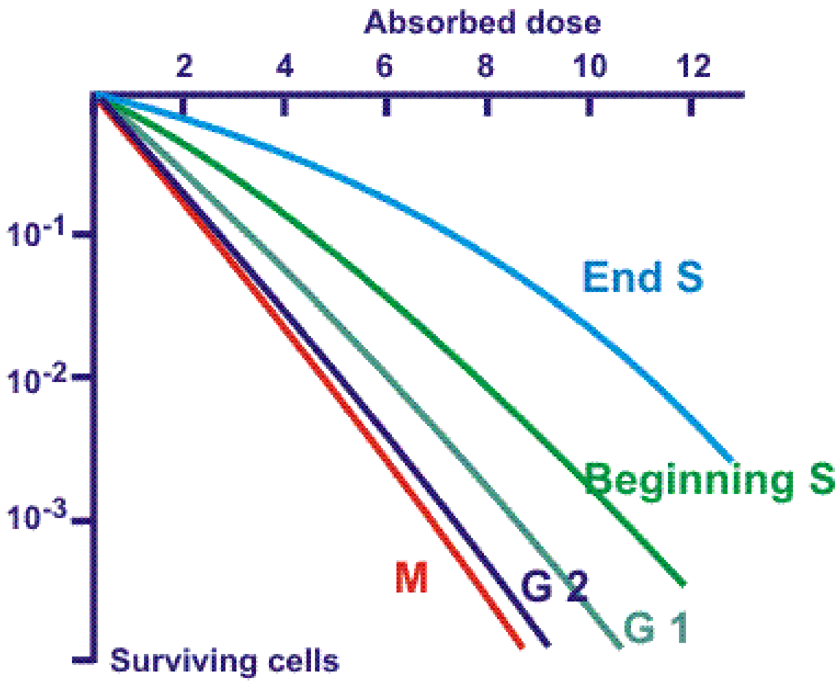
Anoxic – no oxygen
Euoxic – high in oxygen

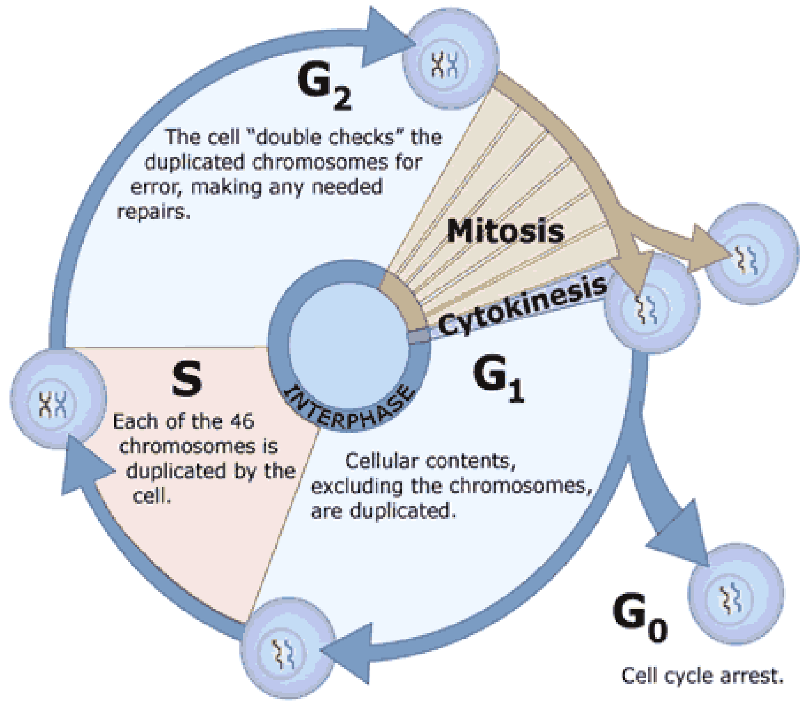
Important effect in treatment of cancer by radiation therapy

Oxygen enhancement ratio (OER)

$$OER = \frac{Dose\ without\ oxygen}{Dose\ with\ oxygen}\Bigg|_{\text{same biological effect}}$$

Impact of the cell cycle on radiosensitivity





Radio-sensitivity varies during the cycle by a factor of 2 to 3:

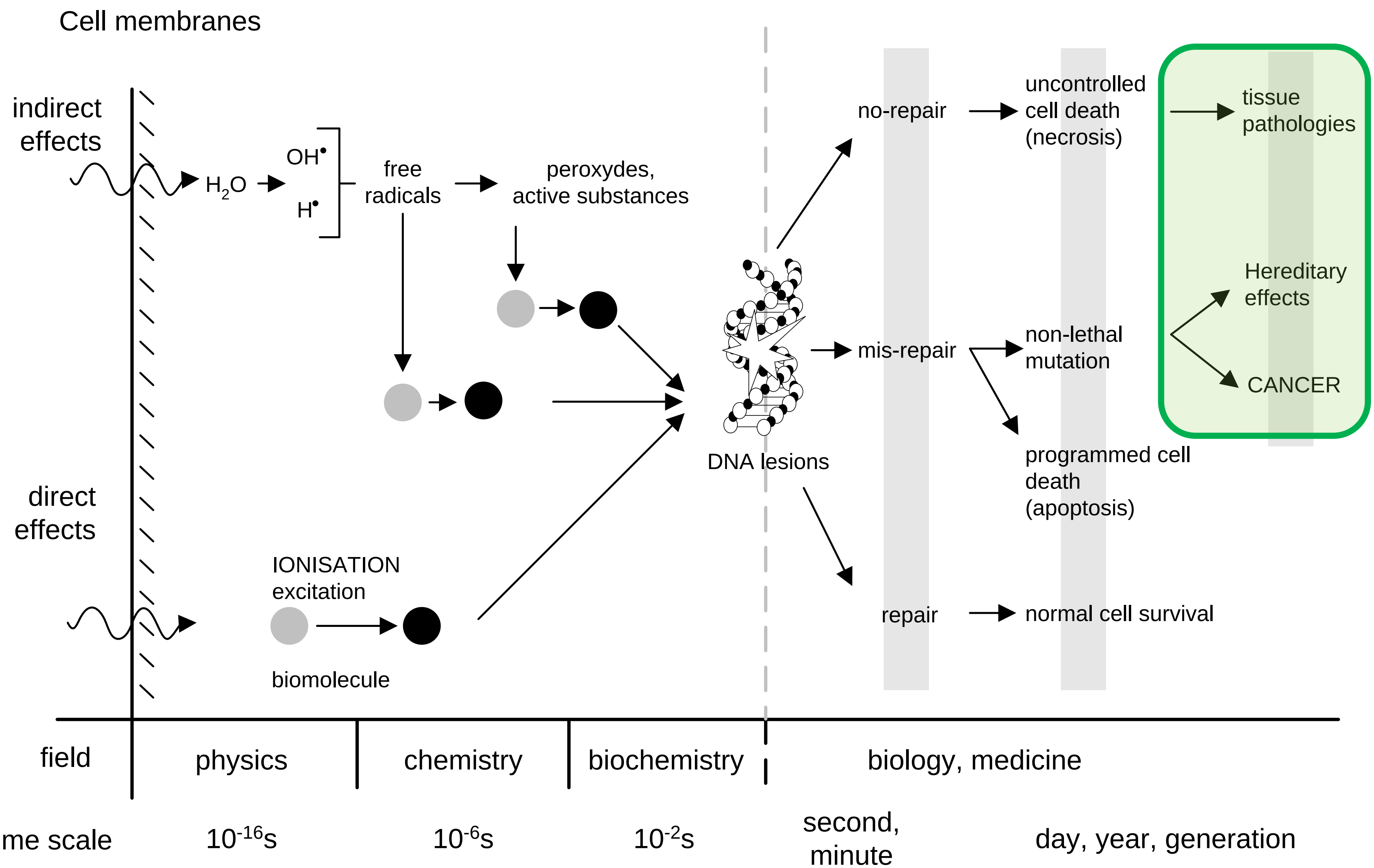
- increased sensitivity in mitosis (M)
- reduced sensitivity during synthesis (S)

3. Radiosensitivity of cells

From the knowledge of effects impacting radiosensitivity of cells, try to explain why is radiation therapy more effective against tumor cells than healthy cells?

Why is radiation therapy more effective in the outer parts of a solid tumor than in the core?

Effects on the organism

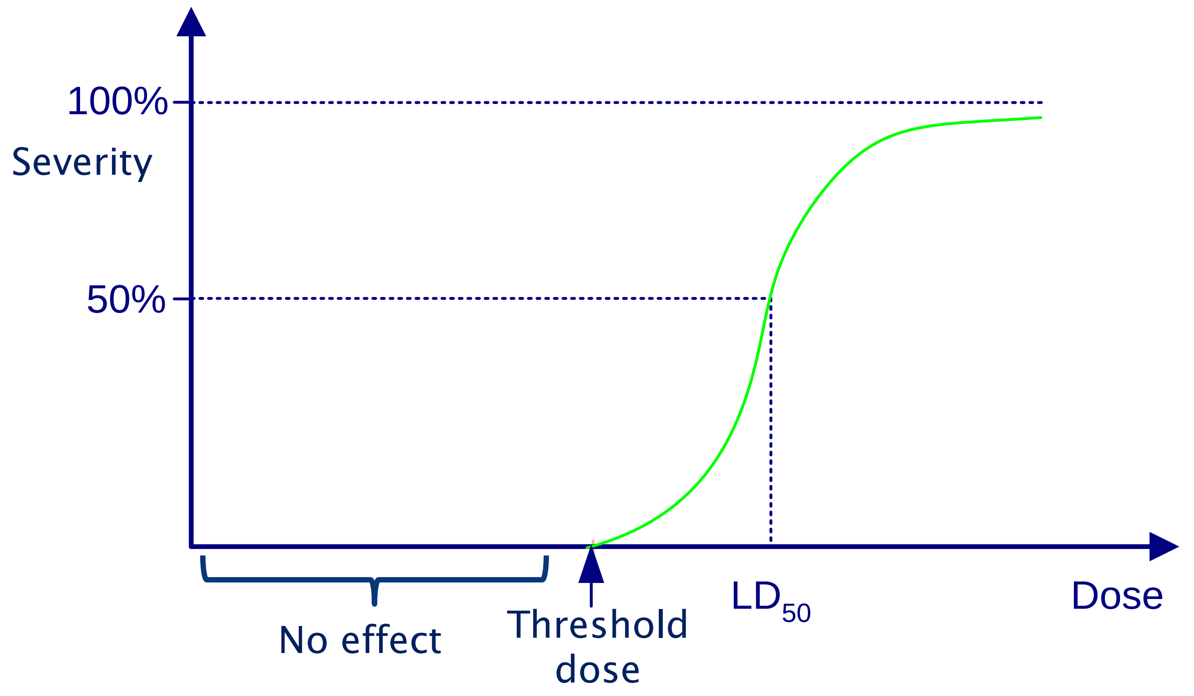


Effects on the organism

Nature	Deterministic	Stochastic
Mechanism	Loss of functionality	Cellular modification
Delay	Quickly after exposure	Latency (~20 yrs)
Effect of dose variation	Severity of effect	Probability of occurrence
Dose level	Only at high doses	Already at low doses
Threshold	Exists	Not proven
Example	Erythema	Cancer induction

Deterministic effects (tissue reactions)

➢ Relationship between dose and the **severity** of a deterministic lethal effect:



- Threshold: dose below which there is no effect (the body manages and repairs)
- $LD_{50/30}$: **semi-lethal dose**; death of 50% of individuals within 30 days of having received this dose

Deterministic effects (tissue reactions)

- Some examples of deterministic effects:
  - Acute radiation syndrome (radiation sickness)
  - Radiation induced skin burns
  - Cataracts
  - Sterility
  - Tumor necrosis

Characterization of deterministic effects

Acute radiation syndrome

- Whole body exposure

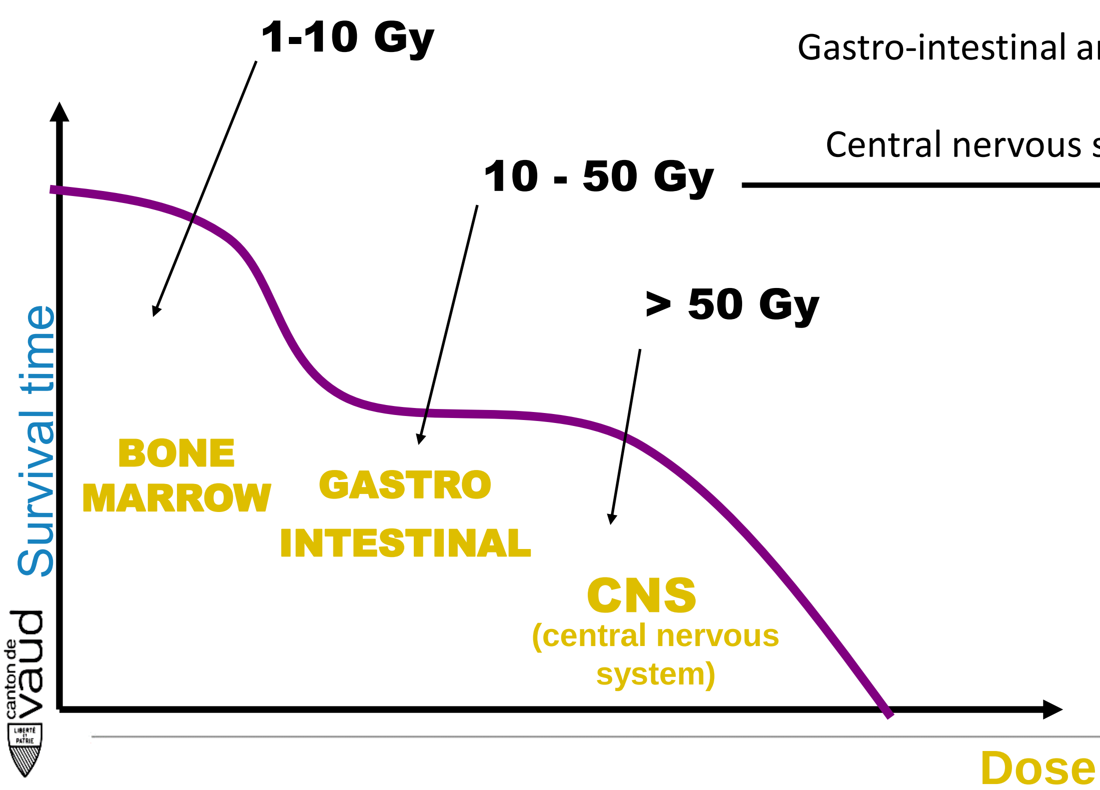
Threshold dose: **0.5 Gy**

Semi-lethal dose: **5 Gy**

Acute radiation syndrome

- Occurs following acute exposure to low LET uniform **whole body** radiation of human being (ICRP 60)

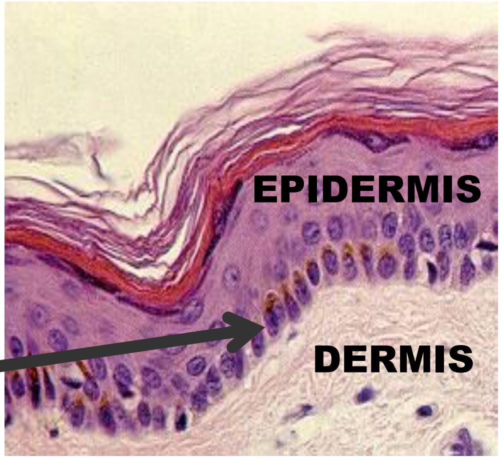
Irradiated organ or tissue	Dose range [Sv]	Latency [days]	Survival [days]
Hematopoietic (bone marrow)	3 – 5	15 – 20	30 – 60
Gastro-intestinal and lungs	5 – 15	3 – 5	10 – 20
Central nervous system	> 50	-	1 – 5



Acute skin irradiation

- Highly radiosensitive cells in skin are from basal stratum of epidermis

Dose (Gy)	Effects
3-5	Erythema and dry desquamation
20	Wet desquamation with blister formation
50	Skin necrosis



Basal stratum

dry desquamation
(fluoroscopy exam)

moist desquamation
(cardiologycal intervention)

Hiroshima survivor

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Characterization of deterministic effects

- Some other threshold doses

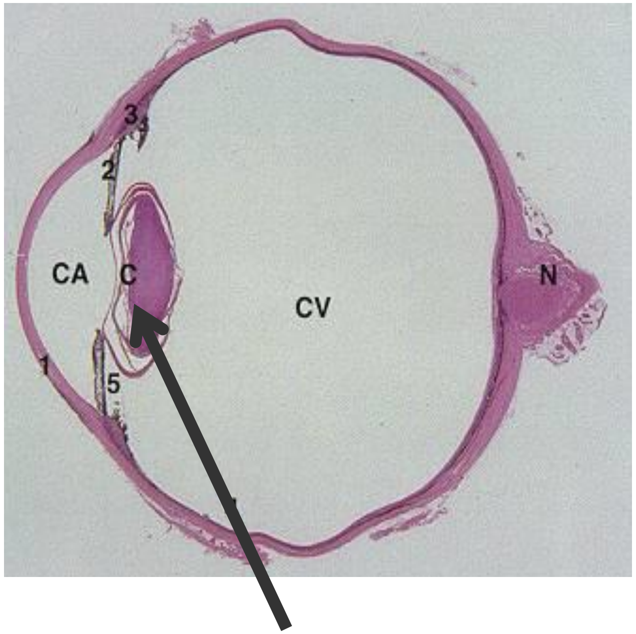
Cataracts of the lens of the eye 0.5 Gy

Permanent sterility

- males 3.5-6 Gy
- females 2.5-6 Gy

Temporary sterility

- males 0.15 Gy



Eye lens is highly radiosensitive, moreover, it is surrounded by highly radiosensitive cuboid cells.

4. High dose irradiation

Indicate the effect of a whole-body dose of 10 Gy on an individual without any subsequent treatment.

Stochastic effects

- Relationship between dose and **probability of occurrence/risk**

Carcinogenesis | **Hereditary effects**

- International Commission on Radiological Protection (ICRP) introduced the concept of **equivalent dose** for radiation protection purposes
  - valid only for small dose values for which stochastic effects may appear
  - takes into account biological effectiveness of different radiation
  - it is used to specify exposure limits of tissues, cannot be measured
  - w_R – conservative judgment of experimental RBE values for low dose exposure

Equivalent dose: $H_T = \sum_R w_R D_{R,T}$

- Unit Sievert (Sv)

Radiation	w_R
X-rays, gamma, electrons	1
protons	2
alpha	20

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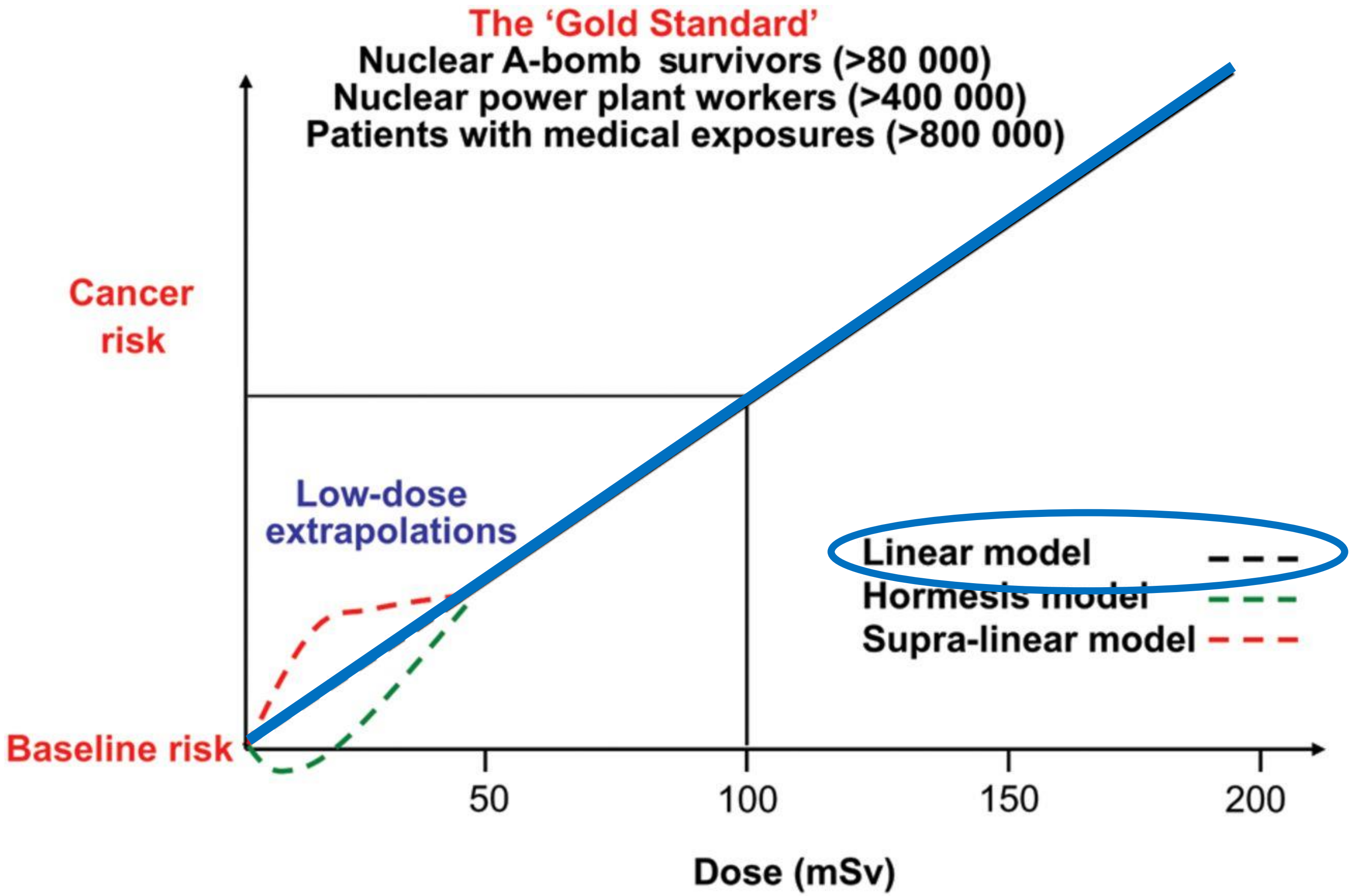
Stochastic effects

- Risk models:



- LNT assumes that radiation is harmful at any dose level

Risk of cancer induction by radiation

- Epidemiological studies:

Survivors of Hiroshima & Nagasaki:

Life Span Study (LSS)

Of the order of 1 Sv (acute irradiation)

120 000 survivors

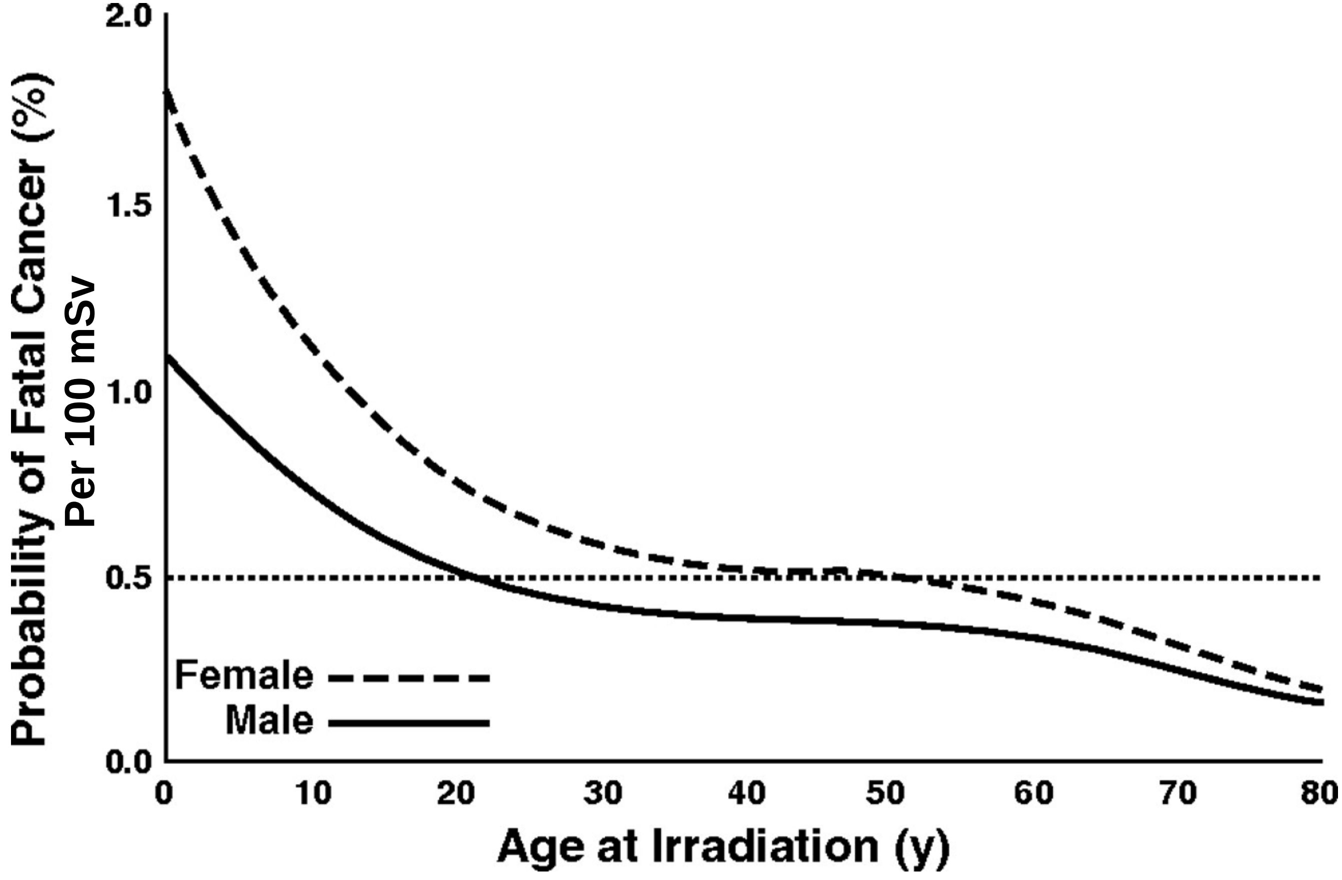
Workers exposed to radiation:

Of the order of 0.1 Sv (chronic irradiation)

95'673 people

Risk coefficient: 5% Sv^{-1}

Risk of cancer induction by radiation vs age at exposure



Risk of hereditary effects

- Radiation damages genetic material in reproductive cells
- Mutations are transmitted from generation to generation

- Epidemiological studies:
  - Experiments on animals (mice)

- Studied effect:
  - Non-specific malformation

- Doubling dose:
  - Dose that induces an additional rate of mutations as large as that which occurs spontaneously
  - 1 Sv

Risk coefficient: 1% Sv^{-1}

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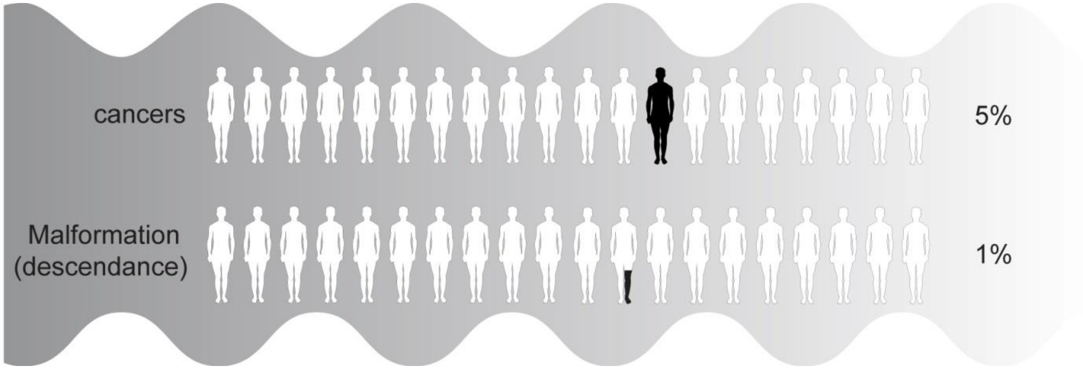
Risk of stochastic effects

1 Sv



	Risk probability per mSv
Cancers	5 out of 100 000
Hereditary effects	1 out of 100 000

5. Natural radiation induced cancer

Calculate for the Swiss population (7 million) the annual number of induced cancers produced by natural radiation whose average effective dose is estimated at 5.5 mSv per year.

Concept of detriment

- Detriment is a concept used to quantify the harmful **stochastic effects** of low-level radiation exposure to the human population

Detriment = "Total harm"

- **Deterministic effects are not considered**

- Detriment is determined from lifetime risk of cancer for a set of tissues and organs and their severity in terms of lethality, years of life lost, quality of life…
    - **Probability** of incidence
    - **Severity** of effects

- ICRP 60 and 103 use concept of detriment to derive **dose limits**

Concept of detriment

- Combination of probability of incidence and severity of effects:

Vest changes the probability of having an accident

Helmet changes the severity of an accident

Detriment = **probability** x **severity**

- Relatively easy to determine
- Incidence probability per dose

- Years of lost life
- Reduction of quality of life
- Lethality of tumor

Concept of detriment

2005 recomm. ICRP

Tissue	Nominal Risk Coefficient (cases per 10,000 PYSv)	Lethality	Lethality-adjusted nominal risk*	Relative cancer free life lost	Detriment	Relative detriment+
Oesophagus	17	0.93	17	0.87	15.0	0.023
Stomach	91	0.83	89	0.88	78.1	0.120
Colon	101	0.48	76	0.97	73.9	0.113
Liver	19	0.95	19	0.88	16.6	0.025
Lung	100	0.89	99	0.80	79.5	0.122
Bone surface	7	0.45	5	1.00	5.1	0.008
Skin	1000	0.002	4	1.00	4.0	0.006
Breast	121	0.29	67	1.29	86.5	0.133
Ovary	13	0.57	10	1.12	11.7	0.018
Bladder	43	0.29	23	0.71	16.3	0.025
Thyroid	24	0.07	7	1.29	9.5	0.015
Bone Marrow	41	0.67	37	1.63	60.8	0.093
Other Solid	214	0.49	164	1.03	169.1	0.259
Gonads / Hereditary	20	0.80	19	1.32	25.4	0.039
Total	1812		638		651.5	1.000

* Defined as $R*q + R*(1-q)*((1 - q_{min})\, q + q_{min})$, where R is the nominal risk coefficient, q is the lethality, and $(1 - q_{min})\, q + q_{min}$ is the weight given to non-fatal cancers and q_{min} is the minimum weight for nonfatal cancers. The q_{min} correction was not applied to skin cancer (see text).
+ The values given should not be taken to imply undue precision but are presented to 3 significant figures to facilitate the traceability of the calculations made.

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Overall detriment

- Detriment-adjusted stochastic risk (% Sv^{-1})

Exposed population	Cancer		Heritable effects		Total	
	ICRP 103	ICRP 60	ICRP 103	ICRP 60	ICRP 103	ICRP 60
Workers	4.1	4.8	0.1	0.8	4.2	5.6
Whole population	5.5	6.0	0.2	1.3	5.7	7.3

Comparison of risks

Risks expressed in number of deaths per million individuals and per year

Professional categories	Risk	Non-professional categories	Risk
Lumberjacks and wood transporters	6000	Smokers	4100
Aerial electric line workers	1550	Windsurfing	1800
Roofers	650	Motorcyclists (20 – 24 years)	420
Aerial service (crew)	540	Mountain climbers	300
Explosive factory employees	380	Falls	230
Truckers	240	Walkers	29
Farming accidents	100	Drowning	12.5
Domestic accidents	70	Death by fire	2.7
Chemical employees (accidents)	51	Food poisoning	1.2

Radiological Field	Risk
Average exposure of the Swiss population (5.5 mSv/year)	200
Occupational limit (20 mSv/year)	800
Standard radiological exams	50 – 500
Thorax exam	2

6. Detriment

Which radiation and non radiation effects are considered in evaluating the detriment?