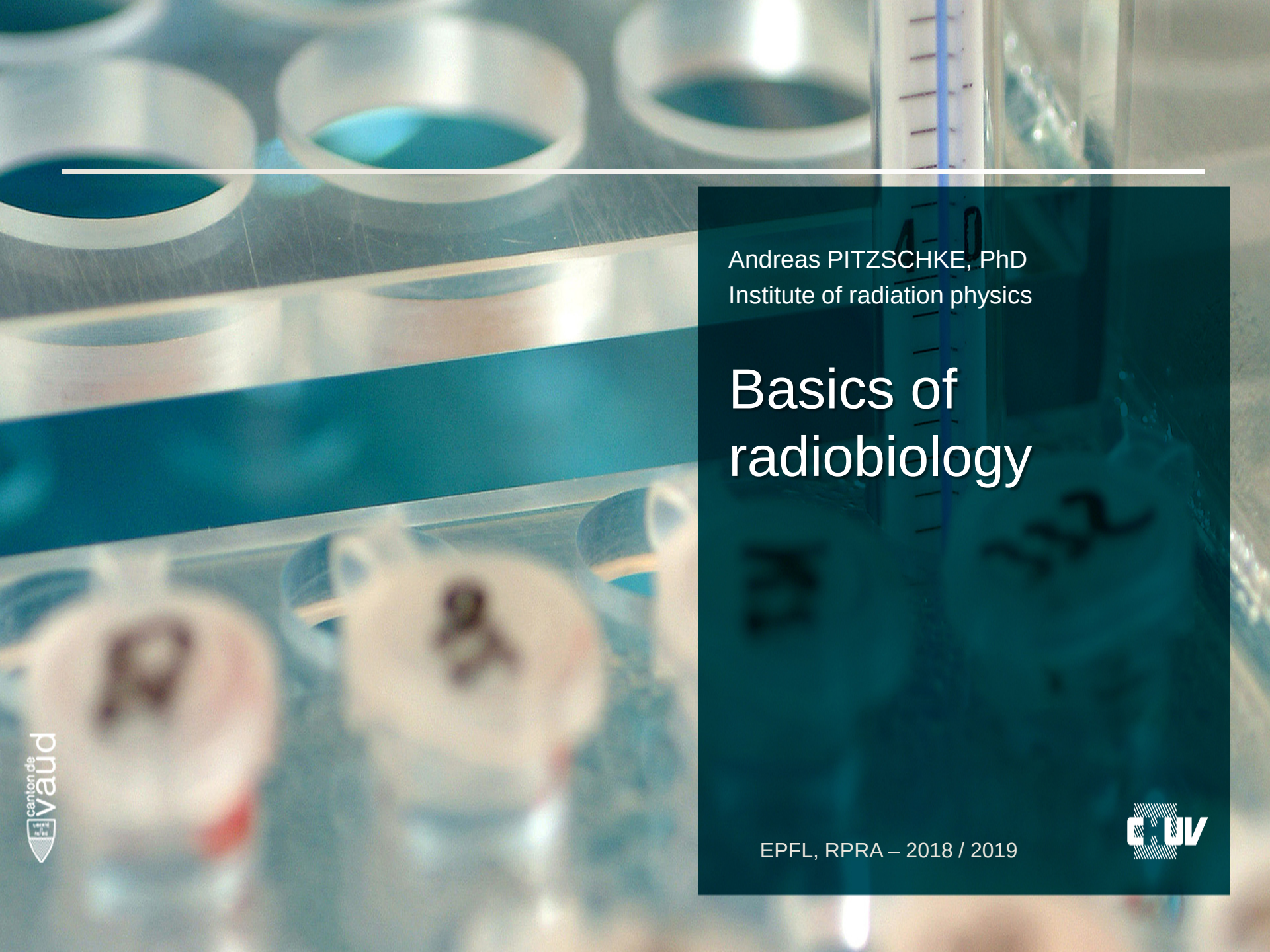


Andreas PITZSCHKE, PhD
Institute of radiation physics

Basics of radiobiology

EPFL, RPRA – 2018 / 2019

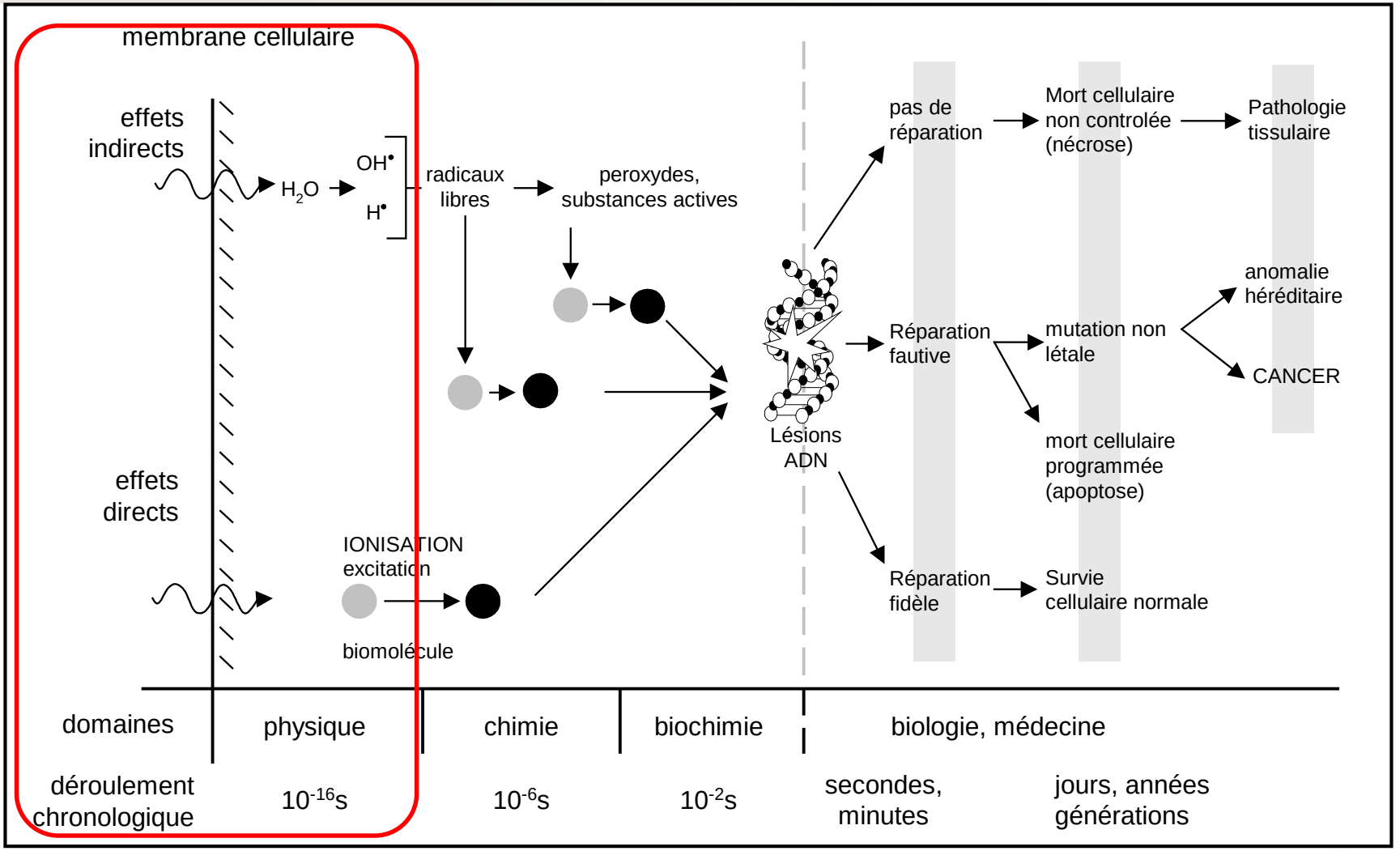
Course objectives

- Be able to describe the **sequence of radiation effects** on organic matter
- Describe the **biological effects** of ionizing radiation
- Explain **deterministic** (tissue based) and **stochastic** effects
- Evaluate the effects expected following either **external** or **internal** exposure in a given situation

Course content

- Physical effects
- Radiochemical effects
- DNA effects
- Cellular effects
- Effects on the organism
  - Tissue Reactions (deterministic effects)
  - Stochastic effects
  - Effects on the embryo and the fetus
  - Other effects
- Radiological risk

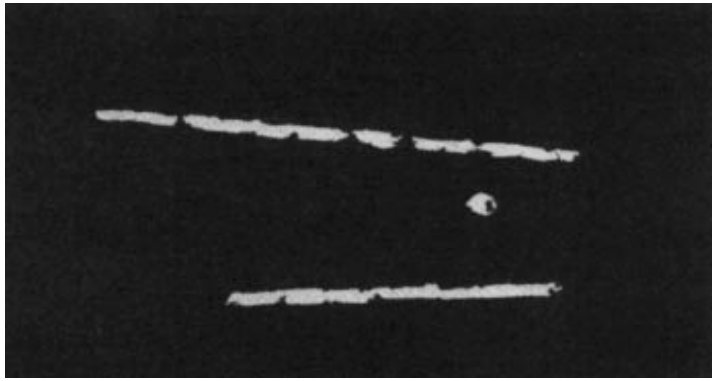
Effects on the organism



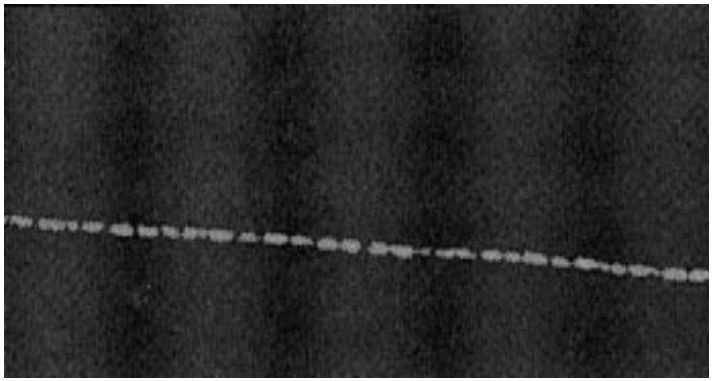
Source: Wikipedia

Cloud chamber

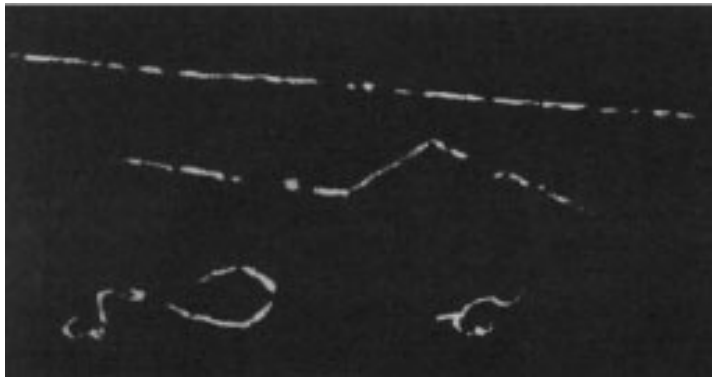
proton



muon



β particle



α particle

Alphas & electrons

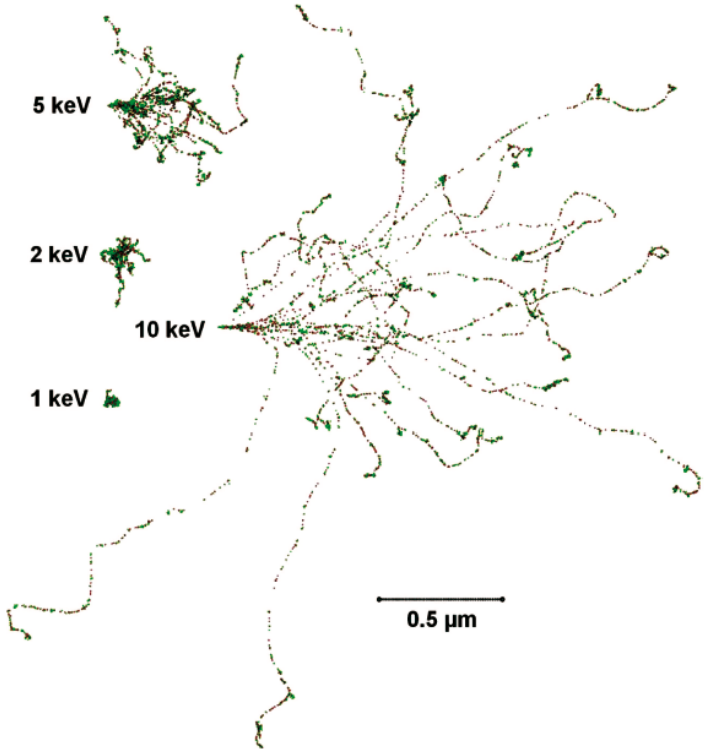


Figure 2.3. Twenty randomly generated electron tracks for initial kinetic energies of 1 keV, 2 keV, 5 keV, and 10 keV. Red points represent ionizations, and green points represent excitations. All tracks of the same energy start at the same point and initially proceed in the same direction (left to right in the figure).

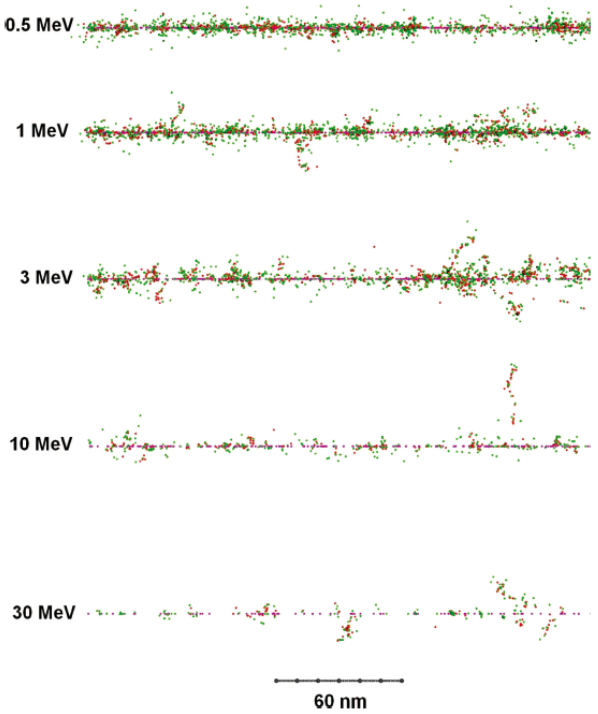


Figure 2.5. Calculated 230 nm track segments for 0.5 MeV, 1 MeV, 3 MeV, 10 MeV, and 30 MeV alpha particles in water. Red points represent ionizations, and green points represent excitations.

ICRU 86

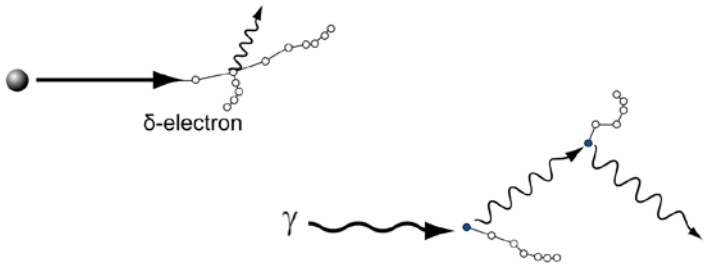
Physical effects of irradiation

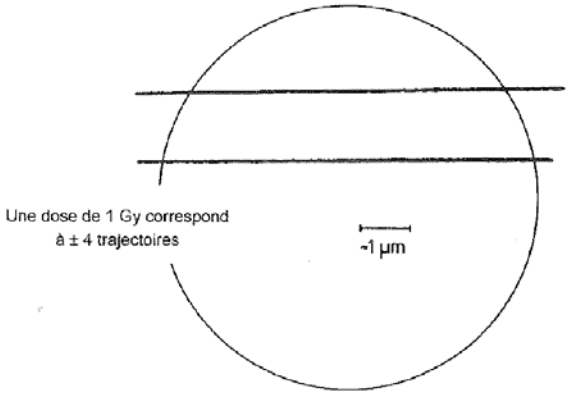
Interactions:

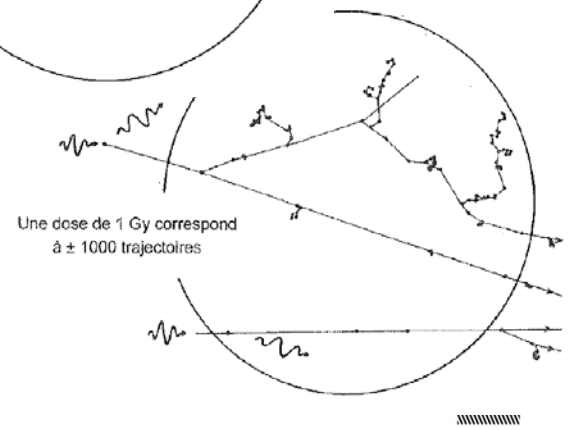
- **Ionisation et excitation** of atoms and molecules:
  - Directly (e±, p, heavy ions) or indirectly ionizing (photons, neutrons)
  - Ionisation energy in the order of 10 e
- **Intra-molecular**:
  - Breaking of chemical bounds
  - Energy below 10 eV

Matter:

- Cells containing **DNA**:
  - α: ~ 2 - 4 trajectories per nucleus for 1 Gy
  - γ: ~ 1000 trajectories per nucleus for 1Gy







canton de vaud

Linear energy transfer (LET)

- At large scale: **absorbed dose**

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

- At the micrometer scale:
  - Absorbed energy is unevenly distributed and discontinuous
  - Biological effects result from the absorption of energy in structures of very **small dimensions**
  - Definition of “absorbed dose” does not express this properties → **micro-dosimetry**

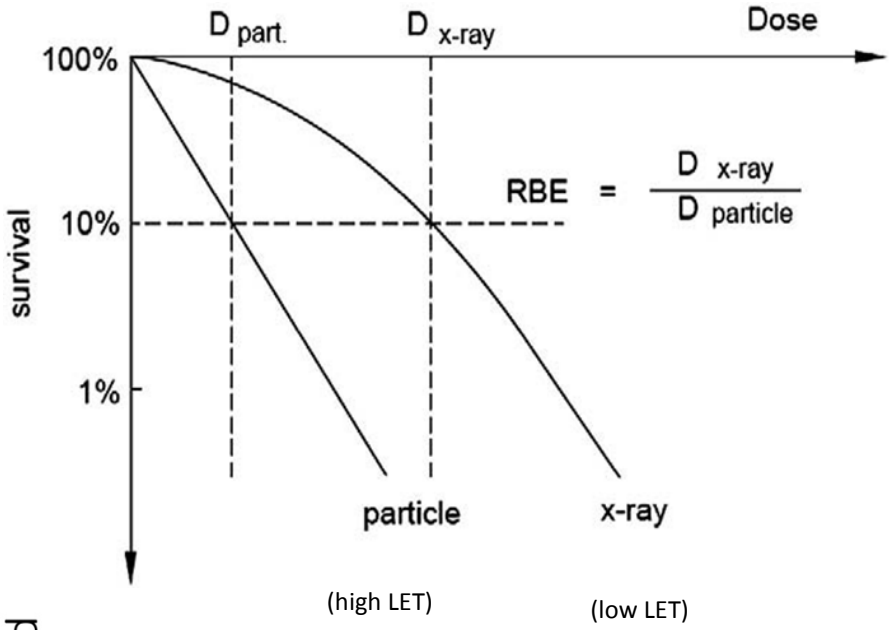
- Energy distribution at the microscopic scale:

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

Relative biological effectiveness (RBE)

Highly ionizing radiation is more effective at destroying cells

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



RBE is used to **compare** the biological effects of two radiations

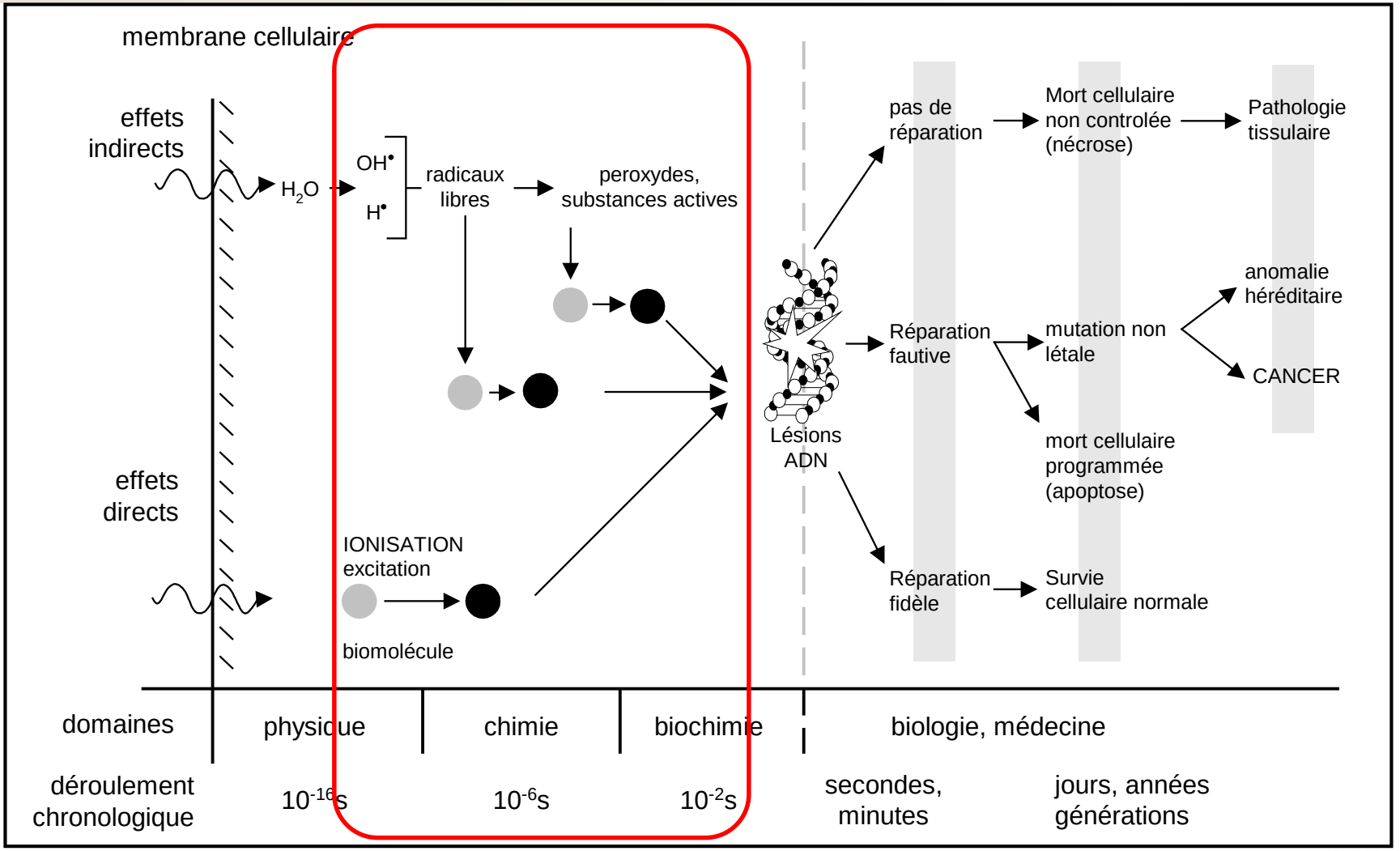
« average » RBE value in radiation protection: w_R

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

Summary: physical step

- Conversion of uncharged particles (γ or n) in charged particles
- Interaction between charged particles with the electrons of matter
  - Ionization
  - Excitation
- Recombination, de-excitation ⇨ heat
- Duration of the process: < 10^{-16} s
- Quantification of the interaction:
  - Macroscopically: absorbed dose $D = \frac{\Delta E}{\Delta m} \qquad [J/kg] = [Gy]$
  - Microscopically: LET $TEL = \frac{\Delta E}{\Delta x} \qquad [eV/\mu m]$

Effects on the organism

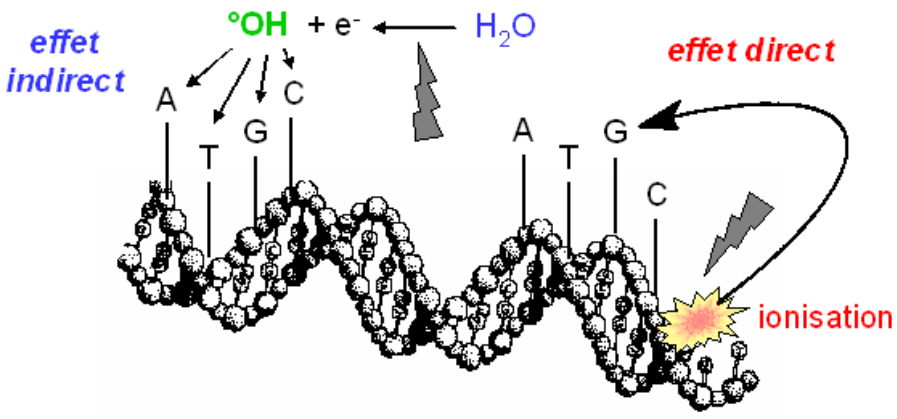


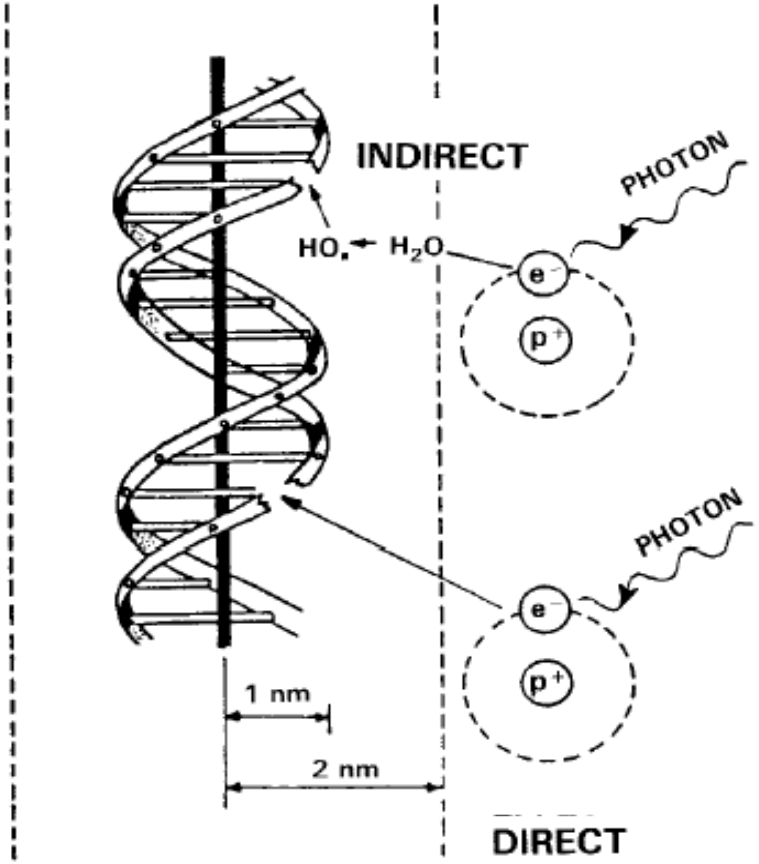
Source: Wikipedia

Direct and indirect effect

Direct :
$DNA + \gamma \rightarrow DNA^{\circ +} + e^-$

Direct ionisation of the DNA by breaking of H-bindings





Indirect :
$H_2O + \gamma \rightarrow H_2O^{\circ +} + e^-$
$H_2O^{\circ +} + H_2O \rightarrow H_3O^+ + {}^\circ OH$
$^\circ OH + DNA \rightarrow DNA^{\circ +} + {}^-OH$

Electron stripping from the electron shell
Production of very reactive radicals

Peroxyl radicals

- Oxygen reacting with free radicals based on **carbon** (R°)
- RO2°: secondary free radicals

➢ Species formed as a result of reactions initiated by free radicals °OH on bio-organic substrates (RH)

$$°OH + RH \rightarrow R° + H_2O$$

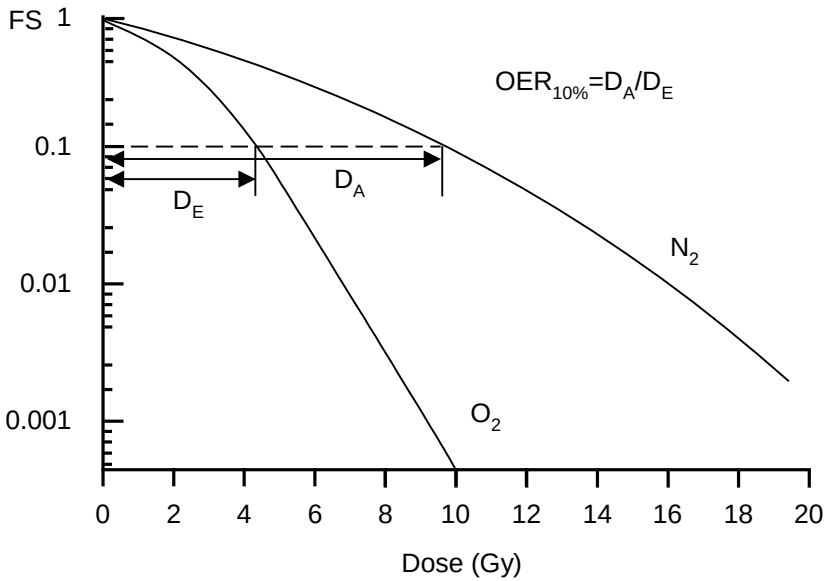
$$R° + O_2 \rightarrow RO_2°$$

➢ **Oxidative degradation of biological membranes (lipids)**

Oxygen enhancement ratio (OER)

Well-oxygenated cells are more sensitive to radiation

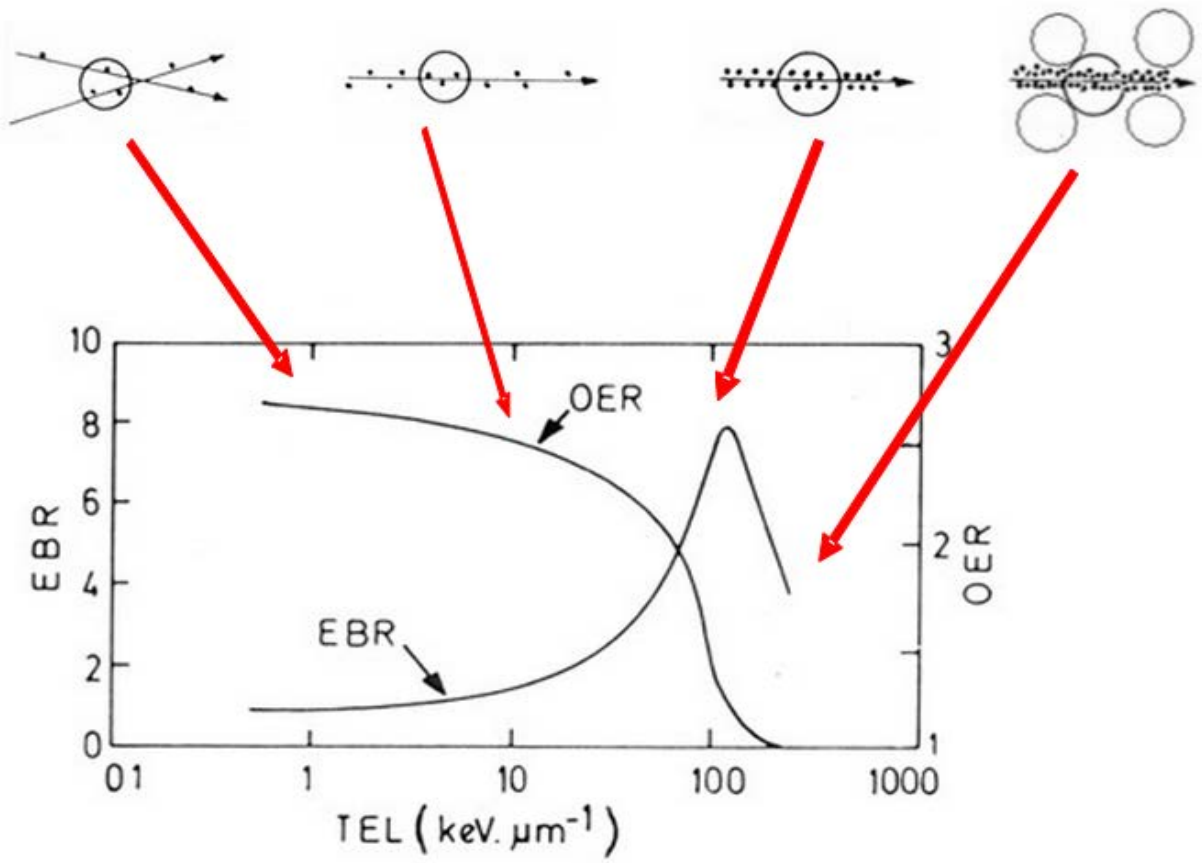
OER : Oxygen enhancement ratio/factor



Important effect in the treatment of cancer by radiation therapy

$$OER = \frac{\text{Dose in hypoxia condition}}{\text{Dose in anoxia condition}}\Bigg|_{\text{Same biological effect}}$$

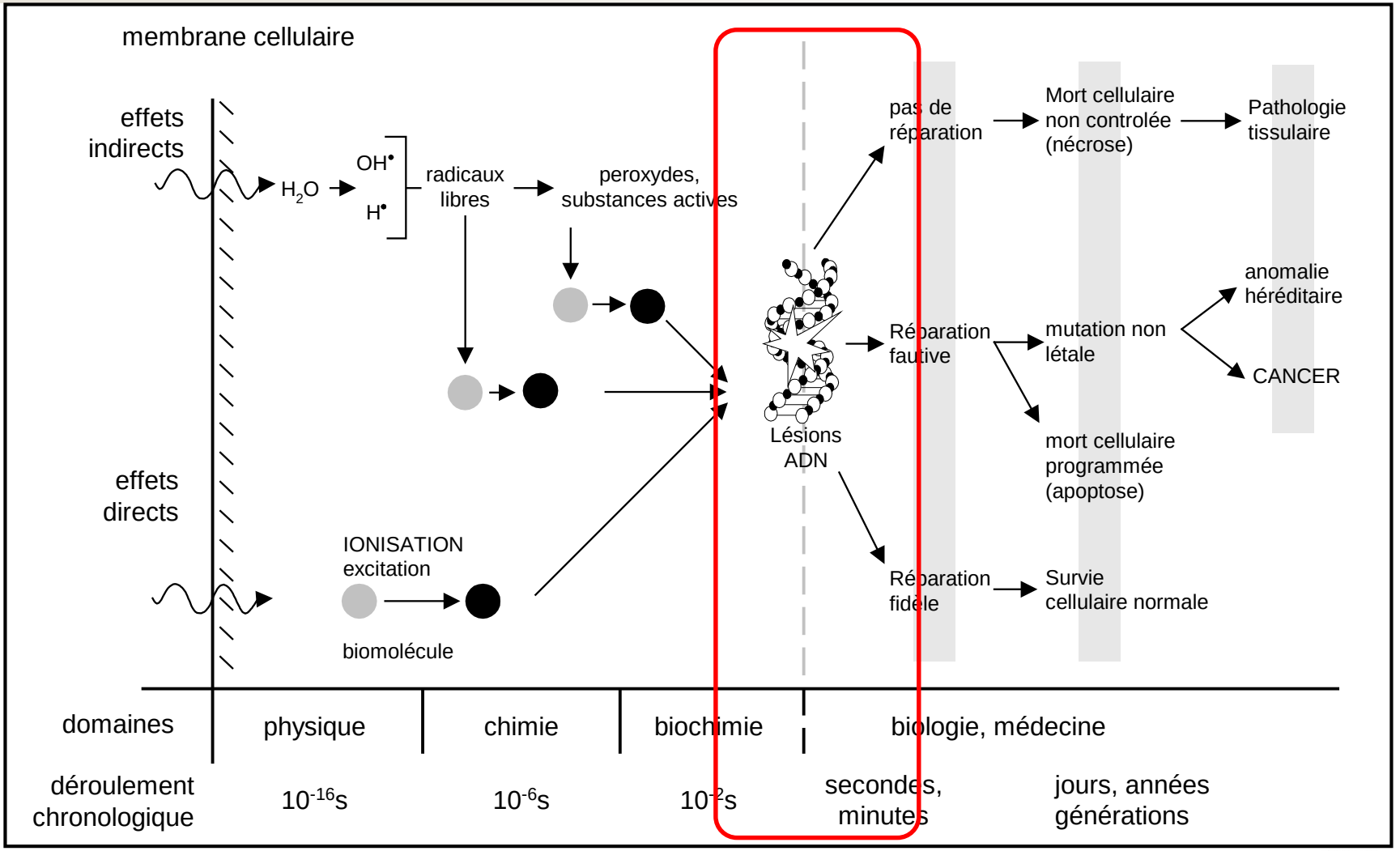
?? LET, RBE and OER ??



Summary: Radiochemistry

- **Direct effect**: direct ionization of DNA
- **Indirect effect**: indirect ionization of DNA by radicals
- Formation of **reactive oxygen species** following the radiolysis of water (indirect effect):
  - Rapid recombination forming molecules of water or hydrogen → no effect
  - Free radical diffusion and molecular alteration inducing breaks in the DNA
  - Formation of peroxides (very reactive)
- The presence of **oxygen promotes the formation of peroxides** and thus increase the biological effect of radiation

Effects on the organism



Source: Wikipedia

Effects of radiation on DNA

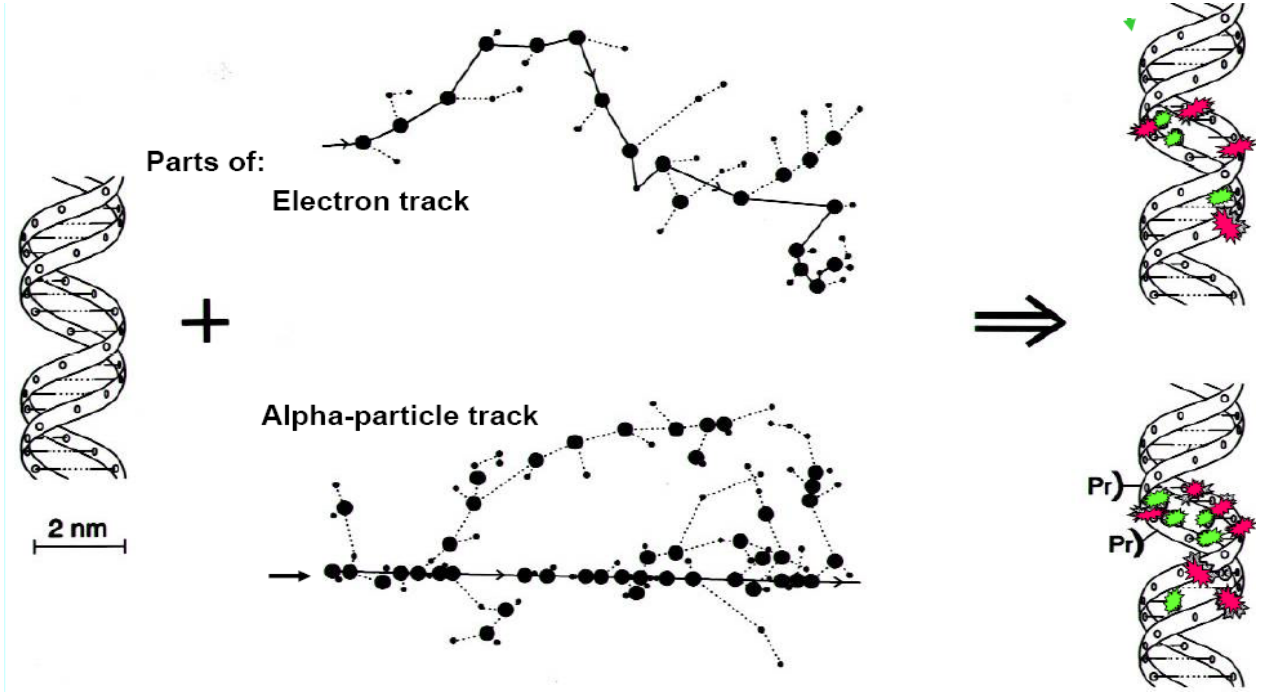
- Contains all **genetic information**:
  - Agent of its own replication (transcription in RNA)
  - Translation of protein information
  - Guarantor of faithful transmission of genetic information

- Any **damage** of or change in the DNA:
  - Inability to reproduce, followed by **cell death**
  - **Mutation** (genetic instability and malignant transformation)
  - Mechanism of repair and defense

Radiation induced DNA lesions

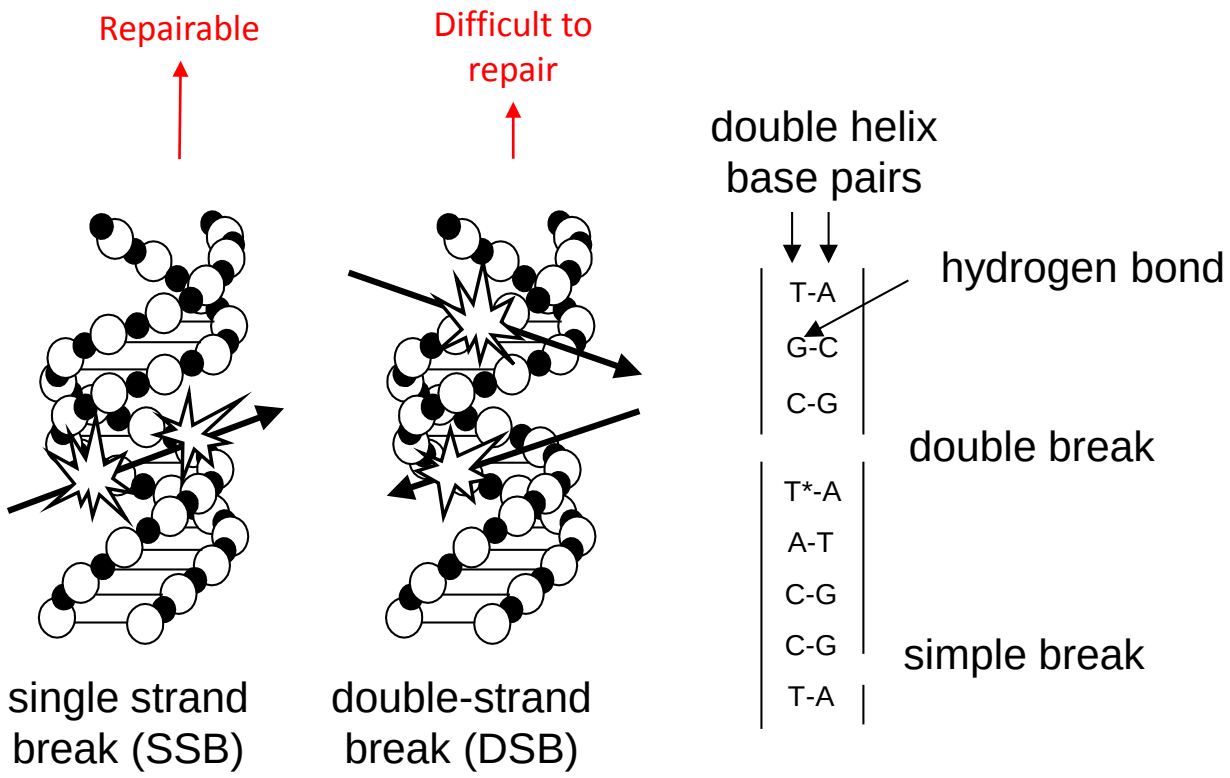
Different effects as function of the LET :

- Low LET: 40% of lesions are due to energy deposition in the DNA and 60% due to indirect effects
- High LET: significant risk of direct DNA lesion

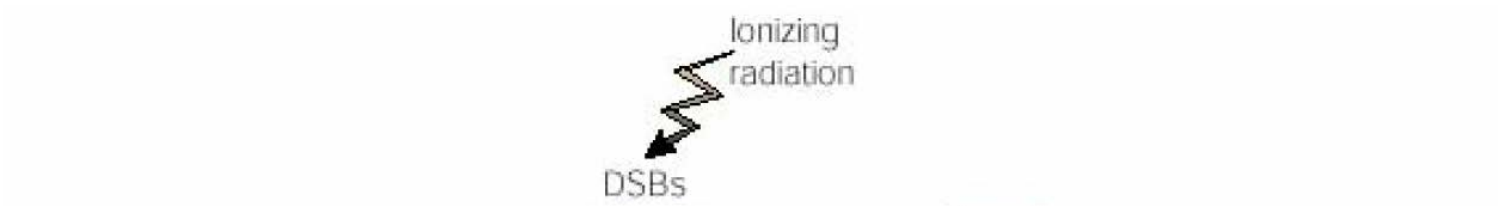


DNA lesions

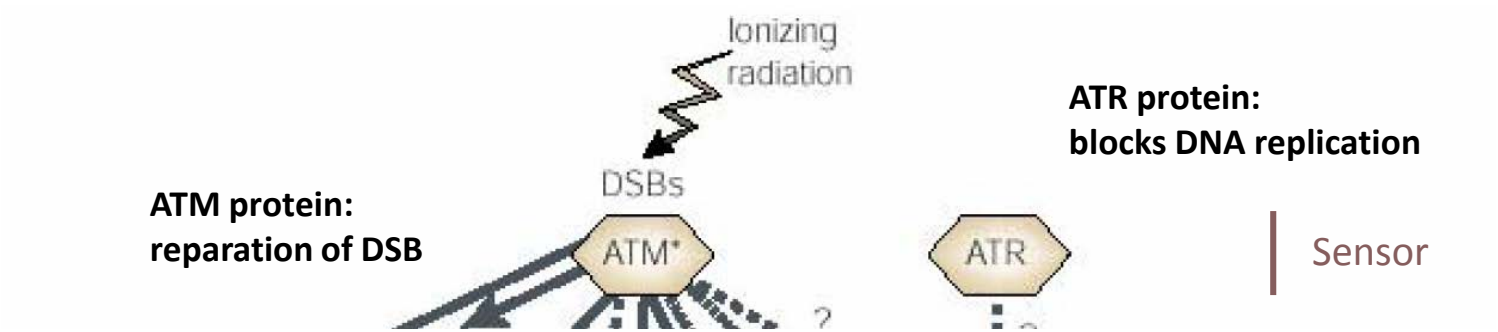
- frequency of “single strand” much higher than “double strand” break
- “double strand” rupture constitutes greatest lesion



Signalling of DNA damage



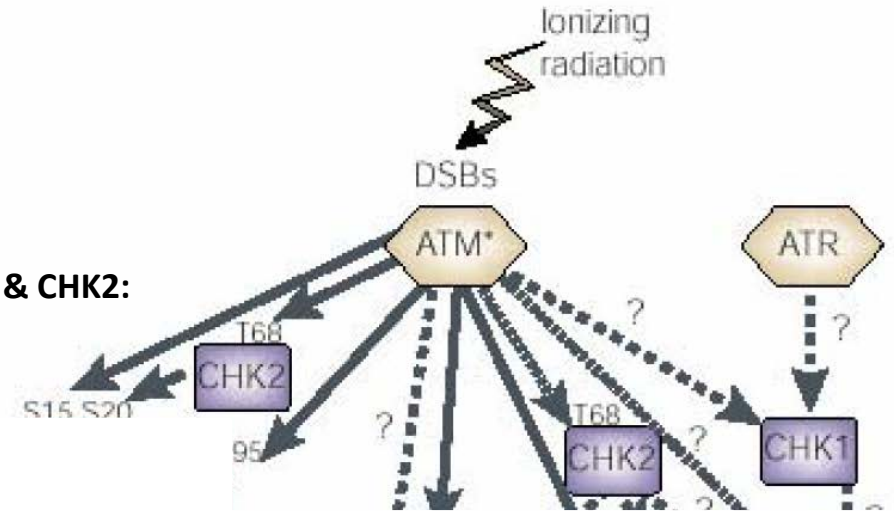
Signalling of DNA damage



(Source : BEIR VII)

Signalling of DNA damage

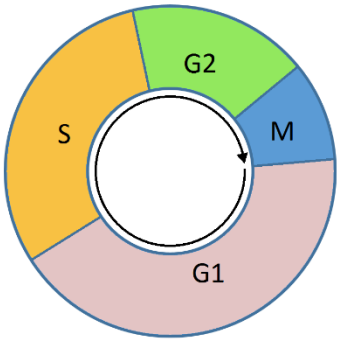
Cellular proteins CHK1 & CHK2: control of cell cycle (progression or stop)



Sensor

Transductor

Signalling of DNA damage



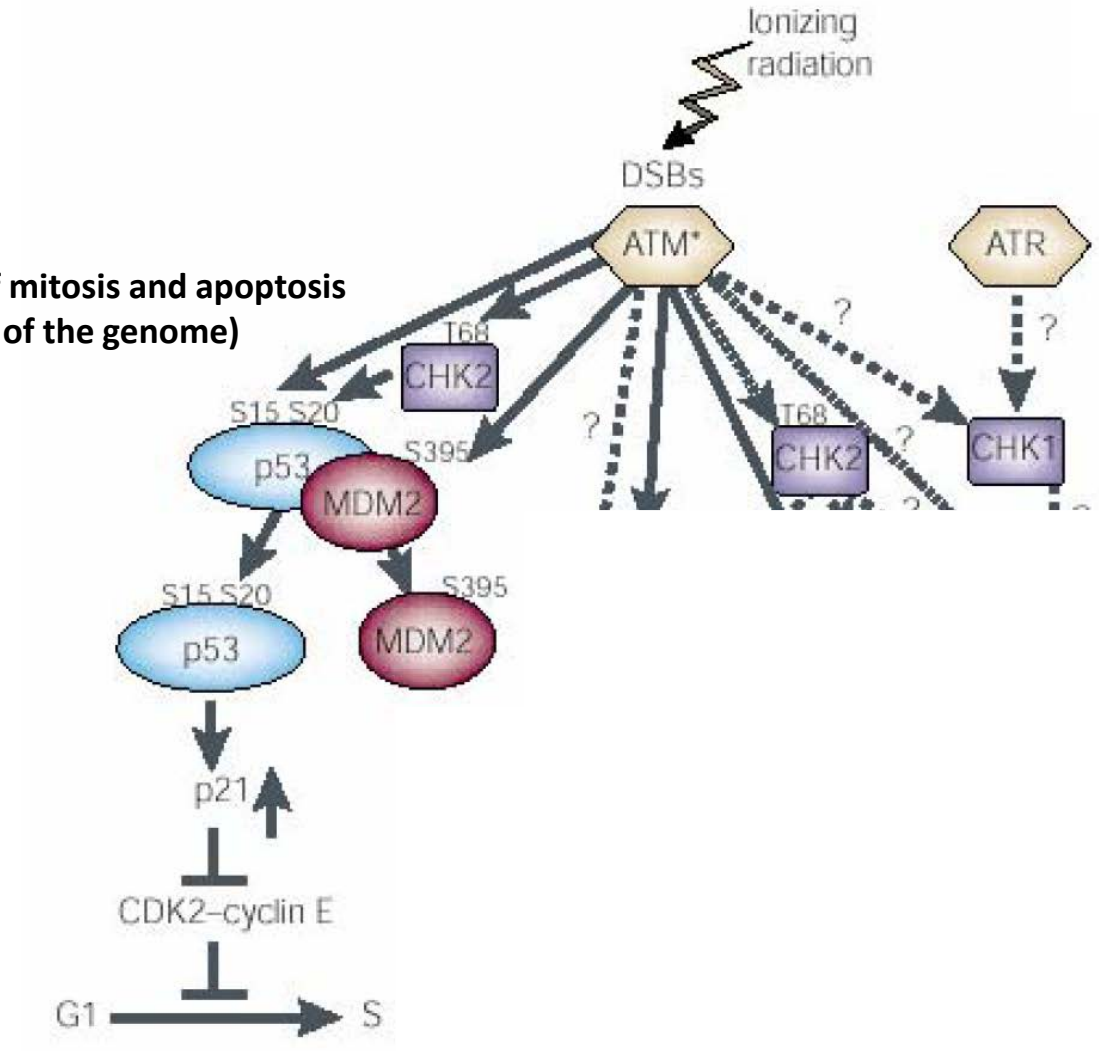
G1 - Growth

S - DNA synthesis

G2 - Growth and preparation for mitosis

M - Mitosis (cell division)

p53:
Control of mitosis and apoptosis (guardian of the genome)

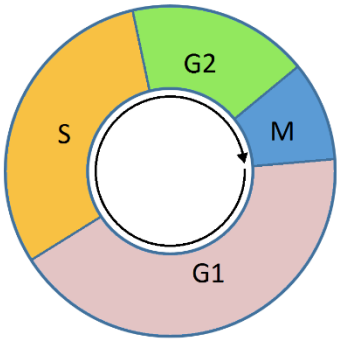


Sensor

Transductor

Effector

Signalling of DNA damage



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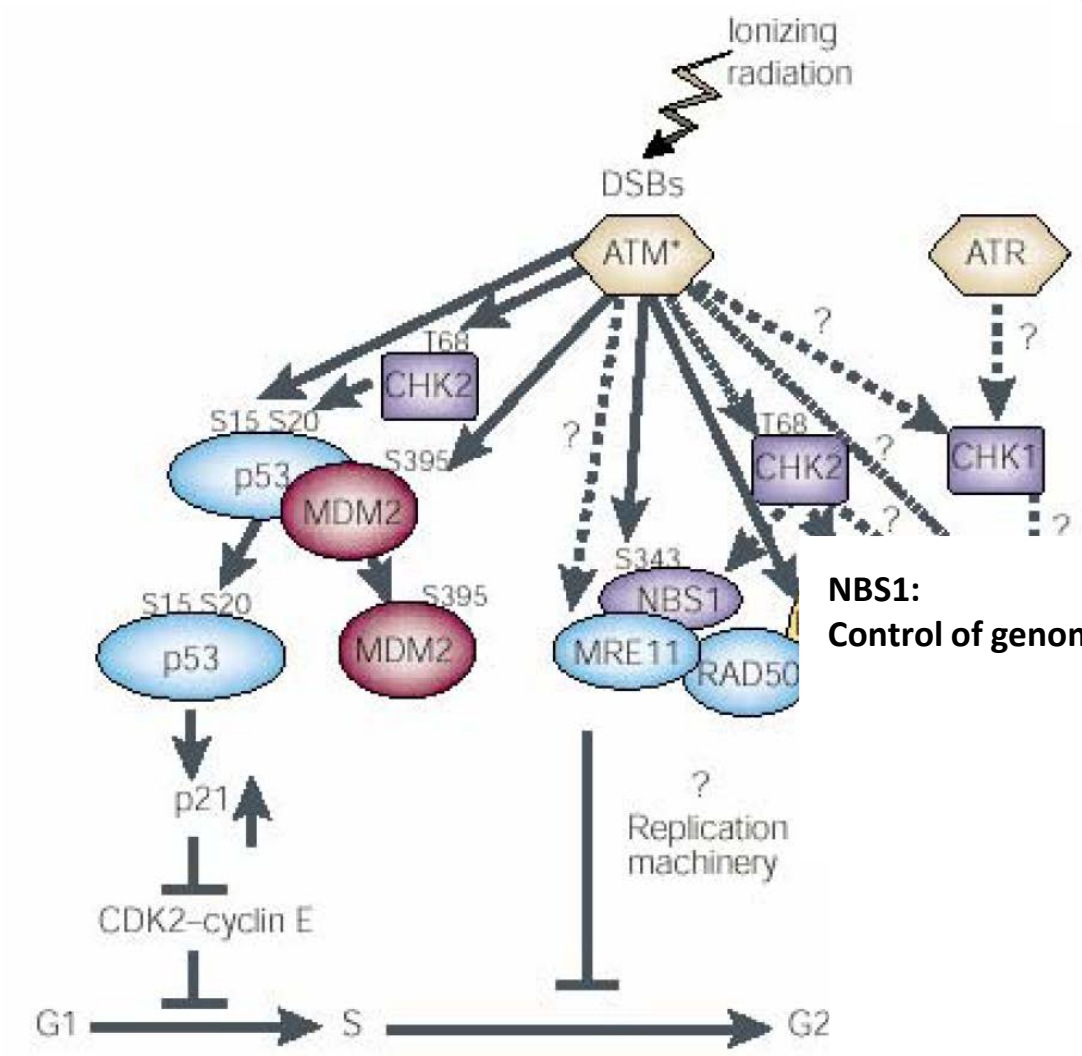


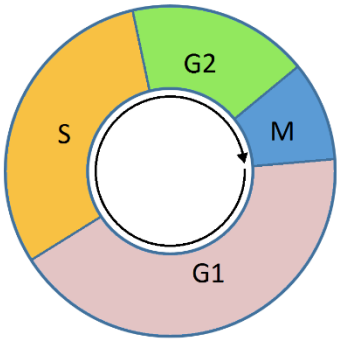
Sensor

Transductor

Effector

NBS1:
Control of genome reparation

Signalling of DNA damage



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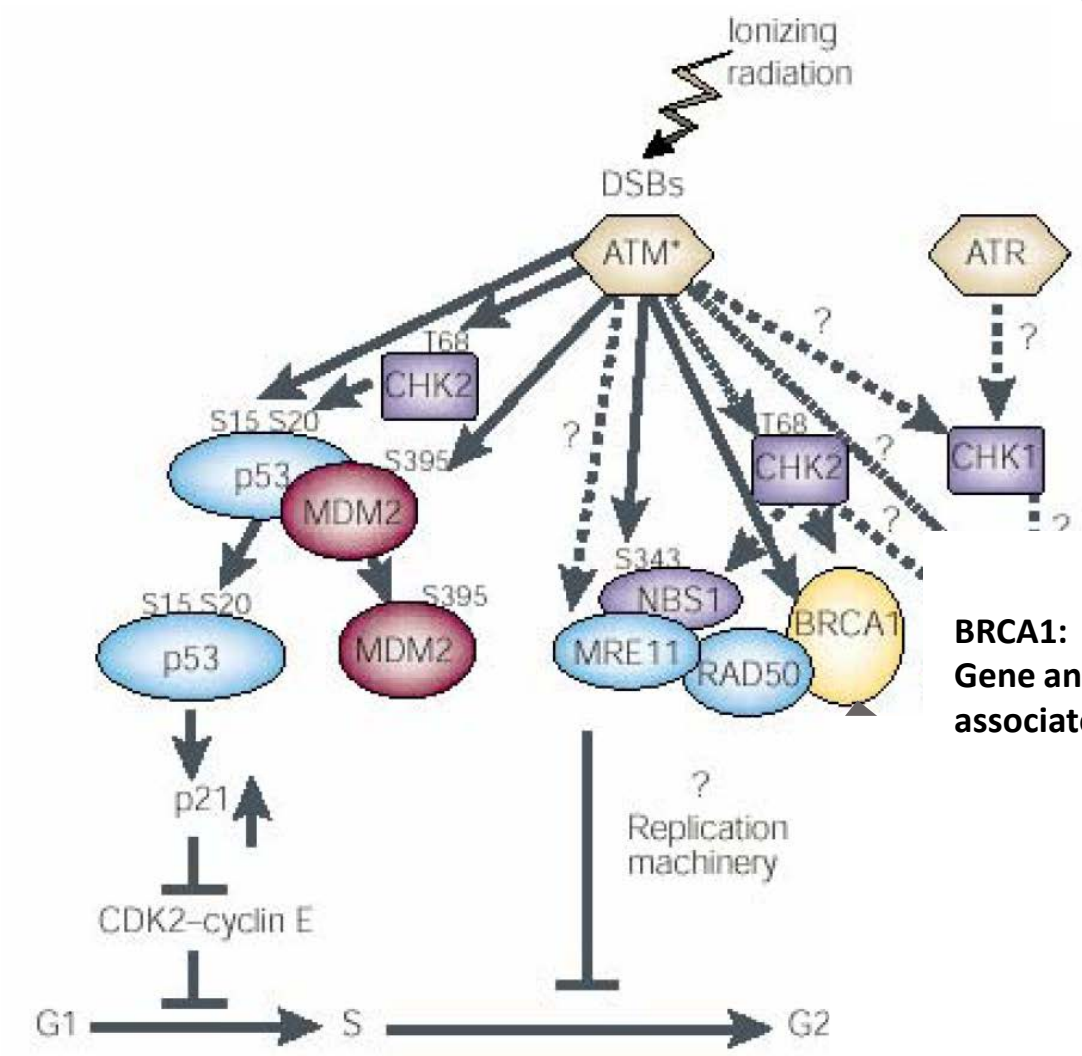


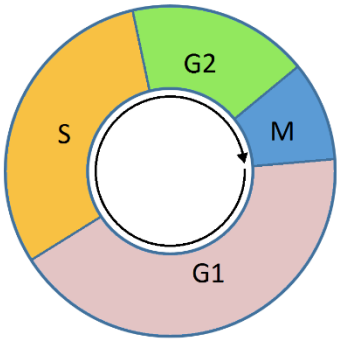
Sensor

Transductor

Effector

BRCA1:
Gene and its protein associated to breast cancer

Signalling of DNA damage



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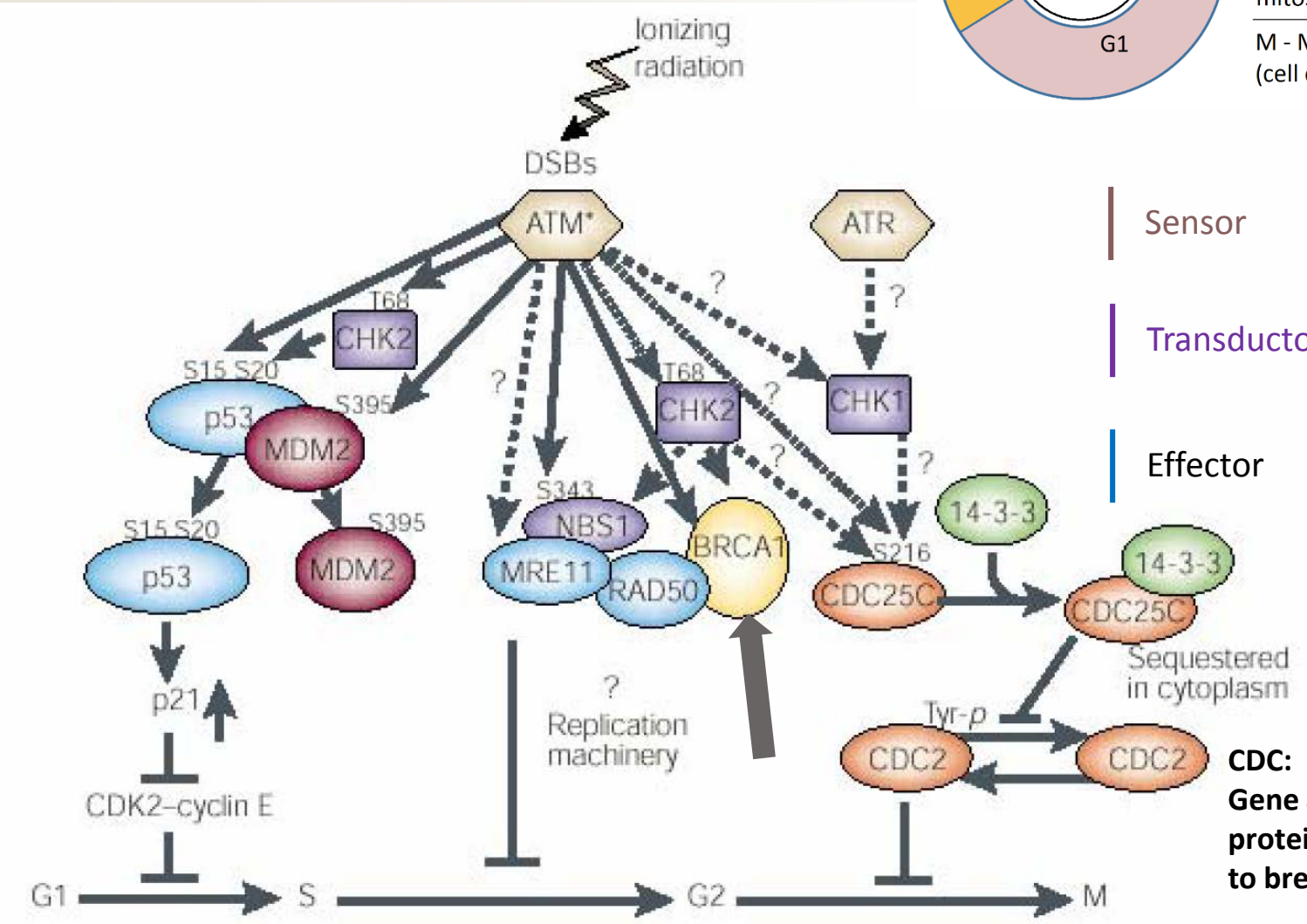


Sensor

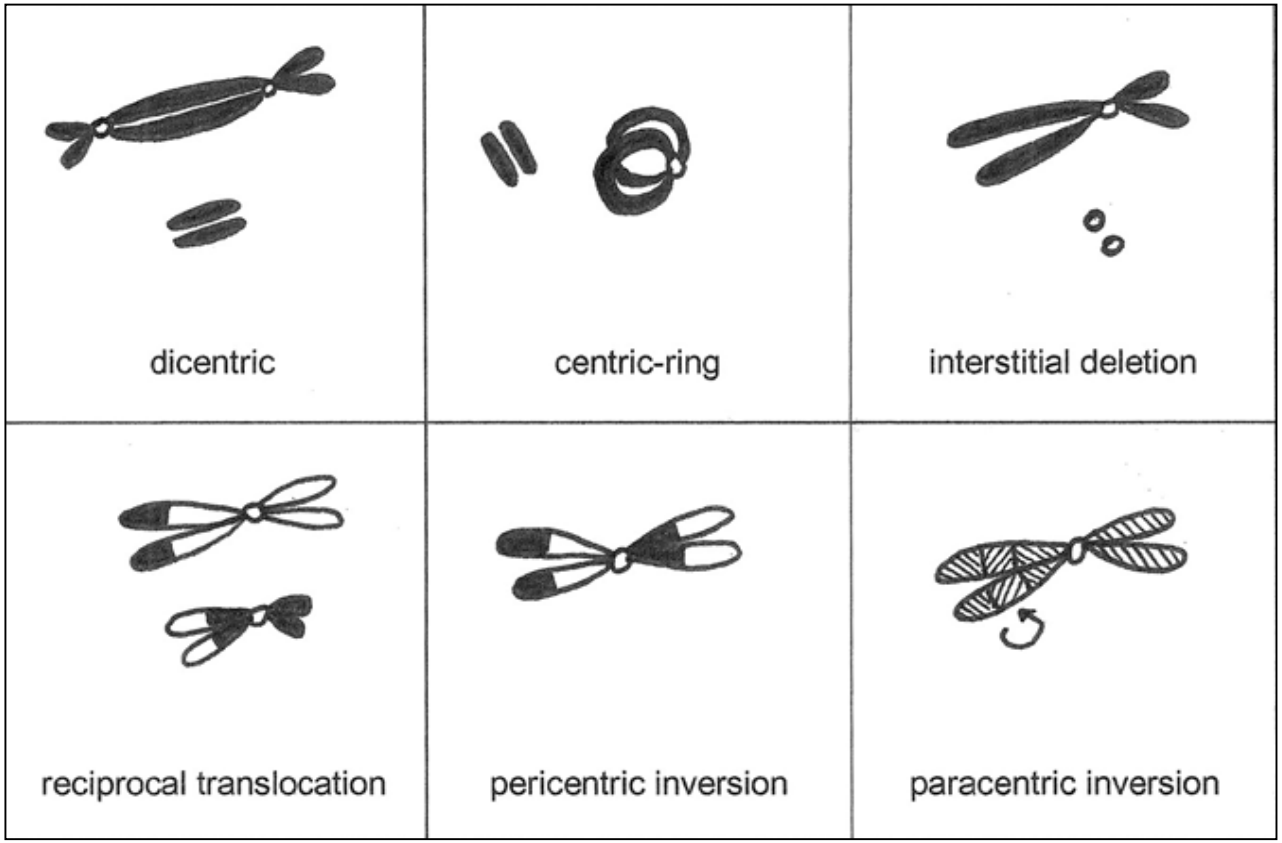
Transductor

Effector

CDC:
Gene and its protein associated to breast cancer

(Source : BEIR VII)

Chromosome aberrations



- Due to breaks and fusions of chromosomes
- Detection of aberrations in lymphocytes

Summary: The effect on DNA

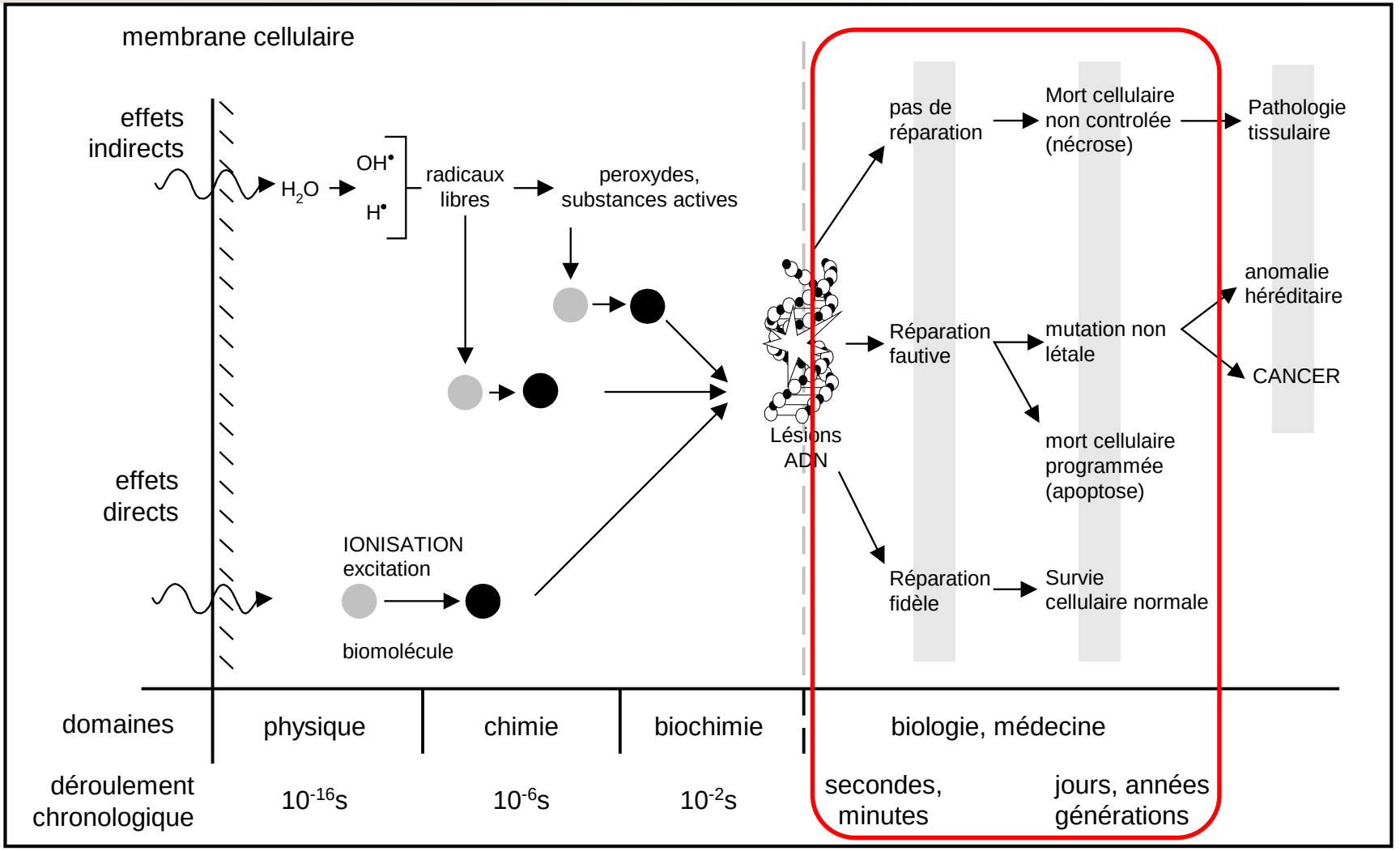
Type of damage caused by radiation:

- damage to a DNA base: 80%
- single-strand break (SSB): 20%
- double-strand break (**DSB**): 1%
- **LMDS** (Locally multiplied damaged site): 0.3%

Existence of **repair genes**:

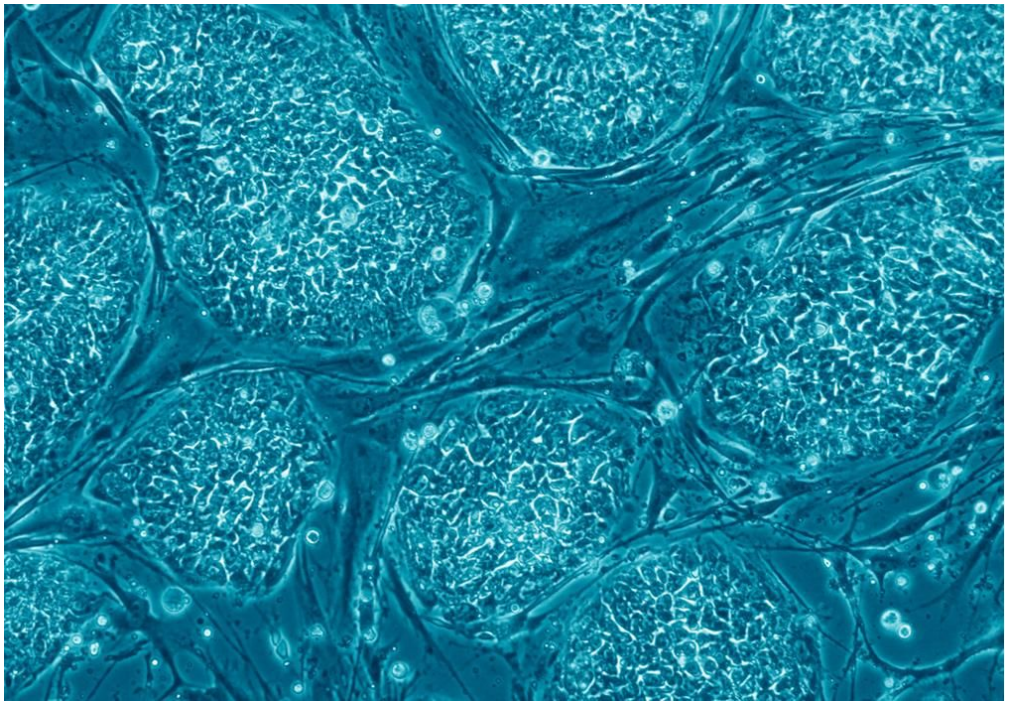
- ATM and ATR detect SSB and DSB
- Chk1 and Chk2 control cell cycle and proliferation
- p53 and BRCA1 control genomic integrity and apoptosis

Effects on the organism



Source: Wikipedia

Effects of radiation on cells



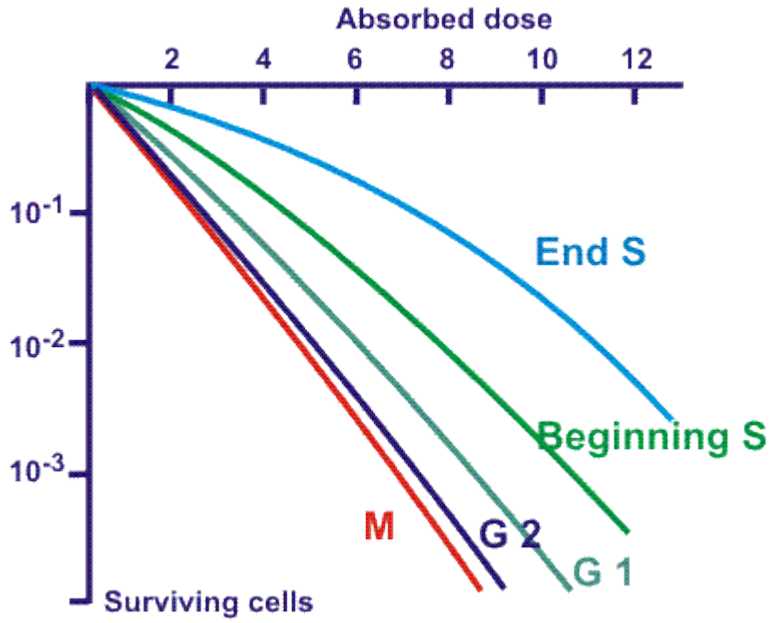
- The effects at the cellular level are studied in **cell culture**
- Development of **theories of the mechanism** of ionizing radiation and evaluation of the effects

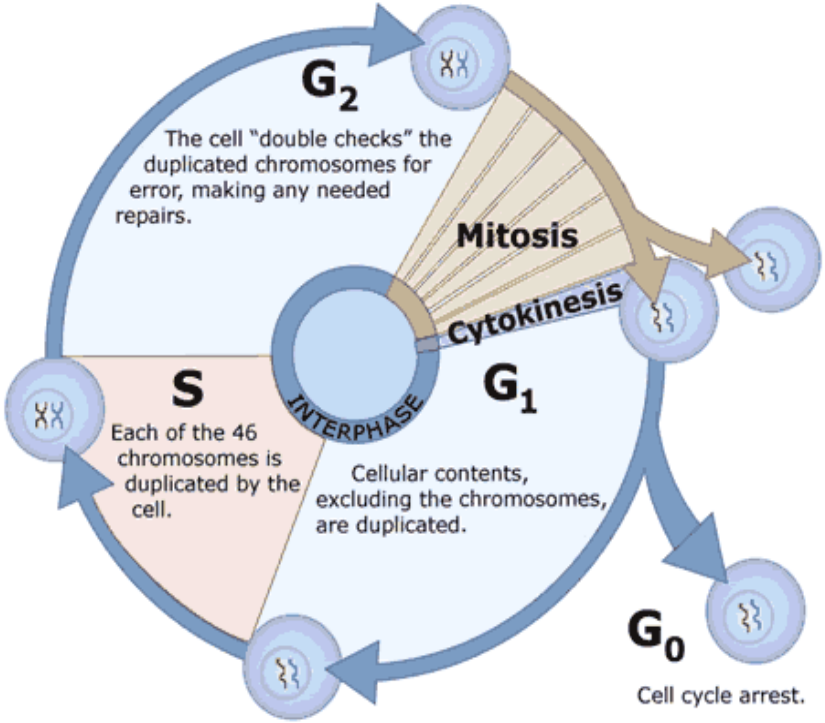
Law of Bergonié and Tribondeau

The **most radiosensitive cells** are:

- those with the highest growth/reproduction rate (hematopoietic tissue, basal layer of the epidermis)
- those with a long karyokinetic future (young cells)
- those that are the least differentiated (embryo tissue, stem cells)

Cellular cycle and radiation

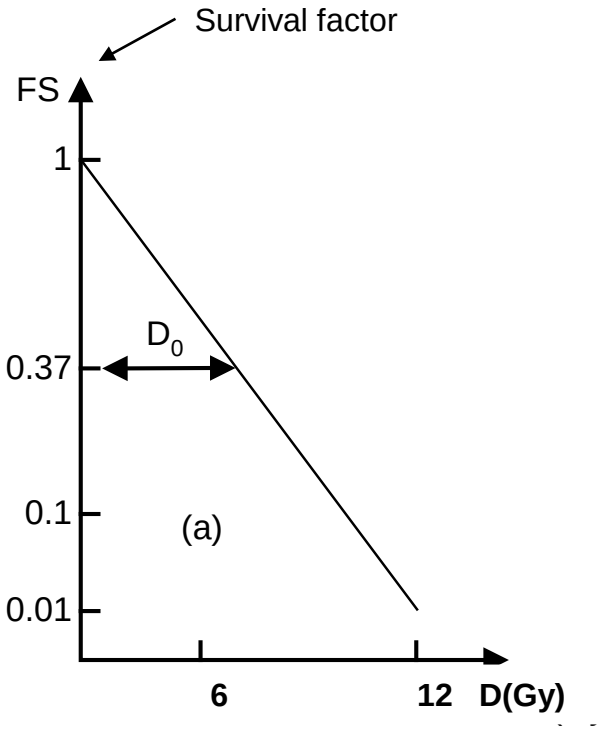




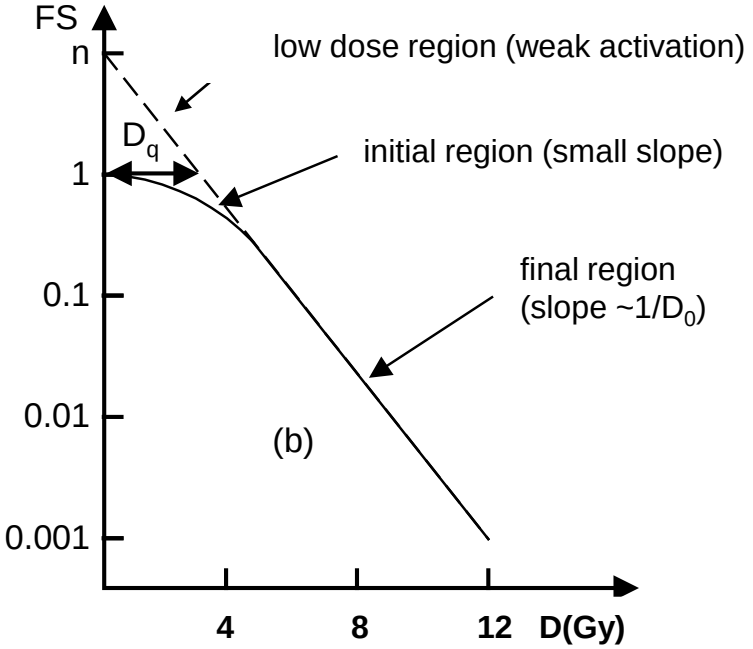
Radio-sensitivity varies during the cycle phases by a factor of 2 to 3:

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

Cellular effects: survival curve



$$\ln(FS) = -\alpha D$$



$$\ln(FS) = -\alpha D - \beta D^2$$

Shoulder:

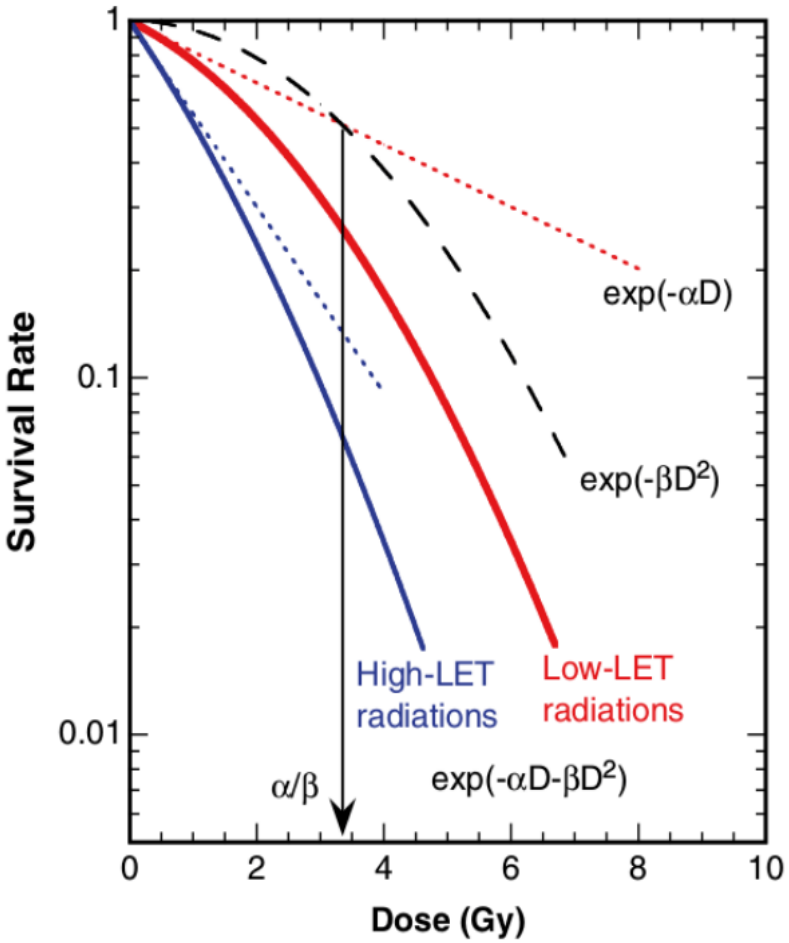
Mechanism of repair at low doses

Linear-quadratic model and LET

α and β depend on LET:

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

Cell survival determines w_R used in radiation protection

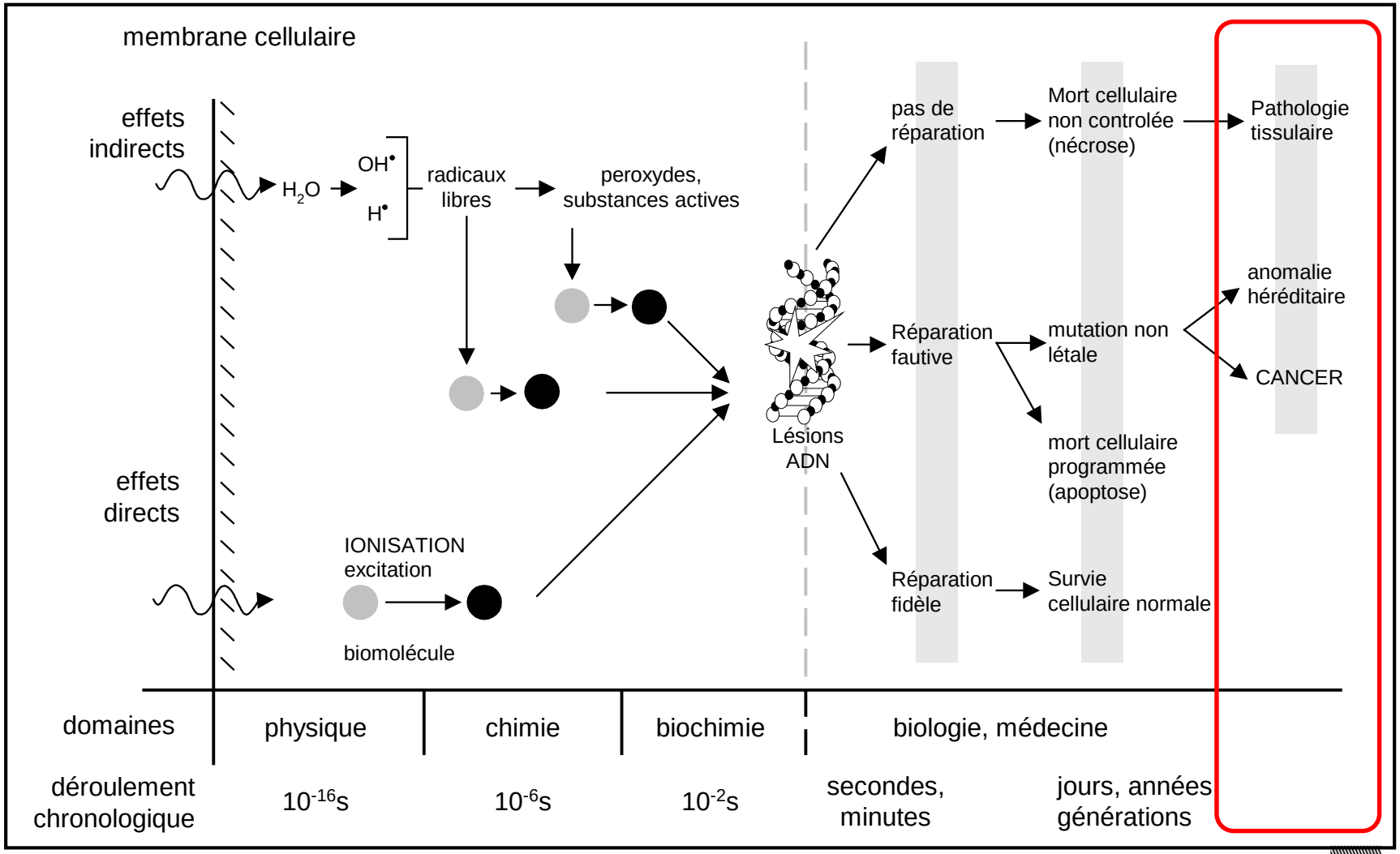


Summary: Effects of radiation on cells

- Radio-sensitivity of the cell:
  - **varies** according to the cell cycle (factor 2 - 3),
  - can be expressed by a **linear-quadratic model**

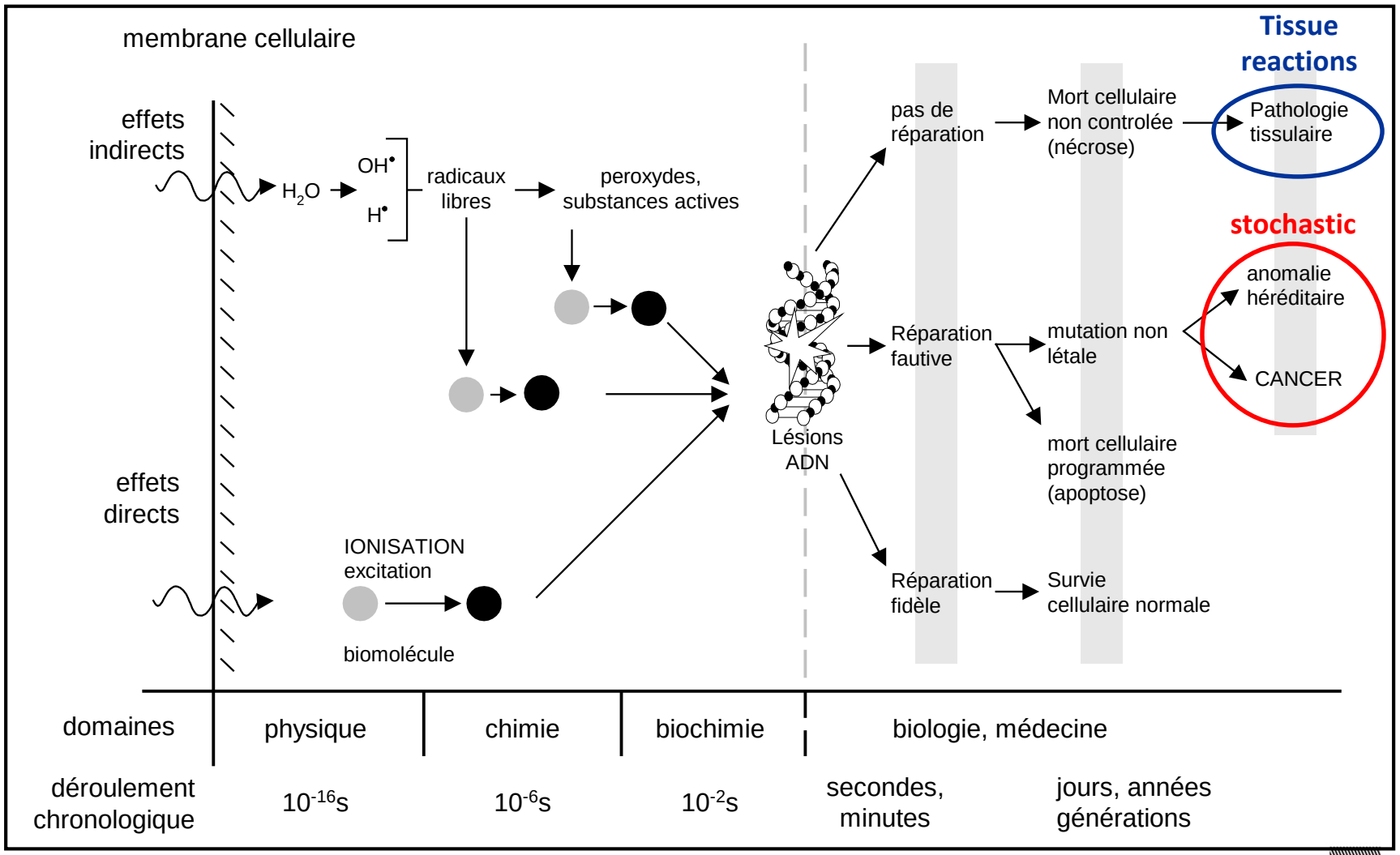
- The **most radiosensitive cells**:
  - highest rate of reproduction/growth
  - long-term
  - less differentiated

Effects on the organism



Source: Wikipedia

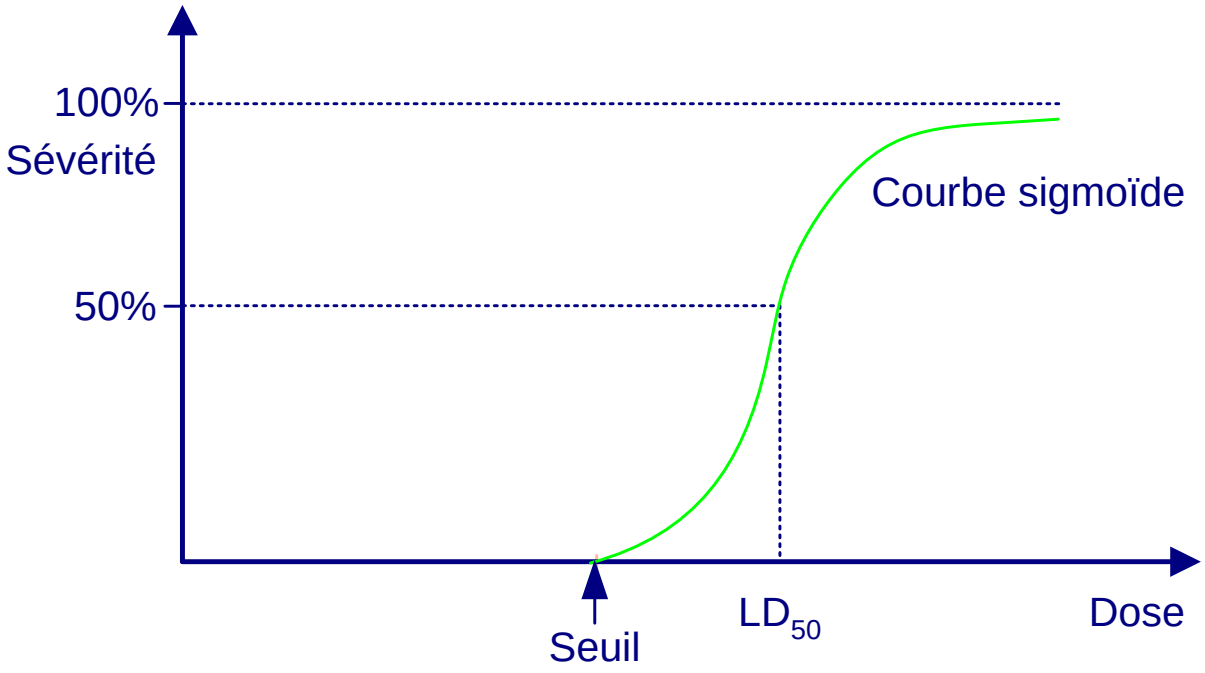
Effects on the organism



Source: Wikipedia

Tissue reactions

- **Relationship between dose and the severity** of a deterministic death effect



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

Characterization of tissue reactions

Dose threshold : ?

Semi-lethal dose : ?

Characterization of tissue reactions

Dose threshold :	0.5 Gy
Semi-lethal dose :	5 Gy

Acute irradiation syndromes

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

The skin is a particularly radiosensitive tissue

3 – 5 Gy : erythema and dry desquamation

20 Gy : humid desquamation (blisters after 4 weeks)

50 Gy : necrosis of the skin after 3 weeks

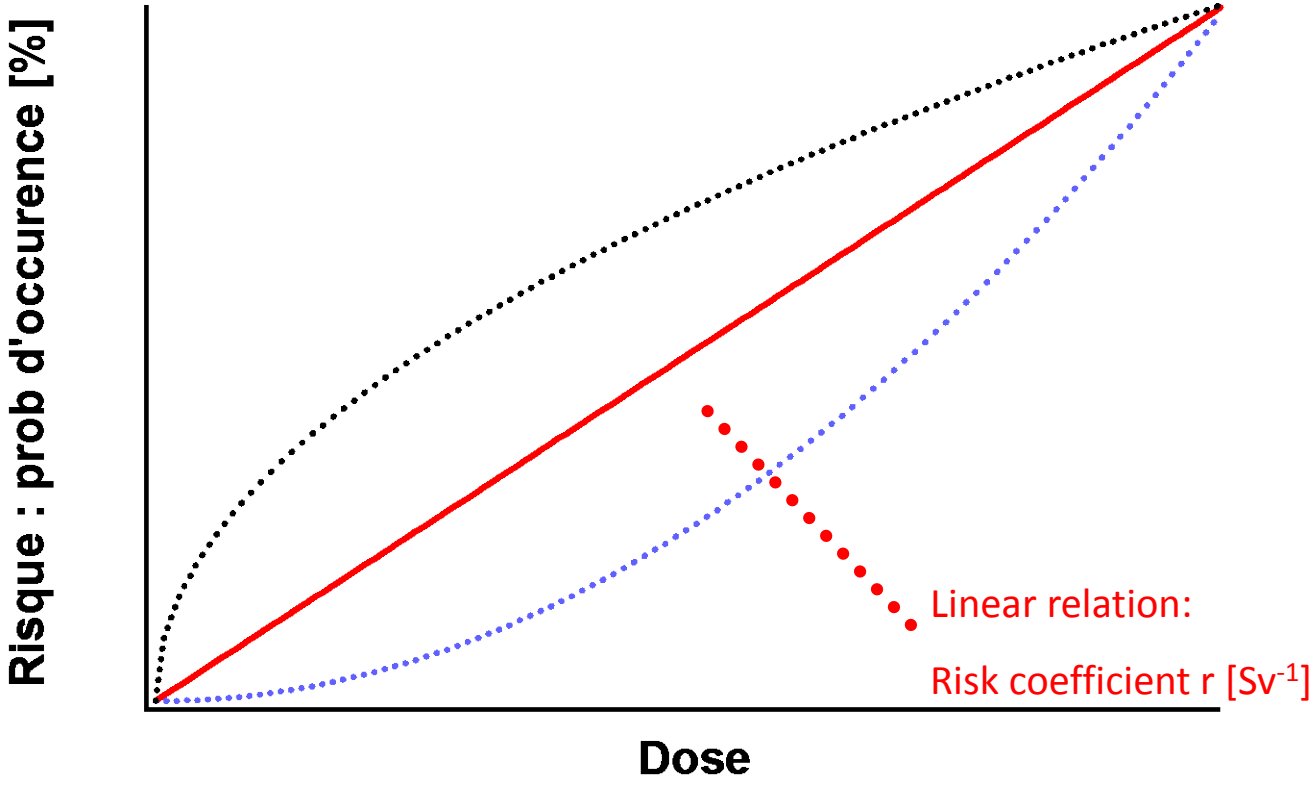
dry desquamation
(fluoroscopy exam)

moist desquamation
(cardiologycal intervention)

Hiroshima survivor

Stochastic effects

Relationship between dose and **probability of occurrence**



Measurement of a stochastic effect

Risk coefficient r :

- Number of occurrences in addition with respect to the magnitude of the cause

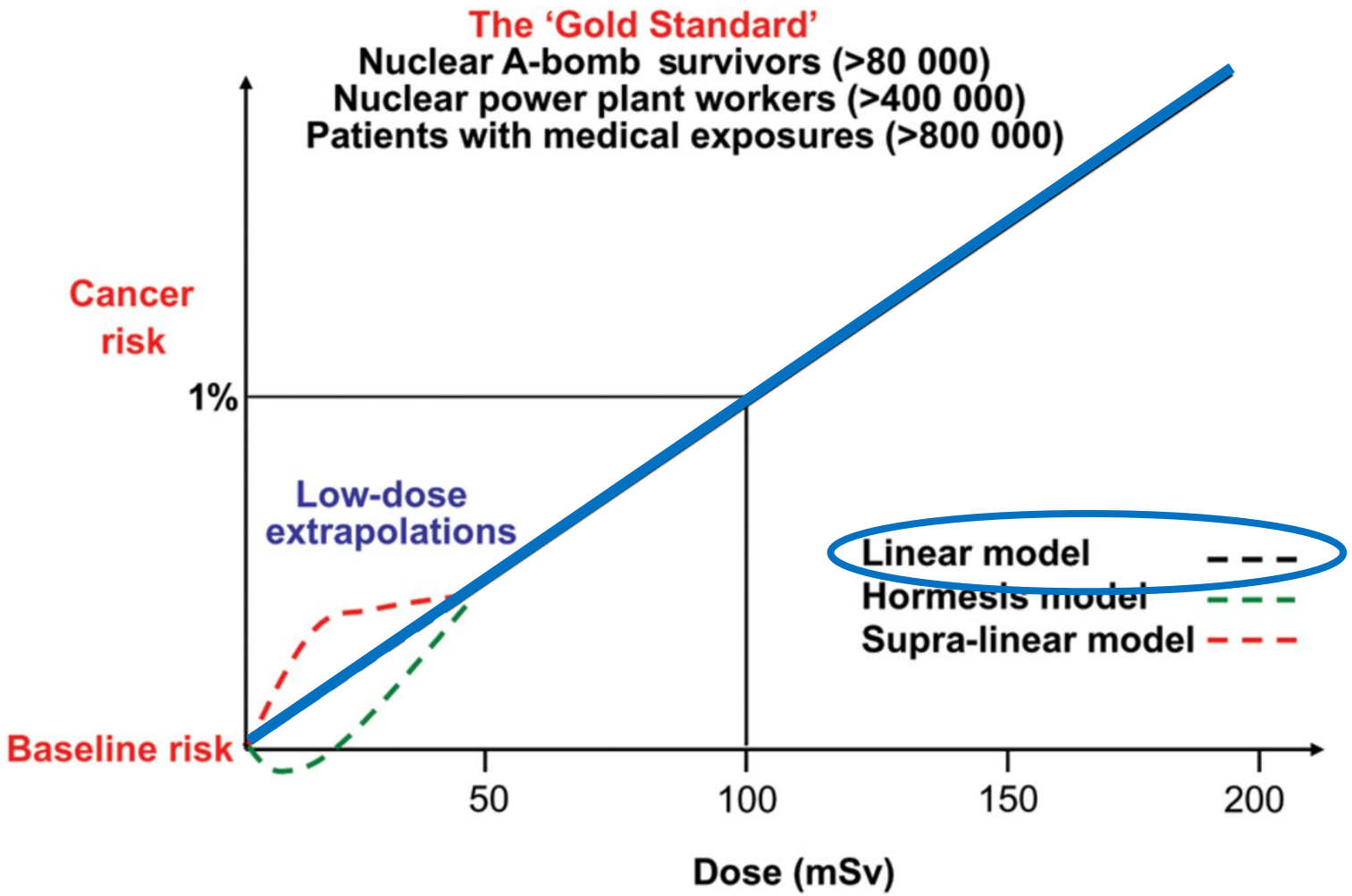
Example:

- Risk of death caused on the road:

$$r = \frac{\text{no. of deaths on the road in Switzerland}}{\text{no. of nbre traveled km}} =$$

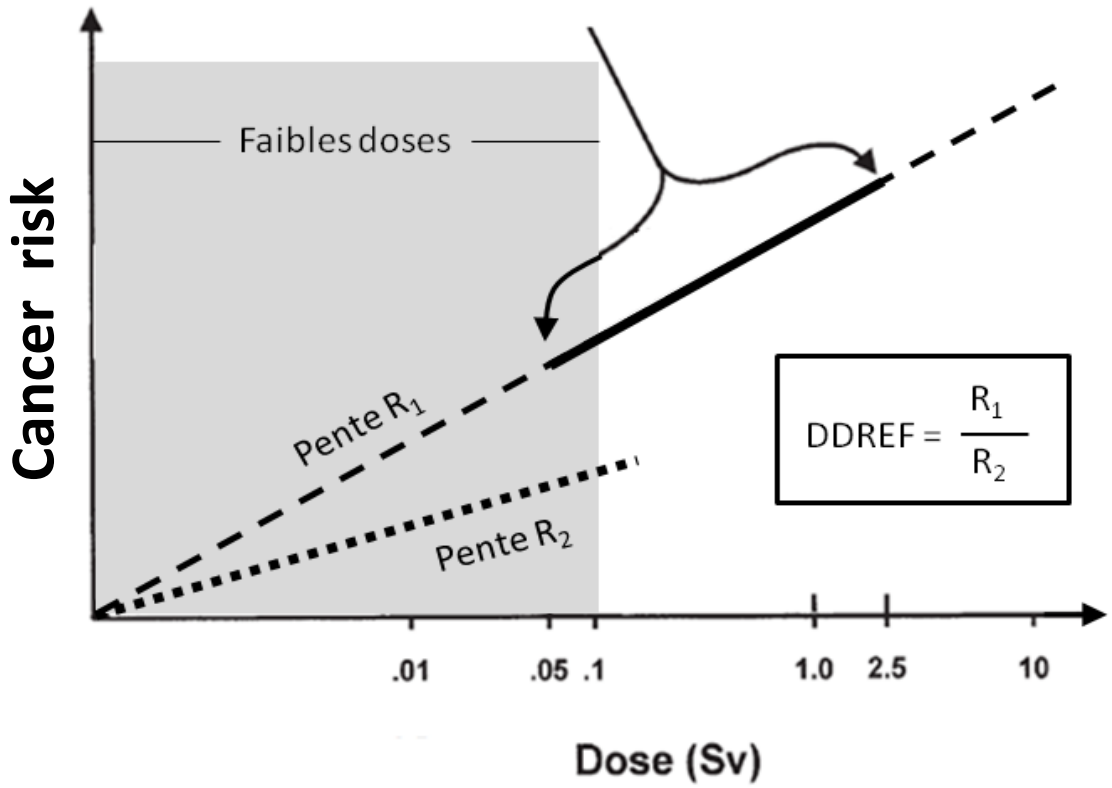
$$= \frac{600}{7'000'000 \times 15'000} \cong 10^{-8}\,\text{km}^{-1}$$

Risk models


The 'Gold Standard'
Nuclear A-bomb survivors (>80 000)
Nuclear power plant workers (>400 000)
Patients with medical exposures (>800 000)
Cancer risk
1%
Low-dose extrapolations
Baseline risk
Linear model
Hormesis model
Supra-linear model
50
100
150
200
Dose (mSv)

Linear no-threshold model (LNT)

Hiroshima & Nagasaki survivors



DDREF : dose and dose-rate effectiveness factor

Q = $DDREF^{-1}$: excess factor for relative risk-per-dose values for cancer

Cancer induction by irradiation

Epidemiological basis:

- Survivors of Hiroshima & Nagasaki:

  Of the order of 1 Sv (acute irradiation)

  86'572 survivors

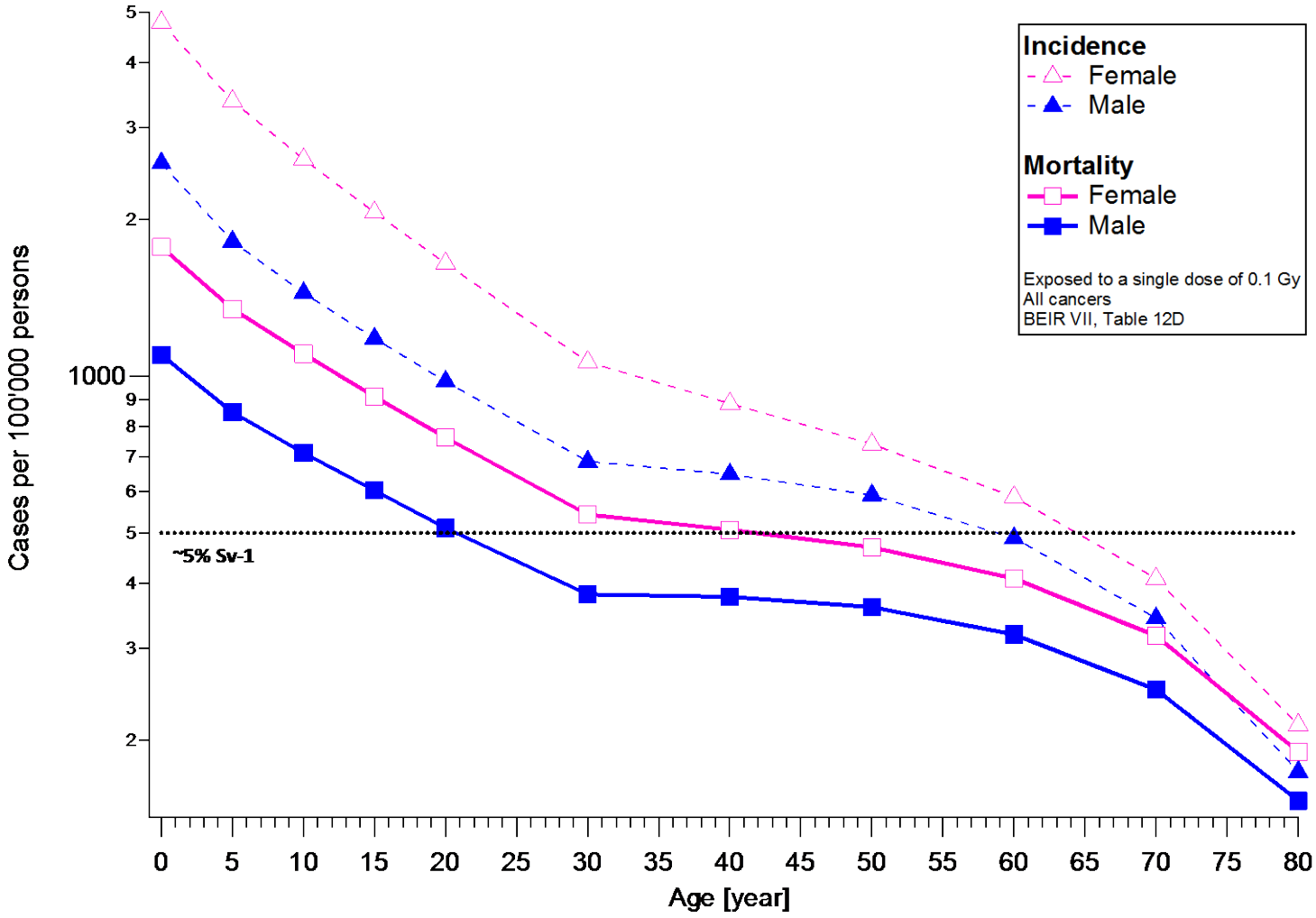
- Workers exposed to radiation:

  Of the order of 0.1 Sv (chronic irradiation)

  95'673 people

⇨ **Risk coefficient: 5% Sv^{-1}**

Probability of developing cancer after **whole-body irradiation** with an absorbed dose of **100 mGy**



Induction of hereditary effects

Base:

- Animal experimentation

Effect:

- Non-specific malformation

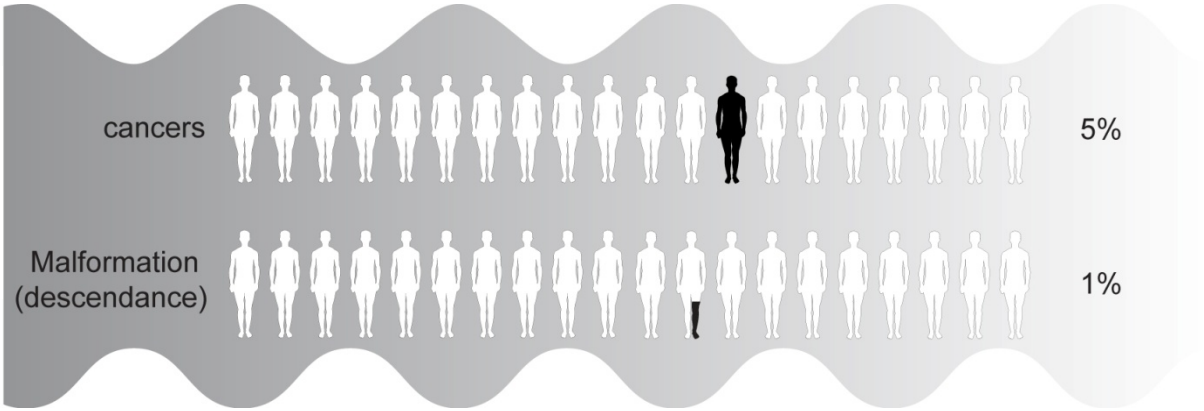
Doubling dose:

- 1 Sv

Risk coefficient: 1% Sv^{-1}

Stochastic effects and risk

1 Sv



	Risk coefficient per mSv
• Cancers • hereditary effects	5 out of 100’000 1 out of 100’000

Stochastic effects and risk

	Detriment (10^{-2} Sv^{-1})			
Exposed population	Fatal cancer	Non-fatal cancer	Serious genetic effects	Total
Adult workers	4.0	0.8	0.8	5.6
Overall population	5.0	1.0	1.3	7.3

Comparison of risks

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

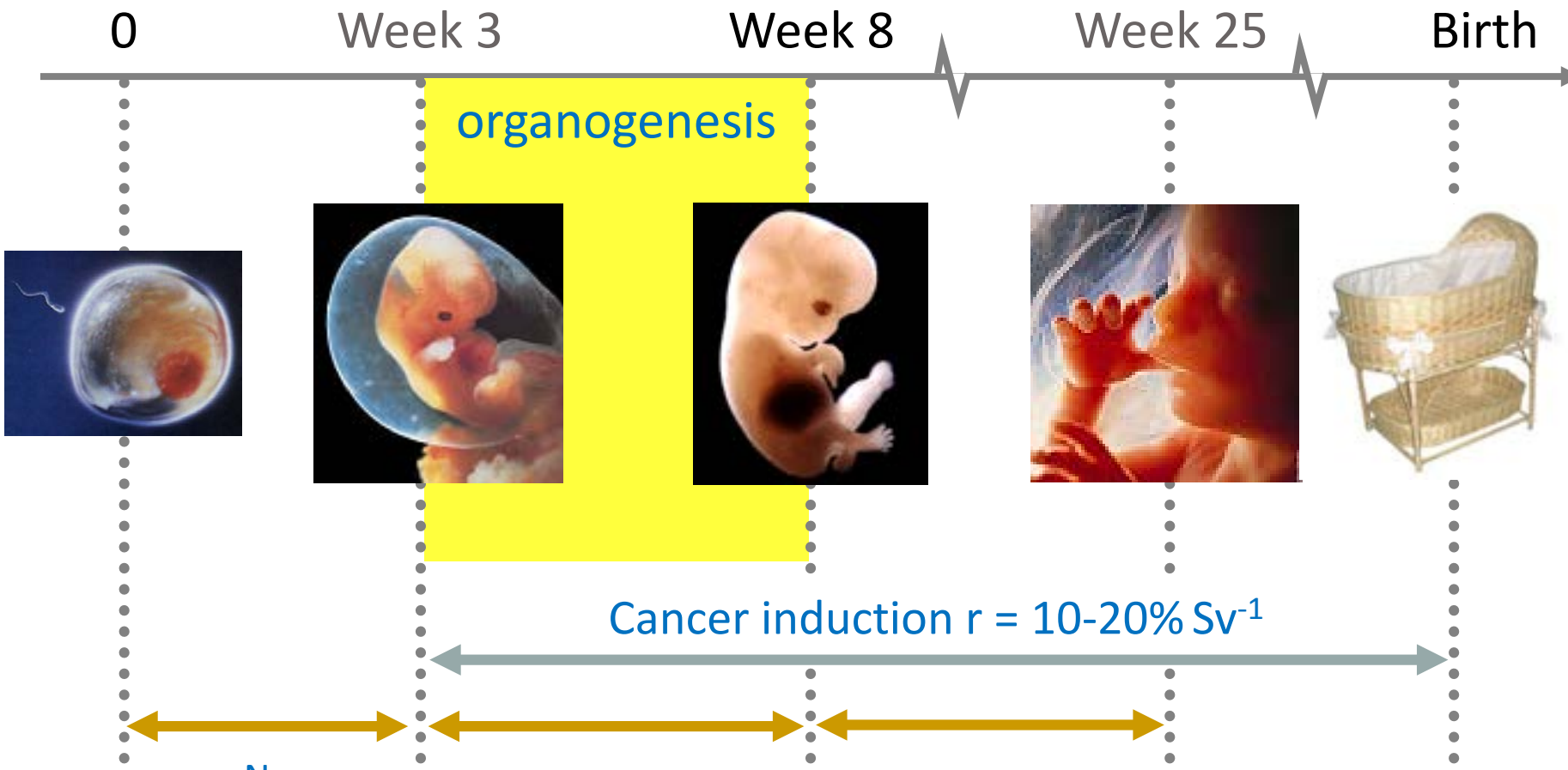
Professional categories	Risk	Non-professional categories	Risk
Lumberjacks and wood transporters	6000	Smokers	4100
Aerial electric line workers	1550	Windsurfing	1800
Roofers	650	Scuba diving	450
Aerial service (crew)	540	Motorcyclists (20 – 24 years)	420
Explosive factory employees	380	Automobile drivers (20 – 24 years)	330
CFF employees	300	Mountain climbers	300
Truckers	240	Falls	230
Coal miners (in GB)	200		
Farming accidents	100	Walkers	29
Domestic accidents	70	Drowning	12.5
Chemical employees (accidents)	51	Death by fire	2.7
Chemical employees (illness)	40	Food poisoning	1.2
Technical office employees	37		
Watchmakers, jewelers	9		

Comparison of risks

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

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

In-utero radiation exposure



Effects other than cancer

- Heart conditions
- Brain attacks
- Digestive and respiratory disorders

The ICRP recommends 100 mSv as threshold for deterministic effect)

How to quantify and combine all these risks?

Concept of detriment

- Detriment is used to describe the '**total harm**' experienced by exposing a population (and their descendant) to ionising radiation
- **Deterministic effects are not considered**

- ICRP: sum of all the risks that exposure to ionising radiation might produce (e.g. probability of fatal and non-fatal cancer induction, years of life lost, ...):
  - **Probability** of incidence
  - **Severity** of effects

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

Concept of detriment

Vest changes the probability of having an accident

Helmet changes the severity of an accident

Detriment = probability x severity

Relatively easy to determine

Years of lost life

Nominal coefficients of risk

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.

Effective dose E

The relative contribution of the organs to the total detriment makes it possible to determine the tissue weighting factors : w_T

$$E = \sum_T w_T \, H_T = [Sv]$$

Tissue	Tissue weighting factor wT	ΣwT
Bone-marrow (red), colon, lung, stomach, breast, remaining tissues(*)	0.12	0.72
Gonads	0.08	0.08
Bladder, oesophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.0

(*) Remaining tissues: Adrenals, extrathoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (♂), small intestine, spleen, thymus, uterus/cervix (♀).

Source: ICRP 103

Overall detriment

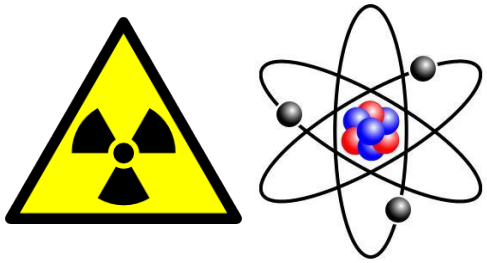
Detriment-adjusted stochastic risk (10^{-2} Sv^{-1})

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

Source: ICRP 103

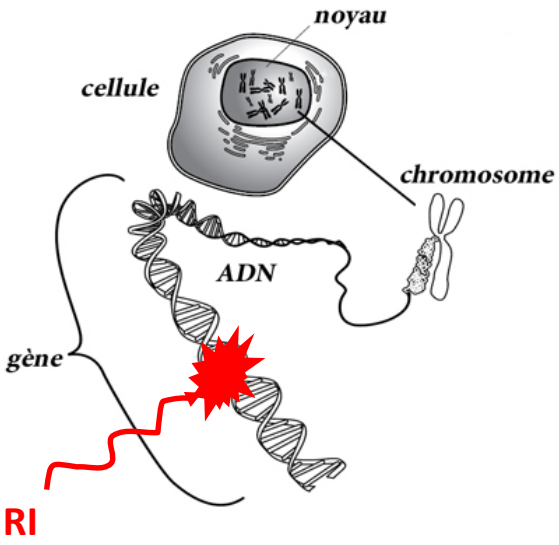
Summary: effects of radiation i

Ionizing radiation



1. **EM-waves**
   - X-rays
   - γ-rays
2. **Particles**
   - β particles
   - α particles
   - neutrons
   - protons
   - …

DNA lesions



Ionisation of atoms and molecules in the cell

No repairing

- Cell death
- **Tissue reactions:**
  - Burns, cataract, sterility, death, …

Faulty repairing

- Lesions and non-lethal mutations
- **Stochastic effects:**
  - Cancer
  - Hereditary anomaly

Repair

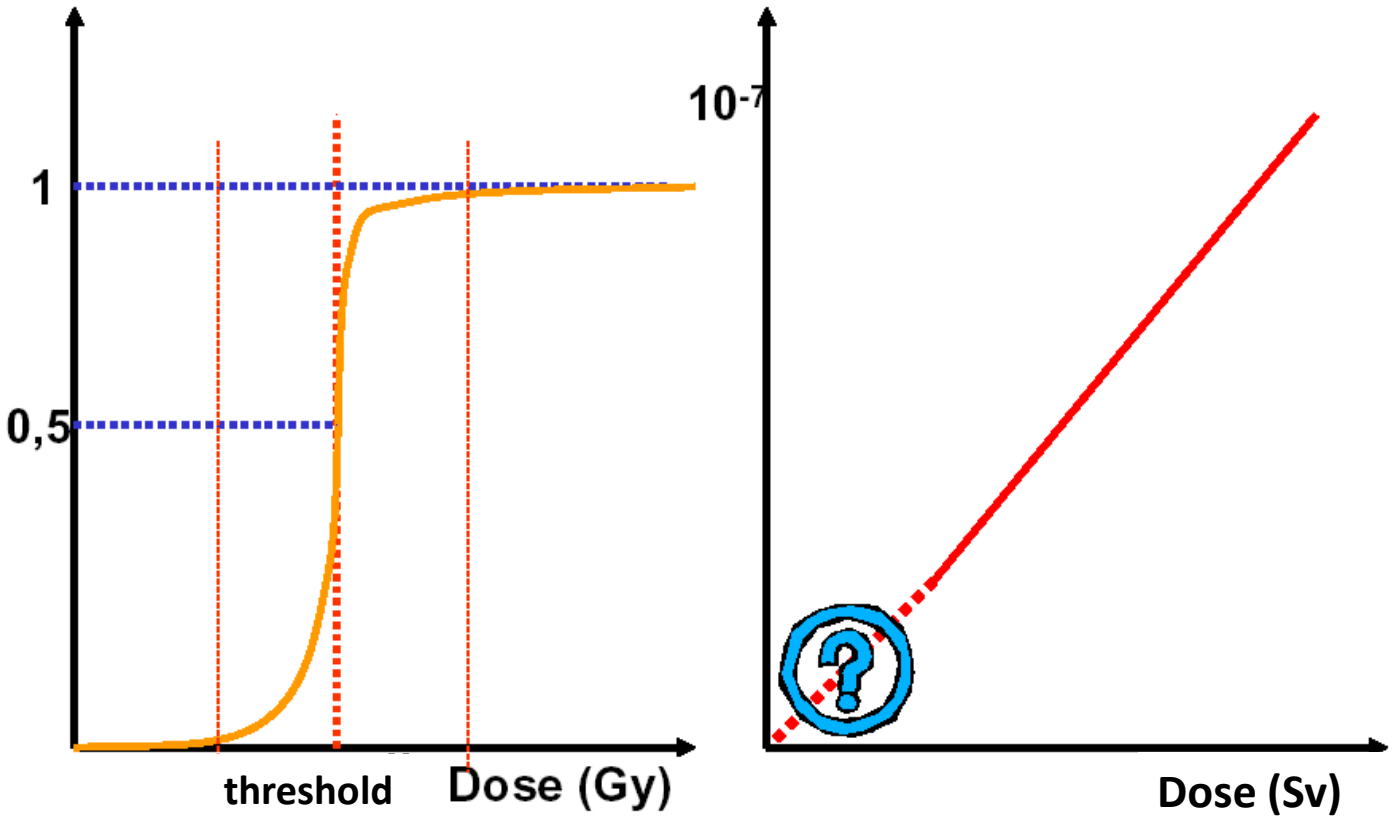
- Cell survival
- No effect

Summary: effects of radiation ii

Tissue reactions

Deterministic effects

Stochastic effects



Course objectives

- Be able to describe the **sequence of radiation effects** on organic matter
- Describe the **biological effects** of ionizing radiation
- Explain **deterministic** (tissue based) and **stochastic** effects
- Evaluate the effects expected following either **external** or **internal** exposure in a given situation