The biological effects of ionizing radiation

by Marilena Streit-Bianchi

CERN Academic Training Lectures

27th, 28th and 29th May 2008

Dedicated to:

M. Quintiliani **and** **A.H. Sullivan**

The biological effects of ionizing radiation

First lecture

- - Ionizing radiations and radiations units
- - Exposure to natural background radiation
- - Exposures by medical usage of radiation
- - Biological effects (cellular damage, genomic instability, bystander effects and adaptive response, dose response as function of radiation quality, dose fractionation and dose rates effects).

Second lecture

- - Biological effects (some particular effects, tissue reactions: skin, intestine, blood, testis, ovary, fetus. Hereditary effects. Lethal doses. Stochastic effects)
- - Health effects of ionizing radiations on short and long terms, from high and low doses (Hiroshima and Nagasaki).

Third lecture

- - Health effects of ionizing radiations on short and long terms, from high and low doses (Chernobyl, radiologists, radon exposures, nuclear workers.)
- - Risk estimate from epidemiological data
- - Radiation limits and ICRP recommendation
- - Future research on radiation effects.

These lectures will review data on the effects of radiation with special emphasis on the health effects from high and low doses exposures.

Radiation risks for long and short term effects as assessed from Hiroshima and Nagasaki, Chernobyl as well as others occupational exposures will be also presented.

Latest ICRP recommendations will be discussed.

A Physical Quantity

The *absorbed dose* in a point is defined as the ratio of the mean energy imparted by ionizing radiation to the matter in a volume element and the mass of the matter in this volume element:

$$D = \frac{d\bar{\varepsilon}}{dm}$$

The unit of absorbed dose is the Gray:

1 Gy = 1 J/kg

Protection quantities

Mean absorbed dose in an organ or tissue:

$$D_T = \frac{1}{m_T} \int_{m_T} D dm$$

Equivalent dose in an organ or tissue:

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

- $D_{T,R}$ is the absorbed dose averaged over the organ or tissue T due to radiation R
- w_R is the radiation weighting factor for radiation R

The unit for the equivalent dose is the Sievert (Sv)

Protection quantities

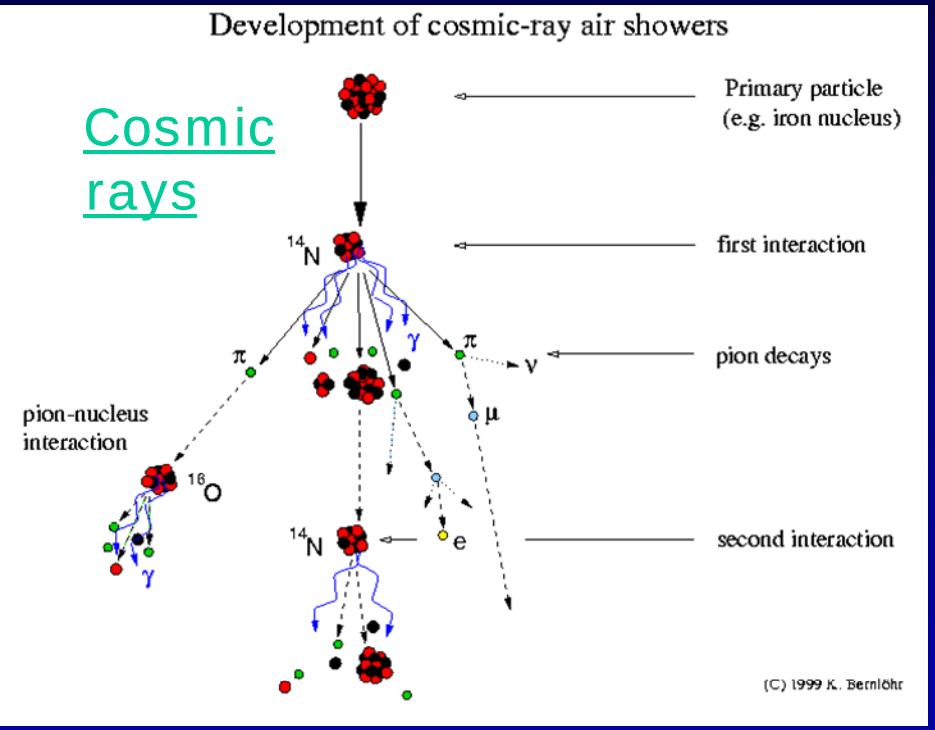
In order to take into account the not uniform irradiation of the human body and the different susceptibility to radiation of different organs and tissues, the ICRP defined the concept of effective dose:

$$E = \sum_T w_T H_T$$

- H_T is the equivalent dose in tissue or organ T
- w_T is the weighting factor for tissue T

The unit for the equivalent dose is also the Sievert

Natural sources of radiation



Cosmic rays

Terrestrial (radionuclides present in the earth's crust, U, Th, Ra, Rn ...)

Human body (radionuclides present in our body, mainly ^{40}K)

Cosmogenic radioactive nuclides (^{14}C, ^{7}Be, ^{3}H)

Doses depend from latitudes and altitudes

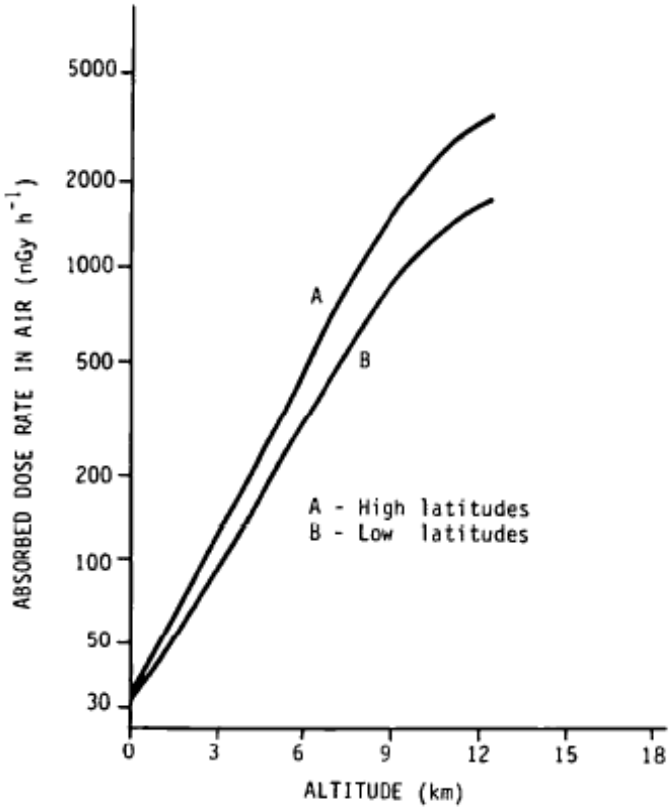


Figure I. Absorbed dose rates in air as a function of altitude and geomagnetic latitude. [H10]

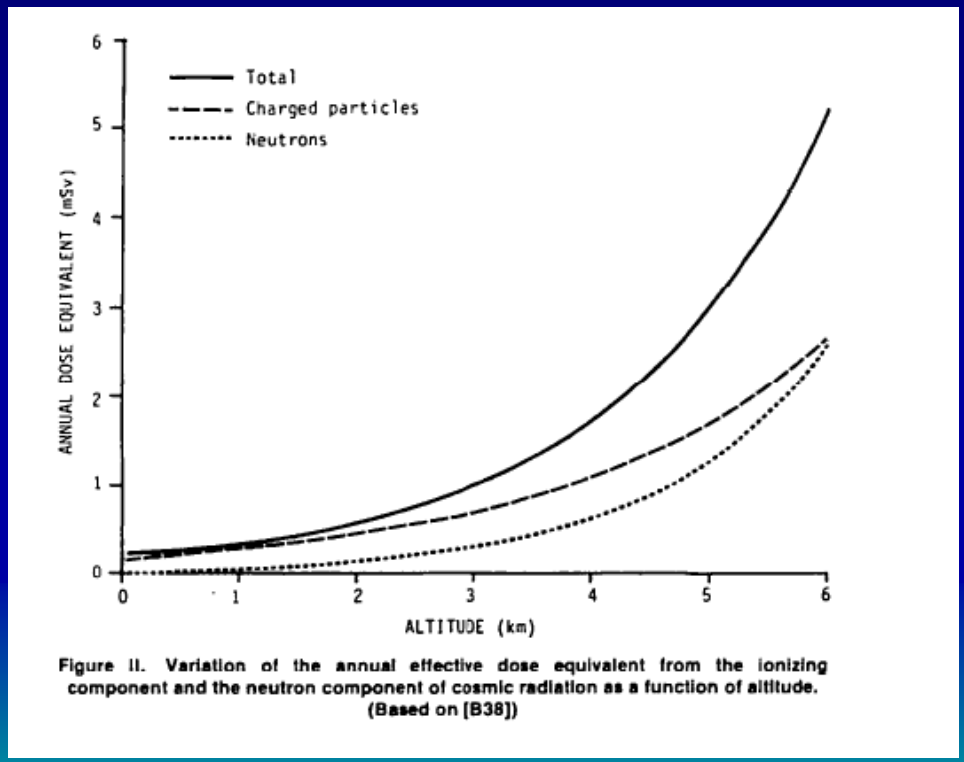


Figure II. Variation of the annual effective dose equivalent from the ionizing component and the neutron component of cosmic radiation as a function of altitude. (Based on [B38])

From UNSCEAR 1988

World wide exposure from natural sources

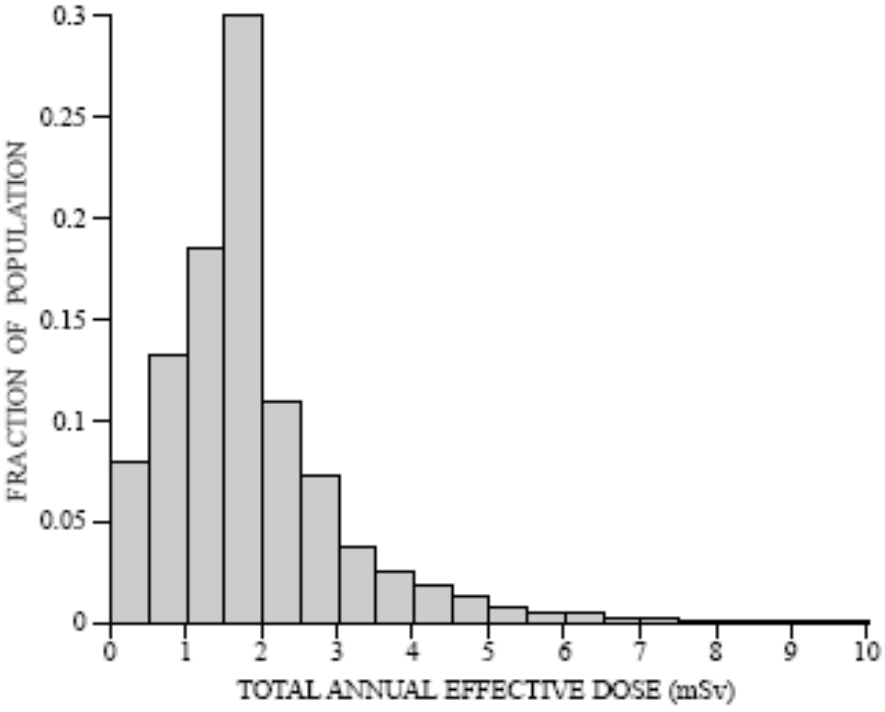


Figure XV. Distribution of population of fifteen countries with respect to total annual effective dose.

From UNSCEAR 2000

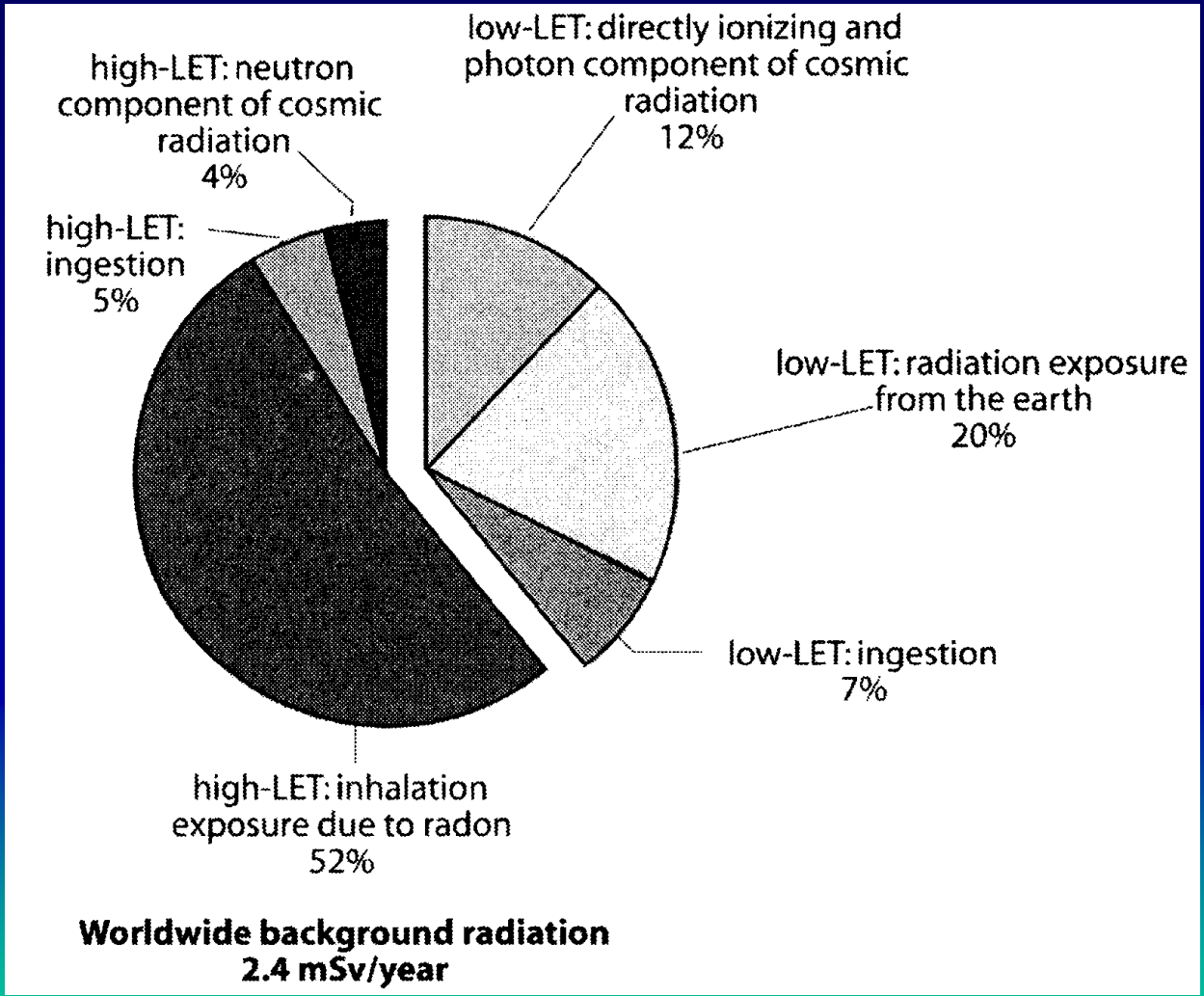
Average worldwide exposure to natural sources

Source of exposure	*Annual effective dose (mSv)*	
	Average	*Typical range*
Cosmic radiation		
Directly ionizing and photon component	0.28 (0.30) [a]	
Neutron component	0.10 (0.08)	
Cosmogenic radionuclides	0.01 (0.01)	
Total cosmic and cosmogenic	0.39	0.3–1.0 [b]
External terrestrial radiation		
Outdoors	0.07 (0.07)	
Indoors	0.41 (0.39)	
Total external terrestrial radiation	0.48	0.3–0.6 [c]
Inhalation exposure		
Uranium and thorium series	0.006 (0.01)	
Radon (^{222}Rn)	1.15 (1.2)	
Thoron (^{220}Rn)	0.10 (0.07)	
Total inhalation exposure	1.26	0.2–10 [d]
Ingestion exposure		
^{40}K	0.17 (0.17)	
Uranium and thorium series	0.12 (0.06)	
Total ingestion exposure	0.29	0.2–0.8 [e]
Total	2.4	1–10

a Result of previous assessment [U3] in parentheses.
b Range from sea level to high ground elevation.
c Depending on radionuclide composition of soil and building materials.
d Depending on indoor accumulation of radon gas.
e Depending on radionuclide composition of foods and drinking water.

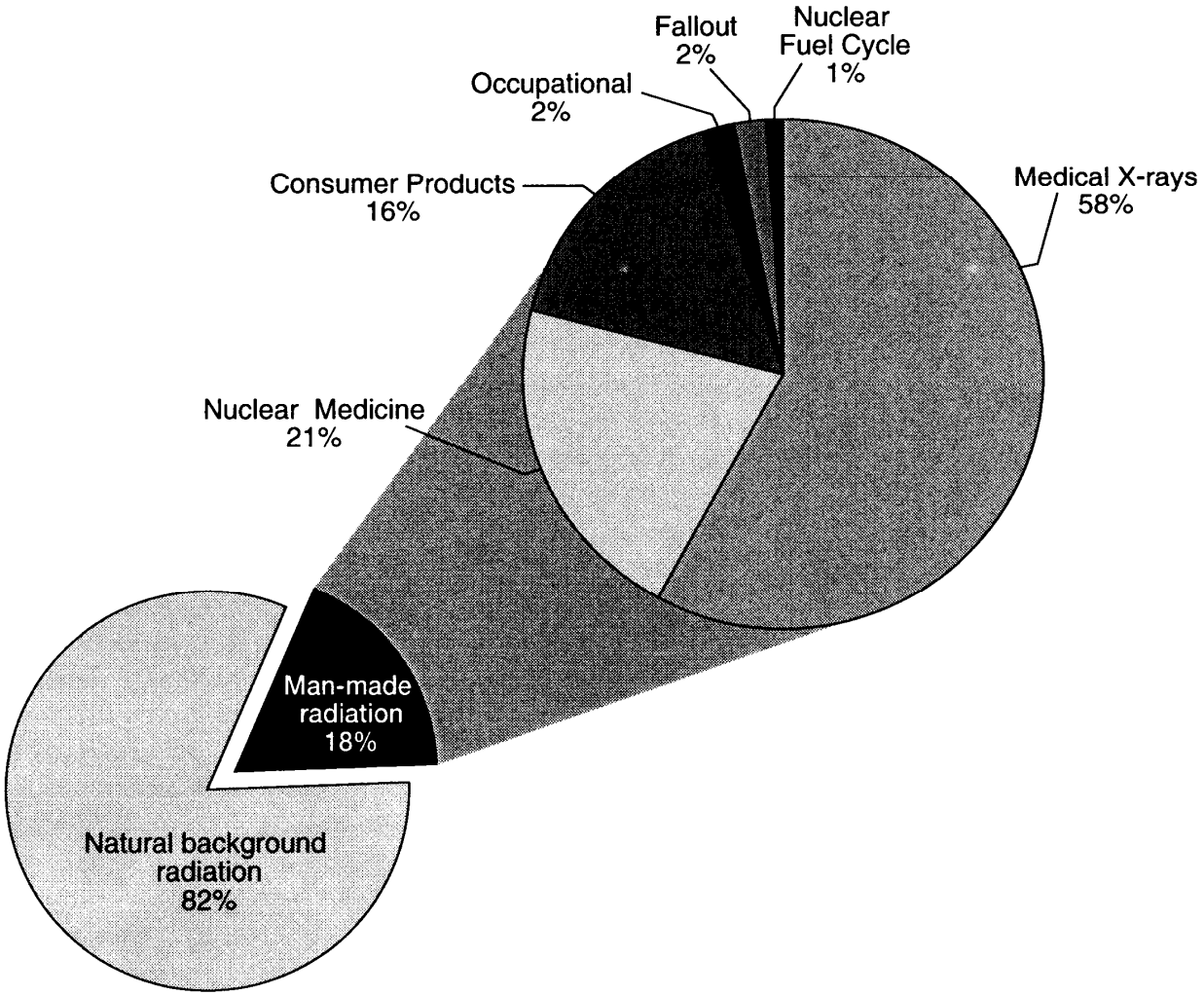
From UNSCEAR 2000

Background radiation



(From BEIR VII, 2006)

Natural and man made radiations



(From BEIR VII, 2006)

Areas of high natural radiation background

Country	*Area*	*Characteristics of area*	*Approximate population*	*Absorbed dose rate in air [a] (nGy h^{-1})*	*Ref.*
Brazil	Guarapari	Monazite sands; coastal areas	73 000	90–170 (streets) 90–90 000 (beaches)	[P4, V5]
	Mineas Gerais and Goias			110–1 300	[A17, P4]
	Pocos de Caldas Araxá	Volcanic intrusives	350	340 average 2 800 average	[V5]
China	Yangjiang Quangdong	Monazite particles	80 000	370 average	[W14]
Egypt	Nile delta	Monazite sands		20–400	[E3]
France	Central region Southwest	Granitic, schistous, sandstone area Uranium minerals	7 000 000	20–400 10–10 000	[J3] [D10]
India	Kerala and Madras	Monazite sands, coastal areas 200 km long, 0.5 km wide	100 000	200–4 000 1 800 average	[S19, S20]
	Ganges delta			260–440	[M13]
Iran (Islamic Rep. of)	Ramsar Mahallat	Spring waters	2 000	70–17 000 800–4 000	[S21] [S58]
Italy	Lazio Campania Orvieto town South Toscana	Volcanic soil	5 100 000 5 600 000 21 000 ~100 000	180 average 200 average 560 average 150–200	[C12] [C12] [C20] [B21]
Niue Island	Pacific	Volcanic soil	4 500	1 100 maximum	[M14]
Switzerland	Tessin, Alps, Jura	Gneiss, verucano, ^{226}Ra in karst soils	300 000	100–200	[S51]

a Includes cosmic and terrestrial radiation.

From UNSCEAR 2000

Classes of HNBRs

VERY HIGH DOSE AREA

Potential Effective Dose > 50 mSv/y

HIGH DOSE AREA

20 mSv/y < Potential Effective Dose ≤ 50 mSv/y

MEDIUM DOSE AREA

5 mSv/y<Potential Effective Dose≤ 20 mSv/y;present ICRP work limit

LOW DOSE AREA

Potential Effective Dose ≤ 5 mSv/y: two times natural average global effective dose of UNSCEAR, or former ICRP Public Dose Limit

By courtesy of J.H. Hendry

Summary of characteristics of HNBRs in different countries

	Brazil	China	India	Iran
Size of population in "radiation area"	Poços 6,000 Araxá 1,300	Cohort with external dose estimates 125,059	359,619 interviewed 76,942 homes measured	Ramsar total 60-70,000 Talesh Mahalleh 1,000
Source of exposures	Monazite sands, Volcanic extrusions Th-232, U-238	Th-232, U-238	Monazite sands: Th-232, ...	Hot springs: Ra^{226} and decay products
Reported dose distribution /year - mean (range)				
• external	1.3 Poços 1.2-6.1 Araxá	2.1 (1-3)	Out. 2.1 (0.5-76)	6 (0.6-135)
• internal	5.9 Pocos NA Araxá	4.3	Ins. 1.8 (0.5-54) NA	(2.4-71)

Note: doses are expressed as effective dose, in mSv – India: medians, not mean; Brazil internal+external

From Cardis E. 2004

Difficulties to assess risk from HBNR studies

- Cofounders
- Ecological fallacy (BEIR VII « Two populations differ in many factors other than that being evaluated, and one or more of these may be underlying reason for any difference noted in their morbidity or mortality experience (Lilienfeld and Stolley 1994))
- High life time occurrence of cancers from all causes.

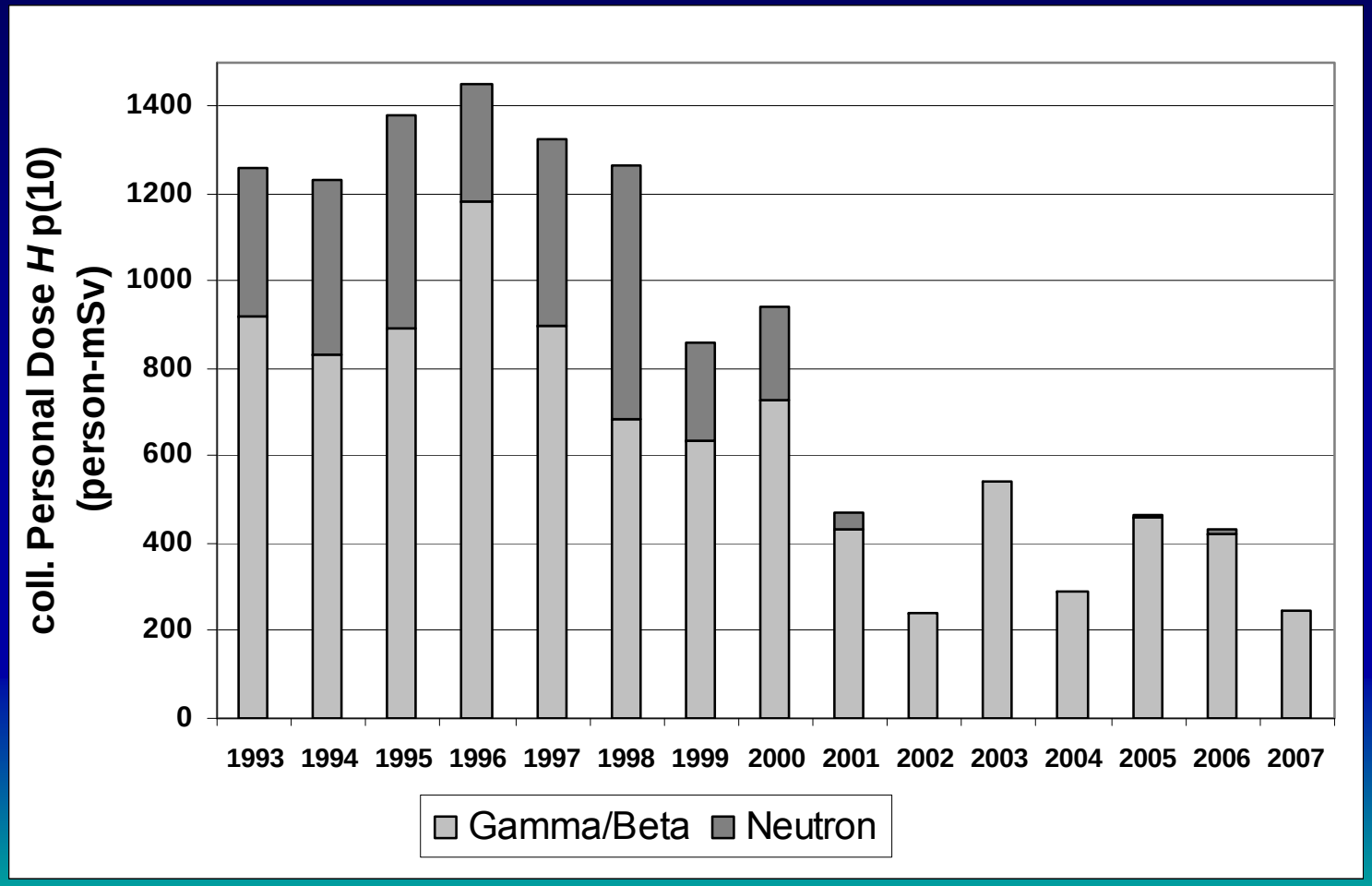
Professional exposures
Average Equivalent Dose (mSv)

- Air travel crew (250000 person) **3.02mSv / y**
- Nuclear workers 600000 (of which 407391 nuclear industry workers) overall average cumulative dose

19.4 mSv

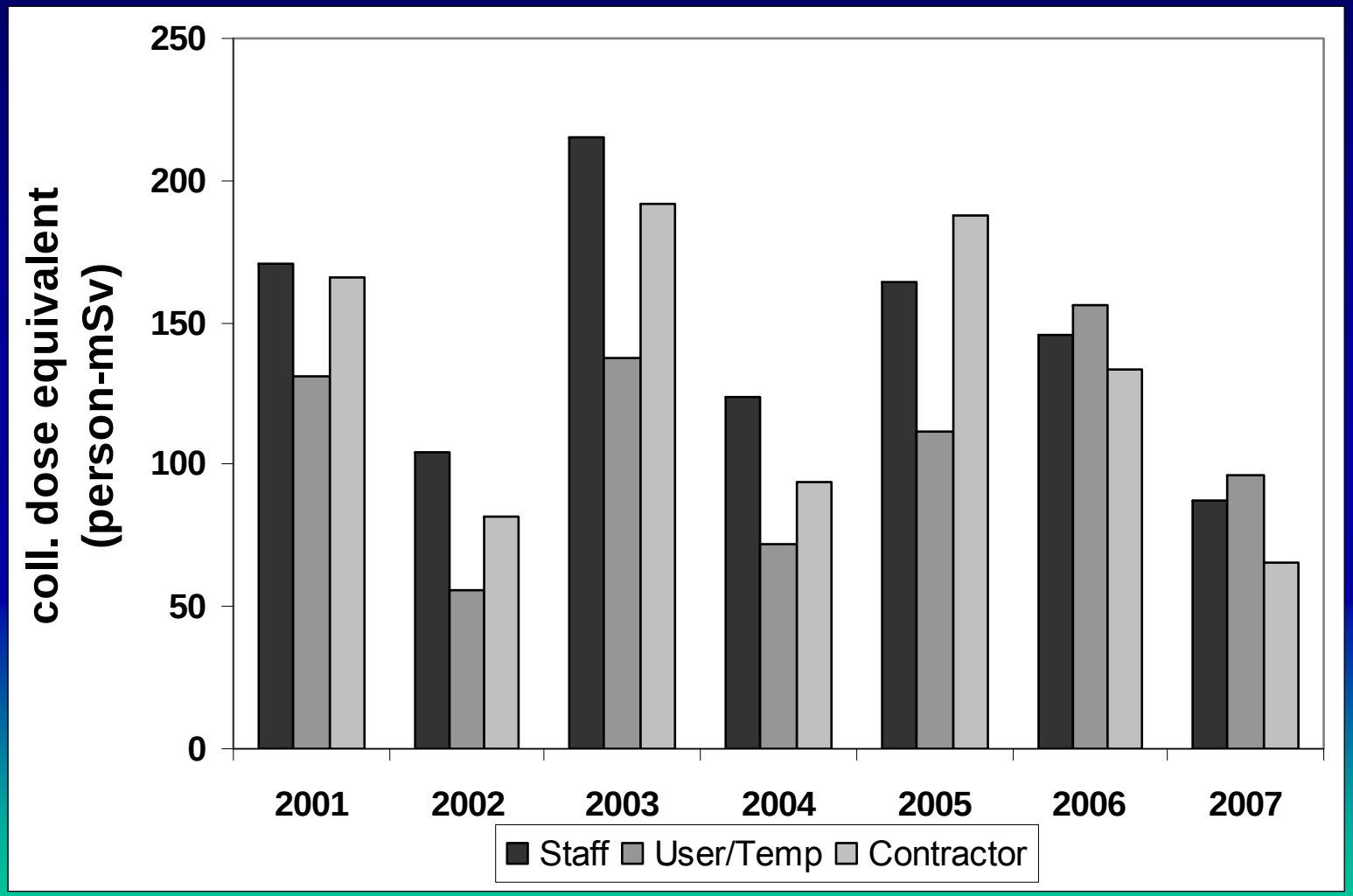
90% < 50 mSV, 0.1% >500 mSv

Collective Personal Dose at CERN



by courtesy of T. Otto, RP group

Personal Dose by Professional Category at CERN



Exposures from medical examinations

	Type of examinations	Equivalent dose mSv
Conventional X rays	Chest (AP – Lat.)	0.02 - 0.04
	Skull (AP – Lat.)	0.03 - 0.01
	Lumbar spine (AP)	0.7
	Mammogram (4 views)	0.7
	Dental (Lat.)	0.02
	Dental (Panoramic)	0.09
	Abdomen	1.2
CT	Head	2.0
	Chest	8.0
	Abdomen	10.0
	Pelvis	10.0
Interventional procedures	Angioplasty (heart study)	7.5 - 57.0
	Coronary angiogram	4.6 - 15.8
	Intravenous pyelogram (kidney 6 films)	2.5

from: Health Physics Society 2006

Interaction of radiations

Marilena Streit-Bianchi

Secondary electrons energy transfer

- Ionization of water molecules H_2O^*, $H_2O^{\cdot+}$,e^- reacts rapidly with the formation of highly reactive ***HO·*** ***and H·*** radicals and e^-_{aq} .
Water radiolisis produces very reactive radicals (HO· and H·)

- direct ionization of cellular macromolecules

- Ionization (> 13 eV)
- excitation (> 7.4 eV)
- thermal transfer

Water molecules get in an excited state in a timescale of **10^{-16} seconds** many reactions occurs in the track of a charged particles and the chemical development of the track is **over by 10^{-6} sec.**

The reaction radii is a measure of the reactivity of the created chemical species and is 2.4 Å for OH to 0.3 Å for H_3O

Are different particles producing different species?

- Electrons, protons and alpha particles produces the **same** chemical species but **different** spatial patterns of energy deposition

Damage occurs in clusters

- Main tracks, secondary electrons and secondary reactive radical species form clusters of chemical alterations giving rise to DNA single strand breaks (SSB) and DNA double strand breaks (DSB). The frequency and the complexity of the clustered damage depends upon the linear energy transfer (LET*) of the radiation. **These clusters arise very infrequently from spontaneous oxidative processes in cells.**

*LET= Mean energy lost by charged particles in electronic collisions per unit track length.

Direct action, Indirect actions and Oxygen effect

- Energy might also be deposited directly in the biological molecule, this will produce radicals in the molecule itself and these radicals can reacts producing damage.
- For High LET particles direct actions is the predominant mechanism for radiation damage
- 60 to 70% of the damage from low LET radiation is caused by $HO^{\cdot}$ radicals.
- Damage get fixed by Oxygen (when oxygen reacts with DNA, before repair has occurred, the damage becomes unrepairable by chemical restitution)

Factors influencing the response to radiation

- Physical:
  - type of radiation [x, γ, n, α]
  - type of exposure
    - internal [by inhalation or ingestion]
    - external
  - local or total body irradiation
  - absorbed dose
  - spatial distribution of the absorbed dose (track structure)
  - time distribution of the absorbed dose

- Biological:
  - intrinsic characteristics of the irradiated biological system: radiation sensitivity (or resistance), number of cells exposed to radiation, kinetics/metabolism, repair capability
  - biological environment: oxygenation, nutrition, etc.

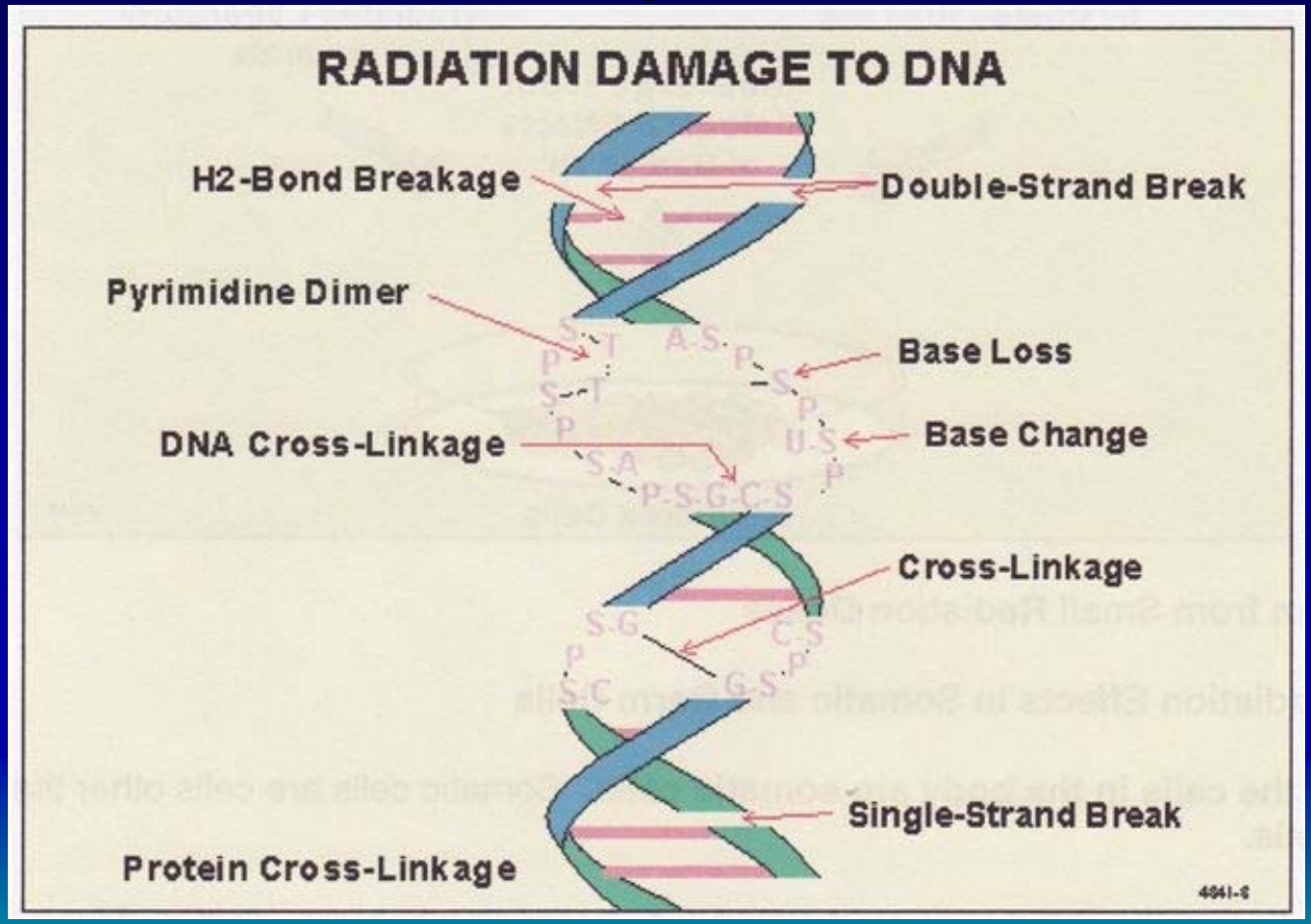
A way to protect from injuries

- Cell cycle checkpoints
- Delaying the passage of cells through their reproductive cycles, this gives time to repair the damage
- Apoptotic death (reduces the frequency of viable cells carrying mutations). This process occurs at doses as low as a few mGy.
- Death of not repaired cells

The damage is repaired or gets fixed

- Biochemical pathways operate to recognize and signal the presence of DNA damage
- Error-prone repair of chemically complex DNA double-strand lesions leads to the induction of chromosome aberrations, gene mutation, and later cell killing
- Direct DNA damage is observable within the first or second post-irradiation cell cycles
- The frequency of genetic changes produced by irradiation is higher than expected from direct DNA damage
- At very low doses < ten of mGy and dose-rates intracellular signalling and repair systems are not activated (threshold level)

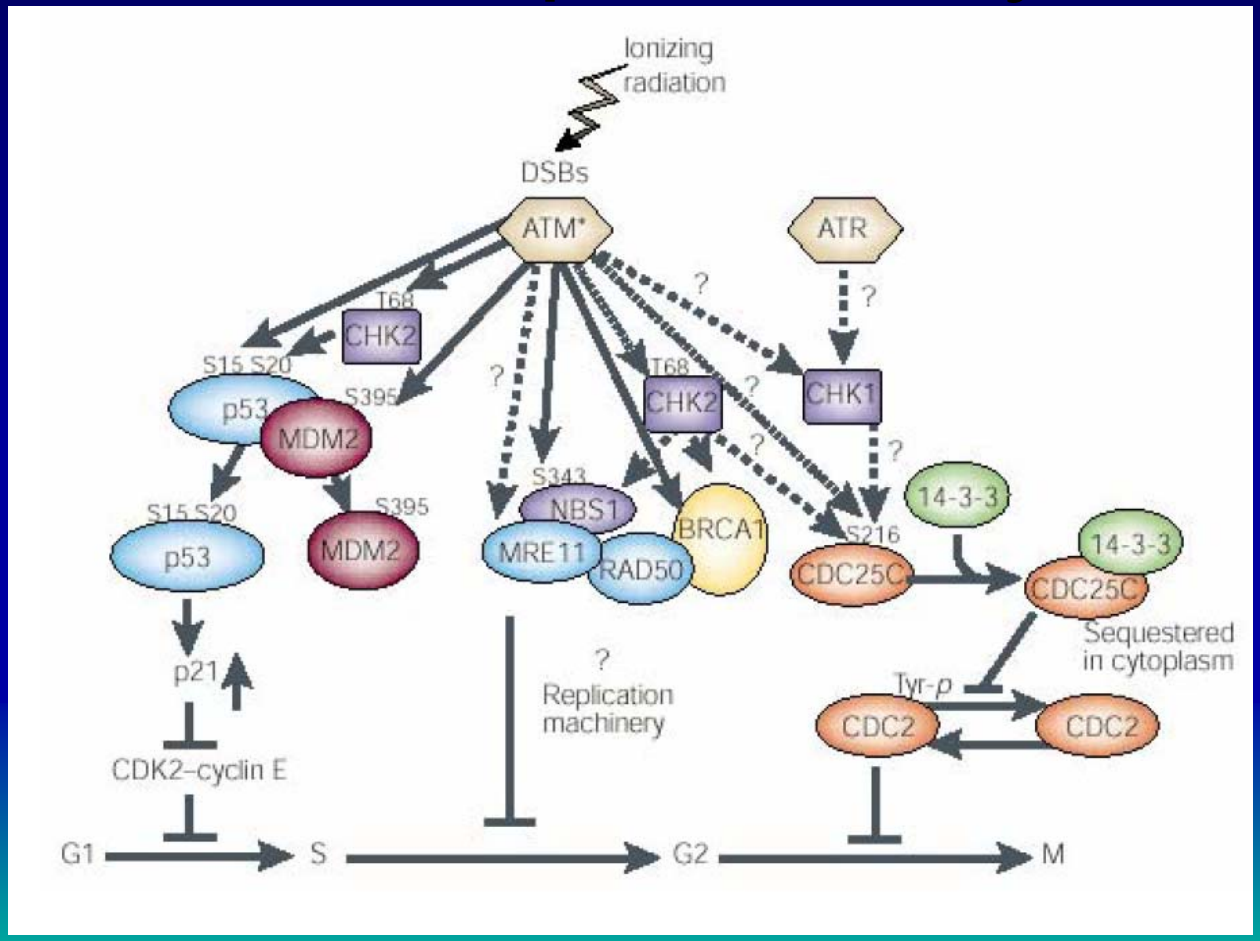
Damage to DNA



From xxxxxx

Strand breaks in DNA may be initiated by low energy electrons

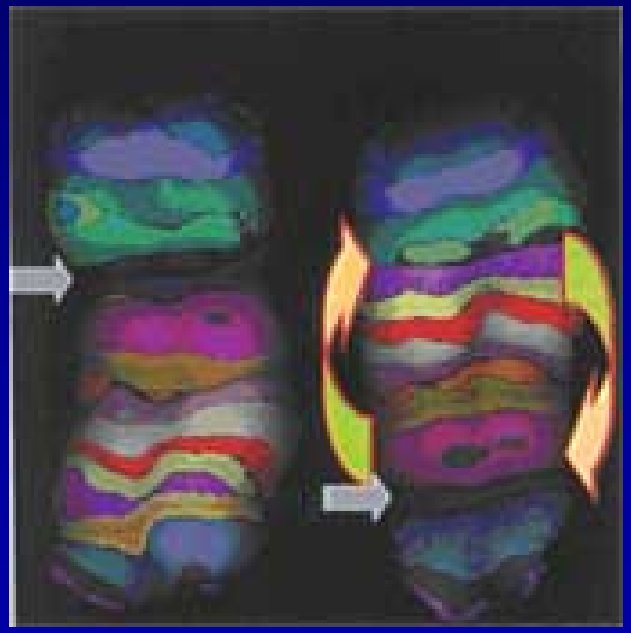
DNA Double Strand Breaks activate numerous proteins kynases



From BEIR VII 2006

The increased p53 protein induce the transcription of p21, inhibit CDK2-cyclin E and cause the arrest in G1

mBAND FISH technique to assess Chromosomal Aberrations



Intrachromosomal aberration in chromosome 2 from peripheral lympocyte from an highly exposed plutonium worker
From Mitchell C.R. et al. 2004

In the FISH technique some or all chromosomes can be stained differently so that any translocations that has occurred due to radiation can be detected. Region specific DNA damage (double and single strand breaks) and site incomplete repair is also made visible. This technique is used to detects the majority of clinically significant chromosome abnormalities

Common Exchange-Type of Chromosome Aberrations

- Within one chromosome:

  Paracentric Inversion: Intra-chromosomal (Intra-arm)

  Interstitial Deletion: Intra-chromosomal (Intra-arm)

  Pericentric Inversion: Intra-chromosomal (Inter-arm)

- Within 2 chromosomes:

  Translocation: Inter-chromosomal

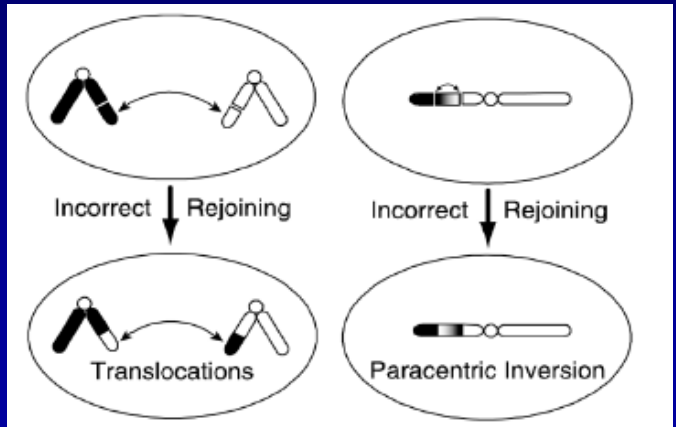


Figure 1. Schematic illustration of the production of inter-chromosomal (left panel) and intra-chromosomal intra-arm aberrations (right panel), in this case for stable aberrations. The H value (see Table 1) is the ratio of the number of induced inter-chromosomal aberrations (translocations or dicentrics) to intra-arm aberrations (paracentric inversions or interstitial deletions).

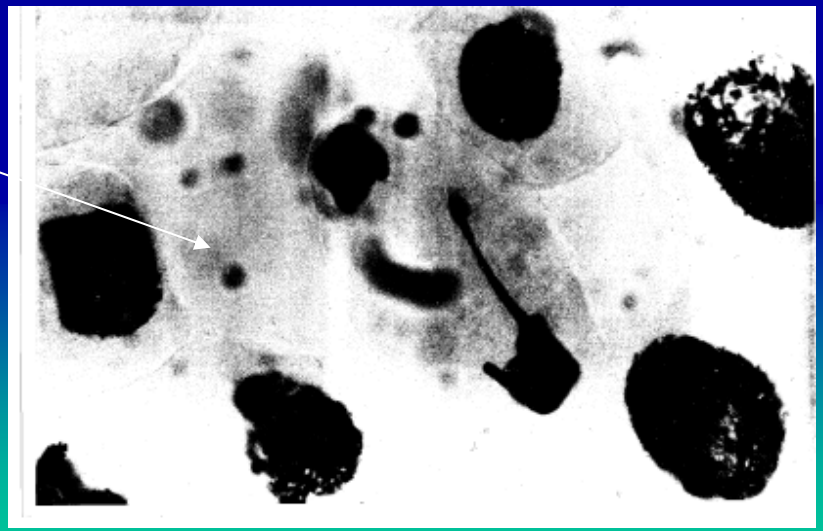
From Brenner D. et al. 2001

http://www.columbia.edu/~djb3/aberrations.html

Chromosome damage visible when cells divide

- Dicentrics, rings and fragments

- Micronuclei



Biochemicals pathways recognise and signal DNA damage, and may lead to:

- Error-prone repair of complex DNA lesions with the induction of mutation, chromosomal aberrations and cell killing
- Error-free repair, this is restricted to the later phases of the cell cycle

From DNA ⟶ to cellular and cancer development effects

1. P53 protein arrests the cell cycle and controls apoptosis (programmed cell death) preventing damaged cells to progress into a proliferation or malignant state.

   - Human tumours show deficiency in apoptotic response.

   - Specific DNA damage by radiation signal apoptosis.

2. Activation of proto-oncogenes by chromosomal translocation
3. Onset of genomic instability (critical event for tumour genesis)
4. Repair of DNA lesions may be error prone

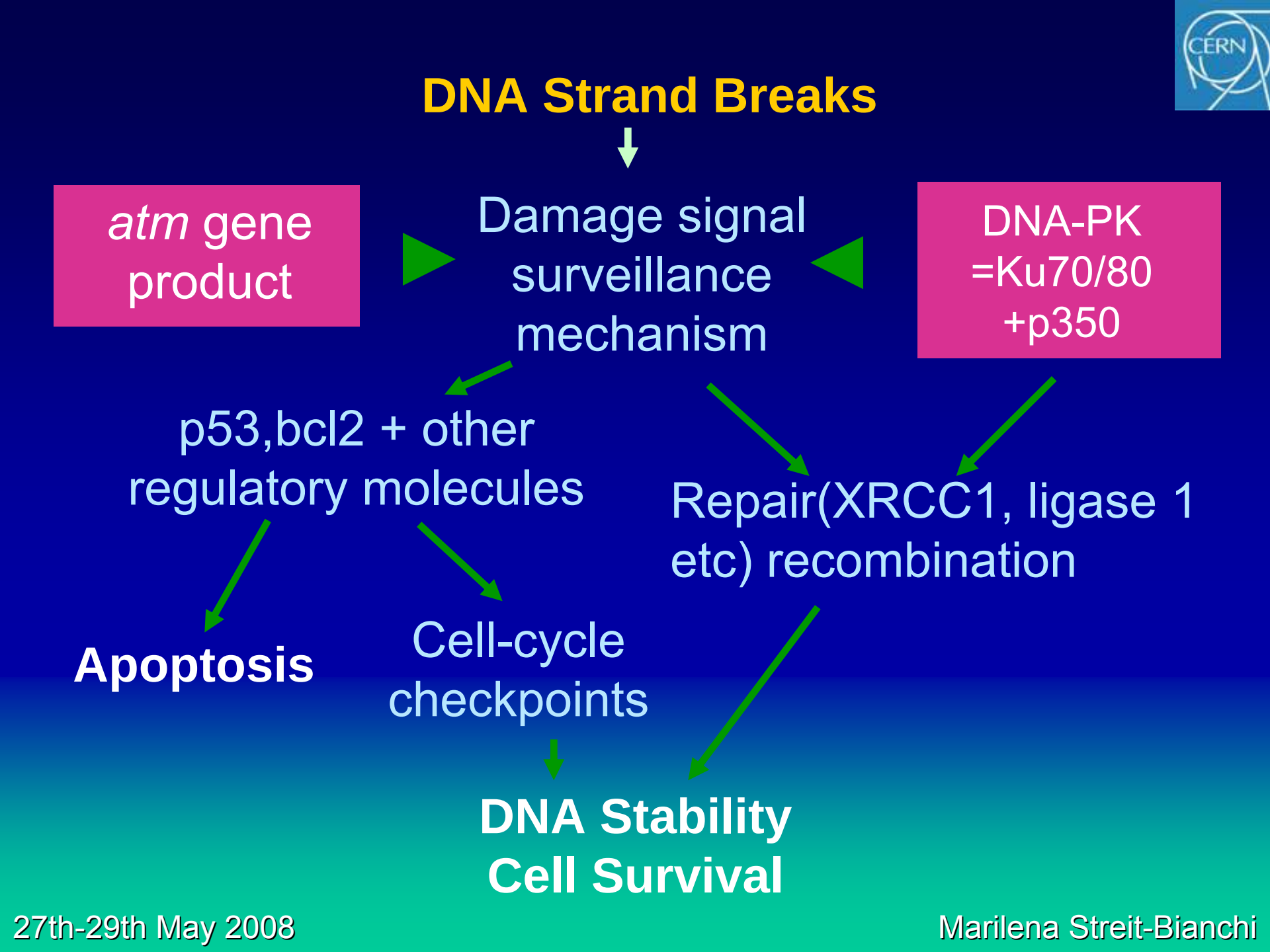
Damage may get repaired

DSBs may be repaired by
a) non-homologous end-joining (NHEJ),
b) single strand annealing or
c) homologous recombination (HR).

- The ATM protein:

- control the rate at which cells grow and divide,
- assists cells in recognizing damaged or broken strands of DNA and
- coordinates DNA repair by activating enzymes that fix the broken strands.

2. DNA-PK kinase activity is involved in DNA double-strand break repair


DNA Strand Breaks
atm gene product
Damage signal surveillance mechanism
DNA-PK =Ku70/80 +p350
p53,bcl2 + other regulatory molecules
Repair(XRCC1, ligase 1 etc) recombination
Apoptosis
Cell-cycle checkpoints
DNA Stability
Cell Survival

Apoptosis in mice intestinal crypts after 600 MeV neutrons irradiations

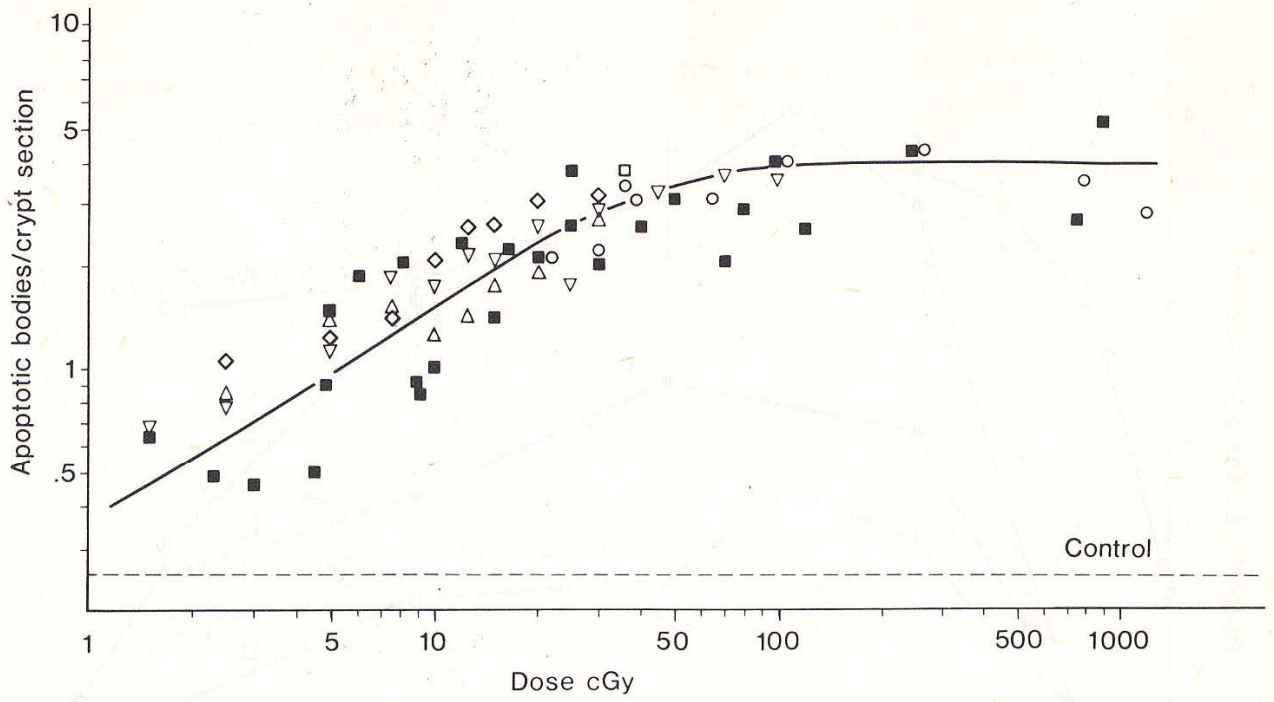
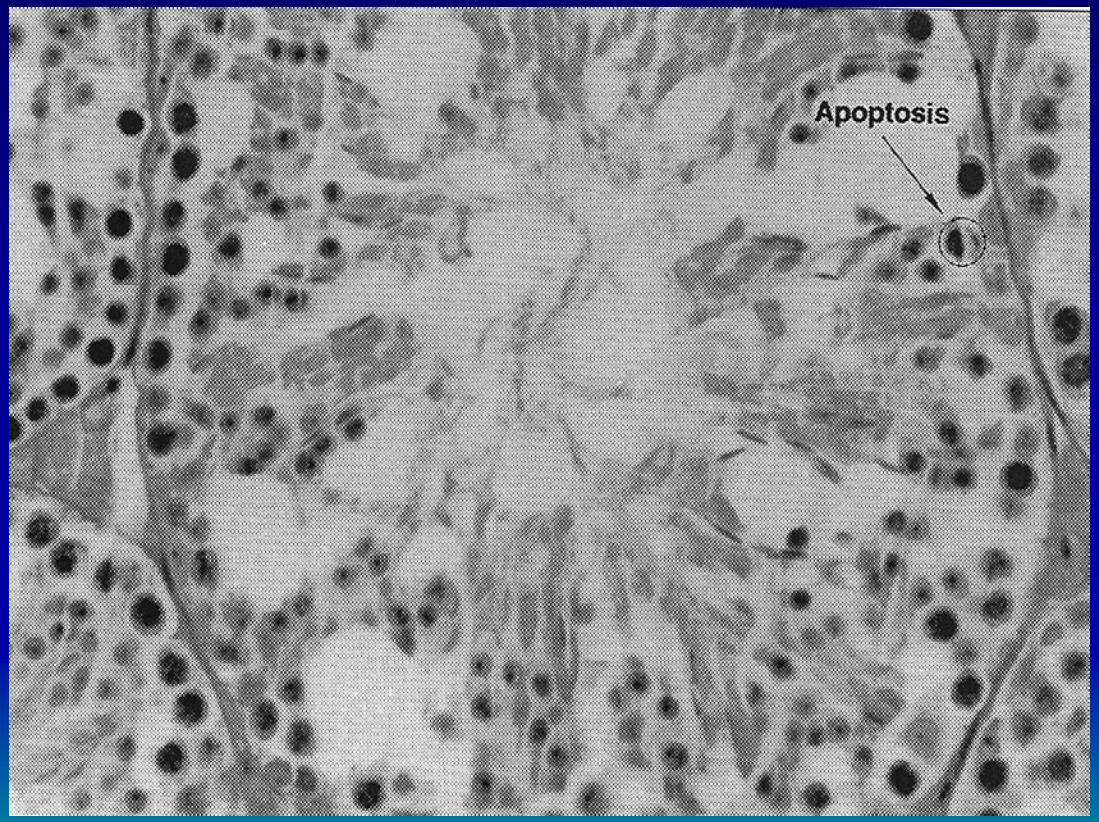


Figure 2. Incidence of apoptotic bodies in crypt sections at 3 hours after various doses of low LET radiation. (○), ^{137}Cs γ-rays at 450 cGy per min (Manchester). (◇), ^{60}Co γ-rays at 82 cGy per min (Manchester). (△), ^{60}Co γ-rays at 0·53 cGy per min (Manchester). (▽), ^{60}Co γ-rays at 0·53 cGy per min (CERN). (□), ^{60}Co γ-rays at 0·27 cGy per min (Manchester). (■), 300 kVp X-rays at 60 cGy per min (Manchester). The curve is based on the exponential line in figure 3.

From Hendry J.H. et al.

Apoptosis in mice germ cells



Perturbation of the

- DNA damage response
- DNA repair and
- apototic process

is linked with tumour genesis

Epigenetic effects of radiations

Post-irradiation cellular responses with genomic change and/or cellular effect without directly induced DNA damage

- They are of 2 types:

  1) Radiation-induced genomic instability observable over many post irradiations cell cycles (i.e. increased frequencies of chromosome aberrations, mutations and apoptosis/cell death). This instability is probably due to persisting oxidative reactions products.

  2) Post-irradiation bystander signaling between cells via intercellular communication or from molecules through the cell culture medium

Bystander effects

- Irradiated cells transmit damage signals to non irradiated cells resulting in

1. **The production of DNA damage (i.e. DSB, loss of nuclear DNA methylation etc.) and**
2. **The alterations in cell fate (i.e. apoptosis, differentiation, senescence or proliferation)**

- *90% of mutations in bystander cells after low doses of α rays are point mutations, whereas in DNA repair deficient cells 80% of the mutants show partial or total gene deletions.*

  Studies carried out using α particles or protons micro beam

Possible reasons for the effect

- Induction of oxidative stress
- Modulation of DNA damage-response pathway
- Release of damaging factors from irradiated cells
- Mobilization of intracellular calcium (culture medium)
- Increase in reactive oxygen species in recipient cells (culture medium)

Others non target effects

- Second neoplastic transformations events with transmissible genetic instability is dose dependent.
- Delayed reproductive failure many generations after irradiations.
- Possible trans-generational effects of radiations due to induction of genomic instability in germ cells.

Cellular adaptive responses

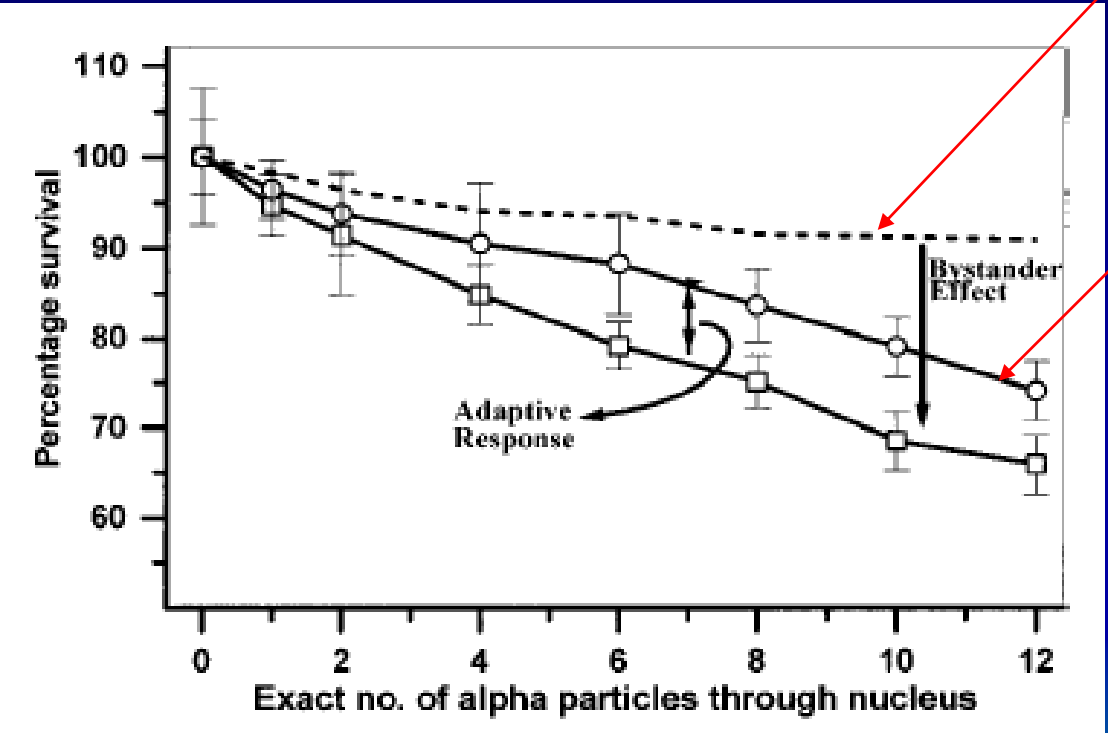
- Exposure to a conditioning dose allows cells to develop increased resistance to a second radiation exposure.
- This effect is function

  a) of the conditioning dose and

  b) time for development and

  c) of the cell system employed
- Varies very much between systems and is not an universal feature

Adaptive response and bystander effects from cell survival

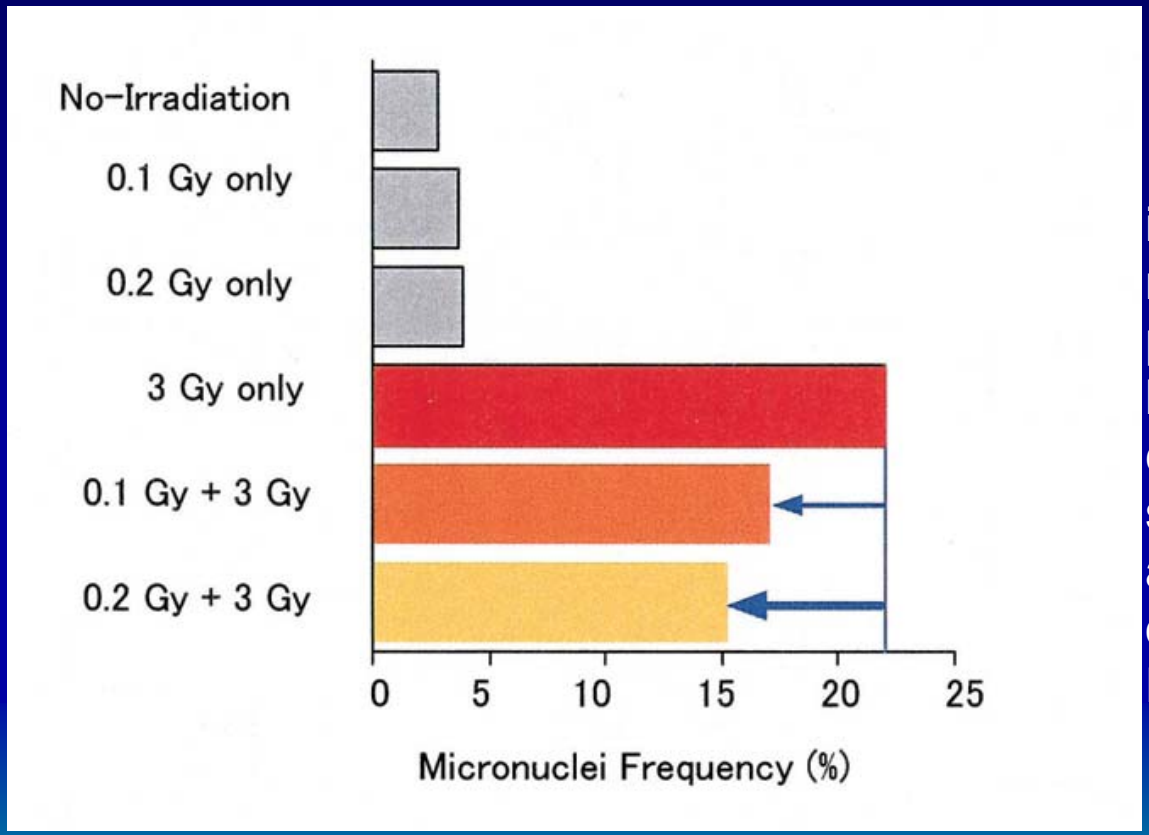


% of cells expected to survive when 10% of cells are exposed

Exposure to 2 cGy of γ rays 6 hours before irradiation with α particles of 10% of cell population

From Sawant et al. 2001 using C3H 10T1/2 cells in culture

Adaptive response in V79 cells in culture



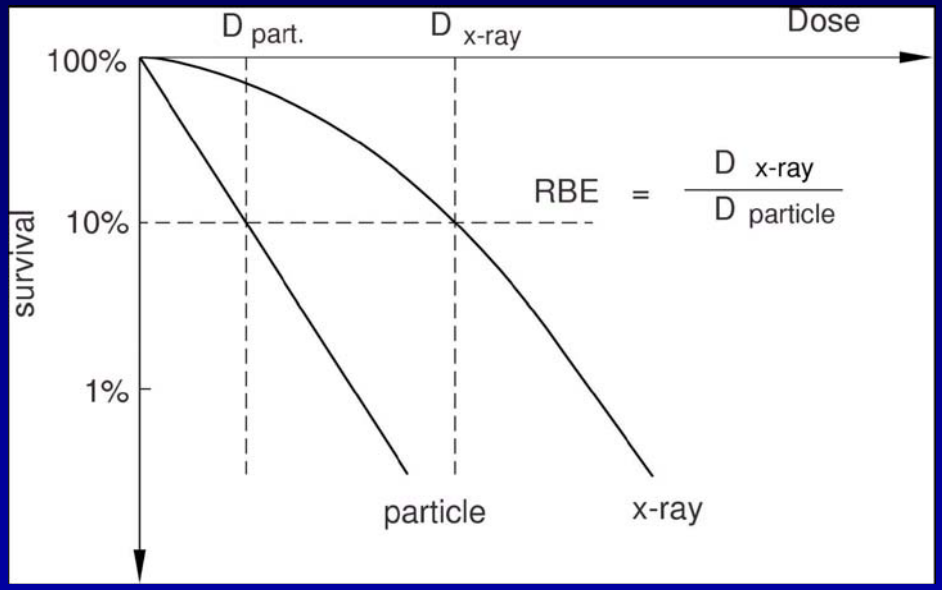
The frequency of micronuclei induced by 3 Gy of X-rays was reduced, when 0.1 or 0.2 Gy of pre-irradiation had been given 4 hours earlier. In HeLa cells (of cancer-origin) treated under the same conditions the radiation adaptive response was not observed.
From Sakai K. 2000

Cellular killing as function of dose

- Survival curves shapes

$S = \exp-(\alpha D+\beta D^2)$

The ratio a/b is the dose at which the linear and quadratic components of cell killing are equal and is a measure of the curvature of the survival curve. a/b ratio is lower for slowly proliferating cell populations. The β component is modified by changing in dose rate and reach 0 at very low dose rates because of repair processes.



Survival curves as well as mutational dose-response curves are linear + quadratic at low LET and tend towards linearity at high LET.

- The **RBE** of a given radiation is the reciprocal of the ratio of the absorbed dose of that radiation to the absorbed dose of a reference radiation (usually x-rays) required to produce the same degree of biological effect.

Particles are characterized by their LET

LET

- Mean energy lost by charged particles in electronic collisions per unit track length.

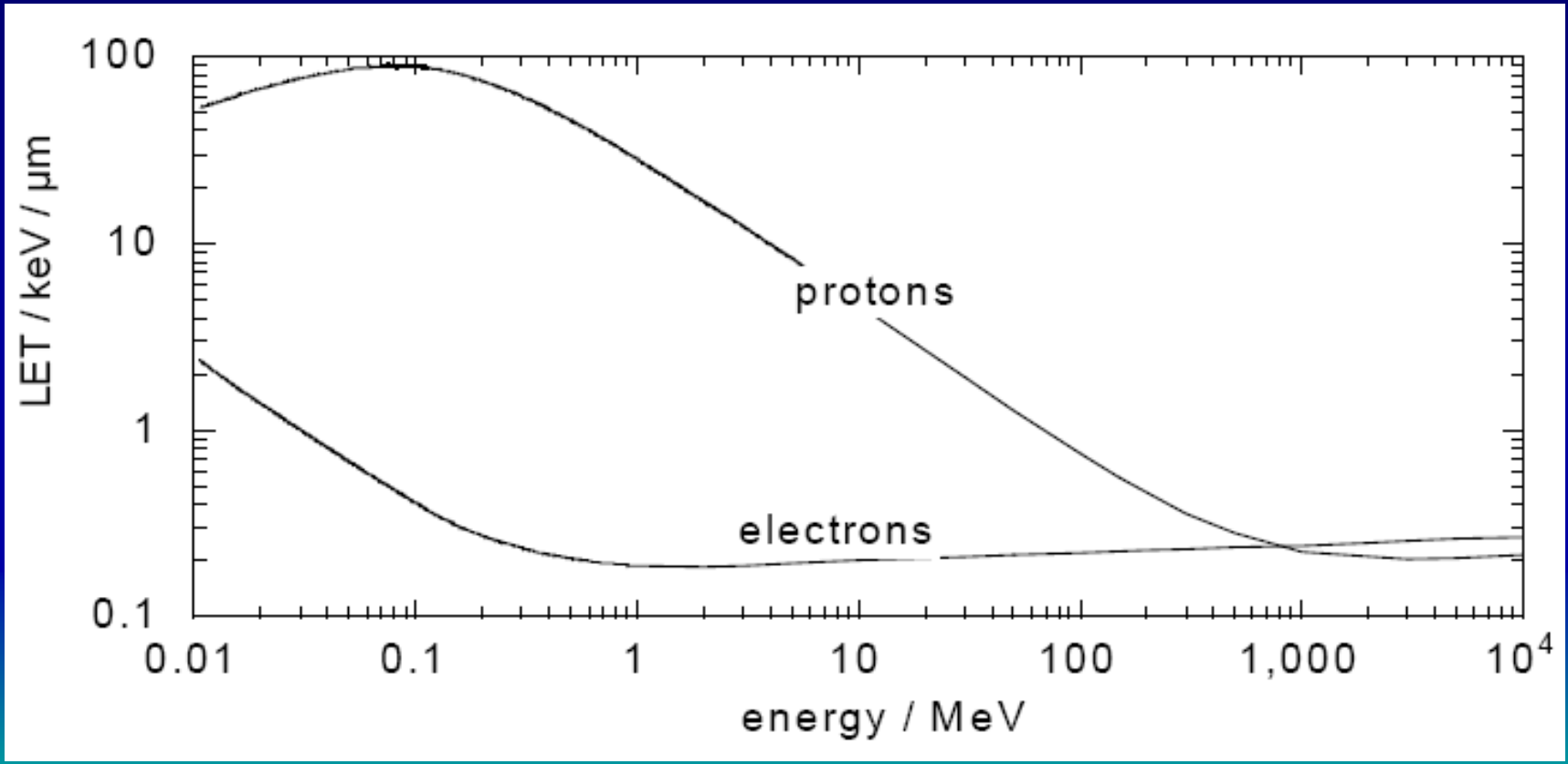
Low-LET radiation

- X-rays and gamma rays or light charged particles such as electrons that produce sparse ionizing events far apart at a molecular scale (L < 10 keV/μm).

High-LET radiation

- Neutrons, heavy charged particles that produce ionizing events densely spaced at a molecular scale (L > 10 keV/μm).

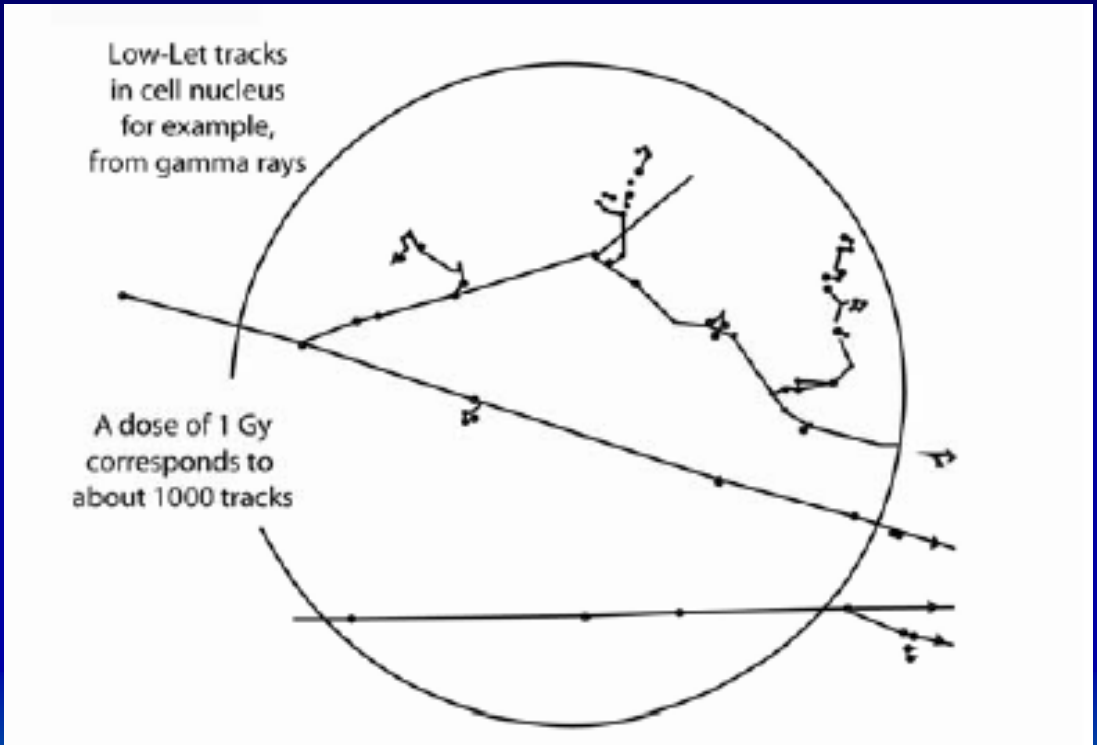
LET of protons and electrons in water



From ICRU 1970

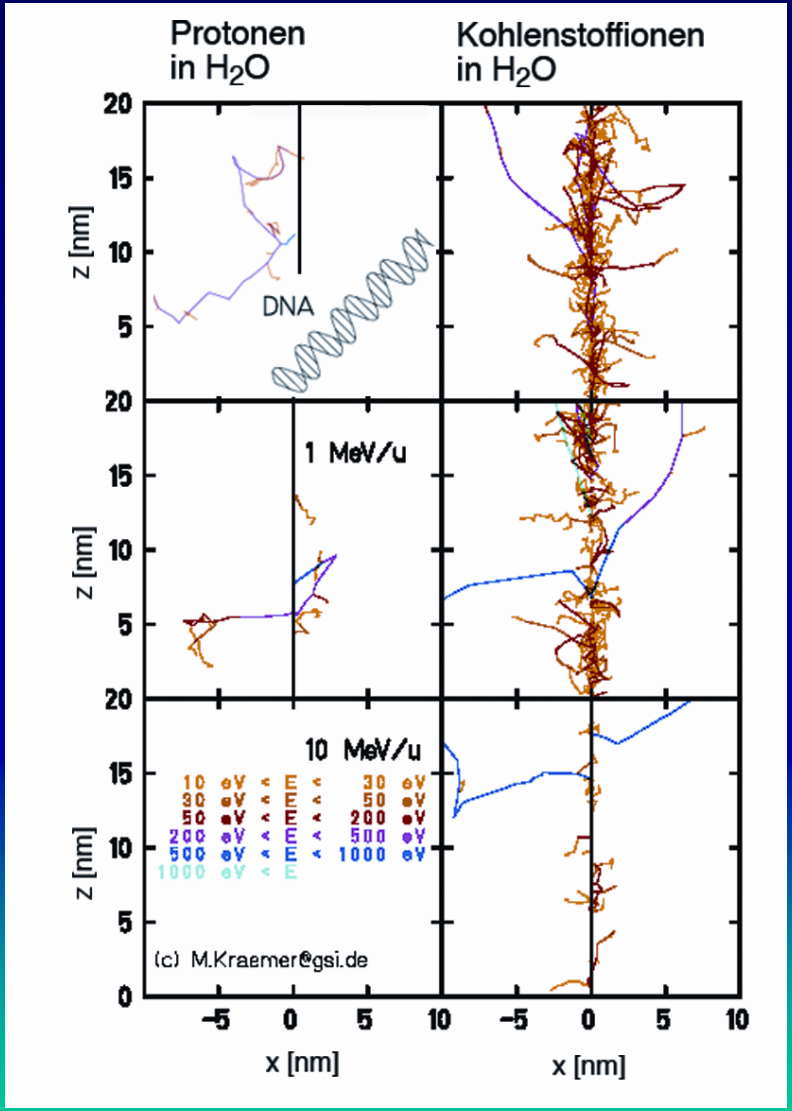
Low LET tracks

Nucleus
of 8 μm diameter



From BEIR VII 2006

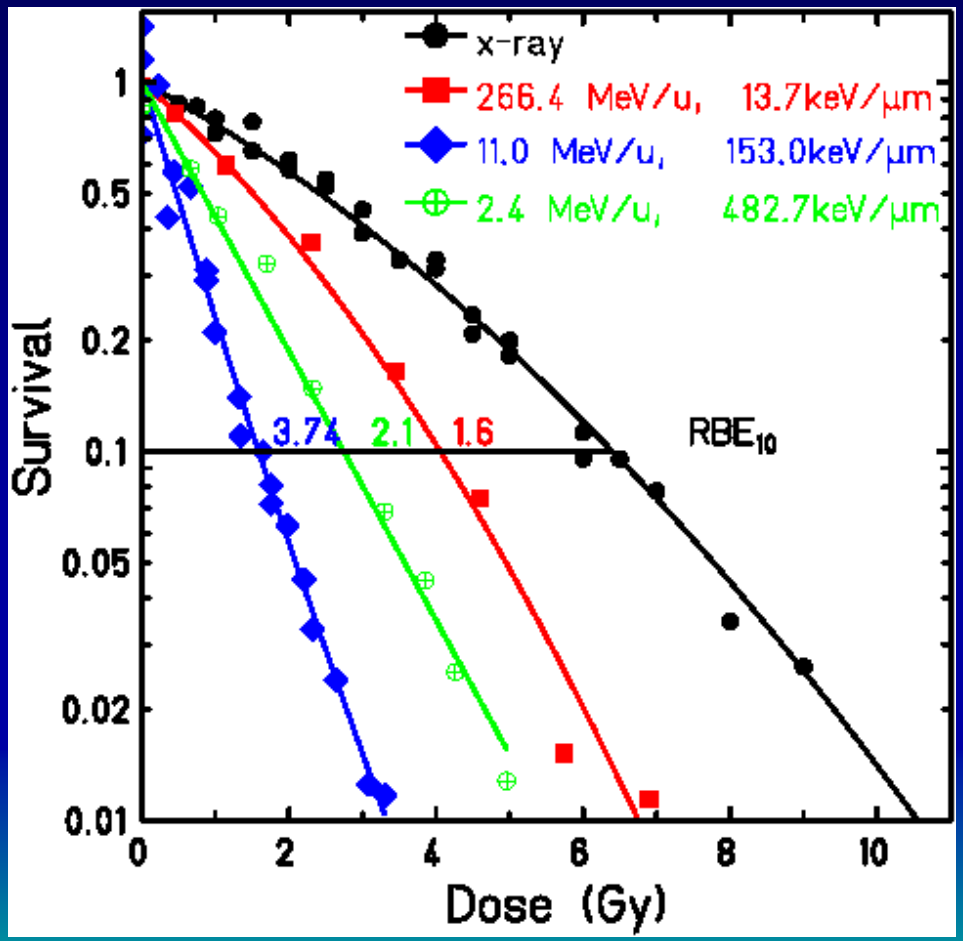
Structure of protons and carbon tracks in matter



Dose distributions as a function of the radial distance from the ion path. For protons the energy loss is small and the events are far from each other. For carbon ions high local ionization densities are reached in the center of each single track when particle energy loss reach a value of 100 keV/µm or more.

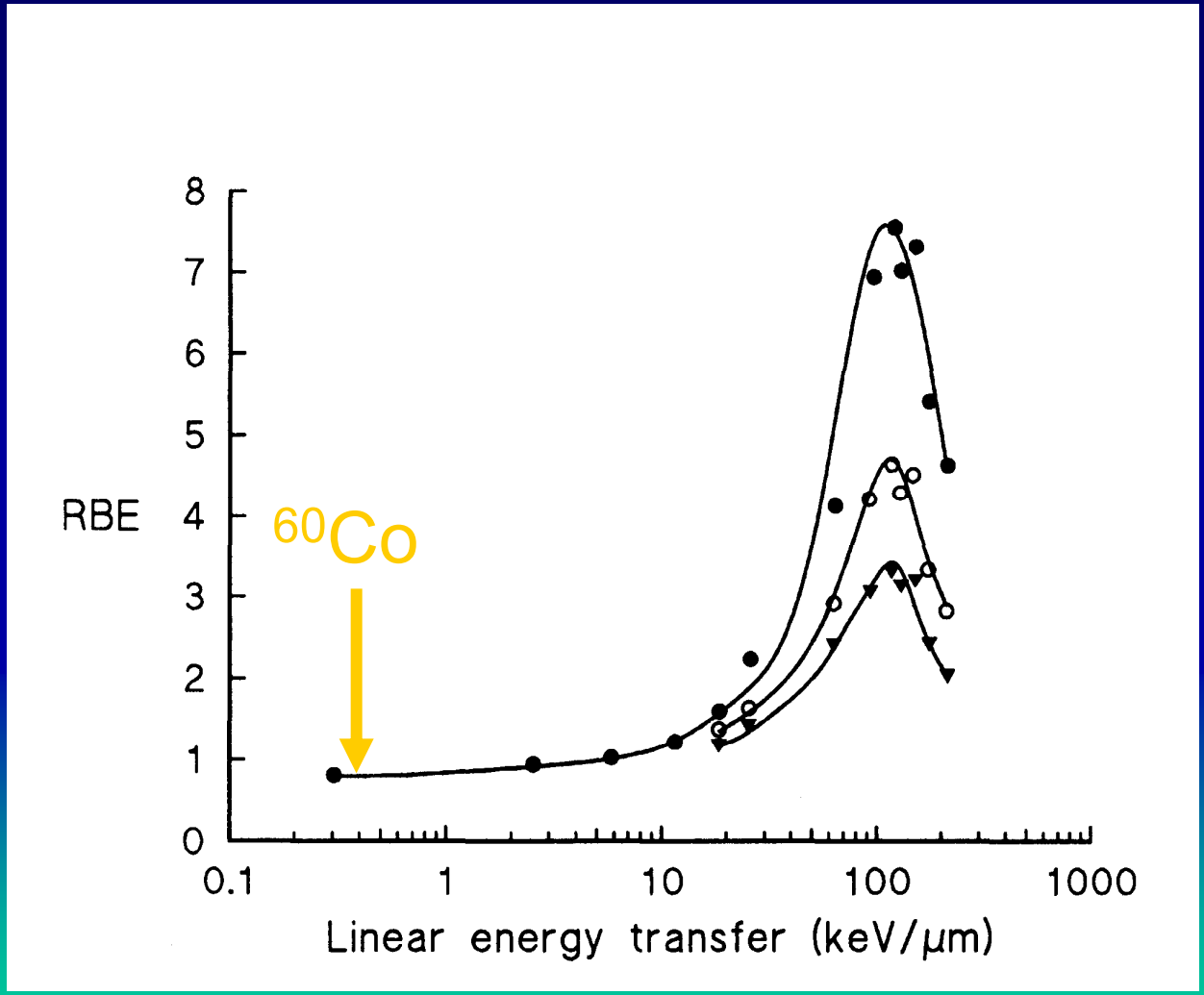
By courtesy of M. Kraemer, GSI

The RBE depend on particles LET

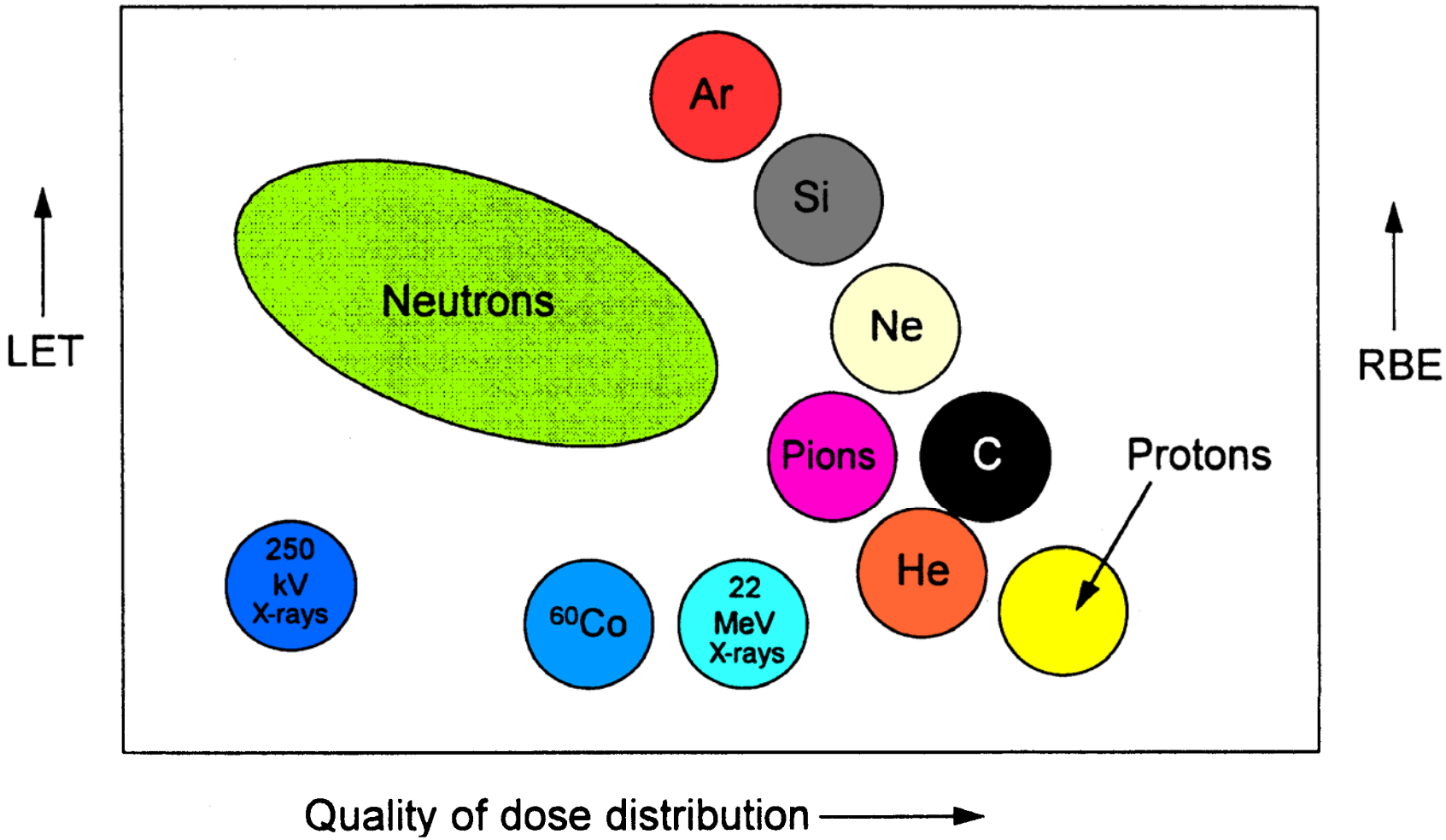


Carbon ions irradiation of different energies
(by courtesy of Kraft G. and Weyrather W. K., GSI)

RBE versus LET



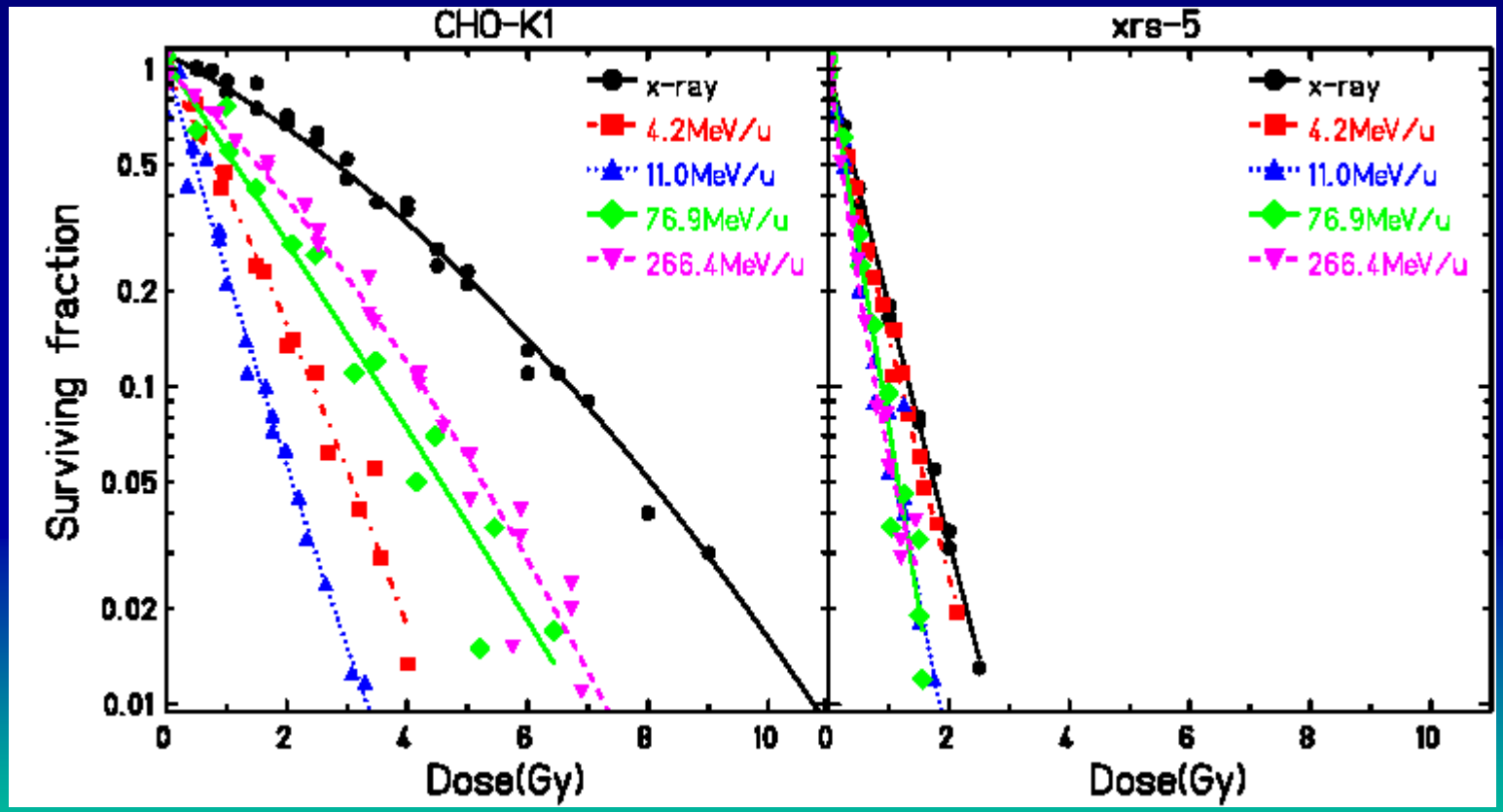
LET and RBE for different radiation types



From. Fowler J. F.

What happen when damage is not recognised?

Xrs-5 is a repair deficient mutant from CHO-K1 with defect in one or two genes needed for damage recognition



from Weyrather W. K. et al. 1999

Neutrons RBE varies with energy and dose and may go >20 at low doses,

Table 3
Estimated RBE_m values for fission neutrons compared with gamma rays [N6]

Endpoint	*RBE_m*
Cytogenetic studies, human lymphocytes in culture	34–53
Cell transformation	3–80
Genetic endpoints in mammalian systems	5–70
Life shortening (mouse)	10–46
Tumour induction	16–59

NCRP Report 1990 and UNSCEAR 2000

Data for cancer induction and life-shortening are extrapolated to low doses and dose-rates

Differences between high and low LET radiations

- the response of cells in the different phases of the cell cycle depend on the radiations quality (Miller R.C. et al. 1995)
- ras mutations in neutron radiation-induced thymic lymphomas is different from that seen in thymic lymphomas induced by gamma radiation in the same strain of mice (Sloan S.R. et al. 1990)

Inactivation α-coefficients for cells in culture irradiated during Mitosis, G1 and stationary phase as function of LET

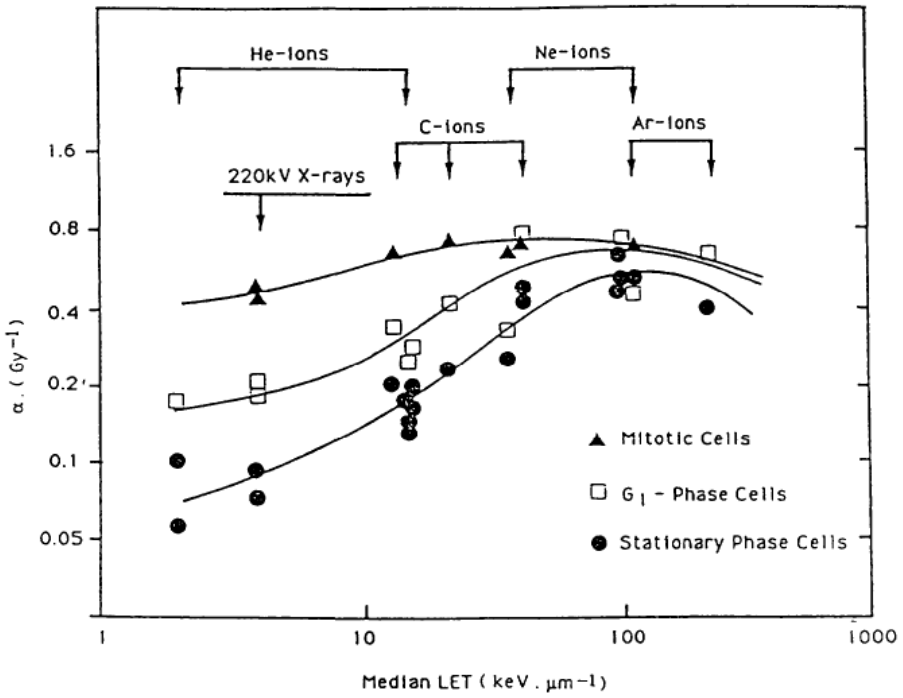


Figure 3: Single-hit inactivation coefficients (α) for homogeneous populations of Chinese hamster cells irradiated in mitosis, G_1 phase and stationary phase, with 220 kV X rays and various beams of charged particles. The α-coefficients are plotted as a function of the median LET (in keV·μm^{-1}). After Chapman (1988).

From IAEA-TECDOC-992, 1997

High LET and DNA damage

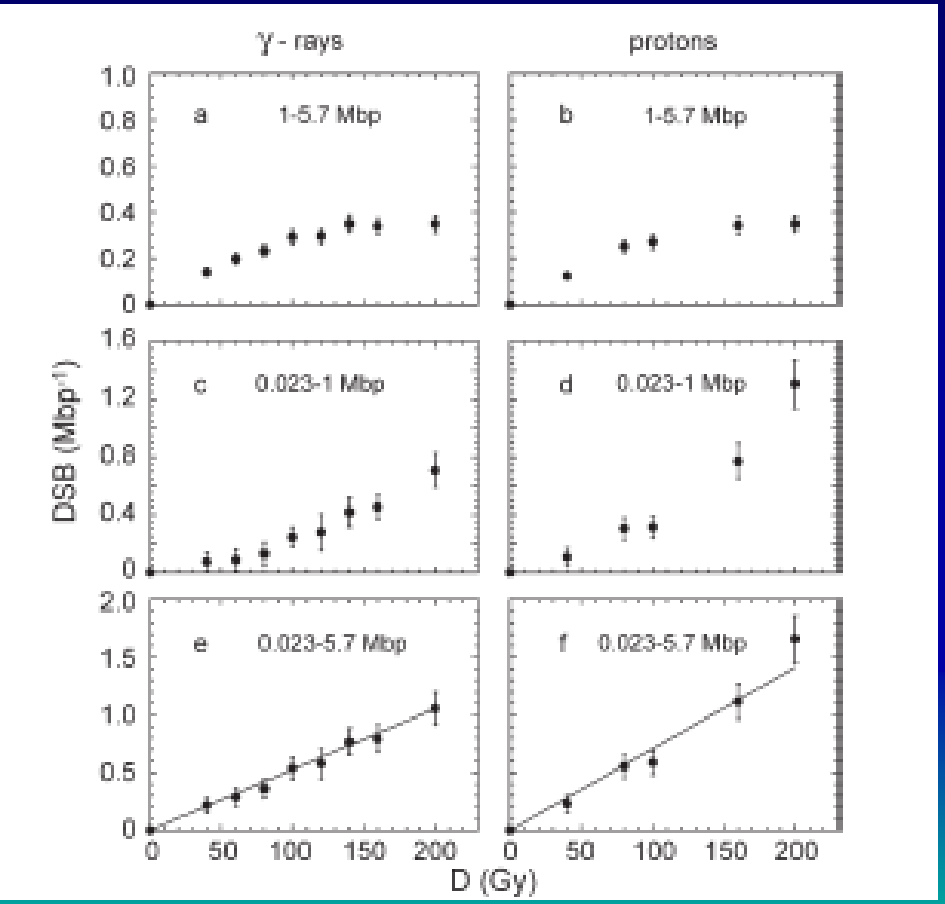
High LET radiations produce complex DNA damage in the form of:

- Double Strand Breaks (DSB) and
- Non DSB Oxydative clustered DNA lesions

(Hada M. and Sutherland B.M. 2006 Hada M. and Georgakilas A.G. 2008)

Complex chromosome exchanges with interaction between more than 2 breakpoints are rare for low doses of low LET radiations and significant for high LET radiations

Importance of track structure in modulating DNA damage



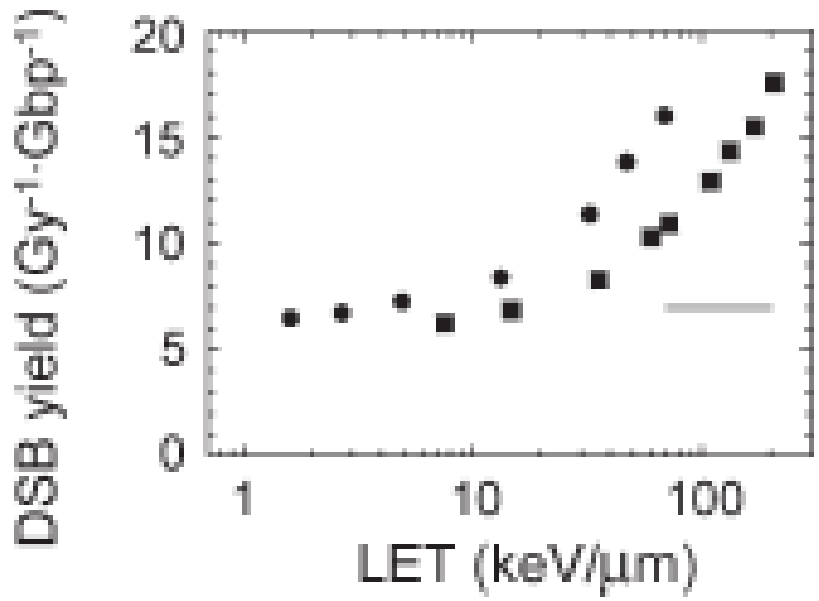
RBE 1.3 ± 0.2

γ rays double strand breaks (DSB) random induction

Protons at low doses show significant deviation from randomness. Small fragments (<23kbp) are produced via non random processes and for protons they represents about 20% of the total number of fragments. For 3.3 MeV α calculations estimates the small fragments to be 50%.

From Campa A. et al. 2005

Importance of the microscopic structure of radiation tracks



The yields of DSB calculated for protons and α increase with LET.
Protons are more effective than α of
the same LET.
From Campa A. et al. 2005

Also for cell inactivation protons are much more efficient than α particles of the same LET
From Goodhead D. et al. 1992

Mutational dose-response

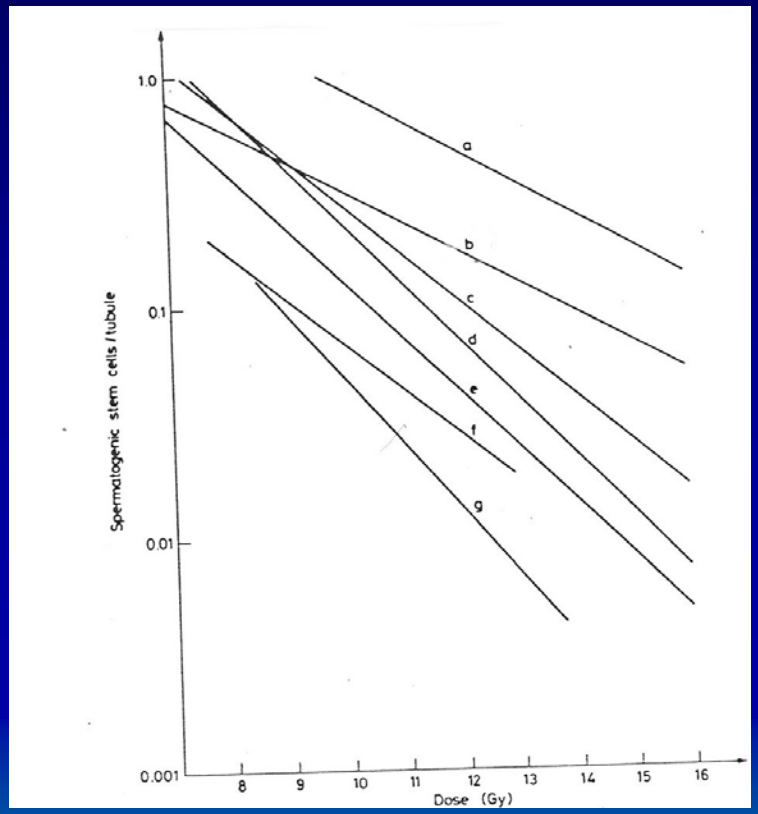
depends on:

- Biological system
- Mutational end-point
- LET
- Dose-rate

Dose-response relation for mutation

- Mutational dose-responses are linear-quadratic for low LET
- For high LET the dose-response tend towards linearity
- RBEs of around 10–20 for LET in the range of 70–200 keV μm
- The induction of blood chromosome aberrations in human lymphocytes is linear for low doses of X rays

Very large differences on radio-sensitivity for different mouse strains



Comparison of survival curves
for clonogenic spermatogonia germ cells
From Bianchi et al. 1985

Genetic susceptibilty to radiations (cataract induction in mice)

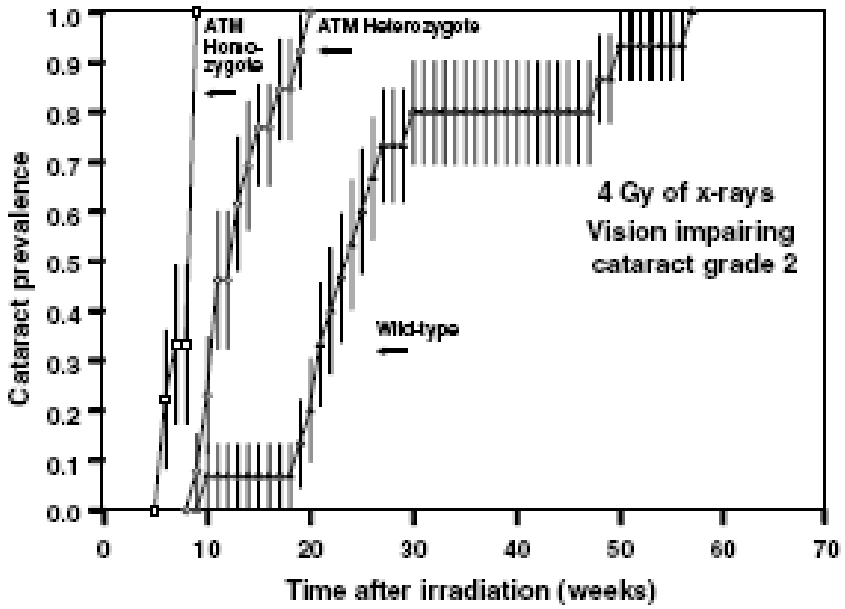


Fig. 3. Prevalence of cataracts of grade 2 (vision impairing) as a function of time after exposure to 4 Gy of X-rays in wild-type mice and in animals homozygous or heterozygous for the ATM gene. The heterozygous animals develop grade 2 (vision impairing) cataracts about 10 weeks earlier than wild-type animals. The vertical bars are standard errors. (Redrawn from Worgul et al., 2002.)

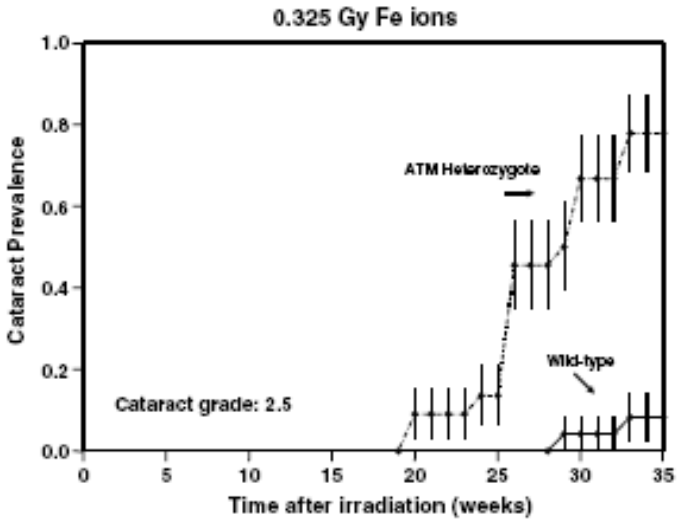


Fig. 6. Prevalence of vision impairing cataracts (grade 2.5) as a function of time after exposure to a dose of 32.5 cGy of high energy Fe ions in wild-type mice of in animals heterozygous for the ATM gene. Note that at this dose, that corresponds to about one particle track per cell nucleus, few wild-type animals develop a vision impairing cataracts, compared with 80% of the heterozygotes.

From Hall et al. 2005
Ataxia Telangiectasia heterozygotes may be a radiosensitive subpopulation

See also experiments on prostate cancer patients (Hall E.J. et al. 1999 and experiments with mouse embryo cells in culture, Smilenov L.B. et al 2001

Male mice germ cells damage in P53 knock-out mice

Genotype	Stage	VI	VII	VIII	IX	P1
(-/-)	D_0(cGy) n	430 ± 140 c. 1.0	230 ± 40 c. 1.0	440 ± 90 c. 1.0	610 ± 190 c. 1.0	0.06
(+/-)	D_0(cGy) n	59 ± 9 1.3 ± 0.3	35 ± 13 3.6 ± 3.5	42 ± 19 4.8 ± 5.2	200 ± 24 1.2 ± 0.2	<0.001
(+/+)	D_0(cGy) n	30 ± 4 2.2 ± 0.9	22 ± 4 4.9 ± 3.5	26 ± 4 8.8 ± 4.8	43 ± 10 6.8 ± 4.0	<0.001
	p_2	<0.001	<0.001	<0.001	-	
$B6D2F_1$	D_0(cGy) n	~25 c. 1.0	27 ± 6 c. 1.0	34 ± 4 c. 1.0	77 ± 10 c. 1.0	<0.001

P53

-/- null

+/- heterozygotes

+/+ homozygotes

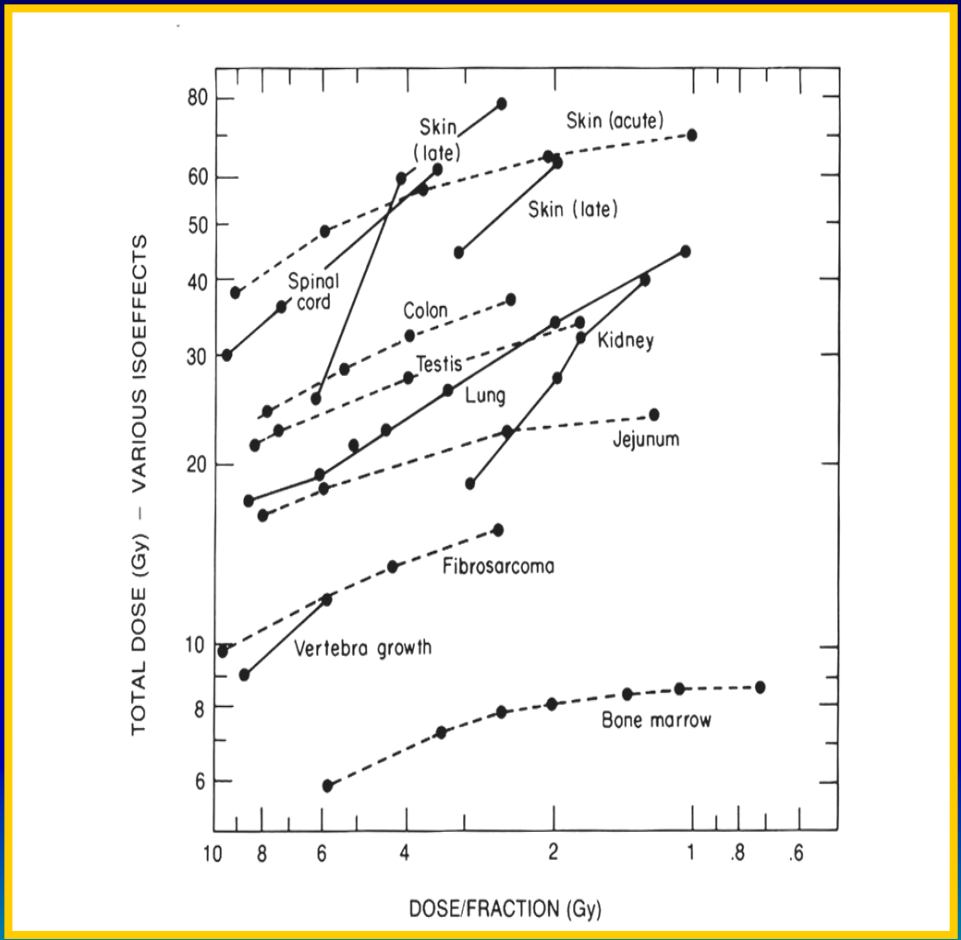
Conventional strain

p53 null mice spermatocytes and other progenitor cells are likely to carry mutations and, as most will not die by apoptosis may contribute to a greater mutational burden with respect to transgenerational effects (From Streit-Bianchi M. et al. 2007)

Genetic susceptibility

- 5 genes have been identified so far in humans to be responsible for increased radiosensitivity. A screening for these genes is possible. Patients carrying these genes, if undergoing radiotherapy, receive less dose or receive alternative treatments.

Effect of fractionation of doses in mouse

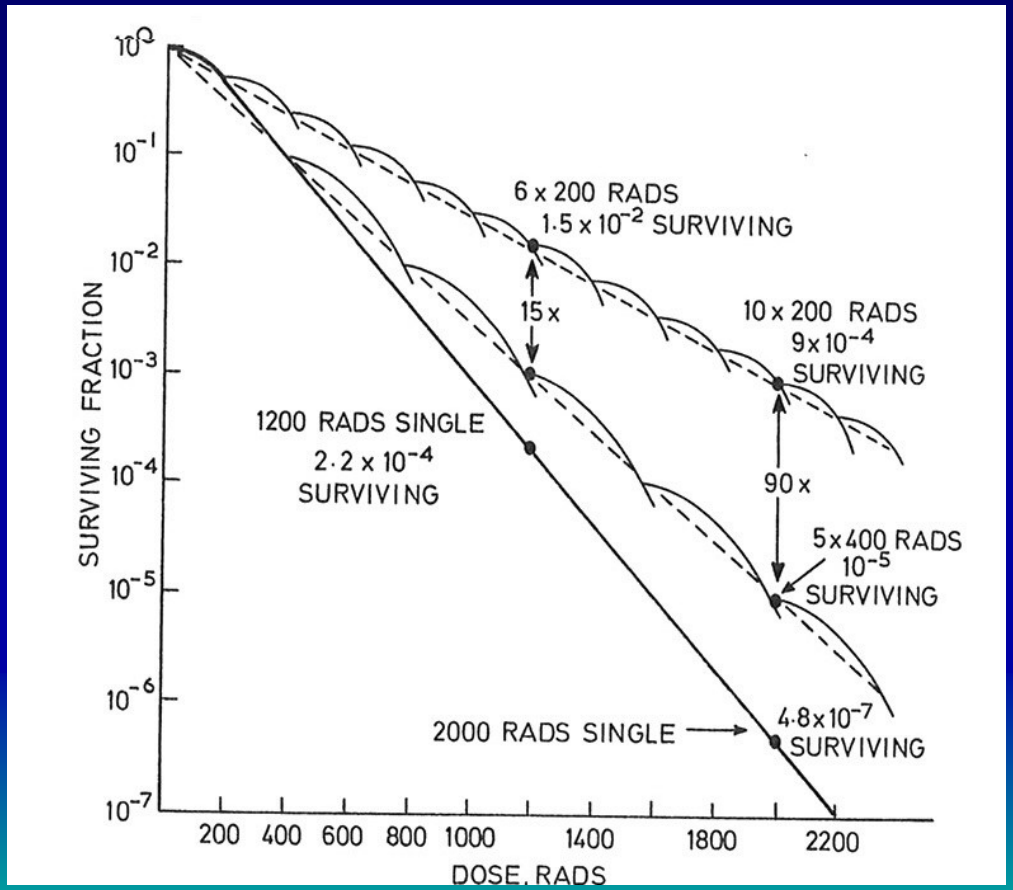


sublethal damage repair:
fast component (i.e. 0.4 h for lung)
and slow component (i.e. 4h for lung)
and
cellular proliferation

From
Thames H. et al.
1982

The increase of total iso-effect dose as a function of decreasing dose per fraction
i.e. increasing number of fractions for various normal-tissue reactions.
The late reactions show a steeper variation than the early reactions

Effect of fractionaction assessed by cell survival



From Duncan W., Nias A.H.W., 1977

Effect of fractionaction in pig skin

Fractionation	Total dose Gy
1 fraction	20
5 fractions in 4 days	36
5 fractions in 28 days	42

Doses required to produce the same skin reaction in pigs
From Duncan W., Nias A.H.W., 1977

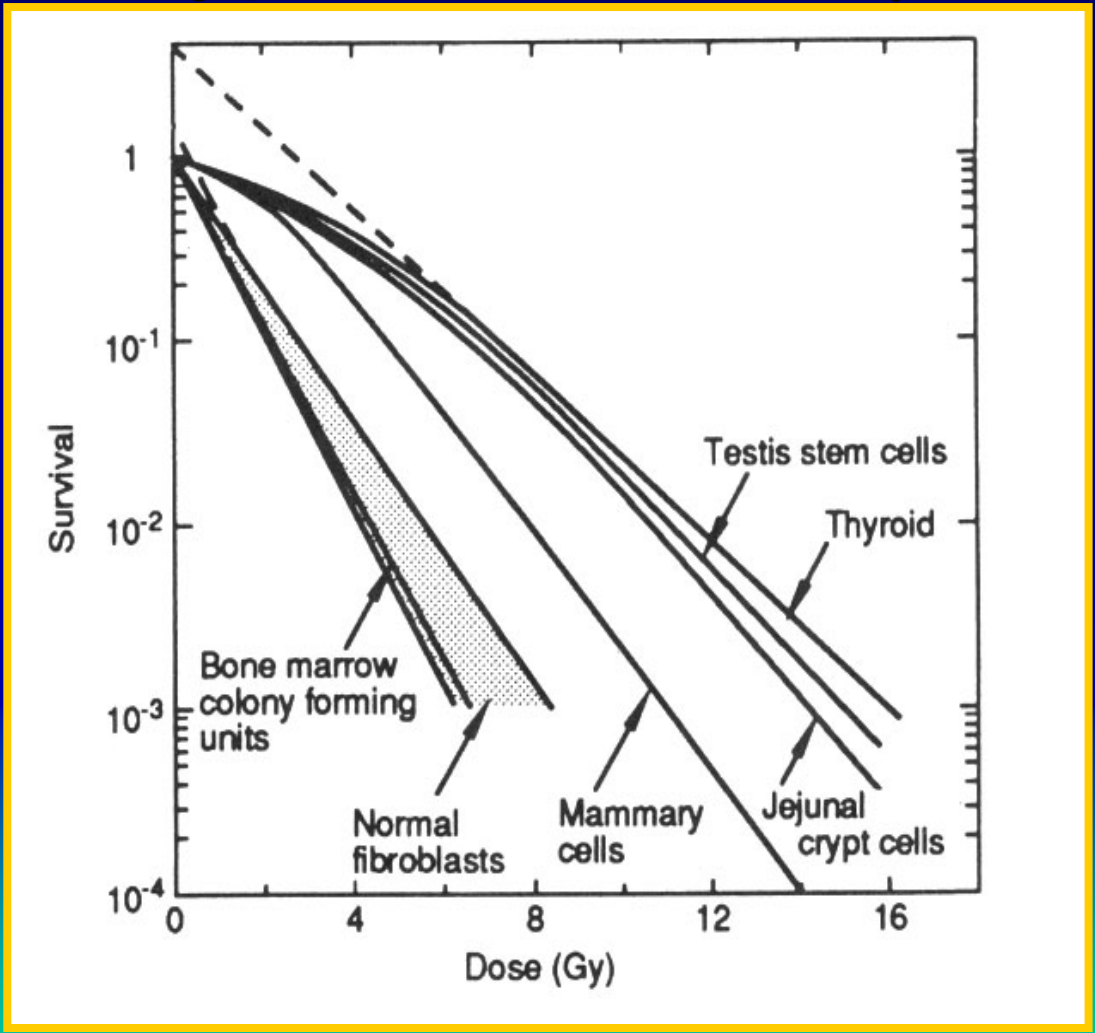
Hypersensitivity by fractionation at low doses

Table 1. Surviving fraction (plating efficiency) for cells irradiated to 6 Gy with different numbers of well-separated fractions

Treatment	(C3H 10T½ cells (plateau phase)	C3H 10T½ cells (exponential phase)	V-79 cells (exponential phase)
Controls	(0.37)	(0.34)	(0.59)
0.3 Gy × 20 fractions	0.30	0.24	0.28
1 Gy × 6 fractions	0.36	0.33	0.34
2 Gy × 3 fractions	0.52	0.55	0.65
3 Gy × 2 fractions	0.11	0.20	0.14
6 Gy × 1 fraction	0.06	0.10	0.08

From Smith L. G. et al. 1999

Cell clonogenic survival for different type of tissues (mouse)



Effect of local or total body irradiations

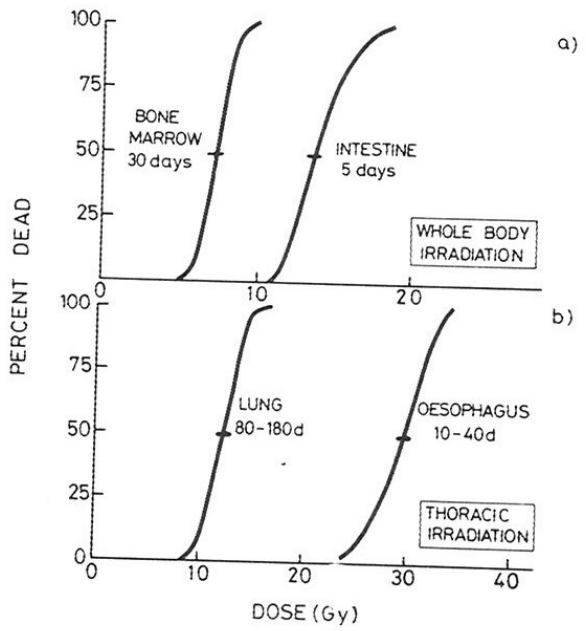
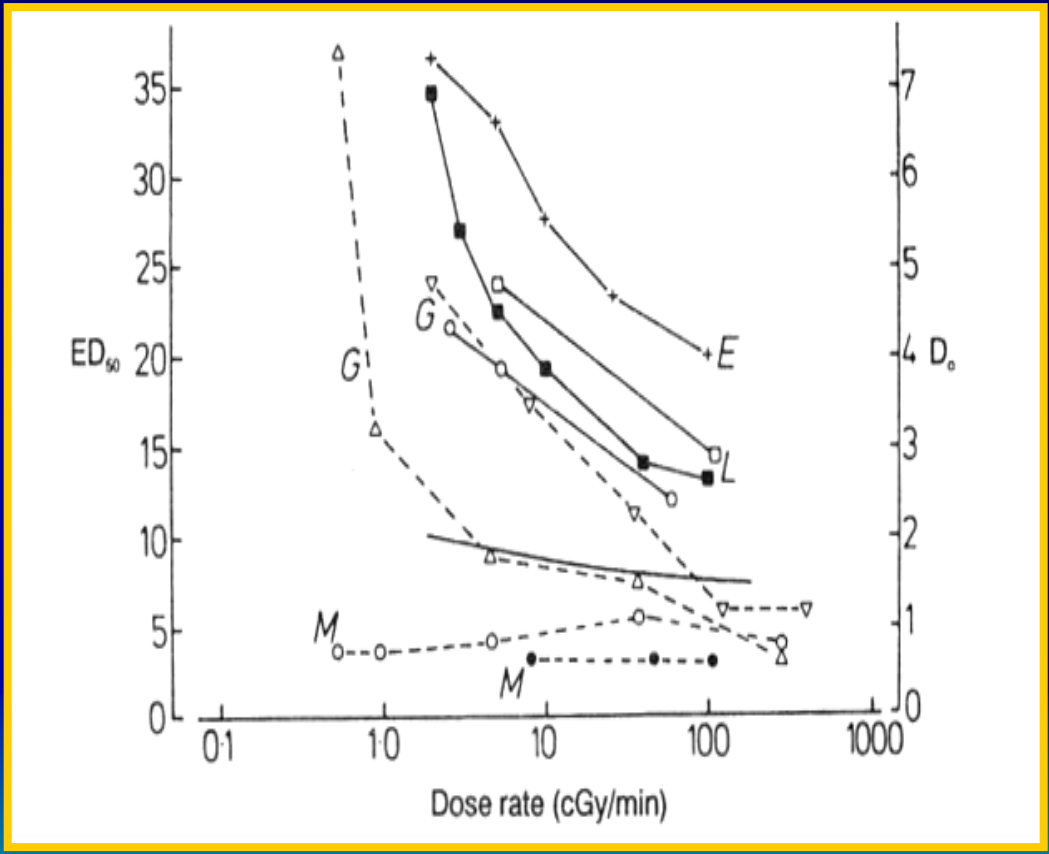


Figure 1. Dose–response curves for lethality after whole body or thoracic irradiation. The mice die at different times and over different time scales according to the turnover time and the radiosensitivity of cells in the indicated organs. Damage is manifest early in rapidly proliferating tissues and late in those with a slow proliferation rate. (Re-drawn from Denekamp (1982).)

Effect of dose rate

- Depend on LET. Smaller or absent for high LET radiations.
- At dose rates around 0.1 Gy/hour repair of cellular radiation injury occur during the irradiation
- Hypersensitivity to doses less than 0.5 Gy, typically at 0.2–0.3 Gy (Joiner et al. 2001) (stimulation of repair processes at doses above 0.2–0.3 Gy?) Joiner, M.C., Marples, B., Lambin, P., et al., 2001.
- *Low-dose hypersensitivity: current status and possible mechanisms. Int. J. Radiat. Oncol. Biol. Phys. 49, 379–389.*

Dose-rate effects in mouse tissues



E = Epidermis
L = Lung
G = Gut
M = Marrows

From Steel G. G. 2002

Depending on dose and dose-rates

- Different genes may get activated
- At very low doses and dose-rates intracellular signalling and repair systems do not get activated
- At high doses repair systems get activated. Cells may survive radiations but carry miss-repair lesions or even irreversible lesions, the latter causing later cellular death.

Are effects detectable at very small doses?

Yes, many are the study carried out at small doses using:

- Cells in culture (oncogenic transformation) ,
- Human lymphocytes
- Tumour induction in animals