Freie Universität Berlin

Radiochemistry and Radiopharmacy II

Compact course held at University of Vigo, June 2012

Ulrich Abram
Freie Universität Berlin
Institute of Chemistry and Biochemistry

Freie Universität Berlin

Radiochemistry and Radiopharmacy

1. **Fundamentals of Radiochemistry.**
2. **Radiation and Biology. Basics in Nuclearmedical Diagnostics and Therapy.**
3. **Positron Emission Tomography (PET) with ^{18}F Compounds.**
4. **Single Photon Computer Tomography (SPECT) with ^{99m}Tc.**
5. **Nuclearmedical Research for Diagnostics (^{99m}Tc, ^{68}Ga) and Therapy (^{186}Re, ^{188}Re).**

Radiochemistry and Radiopharmacy

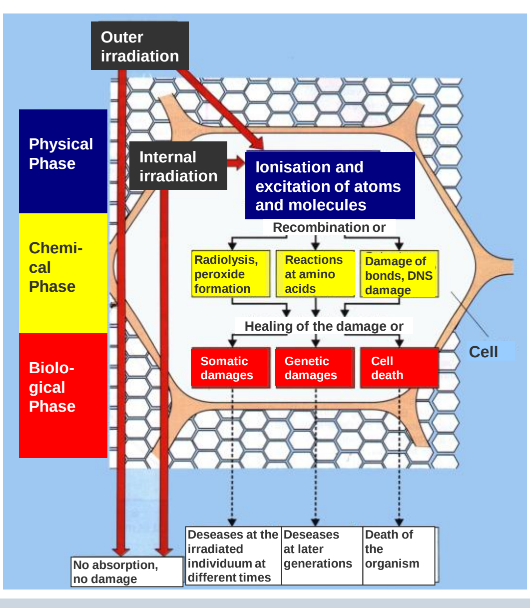
2. Radiation and Biology. Basics in Nuclearmedical Diagnostics and Therapy.

- Interactions between nuclear radiation and biological material
- Radiation protection
- Nuclide properties and nuclearmedical applications
- Nuclearmedical therapy
- Nuclearmedical diagnostics – PET and SPECT

Interactions between nuclear radiation and biological material

Freie Universität Berlin

Three phase model of biological effects on organisms:



Radiation effects in cells

- **Somatic damages** (only the irradiated individuum is damaged)
  - **Long-term damages** (deseases are obvious after years, however damages are set immediately)
    - **Non-cancer deseases** (sterility, turpidity of the eye lenses, minimum dose required)
    - **Cancer deseases** (no minimum dose known, higher dose increases the risk, but not the extend of the desease
  - **Immediate damages** (minimum dose is required, limit at humans is between 200 and 300 mSv; single whole body irradiation of about 7000 mSv is lethal)
- **Genetic damages** (only following generations will be damaged)

Interactions between nuclear radiation and biological material Freie Universität Berlin

Chemical effects of irradiation of cells

Direct interactions with molecules

Amino acids:	Desamination, Ring disruption, Oxidation
Nucleic acids:	Chain disruptions 15 to 29 eV for Single-strand disruptions 100 to 200 eV for Double-strand disruptions

Chemical effects of irradiation of cells

Indirect interactions with molecules („indirect effect“)

- Water is the most common molecule in living cells (≈ 70%)

- Primary radiationreaction on water 10^{-18} bis 10^{-12} s)

Radiolysis: $H_2O + hv \rightarrow H_2O^+ + e^-$ Energy impact 12,56 eV

- Subsequent reactions (simplified):

- Cleavage of H_2O^+ into a OH• radical $H_2O^+ \rightarrow H^+ + OH•$
  - OH• is main product of radiolysis with highly oxidising potential
  - released electron may react in to different ways

$e^- + H_2O \rightarrow OH^- + H•$ $e^- + H_2O \rightarrow e^-_{(aq)}$

DNA damage by ionising radiation

Damages at nucleic bases

- Main damages (removal of a base, desaminination, hydroxylation, ring disrupture, Dimerisation (mainly Thymin)

- Base changes (wrong messenger RNA, repair is possible)

- Frequently with UV radiation

Single-strand disrupture

- Caused by direct and indirect hits, not possible with UV radiation of biologically relevant doses

- Effect depends on the presence of oxygen („oxygen enhancement ratio“, OER), repair possible

- Single-strand disruptures become double-strand damages when they are close together (approxim. 4 bases)

Double-strand disrupture

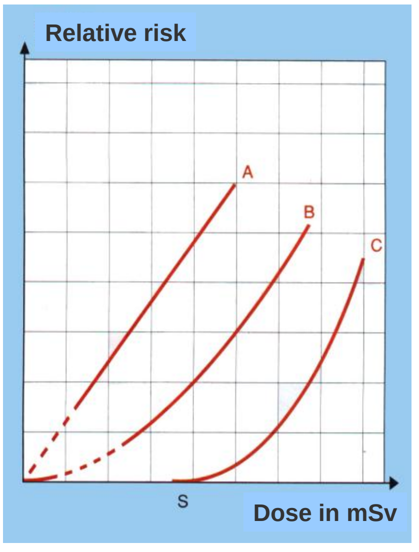
- Caused by direct and indirect hits, not possible with UV radiation of biologically relevant doses

- Effect depends on the presence of oxygen („oxygen enhancement ratio“, OER)

- No repair possible

- Death or mutations

Radiation effects in cells

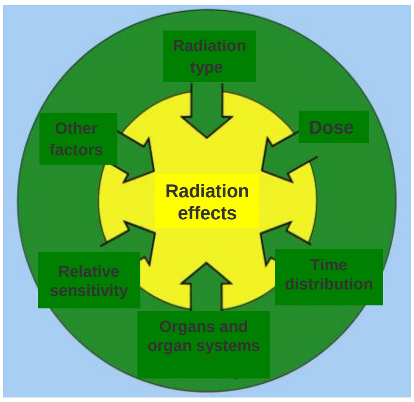


Dose-Risk- relationship at exposition with ionising radiation
(Experimental data at high doses, extrapolation at low doses):

Extrapolation models:
- **A** linear
- **B** linear-squared
- **C** risk slope with lower limit

Sensitivity of organisms against radiation
($D_{50/30}$ value = 50% lethal dose within 30 days)

Organism	$D_{50/30}$
Amoeba	1000 Gy
Drosophila	600 Gy
Shellfish	200 Gy
Goldfish	20 Gy
Rabbit	8 Gy
Monkey	6 Gy
Dog	4 Gy
Man	4 Gy

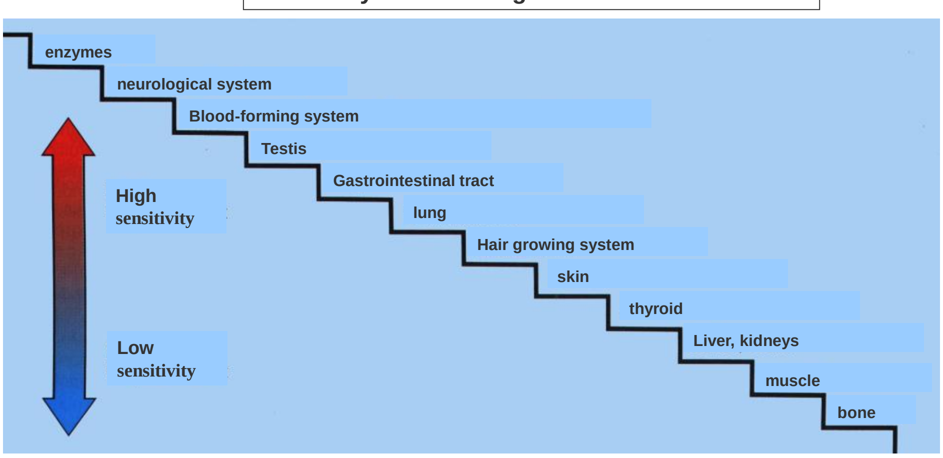


Influence of other factors

- type of radiation ($\alpha > n > \beta, \gamma$)
- value of the dose: higher dose = more damages
- dose distribution (more small doses are less dangerous than one big of the same overall value (repair mechanisms)
- irradiated organs and organ systems (different sensitivity of tissues)
- other factors (e.g. sensibilisation due to drugs, hormons, O_2-level of the organism etc.

Interactions between nuclear radiation and biological material Freie Universität Berlin

Sensitivity of tissues against radiation



Organ weighting factors w_T for the calculation of the organ dose H_T or the effective dose E

Organ dose:
$H_T = \sum w_R D_{T,R}$

Effective Dose:
$E = \sum w_T H_T = \sum w_T \sum w_R D_{T,R}$

Tissues or organs	Tissue weighting factors w_T
Testes	0,20
Bone marrow (red)	0,12
Colon	0,12
Lung	0,12
Stomach	0,12
Bladder	0,05
Breast	0,05
Liver	0,05
Esophagus	0,05
Thyroid	0,05
Skin	0,01
Bone	0,01
Other organs	0,05

Source: German Law

Effects of accidental radiation exposure on man (approximate values)

Whole body irradiation

0.25 Sv	No clinically recognisable damages
0.25 Sv	Decrease of white blood cells
0.5 Sv	Increasing destruction of leukocyte-forming organs (decrease of resistance to infections)
1 Sv	Marked change in the blood picture
2 Sv	Nausea and other symptoms
5 Sv	Damage to the gastrointestinal tract (50% death)
10 Sv	Destruction of the neurological system (100% death)

Irradiation of the hand

2 Gy	No proven effects
4 Gy	Erythema, skin scaling
6 Gy	Skin reddening, pigmentation
8.5 Gy	Irreversible degeneration of the skin
50 Gy	Development of non-healing skin cancer

Note ! By European law the dose limit for people who work with a radiation risk is 0.020 Sv/year

Biological Repair Processes

General Importance of Repair Mechanisms
- not restricted to radiation damages → more general phenomenon
- repair of damages from non-perfect chemical or biological systems or reactions
- sources of the damages can be ionising radiation or chemical noxes
- particularly important in the low-dose range
- important for the maintainance of a stable genetic material and evolution by mutations

Time-Scale
- Repair processes are comparatively slow (0.5 bis 1 hour)
- is used during nuclear medical therapy (intervals of regeneration, irradiation in fractions)

Repair-Mechanisms
- Different sources of energy (light = photorepair, ATP)
- Pre- und postreplicative repair possible

Biological Repair Processes

Excision repair
- pre-replicative, ATP, control by complementary strand
- removal of individual bases: base excision
- removal of base + sugar + phosphate + neighbouring nucleotide : nucleotide excision

Strand-break repair
- pre-replicative, ATP
- works error-free

Photorepair
- pre-replicative, light is source of energy → outer cells only
- cleaves pyrimidine dimers into monomeres
- enzym photolyase absorbs between 300 und 600 nm (with docked DNA)
- works error-free

Recombinationrepair
- post-replicative, when replication produces a defect strand, ATP
- strand-exchange
- works error-free

SOS-Repair
- pre-replicative, closes a gap in the strands after replication, ATP
- works with errors

Conclusion: Repair processes lower the risk of radiation exposure, but cannot remove it completely

Radiation Protection, Protection against external radiation

Always use only that amount of radioactivity you need
→ linear decrease of the exposure

Minimise the time you work near a radiation source
→ linear decrease of the exposure

Work with a maximum distance to the radiation source
→ squared decrease of the exposure

Shielding
→ appropriate materials:

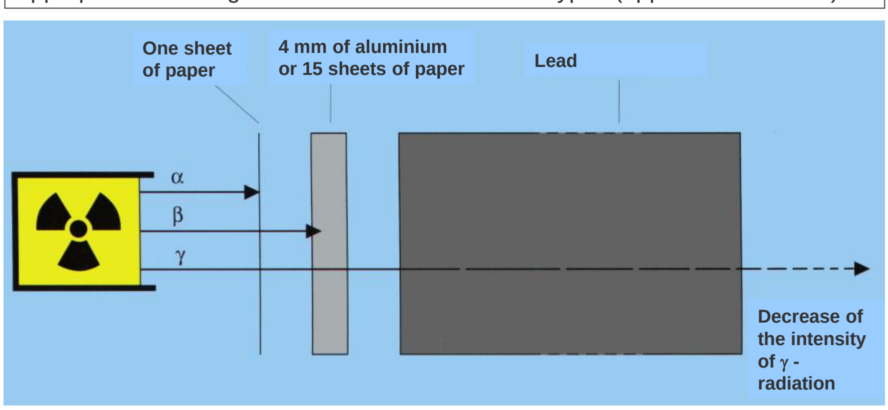
- α, β: Plexiglas
- γ : lead, Uranium
- n : special shields

ALARA
As Low As Reasonbly Achievable

Interactions between nuclear radiation and biological material Freie Universität Berlin

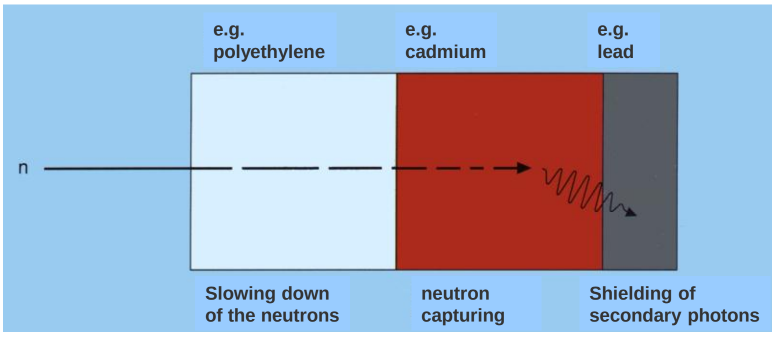
Radiation Protection, Protection against external radiation

Appropriate shielding material for certain radiation types (approximate values)



Radiation Protection, Protection against external radiation

Shielding of neutrons (principle design of a neutron shield)



- Neutrons lose their energy by elastic and inelasic collisions with light nuclei
- capturing of the slow neutrons by neutron absorbers like cadmium or lead
- shielding of the secondary photon radiation by lead walls

Radiation Protection, Protection against internal radiation

- **Special care must be taken during work with nuclides emitting α- and β-radiation (direct interactions with cell material)**
- Reduction of the risk of incorporation by:
  - ♦ radiochemical techniques
  - ♦ frequent contamination checks (hands)
  - ♦ special care when handling volatile or gaseous materials

Nuclearmedical applications, General nuclides properties

Therapy destruction of (cancer) cells	Diagnostics Imaging of organs
- short range - high dose - strongly ionising radiation - β^- - emitter - α - emitter	- medium range - low dose - γ - emitter - β^+ - emitter

Nuclearmedical Therapy

- short range
- high dose
- strongly ionisating radiation
- β^- - emitter
- α - emitter

Problem
Partially high radiations dose to the rest of the organism

β^- - emitter

Isotope	$t_{1/2}$ (d)	Energy (E_{max}, MeV)
^{32}P	14,3	1,71
^{47}Sc	3,4	0,6
^{64}Cu	0,5	0,57
^{89}Sr	50,5	1,46
^{90}Y	2,7	2,27
^{102}Rh	1,5	0,57
^{111}Ag	7,5	1,05
^{131}I	8,0	0,81
^{153}Sm	1,9	0,8
^{186}Re	3,8	1,07

α - emitter

Isotope	$t_{1/2}$ (d)	Energy (E_{max}, MeV)
^{211}At	7,2 h	6,8
^{212}Bi	1,0 h	7,8

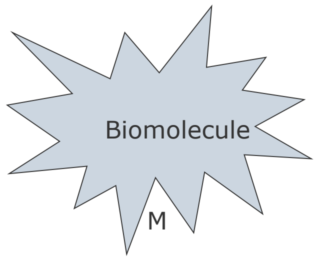
Nuclearmedical Therapy, Targeting

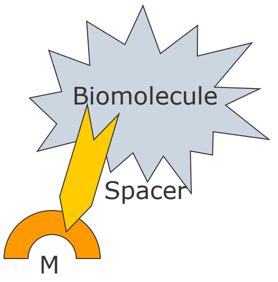
Direct Labeling

- Labeling of a tumor-seeking molecule (e.g. antibody) with a highly ionising radionuclide
- Use of ^{131}I or radioactive metals

Bioconjugate Approach

- Encapsulating of a radionuclide with the help of a chelator and coupling on a biomolecule



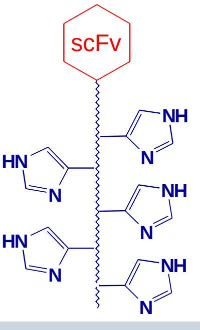


Interactions between nuclear radiation and biological material Freie Universität Berlin

Nuclearmedical Therapy, Targeting

Direct labeling of a tumor-seeking molecule (e.g. antibody) with a highly ionising radionuclide (e.g. ^{186}Re or ^{188}Re)

Example: Binding of a $\{Re(CO)_3\}^+$ centre to a his-tag of an anti-body

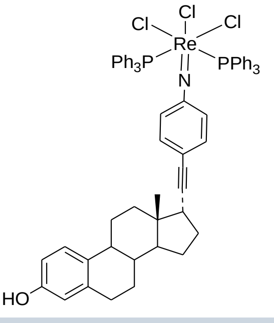


Nuclearmedical Therapy, Targeting

Alternate therapeutic approach

Complexation of a highly ionising radionuclide (e.g. ^{186}Re or ^{188}Re) with a good chelator (e.g. a multidentate ligand system) and coupling of the whole system to a bioactive molecule

Example: Coupling of a rhenium phenylimido complex to a steroid



Interactions between nuclear radiation and biological material Freie Universität Berlin

Nuclearmedical Therapy

Special Approach - Neutron Capturing Therapy

- Application of (nonradioactive) boron compounds that accumulate in tumor tissue
- Irradiation of the patient (after distribution of the boron compound) with neutrons
- Production of destructive radioactivity direct in the tumor

Special Approach - Palliative treatment of cancer and arrthritis

- Application of the radioactive material direct into located tissues
- Use of strong ß$^-$- or α-emitters

Nuclearmedical Diagnostics

- Medium range
- Low dose
- γ - emitter
- β^+ - emitter

β^+ - Emitter

Isotope	$t_{1/2}$	γ - Energy (MeV)
^{11}C	20,4 min	0,5
^{13}N	9,9 min	0,5
^{15}O	2,0 min	0,5
^{18}F	110,0 min	0,5

γ - Emitter

Isotope	$t_{1/2}$	γ - Energy (MeV)
^{131}I	8,0 d	0,36
^{99m}Tc	6,0 h	0,14

PET

(Positron Emission Tomography)

SPECT

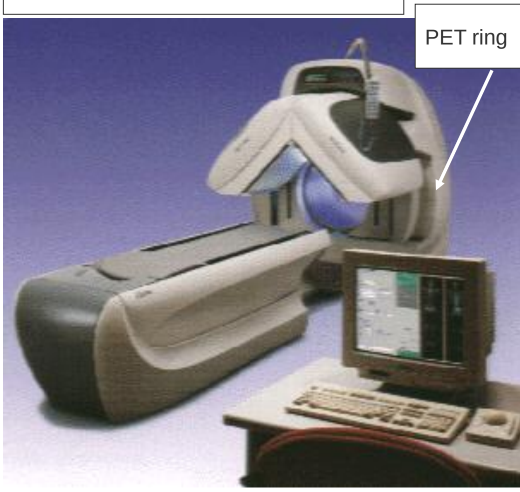
(Single Photon Emission Computer Tomography)

Interactions between nuclear radiation and biological material Freie Universität Berlin

Nuclearmedical Diagnostics

Combined PET / SPECT- Scanner

PET ring



Nuclearmedical Diagnostics, Positron Emission Tomography

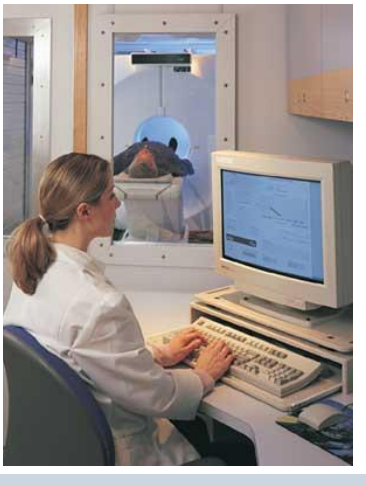
- High end method
- Coincident detection of two γ-quants (cf. Positron decay) provides highly resolved images
- ^{11}C, ^{13}N and ^{15}O are positron emitters, which allow the labeling of biologically active molecules (drugs, antibodies etc.)
- ‚Workhorse‘:. ^{18}F: frequent application in pharmaceutical research, functional diagnostics and medical research

Advantages	Disadvantages
- ‚Biological‘ isotopes	-Extremely short half-lifes of ^{11}C, ^{13}N and ^{15}O
- High resolution	- Production of the isotopes by cyclotrons
- Visualisation of biological activity	- High costs
- Real functional diagnostics	

Nuclearmedical Diagnostics, Positron Emission Tomography

PET scanner

Reconstitution of the images



Nuclearmedical Diagnostics, Single Photon Emission ComputerTomography

Isotope	$t_{1/2}$	γ - Energy (MeV)
^{131}I	8,0 d	0,36
^{99m}Tc	6,0 h	0,14

SPECT Camera

SPECT with integrated computertomograph