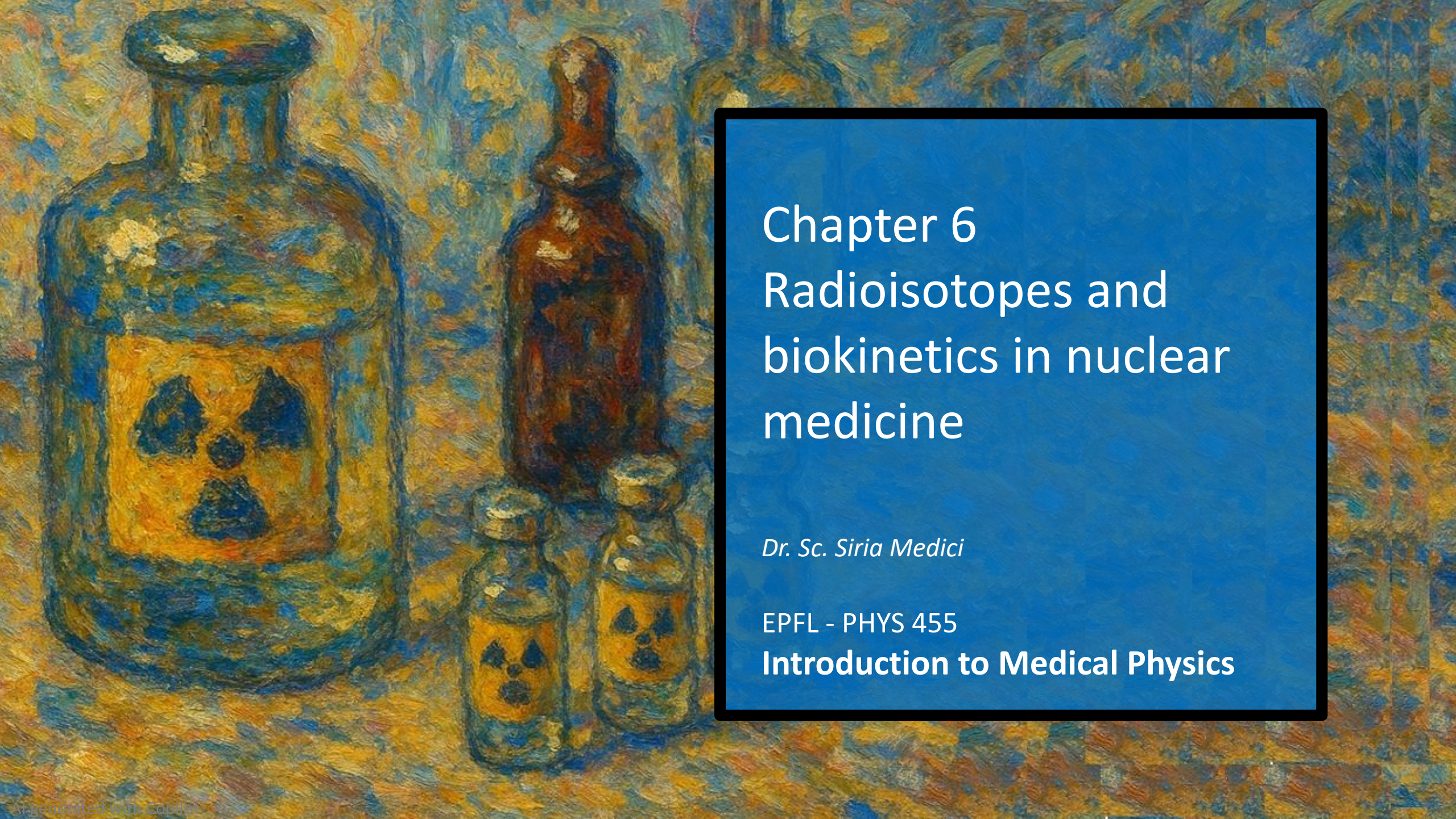

Chapter 6
Radioisotopes and biokinetics in nuclear medicine

Dr. Sc. Siria Medici

EPFL - PHYS 455

Introduction to Medical Physics

Learning objectives

- Distinguish between the different types of **radioactive decay** and their potential **use** in nuclear medicine.

- Illustrate the **mechanisms of action** of a radiopharmaceutical product and their **methods of production**.

- Explain the concept of **biokinetic models** and **internal dosimetry formalism** and use them in applied settings.

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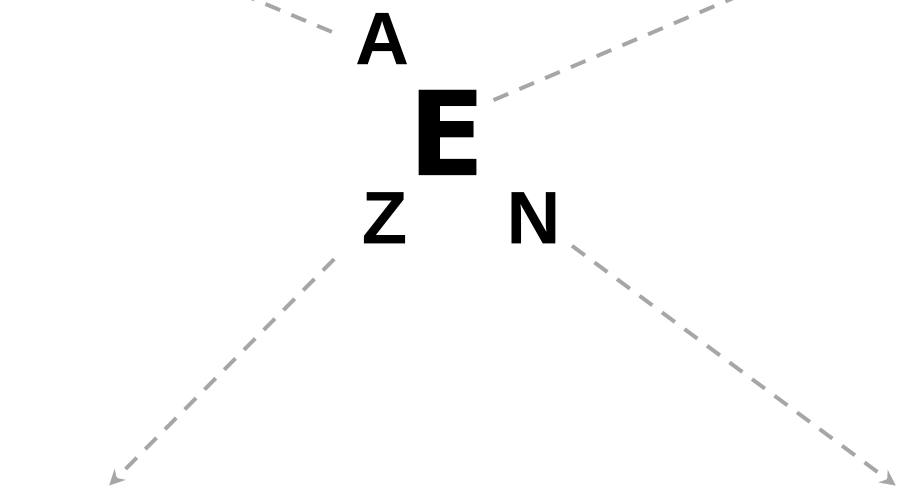
Part 1 - Radioactive decay

Nomenclature

$^{14}_{6}C_{8}$ = ^{14}C



Mass number

of the nucleus : N + Z

Element

C = carbon

Cs = caesium.

characterized by the number of protons (Z).

Number of protons (atomic number)

Chemical characteristics of the element

Number of neutrons

different N's for a given Z

= isotopes

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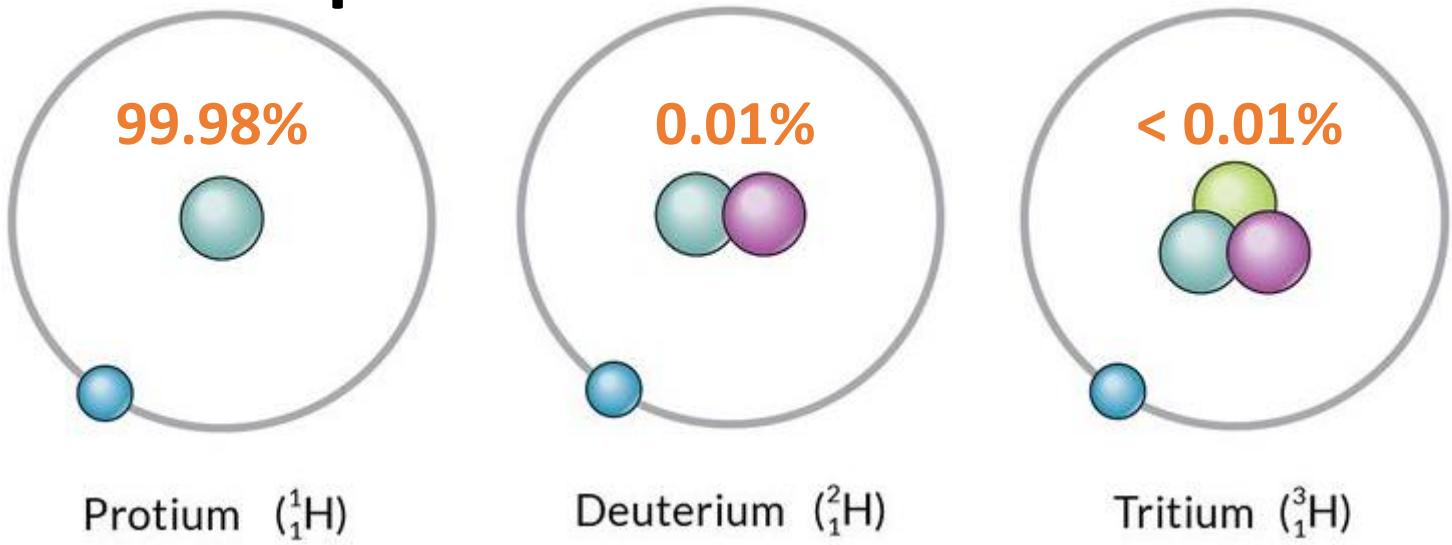
Isotopes, isotones, isobars

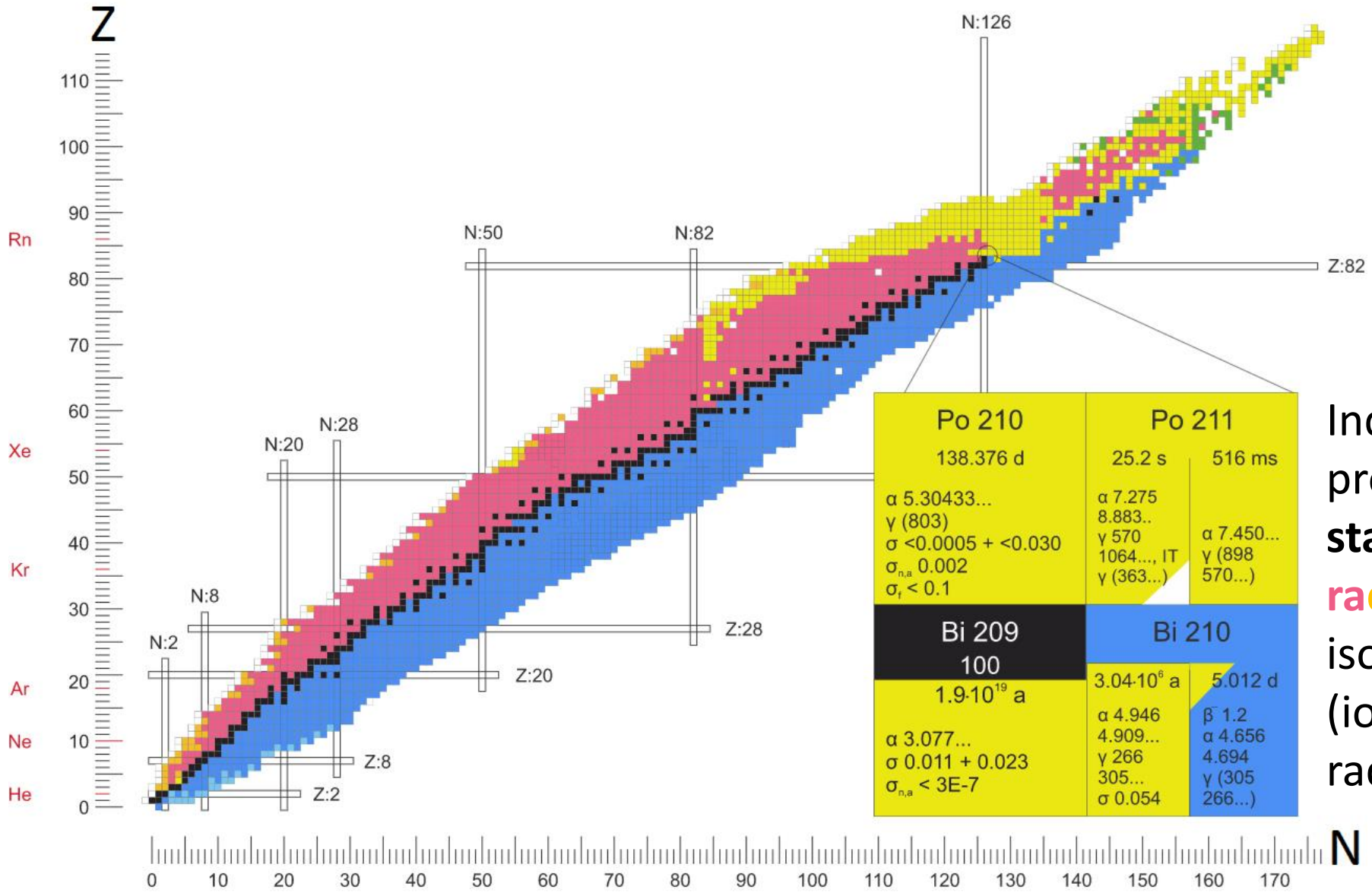
- Isotopes: nuclides sharing the same **Z** (same element), but different **N**
- Isotones: nuclides sharing the same **N**, but different **Z**
- Isobars: nuclides sharing the same **A**, but different Z and N.

- The hydrogen atom has three **isotopes**:
  - Protium: 1 p, 1 e-
  - Deuterium: 1 p, 1 n, 1 e-
  - Tritium: 1 p, 2 n, 1 e-



Source: https://www.daviddarling.info/encyclopedia/T/tritium.html

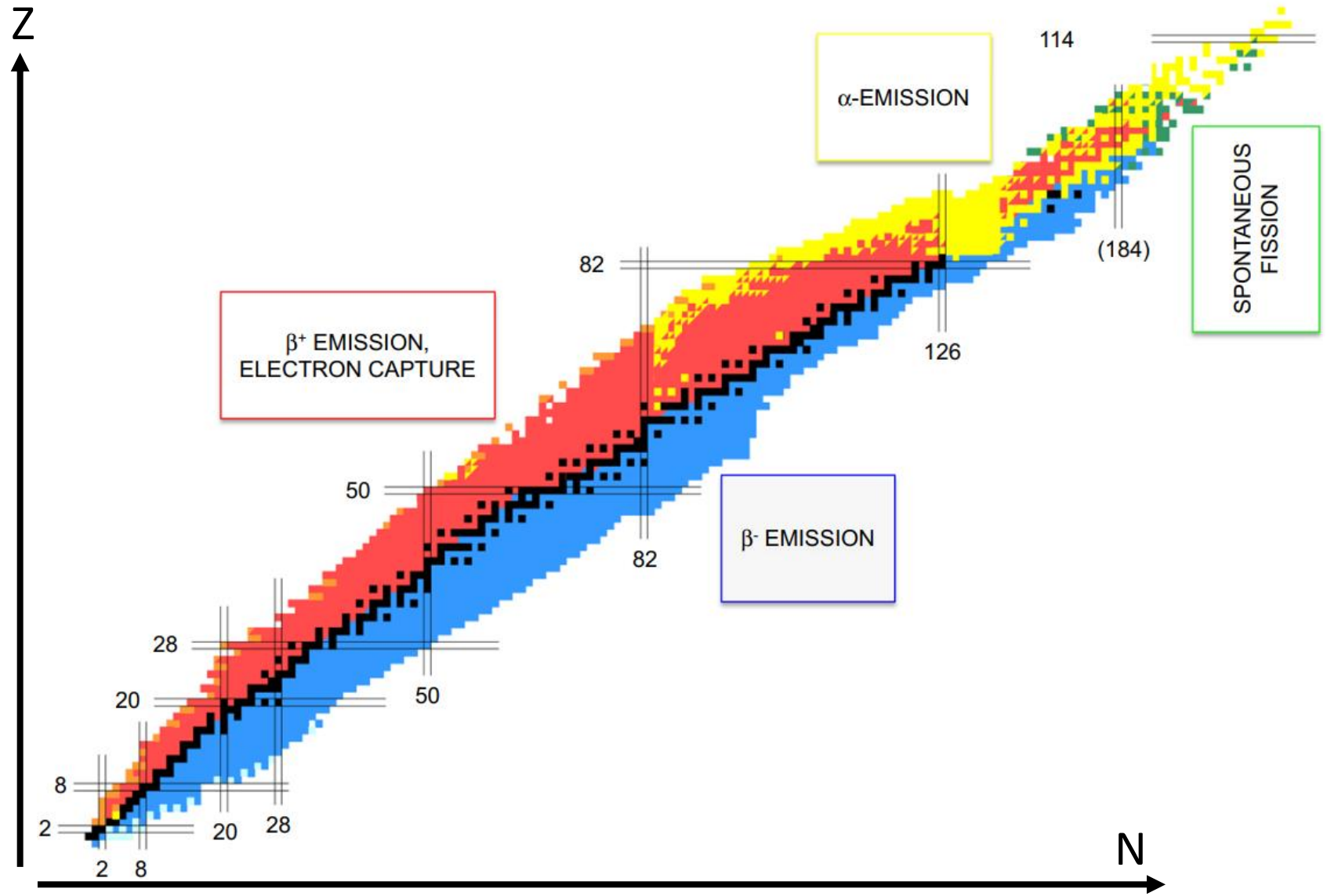
Karlsruhe nuclide chart



Indicates properties of **stable** and radioactive isotopes (ionizing radiation)

Source: https://www.oviss.jp/view/item/000000001879?category_page_id=ct312

Karlsruhe nuclide chart

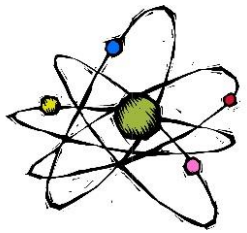


Source: https://doi.org/10.1007/s40828-018-0068-x

Radioactivity

- Activity : # of decays per second (**Becquerel**, s^{-1})

- Old unit (sometimes still used): **Curie** (Ci)



$$A = \lambda \cdot N$$

$$A(t) = A_0 \cdot e^{-\frac{\ln(2)}{T} \cdot t}$$

1852 - 1908

1859 - 1906

1867 - 1934

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Source: https://www.nobelprize.org/prizes/physics/1903/becquerel/facts/; https://explore.psl.eu/fr/decouvrir/expositions-virtuelles/marie-curie-1867-1934/une-nouvelle-vie-parisienne-1891-1897; https://www.pinterest.com/pin/2040762314518118/; https://www.science.org/content/article/perimeter-institute-experiment-research-utopia

Radioactivity - quiz

- A vial containing Tc-99m is labelled «200 MBq/mL» @ 8:00.

- What volume should be withdrawn at 15:00 to prepare an injection of 50 MBq for a patient?

Work in groups of ~3
5 minutes

Ru 98 1.87 σ < 8.0	Ru 99 12.76 σ 7.25	Ru 100 12.60 σ 5.8	Ru 101 17.06 σ 5.2
Tc 97 91.0 d / 4.21·10⁶ a IT (97) e⁻ ε ε no γ	Tc 98 4.2·10⁶ a β⁻ 0.4 γ 745, 652 σ 0.93 + ?	Tc 99 6.0072 h / 2.111·10⁵ a IT (143, 2) e⁻ γ 141 β⁻... γ (90...) β⁻ 0.3... γ (90) σ 22.8	Tc 100 15.65 s β⁻ 3.2... γ 540, 591... ε
Mo 96 16.673 σ 0.55	Mo 97 9.582 σ 2.2, $\sigma_{n,\alpha}$ 4E-7	Mo 98 24.292 σ 0.130	Mo 99 65.924 h β⁻ 1.2... γ 740, 181 778... m, g

Source :Nucleonica ; https://commons.wikimedia.org/wiki/File:SBB_railway_clock_animated.gif ; vial image generated by Copilot

Radioactivity - quiz

- What does 1 Ci correspond to?

- To 37 GBq
- To the activity contained in 1 g of Ra-226
- at 10 times the activity of Ra-226, which Mrs. Curie purified from 13 tons of mine tailings

Source:https://kenyonlyceum.wordpress.com/2019/12/14/the-half-life-of-marie-curie/

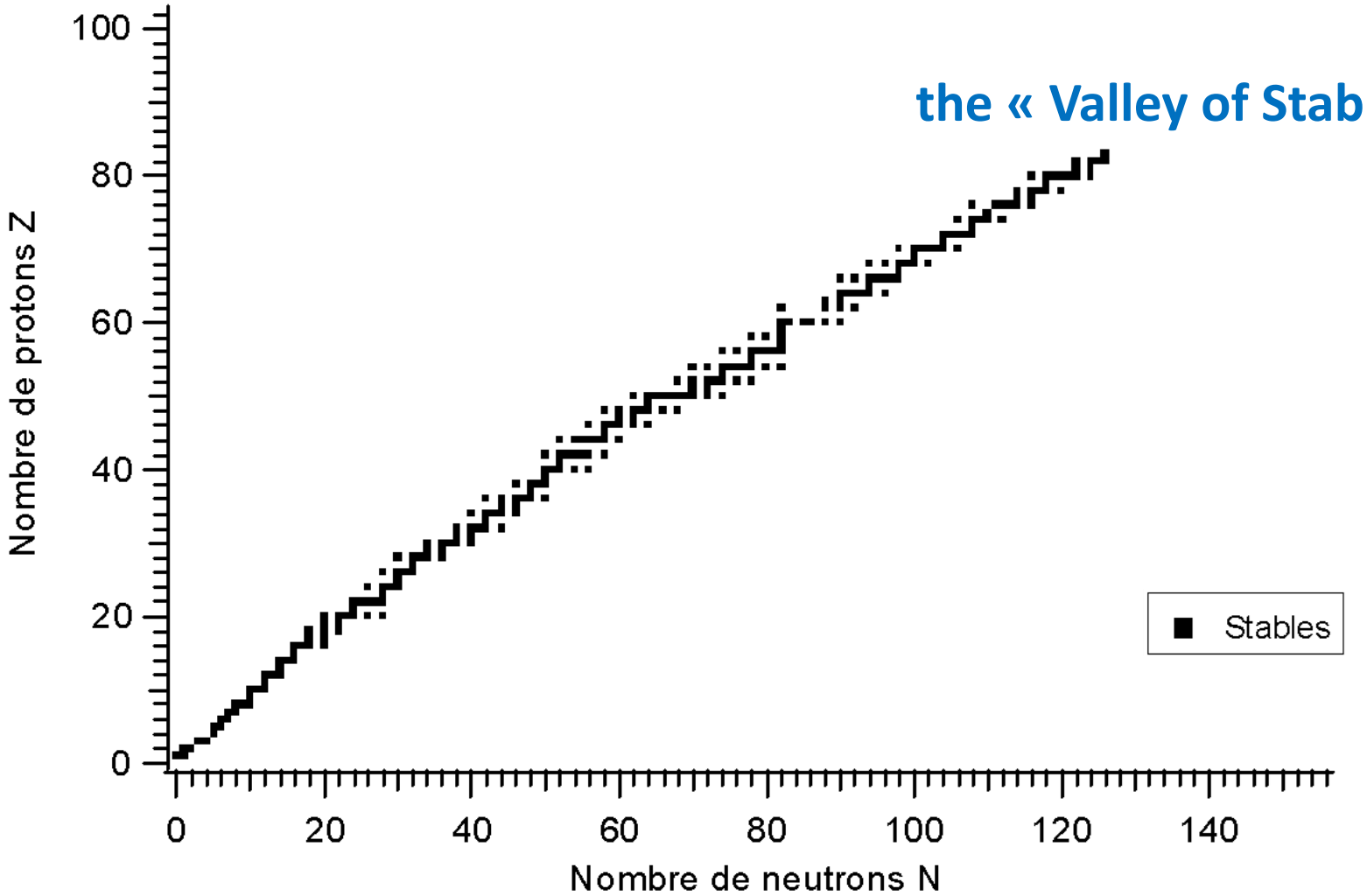
Radioactivity - quiz

- What is the typical half-life of radionuclides used for nuclear medicine applications?

- From ns to ms
- From s to minutes
- From minutes to hours
- From hours to days
- From days to months

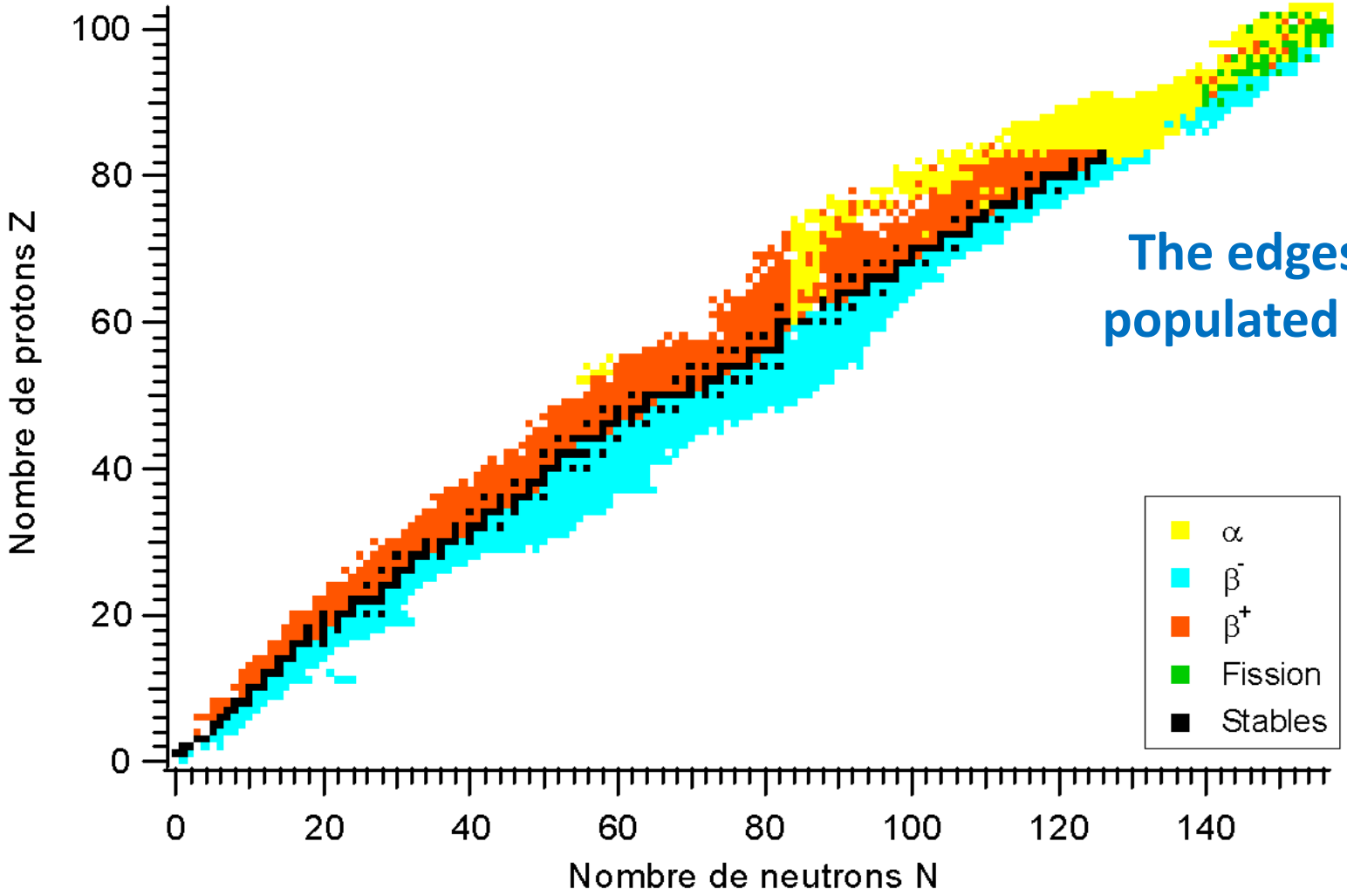
Source:https://kenyonlyceum.wordpress.com/2019/12/14/the-half-life-of-marie-curie/

Nucleus (In)stability



the « Valley of Stability »

Nucleus (In)stability



The edges of the valley are populated by unstable nuclei

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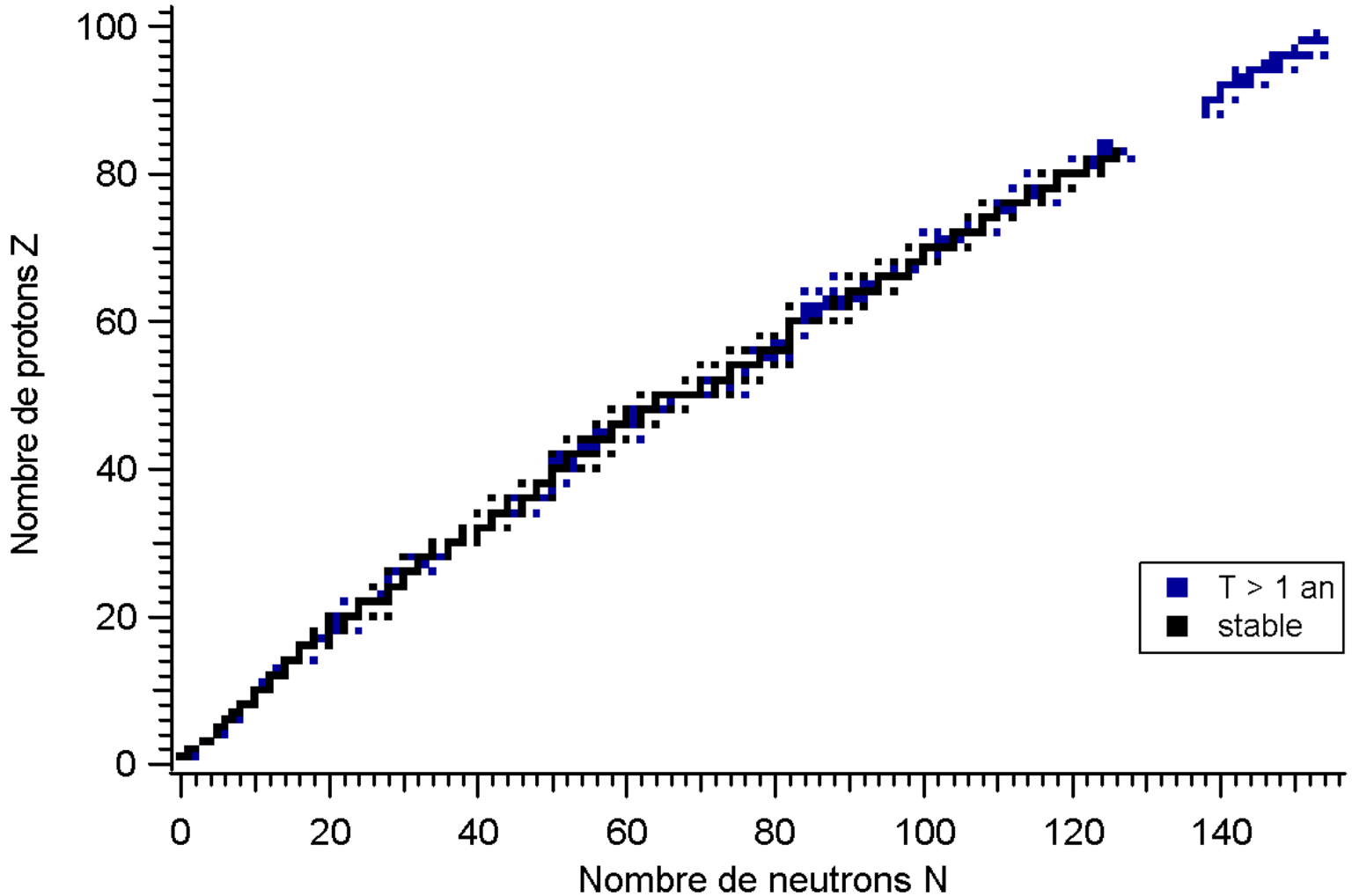
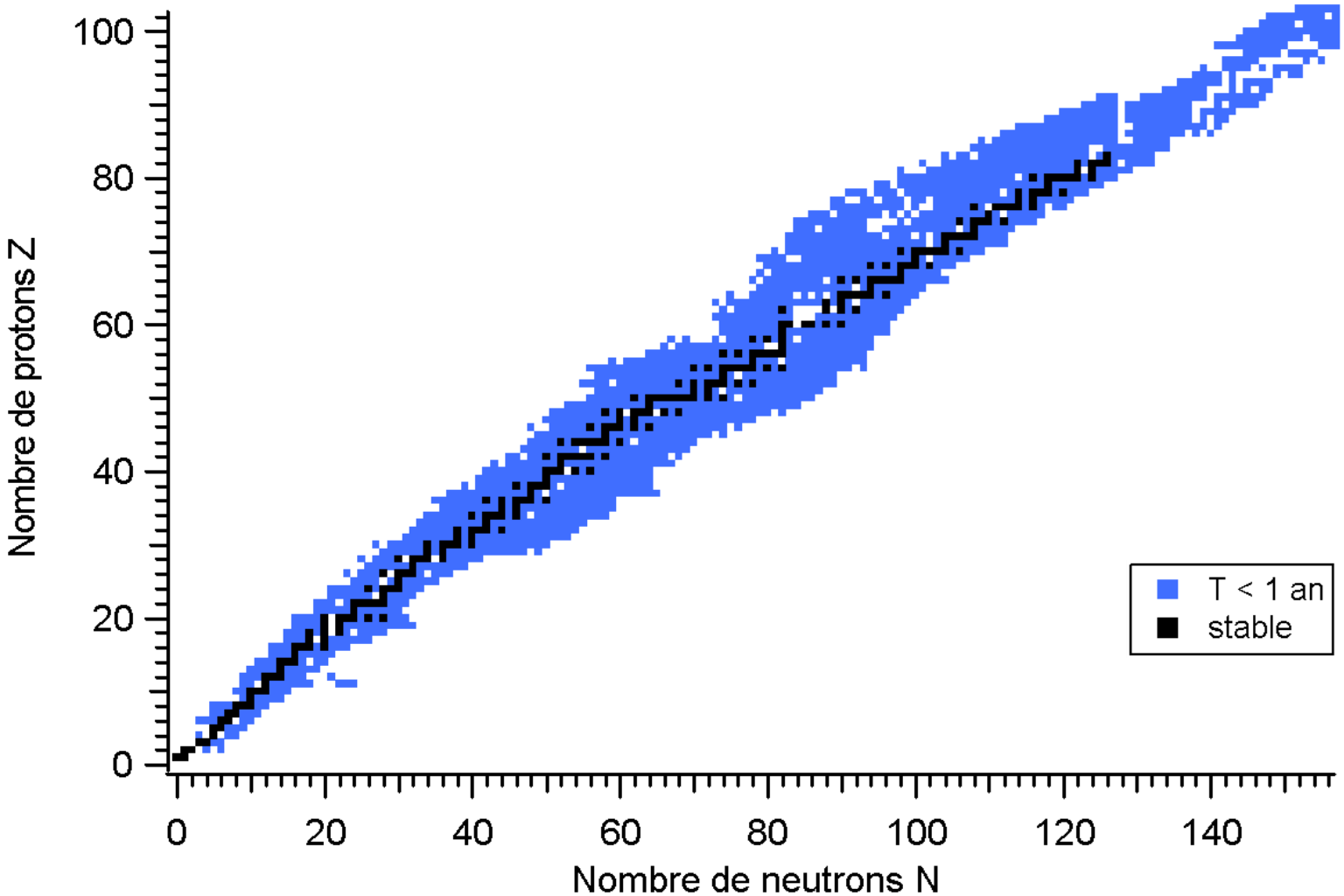
Nucleus (In)stability



Nucleus (In)stability



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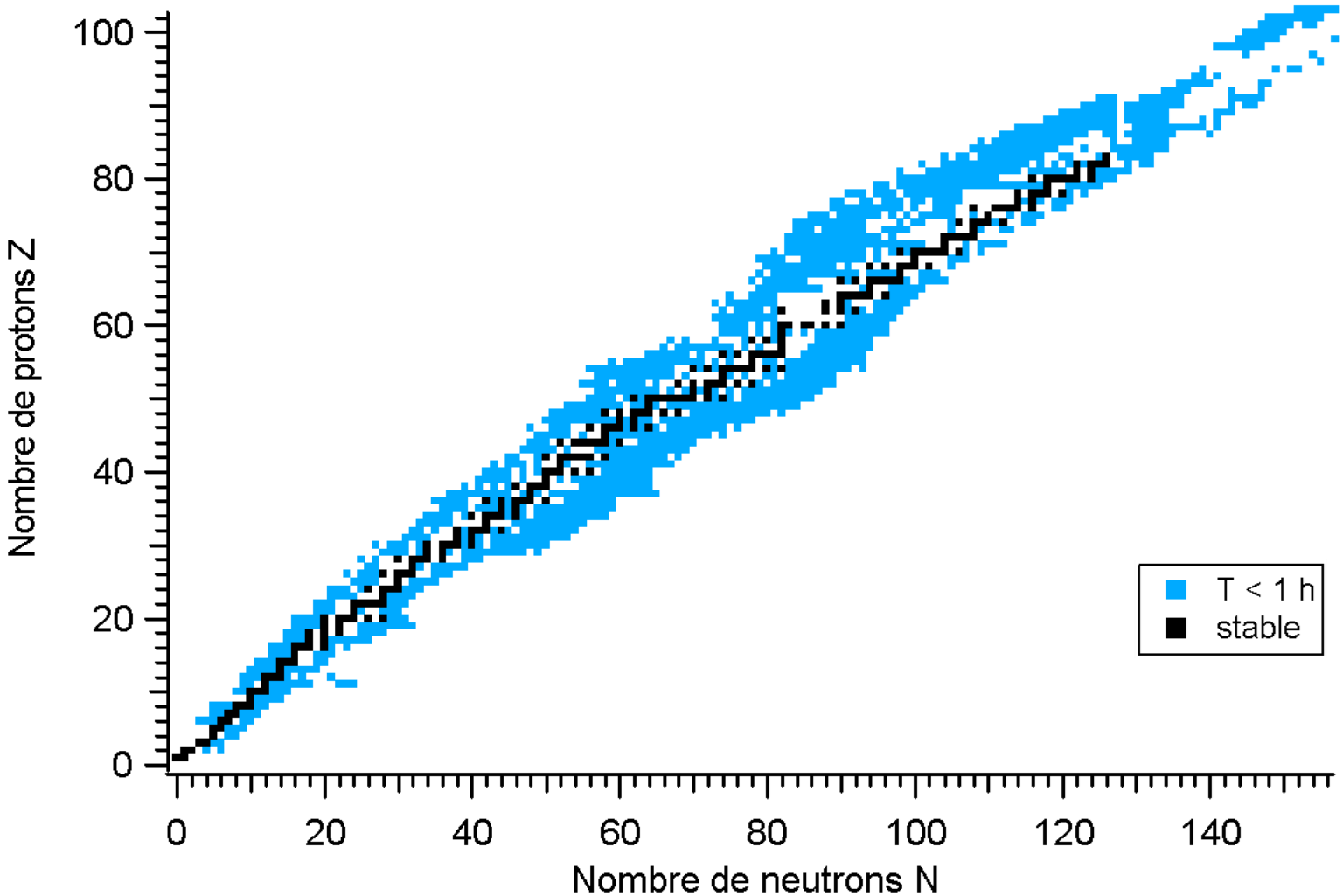
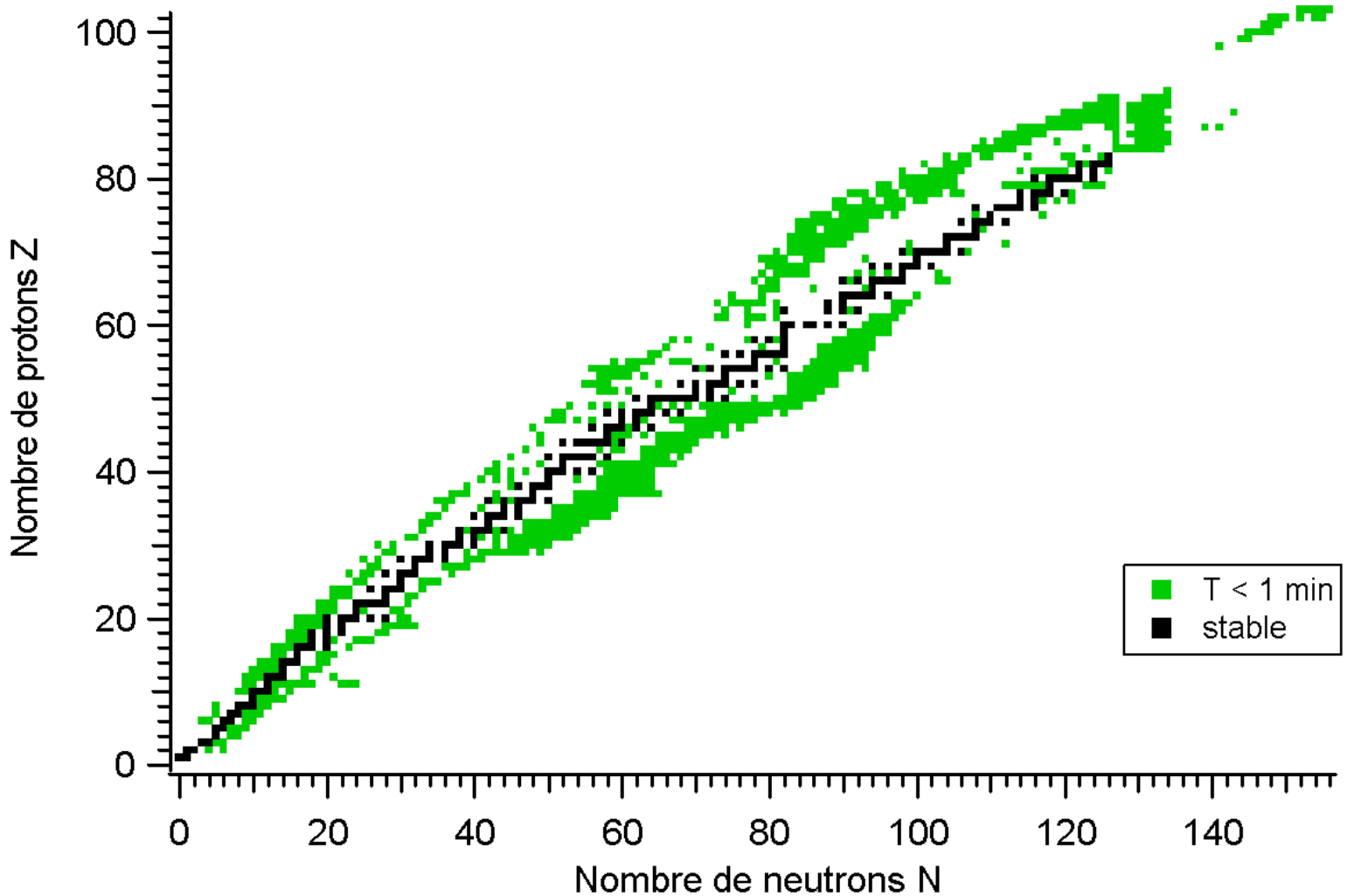
Nucleus (In)stability



Nucleus (In)stability



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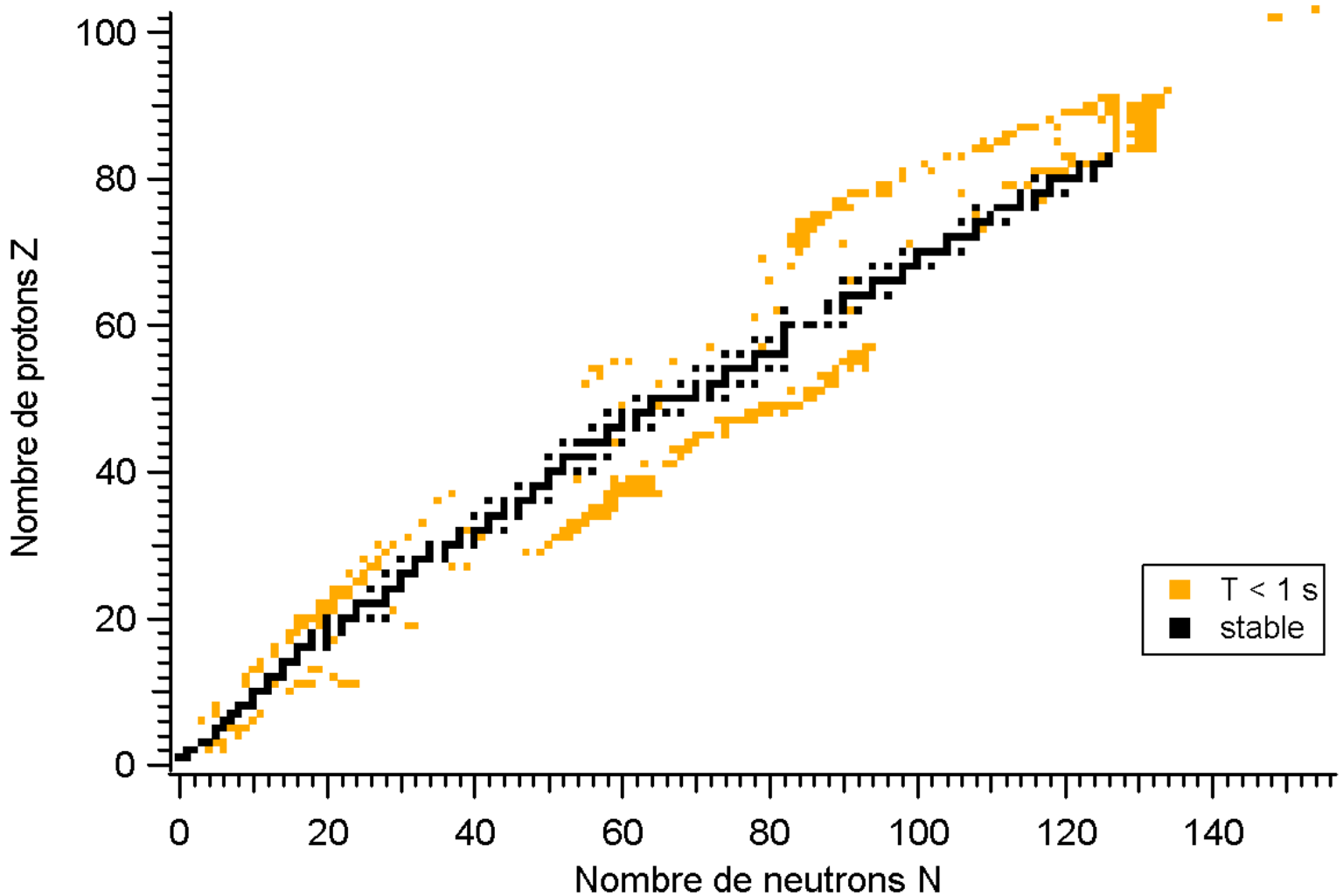
Nucleus (In)stability



Types of radioactive decay

- We can distinguish between different types of radioactive decay used in nuclear medicine :

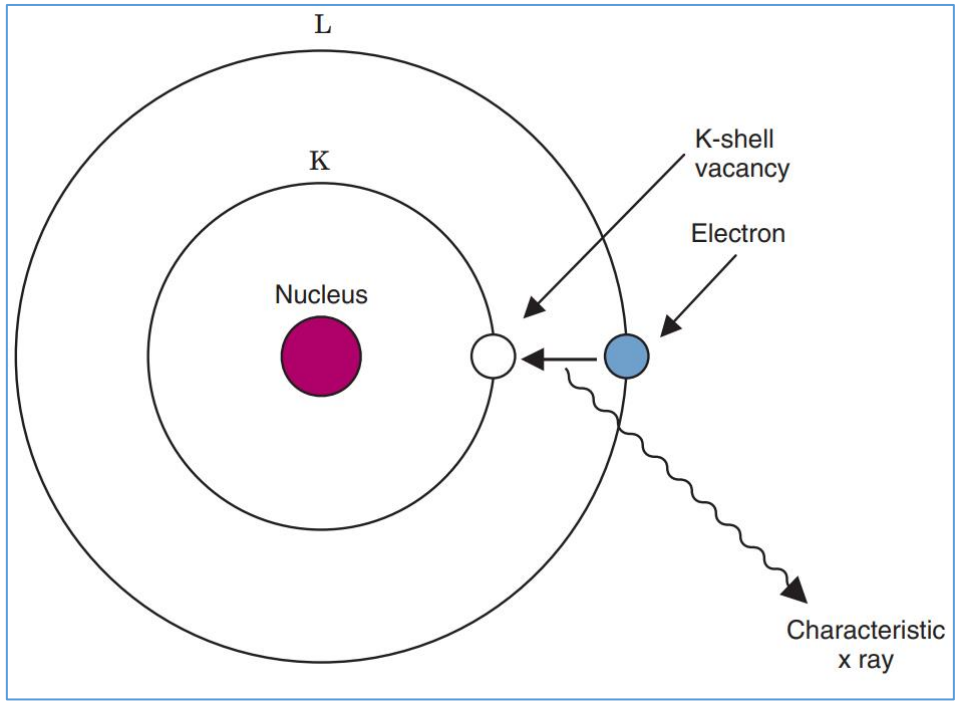
1. **β** decay (**β- and β+/electron capture)**
2. **γ** decay, **isomeric transition** and **internal conversion**
3. **α** decay

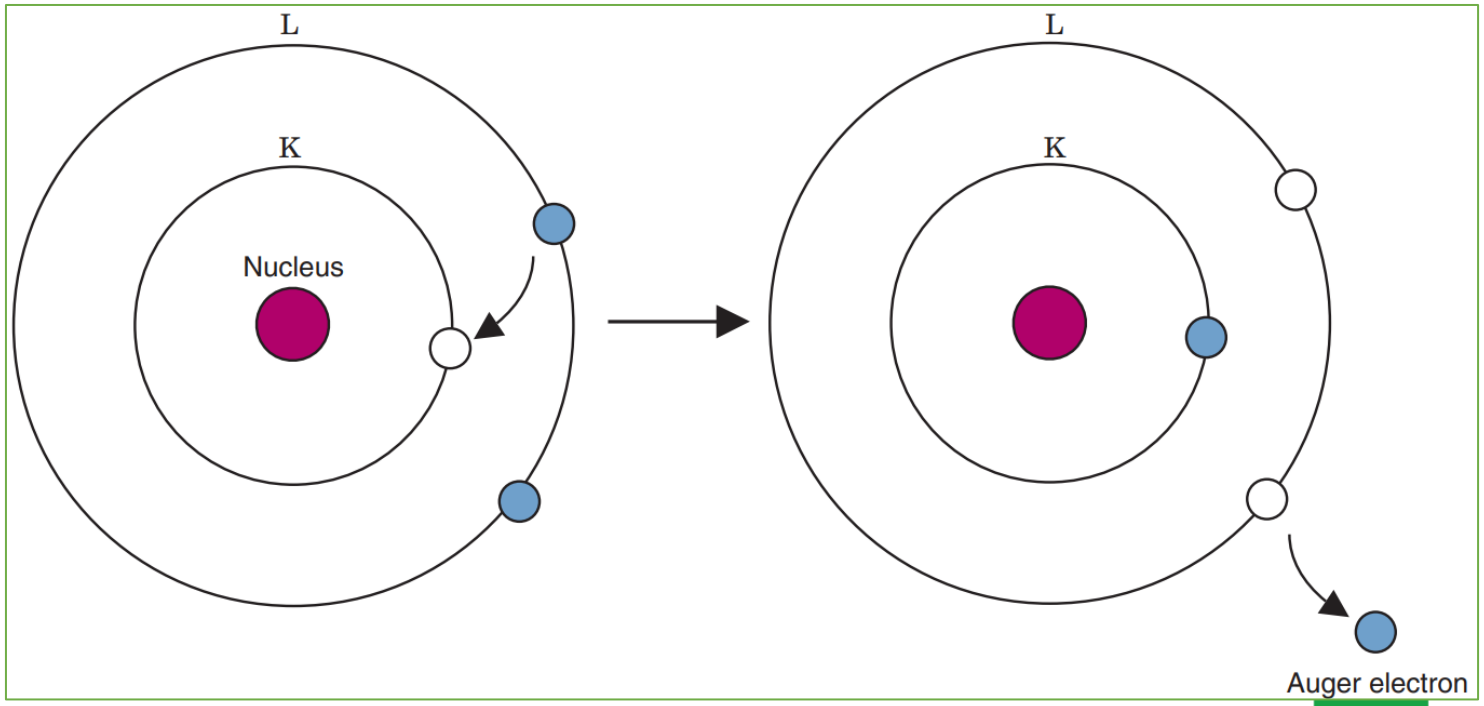
Electron vacancies

- Vacancies are filled by outer shell electrons, resulting in either:

1. Characteristic X-rays emission

2. Auger electrons emission





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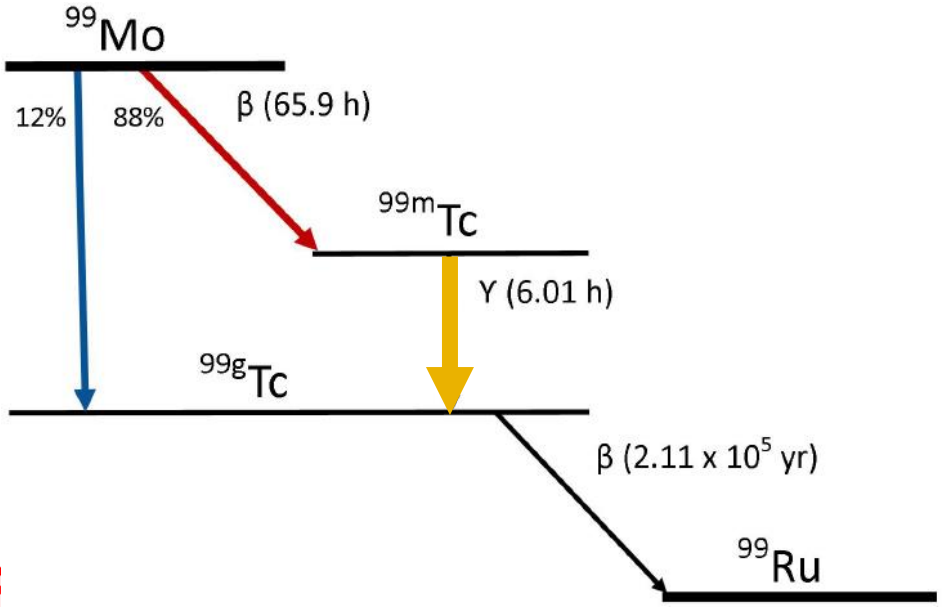
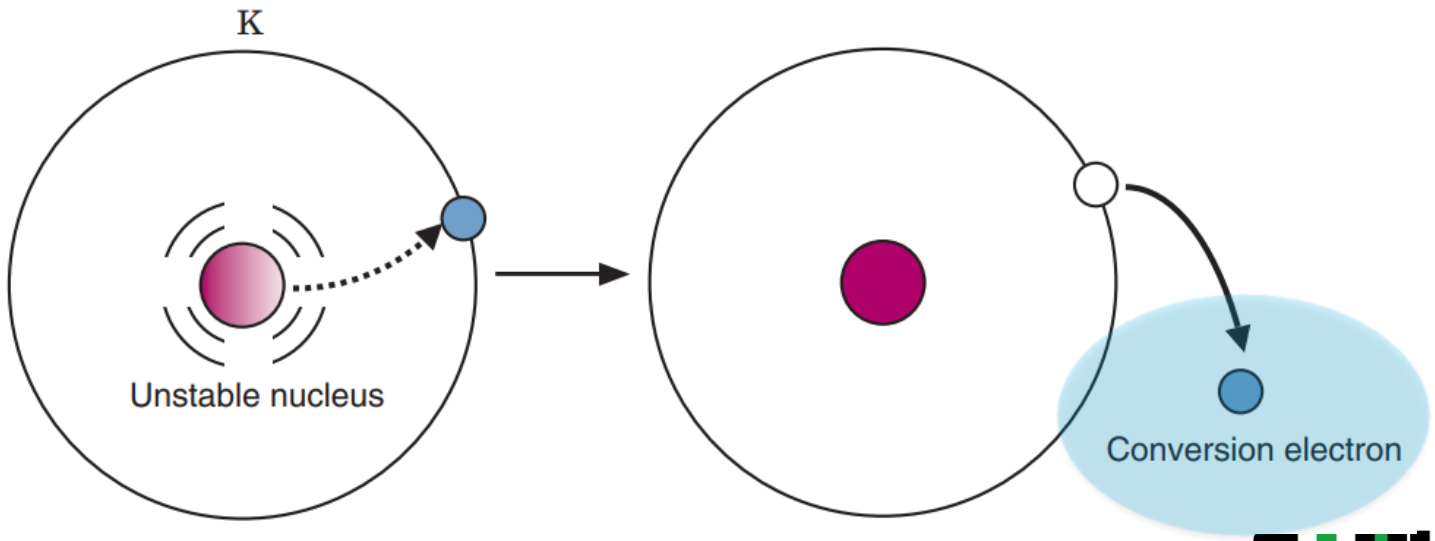
Isomeric transition and internal conversion

- Decay may leave the daughter nucleus in excited state → γ emission possible.
- Daughter nucleus may be left in a <u>metastable</u> state (long-lived excited state).
- Two ways to release the excess energy:
  1. Isomeric transition → decay from excited to ground state by **γ emission**.
  2. Internal conversion → excess energy **transferred to orbital electron** (ejected)





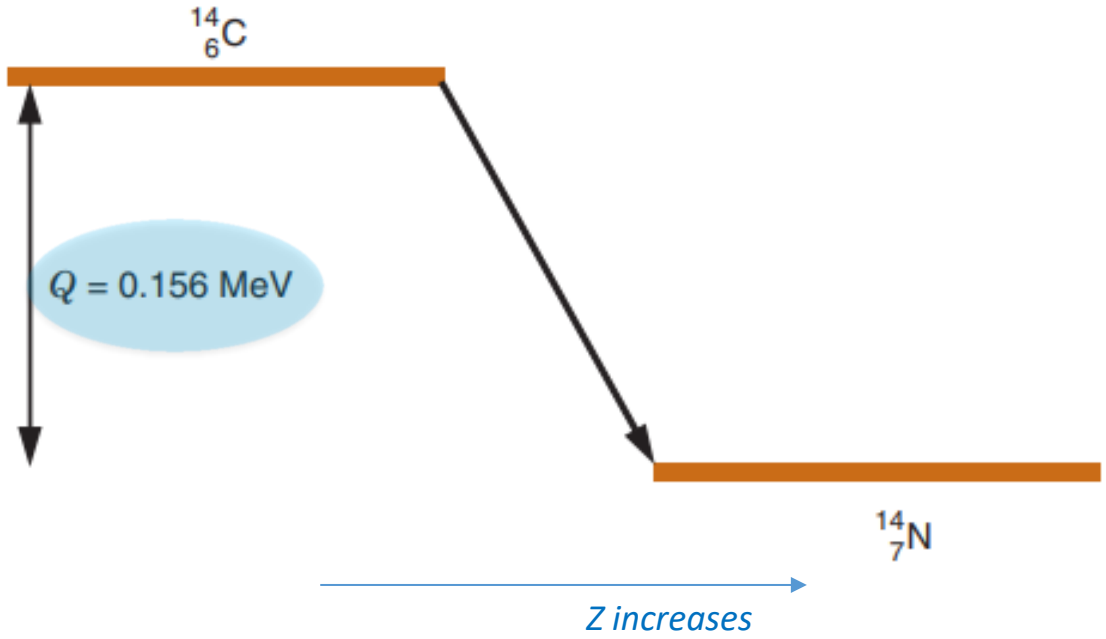
Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985, https://nap.nationalacademies.org/read/23563/chapter/5; https://tenor.com/search/ejection-seat-gifs

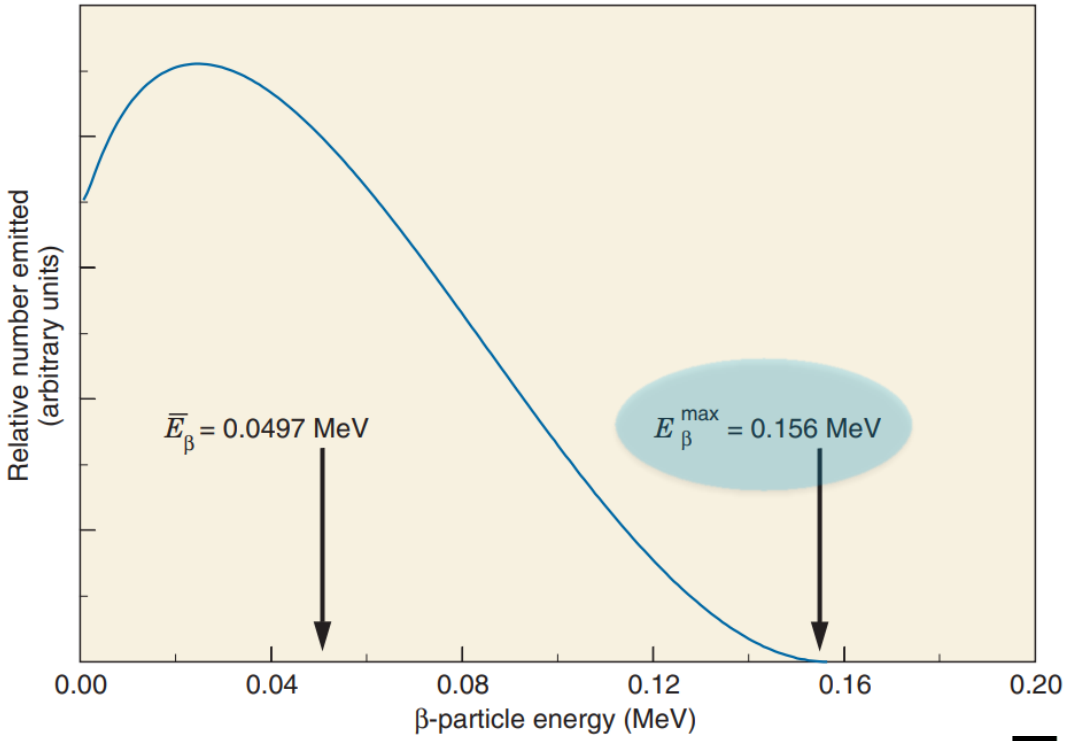
$n \rightarrow p^+ + e^- + \bar{\nu}_e + \text{energy}$

β (β-)

$${}^{A}_{Z}X \xrightarrow{\beta-} {}^{A}_{Z+1}Y$$

- Neutron in the nucleus converted into proton = element transmutation.
- Mother and daughter are isobars: same mass number A
- Released energy is shared between β^- particle and $\bar{\nu}_e$ → continuous spectrum.



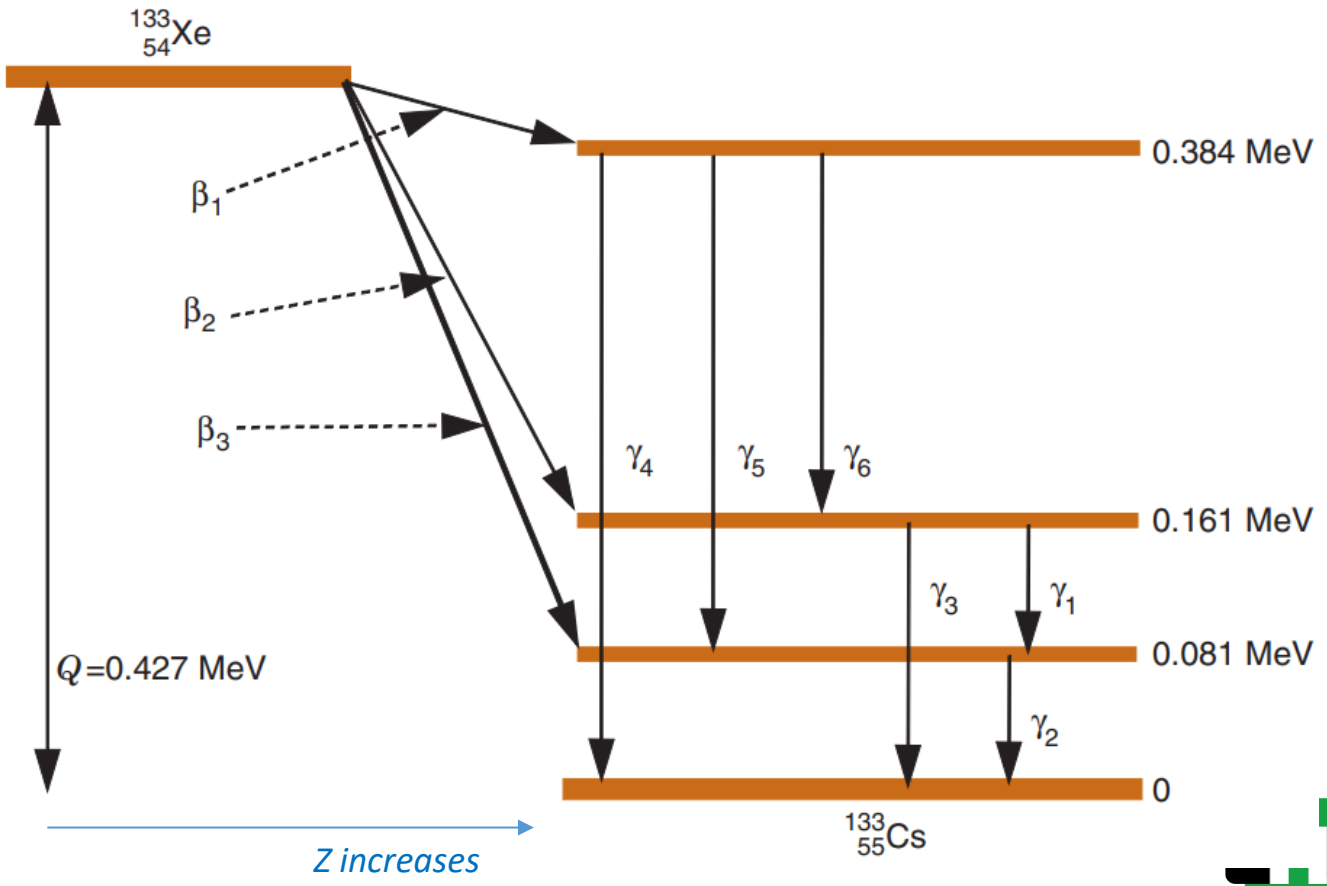


Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

β (β-,γ)

$$ {}^{A}_{Z}X \xrightarrow{\beta-} {}^{A}_{Z+1}Y^{*} \xrightarrow{\gamma} {}^{A}_{Z+1}Y $$

- Mother nucleus may be left in an excited or metastable state.
- The γ emission does not result in further element transmutation
- γ emissions are monoenergetic



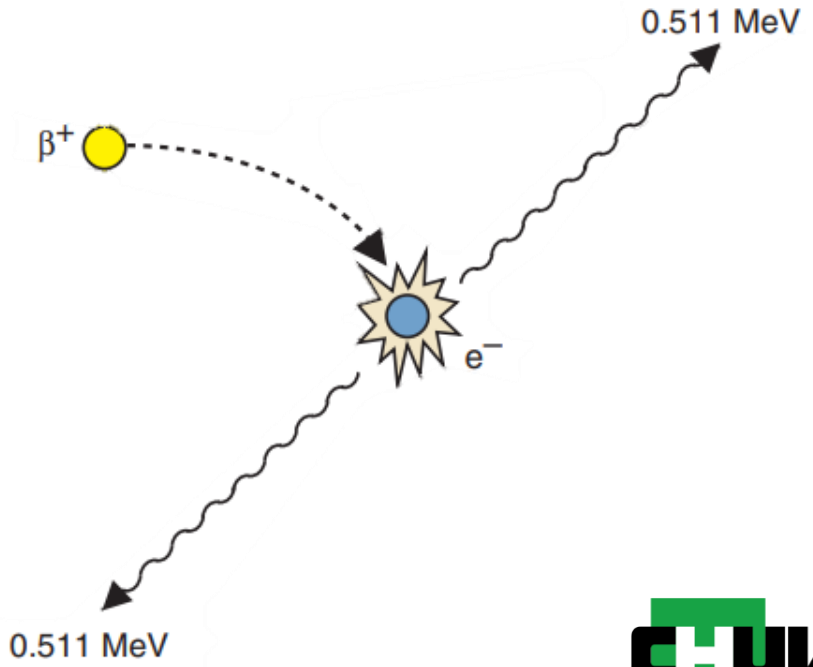
Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

$p^+ \rightarrow n + e^+ + \nu_e + \text{energy}$

β (β+,γ)

$${}^{A}_{Z}X \xrightarrow{\beta+} {}^{A}_{Z-1}Y$$

- Proton in the nucleus converted into neutron = element transmutation.
- Mother and daughter are isobars: same mass number A.
- Excess* energy is shared between β^+ particle and ν_e → continuous spectrum.
- e^+ interacts with e^- in matter (positronium, lifetime of 10^{-10} s) and annihilate.
- Emission of two γ of 511 keV each in nearly opposite directions (momentum conservation).
- Threshold $\Delta E_{min} = 2 \cdot 0.511\ MeV = 1.022\ MeV$
  (rest mass of 1 positron and 1 electron)
  mass of parent atom must exceed that of daughter + 1.022 MeV



excess = above 1.022 MeV

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

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β (β+,γ)

$${}^{A}_{Z}X \xrightarrow{\beta+} {}^{A}_{Z-1}Y$$

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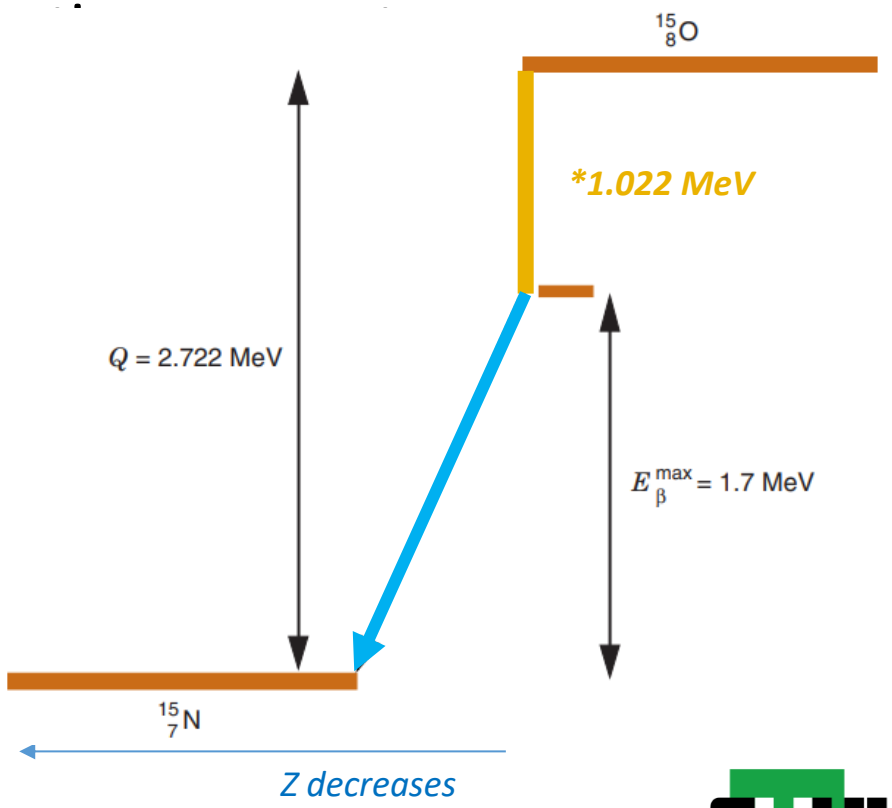


*excess = above 1.022 MeV

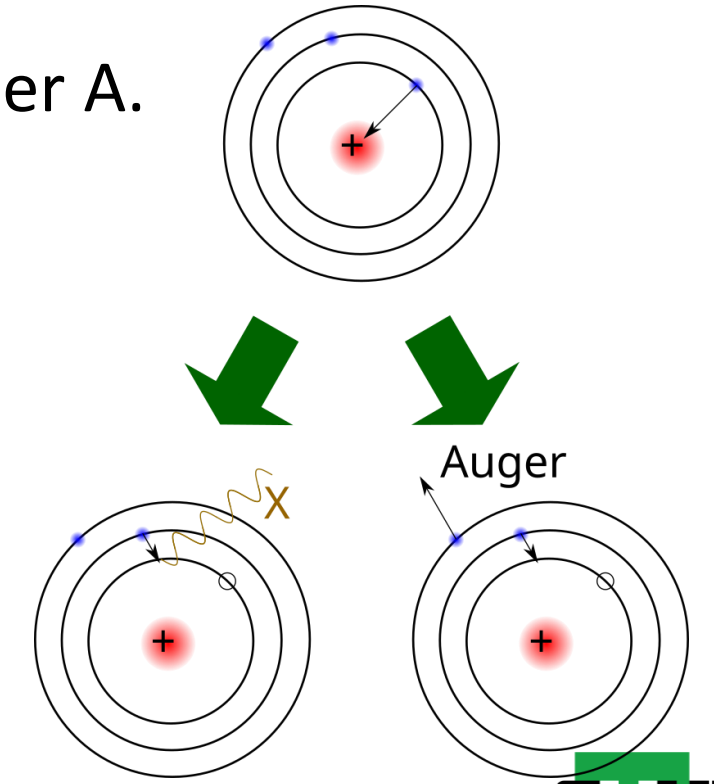
Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Electron capture (EC,γ)

$$^{A}_{Z}X \xrightarrow{EC} {}^{A}_{Z-1}Y$$

$$p^+ + e^- \rightarrow n + \nu_e + \text{energy}$$

- Similar (and sometimes in competition) to β+ decay.
- Proton in the nucleus converted into neutron = element transmutation.
- Mother and daughter are isobars: same mass number A.
- Orbital e^- captured by nucleus combines with p^+ to form a n.
- Energy shared between the ν_e and characteristic X-rays /Auger e^- resulting from the *vacancy*.
- Daughter often left in metastable or excited state → internal conversion is common after (EC,γ).



Source: https://en.wikipedia.org/wiki/Electron_capture

Electron capture (EC,γ)

$${}^{A}_{Z}X \xrightarrow{EC} {}^{A}_{Z-1}Y$$

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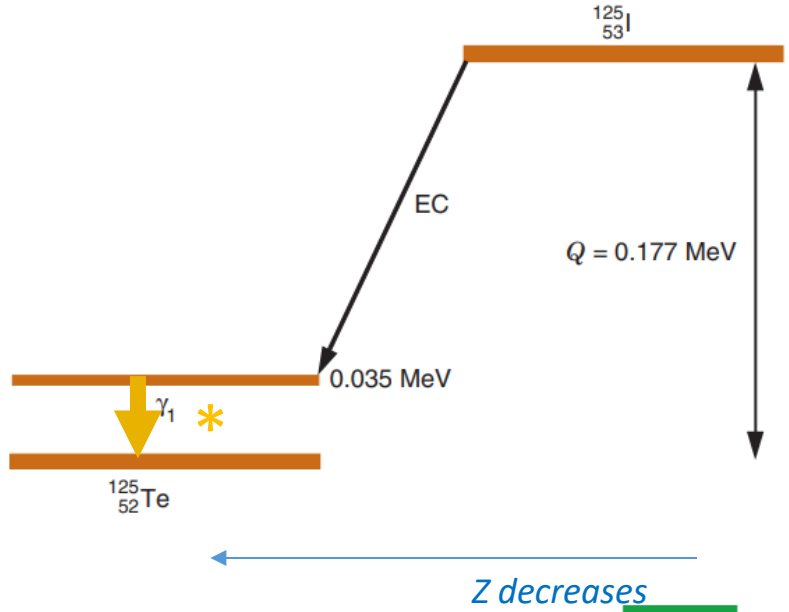
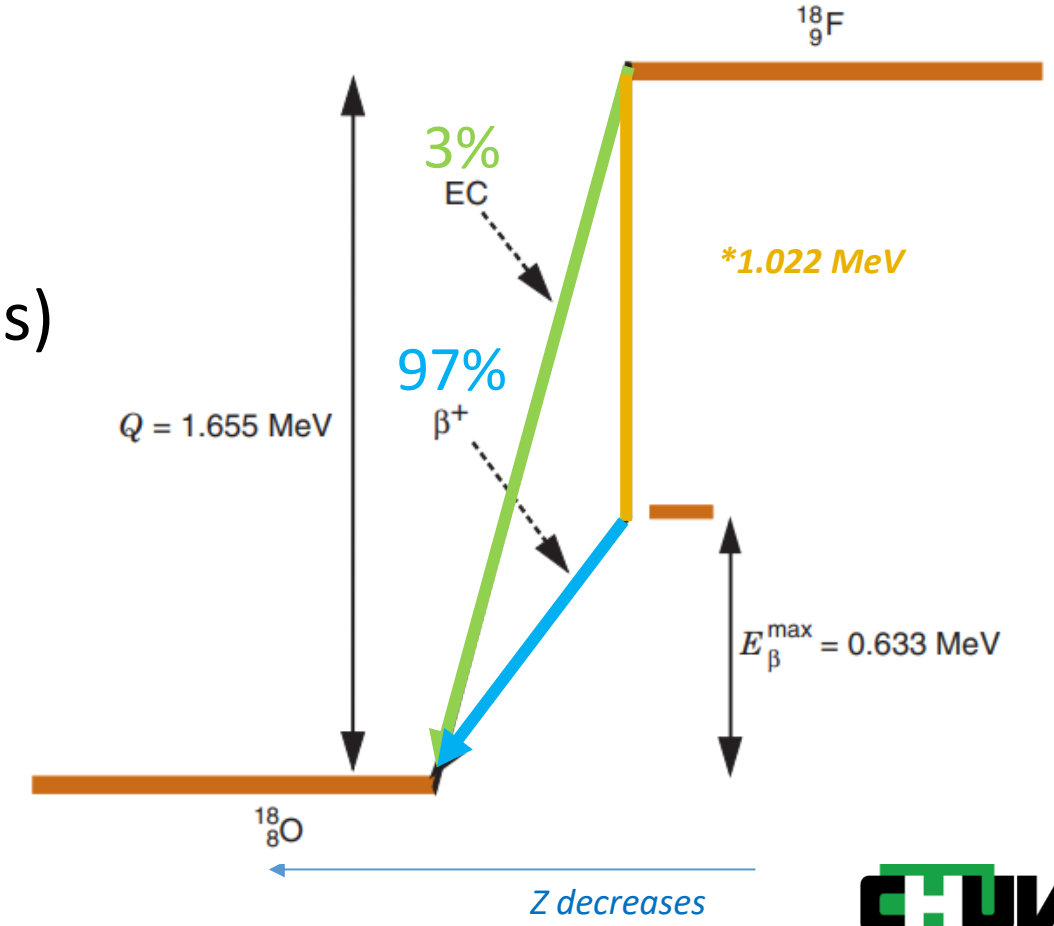


Source: https://en.wikipedia.org/wiki/Electron_capture

Electron capture (EC,γ) and (β+,γ)

- Same (final) effect on parent nucleus:
  - EC more common in heavier radionuclides (orbital e- closer to nucleus),
  - β+ more common in lighter radionuclides

- For the same radionuclide, they can be in competition (with different probabilities)



Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

α decay

"

I. DECAY BY α EMISSION AND BY NUCLEAR FISSION

. . . . . .

Radionuclides that decay by α-particle emission or by nuclear fission are of relatively little importance for direct usage as tracers in nuclear medicine but are described here for the sake of completeness.

"

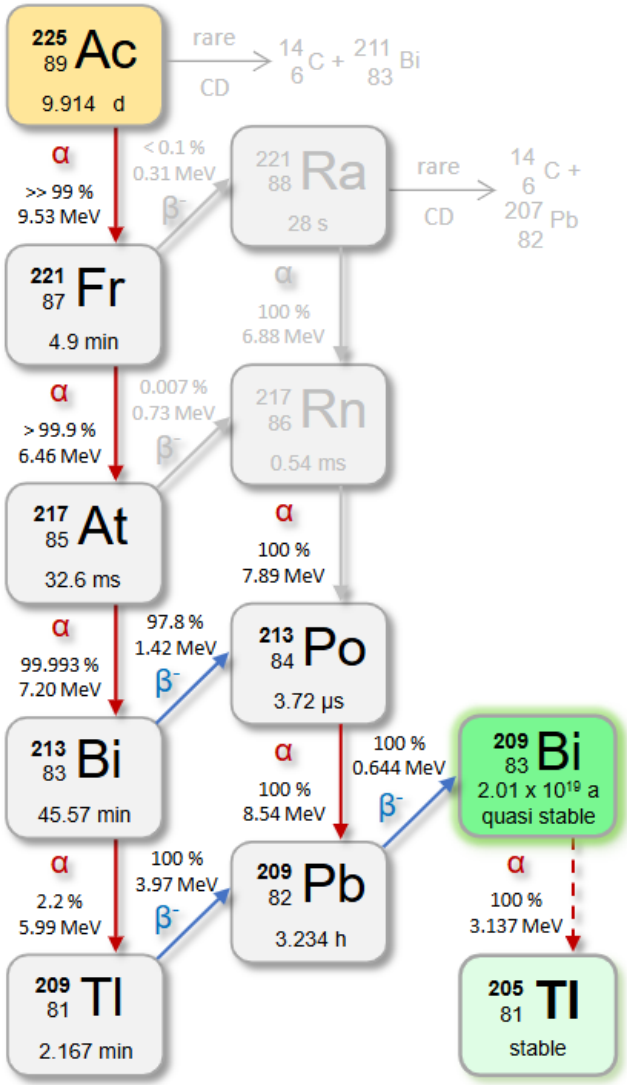
Not the case anymore!

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985 ; https://reactiongifs.me/tag/gandalf/

α decay

$$ {}^{A}_{Z}X \xrightarrow{\alpha} {}^{A-4}_{Z-2}Y $$

- Nucleus ejects an α particle (= a ${}^{4}_{2}\mathrm{He}$ nucleus).
- Element transmutation.
- Monoenergetic emission.
- Mother and daughter are not isobars: A-4.
- For very heavy elements that must lose mass to find stability.
- Typically results in long chains.



Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985 ; https://www.chemlin.org/isotope/actinium-225

….before we move on…

Recap – **photon** emission

- Gamma emission:
  - Nuclear emission of γ (discrete energies, from keV to MeV) to find stability.
  - Special case : isomeric transition
    - from a metastable (i.e. longer-lived) state → «delayed gamma emission»

- Characteristic X-rays:
  - Atomic (electronic) origin.
  - Comes from electron shell rearrangement (discrete photon energies, few keV).

Recap – **electron** emission

- Auger e-:
  - Due to electron shell rearrangement, competitive with characteristic X-rays
  - Atomic e-
  - Discrete energy (few keV)

- Internal conversion e- :
  - Due to nuclear de-excitation, alternative to gamma emission
  - Atomic e-
  - Discrete energy (from keV to MeV)

- Beta-decay e-:
  - Due to nuclear decay
  - Primary decay particle
  - Continuous energy (from keV to MeV)

Radioactive decays : a way towards **stability**

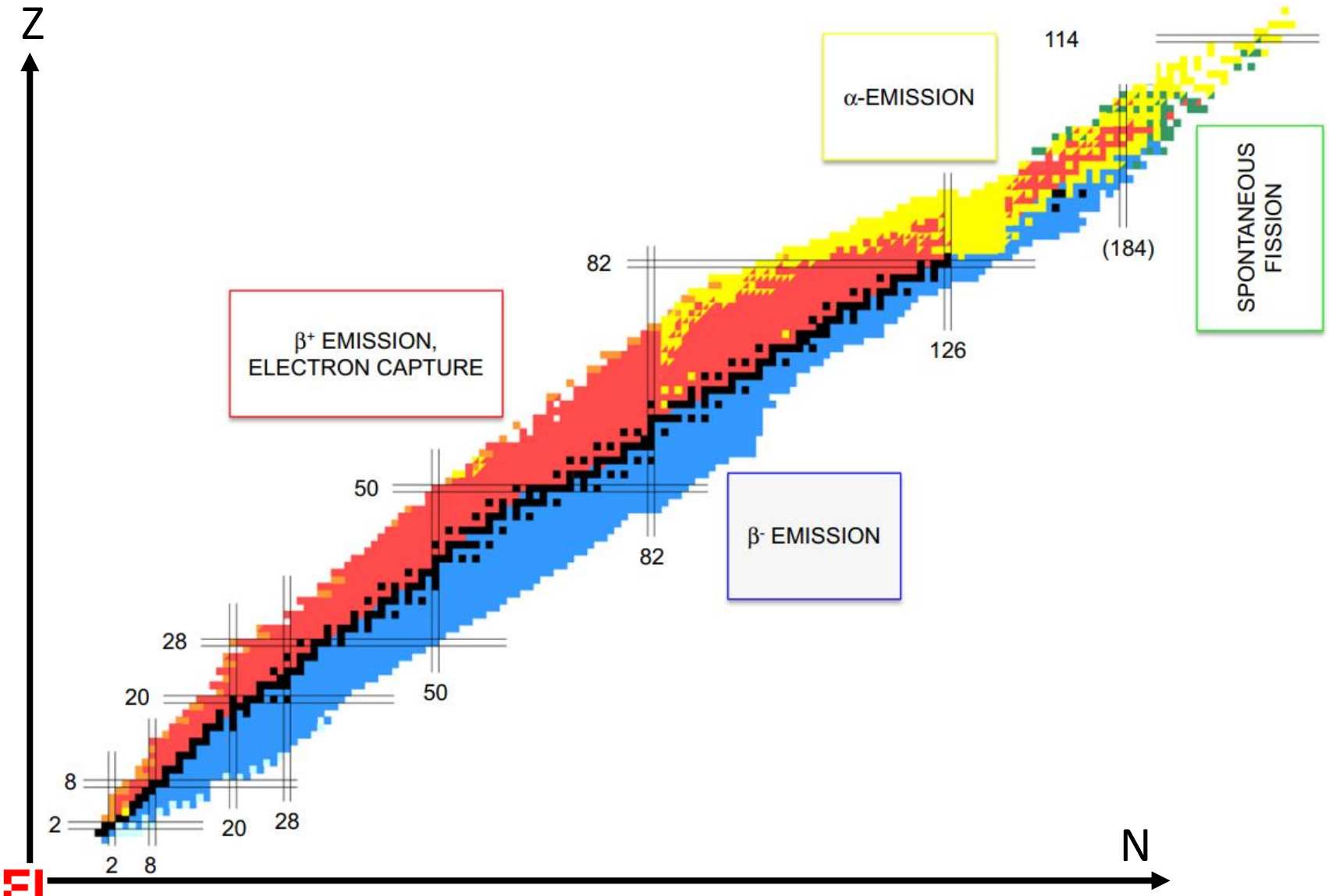
- All radioactive isotopes have excess energy they have to loose to reach a stable state → move closer to the valley of stability.

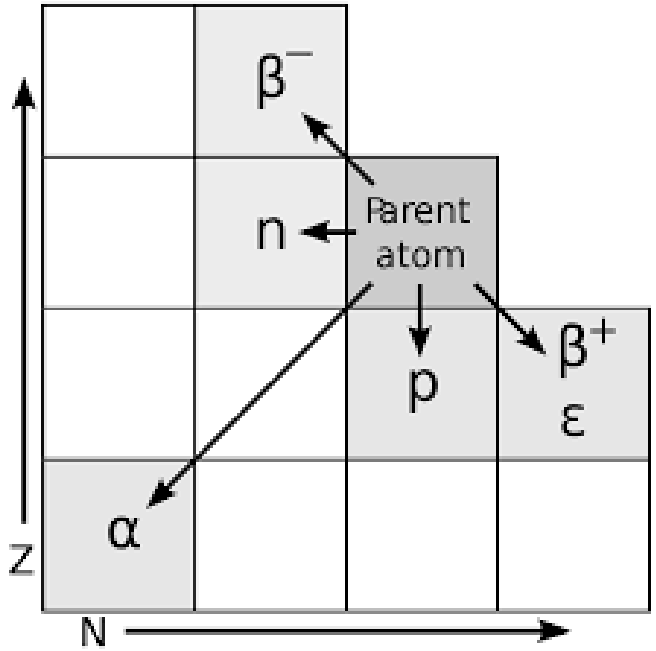
- The way this energy is lost (type of decay) depends on the origin of the instability:

  – Proton-deficient/neutron-rich radionuclides
  – Neutron-deficient/proton-rich radionuclides
  – Very heavy radionuclides

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

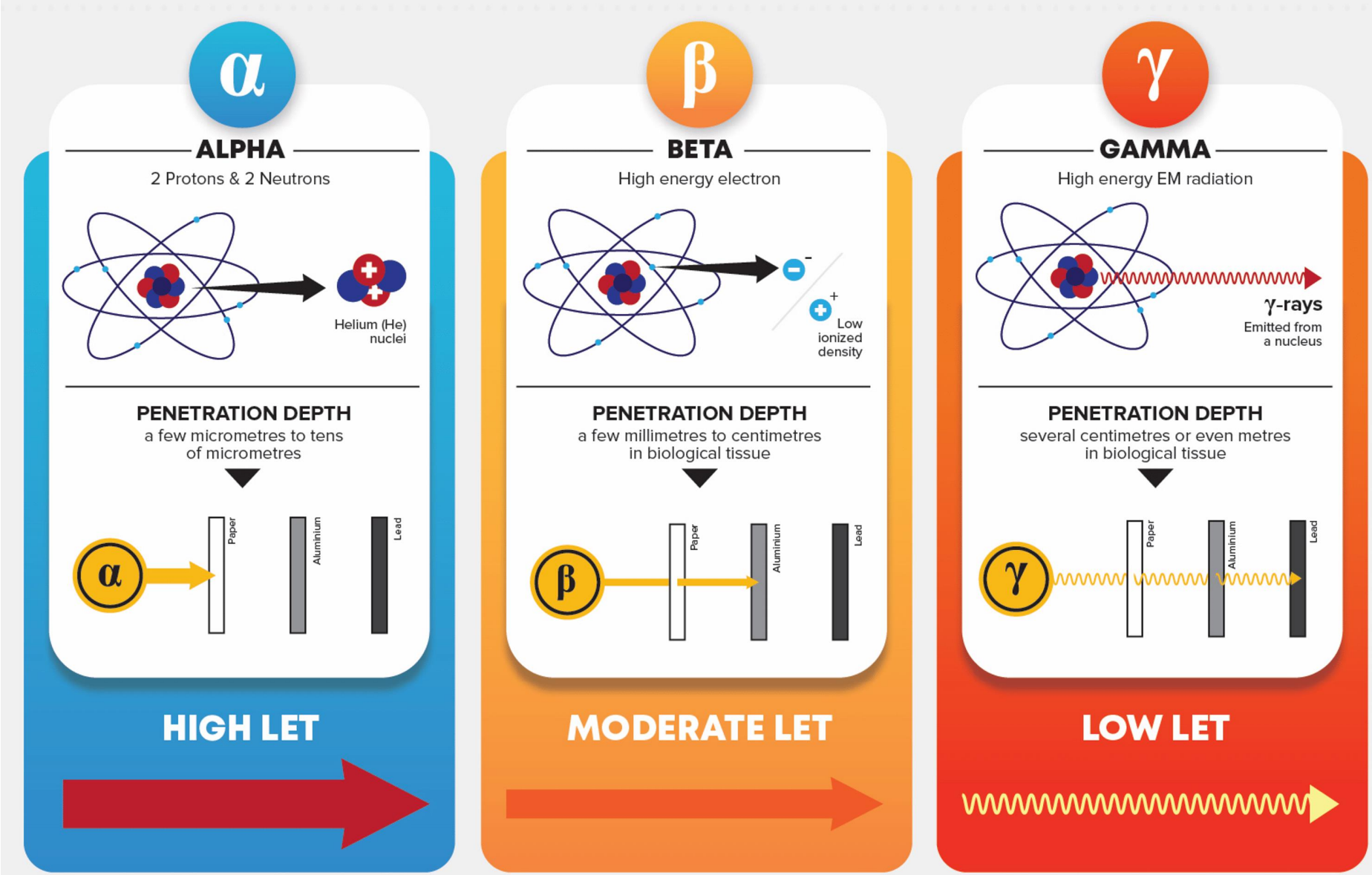
Radioactive decays : a way towards stability





Source: https://doi.org/10.1007/s40828-018-0068-x

α, β, γ



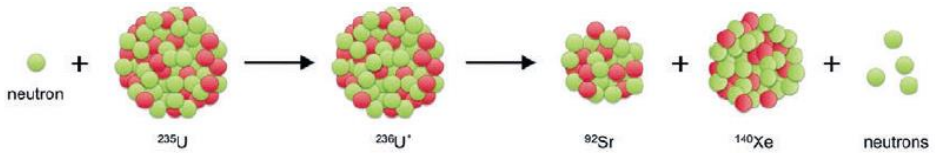
Source: DOI : 10.7759/cureus.41623

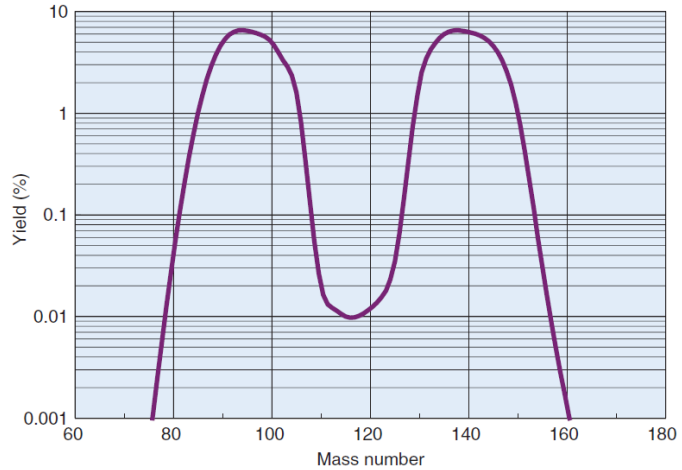
Part 2 – Radionuclide production and radiopharmaceuticals

Radionuclide production

- Three main routes of production:

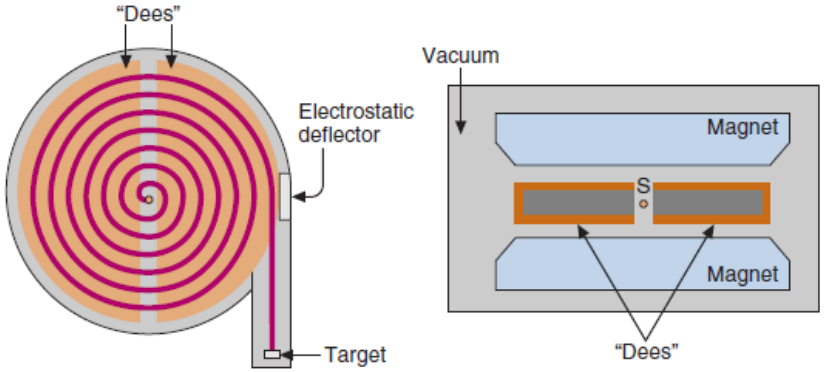
1. **Reactor**-produced (fission fragments / neutron activation)



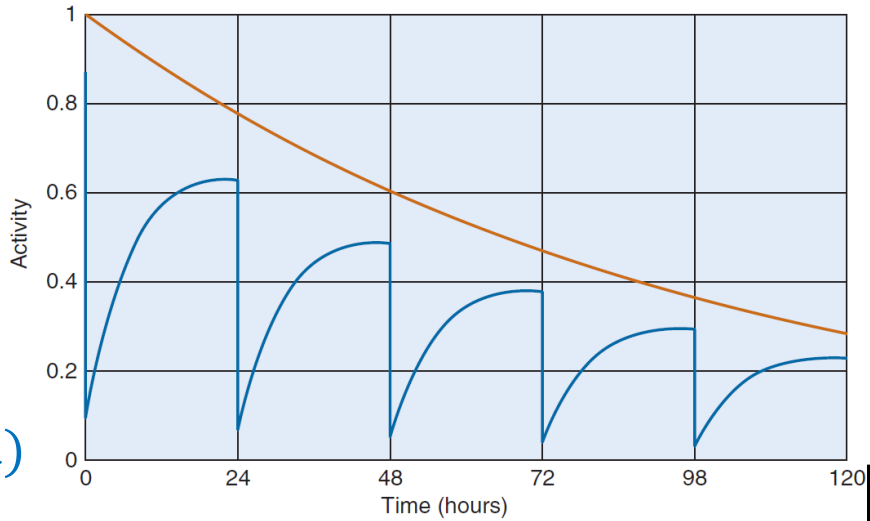


$$^{130}Te\ (n,\gamma)^{131}Te \xrightarrow{\beta-\ (25\ m)} \mathbf{^{131}I} \xrightarrow{\beta-,\gamma=364\ keV\ (8\ d)} {}^{131}Xe$$

2. **Accelerator**-produced



$$^{18}O(p,n)\mathbf{^{18}F}$$



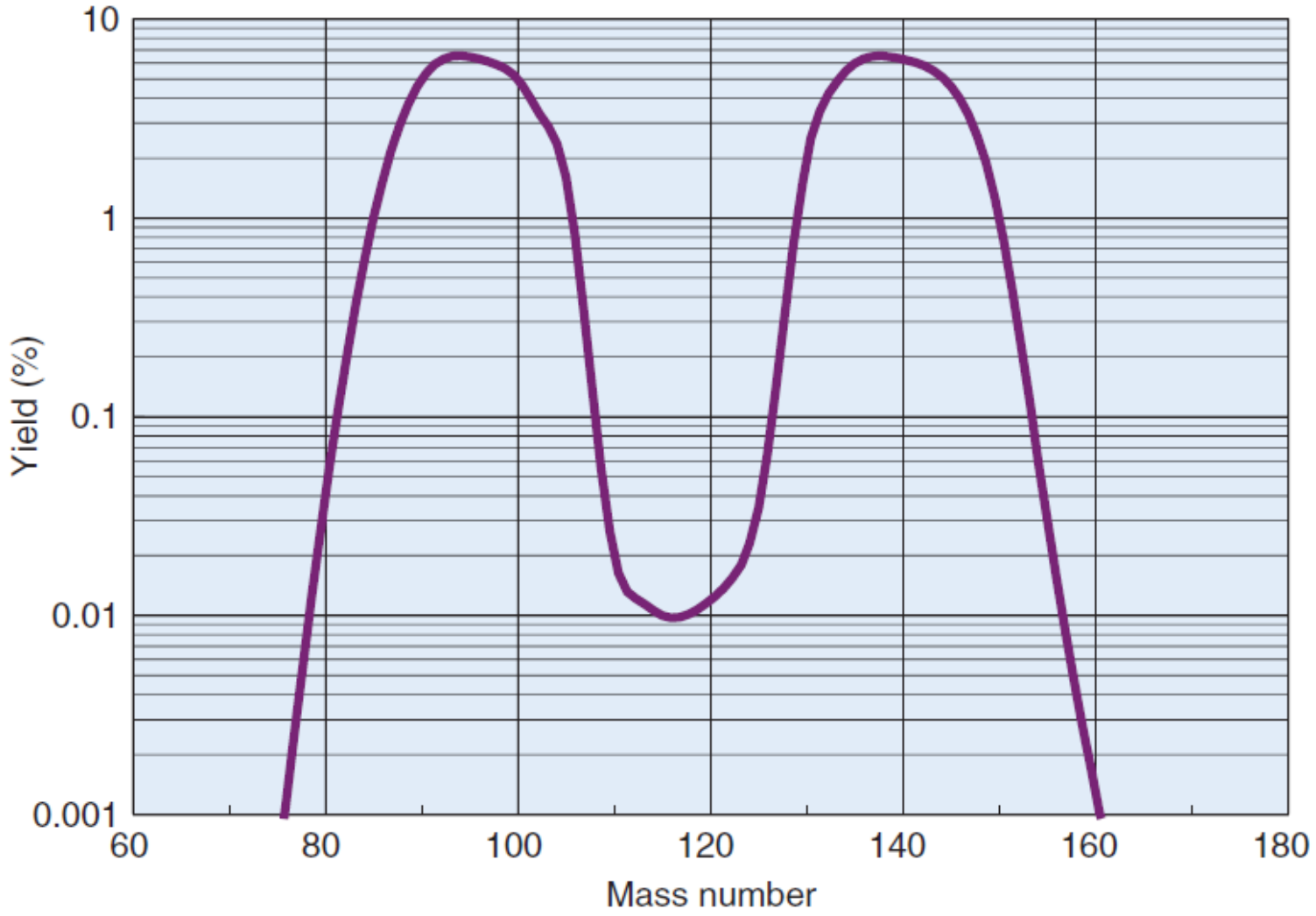
3. Radionuclide **generators**

$$^{99}Mo \xrightarrow{\beta-(66\ h)} \mathbf{^{99m}Tc}\ (6\ h)$$

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Radionuclide production : **reactors**

1. Reactor-produced radionuclides: **fission fragments**



Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Radionuclide production : **reactors**

1. Reactor-produced radionuclides: **fission fragments**

$$^{235}\mathrm{U} + \mathrm{n} \longrightarrow {}^{236}\mathrm{U}^{*} + \text{fission fragments}$$

$$^{99}_{39}Y \xrightarrow{\beta-(1.5\ s)} {}^{99}_{40}Zr \xrightarrow{\beta-(21\ s)} {}^{99}_{41}Nb \xrightarrow{\beta-(15\ s)} {}^{99}_{42}Mo \xrightarrow{\beta-(66\ h)} {}^{99m}_{43}Tc \xrightarrow{\gamma=140\ keV\ (6\ h)} {}^{99}_{43}Tc \xrightarrow{\beta-(2.111\cdot10^{5}\ \mathrm{y})} {}^{99}_{44}Ru$$

- Fission products have excess of neutrons → β- decay.
- Fission products may be carrier-free* (no stable isotope of the radionuclide of interest → high specific activity can be achieved after chemical separation).
- Fission processes lack in specificity : low yield of the radionuclide of interest.
- Example of isotopes used in nuclear medicine : Mo-99, Xe-133, I-131.

* carrier-free: no stable isotopes of the same elements are present.

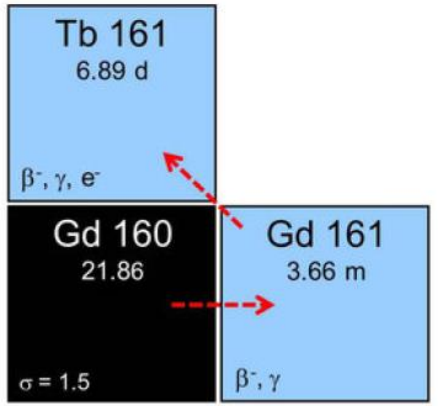
Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Radionuclide production : **reactors**

1. Reactor-produced radionuclides: **neutron activation**

$$ {}^{A}_{Z}\mathrm{X}(\mathrm{n},\gamma)^{A+1}_{Z}\mathrm{X} \qquad {}^{A}_{Z}\mathrm{X}(\mathrm{n},\mathrm{p})_{Z-1}{}^{A}\mathrm{Y} $$

$$ {}^{130}Te\ (n,\gamma)^{131}Te \xrightarrow{\beta-\ (25\ m)} {}^{131}I \xrightarrow{\beta-,\gamma=364\ keV\ (8\ d)} {}^{131}Xe $$



- Neutron activation products have excess of neutrons → β- decay
- Most common production mode is (n,γ) → same element, not carrier-free.
  - Carrier-free by possible by using (n,p) reaction or by activating a short lived radionuclide using the (n,γ) reaction and waiting for its decay.
- Small fraction of target nuclei are activated, even at high neutron fluxes
  → low specific activity due to presence of unactivated stable carrier (target).

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

NEUTRON-ACTIVATED RADIONUCLIDES OF IMPORTANCE IN BIOLOGY AND MEDICINE

Radionuclide	Decay Mode	Production Reaction
^{14}C	β^-	$^{14}N(n,p)^{14}C$
^{24}Na	(β^-,γ)	$^{23}Na(n,\gamma)^{24}Na$
^{32}P	β^-	$^{31}P(n,\gamma)^{32}P$ $^{32}S(n,p)^{32}P$
^{35}S	β^-	$^{35}Cl(n,p)^{35}S$
^{42}K	(β^-,γ)	$^{41}K(n,\gamma)^{42}K$
^{51}Cr	(EC,γ)	$^{50}Cr(n,\gamma)^{51}Cr$
^{59}Fe	(β^-,γ)	$^{58}Fe(n,\gamma)^{59}Fe$
^{75}Se	(EC,γ)	$^{74}Se(n,\gamma)^{75}Se$
^{125}I	(EC,γ)	$^{124}Xe(n,\gamma)^{125}Xe \xrightarrow{EC} {}^{125}I$
^{131}I	(β^-,γ)	$^{130}Te(n,\gamma)^{131}Te \xrightarrow{\beta^-} {}^{131}I$

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Radionuclide production : **accelerators**

2. **Accelerator**-produced radionuclides

$$ {}^{A}_{Z}\mathrm{X}(\mathrm{p},\mathrm{n})_{Z+1}{}^{A}\mathrm{Y} \qquad {}^{A}_{Z}\mathrm{X}(\mathrm{d},\mathrm{n})^{A+1}_{Z+1}\mathrm{Y} $$

$$ {}^{18}O(p,n)^{18}F \qquad {}^{109}Ag(\alpha,2n)^{111}In \qquad {}^{122}Te(d,n)^{123}I $$

- In most activation processes, positive charge is added to the nucleus
  → β+ / EC decay

- Addition of positive charge changes to atomic number Z → generally different element, carrier-free.

- Smaller quantities of radioactivity when compared to reactor-produced radionuclides (due to generally higher activation cross-section for neutrons than for charged particles + lower beam intensities).

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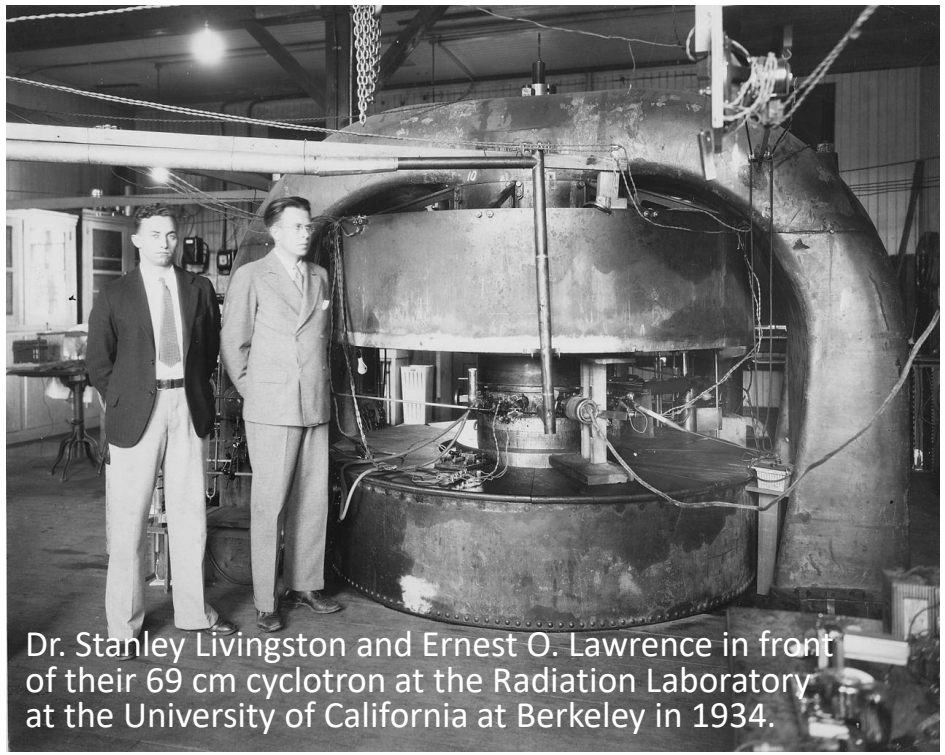
CHUV

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

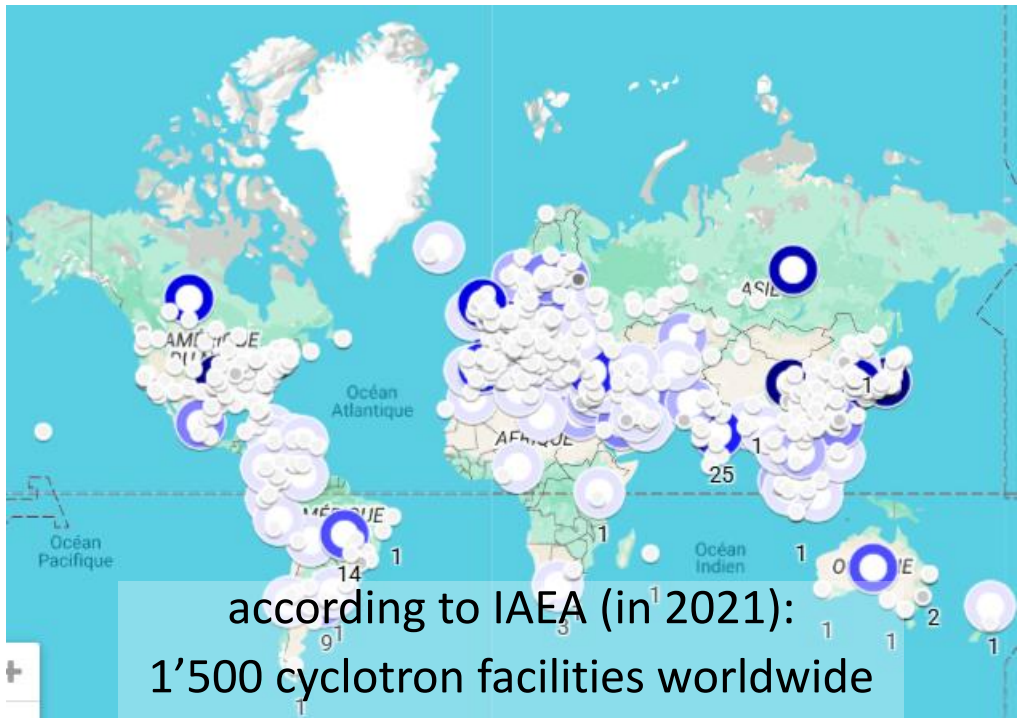
Radionuclide production : **accelerators**

Charged particle accelerators:

- Accelerate electrically charged particles (such as *p*, *d*, *α*)
- 3 main types of accelerators: cyclotrons, synchrotrons, and linear accelerators (LINAC).
- Main difference wrt *n* activation: higher energies required (~10-20 MeV) → Coulomb forces!
- Cyclotrons are the most widely used for radionuclide production for medical applications.



Dr. Stanley Livingston and Ernest O. Lawrence in front of their 69 cm cyclotron at the Radiation Laboratory at the University of California at Berkeley in 1934.



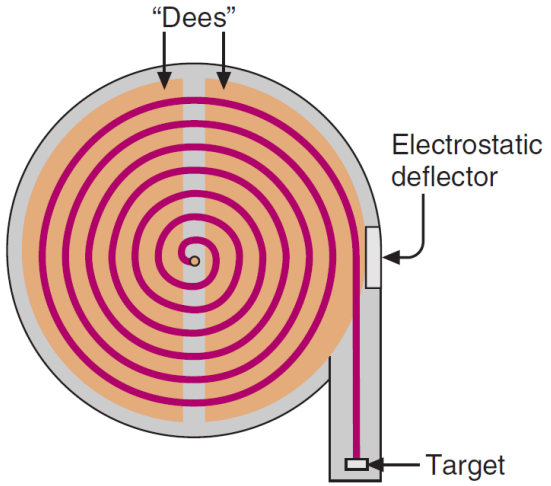
according to IAEA (in 2021):
1'500 cyclotron facilities worldwide

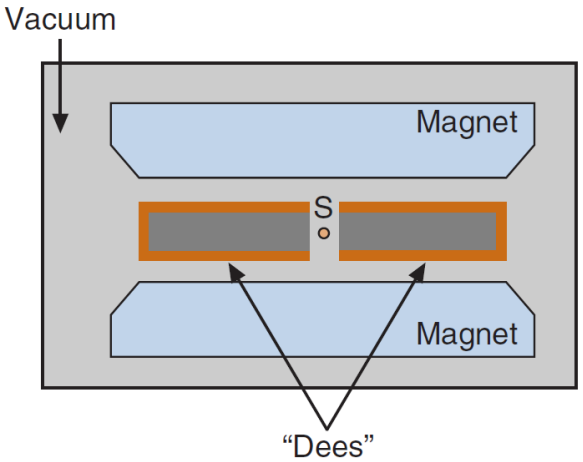
Source: https://en.wikipedia.org/wiki/Cyclotron; https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx

Radionuclide production : **accelerators**

Cyclotron

- Pair of semicircular electrodes placed between poles of an electromagnet (vacuum).
- An ion source is placed at the centre of the electrodes.





- High frequency oscillators generates AC current that is applied across the electrodes.
- Charged particles follow a circular path due to the B field.
- Particles reach the gap between the electrodes when the voltage across them reaches its max value.
- Particles are accelerated across the gap and gain energy in the process (outward spiral path).
- Increasing speed compensates for increasing travel distance.
- Energy achievable: limited by B strength and electrodes size (B = 1.5 T, electrode ⌀ 76 cm, p ~15 MeV)
- When max radius reached: beam is deflected towards a target (RP!).

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

SOME CYCLOTRON-PRODUCED RADIONUCLIDES USED IN NUCLEAR MEDICINE

Product	Decay Mode	Common Production Reaction
^{11}C	β^+, EC	$^{14}N(p,\alpha)^{11}C$
		$^{10}B(d,n)^{11}C$
^{13}N	β^+	$^{16}O(p,\alpha)^{13}N$
		$^{12}C(d,n)^{13}N$
^{15}O	β^+	$^{14}N(d,n)^{15}O$
		$^{15}N(p,n)^{15}O$
^{18}F	β^+, EC	$^{18}O(p,n)^{18}F$
		$^{20}Ne(d,\alpha)^{18}F$
^{67}Ga	(EC,γ)	$^{68}Zn(p,2n)^{67}Ga$
^{111}In	(EC,γ)	$^{109}Ag(\alpha,2n)^{111}In$
		$^{111}Cd(p,n)^{111}In$
^{123}I	(EC,γ)	$^{122}Te(d,n)^{123}I$
		$^{124}Te(p,3n)^{123}I$
^{201}Tl	(EC,γ)	$^{201}Hg(d,2n)^{201}Tl$

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

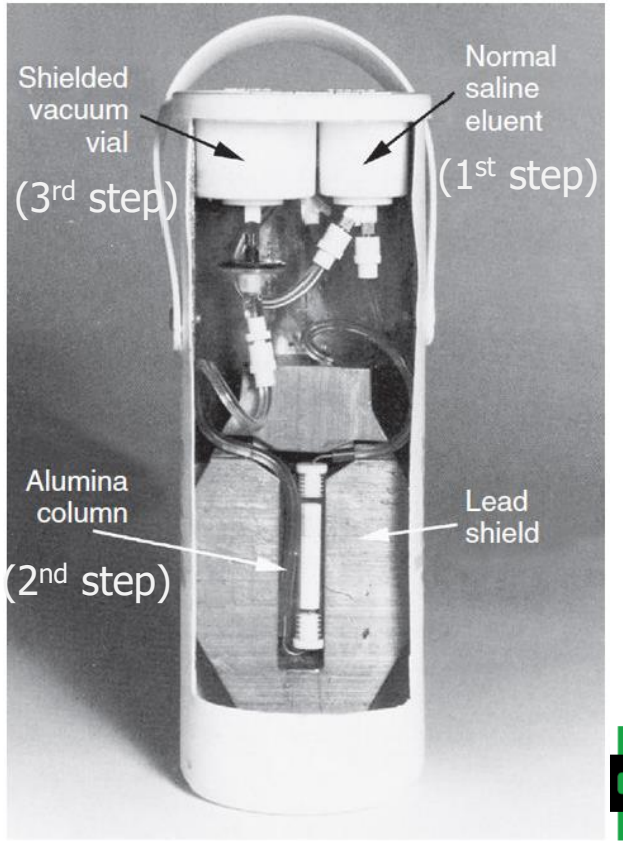
Radionuclide production : **generators**

3. **Generator**-produced radionuclides

Mother (long-lived) → daughter

$$^{82}Sr \xrightarrow{EC\ (25\ d)} {}^{82}Rb\ (75\ s)$$

$$^{99}Mo \xrightarrow{\beta-(66\ h)} {}^{99m}Tc\ (6\ h)$$

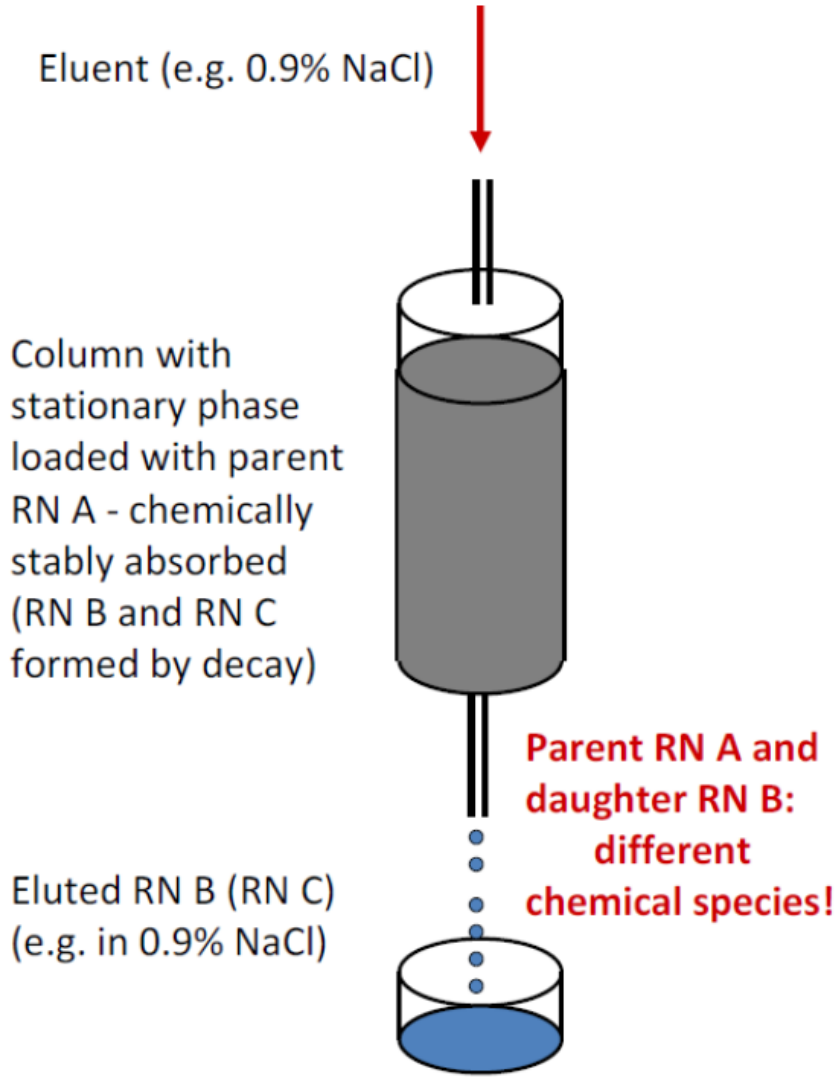


- Elution efficiency may vary from one generator to the other.
- Impurities (partial elution of the parent) may occur.
- Dependent on reactor operations (shortages!)

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Radionuclide production : **generators**

- A long-lived parent radionuclide “A” is absorbed on a stationary phase of a column.
- The long-lived parent decays and generate daughter radionuclide “B”.
- B is eluted while A sticks on the column.
- B is used for (medical) applications.



EPFL

Source: Dr. Ruslan Cusnir (IRA/CHUV) ;

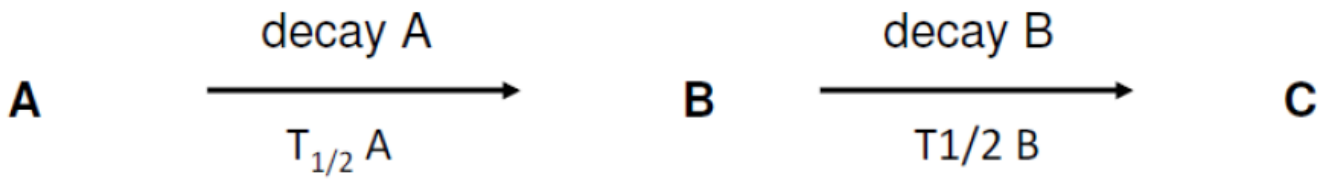
CHUV

Radionuclide production : **generators**

parent (mother) nuclide
- radioactive -

daughter nuclide
- radioactive -

granddaughter nuclide
- best case: non-radioactive -



Transient equilibrium

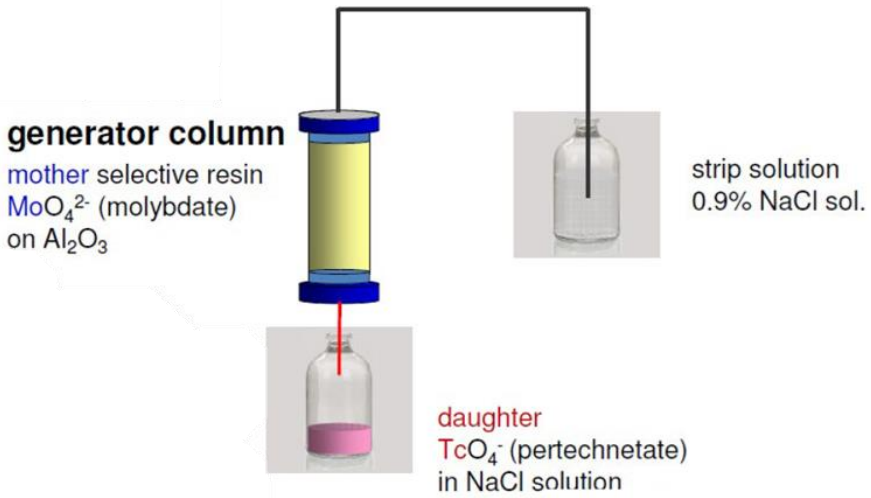
Conditions for an ideal generator:

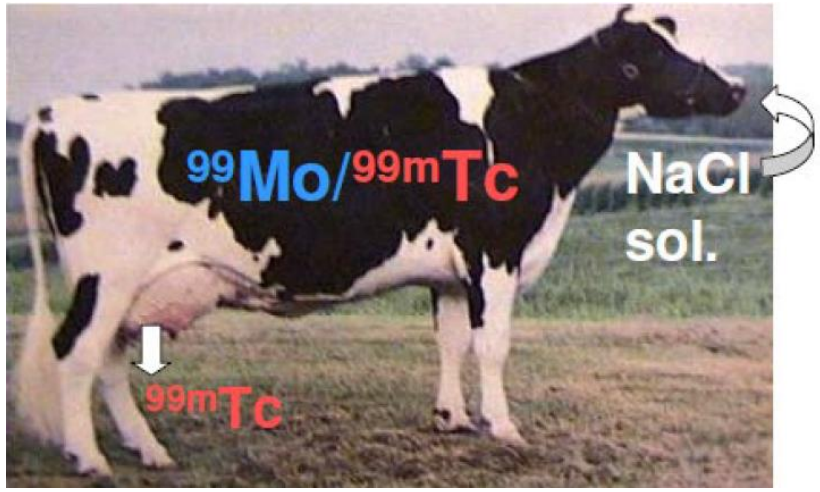
- T_A (ideal: some days − years) > T_B (ideal: some minutes or hours − days) and C stable
- B has suitable nuclear properties (half-life, decay modes, energies,…)
- Separation of B from A is simple (high yield, low breakthrough, suitable chemical form, high consistency….)

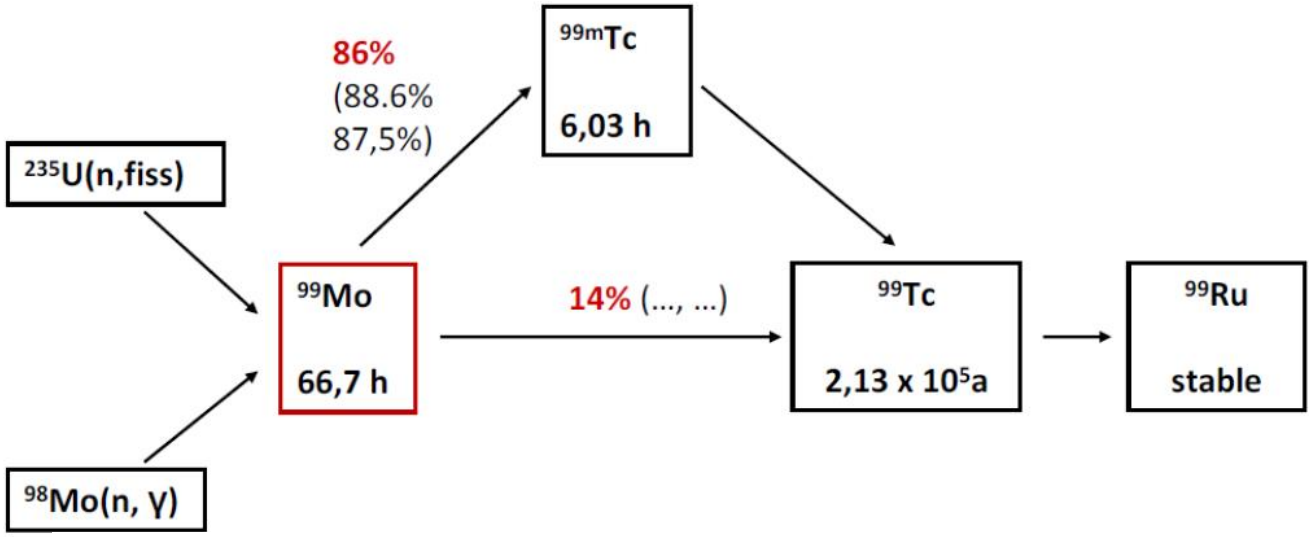
Source: Dr. Ruslan Cusnir (IRA/CHUV)

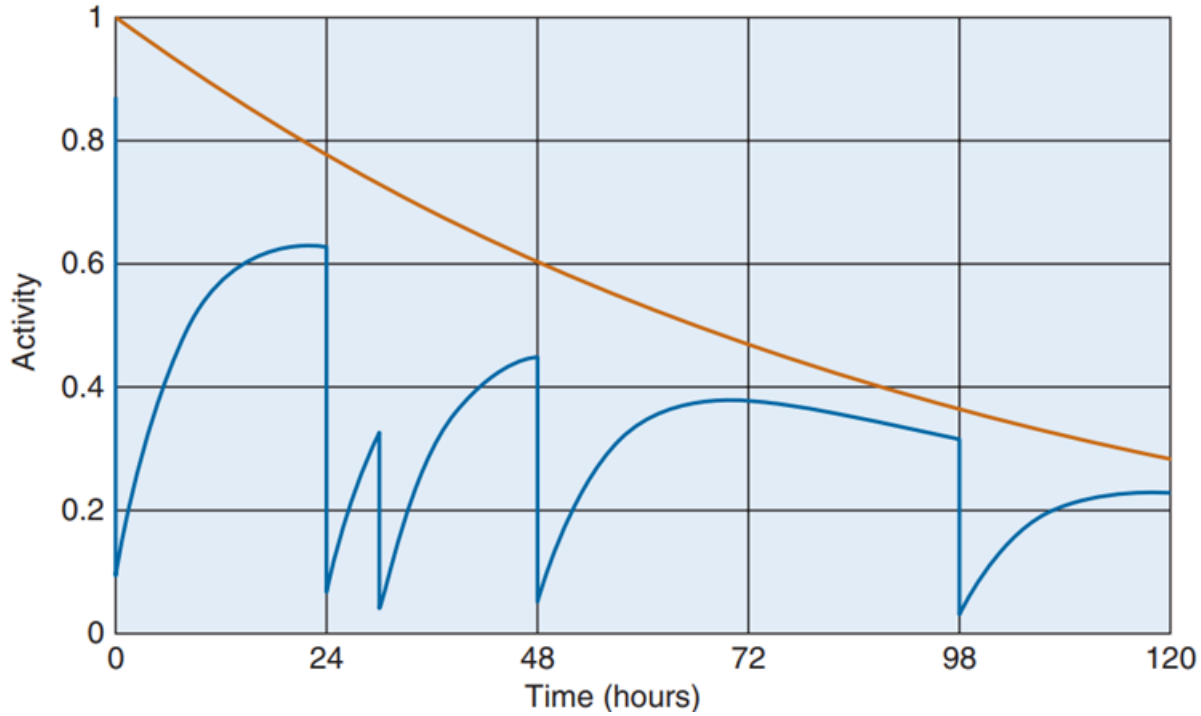
Radionuclide production : **generators**

mother nuclide: ^{99}Mo
daughter nuclide: ^{99m}Tc









^{99}Mo

^{99m}Tc

EPFL

Source: Dr. Ruslan Cusnir (IRA/CHUV); Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

CHUV

Radionuclide production : **shortage**

FORBES > INNOVATION > HEALTHCARE

Technetium Is In Short Supply. Here's How That Affects Public Health

Omer Awan Senior Contributor ⓘ

Dr. Omer Awan is a practicing physician who covers public health.

Follow

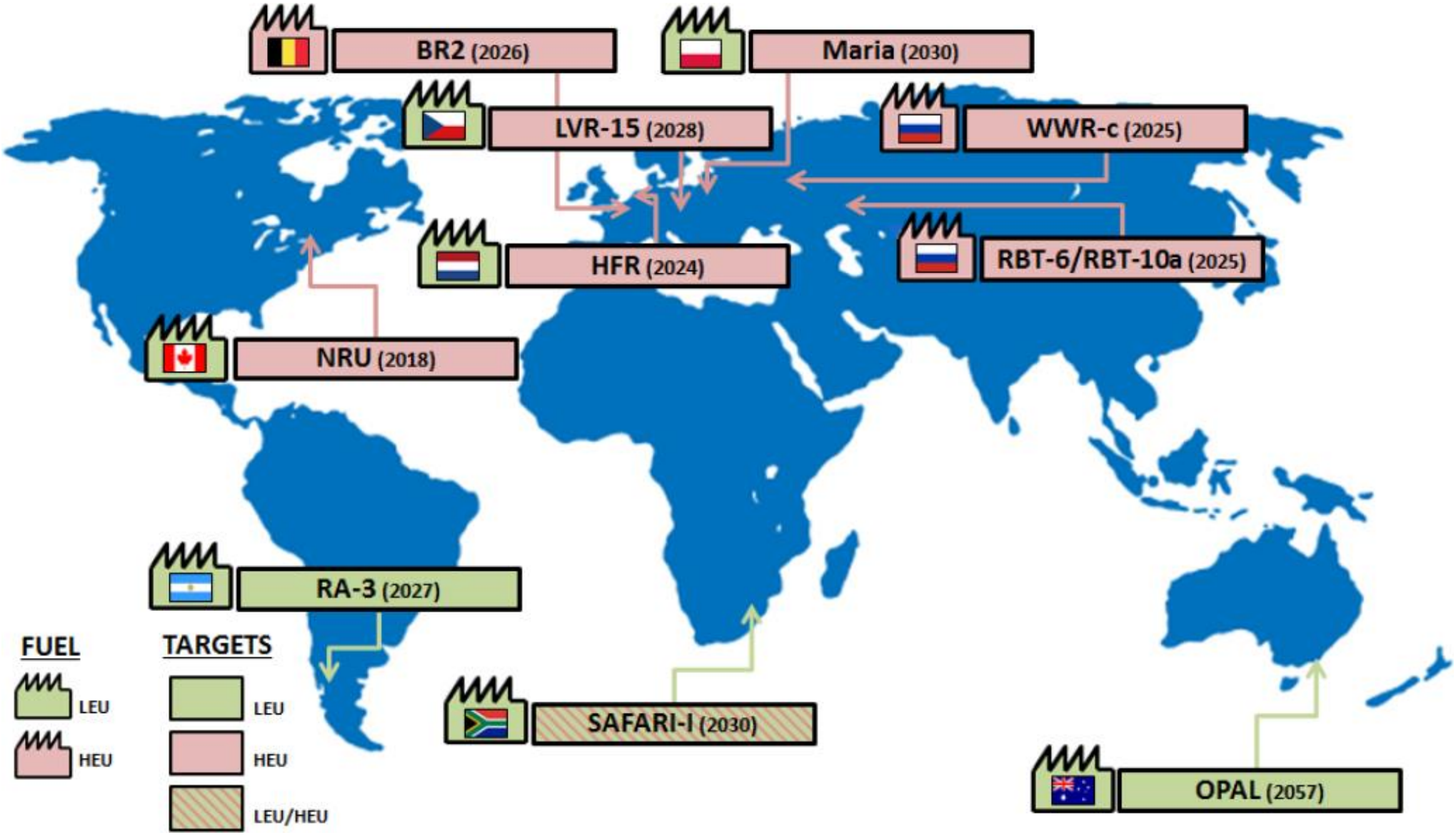
0

Oct 24, 2024, 06:45am EDT

"Technetium-99m, a critical nuclear imaging radioisotope, is in short supply and could cause delays or cancellations of over 40,000 medical imaging studies daily in the United States.

The global shortage of Tc-99m stems for issues related to its production. Normally, Tc-99m decays and is eluted from Molybdenum-99, which is generated from a high-flux reactor. The parent isotope Molybdenum-99 is only produced in a few nuclear reactors worldwide, such as in Petten, Netherlands. A structural issue within a pipe from this reactor in the Netherlands will require repair that may delay the production of Tc-99m well into November, according to reports from the Society of Nuclear Medicine and Molecular Imaging.

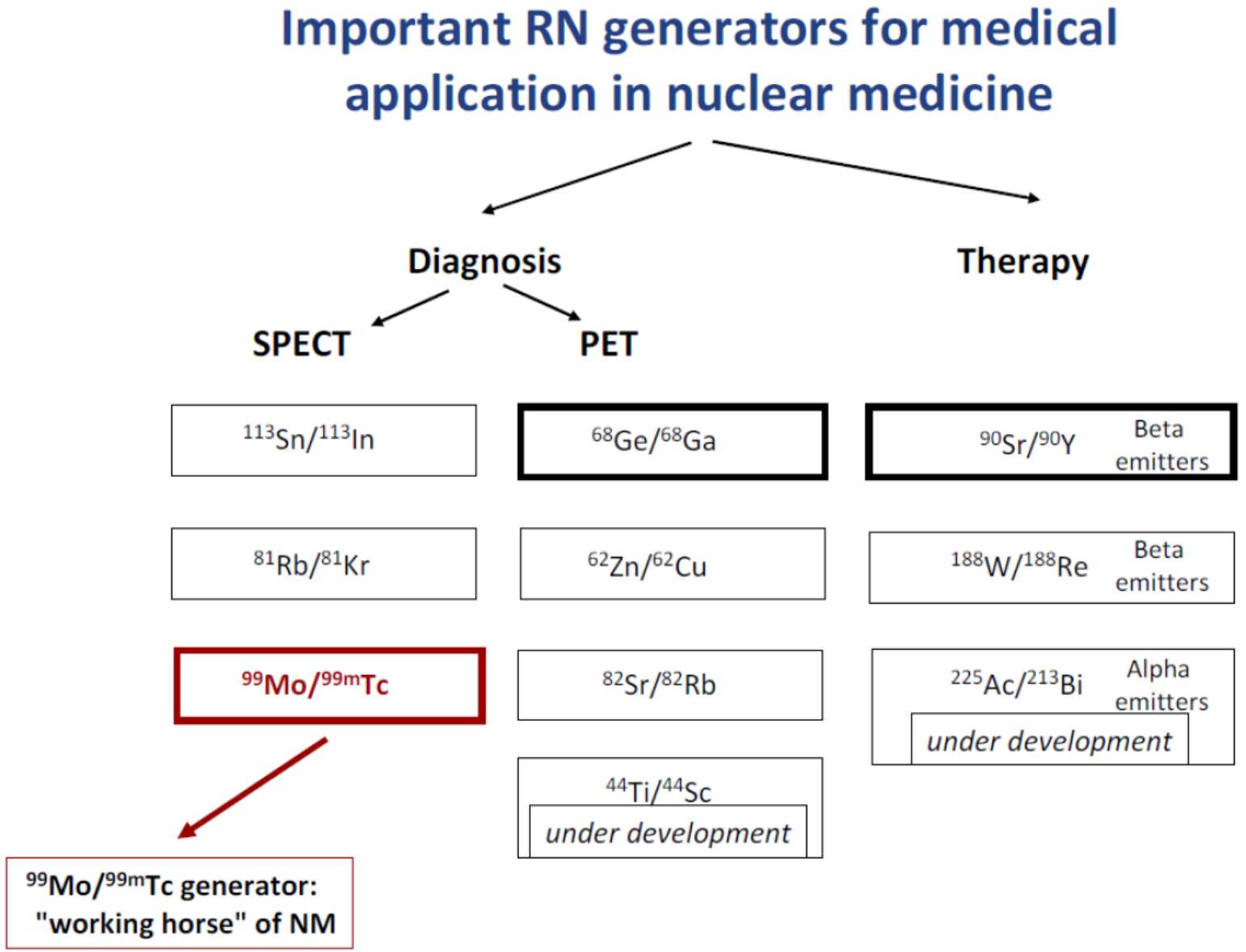
Sources: https://nap.nationalacademies.org/read/24909/chapter/5#14, https://www.forbes.com/sites/omerawan/2024/10/24/technetium-is-in-short-supply-heres-how-that-affects-public-health/



Current Mo-99 supply map as of July 2017. The estimated end of operation for the reactors is shown in parentheses. https://doi.org/10.17226/24909.

Sources: https://nap.nationalacademies.org/read/24909/chapter/5#14, https://www.forbes.com/sites/omerawan/2024/10/24/technetium-is-in-short-supply-heres-how-that-affects-public-health/

Radionuclide production : **generators**



Source: Dr. Ruslan Cusnir (IRA/CHUV)

SOME RADIONUCLIDE GENERATORS USED IN NUCLEAR MEDICINE

Daughter*	Decay Mode	$T_{1/2}$	Parent	$T_{1/2}$
^{62}Cu	β^+,EC	9.7 min	^{62}Zn	9.3 hr
^{68}Ga	β^+,EC	68 min	^{68}Ge	271 d
^{82}Rb	β^+,EC	1.3 min	^{82}Sr	25 d
^{87m}Sr	IT	2.8 hr	^{87}Y	80 hr
^{99m}Tc	IT	6 hr	^{99}Mo	66 hr
^{113m}In	IT	100 min	^{113}Sn	120 d

Source: Physics in Nuclear Medicine, 4th edition, ISBN: 978-1416051985

Common radionuclides in NM

SPECT		
Tc-99m	6 h	γ 140 keV (89%)
I-123	13 h	γ 159 keV (83%)
I-131	8 d	γ 284 keV (6%), 364 (81%), 637 (7%)
In-111	2.2 d	γ 171 keV (90%), 245 keV (94%)
PET		
F-18	1.8 h	Mean β+ 250 keV + 2x γ 511 keV
Ga-68	1.2 h	Mean β+ 830 keV + 2x γ 511 keV
O-15	2 min	Mean β+ 735 keV + 2x γ 511 keV
C-11	20 min	Mean β+ 386 keV + 2x γ 511 keV
Therapy		
I-131	8 d	Max β- 0.6 MeV
Y-90	2.7 d	Max β- 2.3 MeV
Lu-177	6.6 d	Max β- 0.5 MeV
Ra-223	11.4 d	Max α 5.78 MeV

Nuclear medicine and radiopharmaceuticals

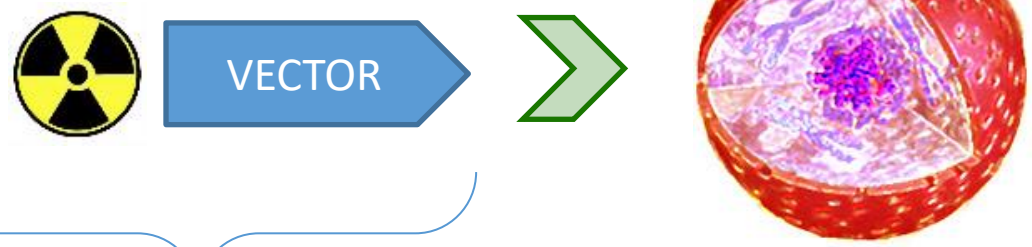
- Nuclear medicine:
  - A branch of medicine dealing with the use of radioactive materials in the diagnosis and treatment of disease (Merriam-Webster dictionary).

- Radiopharmaceutical :
  - a radioactive compound used to assess bodily functions, diagnose a condition, and treat diseases.

Radiopharmaceuticals

Radioisotope

Specific binding site

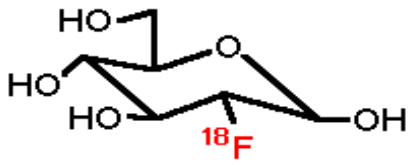


Cell/Target tissue

radiopharmaceutical product

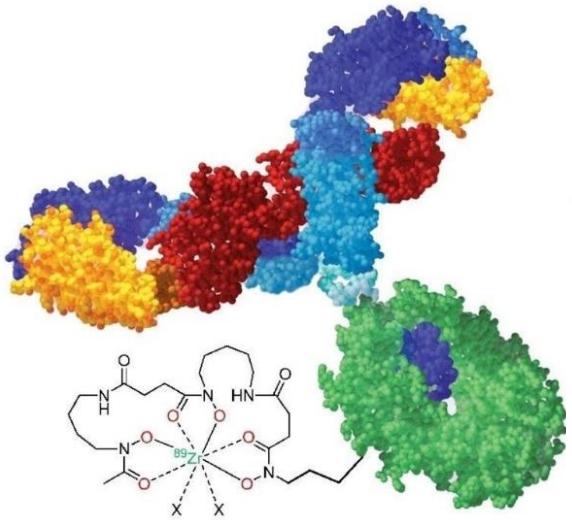
Radio-**diagnostic** and/or radio-**therapeutic** (if both: "*theranostic*")

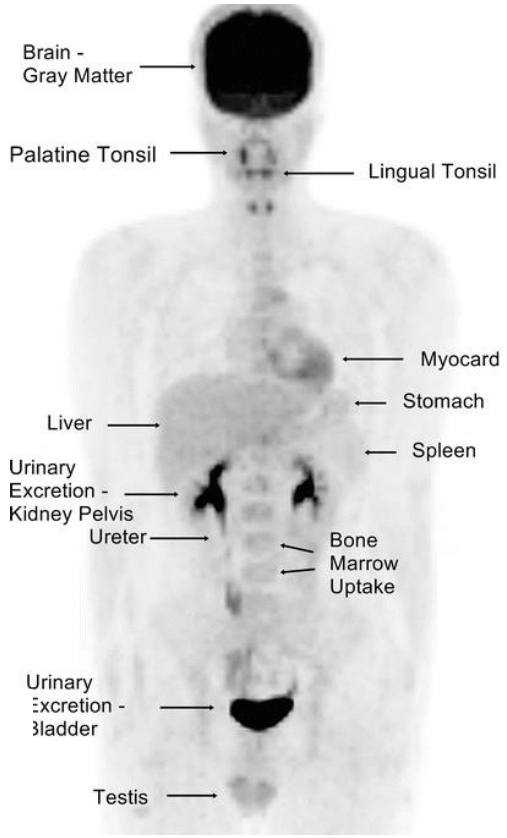
γ γ + β and/or α

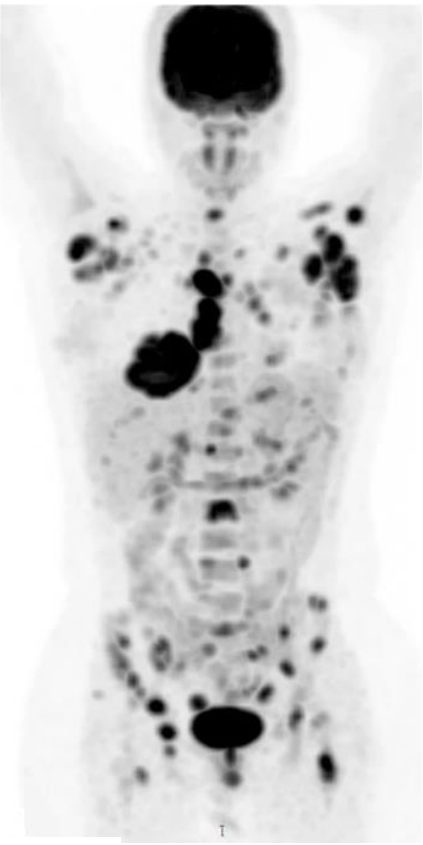


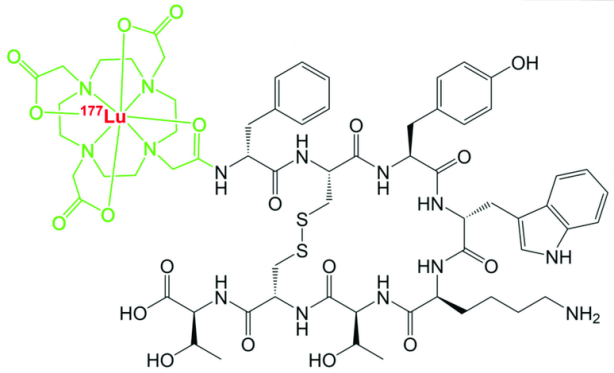
Vectors:

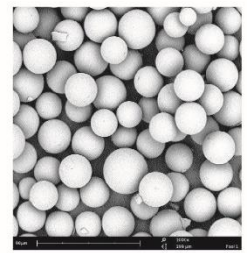
- Molecules, peptides, antobodies, microspheres, …









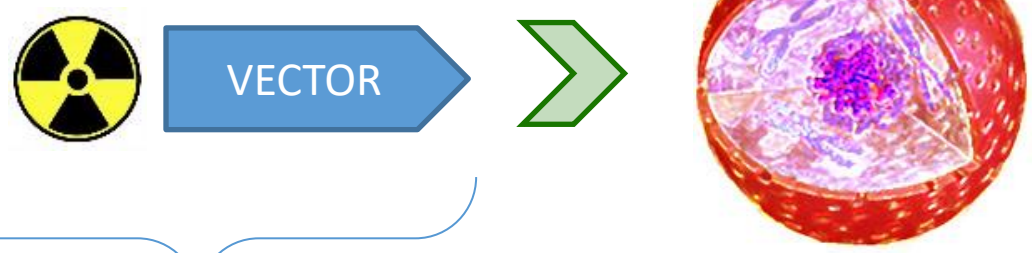


EPFL

Radiopharmaceuticals and theranostics

Radioisotope

Specific binding site



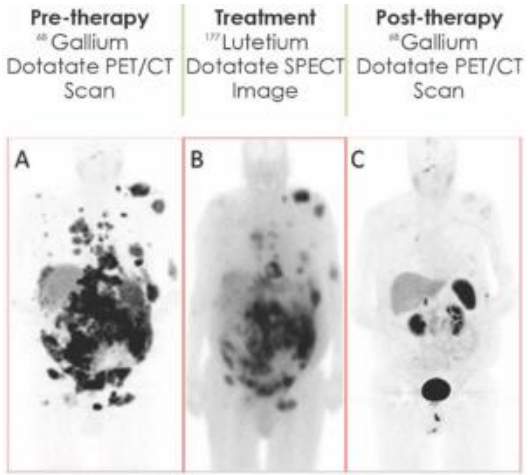
radiopharmaeutical product

Cell/Target tissue

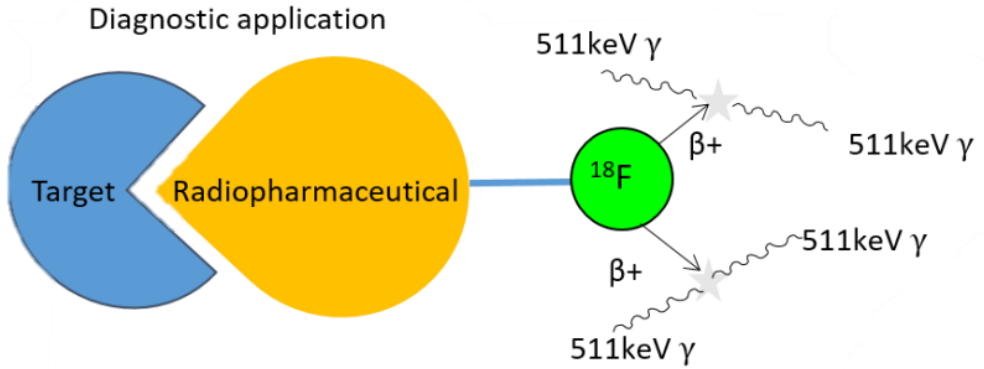
Radio-**diagnostic** and/or radio-**therapeutic** (if both: "*theranostic*")

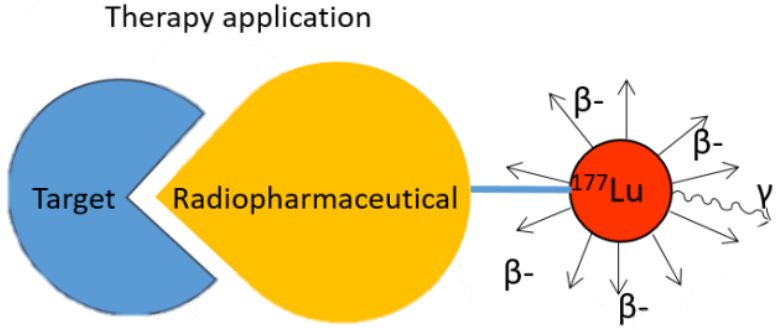
γ

γ + β and/or α



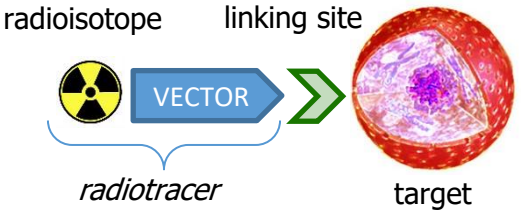
Same vector (i.e. biodistribution) but different radionuclide (i.e. dose delivery)!





Source: https://doi.org/10.48550/arXiv.2107.13913 ; https://www.misrradiologycenter.com/theranostics/lutetium-dotatate/

Nuclear Medicine applications



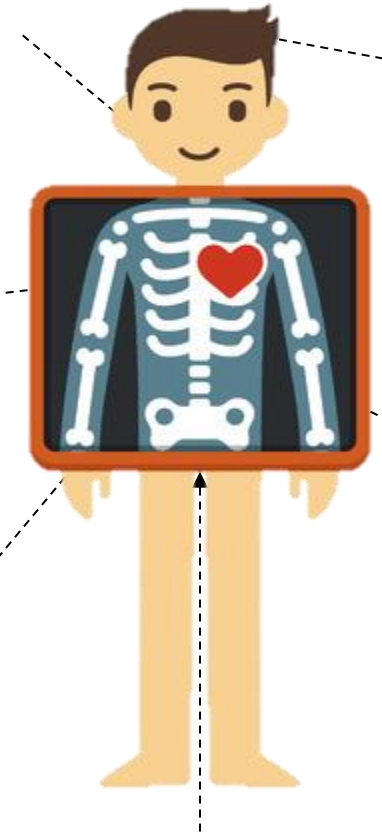
Diagnostics
Therapy

... and many more!

Oncology
F-18 FDG (PET)

Thyroid diseases
I-131 (T+SPECT)
I-124 (PET)
I-123 (SPECT)

Brain diseases
F-18 FET/FDG (PET)
I-123 DaTscan (SPECT)



Heart Disease
Rb-82 (PET)
Tl-201 (SPECT)
Tc-99m MIBI (SPECT)

Neuroendocrine tumors
Lu-177-peptide (T+SPECT)
Y-90-peptide
Ga-68/Sc-44-peptide (PET)
I-131-MIBG (T+SPECT)

Lymphoma (NHL)
Y-90-mAb (T + Scintigraphy)
In-111 (SPECT)/Zr-89 (PET)

Bone & joint pain
Sr-89 (T + Scintigraphy)
P-32 (T + Scintigraphy)
Sm-153-EDTMP (T + Scintigraphy)
Re-188-HEDP (T + Scintigraphy)
Y-90-HEDP
Ra-223 (T + Scintigraphy)
Y-90, Re-186, Er-169
Tc-99m DTPA

Liver tumors
Selective Internal Radiotherapy (SIRT)
Y-90 microspheres (T+PET+SPECT)
Tc-99m-MAA (SPECT)

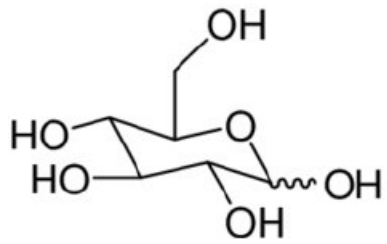
Prostate cancer
Lu-177-PSMA (T+SPECT)
Ga-68/Sc-44-PSMA (PET)

EPFL

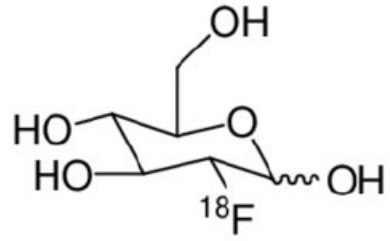
CHUV

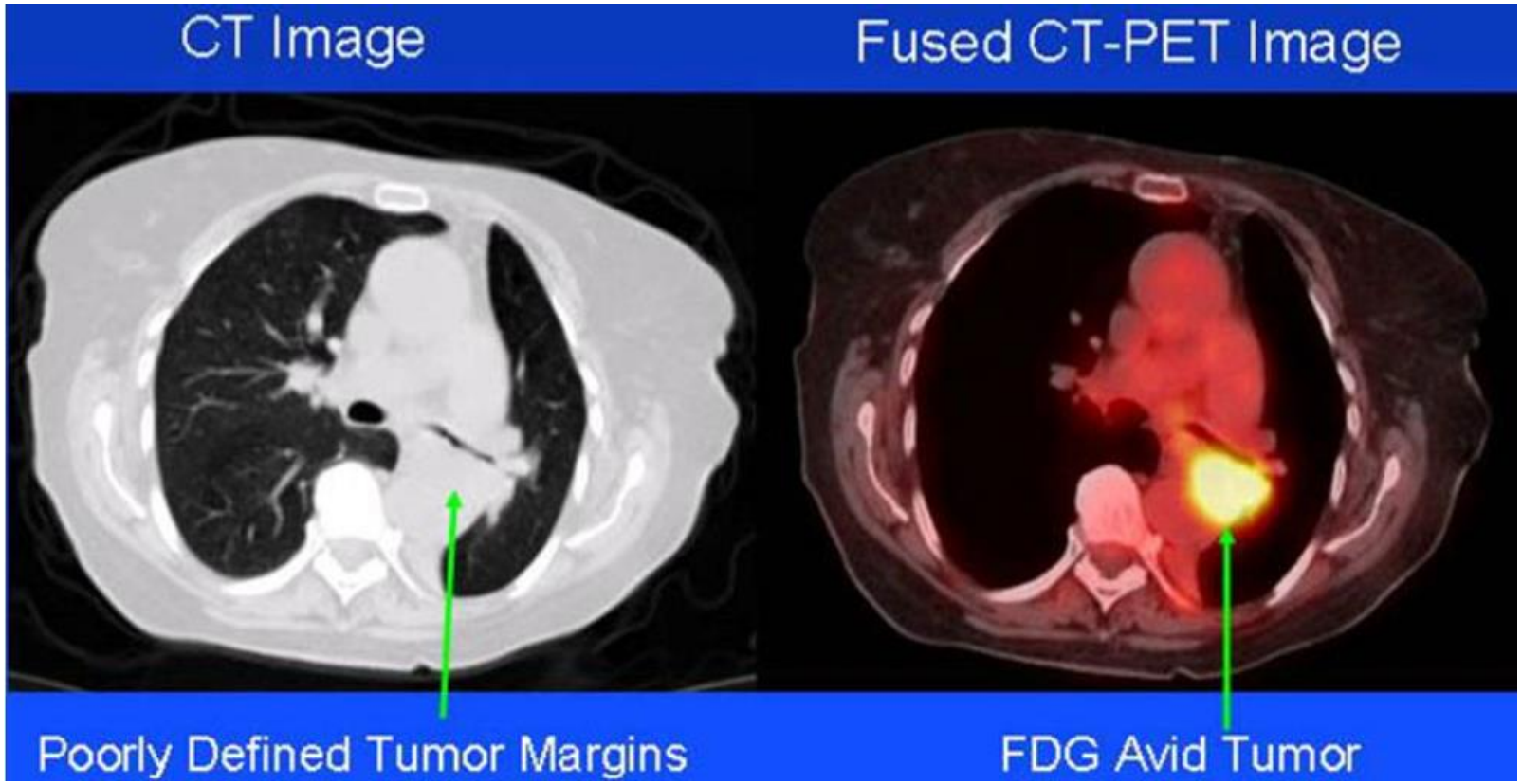
Example of radiopharmaceutical

glucose – a universal source of energy



«radioactive sugar»
[^{18}F]fluorodeoxyglucose





Source: https://www.nibib.nih.gov/science-education/science-topics/nuclear-medicine

Ideal radiopharmaceutical characteristics

Work in groups of ~3
2 minutes

Source: Dr. Ruslan Cusnir (IRA/CHUV) ; https://www.flaticon.com/free-icon/target_2313848?term=effective&page=1&position=3&origin=search&related_id=2313848

Ideal radiopharmaceutical characteristics

- **Nuclear** and **biokinetic** properties :
  - Physical and effective half-lives adapted to application (diagnostic: short-lived / therapeutic: longer-lived)
  - Diagnostics : γ between 100 and 511 keV
  - Therapy : α, β-, Auger e- (and preferably γ for visualization)
- High **target to non-target** ratio:
  - High affinity with targeted disease
- **Biological** stability:
  - Prevents degradation due to chemical or metabolic changes

- **Purity**:
  - Chemical : proportion of desired chemical compound vs. non-radioactive impurities (e.g. synthesis by-products)
  - Radiochemical : proportion of radioactive compound in the desired chemical form (e.g. only bound to ligand, not in a free form)
  - Radionuclidic : proportion of the desired radionuclide vs. other radioactive contaminants (e.g. unwanted Mo-99 breakthrough)
- Operational **feasibility**:
  - Simple preparation
  - Wide availability
  - Production costs

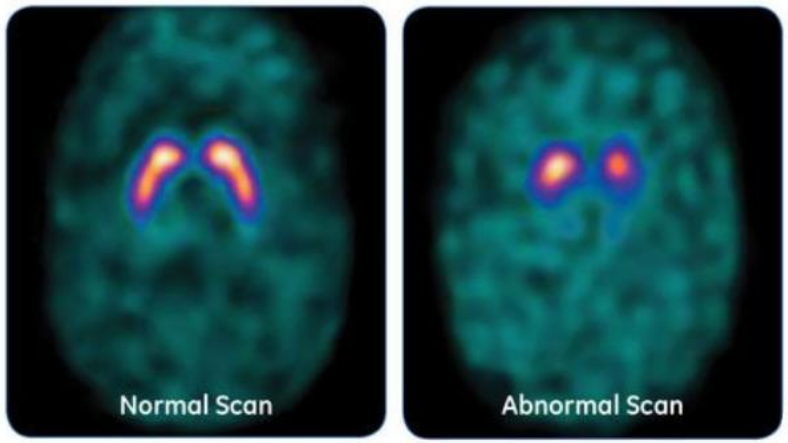
EPFL

Source: Dr. Ruslan Cusnir (IRA/CHUV) ; https://www.flaticon.com/free-icon/target_2313848?term=effective&page=1&position=3&origin=search&related_id=2313848

CHUV

From radionuclides to radiopharmaceuticals

1. **Ready to use :** directly delivered to be administered (e.g. DaTscan; therapies)
2. **Kits :** “cold”, to be combined with radionuclides (cf. most Tc-99m-based radioph.)
3. **Radionuclide precursors :** *in-house* produced radiopharmaceuticals, e.g. labelled peptides or antibodies



“Comma”-shaped
Possible essential tremor

“Period”-shaped
Possible parkinsonian syndrome

Source: Dr. Ruslan Cusnir (IRA/CHUV); https://www.apdaparkinson.org/article/what-is-a-datscan-and-should-i-get-one/; https://www.drugs.com/pro/pluvicto.html; https://nuclearsupplies.co.nz/products/technescan-mag3; https://medical.ezag.com/en/products/modular-lab-pharmtracer/

From radionuclides to radiopharmaceuticals

Kits:

- Commercialised, quality guaranteed by the producer.

- Contains:
  - Active ligand system
  - Reducing agent (to reduce oxidation state of Tc-99m)
  - Antioxidants
  - Buffer components (physiological pH)
  - Auxiliary ligand systems
  - Auxiliary components

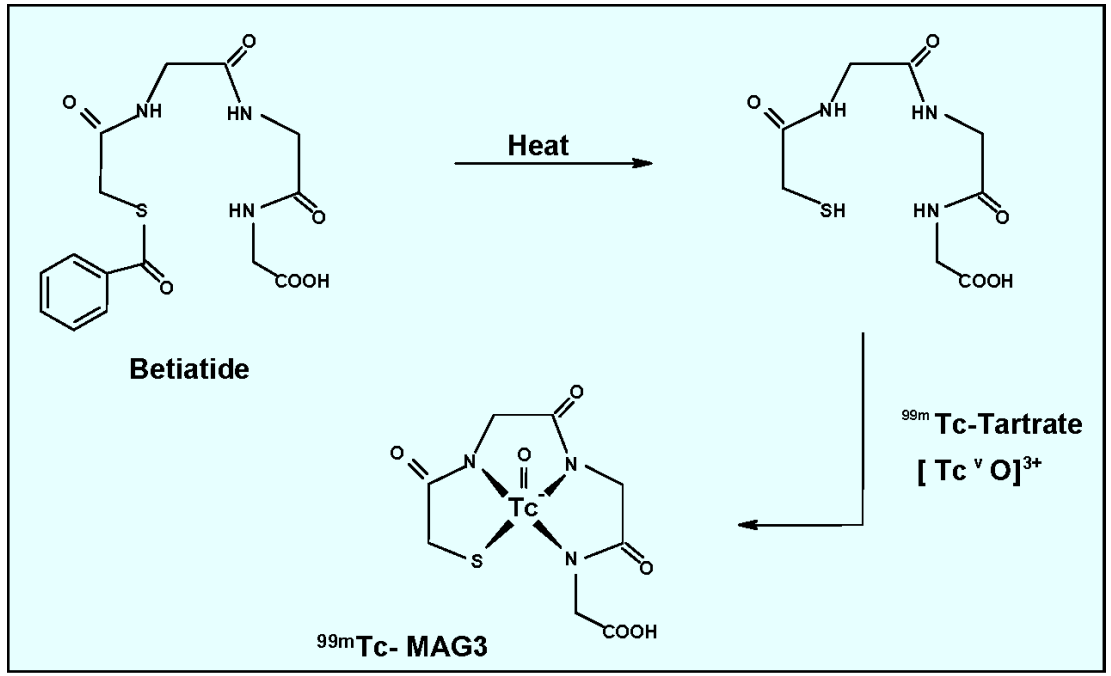


Figure 18. Synthetic pathway for labeling ^{99m}Tc-mertiatide (^{99m}Tc-MAG3).

- Radioactive solution (e.g. pertechnetate from generator) added <u>immediately before use</u>.

Source: Dr. Ruslan Cusnir (IRA/CHUV); Technetium Radiopharmaceutical Chemistry (Continuing Education for Nuclear Pharmacists and Nuclear Medicine Professionals), available : https://pharmacyce.unm.edu/nuclear_program/freelessonfiles/vol12lesson3.pdf ; https://radiopaedia.org/articles/tc-99m-mag3

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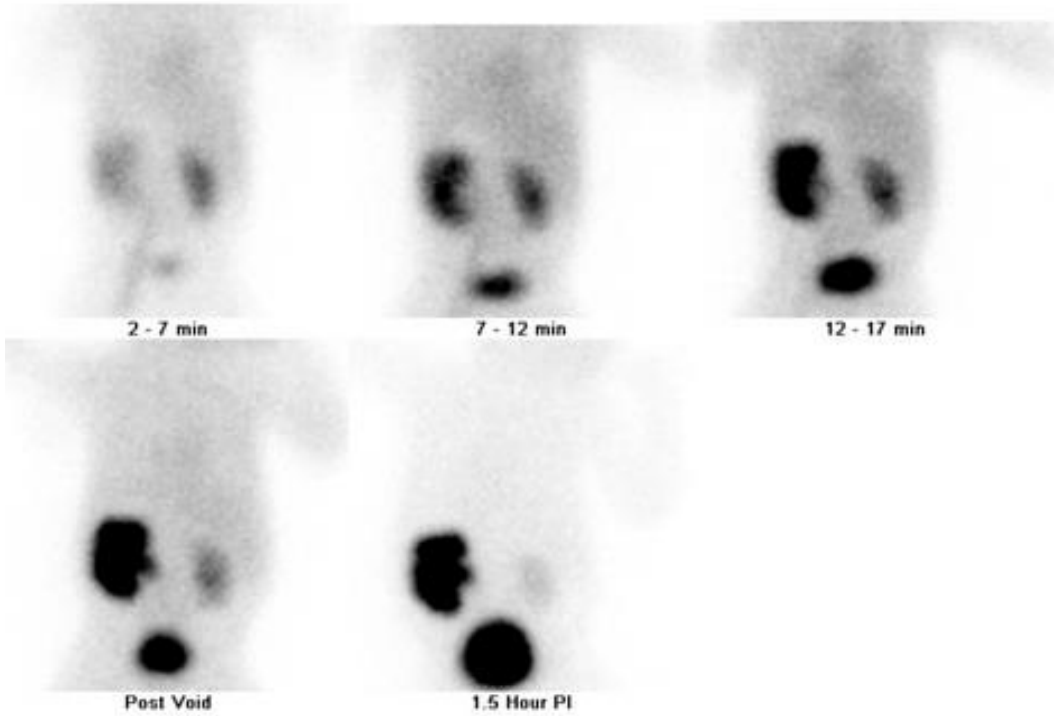

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Source: Dr. Ruslan Cusnir (IRA/CHUV); Technetium Radiopharmaceutical Chemistry (Continuing Education for Nuclear Pharmacists and Nuclear Medicine Professionals), available : https://pharmacyce.unm.edu/nuclear_program/freelessonfiles/vol12lesson3.pdf ; https://radiopaedia.org/articles/tc-99m-mag3

Radiopharmaceuticals quality control

Preparation of all radiopharmaceuticals must happen under aseptic conditions to ensure sterility and prevent microbial contamination! → patients may have weak immune system

More generally, information for quality controls can be found:

- SPC (summary of product characteristics) of Kits and radiopharmaceuticals,
- Pharmacopoeia monographs,
- Legal notices from the Federal Office of Public Health / Swissmedic,
- Publications & Literature.

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Federal Department of Home Affairs FDHA
Federal Office of Public Health FOPH

swissmedic

The nature of the QC changes according to the type of radiopharmaceutical!

Source: Dr. Ruslan Cusnir (IRA/CHUV); https://fr.wikipedia.org/wiki/Swissmedic ; https://cancerscreeningcommittee.ch/fr/logo-foph-2/

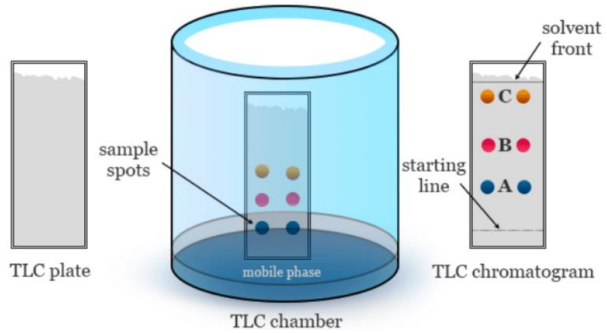
Radiopharmaceuticals quality control

Ready-to-use	Kit (e.g. ^{99m}Tc)	Generators	Precursor (synthesis)
activity	activity	Breakthroug (of ^{99}Mo for ^{99m}Tc and of ^{68}Ge for 68Ga)	activity
(sterility, apyrogenicity, purity are guaranteed by manufacturer)	Radiochemical purity	breakthrough (^{68}Ga)	Purity (chemical, radiochemical, radionuclidic)
	(chemical purity, apyrogenicity, particle size, pH generally guaranteed by manufacturer)	Aluminium content	Particle size
		pH	pH
			Sterility and endotoxins
			Mother breakthrough
			Quantification of residual solvents from synthesis

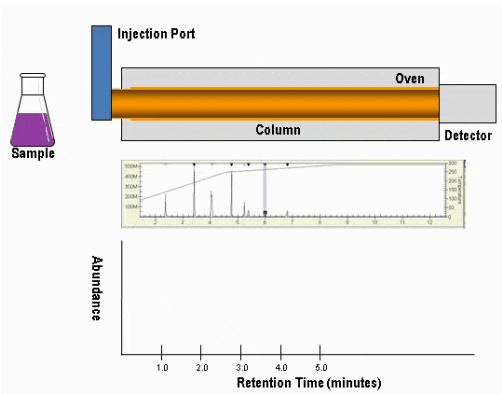
Source: Dr. Ruslan Cusnir (IRA/CHUV); https://fr.wikipedia.org/wiki/Swissmedic ; https://cancerscreeningcommittee.ch/fr/logo-foph-2/ ; https://www.mirion.com/products/medical/nuclear-medicine-instrumentation/lab-supplies/nuclear-medicine-lab-equipment/radiopharmacy-equipment/tec-control-aluminum-breakthru-kit

Radiopharmaceuticals quality control

- Instrumentation for CQ:
  - Activimeters (or radionuclide calibrators)
    - activity measurements
  - Thin layer chromatography (TLC)
    - radiochemical purity
  - High-performance liquid chromatography (HPLC)
    - identification, radiochemical purity, quantification
  - Gas chromatography
    - residual solvent identification (acetone, ethanol)



Pressurized liquid solvent containing the sample mixture flows through a column filled with a solid adsorbent material which retains the individual components.



Used for separating and analyzing compounds that can be vaporized without decomposition.

Source: Dr. Ruslan Cusnir (IRA/CHUV); https://www.comecer.com/dose-calibrator-vdc-505-4/ ; https://www.careerpower.in/school/chemistry/thin-layer-chromatography ; https://noguchi.ug.edu.gh/services/hplc-analysis/ ; https://instrumentationtools.com/working-principle-of-gas-chromatograph/

Radiopharmaceutical facilities

- Requirements change according to the radiopharmaceutical production.
- In every case → trained personnel in:
  - aseptic working techniques
  - radiation protection

Small-scale (KIT and ready-to use)	**Large-scale**, including in-house productions
Ideally dedicated room for production	Supervision of a radiopharmacist
Shielded laminar flow hood, grade A	Dedicated room for production
	Dedicated room for QC
	Hot cells grade A, environment grade B, C, D
	GMP certified by the regulatory authorities

EPFL

Source: Dr. Ruslan Cusnir (IRA/CHUV); https://isovax.in/specialised-isolators/; https://www.radioprotech.com/en/15-shieldedbiosafetycabinet/36-labellingbiosafetycabinet

CHUV

Radiopharmaceutical facilities

EUROPEAN COMMISSION

Brussels, 22.8.2022
C(2022) 5938 final

GUIDELINES

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Table 4: Examples of operations and grades for aseptic preparation and processing operations

Grade A	- Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam-in-place whenever possible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	- Background support for grade A (when not in an isolator). - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	- Preparation of solutions to be filtered including sampling and dispensing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning. - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. - Assembly of closed and sterilised SUS using intrinsic sterile connection devices.

EPFL

CHUV

Radiopharmaceutical facilities

- GMP = good manufacturing practice
  - Adequate **premises**, **space**, **equipment** and **materials**.
  - Appropriately **qualified** and **trained** personnel.
  - Clear **definition** of manufacturing process.
  - **Validation** of critical steps in the process.
  - Validation of any significant **changes** to the process.
  - Approved **instructions** and procedures for production, quality control, product release, etc.
  - **Quality assurance and quality control** independent of production.
  - **Traceability** of manufacture.
  - Examination of complaints and **investigation** of quality defects.
  - …

EPFL

Source: Dr. Ruslan Cusnir (IRA/CHUV); https://www.smrtinc.com/news/considerations-in-navigating-radiopharmaceutical-facility-design/

CHUV

Part 3 – Biokinetic models and internal dosimetry

Glossary : sealed vs unsealed sources

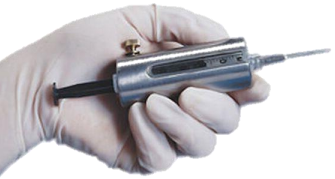
sealed sources

sources whose construction prevents the dispersion of radioactive material under normal working conditions.

unsealed sources

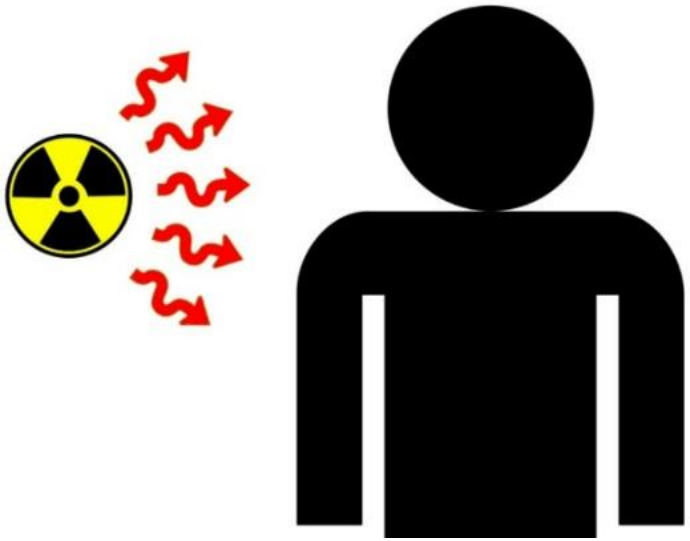
sources whose construction does not allow to prevent the dispersion of radioactive material
(ex : liquids, powders).

Source: https://www.suva.ch/fr-ch/prevention/par-danger/materiaux-rayonnements-et-situations-a-risque/rayonnement-et-radioactivite/rayonnement-ionisant/controle-de-letancheite-des-sources-de-rayonnements-scellees#state=%5Banchor-C9332EBB-08A3-40ED-8664-7F8D9BB05301%26A3AB243DFCA44363AB2CF15F0992E007%5Bopen%5D%3Dtrue%5D;
https://www.mirion.com/fr/products/medical/nuclear-medicine-instrumentation/lab-supplies/shielding-storage/syringe-shields/pro-tec-pet-syringe-shield;
https://www.world-nuclear-news.org/Articles/Companies-work-on-securing-medical-isotope-supplie

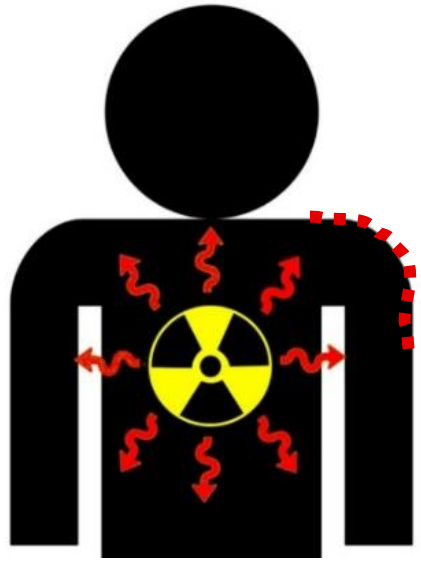


Glossary

«irradiation»



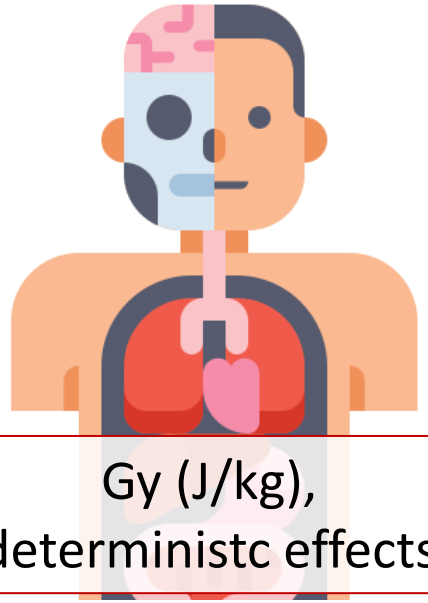
«contamination»



Recap : the concept of dose

- How to evaluate the quantity of radiation, taking into account its effect on the human body?

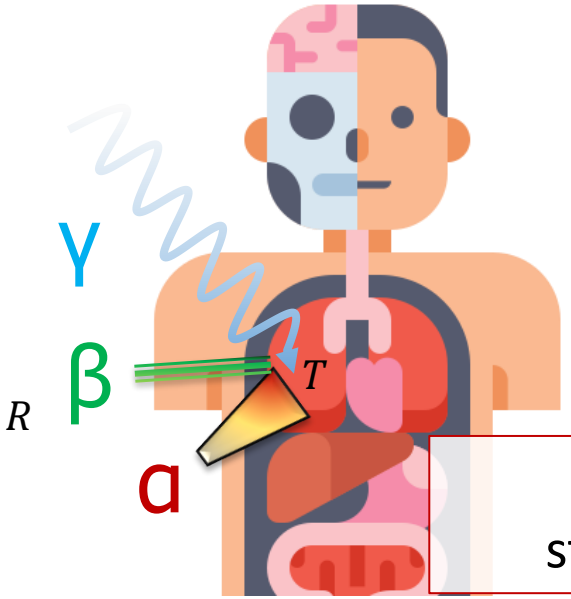
Absorbed dose, *D* :
Amount of energy delivered per unit mass



Gy (J/kg), deterministc effects

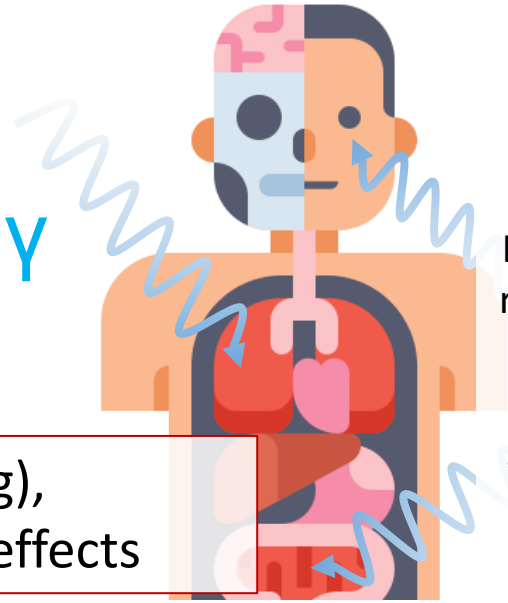
$$D$$

Equivalent dose, *H* :
Takes into account the detriment induced by the type of radiation



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

Effective dose, *E* :
Takes into account the radiosensibility of the different organs



Sv (J/kg), stochastic effects

$$E = \sum_T w_T H_T$$

It expresses the overall risk to the human body regarding the occurrence of stochastic effects for a reference individual

Disclaimer!

- In the following slides we are going to see similar concepts applied to:

1. Radiation protection (occupational exposure)
   - **Workers** exposed to accidental intake of radionuclides

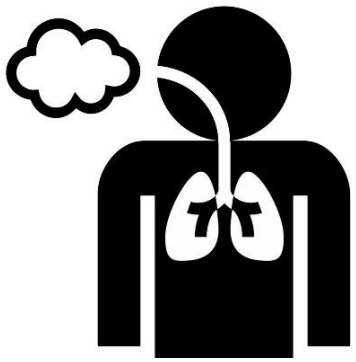
RP

2. Nuclear medicine (medical exposure)
   - **Patients** administered with radiopharmaceuticals on purpose

NM

Briefly : committed effective dose *E*

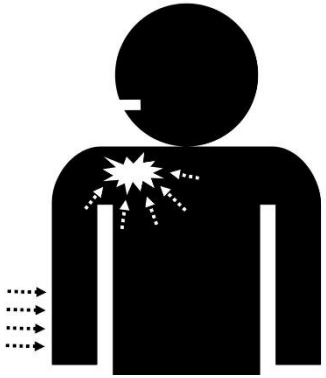
RP NM



Inhalation

Ingestion

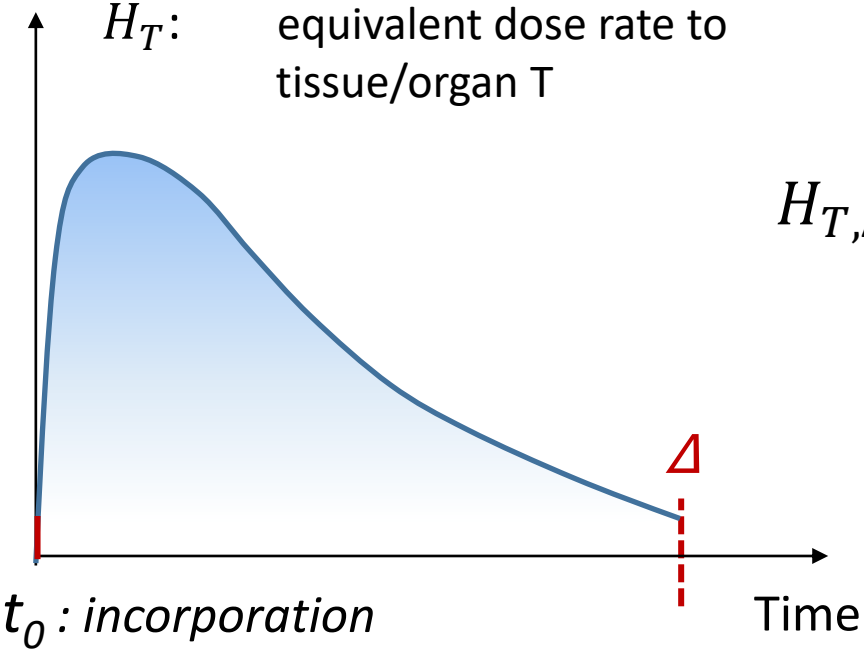
Injection



Absorption
(intact skin or wounds)

Effective dose received by the whole body during the Δ years that follow an intake

- Δ = 50 for a worker (occupational exposure)
- Δ = ∞ for a NM patient (because short-lived isotopes!)



$$H_{T,\Delta} = \int_{t_0}^{t_0+\Delta} \dot{H}_T(t)\,dt$$

$$\boldsymbol{E}_\Delta = \sum_T w_T \cdot H_{T,\Delta}$$

EPFL Not a directly measurable quantity → indirect estimation from *in vivo* and *in vitro* measurements. CHUV

RP

Determination of the effective dose

NM

$$E_{50} = I_{inh} \cdot \mathbf{e_{inh}}$$

$$E_{50} = I_{ing} \cdot \mathbf{e_{ing}}$$

e_{inh} and e_{ing} take into account:

- Radionuclide and radiation type / energy
- Incorporation route (inhalation or ingestion)
- Metabolism of the incorporated radionuclide

$$E = I_{adm} \cdot \mathbf{e}$$

e takes into account:

- Radionuclide and radiation type / energy
- Incorporation route (mostly injection)
- Metabolism of the radiopharmaceutical

EPFL

CHUV

RP

Determination of the effective dose

NM

inhaled activity

$$E_{50} = I_{inh} \cdot \mathbf{e_{inh}}$$

dose conversion coefficient

$$E_{50} = I_{ing} \cdot \mathbf{e_{ing}}$$

ingested activity

$$E = I_{adm} \cdot \mathbf{e}$$

Radionuclide	Half-life	Type of decay/ radiation	Assessment quantities e_{inh} Sv/Bq	e_{ing} Sv/Bq	h_{10} (mSv/h)/ GBq at 1 m distance	$h_{0,07}$ (mSv/h)/ GBq at 10 cm distance
1	2	3	4	5	6	7
Tc-97	2.6 E6 a	ec / ph	1.60E-10	8.30E-11	0.017	4
Tc-97m	90.1 d	it / ph	2.70E-09	6.60E-10	0.014	30
Tc-98	4.2 E6 a	β^- / ph	6.10E-09	2.30E-09	0.215	2000
Tc-99	2.111 E5 a	β^-	3.20E-09	7.80E-10	<0.001	1000
Tc-99m	6.015 h	it, β^-/ ph	2.90E-11	2.20E-11	0.022	300
Tc-101	14.2 min	β^- / ph	2.10E-11	1.90E-11	0.055	1000
Tc-104	18.3 min	β^- / ph	4.80E-11	8.10E-11	1.219	1000
Ru-94	51.8 min	ec, β^+ / ph	7.40E-11	9.40E-11	0.100	20
Ru-97	2.9 d	ec / ph	1.60E-10	1.50E-10	0.055	100

Swiss Radiological Protection Ordinance (taken from ICRP for occupational exposures)

Radiation dose to patients from radiopharmaceuticals

Table C.31. Absorbed doses for ^{18}F-fluoro-2-deoxy-D-glucose.

Organ	Absorbed dose per unit activity administered (mGy MBq^{-1}) Adult	15 years	10 years	5 years	1 year
Adrenals	1.2E−02	1.6E−02	2.4E−02	3.9E−02	7.1E−02
Bone surfaces	1.1E−02	1.4E−02	2.2E−02	3.4E−02	6.4E−02
Brain	3.8E−02	3.9E−02	4.1E−02	4.6E−02	6.3E−02
Breast	8.8E−03	1.1E−02	1.8E−02	2.9E−02	5.6E−02
Gallbladder wall	1.3E−02	1.6E−02	2.4E−02	3.7E−02	7.0E−02
Effective dose (mSv MBq^{-1})	1.9E−02	2.4E−02	3.7E−02	5.6E−02	9.5E−02

The physical half-life of ^{18}F is 1.83 h.

... incorporation route (mostly injection)

ICRP 128 – for medical exposures

How fast does radioactivity decays *inside* the body?

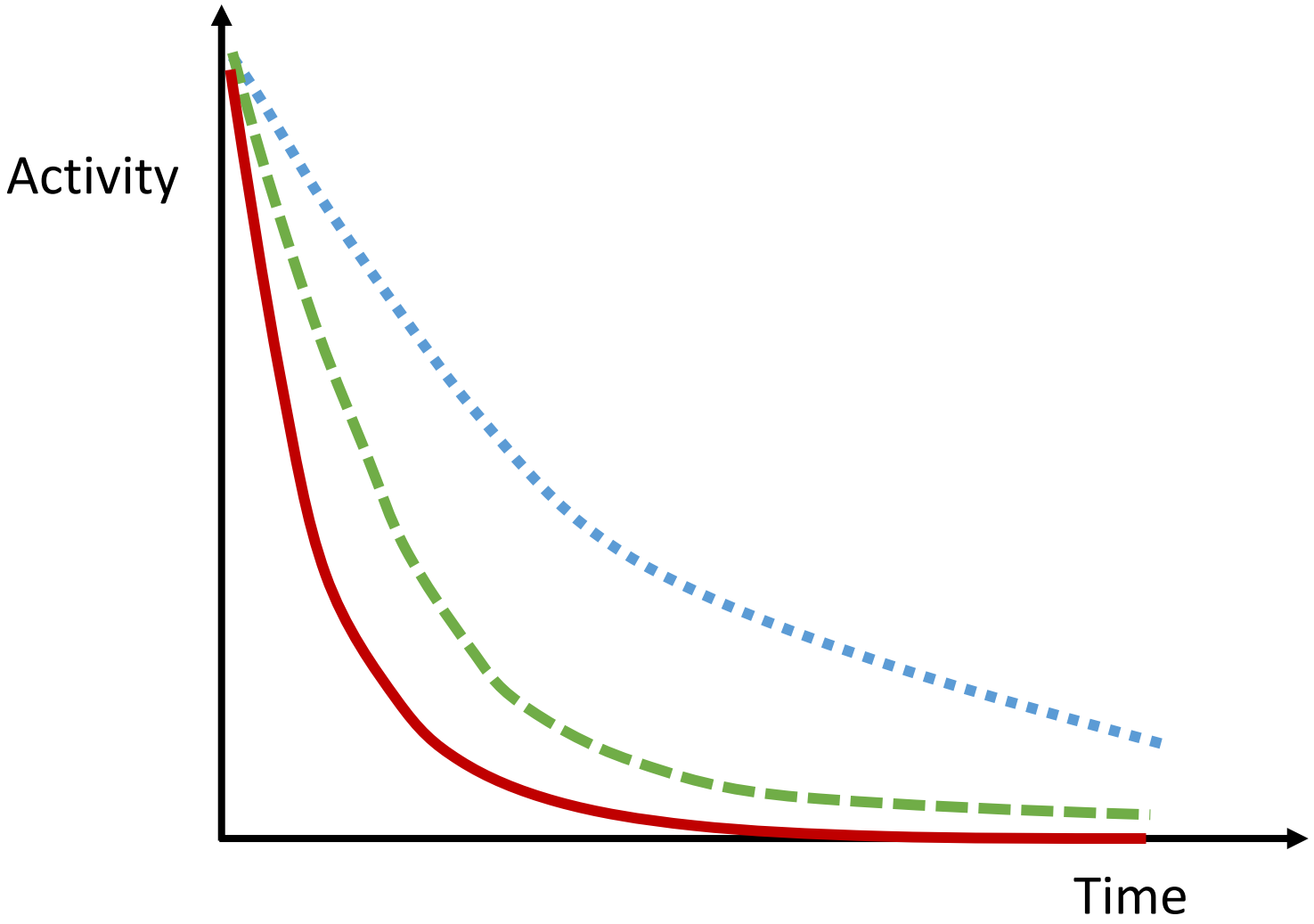
- Physical half-life T_{phys} :
  - given by radioactive decay, radionuclide specific
    - E.g. I-131 has a physical half-life of 8 days

$$\frac{1}{T_{\text{eff}}} = \frac{1}{T_{\text{phys}}} + \frac{1}{T_{\text{bio}}}$$

- Biological half-life T_{bio} :
  - Given by metabolic data, element / substance specific
    - E.g. iodine has a biological half-life of 90 days in the thyroid

- Effective half-life T_{eff} :
  - Combination of physical decay and biological clearance
    - E.g. the effective half-life of I-131 in the thyroid is ~7 days

How fast does radioactivity decays *inside* the body?

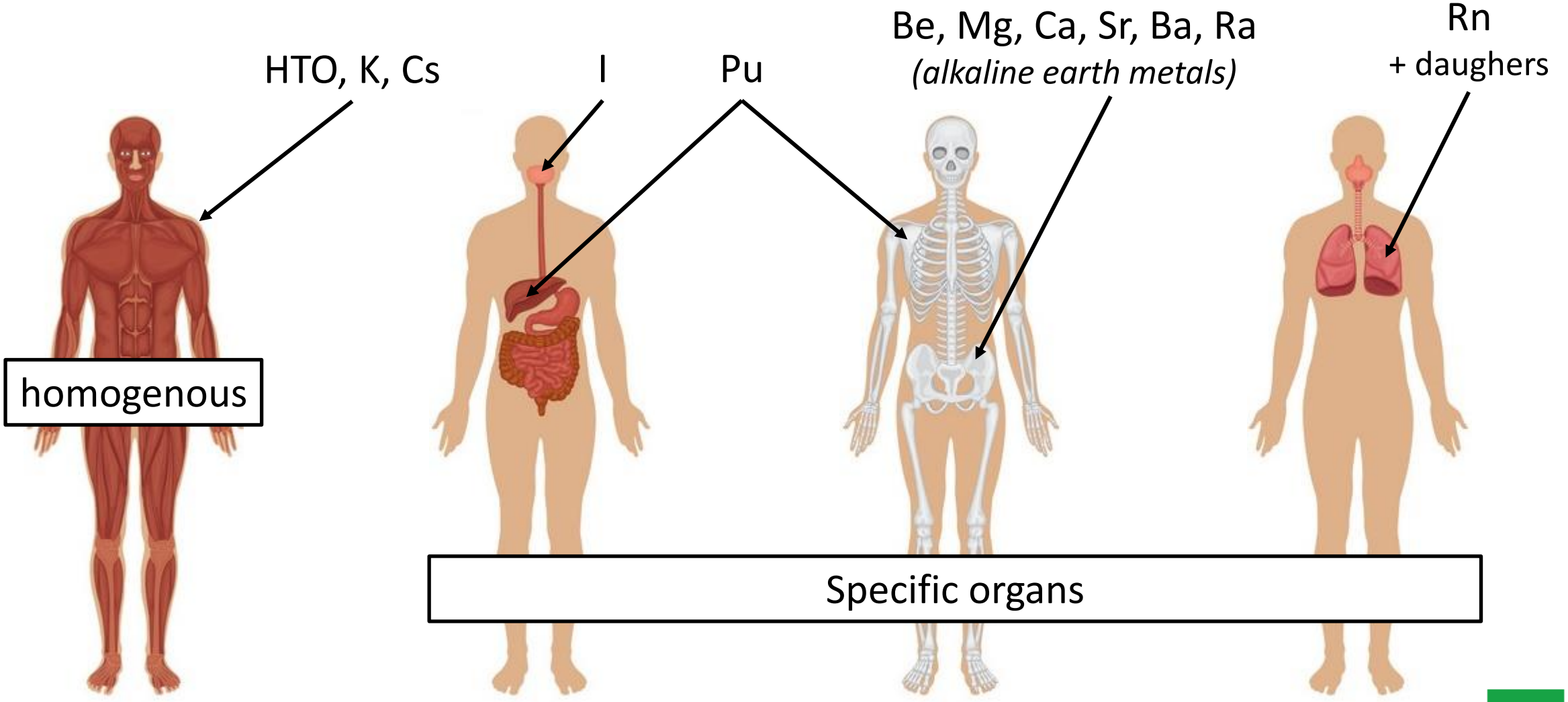


$$\frac{1}{T_{\text{eff}}} = \frac{1}{T_{\text{phys}}} + \frac{1}{T_{\text{bio}}}$$

Source: adapted from https://rajeshvcet.home.blog/wp-content/uploads/2022/04/mlt-unit-vi.pdf

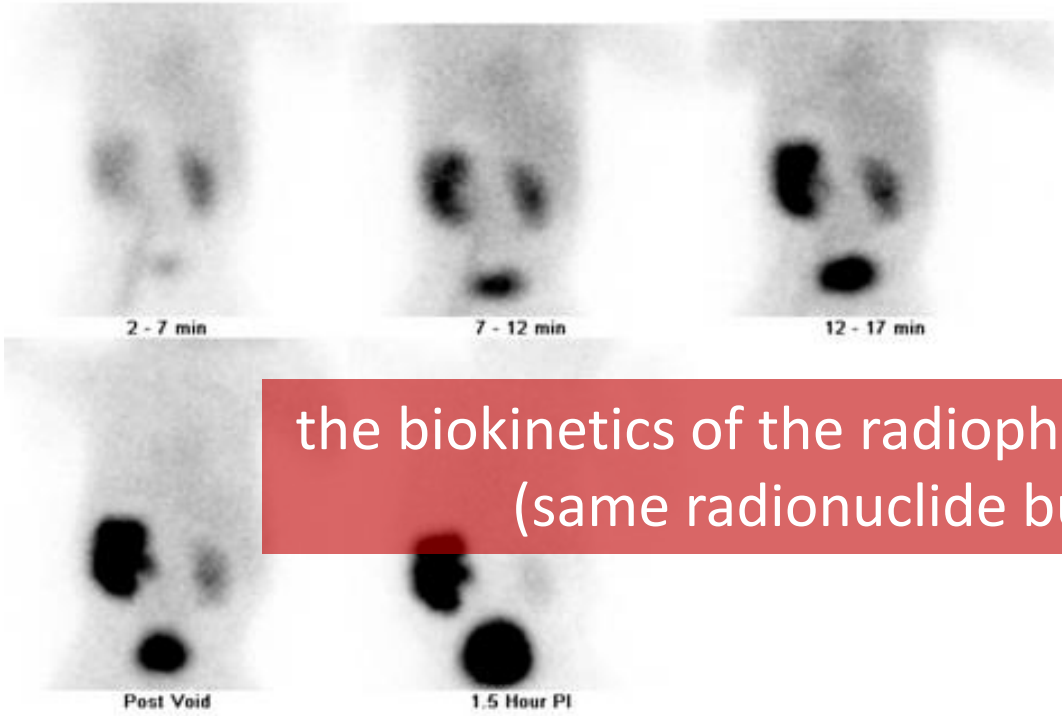
Biokinetics of (unbound) radionuclides

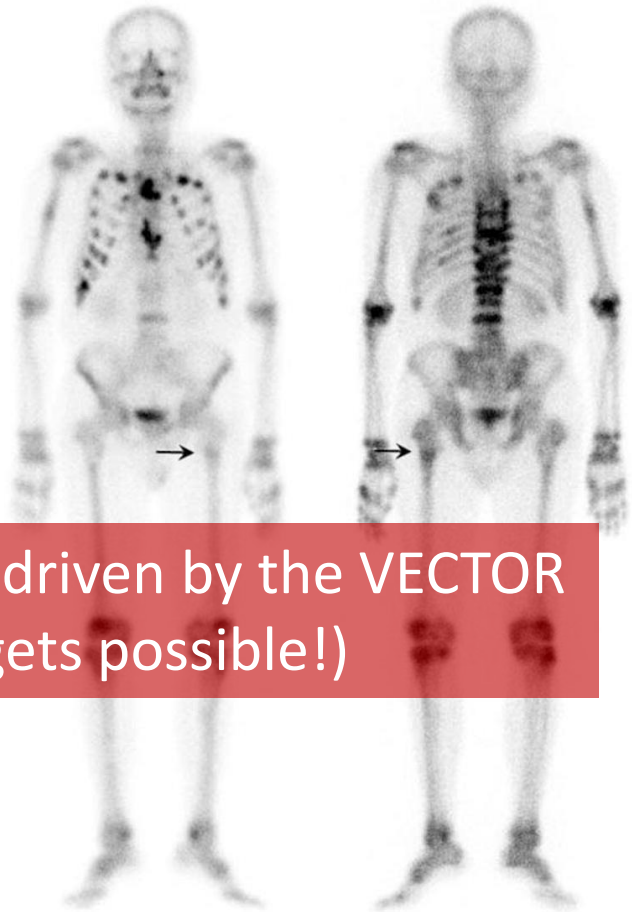
RP



Biokinetics of radiopharmaceuticals

NM





the biokinetics of the radiopharmaceutical is driven by the VECTOR
(same radionuclide but different targets possible!)

^{99m}Tc MAG3 (mercaptoacetyltriglycine)
Dynamic renal scintigraphy

^{99m}Tc MDP (methylene diphosphonate)
bone scan

EPFL

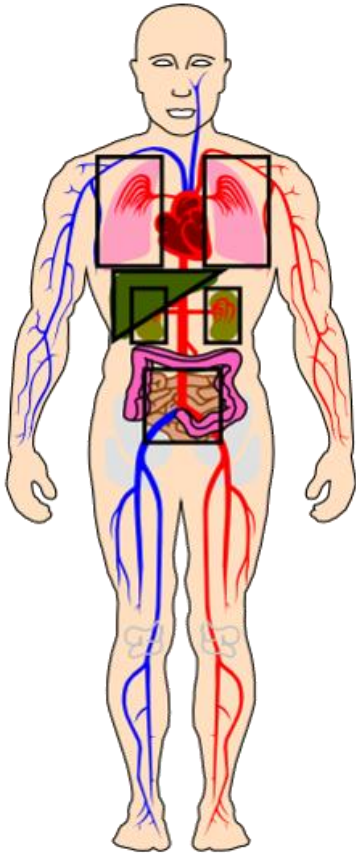
CHUV

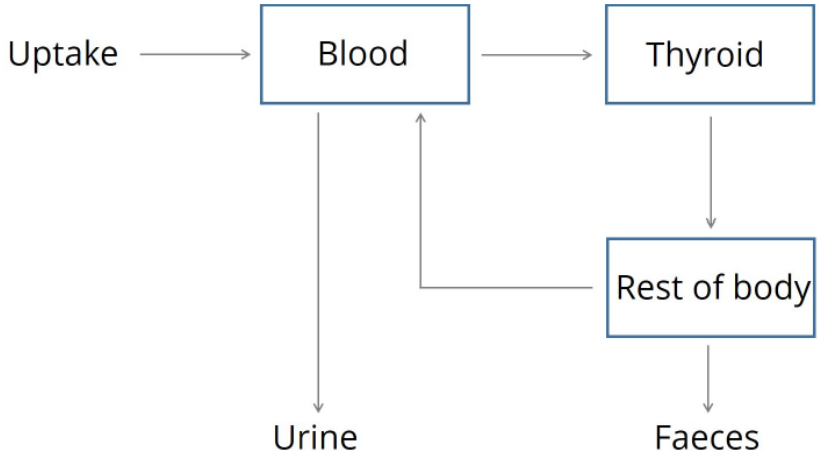
Source: DOI:10.1097/MD.0000000000000995 ; https://radiopaedia.org/cases/pelviureteric-obstruction-high-grade-99m-tc-mag3-scan?lang=gb

Compartmental models : a preview

RP NM

- **ICRP*** approach:
- The distribution of a radioactive substance within the body is modelled by a group of compartments:
  - The body is modelled as a group of compartments.
  - The exchange of a radioactive substance within the different compartments is described by a transfer rate.
  - The time evolution of the substance follows a first order kinetics.



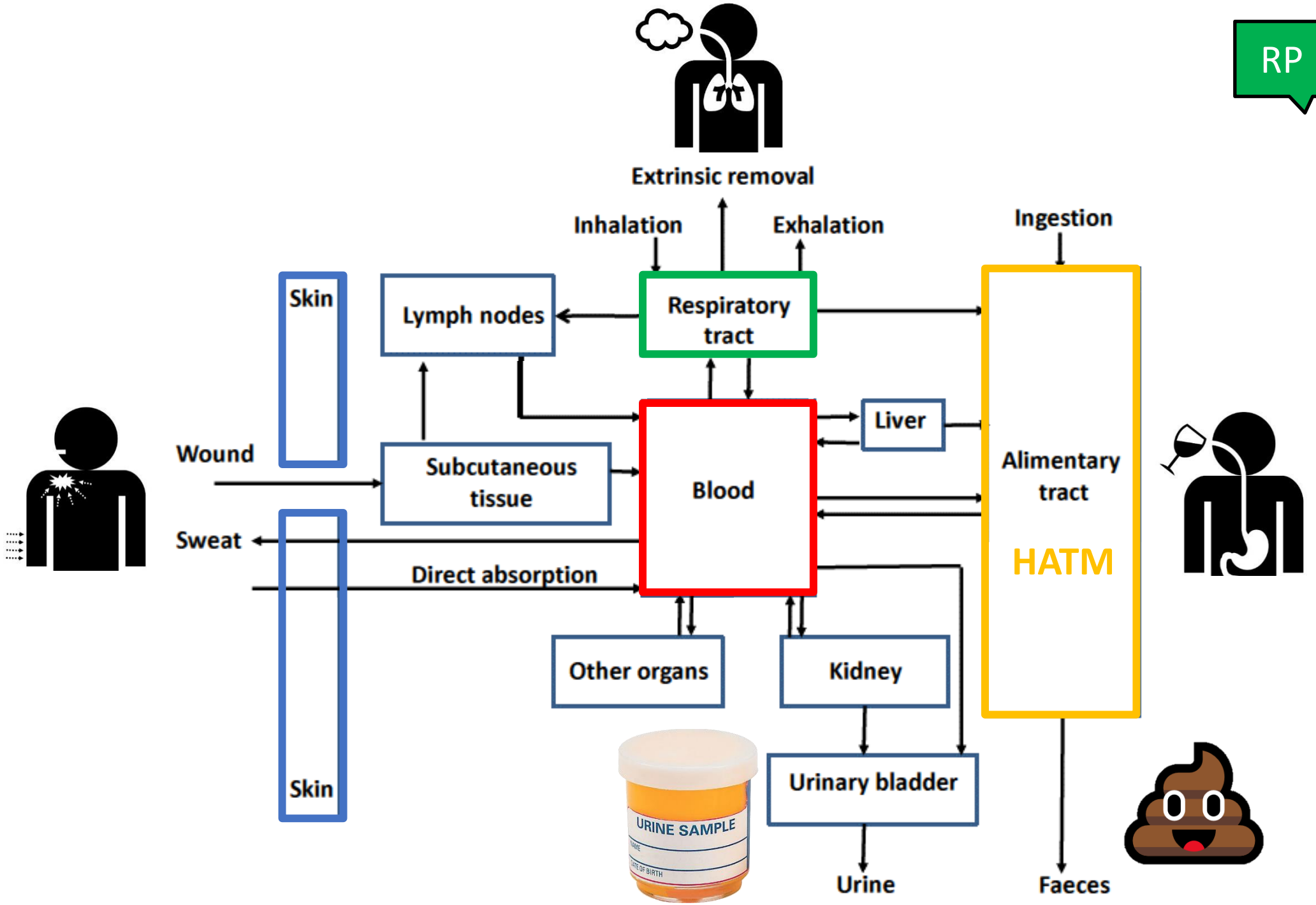


Model for iodine (ICRP Publication 30)

*International Commission for Radiological Protection

RP

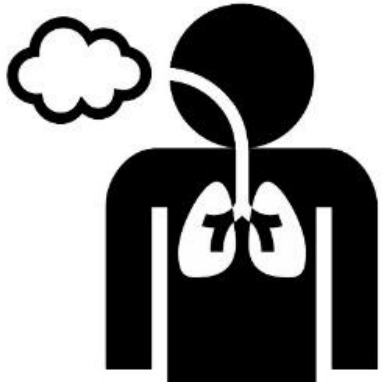
NM
(diag)



EPFL

CHUV

RP

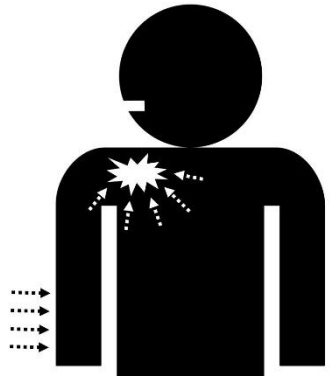


HRTM

Human Respiratory Tract Model

HATM

Human Alimentary Tract Model



skin + wound

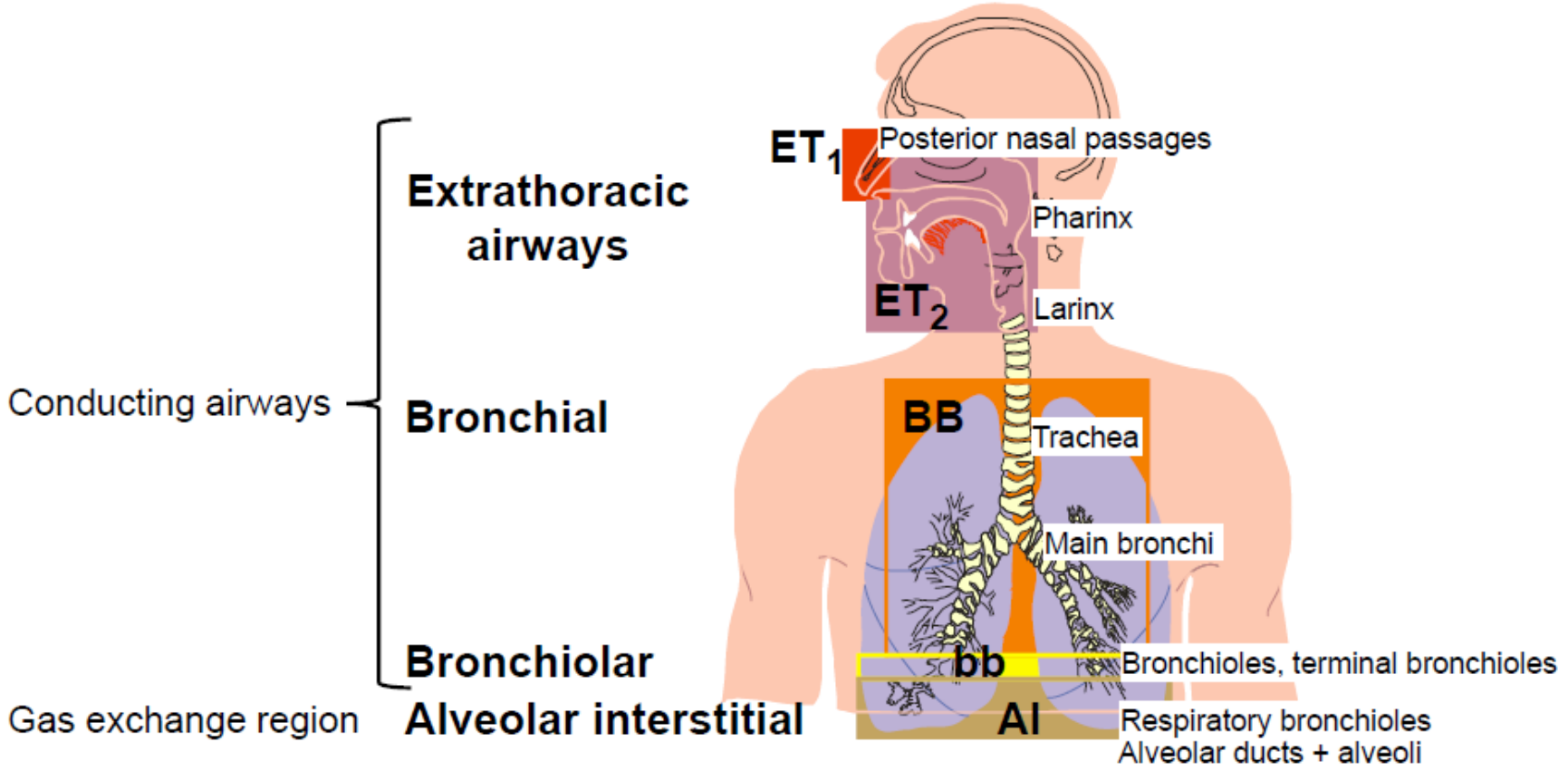
element-specific systemic models

RP

HRTM

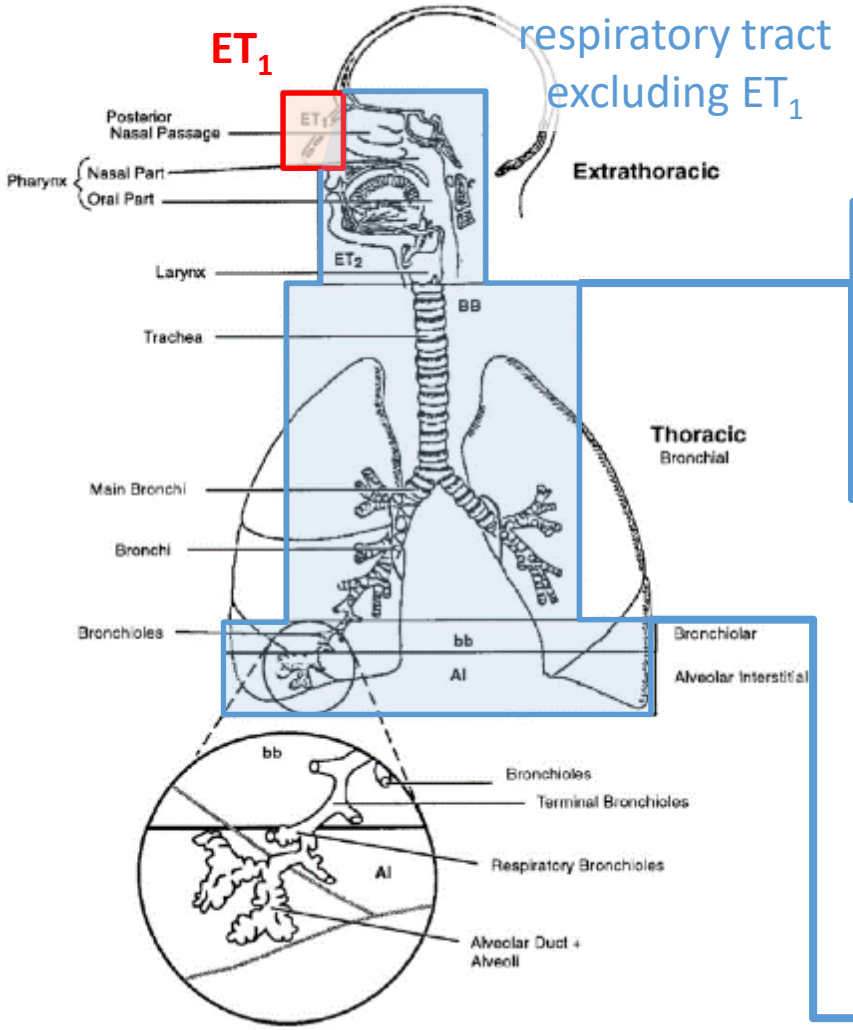
Human Respiratory Tract Model

Anatomy: respiratory tract regions ET, BB, bb, AI



HRTM

Human Respiratory Tract Model



RP

HATM

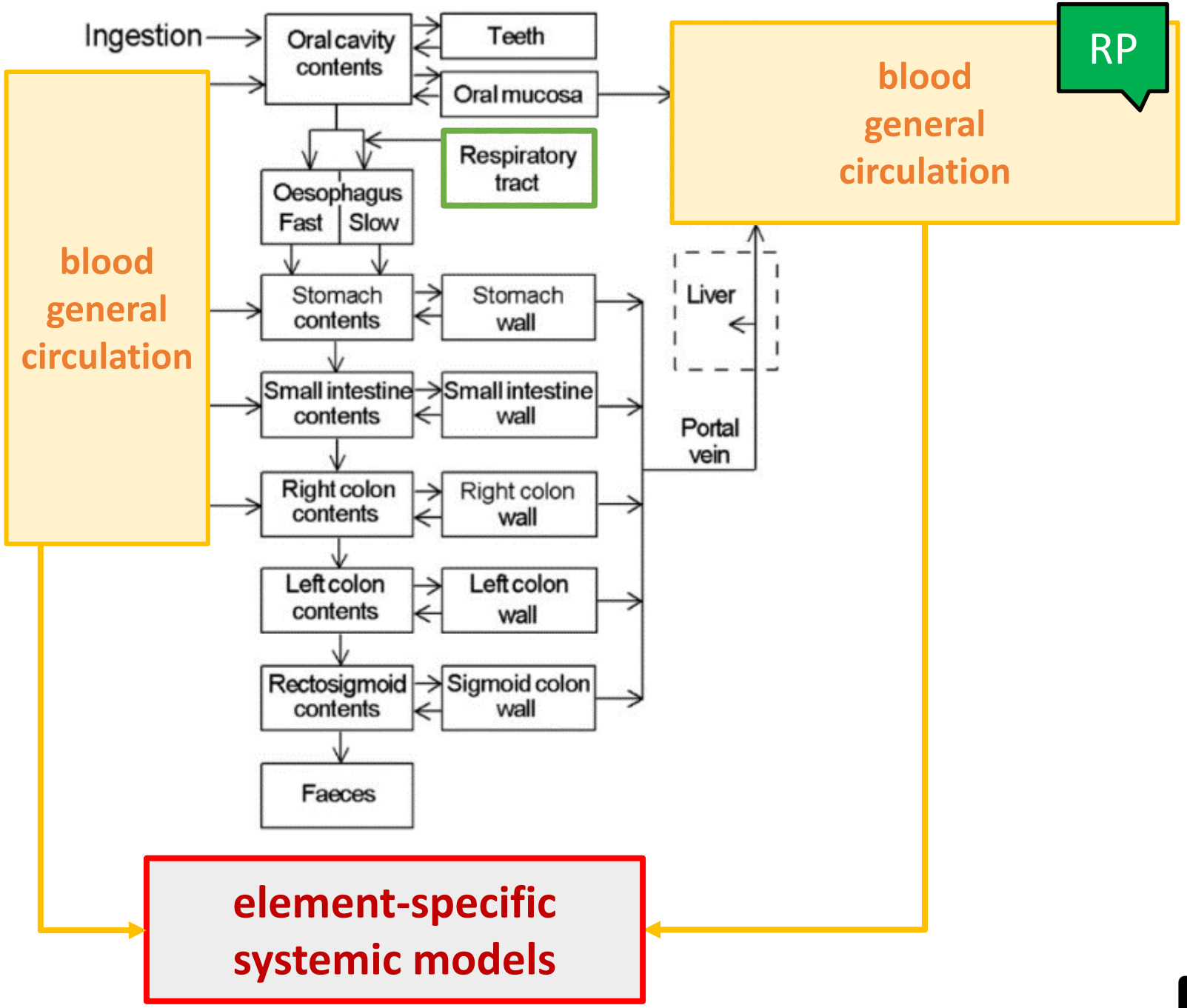
lymph nodes

blood general circulation

element-specific systemic models

HATM

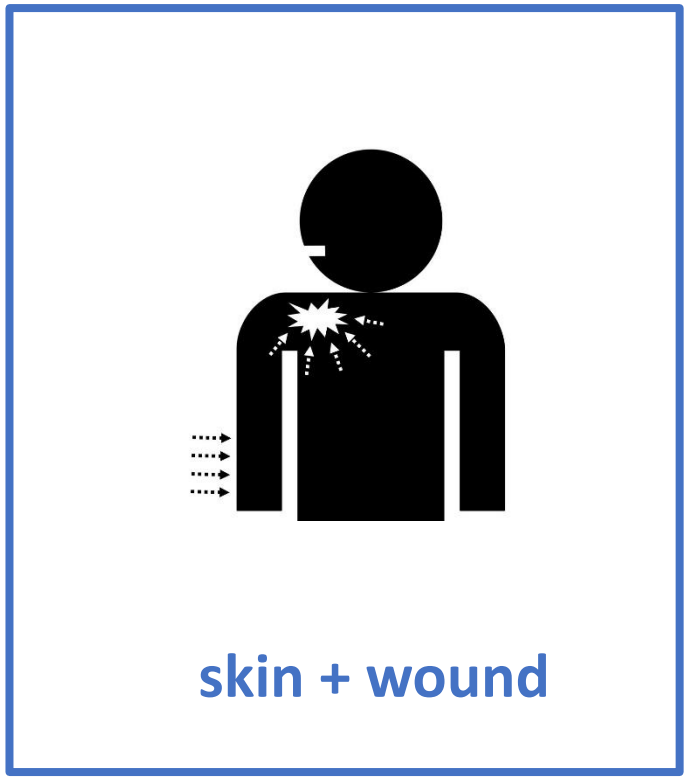
Human Alimentary Tract Model



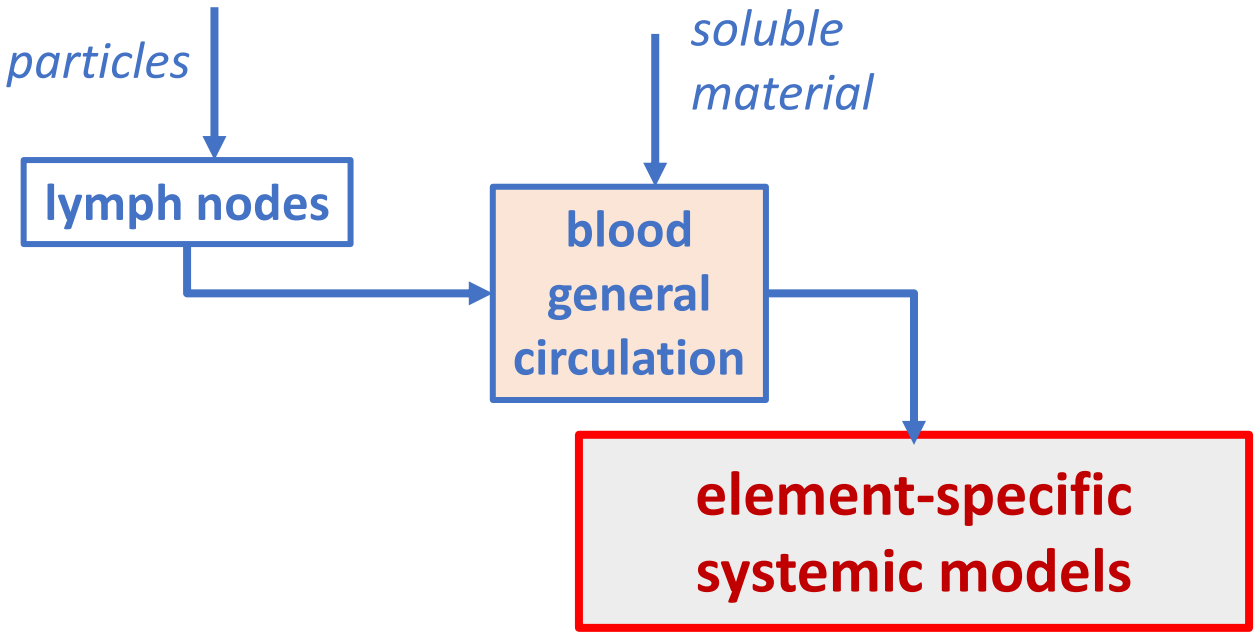
RP

intact skin is a **good barrier**, except for :

- tritiated water, in vapor or liquid form
- organic carbon compounds
- iodine in vapor form or in solution



wound is considered on a case-by-case basis (very complex!):



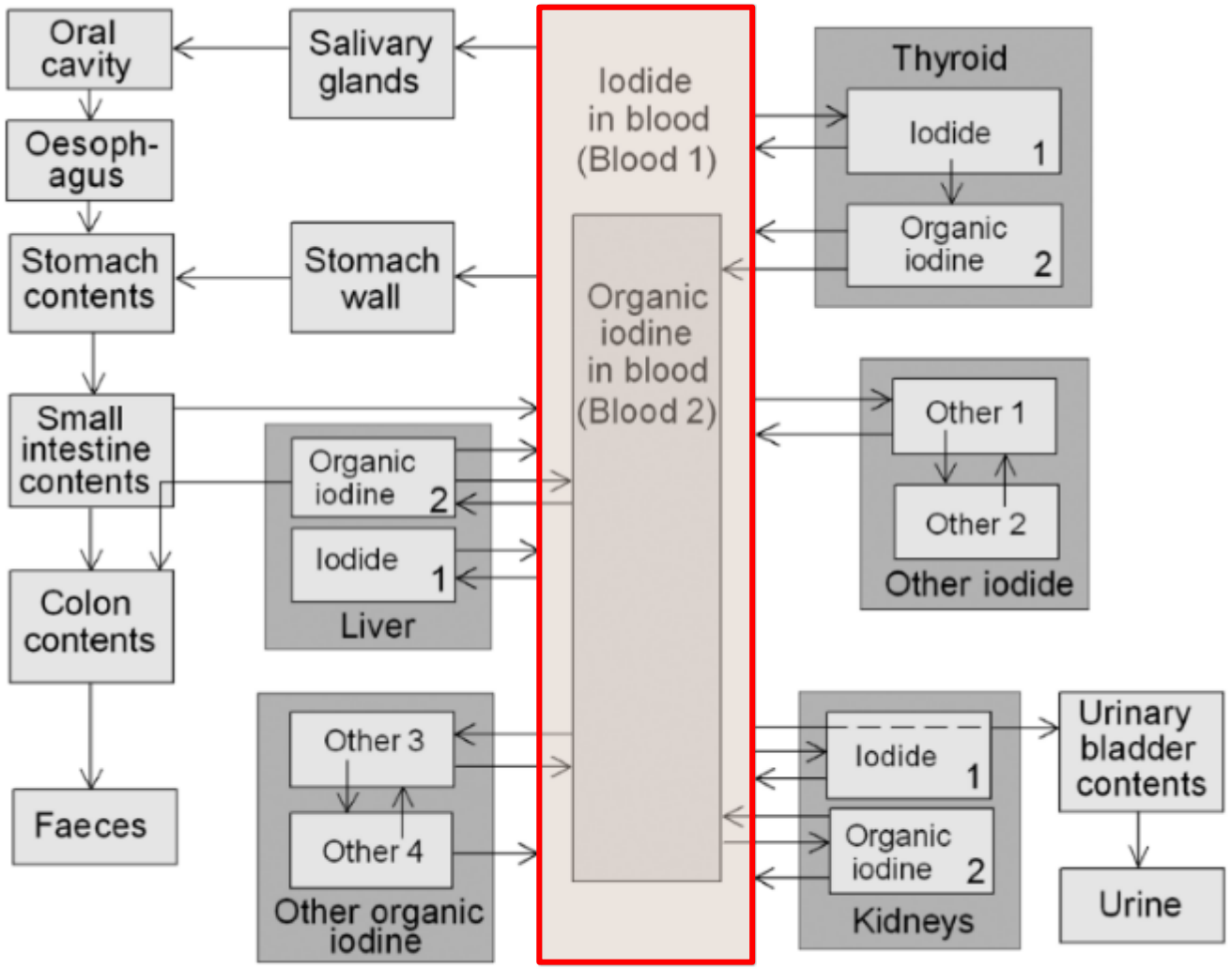


Fig. 5.2. Structure of the biokinetic model for systemic iodine used in this publication.

Pathway	Transfer coefficient (d^{-1})
Blood 1 to Thyroid 1	7.26*
Blood 1 to urinary bladder contents	11.84
Blood 1 to salivary gland	5.16
Blood 1 to stomach wall	8.60
Blood 1 to Other 1†	600
Blood 1 to Kidneys 1	25
Blood 1 to Liver 1	15
Salivary gland to oral cavity	50
Stomach wall to stomach contents	50
Thyroid 1 to Thyroid 2	95
Thyroid 1 to Blood 1	36
Thyroid 2 to Blood 2‡	0.0077
Thyroid 2 to Blood 1	0§
Other 1 to Blood 1	330
Other 1 to Other 2†	35
Other 2 to Other 1	56
Kidneys 1 to Blood 1	100
Liver 1 to Blood 1	100
Blood 2 to Other 3†	15
Other 3 to Blood 2	21
Other 3 to Other 4	1.2
Other 4† to Other 3	0.62
Other 4 to Blood 1	0.14
Blood 2 to Kidneys 2	3.6
Kidneys 2 to Blood 2	21
Kidneys 2 to Blood 1	0.14
Blood 2 to Liver 2	21
Liver 2 to Blood 2	21
Liver 2 to Blood 1	0.14
Liver 2 to right colon contents	0.08

RP

element-specific systemic models

Example of **iodine**

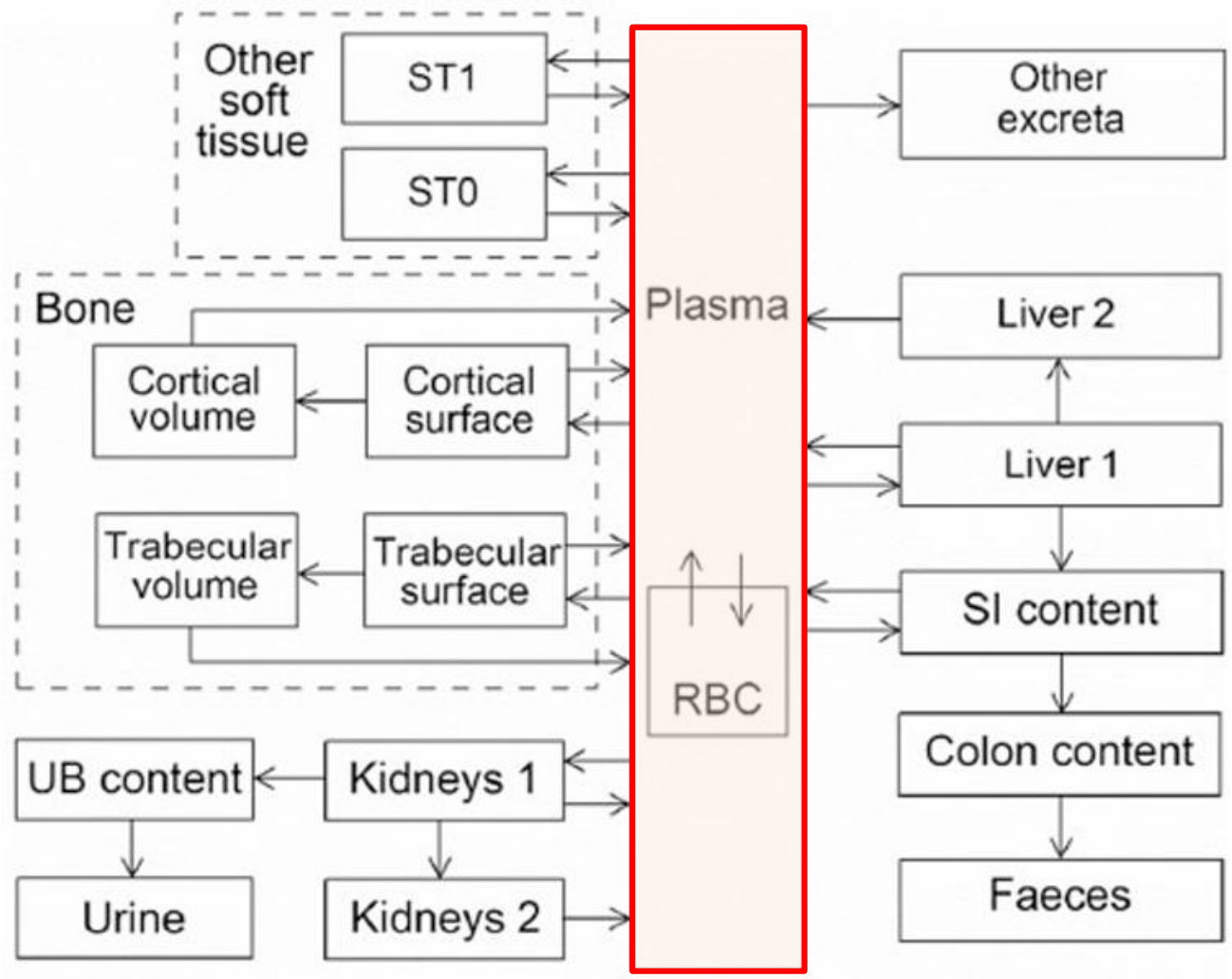


Table 15.4. Transfer coefficients in the biokinetic model for systemic nickel.

From	To	Transfer coefficient (d^{-1})
Plasma	Kidneys 1	12.7
Plasma	Small intestine content	0.18
Plasma	Liver 1	0.45
Plasma	Cortical bone surface	0.675
Plasma	Trabecular bone surface	0.675
Plasma	ST0	7.2
Plasma	ST1	1.2
Plasma	RBC	0.075
Plasma	Other excreta	0.34
RBC	Plasma	0.231
Kidneys 1	Plasma	35
Kidneys 1	Urinary bladder content	15
Kidneys 1	Kidneys 2	0.0013
Kidneys 2	Plasma	0.00173
Liver 1	Plasma	1.9
Liver 1	Liver 2	0.29
Liver 1	Small intestine content	1.46
Liver 2	Plasma	0.00173
ST0	Plasma	1.9
ST1	Plasma	0.00173
Cortical bone surface	Plasma	1.9
Cortical bone surface	Cortical bone volume	0.0192
Trabecular bone surface	Plasma	1.9
Trabecular bone surface	Trabecular bone volume	0.0192
Cortical bone volume	Plasma	0.0000821
Trabecular bone volume	Plasma	0.000493

RBC, red blood cells. ST, soft tissue. ST0 and ST1 are compartments of other soft tissues representing two phases of biological removal to blood.

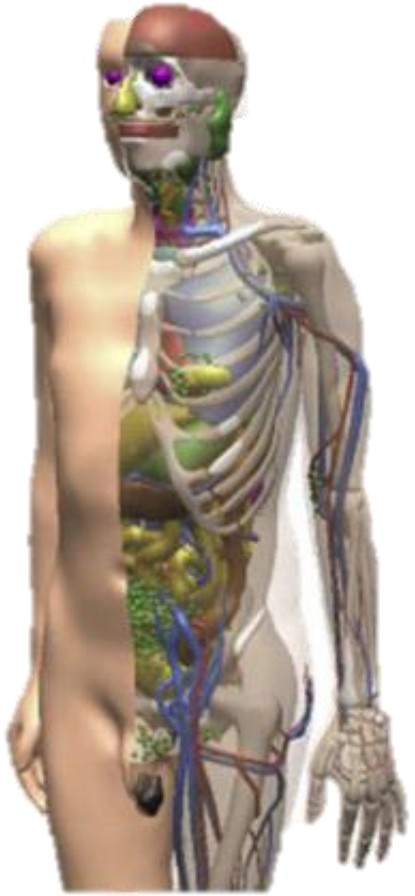
RP

element-specific systemic models

Example of **nickel**

Compartmental models for RP: physiological data for **reference worker**

RP



Deposition and clearance parameter values of a:

- healthy
- non-smoking
- normal nose-breathing
- **adult male** at **light work**

Light work

- 2.5 h sitting
  - 0.54 m^3 h^{-1} (inhaled air)
- 5.5 h light exercise
  - 1.5 m^3 h^{-1}
- All the inhaled air enters through the nose

EPFL

CHUV

Compartmental models for NM *(mostly diagnostics):* physiological data for **reference patients**

NM (diag)

Radiation dose to patients from radiopharmaceuticals

Table A.7. Uptake values (fractions) for small colloids (<100 nm diameter).*

Organ	Condition 1†	Condition 2‡	Condition 3§
Liver	0.70	0.50	0.30
Spleen	0.10	0.20	0.30
Red marrow	0.15	0.25	0.30
Remaining tissue	0.05	0.15	0.10

*Example: ^{99m}Tc mini-/micro-aggregated albumin.
†Normal liver.
‡Early to intermediate diffuse parenchymal liver disease.
§Intermediate to advanced diffuse parenchymal liver disease.

- Disease can modify the "reference" transfer and clearance parameters.
- Effects of the pathology have to be taken into account for the biokinetics.
- This mainly applies to diagnostic radionuclides, for which we may be interested in knowing the effective dose received by the patient (stochastic risk).
- For therapeutic radionuclides, we are mainly interested in the absorbed dose received by the lesions (e.g. tumor) and the healthy organs at risk (expected short-term deterministic effects).

EPFL

Source: ICRP Publication 128

CHUV

Compartmental models for NM *(mostly diagnostics):* physiological data for **reference patients**

NM (diag)

ICRP Publication 128

Table C.76. Biokinetic data for ^{99m}Tc-labelled mercaptoacetyl triglycine.

Organ (S)	F_s	T (h)	a	$\tilde{A}_s/A_0$ (h)
Normal renal function				
Total body (excluding urinary bladder contents and kidneys)	1.0	0.028 0.053 0.72	0.40 0.40 0.20	0.23
Kidneys	1.0			0.065
Urinary bladder contents	1.0			
Adult, 15 years				2.7
10 years				2.3
5 years, 1 year				1.6
Abnormal renal function				
Total body (excluding urinary bladder contents and kidneys)	1.0	0.28 0.53 7.2	0.40 0.40 0.20	1.4
Kidneys	1.0			0.28
Liver	0.04	0.28 0.53 7.2	0.40 0.40 0.20	0.055
Urinary bladder contents	1.0			
Adult, 15 years				2.0
10 years				1.7
5 years, 1 year				1.1

- Disease can modify the "reference" transfer and clearance parameters.
- Effects of the pathology have to be taken into account for the biokinetics.
- This mainly applies to diagnostic radionuclides, for which we may be interested in knowing the effective dose received by the patient (stochastic risk).
- For therapeutic radionuclides, we are mainly interested in the absorbed dose received by the lesions (e.g. tumor) and the healthy organs at risk (expected short-term deterministic effects).

EPFL

CHUV

Source: ICRP Publication 128

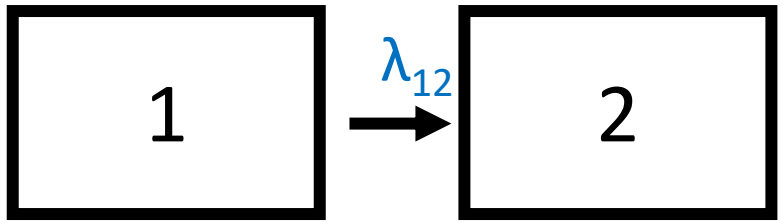
The usefulness of compartmental models

- They describe the transfer of activity and its clearance, allowing to **compute the activity content** of the whole body/specific compartments according to time.

- This information can be used for **dosimetric purposes**.

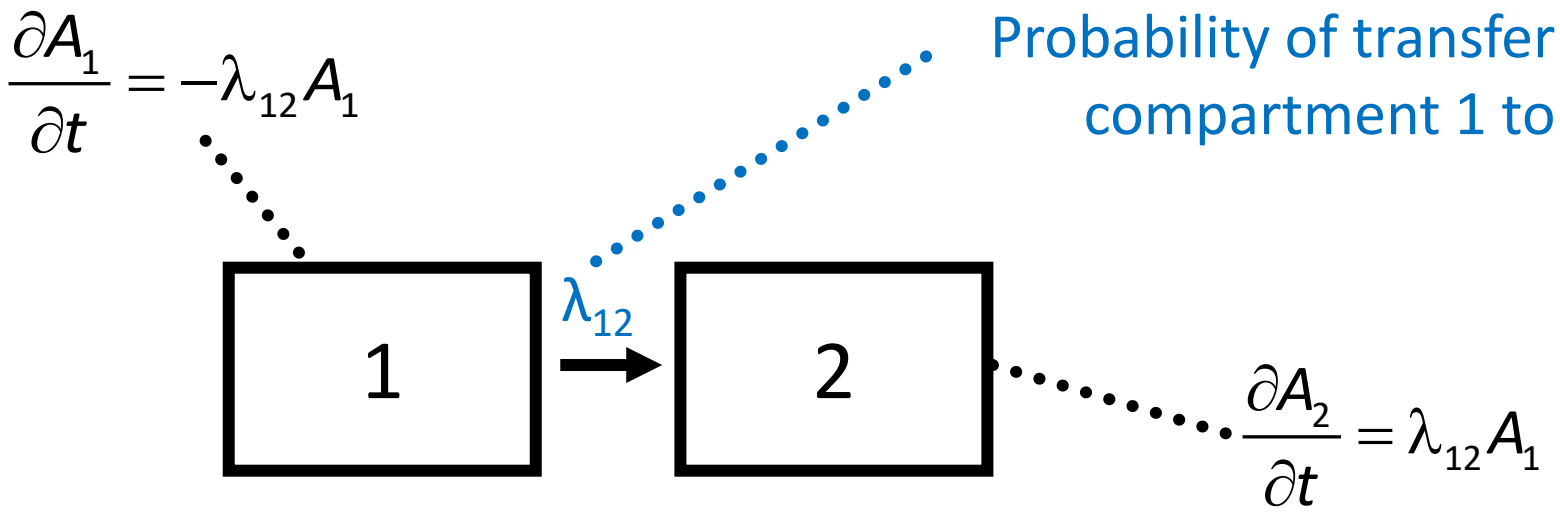
- *How ?*

Solving the compartmental models



- The compartments are considered as **instantaneously homogenous**.
- **Continuous transfer** between the compartments.
- Transfer **proportional** to A in the source
- λ **fractional transfer rate :**probability of transfer from one compartment to another per unit of time.

Solving the compartmental models



flux proportional to the source content

***Solution** of the differential equation (simple case)*

$$A_1(t) = A_{1,0} e^{-\lambda_{12} t}$$

***Generalization** to **N** compartments*

*N*x1 vector containing the activities in each compartment

*N*x*N* matrix containing the fractional transfer rate coefficients

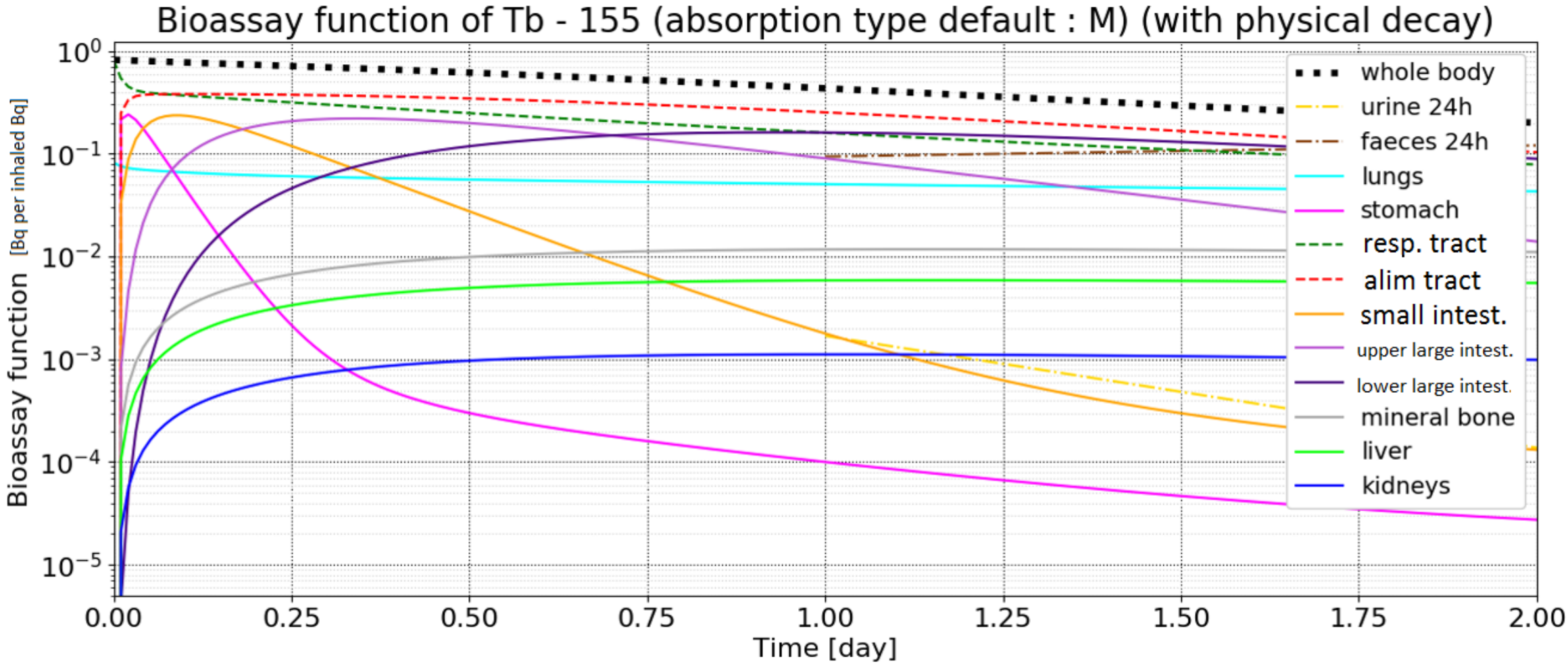
$$\frac{\partial \mathbf{A}}{\partial t} = \mathbf{\Lambda A} \quad \text{solution} \quad \mathbf{A}(t) = \mathbf{A}_0 e^{\mathbf{\Lambda} t}$$

Compartmental models : analytical approach

RP

NM (diag)

- By solving the first order differential equations describing the models we obtain the retention and excretion functions (activity evolution in compartments according to time).

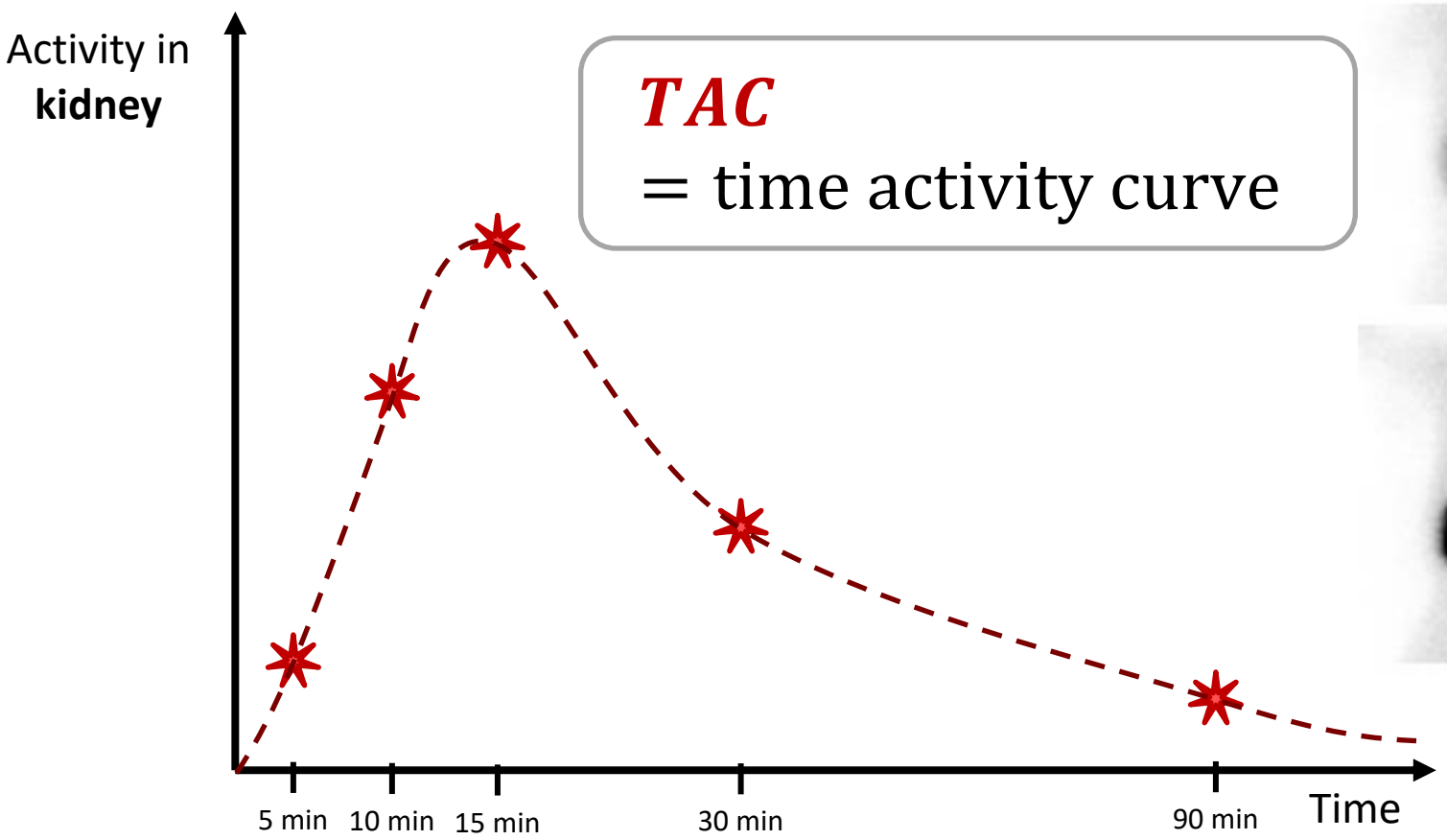


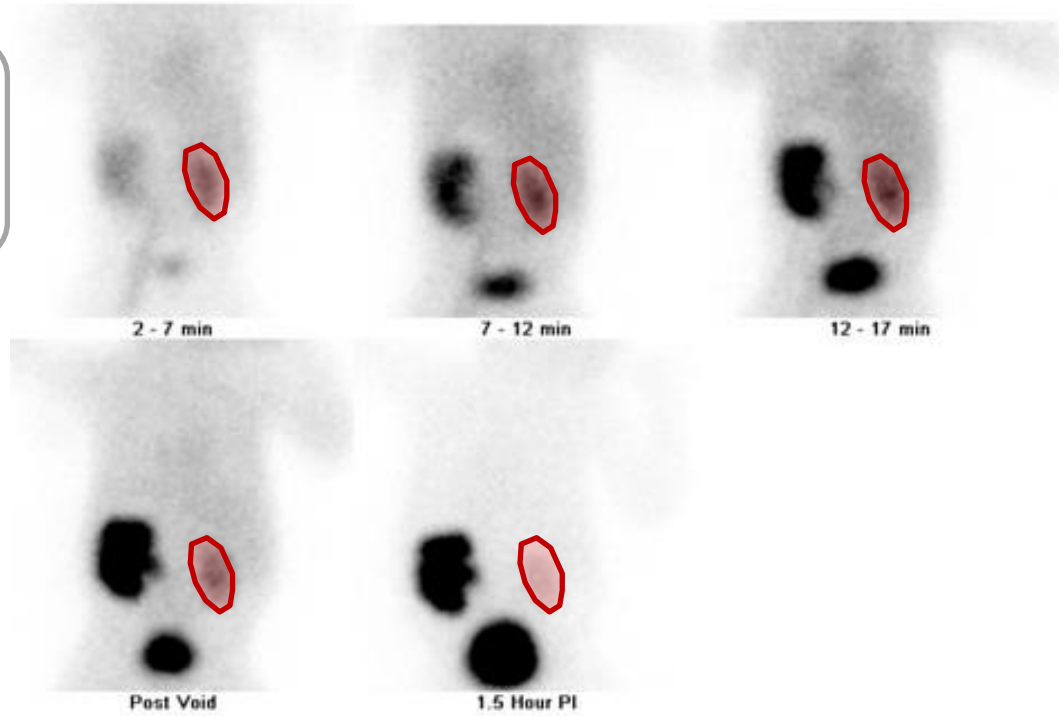
Compartmental models : empirical approach

NM (diag) NM (therapy)

(cf. following lectures!)

- By taking patient images at different time steps it is possible to draw the evolution of activity according to time in specific organs of interest.





Source: Technetium Radiopharmaceutical Chemistry (Continuing Education for Nuclear Pharmacists and Nuclear Medicine Professionals), available : https://pharmacyce.unm.edu/nuclear_program/freelessonfiles/vol12lesson3.pdf ; https://radiopaedia.org/articles/tc-99m-mag3

Dosimetry formalism

- Now we know how to represent the evolution of the activity according to time (analytic solution of biokinetic models / empiric definition of time-activity-curves).

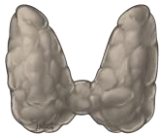
- How can we use this information to compute a dose?

  → internal dosimetry formalism

Dose calculation to a target r_T – MIRD formalism

Absorbed dose in target region r_T [Gy]

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S)\, S(r_T \leftarrow r_S)$$

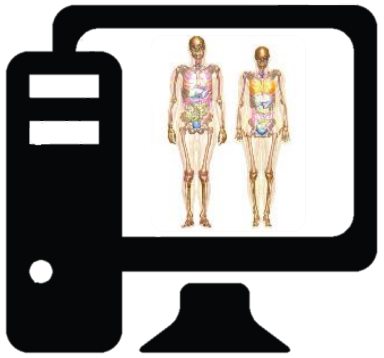


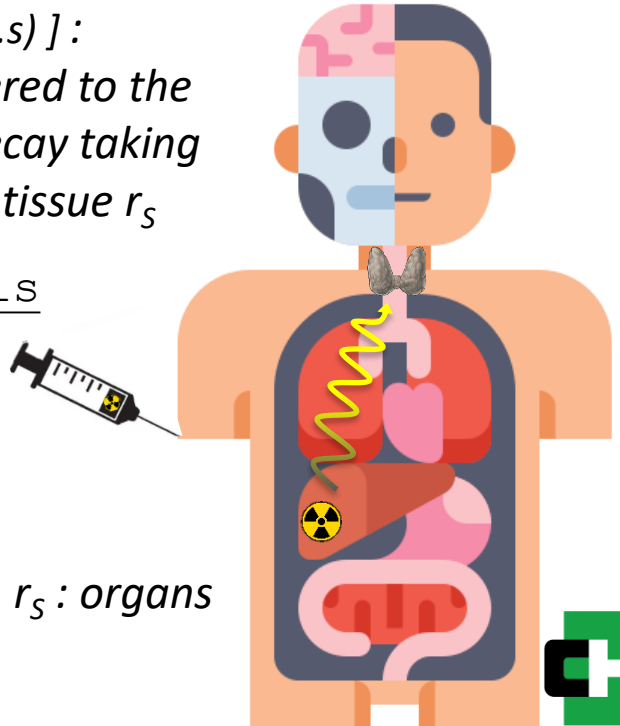
r_T : thyroid

$$S(r_T \leftarrow r_S) = \sum_i \frac{\Delta_i\, \phi(r_T \leftarrow r_S, i)}{M(r_T)}$$

S-factor [Gy/(Bq.s)] :
Absorbed dose delivered to the target tissue r_T per decay taking place in the source tissue r_S

Dosimetric models





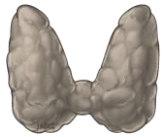
r_S : organs

EPFL MIRD = Medical Internal Radiation Dosimetry (MIRD)

CHUV

Dose calculation to a target r_T – MIRD formalism

Absorbed dose in target region r_T [Gy]



r_T : thyroid

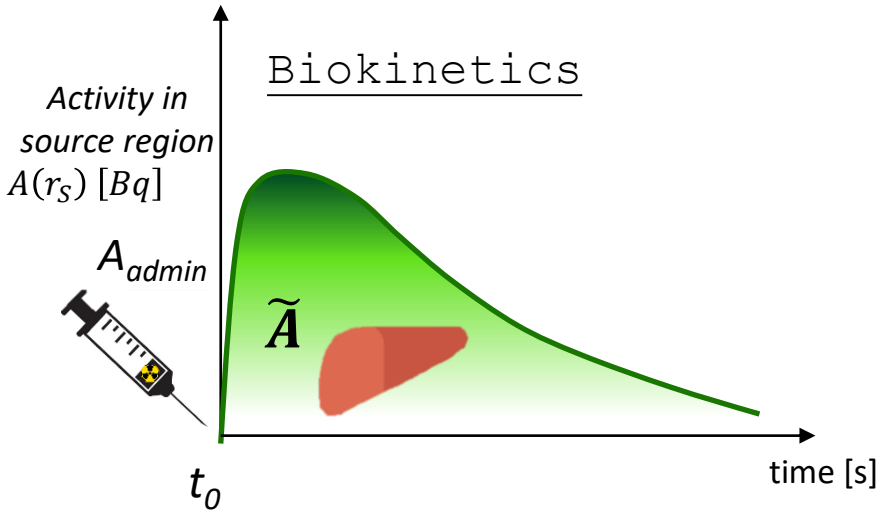
$$D(r_T) = \sum_{r_S} \tilde{A}(r_S)\, S(r_T \leftarrow r_S)$$

$$\tilde{A}(r_S) = \int_{t_0}^{\infty} A(r_S, t)\, dt$$

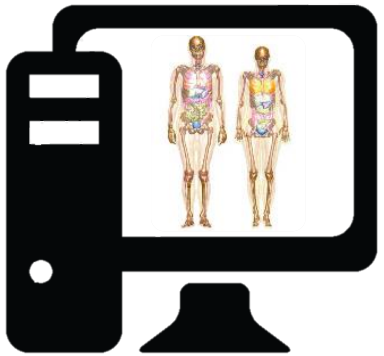
number of decays in r_s

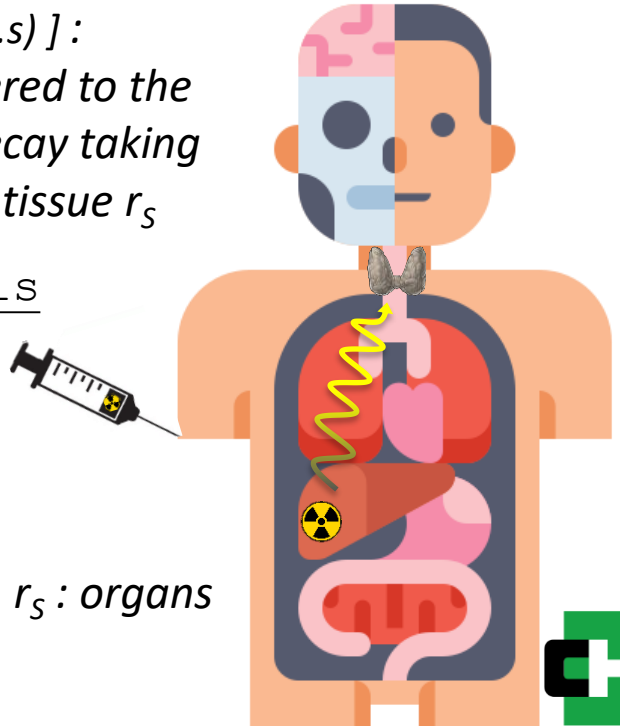
$$S(r_T \leftarrow r_S) = \sum_i \frac{\Delta_i\, \phi(r_T \leftarrow r_S, i)}{M(r_T)}$$

S-factor [Gy/(Bq.s)] :
Absorbed dose delivered to the target tissue r_T per decay taking place in the source tissue r_S



Dosimetric models



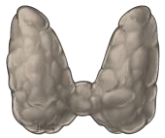


r_S : organs

MIRD = Medical Internal Radiation Dosimetry (MIRD)

Dose calculation to a target r_T – MIRD formalism

Absorbed dose in target region r_T [Gy]



r_T : thyroid

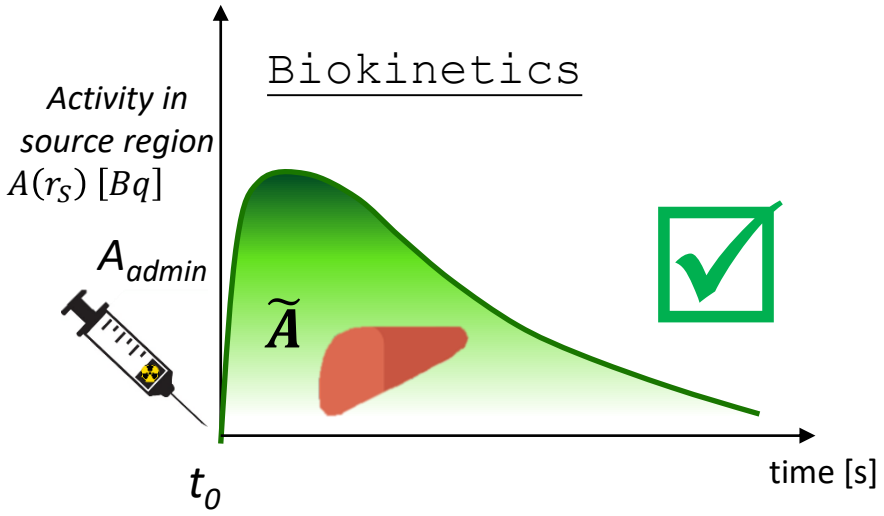
$$D(r_T) = \sum_{r_S} \tilde{A}(r_S)\, S(r_T \leftarrow r_S)$$

$$\tilde{A}(r_S) = \int_{t_0}^{\infty} A(r_S, t)\, dt$$

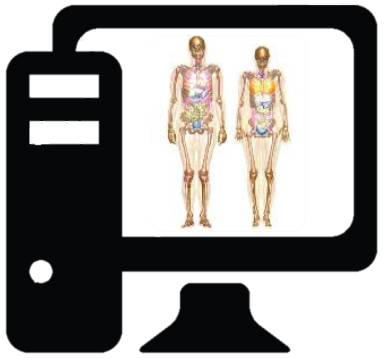
number of decays in r_s

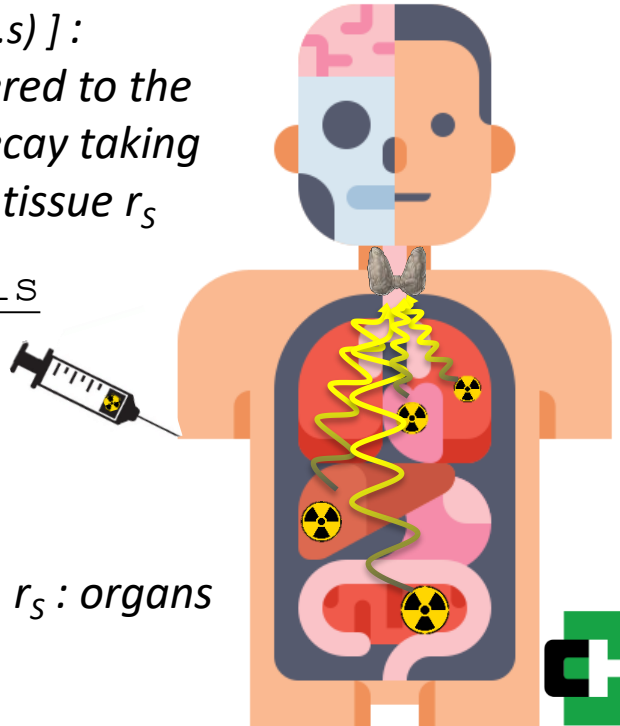
$$S(r_T \leftarrow r_S) = \sum_i \frac{\Delta_i\, \phi(r_T \leftarrow r_S, i)}{M(r_T)}$$

S-factor [Gy/(Bq.s)] :
Absorbed dose delivered to the target tissue r_T per decay taking place in the source tissue r_S



Dosimetric models





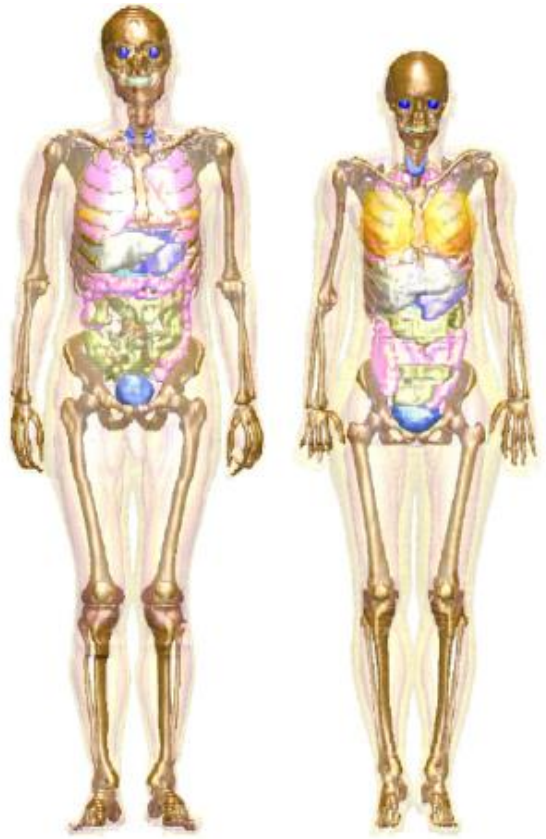
r_S : organs

MIRD = Medical Internal Radiation Dosimetry (MIRD)

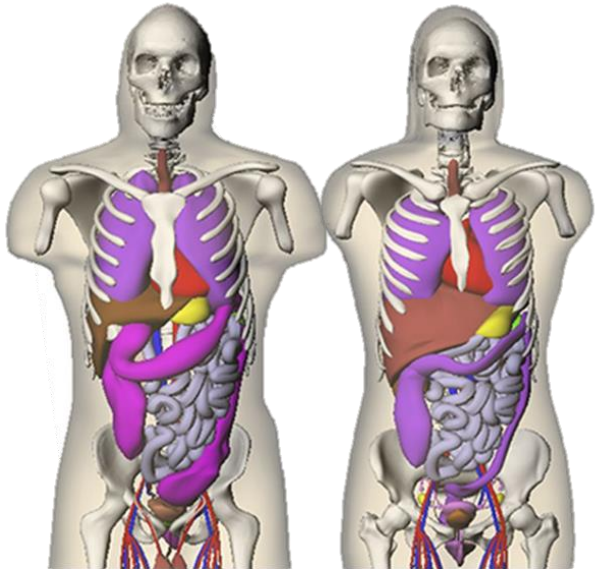
$S(r_t \leftarrow r_s)$ can be computed:

By Monte Carlo simulation transport codes on test objects = phantoms:

- Transport of energy from r_S to r_T is computed.
- Individual tracking of a large number of emitted radiations.
- Computed from each source region r_S
- For different particles (photons, electrons, positrons, alphas…) and energies



ICRP-110 voxel phantoms



Example of other phantoms : **RADAR**

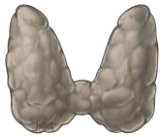
EPFL

Sources: ICRP Publication 110; https://doi.org/10.2967/jnumed.117.196261

CHUV

Dose calculation

RP NM (diag)



r_T : thyroid

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S)\, S(r_T \leftarrow r_S)$$

$$H(r_T) = \sum_{r_S} \tilde{A}(r_S)\, S_w(r_T \leftarrow r_S)$$

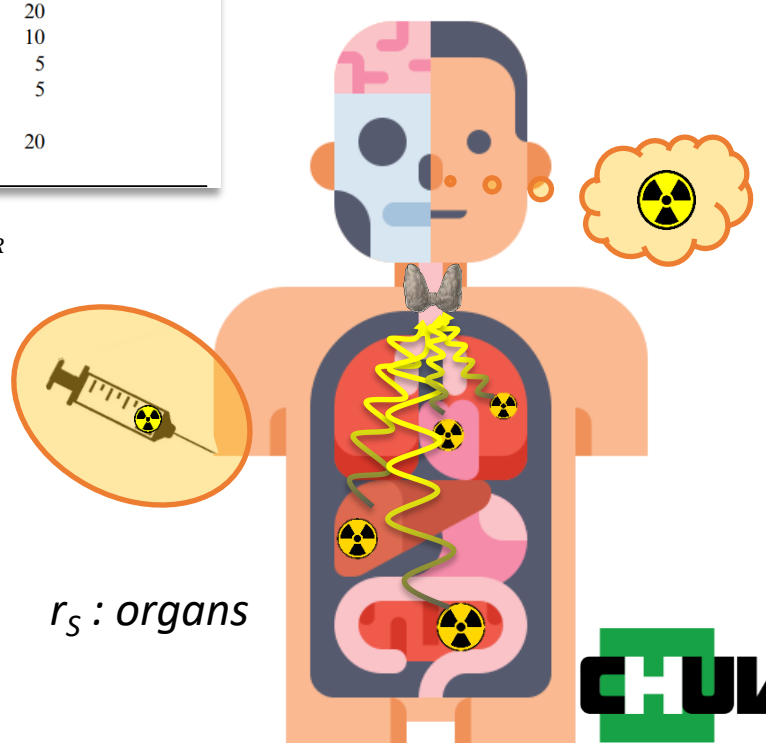
$$h(r_T) = \sum_{r_S} \frac{\tilde{A}(r_S)}{I}\, S_w(r_T \leftarrow r_S)$$

ICRP Publication 103

Table B.3. Radiation weighting factors[1] (ICRP 1991b).

Type and energy range[2]	Radiation weighting factors, w_R
Photons, all energies	1
Electrons and muons, all energies[3]	1
Neutrons, energy < 10 keV	5
10 keV to 100 keV	10
> 100 keV to 2 MeV	20
> 2 MeV to 20 MeV	10
> 20 MeV	5
Protons, other than recoil protons, energy>2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

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



r_S : organs

MIRD = Medical Internal Radiation Dosimetry (MIRD), w stands for «weighted». Source: ICRP 103

Dose calculation

$$h(r_T) = \sum_{r_S} \frac{\tilde{A}(r_S)}{I} S_w(r_T \leftarrow r_S)$$

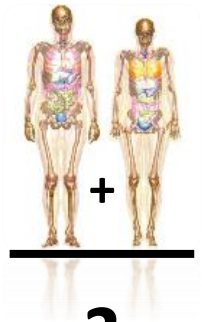
equivalent dose coefficients (h) in the **target region** r_T summed over *N* regions for each phantom

$$h^M(r_T, \tau) = \sum_{r_S}^{N} \frac{\tilde{A}_i(r_S, \tau)}{I} S_w^M(r_T \leftarrow r_S)$$

$$h^F(r_T, \tau) = \sum_{r_S}^{N} \frac{\tilde{A}_i(r_S, \tau)}{I} S_w^F(r_T \leftarrow r_S)$$

committed effective dose coefficient **(e)** **over all target tissues T**

(committed effective dose for 1 Bq intake)



2

$$e(\tau) = \sum_T w_T \left[\frac{h_T^M(\tau) + h_T^F(\tau)}{2} \right]$$

Tissue	w_T	$\sum w_T$
Active bone marrow, breast, colon, lung, stomach, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Urinary bladder, oesophagus, liver, thyroid	0.04	0.16
Bone endosteum, brain, salivary glands, skin	0.01	0.04

Sources: ICRP Publication 133 and 103

Reminder on the use of E

(57) Effective dose can be of practical value for comparing doses related to stochastic effects from: different diagnostic examinations and interventional procedures; the use of similar technologies and procedures in different hospitals and countries;

(58) Effective dose should not be used to assess risks of stochastic effects in retrospective situations for exposures in identified individuals, nor should it be used in epidemiological evaluations of human exposure.

(59) Risk assessment for medical uses of ionising radiation is best evaluated using appropriate risk values for the individual tissues at risk, and for the age and gender distribution of the population groups undergoing the medical procedures.

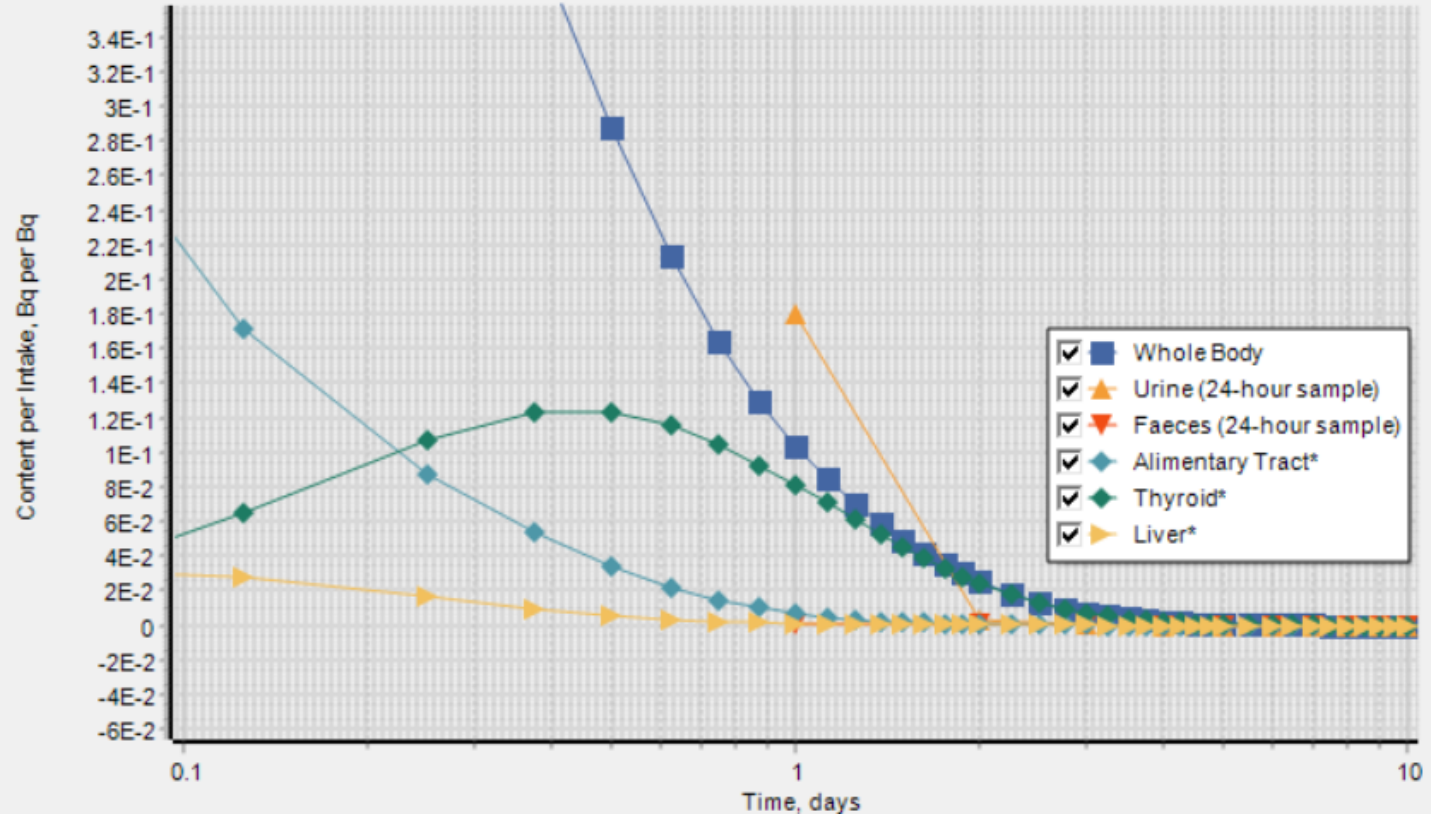
Dose calculation - quiz

Work in groups of ~3
5 minutes

Radionuclide: I 123

Route of Intake: Ingestion

Element	Radionuclide	Route of Intake	Material	AMTD/AMAD, µm	Dose Coefficient e(50), Sv/Bq
I	I-123	Ingestion	All unspecified forms, f_A=0.99	-	1.8E-10



- An adult patient has been orally administered I-123.

→ Compute the effective dose, knowing that after 1 day the I-123 content in the thyroid was 296 kBq.

Sources: ICRP OIR Data Viewer (for occupational exposures)

Dose calculation - quiz

Work in groups of ~3
5 minutes

ICRP Publication 128

Table C.107. *(continued)*

Organ	Absorbed dose per unit activity administered (mGy MBq^{-1})				
	Adult	15 years	10 years	5 years	1 year
Thyroid blocked, oral administration					
Adrenals	8.3E−02	1.0E−01	1.6E−01	2.4E−01	4.3E−01
Bone surfaces	5.0E−02	6.3E−02	9.8E−02	1.5E−01	2.9E−01
Brain	3.4E−02	4.2E−02	6.8E−02	1.1E−01	2.0E−01
Breast	3.6E−02	4.5E−02	7.3E−02	1.2E−01	2.2E−01
...					
Urinary bladder wall	7.0E−01	8.9E−01	1.3E+00	1.7E+00	2.2E+00
Uterus	9.7E−02	1.2E−01	1.9E−01	2.8E−01	4.2E−01
Remaining organs	5.4E−02	6.8E−02	1.1E−01	1.7E−01	2.9E−01
Effective dose (mSv MBq^{-1})	3.5E−01	4.9E−01	7.3E−01	1.3E+00	2.5E+00

(continued on next page)

→ How does the result change using the dose coefficients on the left? why?

Sources: ICRP 128 :ICRP, 2015. Radiation Dose to Patients fromRadiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances. ICRP Publication 128. Ann. ICRP 44(2S).

Summary

- Distinguish between the different types of **radioactive decay** and their potential **use** in nuclear medicine.
- Illustrate the **mechanisms of action** of a radiopharmaceutical product and their **methods of production**.
- Explain the concept of **biokinetic models** and **internal dosimetry formalism** and use them in applied settings.