Reactor produced medical radionuclides

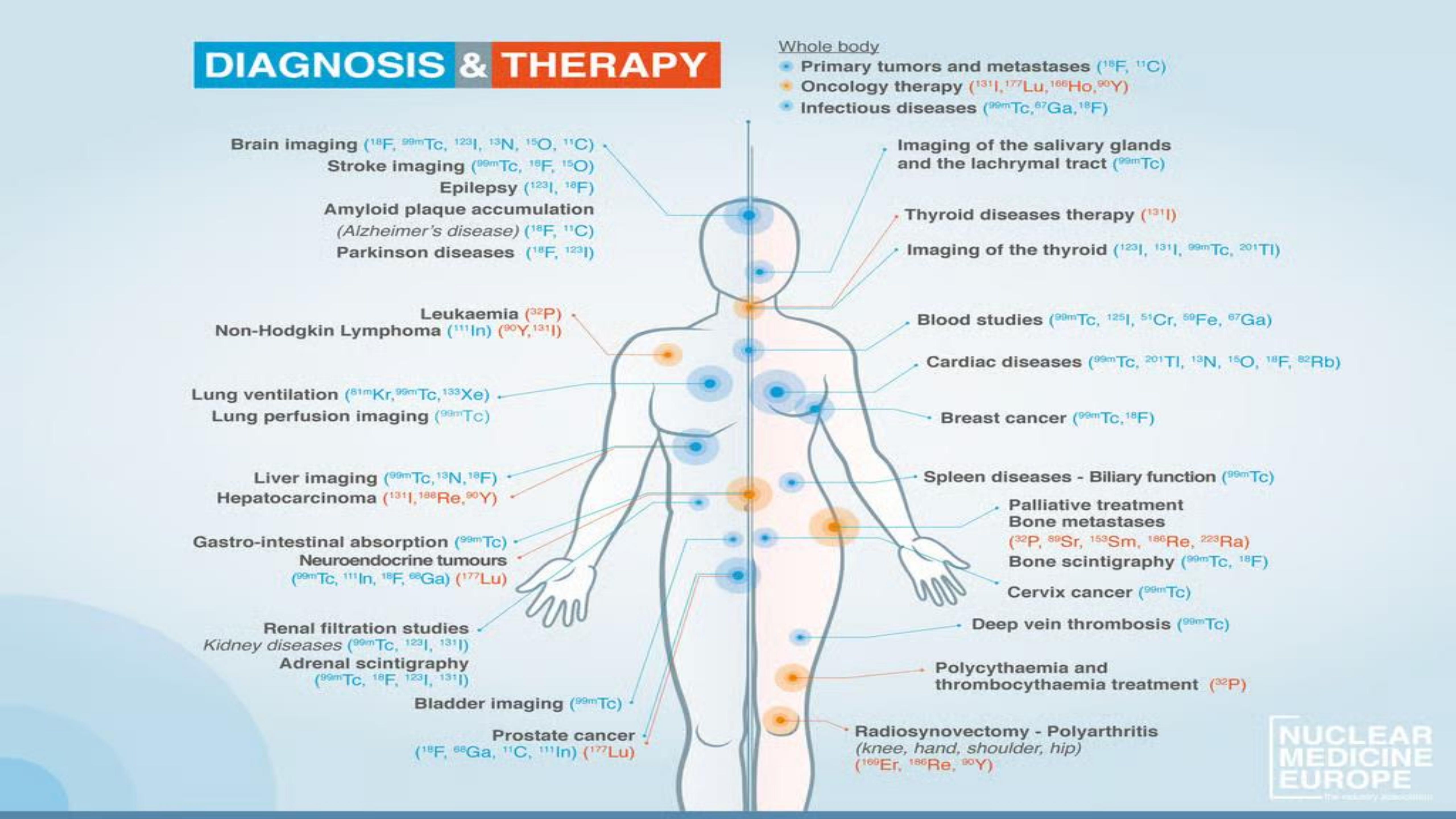
Michiel Van de Voorde – PRISMAP School on Radionuclide Production – May 2024

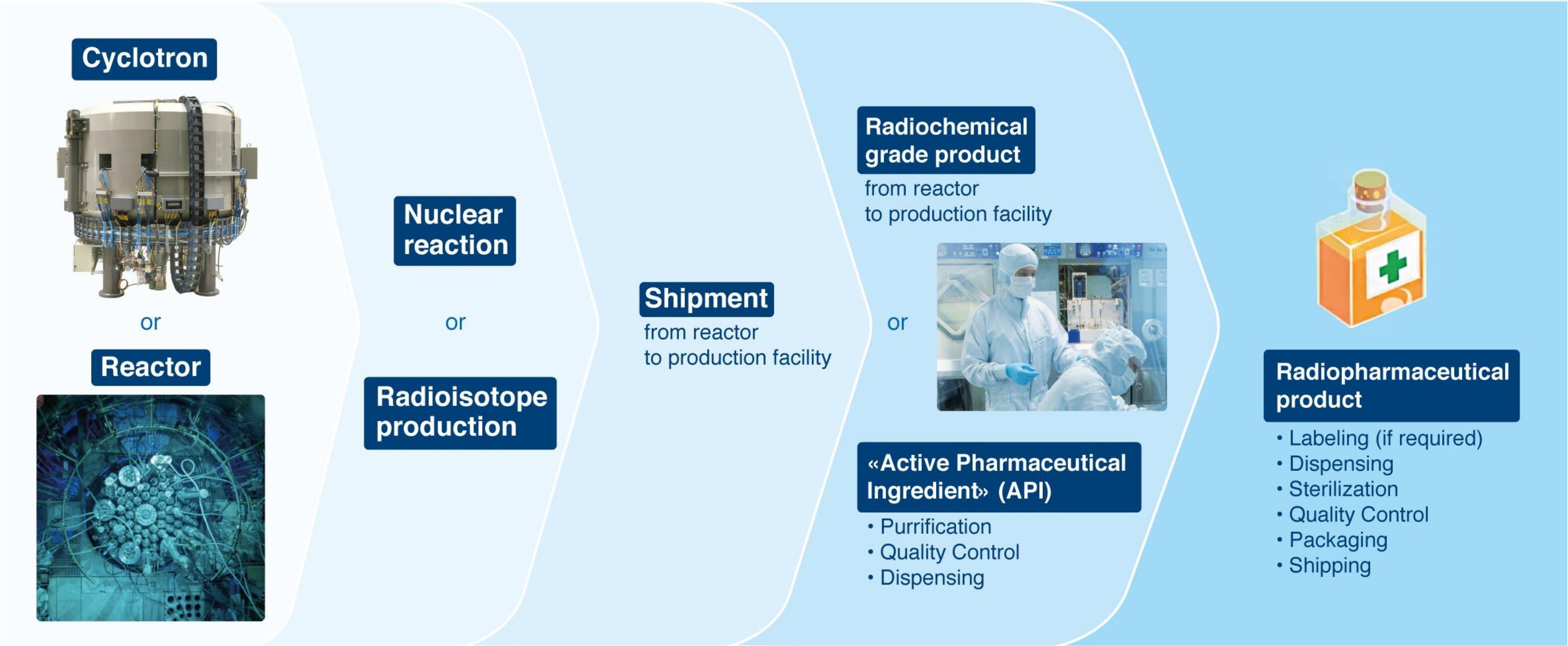
Outline

- Introduction
- **Basic concepts**
- **Production** strategies
- Radiochemical **processing**

Learning outcomes

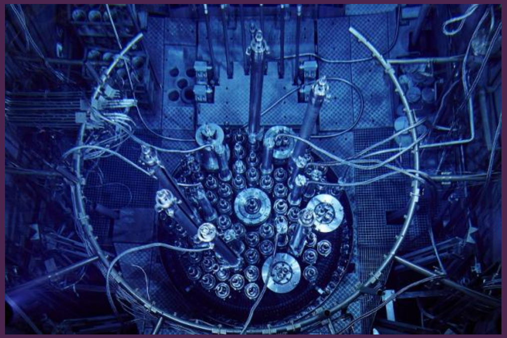
- Know the **difference** between reactor and accelerator produced radionuclides
- **Basic understanding** of how radionuclides are produced in a nuclear reactor
- Estimating a **production yield** and evaluating a **production strategy**


DIAGNOSIS & THERAPY
Whole body
Primary tumors and metastases (^{18}F, ^{11}C)
Oncology therapy (^{131}I, ^{177}Lu, ^{166}Ho, ^{90}Y)
Infectious diseases (^{99m}Tc, ^{67}Ga, ^{18}F)
Brain imaging (^{18}F, ^{99m}Tc, ^{123}I, ^{13}N, ^{15}O, ^{11}C)
Stroke imaging (^{99m}Tc, ^{18}F, ^{15}O)
Epilepsy (^{123}I, ^{18}F)
Amyloid plaque accumulation
(Alzheimer's disease) (^{18}F, ^{11}C)
Parkinson diseases (^{18}F, ^{123}I)
Imaging of the salivary glands
and the lachrymal tract (^{99m}Tc)
Thyroid diseases therapy (^{131}I)
Imaging of the thyroid (^{123}I, ^{131}I, ^{99m}Tc, ^{201}Tl)
Leukaemia (^{32}P)
Non-Hodgkin Lymphoma (^{111}In) (^{90}Y, ^{131}I)
Blood studies (^{99m}Tc, ^{125}I, ^{51}Cr, ^{59}Fe, ^{67}Ga)
Cardiac diseases (^{99m}Tc, ^{201}Tl, ^{13}N, ^{15}O, ^{18}F, ^{82}Rb)
Lung ventilation (^{81m}Kr, ^{99m}Tc, ^{133}Xe)
Lung perfusion imaging (^{99m}Tc)
Breast cancer (^{99m}Tc, ^{18}F)
Liver imaging (^{99m}Tc, ^{13}N, ^{18}F)
Hepatocarcinoma (^{131}I, ^{188}Re, ^{90}Y)
Spleen diseases - Biliary function (^{99m}Tc)
Palliative treatment
Bone metastases
(^{32}P, ^{89}Sr, ^{153}Sm, ^{186}Re, ^{223}Ra)
Bone scintigraphy (^{99m}Tc, ^{18}F)
Gastro-intestinal absorption (^{99m}Tc)
Neuroendocrine tumours
(^{99m}Tc, ^{111}In, ^{18}F, ^{68}Ga) (^{177}Lu)
Cervix cancer (^{99m}Tc)
Deep vein thrombosis (^{99m}Tc)
Renal filtration studies
Kidney diseases (^{99m}Tc, ^{123}I, ^{131}I)
Adrenal scintigraphy
(^{99m}Tc, ^{18}F, ^{123}I, ^{131}I)
Polycythaemia and
thrombocythaemia treatment (^{32}P)
Bladder imaging (^{99m}Tc)
Prostate cancer
(^{18}F, ^{68}Ga, ^{11}C, ^{111}In) (^{177}Lu)
Radiosynovectomy - Polyarthritis
(knee, hand, shoulder, hip)
(^{169}Er, ^{186}Re, ^{90}Y)
NUCLEAR
MEDICINE
EUROPE



Source: www.nuclearmedicineeurope.eu/nuclear-medicine

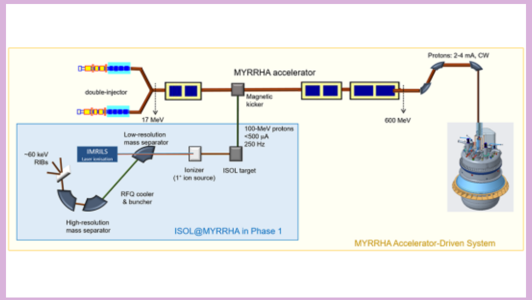
Production methods



Reactor produced

Cyclotron produced

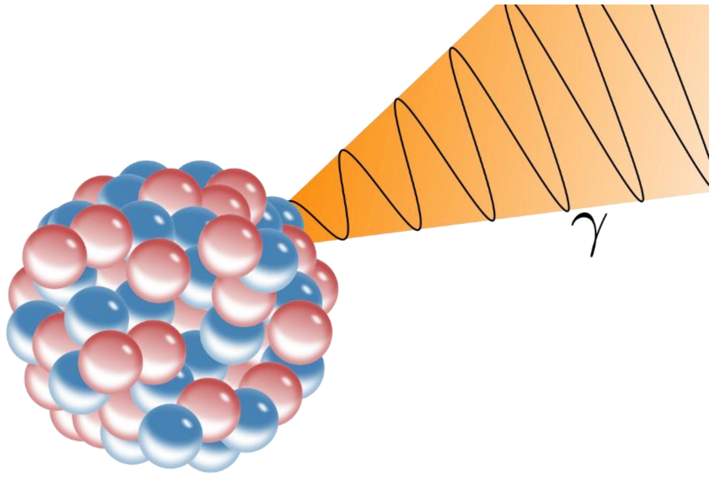
Gamma produced

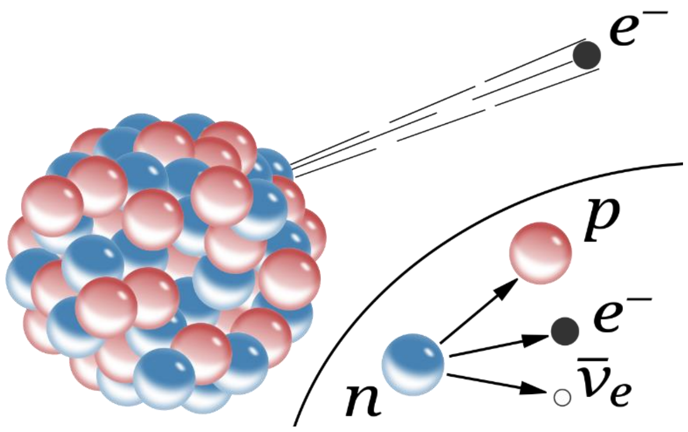


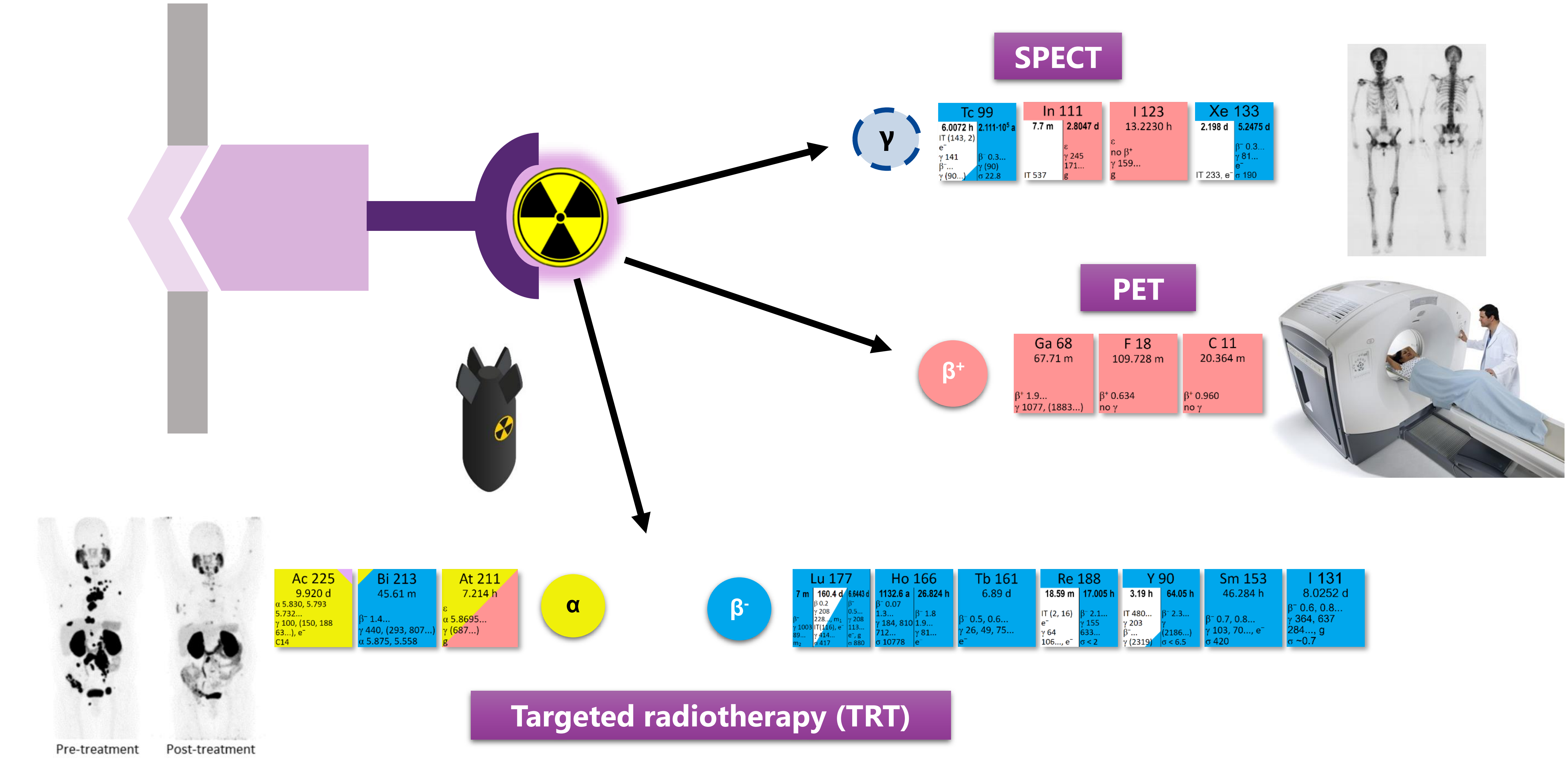
ISOL produced

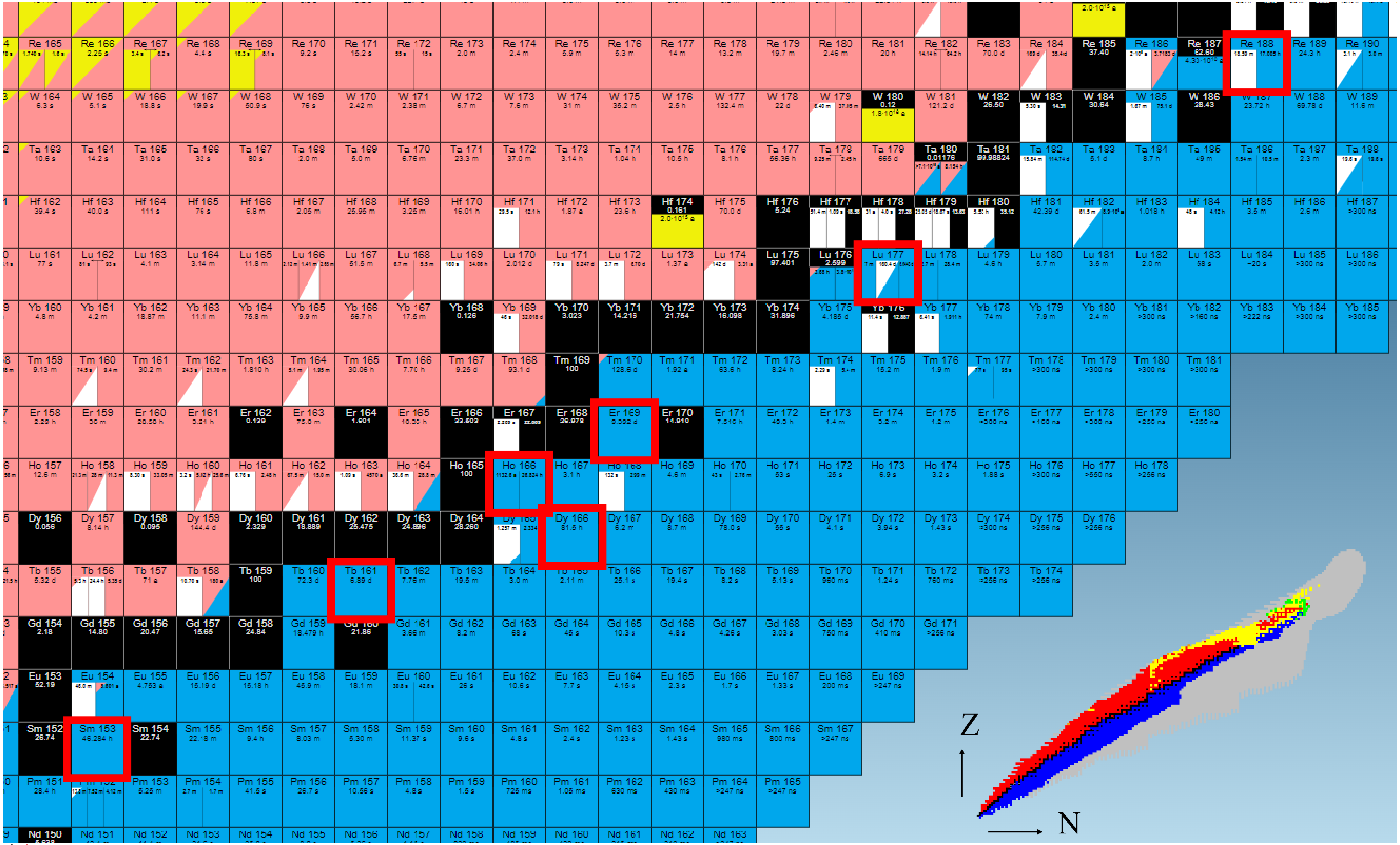
General classification

- Radionuclides for SPECT
    - Reactor and cyclotron produced
- Radionuclides for PET
    - Cyclotron produced
- Radionuclides for therapy
    - Reactor produced
    - Naturally occurring
    - Accelerator produced

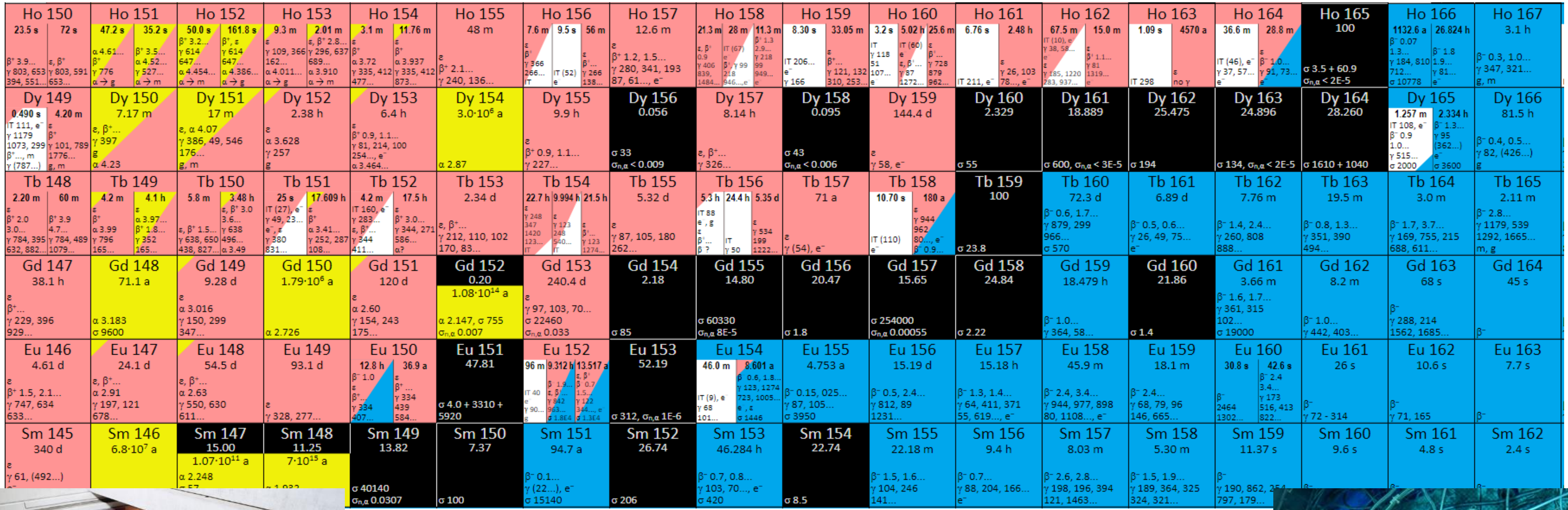





SPECT
γ
Tc 99
6.0072 h
In 111
7.7 m
2.8047 d
I 123
13.2230 h
Xe 133
2.198 d
5.2475 d
PET
β+
Ga 68
67.71 m
β+ 1.9...
γ 1077, (1883...)
F 18
109.728 m
β+ 0.634
no γ
C 11
20.364 m
β+ 0.960
no γ
Ac 225
9.920 d
Bi 213
45.61 m
At 211
7.214 h
α
β-
Lu 177
160.4 d
Ho 166
1132.6 a
26.824 h
Tb 161
6.89 d
β- 0.5, 0.6...
γ 26, 49, 75...
Re 188
18.59 m
17.005 h
Y 90
3.19 h
64.05 h
Sm 153
46.284 h
I 131
8.0252 d
Pre-treatment
Post-treatment
Targeted radiotherapy (TRT)


Re 165
Re 166 2.25 s
Re 167
Re 168 4.4 s
Re 169
Re 170 9.2 s
Re 171 15.2 s
Re 172
Re 173 2.0 m
Re 174 2.4 m
Re 175 5.9 m
Re 176 5.3 m
Re 177 14 m
Re 178 13.2 m
Re 179 19.7 m
Re 180 2.46 m
Re 181 20 h
Re 182
Re 183 70.0 d
Re 184
Re 185 37.40
Re 186
Re 187 62.60
Re 188
Re 189 24.3 h
Re 190
W 164 6.3 s
W 165 5.1 s
W 166 18.8 s
W 167 19.9 s
W 168 50.9 s
W 169 76 s
W 170 2.42 m
W 171 2.38 m
W 172 6.7 m
W 173 7.6 m
W 174 31 m
W 175 35.2 m
W 176 2.5 h
W 177 132.4 m
W 178 22 d
W 179
W 180 0.12
W 181 121.2 d
W 182 26.50
W 183
W 184 30.64
W 185
W 186 28.43
W 188 69.78 d
W 189 11.6 m
Ta 163 10.6 s
Ta 164 14.2 s
Ta 165 31.0 s
Ta 166 32 s
Ta 167 80 s
Ta 168 2.0 m
Ta 169 5.0 m
Ta 170 6.76 m
Ta 171 23.3 m
Ta 172 37.0 m
Ta 173 3.14 h
Ta 174 1.04 h
Ta 175 10.5 h
Ta 176 8.1 h
Ta 177 56.36 h
Ta 178
Ta 179 665 d
Ta 180 0.01176
Ta 181 99.98824
Ta 182
Ta 183 5.1 d
Ta 184 8.7 h
Ta 185 49 m
Ta 186
Ta 187 2.3 m
Ta 188
Hf 162 39.4 s
Hf 163 40.0 s
Hf 164 111 s
Hf 165 76 s
Hf 166 6.8 m
Hf 167 2.05 m
Hf 168 25.95 m
Hf 169 3.25 m
Hf 170 16.01 h
Hf 171
Hf 172 1.87 a
Hf 173 23.6 h
Hf 174 0.161
Hf 175 70.0 d
Hf 176 5.24
Hf 177
Hf 178
Hf 179
Hf 180
Hf 181 42.39 d
Hf 182
Hf 183 1.018 h
Hf 184
Hf 185 3.5 m
Hf 186 2.6 m
Hf 187 >300 ns
Lu 161 77 s
Lu 162
Lu 163 4.1 m
Lu 164 3.14 m
Lu 165 11.8 m
Lu 166
Lu 167 51.5 m
Lu 168
Lu 169
Lu 170 2.012 d
Lu 171
Lu 172
Lu 173 1.37 a
Lu 174
Lu 175 97.401
Lu 176 2.599
Lu 177
Lu 178
Lu 179 4.6 h
Lu 180 5.7 m
Lu 181 3.5 m
Lu 182 2.0 m
Lu 183 58 s
Lu 184 ~20 s
Lu 185 >300 ns
Lu 186 >300 ns
Yb 160 4.8 m
Yb 161 4.2 m
Yb 162 18.87 m
Yb 163 11.1 m
Yb 164 75.8 m
Yb 165 9.9 m
Yb 166 56.7 h
Yb 167 17.5 m
Yb 168 0.126
Yb 169
Yb 170 3.023
Yb 171 14.216
Yb 172 21.754
Yb 173 16.098
Yb 174 31.896
Yb 175 4.185 d
Yb 177
Yb 178 74 m
Yb 179 7.9 m
Yb 180 2.4 m
Yb 181 >300 ns
Yb 182 >160 ns
Yb 183 >222 ns
Yb 184 >300 ns
Yb 185 >300 ns
Tm 159 9.13 m
Tm 160
Tm 161 30.2 m
Tm 162
Tm 163 1.810 h
Tm 164
Tm 165 30.06 h
Tm 166 7.70 h
Tm 167 9.25 d
Tm 168 93.1 d
Tm 169 100
Tm 170 128.6 d
Tm 171 1.92 a
Tm 172 63.6 h
Tm 173 8.24 h
Tm 174
Tm 175 15.2 m
Tm 176 1.9 m
Tm 177
Tm 178 >300 ns
Tm 179 >300 ns
Tm 180 >300 ns
Tm 181 >300 ns
Er 158 2.29 h
Er 159 36 m
Er 160 28.58 h
Er 161 3.21 h
Er 162 0.139
Er 163 75.0 m
Er 164 1.601
Er 165 10.36 h
Er 166 33.503
Er 167
Er 168 26.978
Er 169 9.392 d
Er 170 14.910
Er 171 7.516 h
Er 172 49.3 h
Er 173 1.4 m
Er 174 3.2 m
Er 175 1.2 m
Er 176 >300 ns
Er 177 >160 ns
Er 178 >300 ns
Er 179 >256 ns
Er 180 >256 ns
Ho 157 12.6 m
Ho 158
Ho 159
Ho 160
Ho 161
Ho 162
Ho 163
Ho 164
Ho 165 100
Ho 166
Ho 167 3.1 h
Ho 169 4.6 m
Ho 170
Ho 171 53 s
Ho 172 25 s
Ho 173 6.9 s
Ho 174 3.2 s
Ho 175 1.88 s
Ho 176 >300 ns
Ho 177 >550 ns
Ho 178 >256 ns
Dy 156 0.056
Dy 157 8.14 h
Dy 158 0.095
Dy 159 144.4 d
Dy 160 2.329
Dy 161 18.889
Dy 162 25.475
Dy 163 24.896
Dy 164 28.260
Dy 166 81.5 h
Dy 167 6.2 m
Dy 168 8.7 m
Dy 169 39 s
Dy 170 55 s
Dy 171 4.1 s
Dy 172 3.94 s
Dy 173 1.43 s
Dy 174 >300 ns
Dy 175 >256 ns
Dy 176 >256 ns
Tb 155 5.32 d
Tb 156
Tb 157 71 a
Tb 158
Tb 159 100
Tb 160 72.3 d
Tb 161 6.89 d
Tb 162 7.76 m
Tb 163 19.5 m
Tb 164 3.0 m
Tb 166 25.1 s
Tb 167 19.4 s
Tb 168 8.2 s
Tb 169 5.13 s
Tb 170 960 ms
Tb 171 1.24 s
Tb 172 760 ms
Tb 173 >256 ns
Tb 174 >256 ns
Gd 154 2.18
Gd 155 14.80
Gd 156 20.47
Gd 157 15.65
Gd 158 24.84
Gd 159 18.479 h
21.86
Gd 161 3.66 m
Gd 162 8.2 m
Gd 163 68 s
Gd 164 45 s
Gd 165 10.3 s
Gd 166 4.8 s
Gd 167 4.26 s
Gd 168 3.03 s
Gd 169 750 ms
Gd 170 410 ms
Gd 171 >256 ns
Eu 153 52.19
Eu 154
Eu 155 4.753 a
Eu 156 15.19 d
Eu 157 15.18 h
Eu 158 45.9 m
Eu 159 18.1 m
Eu 160
Eu 161 26 s
Eu 162 10.6 s
Eu 163 7.7 s
Eu 164 4.15 s
Eu 165 2.3 s
Eu 166 1.7 s
Eu 167 1.33 s
Eu 168 200 ms
Eu 169 >247 ns
Sm 152 26.74
Sm 153 46.284 h
Sm 154 22.74
Sm 155 22.18 m
Sm 156 9.4 h
Sm 157 8.03 m
Sm 158 5.30 m
Sm 159 11.37 s
Sm 160 9.6 s
Sm 161 4.8 s
Sm 162 2.4 s
Sm 163 1.23 s
Sm 164 1.43 s
Sm 165 980 ms
Sm 166 800 ms
Sm 167 >247 ns
Pm 151 28.4 h
Pm 153 5.25 m
Pm 154
Pm 155 41.5 s
Pm 156 26.7 s
Pm 157 10.56 s
Pm 158 4.8 s
Pm 159 1.5 s
Pm 160 725 ms
Pm 161 1.05 ms
Pm 162 630 ms
Pm 163 430 ms
Pm 164 >247 ns
Pm 165 >247 ns
Nd 150
Nd 151
Nd 152
Nd 153
Nd 154
Nd 155
Nd 156
Nd 157
Nd 158
Nd 159
Nd 160
Nd 161
Nd 162
Nd 163
Z
N

Nuclear transmutation



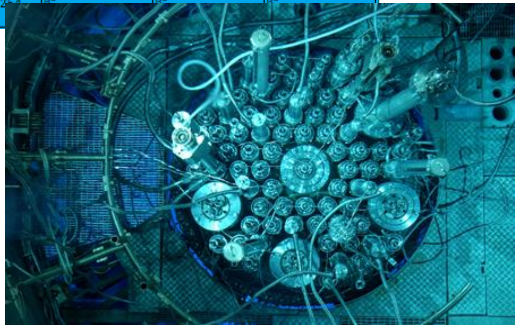
- Stable
- β⁻ decay
- α decay
- β⁺ decay

← **Neutron-deficient**

Acquired by particle accelerators

Proton-deficient →

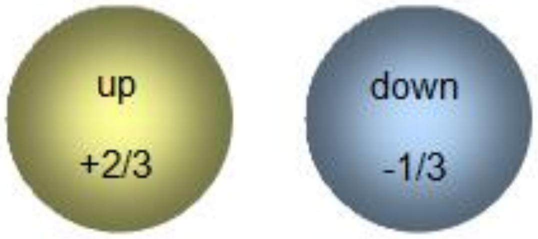
Acquired by thermal neutron flux in nuclear research reactors



β decay

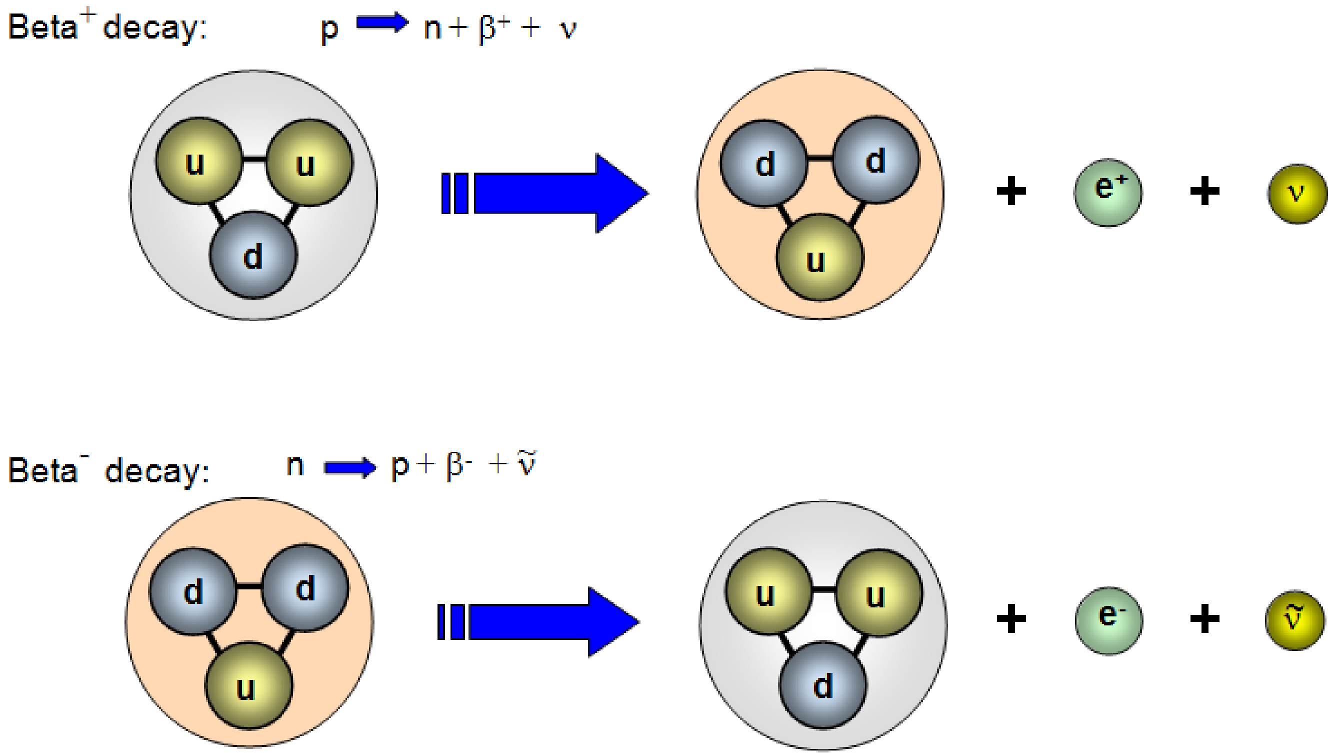
- β^- decay: proton (quarks: u, u, d) → neutron (quarks: u, d, d)
- β^+ decay: neutron (quarks: u, d, d) → proton (quarks: u, u, d)

Quarks



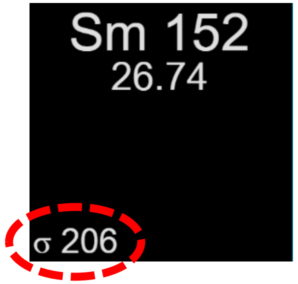
$$\text{Proton} = \text{u u d} = +\frac{2}{3} + \frac{2}{3} - \frac{1}{3} = +1$$

$$\text{Neutron} = \text{u d d} = +\frac{2}{3} - \frac{1}{3} - \frac{1}{3} = 0$$



Neutron – nucleus interactions

- 3 main types
  - Elastic collisions = scattering (billiard ball interactions) → Moderation (slowing down neutrons)
  - Neutron absorption
    - Nuclear fission → Nuclear chain reaction (splitting of atoms)
    - Nuclear transmutation → Isotope production
- Nuclear cross section → Describes probability of a nuclear reaction to occur → characteristic area
  → Higher nuclear cross section => higher probability of interaction
  → Expressed in barn (10^{-24} cm²)
- Thermal neutrons → Larger probability of interaction
  → Larger effective neutron absorption cross-section
  → Can be absorbed more easily by an atomic nucleus
  → Creates more heave isotope of the same chemical element (often unstable)



NEUTRON ACTIVATION

Neutron activation

Process where neutron radiation induces radioactivity in materials

→ Atomic target nucleus captures free neutron, becoming heavier and entering excited state

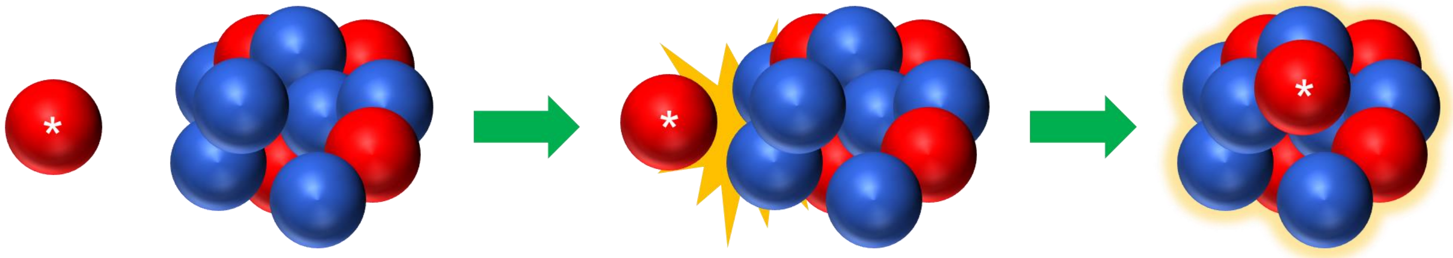
→ Immediately followed by gamma emission (photon) → (n,γ) reaction

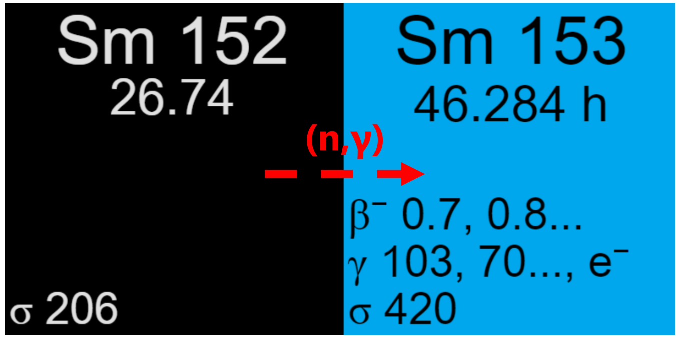
→ Typically yields an unstable (i.e. radioactive) activation product

  → Emits particles to become stable again → electrons (β^-), ^4He (α), neutrons, fission products

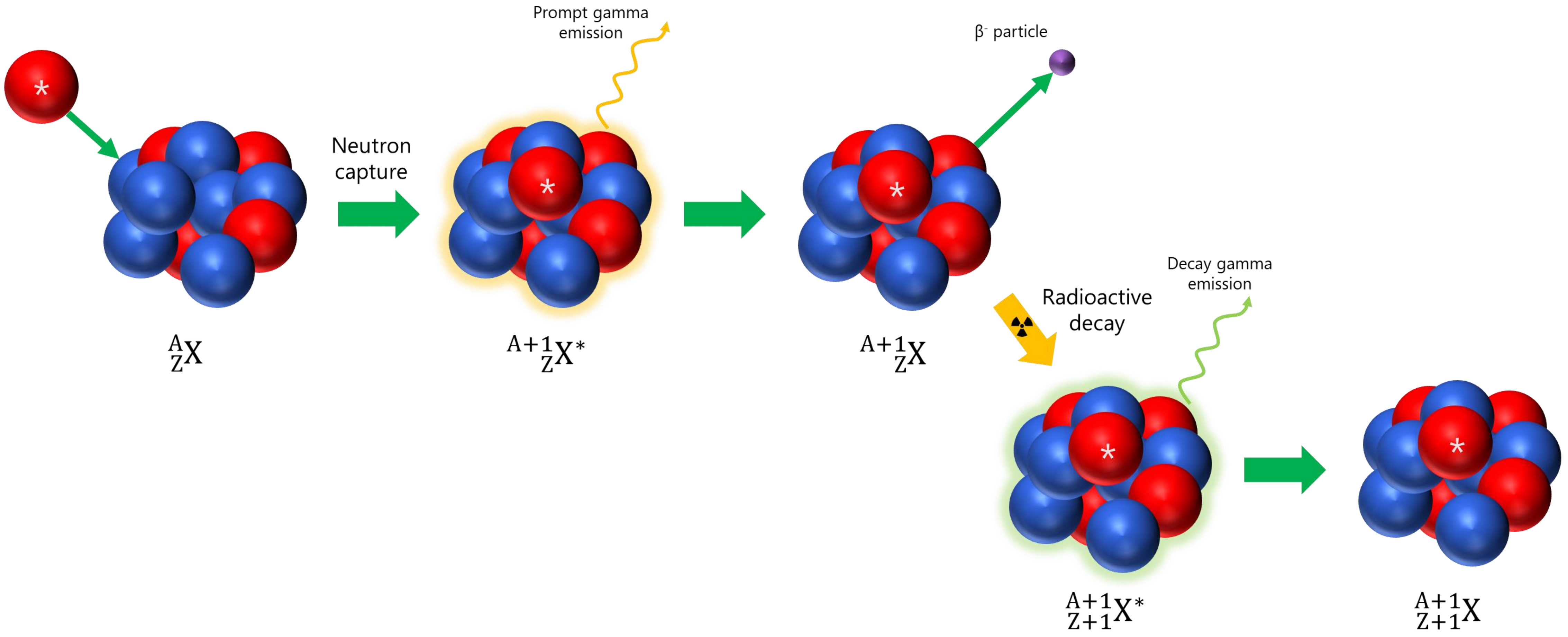
  → Half-lives range from fractions of a second till many thousands of years

→ Production of neutron-rich isotopes

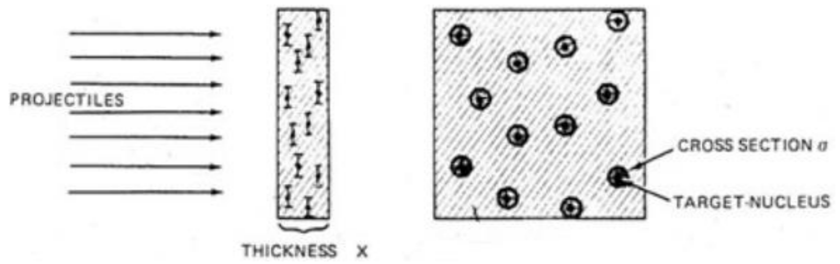




Neutron activation



Neutron activation *(simplified)*



$$\mathbf{A = A_0 \cdot e^{-\lambda \cdot t}}$$

$$\mathbf{A = N_{target} \cdot \chi_{target} \cdot \sigma_{target} \cdot \phi_{reactor} \cdot \left(1 - e^{-\lambda_{isotope} \cdot t_{irradiaiton}}\right)}$$

- $A_{isotope}$ = activity of isotope (Bq = s^{-1})
- N_{target} = number of particles in target
- χ_{target} = isotopic and chemical purity of the target (enrichment)
- $\sigma_{th,\ target}$ = cross section of target for neutrons (barn = 10^{-24} cm^2)
- $\Phi_{reactor}$ = neutron flux (neutrons/cm^2/s)
- $\lambda_{isotope}$ = radioactive decay constant of produced radionuclide (s^{-1})

  = ln(2) / $t_{1/2,\ isotope}$
- $t_{irradiation}$ = target irradiation time (s)

Not considered

- Self-shielding in the target
- Flux variations
- Burn-up of the target material with time
- Subsequent neutron capture

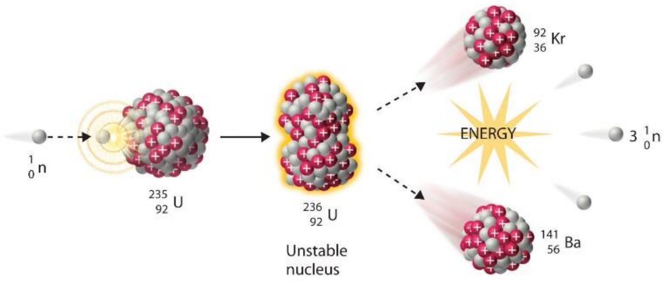
Neutron source

Production of neutron-rich radionuclides require neutrons

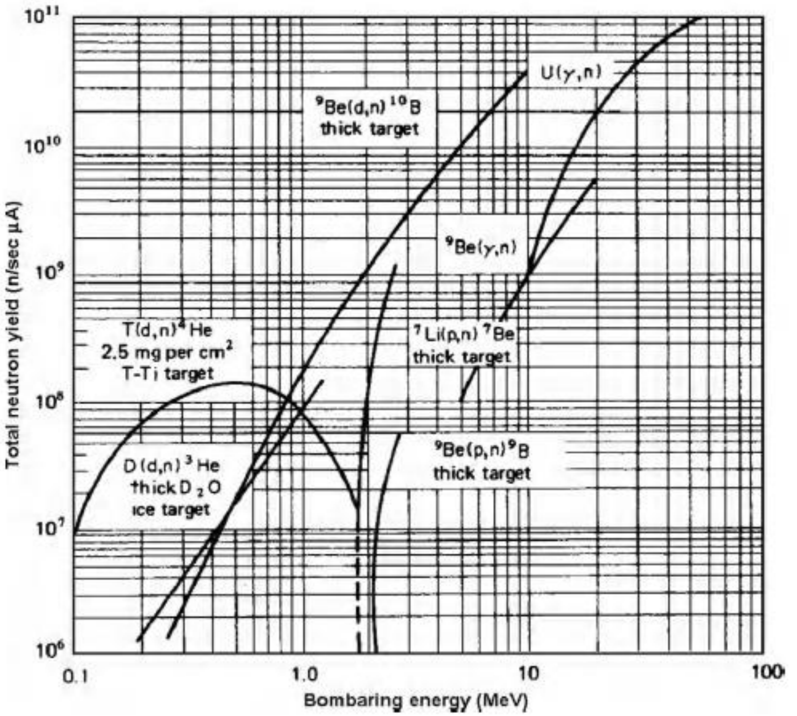
→ Neutrons are bound to a nucleus, and do not exist free for long in nature

→ Neutron source needed

- → Nuclear fission
- → Nuclear reactions induced by radioisotopes
- → Accelerator-induced reaction



Material	Half-life	Neutron yield ($n\ s^{-1}\ Bq^{-1}$)	γ-dose rate[a] ($mSv\ h^{-1}\ m^2\ Bq^{-1}$)
$^{226}Ra + Be$	1600 y	3.5×10^{-4}	850
$^{239}Pu + Be$	24110 y	2.4×10^{-4}	4
$^{239}Pu + ^{18}O$	24110 y	7.8×10^{-6}	(b)
$^{241}Am + Be$	433 y	6.8×10^{-5}	2.5
$^{210}Po + Be$	138 d	6.8×10^{-5}	<0.3[c]
$^{124}Sb + Be$	60 d	$\sim5\times10^{-6}$	1000
^{252}Cf	2.6 y	$5\times10^{12}\ n\ s^{-1}\ g^{-1}$	(d)



Source: G.R. Choppin, J.R. Rydberg, J.-O. Liljenzin, C. Ekberg, "Radiochemistry and Nuclear Chemistry"

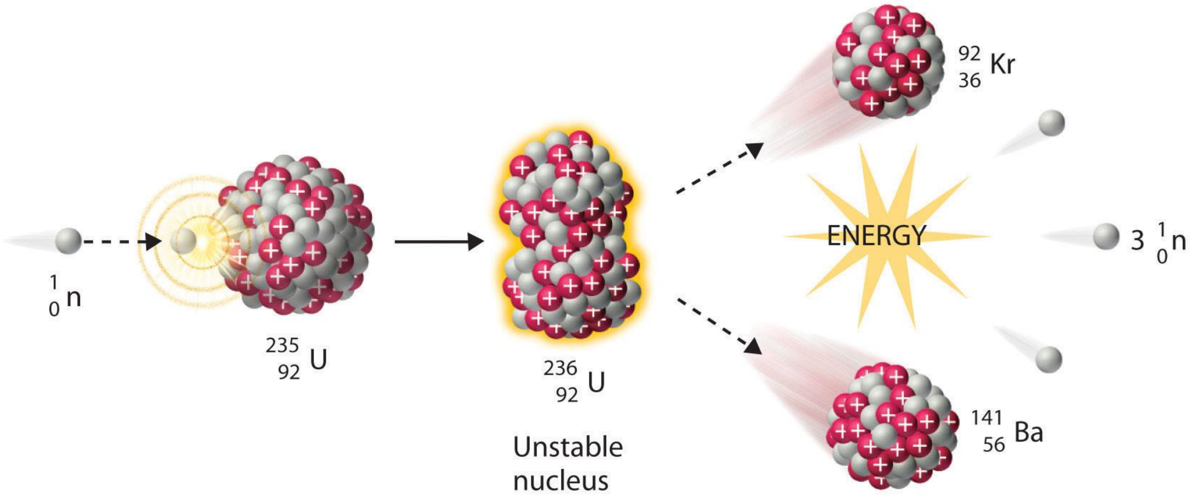
Neutron source – Fission

Nuclear fission $^{235}U(n,f)$ yields fission products + ±2.5 n^0 + energy (ca. 200 MeV)

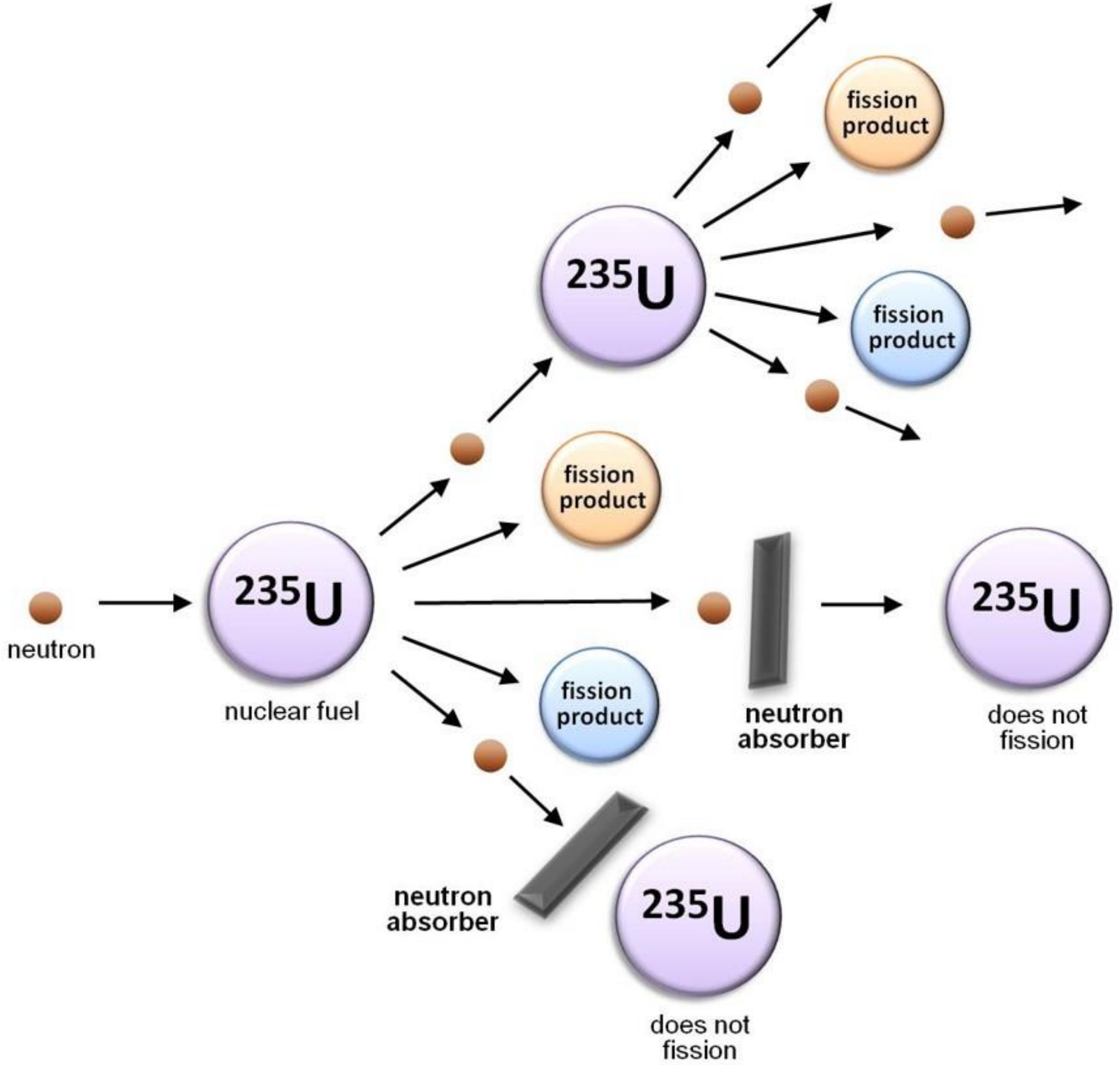
→ Highly efficient neutron source

→ Nuclear chain reaction → needs to be controlled once critical

→ Takes place in a nuclear reactor

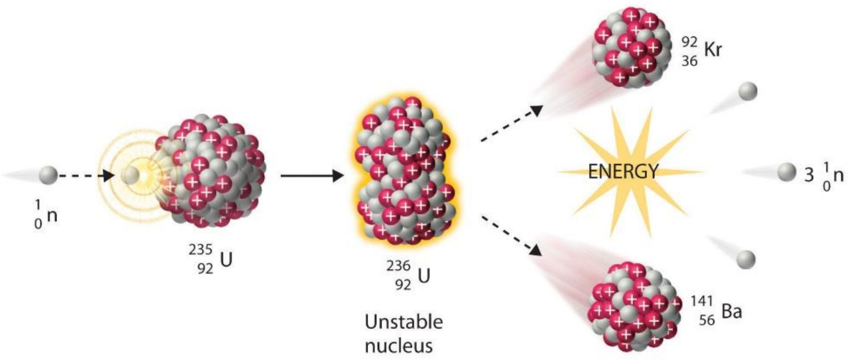


Neutron source



Source: https://nuclear.mcmaster.ca/

Neutron energy



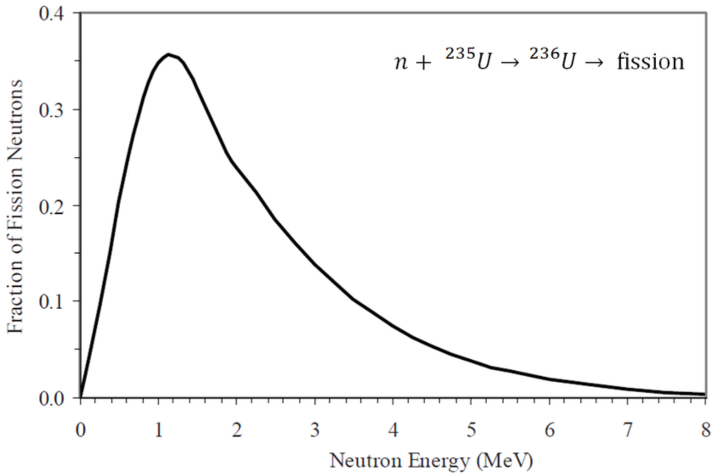
$^{235}U(n,f) \rightarrow$ Unstable ^{236}U nucleus 'explodes', ejecting fission products and neutrons at high kinetic energy and velocity

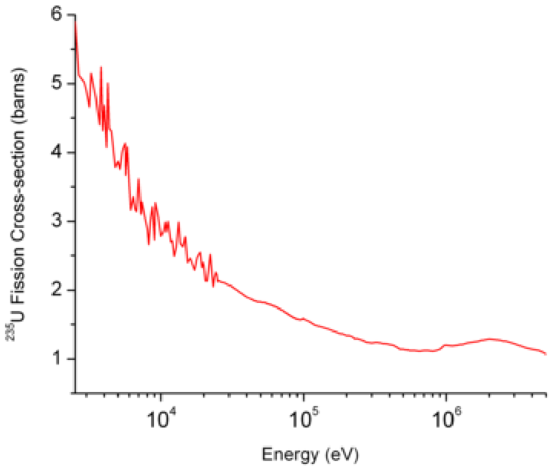
→ Release of neutrons from nucleus requires exceeding binding energy (7-9 MeV)

→ 'Fast neutrons' – 1-20 MeV, traveling ca 20,000 km/s

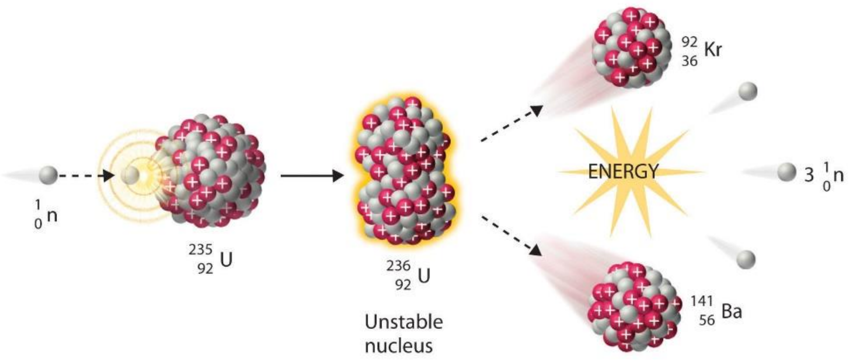
→ Low probability of being captured by ^{235}U atoms (or other target atoms)

→ Not very suitable for maintaining fission reaction or radionuclide production





Neutron energy



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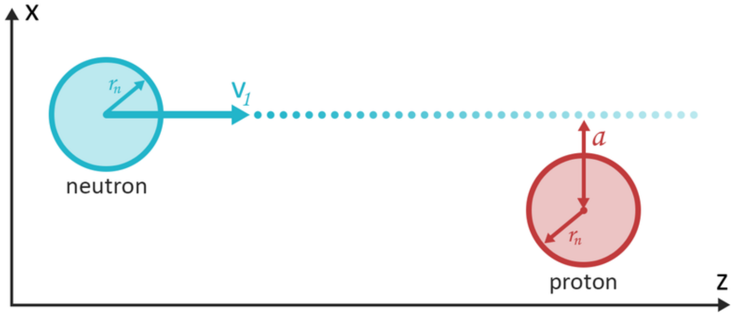
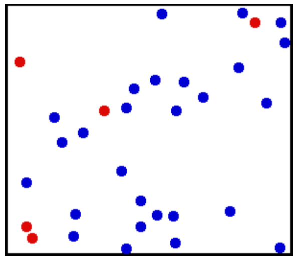
→ 'Fast neutrons' – 1-20 MeV, traveling ca 20,000 km/s
→ Low probability of being captured by ^{235}U atoms (or other target atoms)
→ Not very suitable for maintaining fission reaction or radionuclide production

→ **Neutrons must be slowed down without being captured**
→ Transfer of energy to a moderator

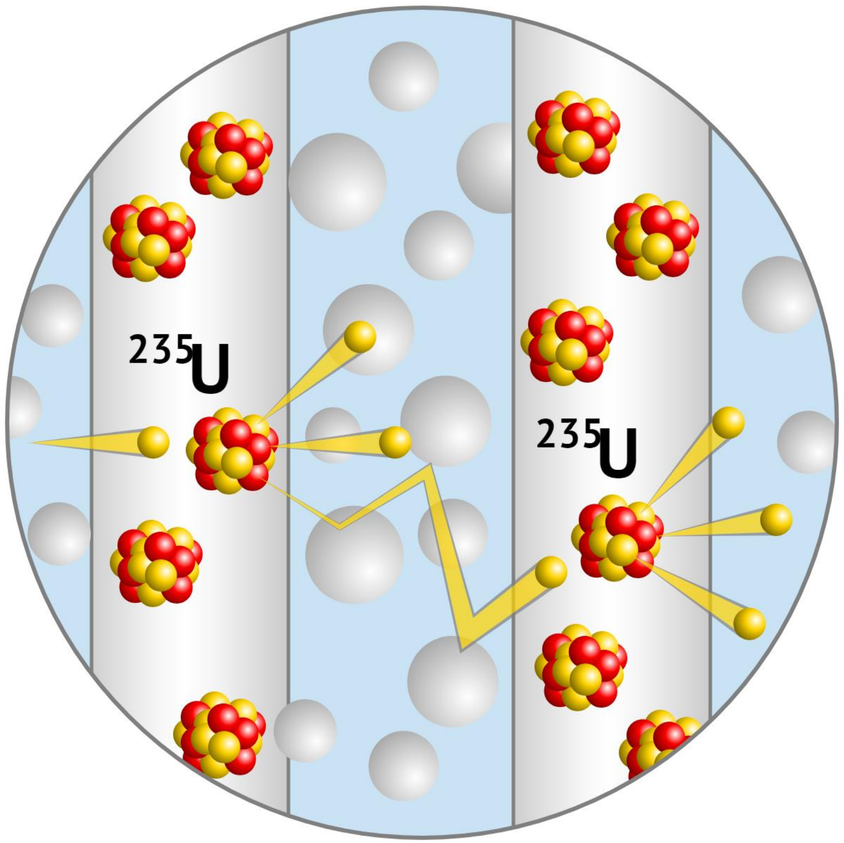
Neutron energy

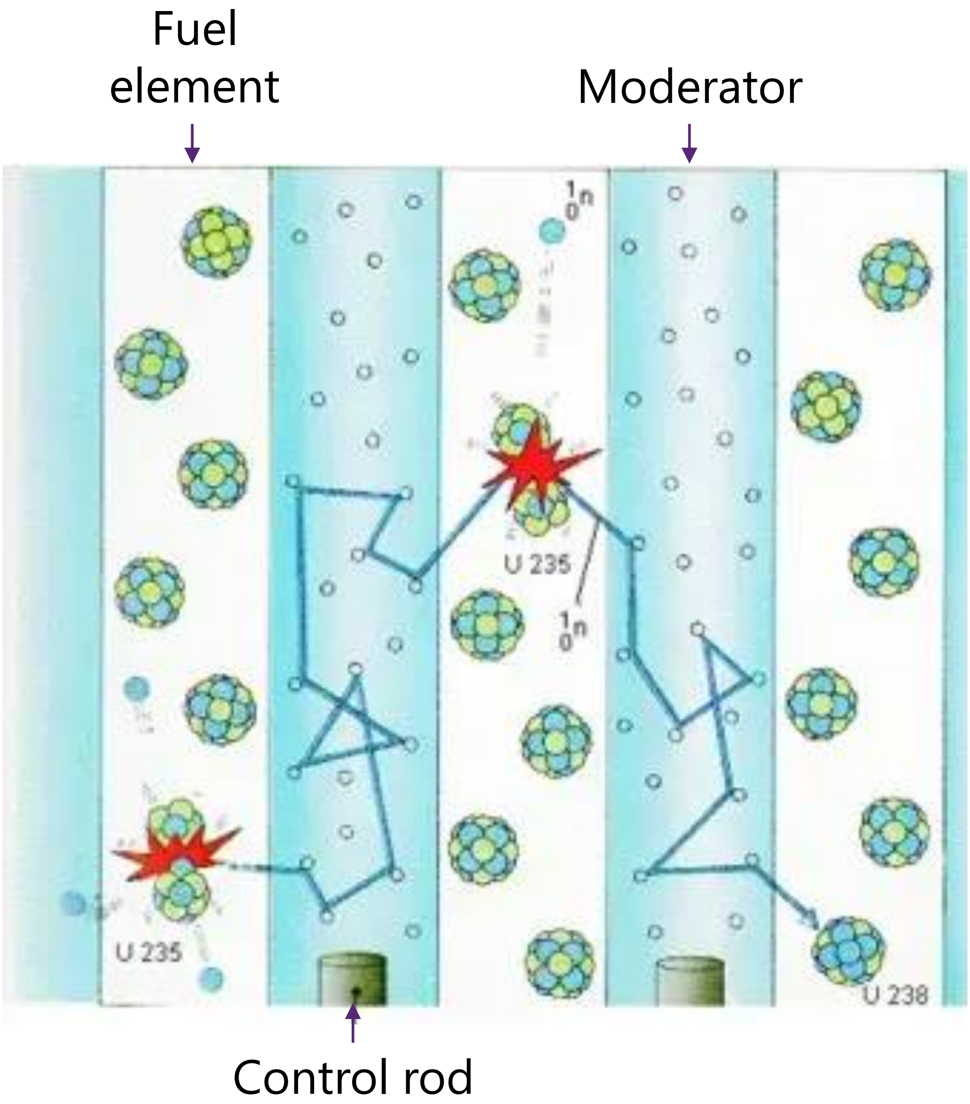
- **Neutron moderation** → Reduction of the initial high speed, i.e. high kinetic energy, of the free neutron
- Conservation of energy → reduction of energy = transfer of energy to another material, i.e. the moderador (= the medium)
- Performed by a large number of successive collisions with a material that scatters strongly, but absorbs weakly → High neutron scatter cross section
  - Energy is predominantly transfered by elastic collisions
  - Most efficient removal of $E_{k,n}$ by moderating nucleus with near-identical mass
  - ^1H is an almost perfect choice ($m_p \approx m_n$)
  - Maxwell-Boltzmann distribution of E_k
  - H_2O, D_2O, graphite, Be





Neutron energy





Neutron energy

'Neutron temperature' → indicates a free neutron's kinetic energy (eV)

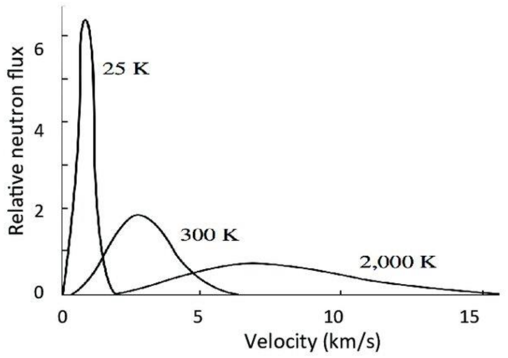
- $\bar{E} = \frac{1}{2} m_n \langle v_n{}^2 \rangle = \frac{3}{2} k_B T$

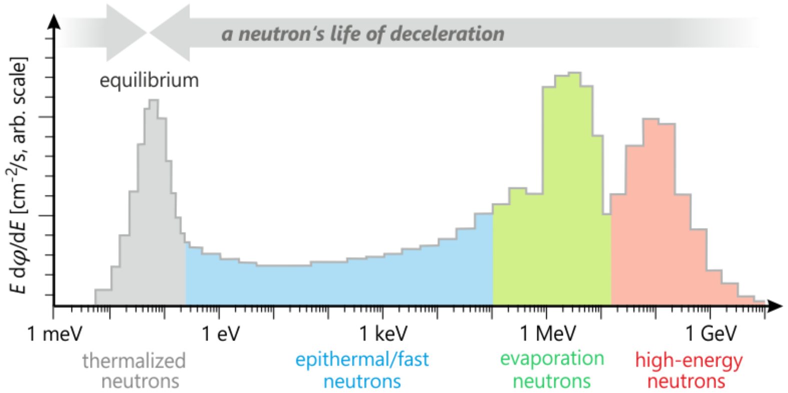
  m_n = the neutron mass
  $v_n{}^2$ = the average squared neutron speed
  k_B = Boltzmann constant (1.38E-23 J/K = 8.62E-5 eV/K)

- 1 MeV → T ≈ 7.7E9 K (thermodynamic temperature)
- Fast neutron: 1 – 20 MeV → 7.7 – 154 billion K → 'Hot neutrons'
- Neutron energy comparible to energy of surrounding particles → 'Thermalized'

  → Thermal neutrons (≈ 0.025 eV, traveling at 2.2 km/s)

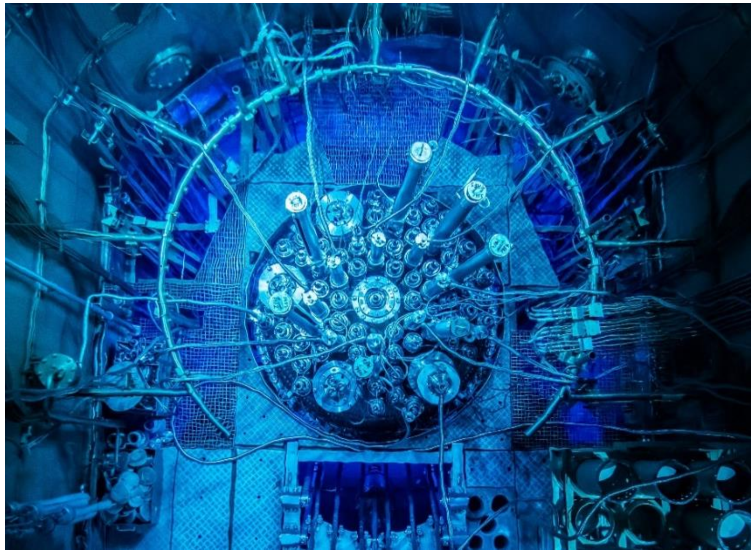
  → Energy corresponding to most probable speed at 300 K (H_2O medium in water tank)





Research reactors

- Developed and designed for material testing
  - Purpose = neutron flux irradiations and impact studies
  - Powerful high flux neutron source → 'Neutron factory'
  - Not for electricity production → All produced heat is evacuated by cooling water = by-product
- Allow for ease of access to neutrons
  → Access during operation
  → Shielding compatible with installation of experimental devices
- Provide flexibility in utilization
  → Configuration and operation parameters can be varied



Research reactors

NDA

III. INTRODUCTION

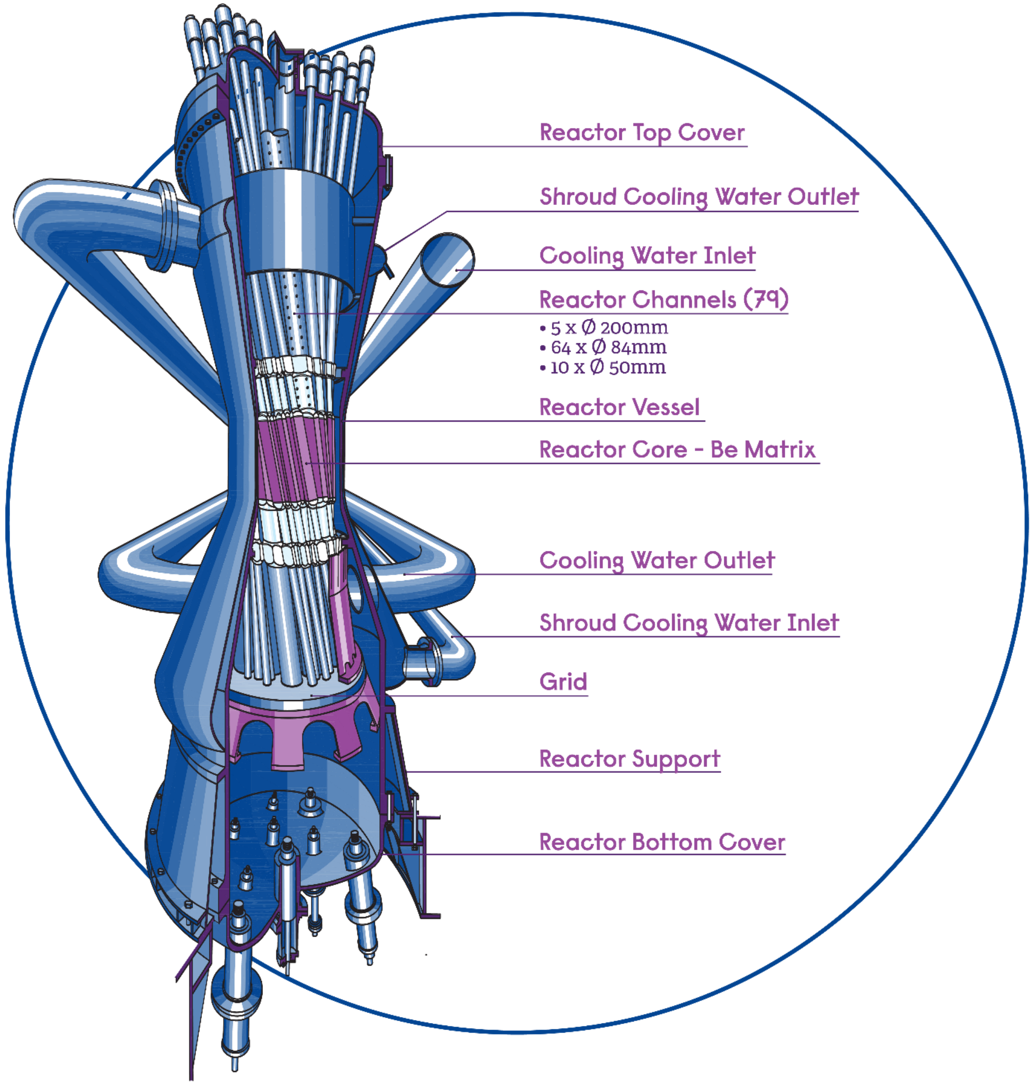
A. PURPOSE OF PROJECT AND PHASE I

Under terms of a contract with the Centre d'Etudes pour les Applications de l'Energie Nucleaire (CEAN), the Nuclear Development Corporation of America (NDA) undertook the design of an engineering test reactor for Belgium. This reactor is intended to provide CEAN with a test facility of greatest overall usefulness in a future power reactor development program. Inasmuch as the present CEAN graphite reactor, BR I, already provides low neutron flux facilities, a basic objective of this program was to provide high flux test facilities of ready accessibility.

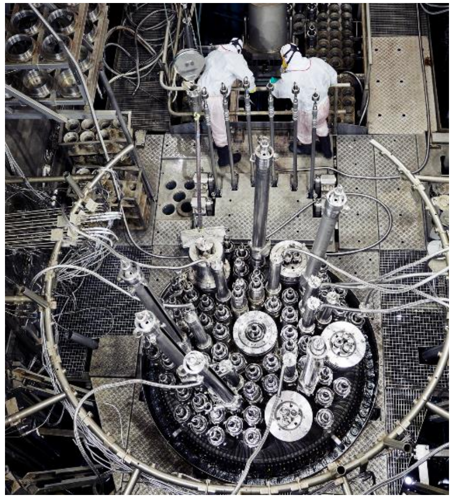
Research reactors

Flux results from power and size

- Thermal spectrum most favorable
  1. Compact design
  2. Water cooling
  3. Metallic
- Pool type reactors allow for
  - Easy access
  - Shielding
  - Heat sink
- Large (= high power) reactors allow wider range of conditions
  - Flux ranges and reactivity variation
  - More flexible core configuration



Research reactors



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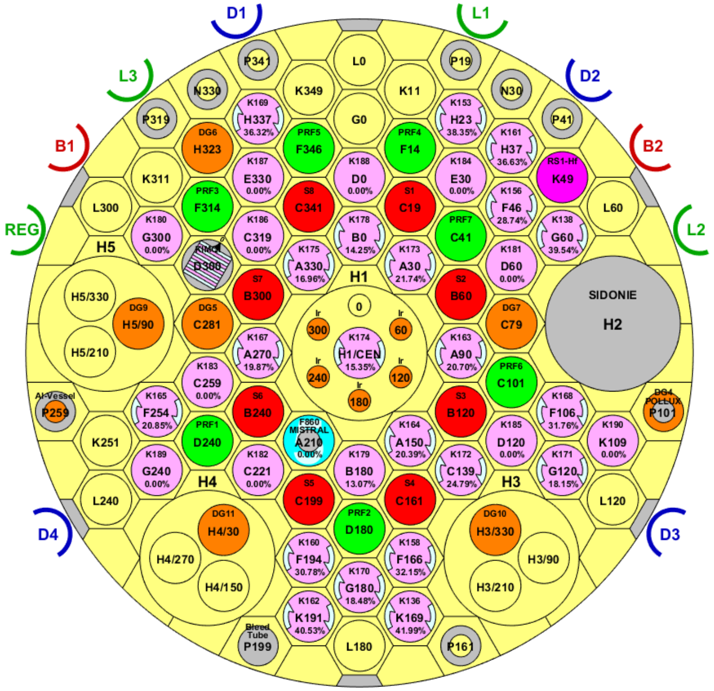
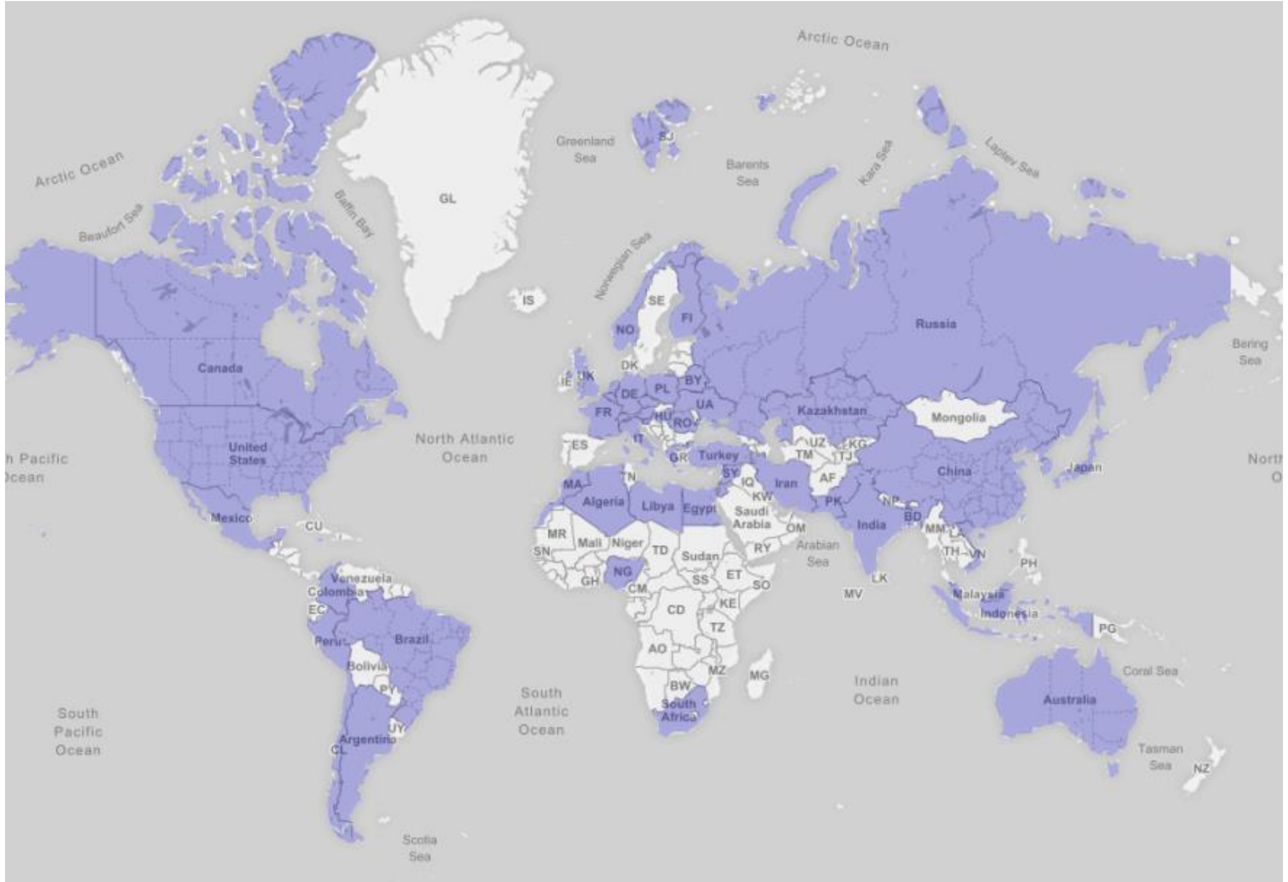


Research reactors available



Total

840 Reactors
in 70 countries

Operational

226 Reactors
in 54 countries

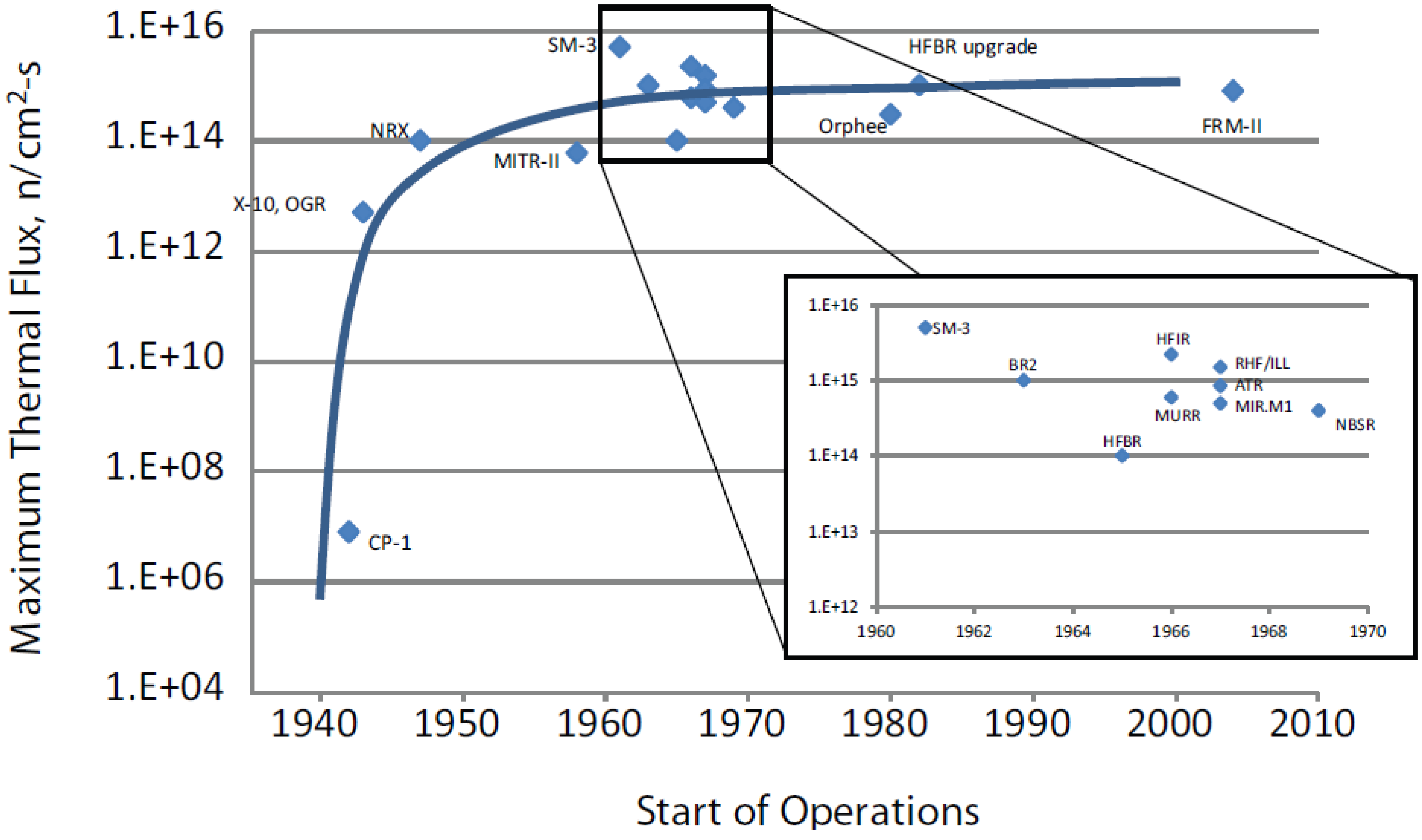
81 are utilized for Isotope production

Under construction/Planned

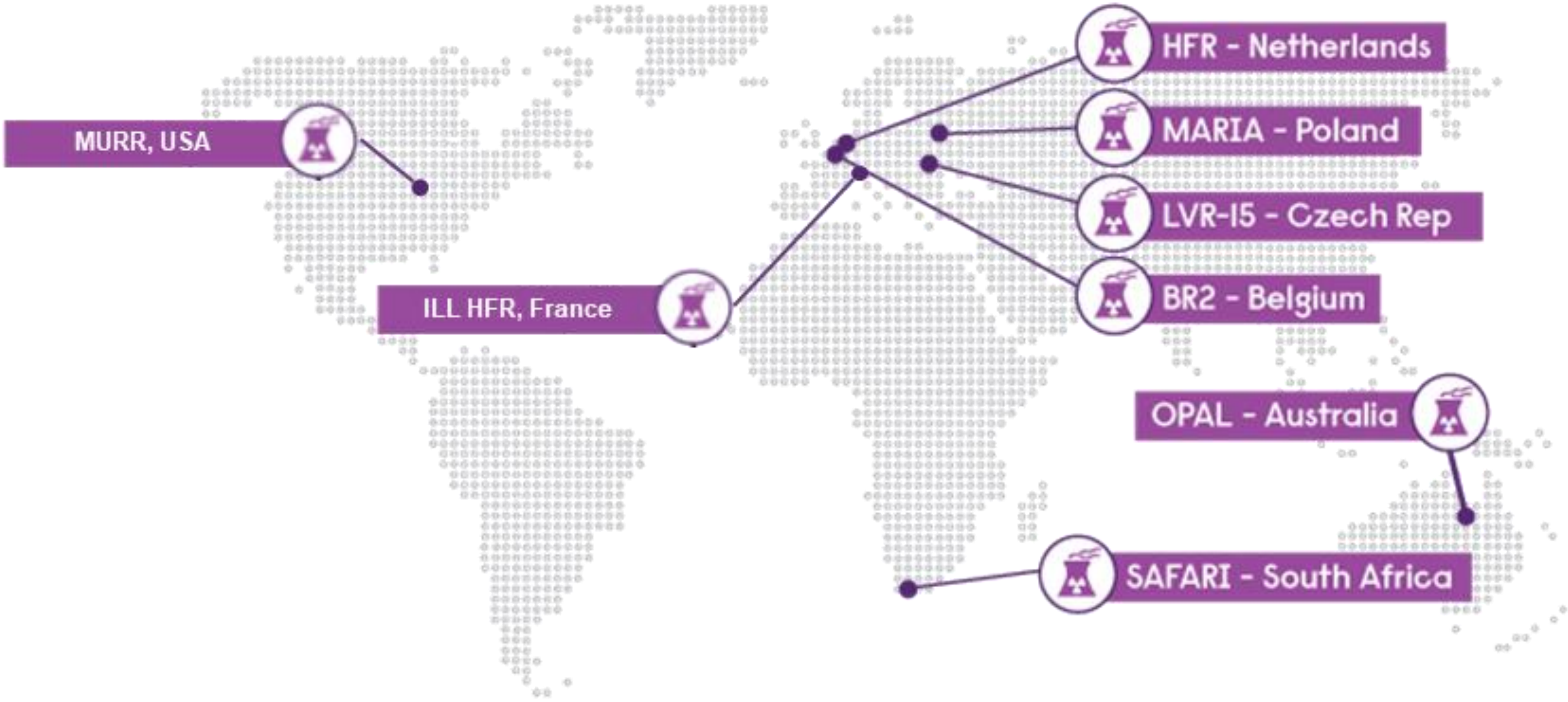
20 Reactors
in 15 countries

Source: IAEA Research reactors database, https://nucleus.iaea.org/RRDB/ (February 2024)

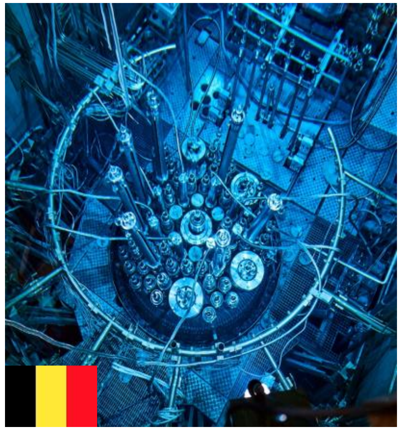
Research reactors



Research reactors

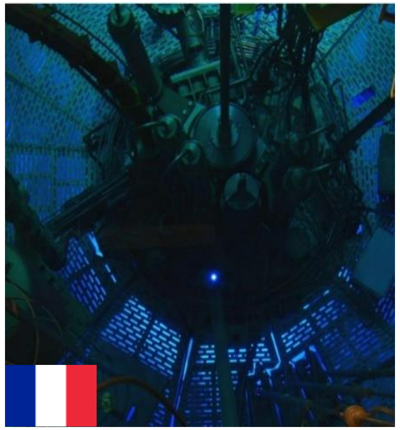


Research reactors *(current capacity in EU)*



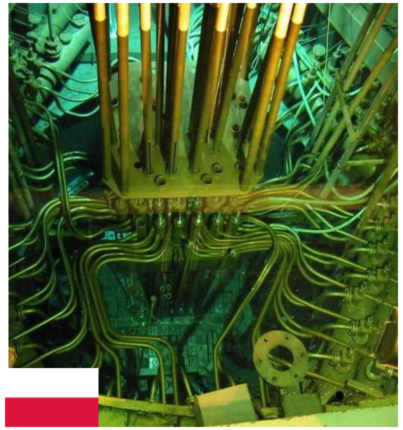
BR2 – SCK CEN

ϕ_{th} up to 4×10^{14} neutrons/cm^2/s (flexible)
1×10^{15} neutrons/cm^2/s (pressure vessel)



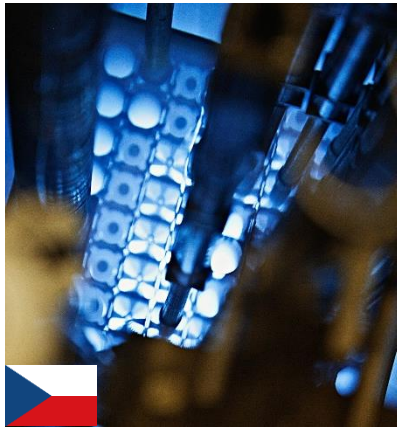
RHF – ILL

Φ_{th} up to 1.5×10^{15} neutrons/cm^2/s



MARIA – Polatom

Φ_{th} up to 3×10^{14} neutrons/cm^2/s



LVR-15 – CICRR

ϕ_{th} up to 1×10^{14} neutrons/cm^2/s

HFR - NRG

ϕ_{th} up to 2.6×10^{14} neutrons/cm^2/s

FRM II - TUM

ϕ_{th} up to 1.3×10^{14} neutrons/cm^2/s

Research reactors *(future capacity in EU)*

JHR – CEA
Operational: ca. 2032

PALLAS - NRG
Operational: ca. 2030

Potential difficulties

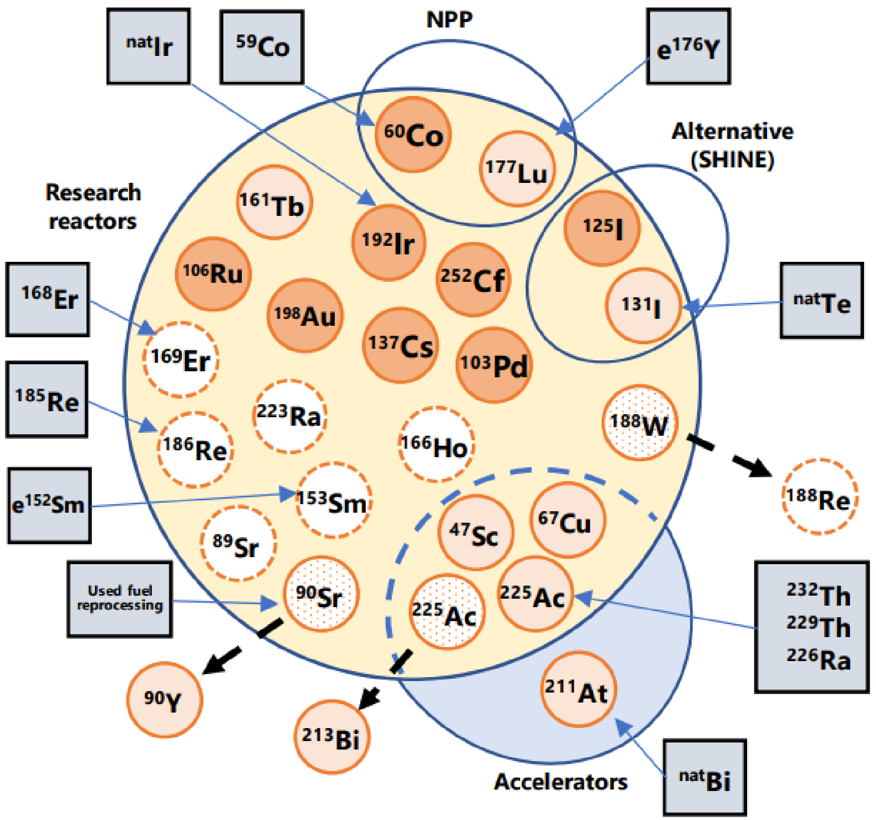
- Proliferation of fissile material → Conversion to LEU (< 20% ^{235}U enrichment)
- Ageing research reactor fleet → Most reactors were constructed in 1960s
- Strong support by public subsidies
- Operation cycles altered with maintenance cycles
- Severe safety measurements
- Current research reactors were designed and optimized for material testing, not for medical radionuclide production
- Irradiation positions are limited, especially the very high flux ones

  → High demand = high competitions = increasing prices

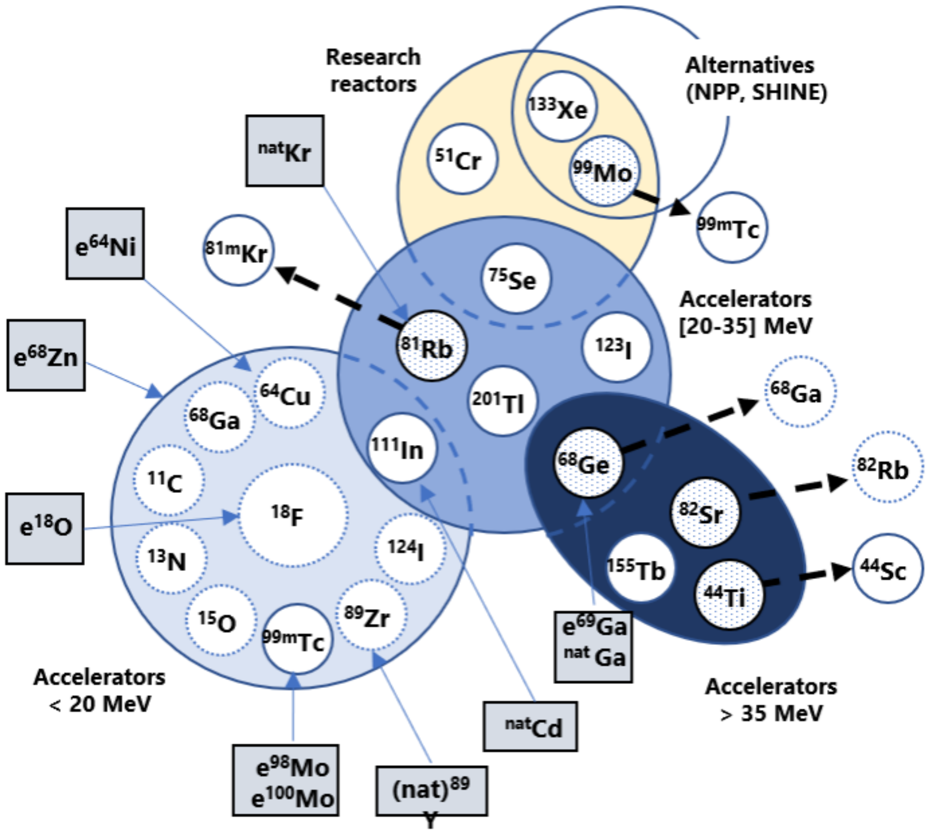
  → Find alternative high thermal neutron sources (e.g. CANDU commercial power reactors)

	Nuclear reactors	Cyclotrons
Principle of production	Target material inserted in the neutron flux field undergoes fission or neutron activation transmuting into radionuclide of interest	Target material irradiation by charged particle beams. Inlcuding nuclear reactions that transmute the material into radionuclide of interest
Transmutation base	Neutrons	p, d, t, ^{3}He, α or heavy ion beams
Advantages	• Production of neutron rich radionuclides, mostly for **therapeutic use** • High production yield and production efficiency • Centralized production: one research reactor able to supply to large regions, in some cases even globally	• Production of proton rich elements used as β^+ emitters for PET scans → **diagnositc use** • Decentralized production allows for back-up chains • High up-time • High specific activity in most cases • Small initial investment in comparison to nuclear reactor • Lilltle long-lived radioactive waste
Disadvantages	• Extremely high initial investment cost • High operational costs • Considerable amounts of long-lived radioactive waste • Long out-of-service periods • Trouble to back-up in case of unforeseen downtime • Demanding ligistics, often involving air transport • Public safety concerns • Non-proliferation treaty concerns → **Conversion to LEU**	• Regional network of cyclotrons and complex logistics needed for short-lived produced radionuclides • Radionuclide production limited depending on installed beam energy • Lower production yield

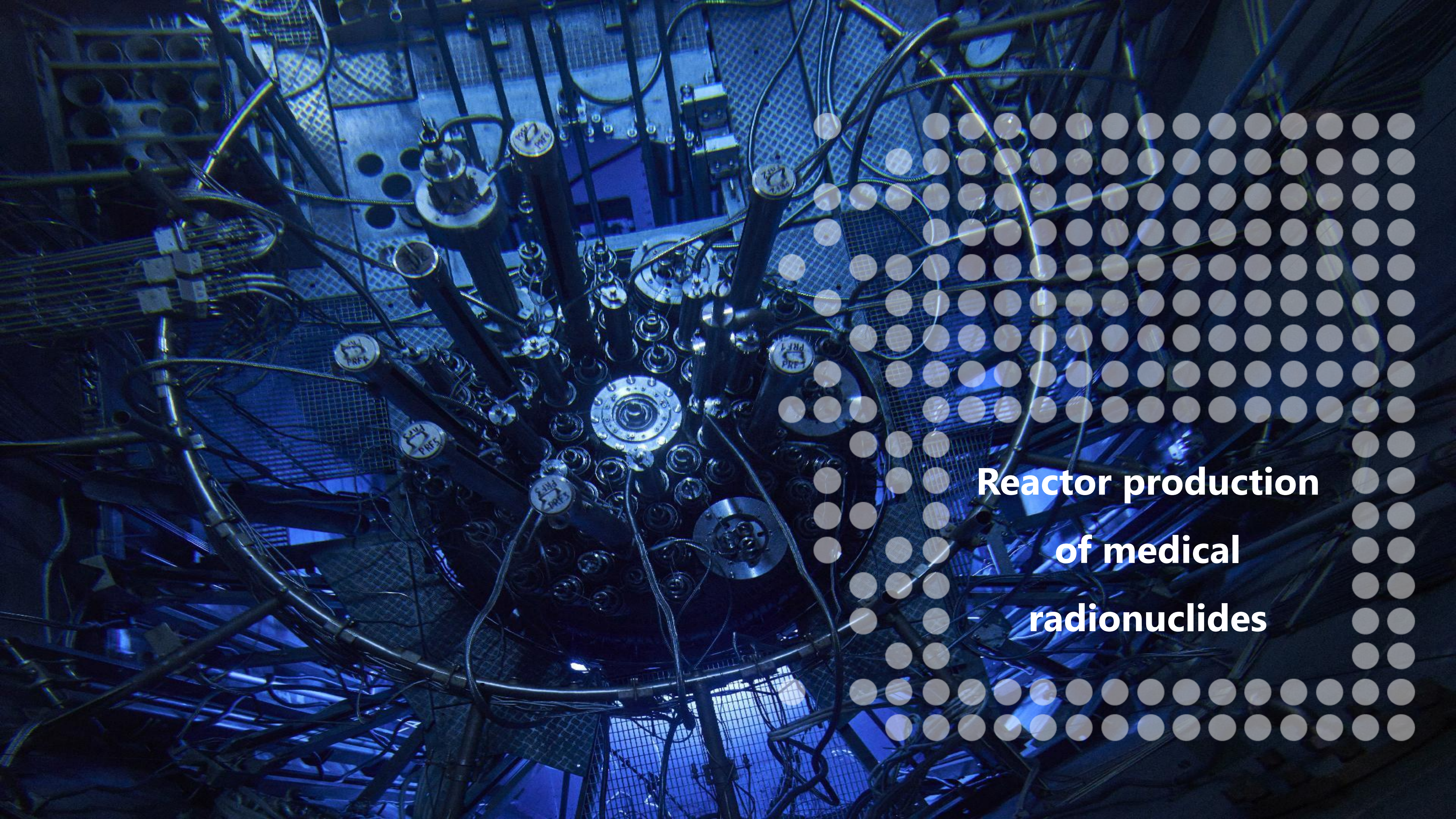
Therapeutic radionuclides



Diagnostic radionuclides

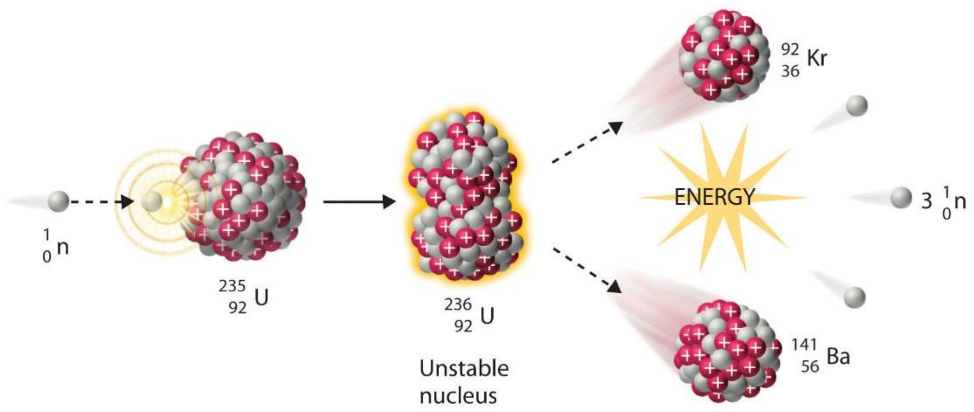


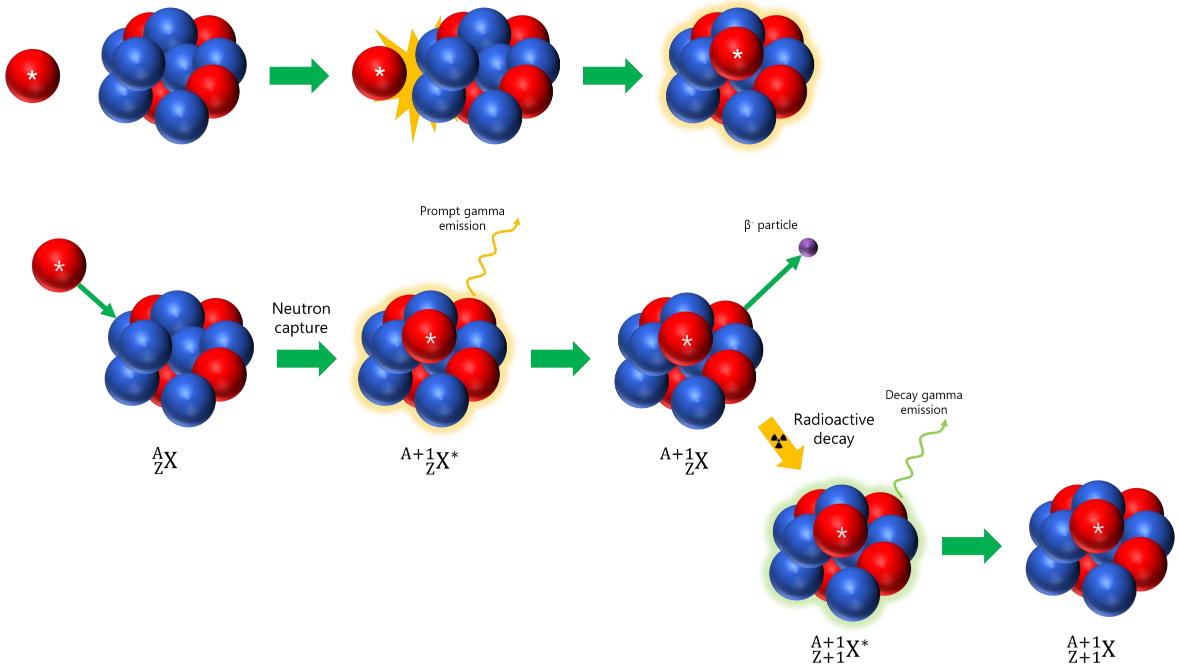
Source: *Co-ordinated Approach to the Development and Supply of Radionuclides in the EU (2021)*


Reactor production
of medical
radionuclides

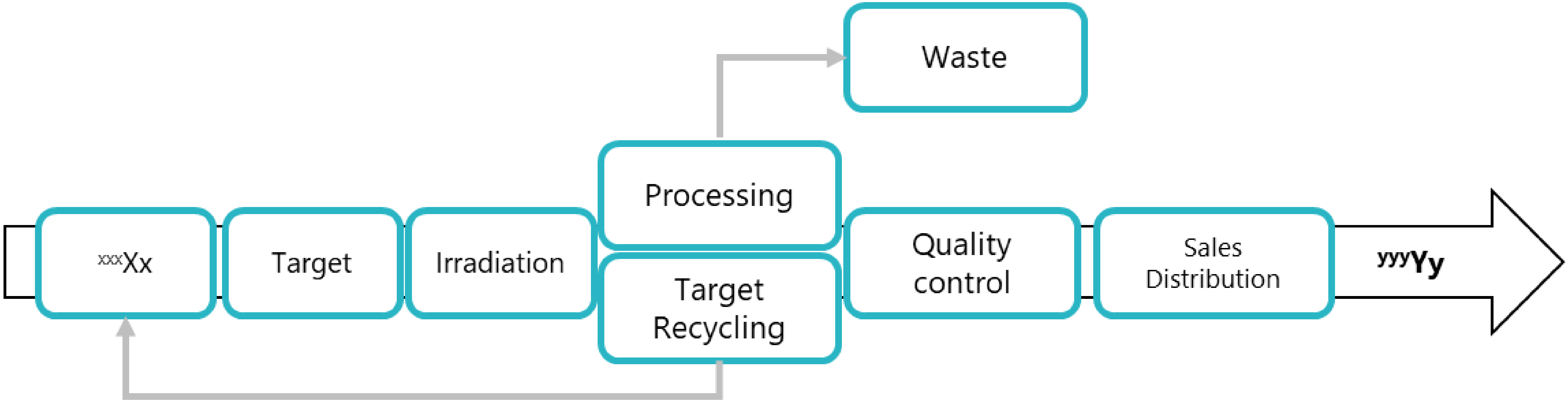
Production strategies

1. Fission $^{235}U(n,f)$
2. Neutron activation (n,γ) of highly enriched targets
   - Carrier added
   - Non-carrier added



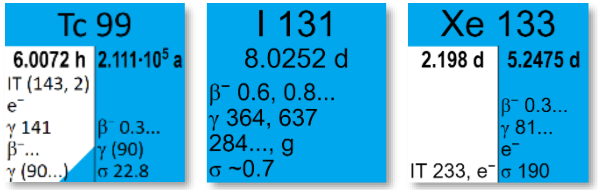


Production strategies



Radionuclide	Half life	Application	Production method
$^{99}Mo/^{99m}Tc$	66 h/6 h	SPECT	^{235}U fission $^{98}Mo(n,\gamma)^{99}Mo$
^{131}I	8 d		^{235} U fission $^{130}Te(n,\gamma)^{131}Te \rightarrow ^{131}I$
^{51}Cr	28 d	Radionuclide therapy	$^{50}Cr(n,\gamma)^{51}Cr$
^{153}Sm	46 h		$^{152}Sm(n,\gamma)^{153}Sm$
^{161}Tb	6.95 d		$^{160}Gd(n,\gamma)^{161}Gd \rightarrow ^{161}Tb$
^{166}Ho	27 h		$^{165}Ho(n,\gamma)^{166}Ho$ $^{164}Dy(2n,\gamma)^{166}Dy \rightarrow ^{166}Ho$
^{177}Lu	6.65 d		$^{176}Lu(n,\gamma)^{177}Lu$ $^{176}Yb(n,\gamma)^{177}Yb \rightarrow ^{177}Lu$
^{90}Y	64 h		$^{89}Y(n,\gamma)^{90}Y$
$^{188}W/^{188}Re$	69.8 d/17 h		$^{186}W(2n,\gamma)^{188}W \rightarrow ^{188}Re$
^{125}I	60 d	Brachytherapy	$^{124}Xe(n,\gamma)^{125m}Xe \rightarrow ^{125}I$
^{192}Ir	74 d		$^{191}Ir(n,\gamma)^{192}Ir$

Production strategies – Fission



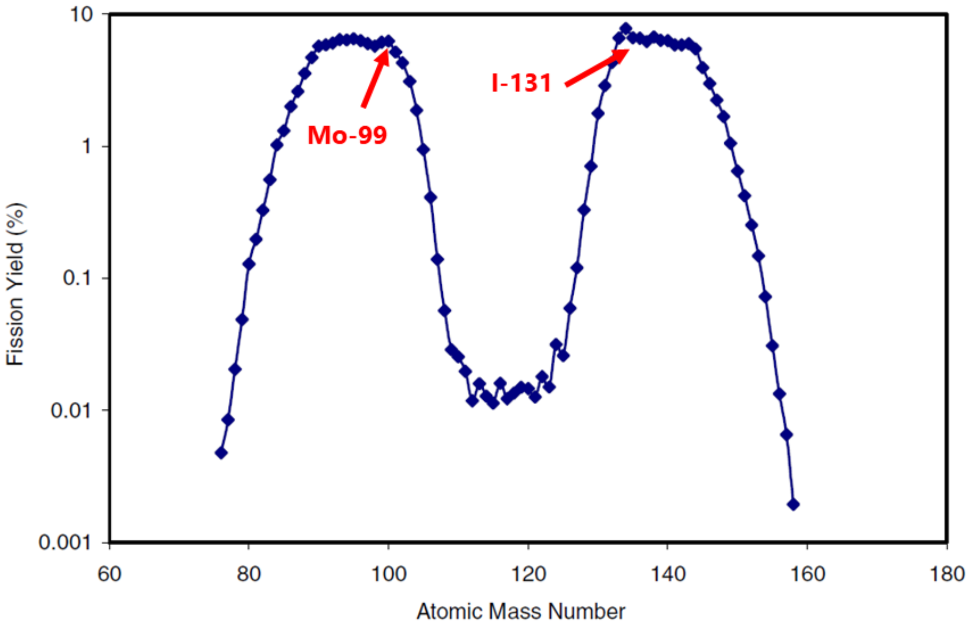
Fission $^{235}U(n,f)$

→ Produces wide range of fission products

→ Predominant way for $^{99}Mo/^{99m}Tc$ production, ^{131}I and ^{133}Xe are by-products

→ Initially by use of HEU (90-95% ^{235}U), now by use of LEU (<20% ^{235}U)

→ $$N_{^{99}Mo} = \frac{\varphi \sigma_{^{235}U_f} \gamma_{^{99}Mo} N_{^{235}U_0}}{\lambda_{^{99}Mo}} \left[1 - e^{-\lambda_{^{99}Mo} t}\right]$$ *(γ = fission production probability)*



Reference Target	HEU (93%-^{235}U)	LEU (19.8%-^{235}U)
^{99}Mo yield, Ci	530	540
Total U (^{235}U), g	16 (15)	94 (18)
^{239}Pu, µCi	30	720
$^{234, 235, 238}U$, µCi	1280	840
Total α, µCi	1310	1560

Source: https://www-nds.iaea.org/sgnucdat/c1.htm

Mo-99/Tc-99m production

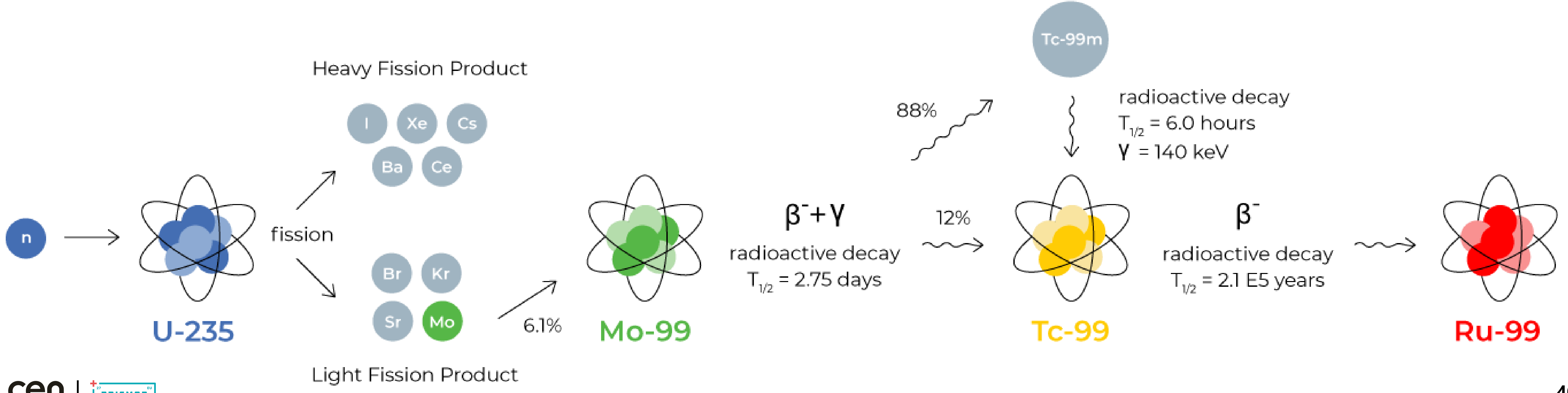
→ Used for diagnosis in hospitals (SPECT imaging)

→ ^{99}Mo yield accounts for 5-7% of fission products

→ ^{99}Mo/^{99m}Tc generators, locally milked for ^{99m}Tc

→ Currently the working horse in nuclear medicine (80% ~ 40 million procedures)

→ ^{99}Mo ($t_{1/2}$ = 2.75 d), ^{99m}Tc ($t_{1/2}$ = 6 h) → Supply chain is race against time!



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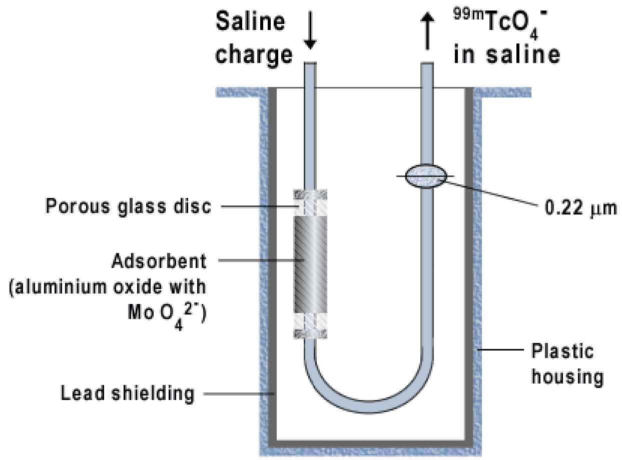
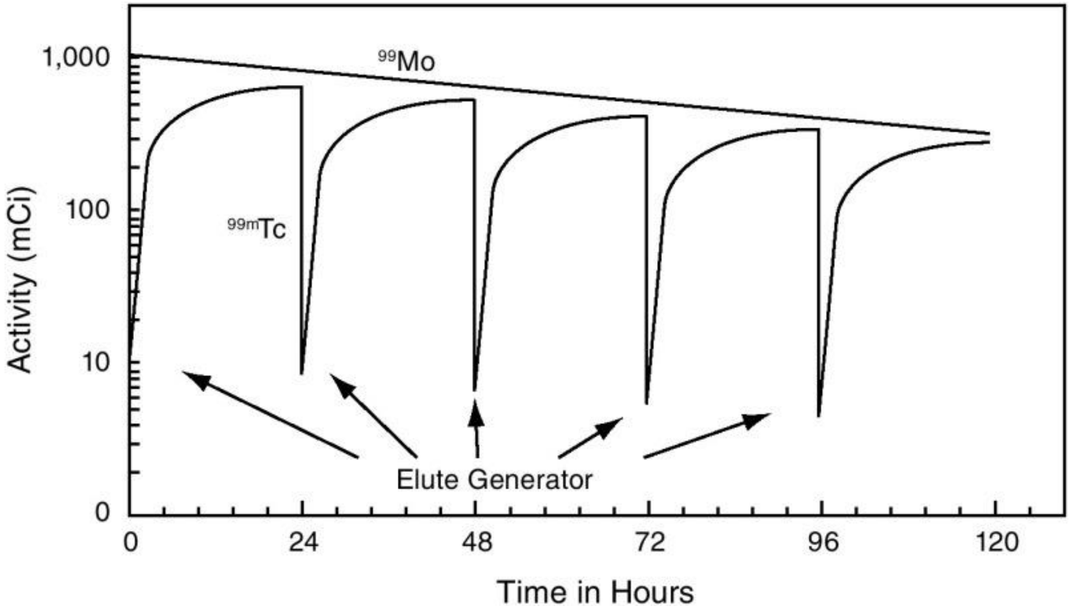
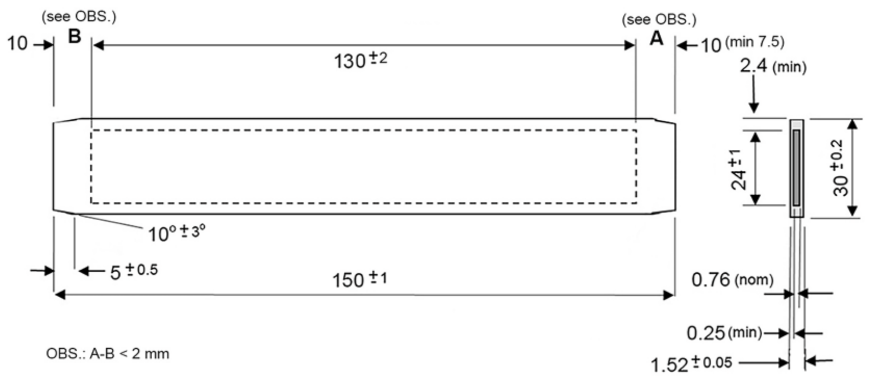




Mo-99/Tc-99m production

1. Target manufacuturing (LEU)
2. Production by $^{235}U(n,f)$
3. Chemical extraction



Target criteria

- **Properly sized** to fit into the irradiation position/canister
- Must contain a **suffient amount of ^{235}U** to produce required amount of ^{99}Mo
- **Good heat transfer properties** to prevent over-heating during irradiation
- **Provide a barrier** to the release of radioactive products during and after irradation
- Target material must be **compatible with chemical processing steps** to recover and purify ^{99}Mo

Mo-99/Tc-99m production

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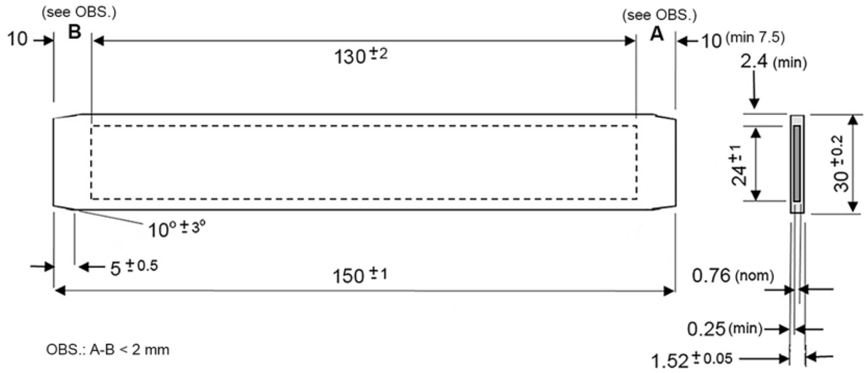
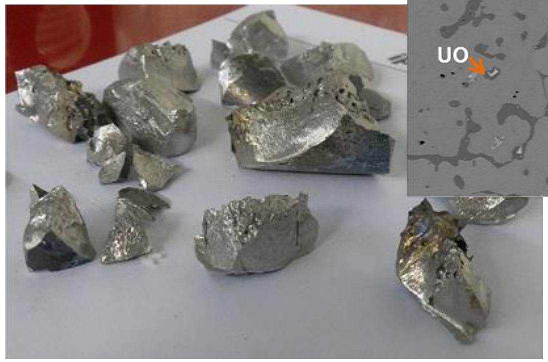
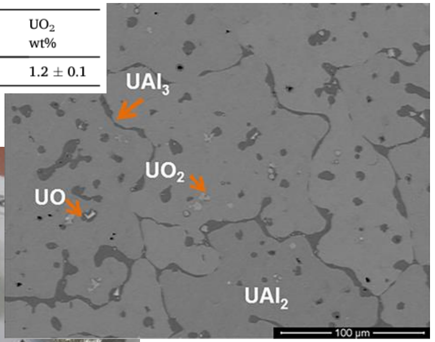


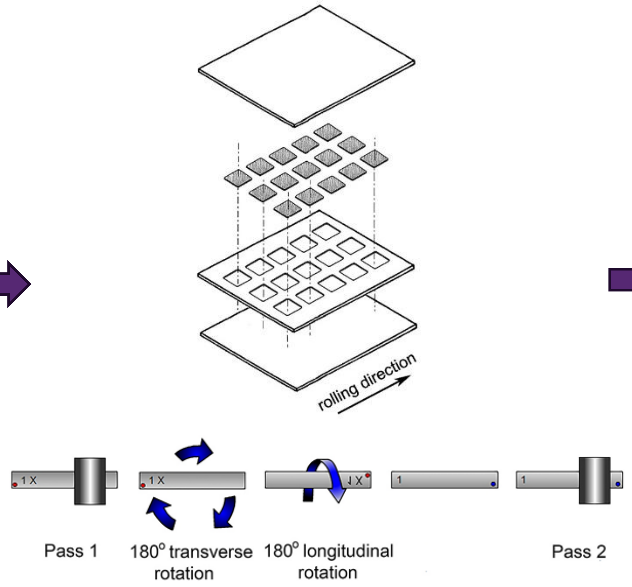
Phase composition in primary UAl_2 ingot.

UAl_2 wt%	UAl_3 wt%	UAl_4 wt%	UO wt%	UO_2 wt%
87.1 ± 0.3	10.2 ± 0.3	N.D	1.6 ± 0.1	1.2 ± 0.1





UAl_2 ingots after induction melting (87 wt% UAl_2)



Hot-rolling to convert UAl_2 into UAl_3 nad UAl_4 according to picture-frame technique

Phase composition in the finished target.

UAl_2 wt%	UAl_3 wt%	UAl_4 wt%	UO wt%	UO_2 wt%
0.3 ± 0.1	30.1 ± 1.5	68.1 ± 1.6	0.3 ± 0.1	1.3 ± 0.2

N.D = not detected.

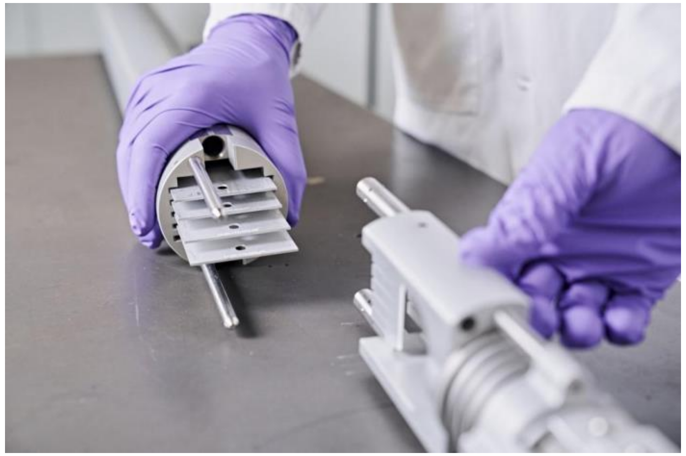
UAlx meat completely surrounded by aluminium (cladding), guaranteeing removal of heat + isolation from reactor environment (0 wt% UAl_2)

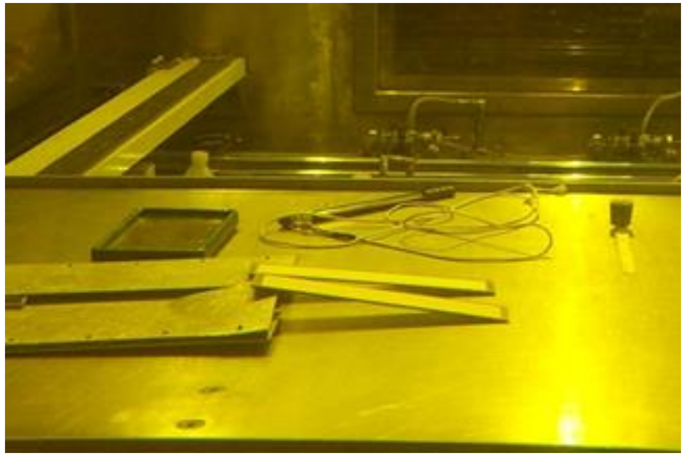
Source: M. Durazzo, Progress in Nuclear Energy 140 (2021)

Mo-99/Tc-99m production

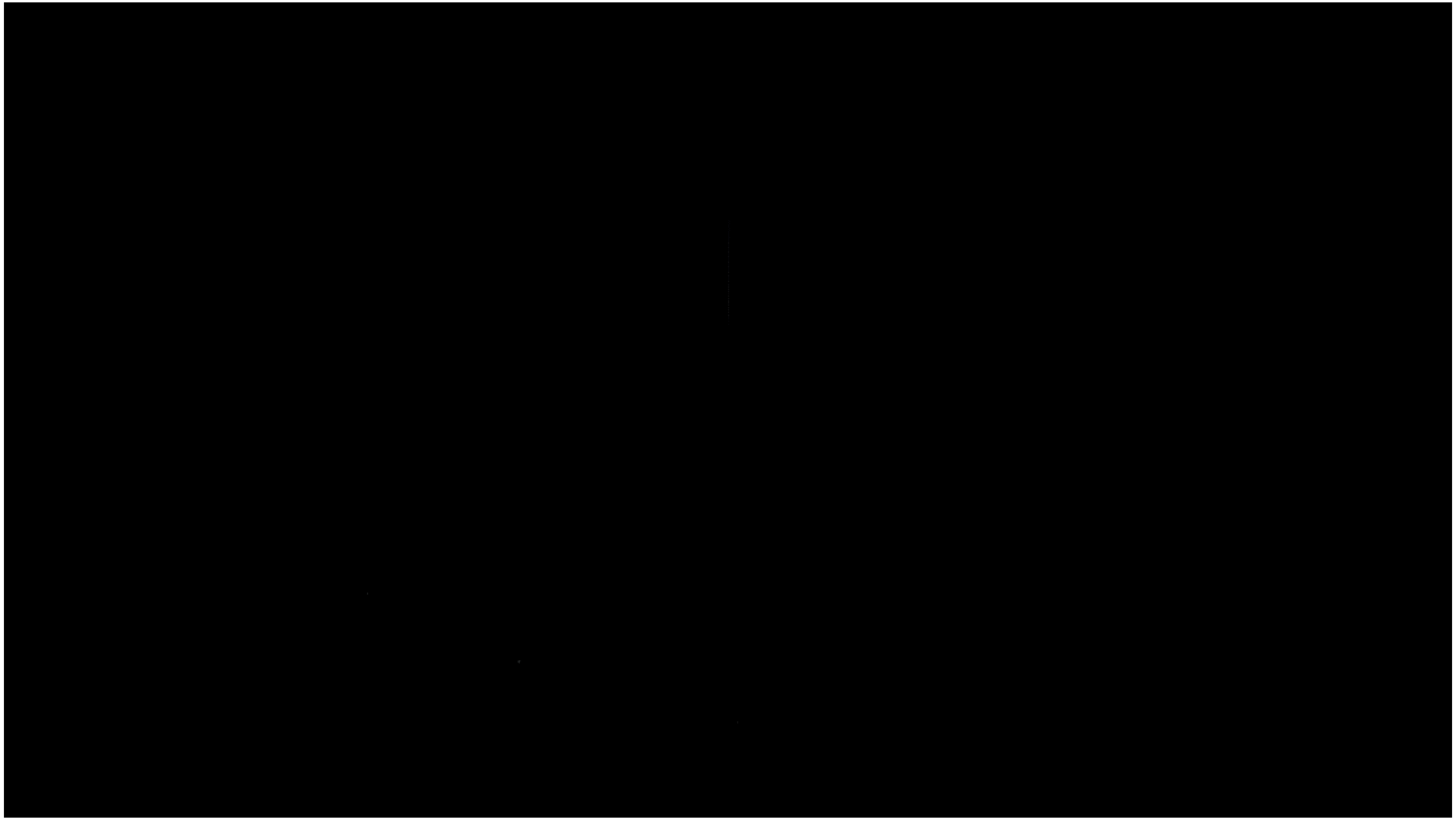
1. Target manufacuting (LEU)
2. Production by $^{235}U(n,f)$
3. Chemical extraction





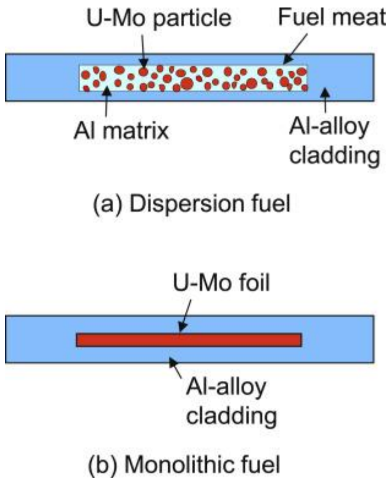
Mo-99/Tc-99m production



Video shared by the courtesy of CEA, kindly provided by Dr. M. Libessart
https://www.youtube.com/watch?v=eMWaVurRX78

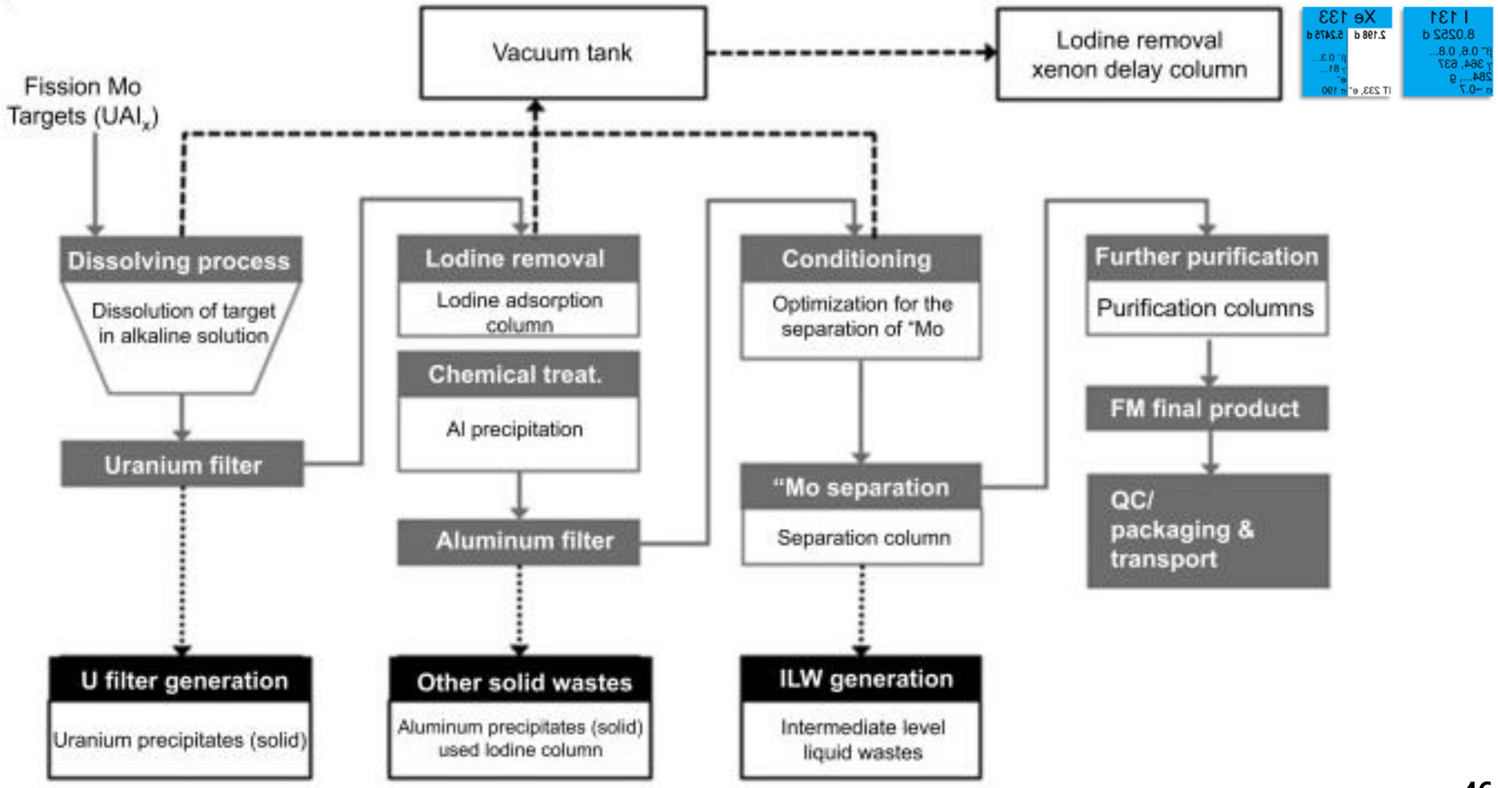
Mo-99/Tc-99m production

1. Target manufacuting
2. Production by ^{235}U(n,f)
3. Chemical extraction



Dissolution of target by NaOH

Yields a $NaAlO_2$ + Na_2MoO_4 solution and solid oxide/hydroxide residu (U and most fission products)



Source: *S. Seung-Lee, Nuclear Engineering and Technology 48:3 (2016)*

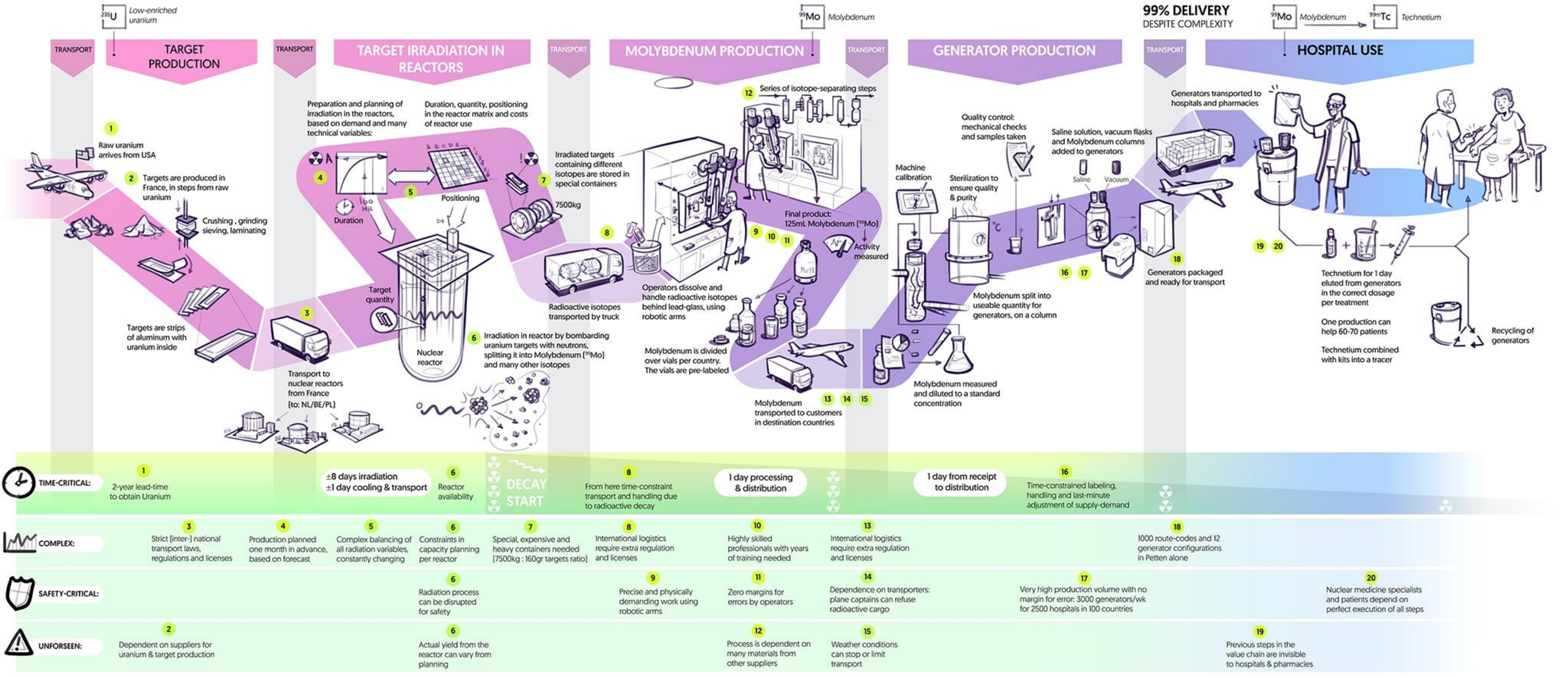
Mo-99/Tc-99m production

Source: IRE
https://www.youtube.com/watch?v=C0FfTSLmK9E&t=13s

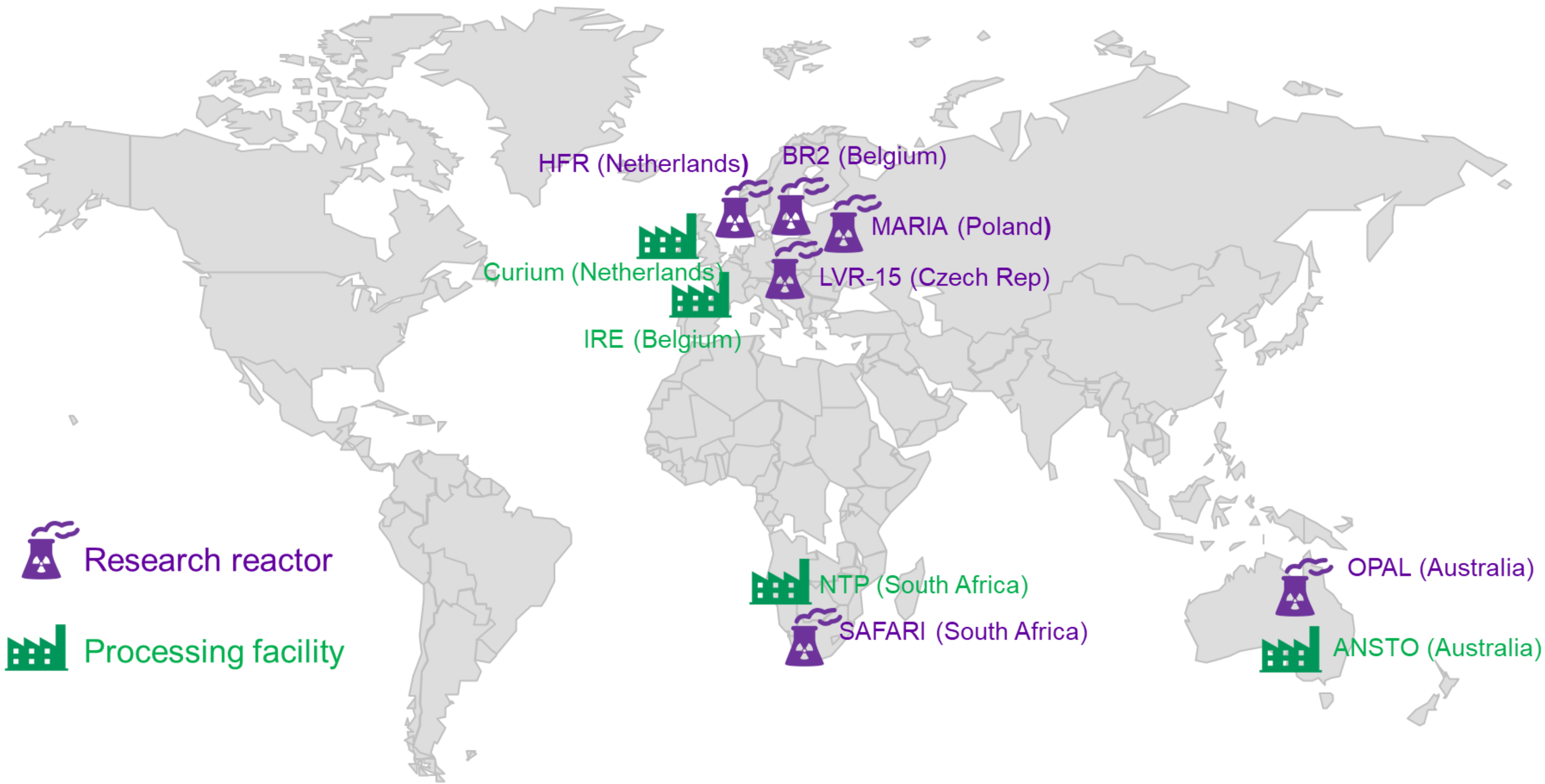
CURIUM™ LIFE FORWARD

COMPLEXITY OF GLOBAL MOLYBDENUM-99 SUPPLY CHAIN

From target production to generator delivery

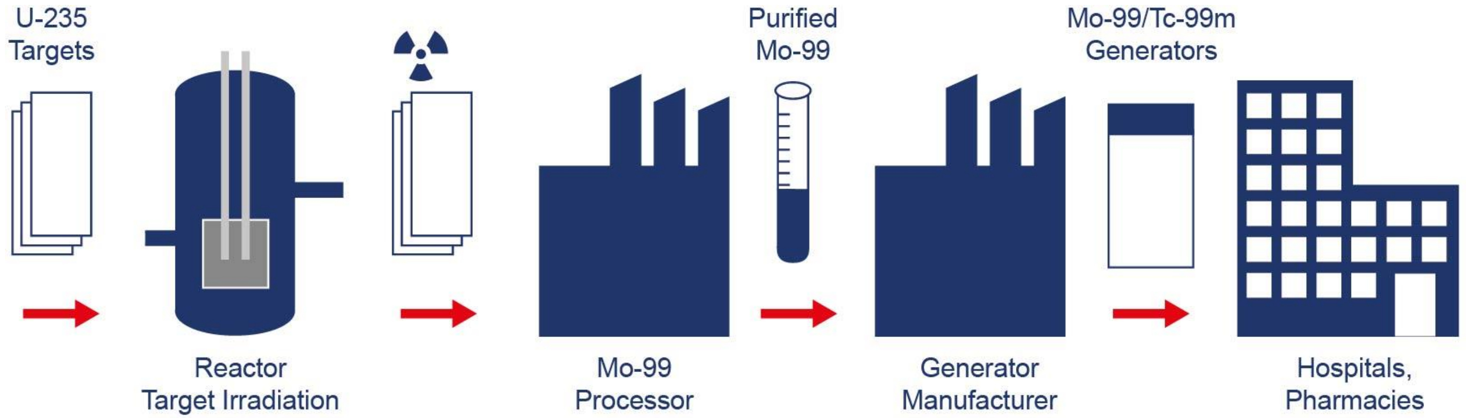


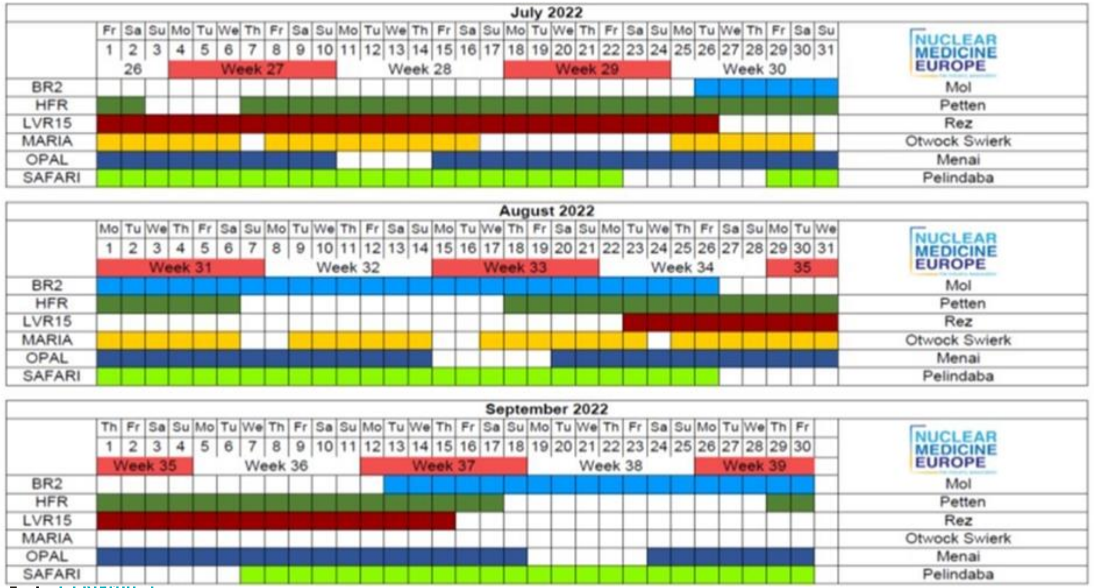
Mo-99/Tc-99m production

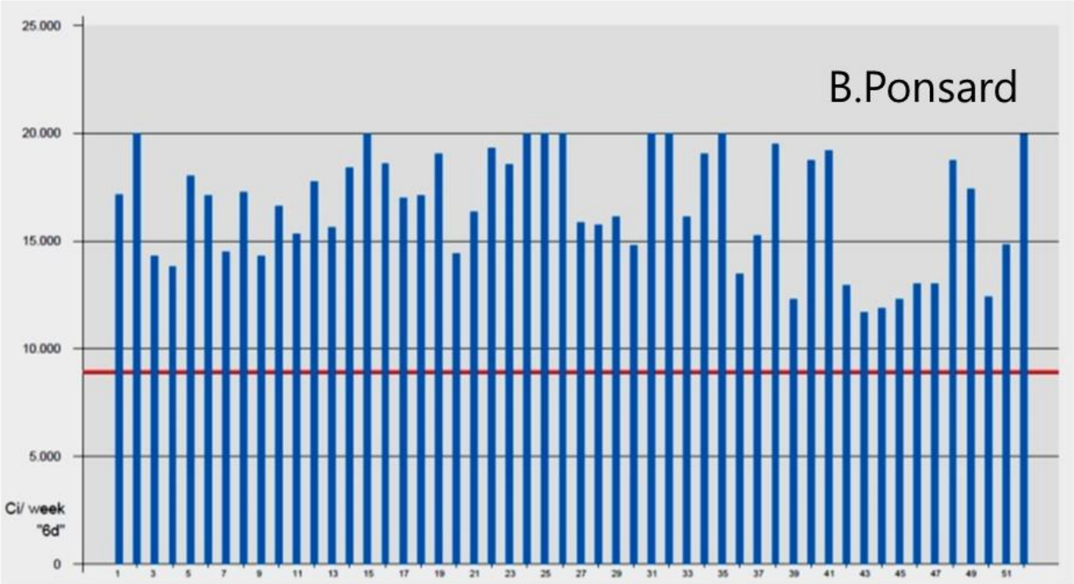


Source: B. Ponsard, SCK CEN

Mo-99/Tc-99m production – Security of supply







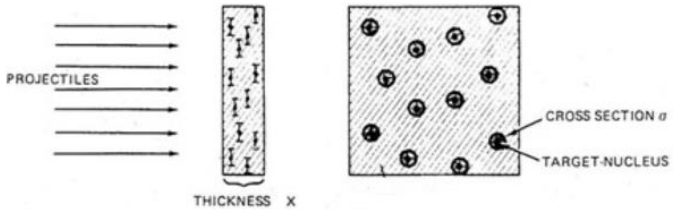
Mo-99/Tc-99m production

Reactor	Targets	Operating days/year	Mo-99 irradiation weeks/year	Irradiation capacity per week (6-day Ci Mo-99)	Irradiation capacity per year (6-day Ci Mo-99)	Estimated end of operation
BR2	LEU	203	29	8 600	249 400	2036
HFR	LEU	265	38	6 200	235 600	2030
LVR-15	LEU	210	30	3 000	90 000	2028
MARIA	LEU	200	36	2 200	79 200	2040
OPAL	LEU	308	44	3 200	140 800	2057
SAFARI-1	LEU	305	44	3 000	130 700	2030

Processor	Targets	Mo -99 production weeks/year	Processing capacity per week (6-day Ci Mo-99)	Processing capacity per year (6-d Ci Mo-99)	Estimated end of operation
ANSTO	LEU	44	3 200	140 800	2057
CURIUM	LEU	52	5 000	260 000	Not Known
IRE	LEU	52	3 500	182 000	At least until 2032
NTP	LEU	44	3 000	130 700	At least until 2030

Source: B. Ponsard, SCK CEN

Production strategies – Neutron activation

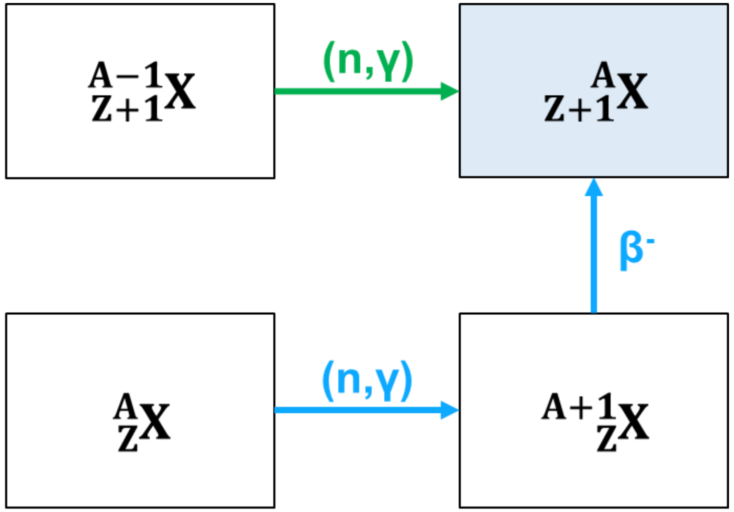


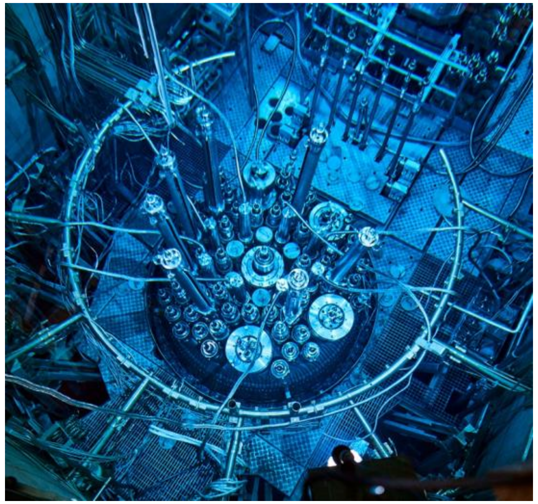
Neutron activation $^{A}X(n,\gamma)^{A+1}X$

$$\mathbf{A = N_{target} \cdot \text{Ѧ}_{target} \cdot \sigma_{target} \cdot \phi_{reactor} \cdot \left(1 - e^{-\lambda_{isotope} \cdot t_{irradiaiton}}\right)}$$

Carrier added → = direct route

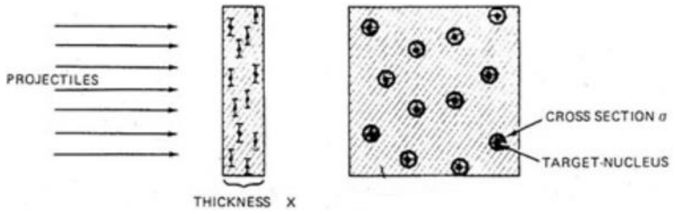
Non-carrier added → = indirect route





Production strategies – Neutron activation

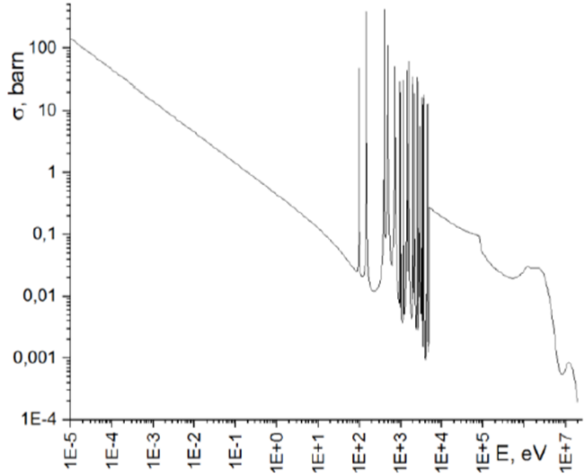
Neutron activation $^{A}X(n,\gamma)^{A+1}X$



$$A = N_{target} \cdot \text{Ѧ}_{target} \cdot \sigma_{target} \cdot \phi_{reactor} \cdot \left(1 - e^{-\lambda_{isotope} \cdot t_{irradiaiton}}\right)$$

Main factors that determine the production yield of the radionuclide of intrest are:

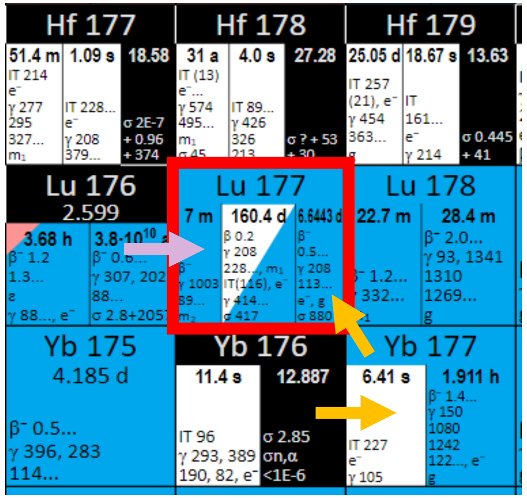
- **Energy** of the neutrons and the **neutron flux**
- Characteristics of the **target material** (purity, enrichment, matrix, dimensions)
- **Activation cross-section** for the desired reaction

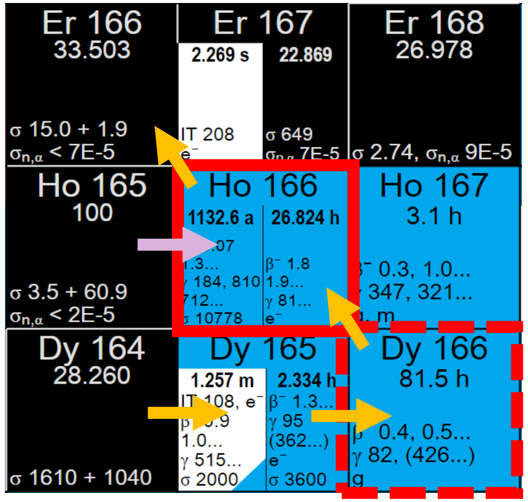


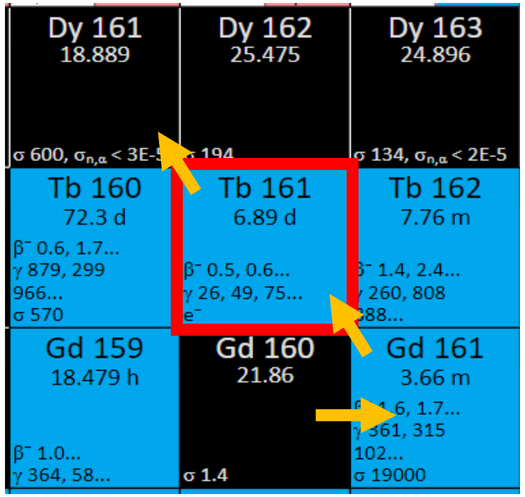
Cross-section of ^{176}Yb

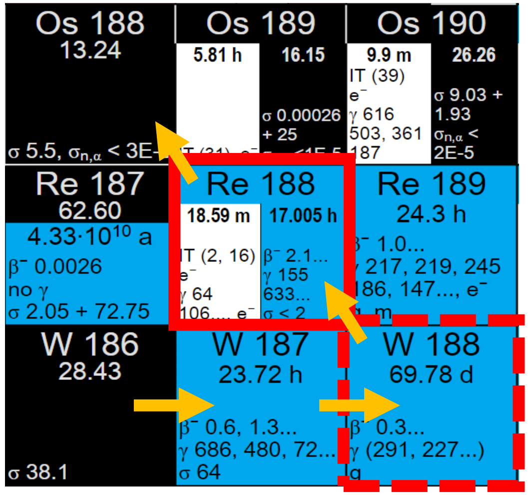
Radionuclide	Half life	Application	Production method
$^{99}Mo/^{99m}Tc$	66 h/6 h	SPECT	^{235}U fission $^{98}Mo(n,\gamma)^{99}Mo$
^{131}I	8 d		^{235} U fission $^{130}Te(n,\gamma)^{131}Te \rightarrow ^{131}I$
^{51}Cr	28 d	Radionuclide therapy	$^{50}Cr(n,\gamma)^{51}Cr$
^{153}Sm	46 h		$^{152}Sm(n,\gamma)^{153}Sm$
^{161}Tb	6.95 d		$^{160}Gd(n,\gamma)^{161}Gd \rightarrow ^{161}Tb$
^{166}Ho	27 h		$^{165}Ho(n,\gamma)^{166}Ho$ $^{164}Dy(2n,\gamma)^{166}Dy \rightarrow ^{166}Ho$
^{177}Lu	6.65 d		$^{176}Lu(n,\gamma)^{177}Lu$ $^{176}Yb(n,\gamma)^{177}Yb \rightarrow ^{177}Lu$
^{90}Y	64 h		$^{89}Y(n,\gamma)^{90}Y$
$^{188}W/^{188}Re$	69.8 d/17 h		$^{186}W(2n,\gamma)^{188}W \rightarrow ^{188}Re$
^{125}I	60 d	Brachytherapy	$^{124}Xe(n,\gamma)^{125m}Xe \rightarrow ^{125}I$
^{192}Ir	74 d		$^{191}Ir(n,\gamma)^{192}Ir$

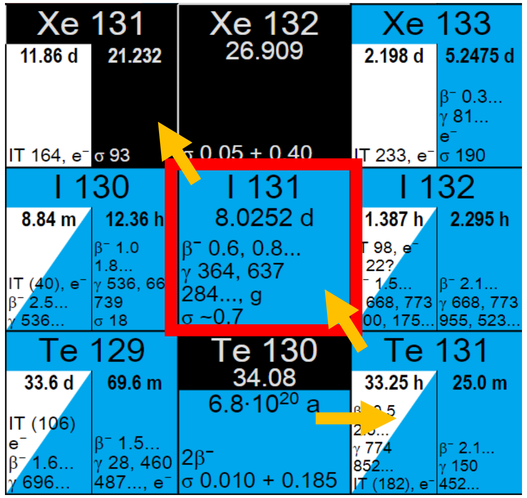
Neutron activation – Examples

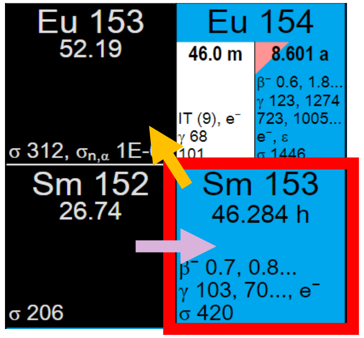


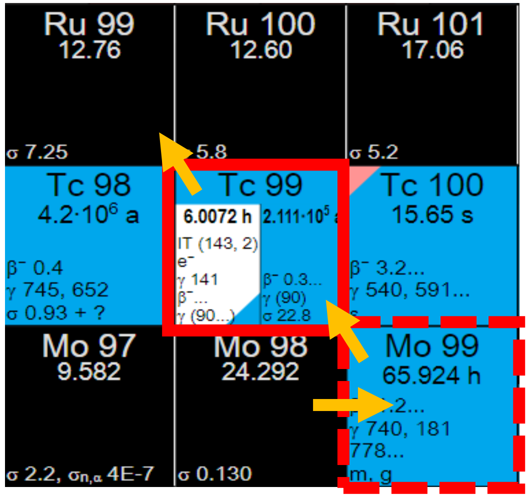










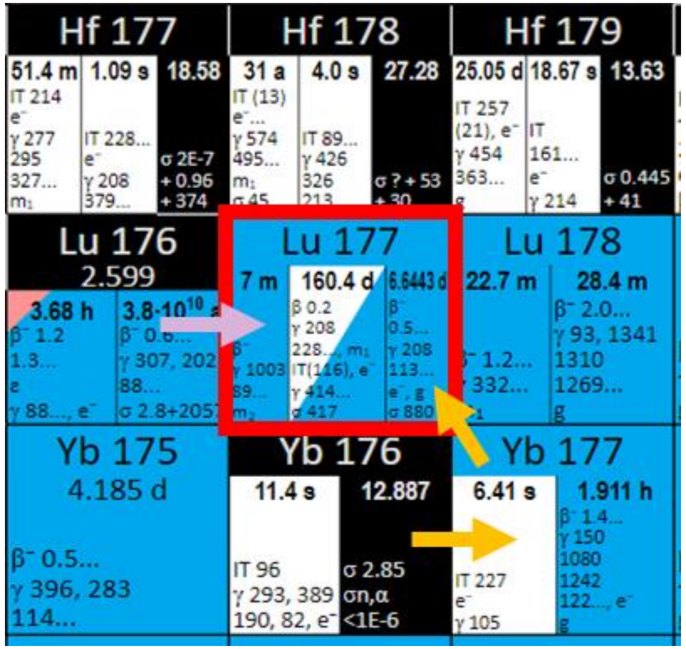


Production strategies – ^{177}Lu example

$^{176}Lu(n,\gamma)^{177}Lu$ (σ_{th} = 2057 barn) but $^{176}Lu(n,\gamma)^{177m}Lu$ (σ_{th} = 2.8 barn)

↕

$^{176}Yb(n,\gamma)^{177}Lu$ (σ_{th} = 2.85 barn)

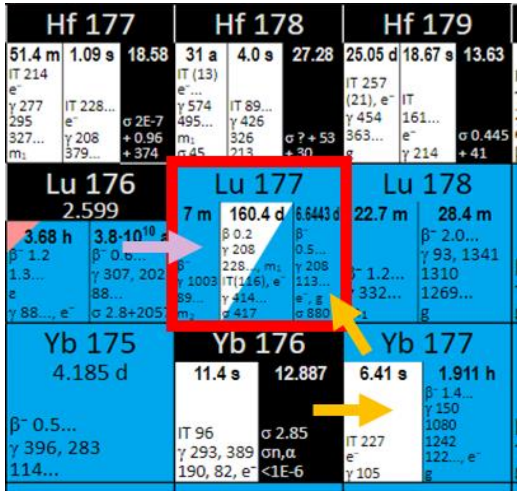


Tradeoff between

- Production yield
- Specific activity
- Chemical and radionuclidic purity

→ Depends on available target material and final application

Production strategies – ^{177}Lu example



^{176}Lu(n,γ)^{177}Lu (σ_{th} = 2057 barn)

A(^{177}Lu) = 1115 TBq at EOI

→ SA(^{177}Lu) = 1115 GBq/mg

A(^{177}Lu) = 527 TBq at EOI+7d

→ SA(^{177}Lu) = 527 GBq/mg

but ^{176}Lu(n,γ)^{177m}Lu (σ_{th} = 2.8 barn)

A(^{177m}Lu) = 86 GBq at EOI

LuMark® Lu-177 chloride

SA ≥ 500 GBq/mg at ART

^{176}Yb(n,γ)^{177}Lu (σ_{th} = 2.85 barn)

A(^{177}Lu) = 1.5 TBq at EOI

→ SA(^{177}Lu) = 4106 GBq/mg

A(^{177}Lu) = 0.8 TBq at EOI+7d

→ SA(^{177}Lu) = 4106 GBq/mg

endolucin beta

SA ≥ 3000 GBq/mg at ART

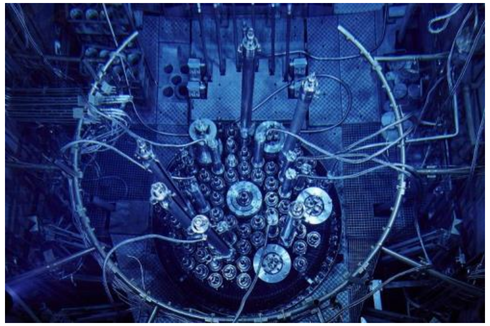
Activation parameters

- 100% enriched target
- Φ_{th} = 3E14 neutrons/cm^2/s
- No epithermal or fast neutrons
- No self-shielding
- 7 days irradiation
- 1 g target

$$A = N_{target} \cdot \sigma_{th,\ target} \cdot \phi_{th,reactor} \cdot \left(1 - e^{-\lambda_{isotope} \cdot t_{irr}}\right) \cdot e^{-\lambda_{isotope} \cdot t_{cool}}$$

Production n.c.a. ^{177}Lu – General approach

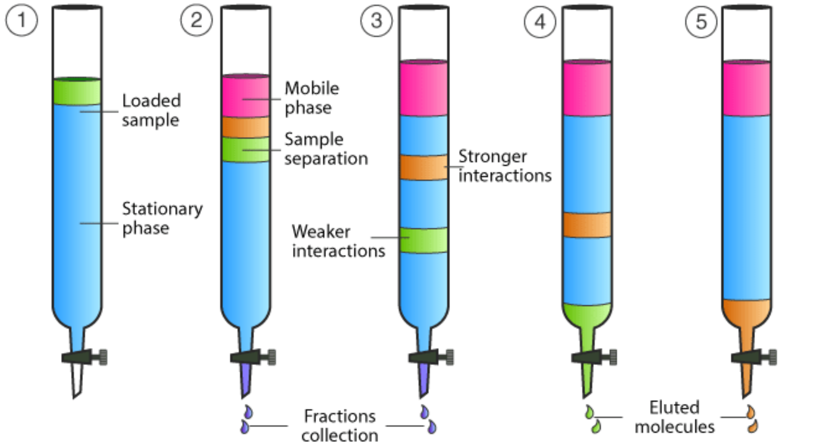
Transport



Transport

1. Ampoule crushing
2. target dissolution

3. pH adjustment target solution

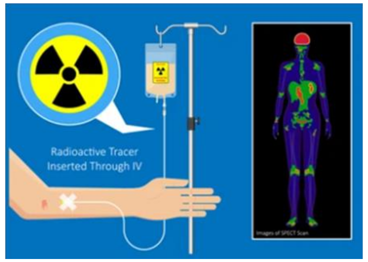


^{177}Lu

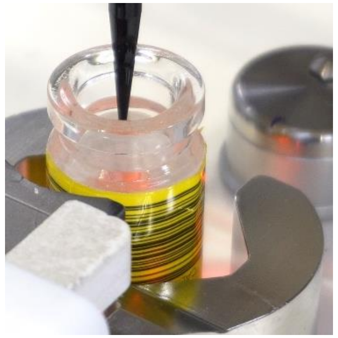
^{176}Yb

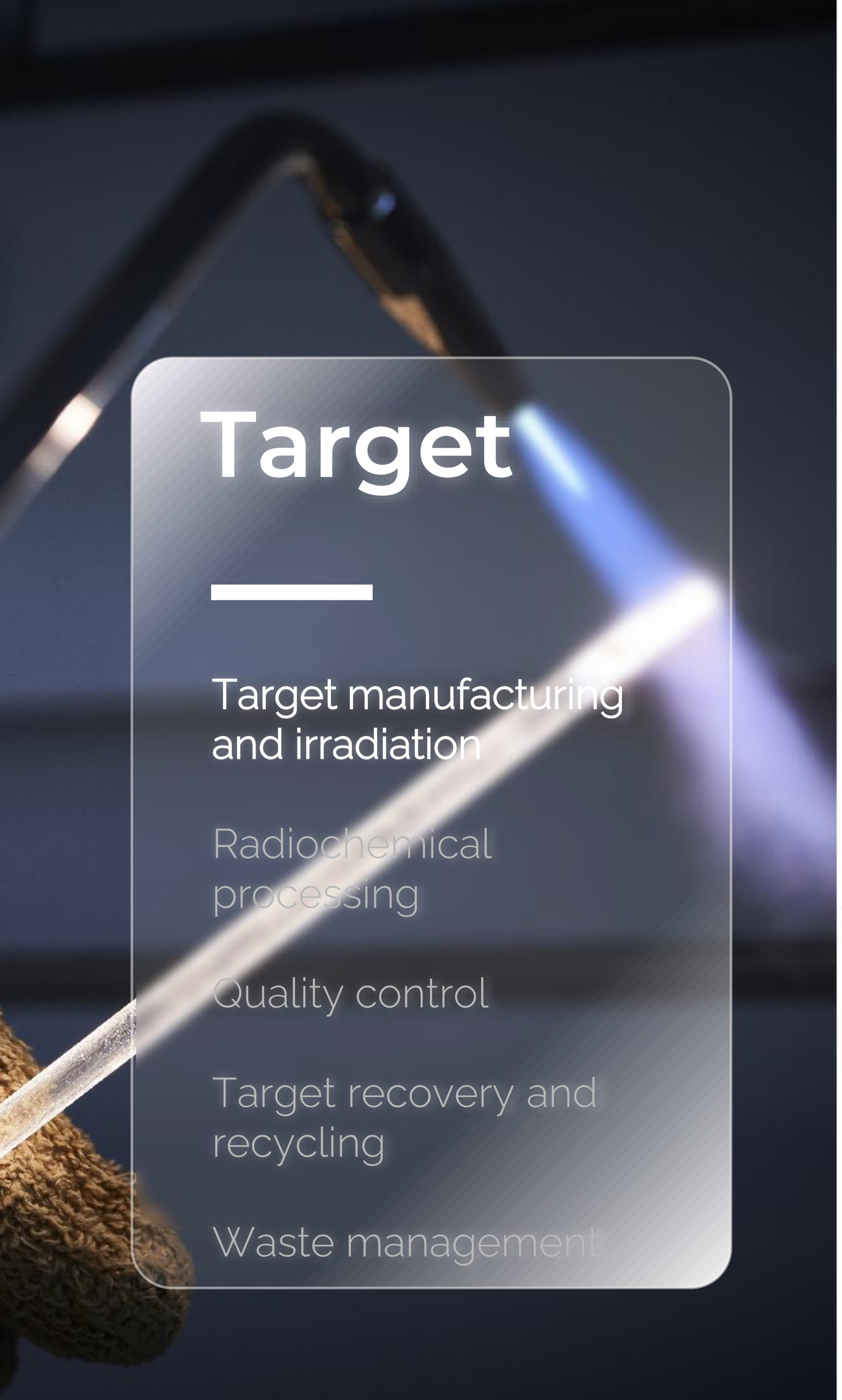
- ^{177}Lu conversion to chloride
- Final [^{177}Lu]$LuCl_3$ for dispensing
- QC

Target recycling and QC



Transport

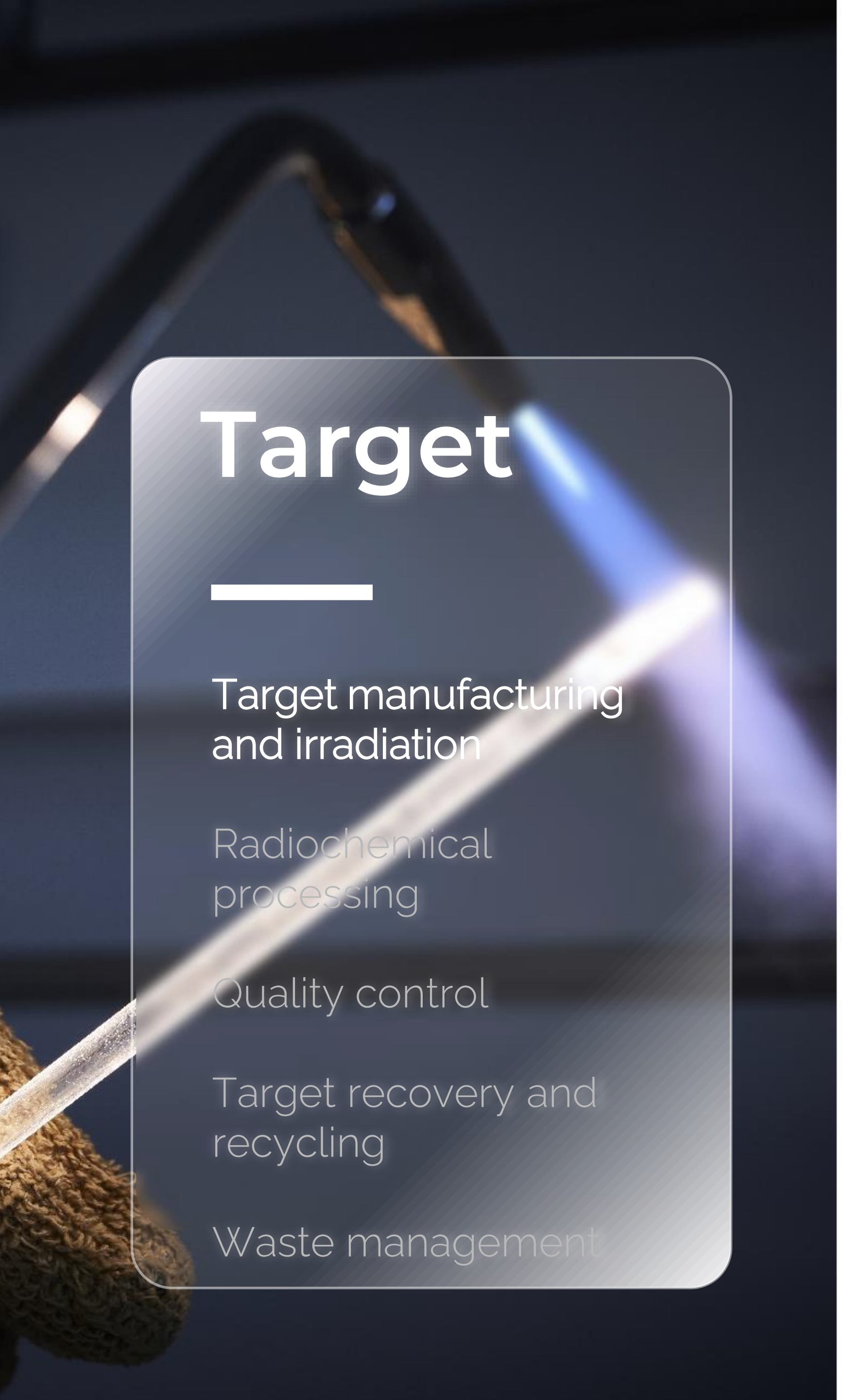




Target preparation

Target criteria

- **Properly sized** to fit into the irradiation position/canister
- Sufficient amount to produce desired amount of activity
- **Good heat transfer properties** to prevent over-heating during irradiation
- **Thermally stable compounds** to prevent pressure build-up and target failure → typically metal or oxide compounds
- **Provide a barrier** to the release of radioactive products during and after irradiation
- Target material must be **compatible with chemical processing steps** to recover and purify desired radioactive compoud

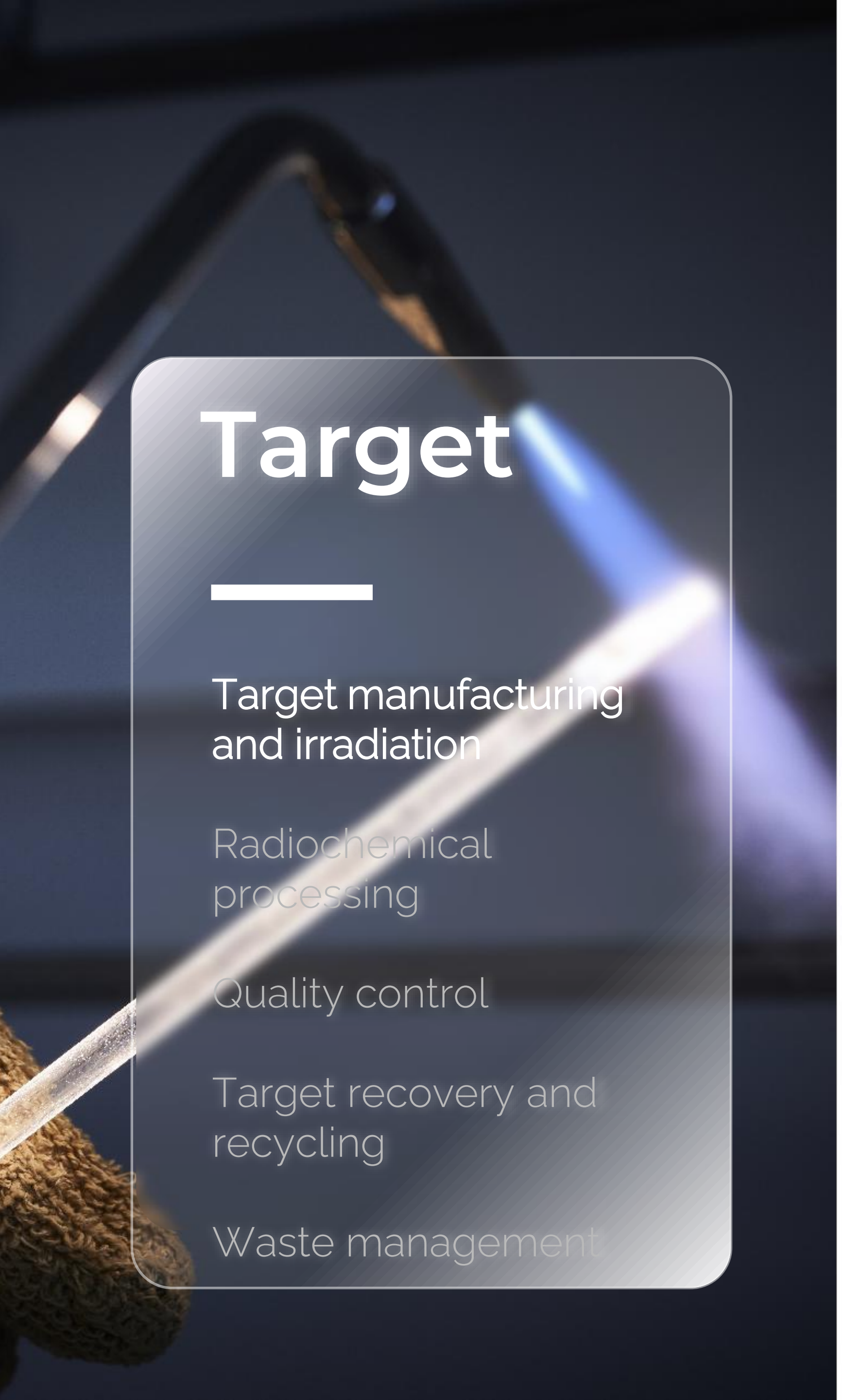


Target preparation

Target matrix should be suitable for neutron activation

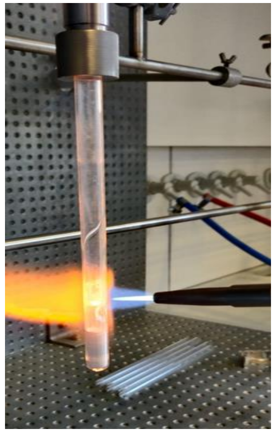
→ **Radiolanthanides**: typically Ln_2O_3 target material sealed in a quartz glass ampoule (1 mm wall thickness) in cold welded aluminium irradiation can

$Ln(NO_3)\cdot xH_2O$		Ln_2O_3	
More time-consuming target preparation	☹	Simple target preparation	☺
Easy to dissolve for chemical separation	☺	More challenging to dissolve	😐
Hygroscopic nature	☹	Not hygroscopic	☺
Low thermal stability, increased risk of ampoule failure	☹	High thermal stability, enhancing target stability	☺
Lower density = lower loading capacity	☹	Higher density = higher loading capacity	☺

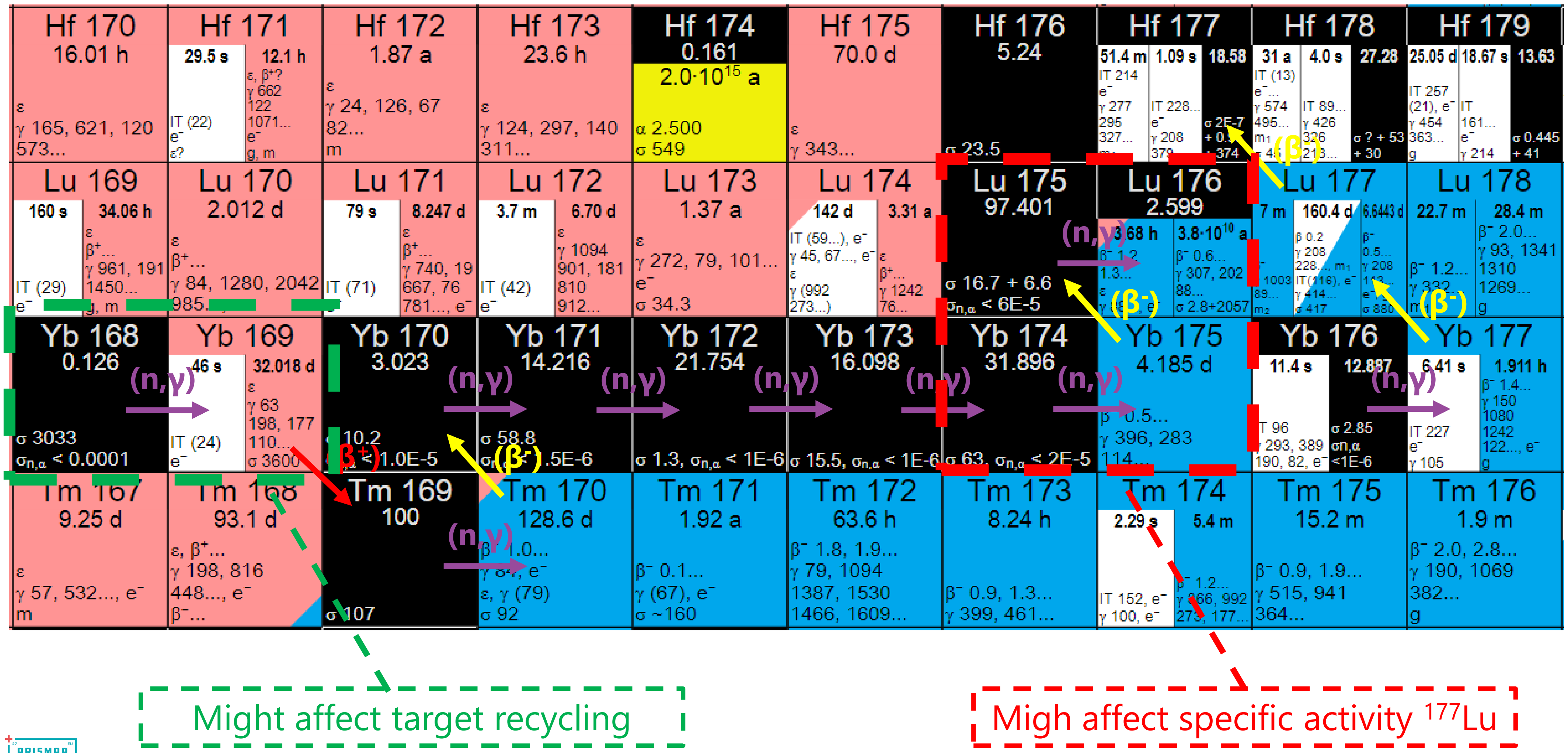


Target preparation

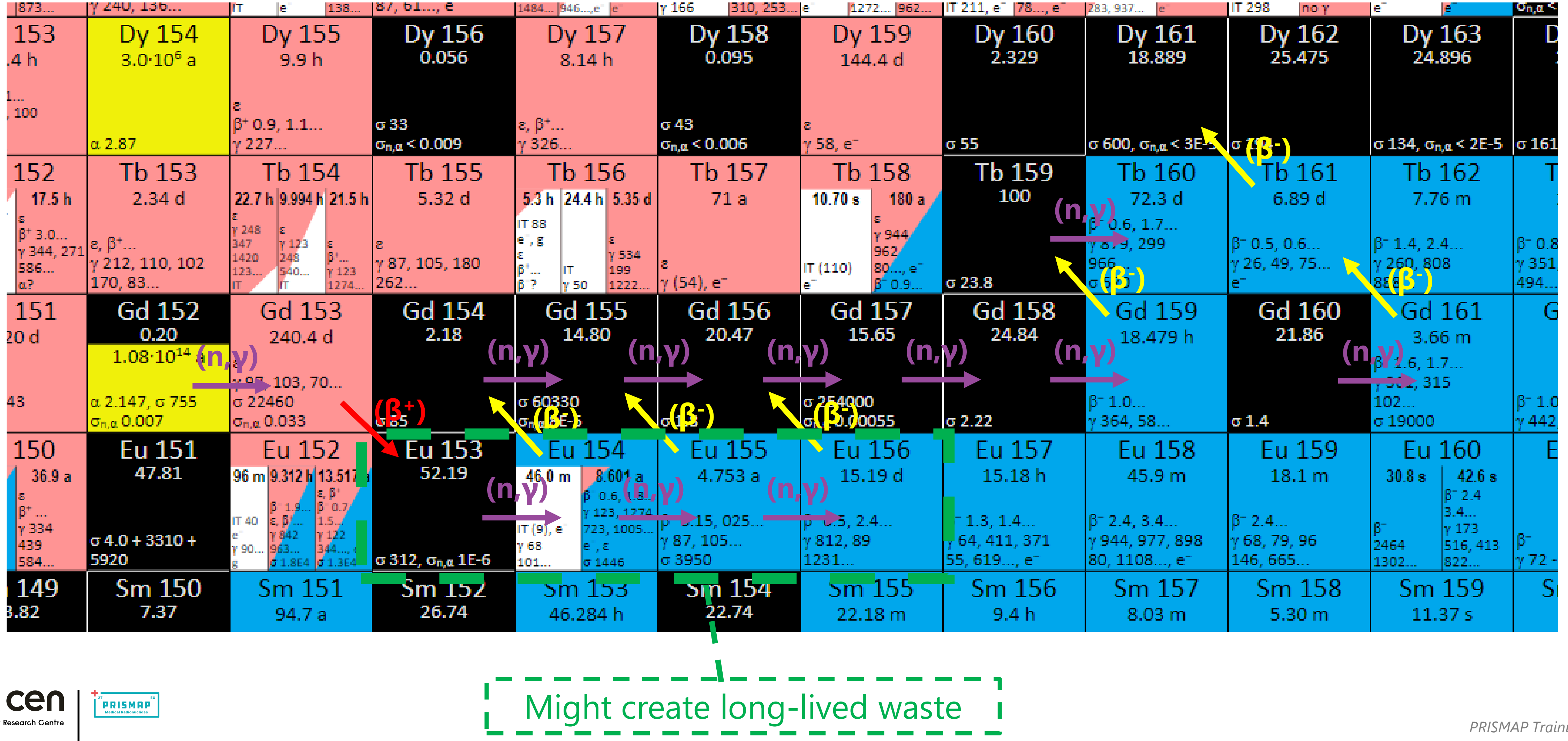
- Target matrix should be suitable for neutron activation
  - → **Radiolanthanides**: typically Ln_2O_3 target material sealed in a quartz glass ampoule (1 mm wall thickness) in cold welded aluminium irradiation can
  - → Metal compounds (e.g. ^{186}W rings, ^{176}Yb in SHINE process)
- Ampoule size limited to dimensions of aluminium irradiation can
  - → Relatively uniform, but small variations between different research reactors

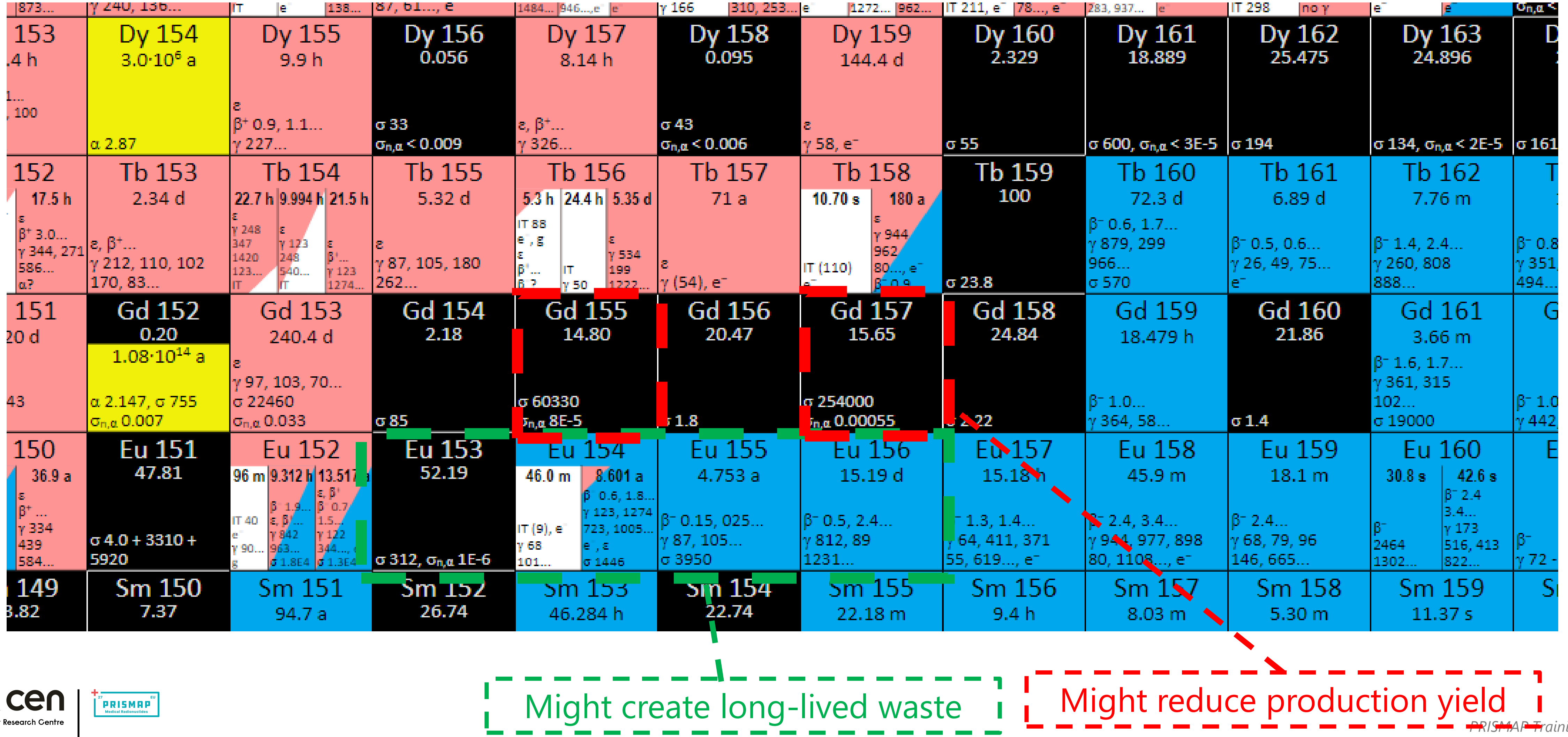
^{177}Lu production – Target quality



^{161}Tb production – Target quality

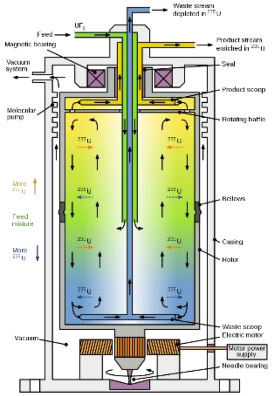


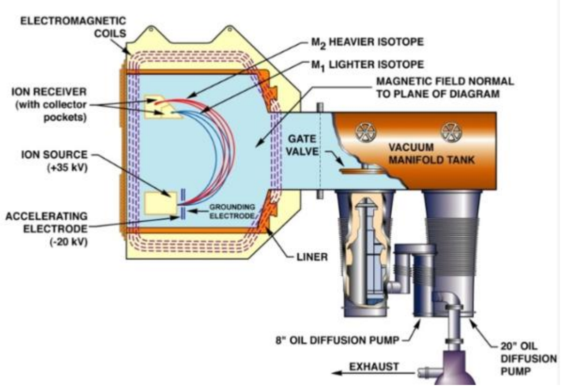
^{161}Tb production – Target quality



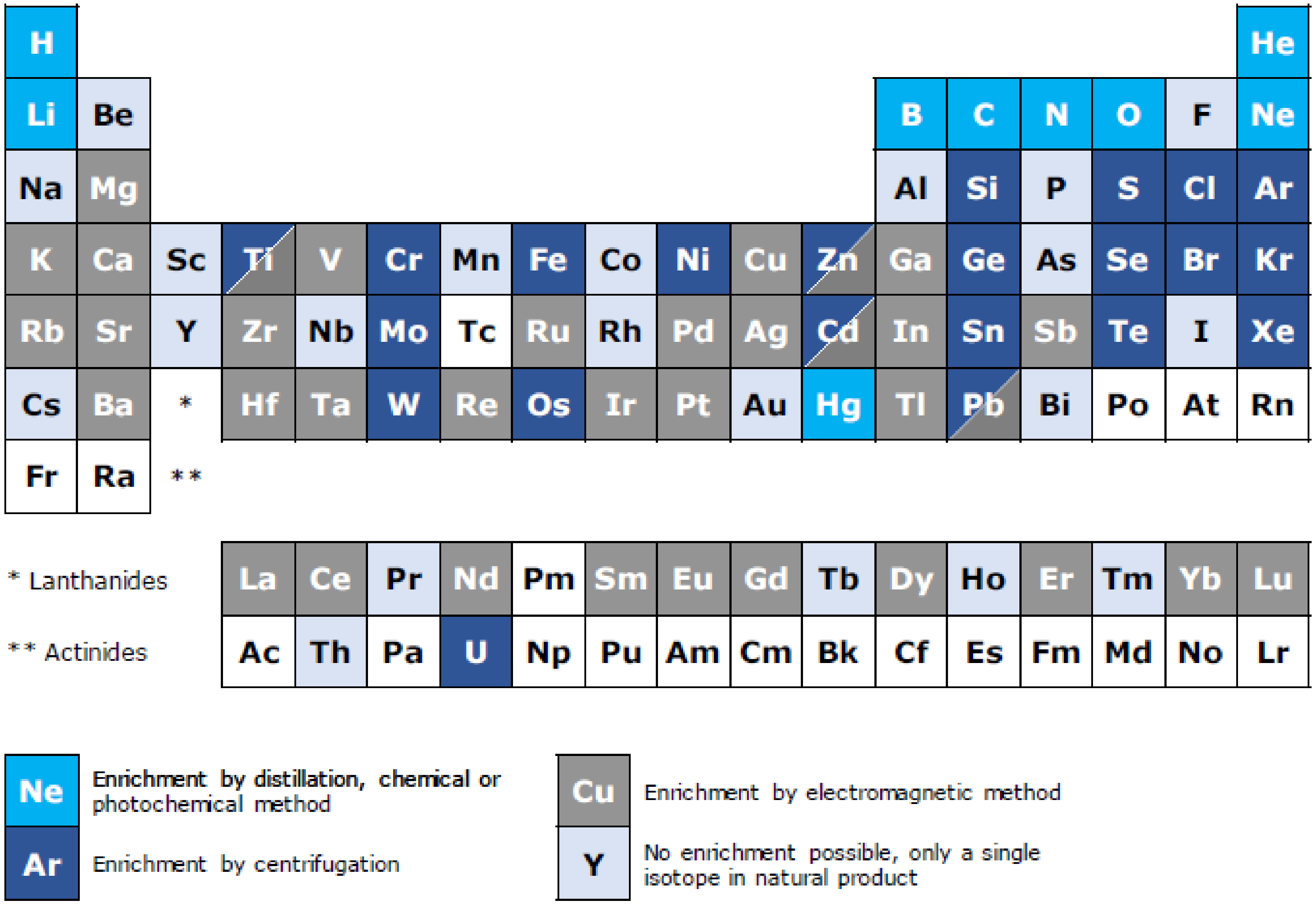
Stable isotope enrichment

- High radionuclidic purity and specific activity required
  → (Highly) enriched isotopes needed
- Enrichment techniques
  - **Distillation** – only works effectifiely when large relative mass differences between different isotopes of an element → light isotopes
  - **Gaseous centrifugation** – only works when gaseous compound of the element exists. Most cost-efficient for enrichment of elements too heavy for distillation
  - **Electromagnetic isotope separator (EMIS)** – magnetic and electronic forces separate charged isotopic species. More costly to operate and smaller production quantities

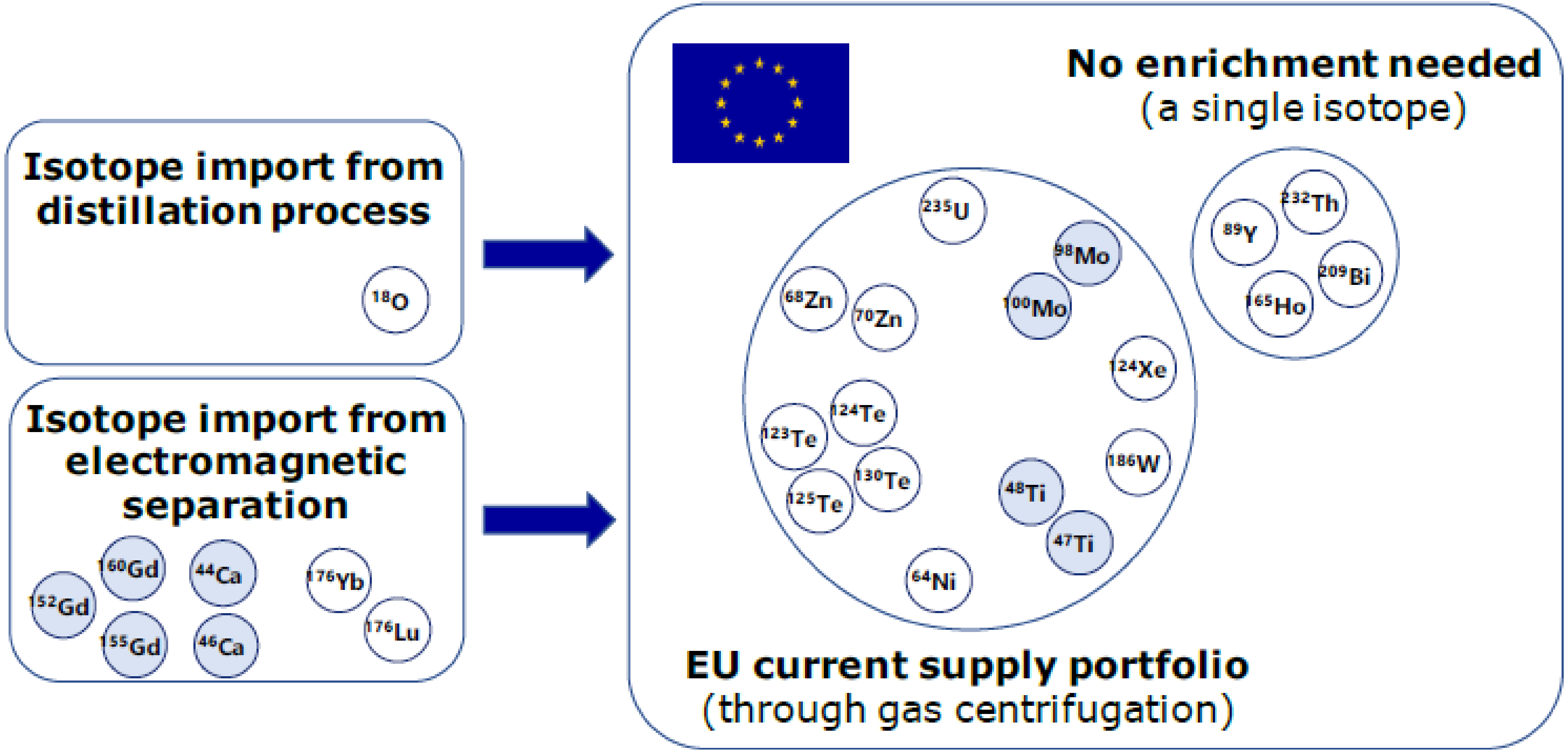


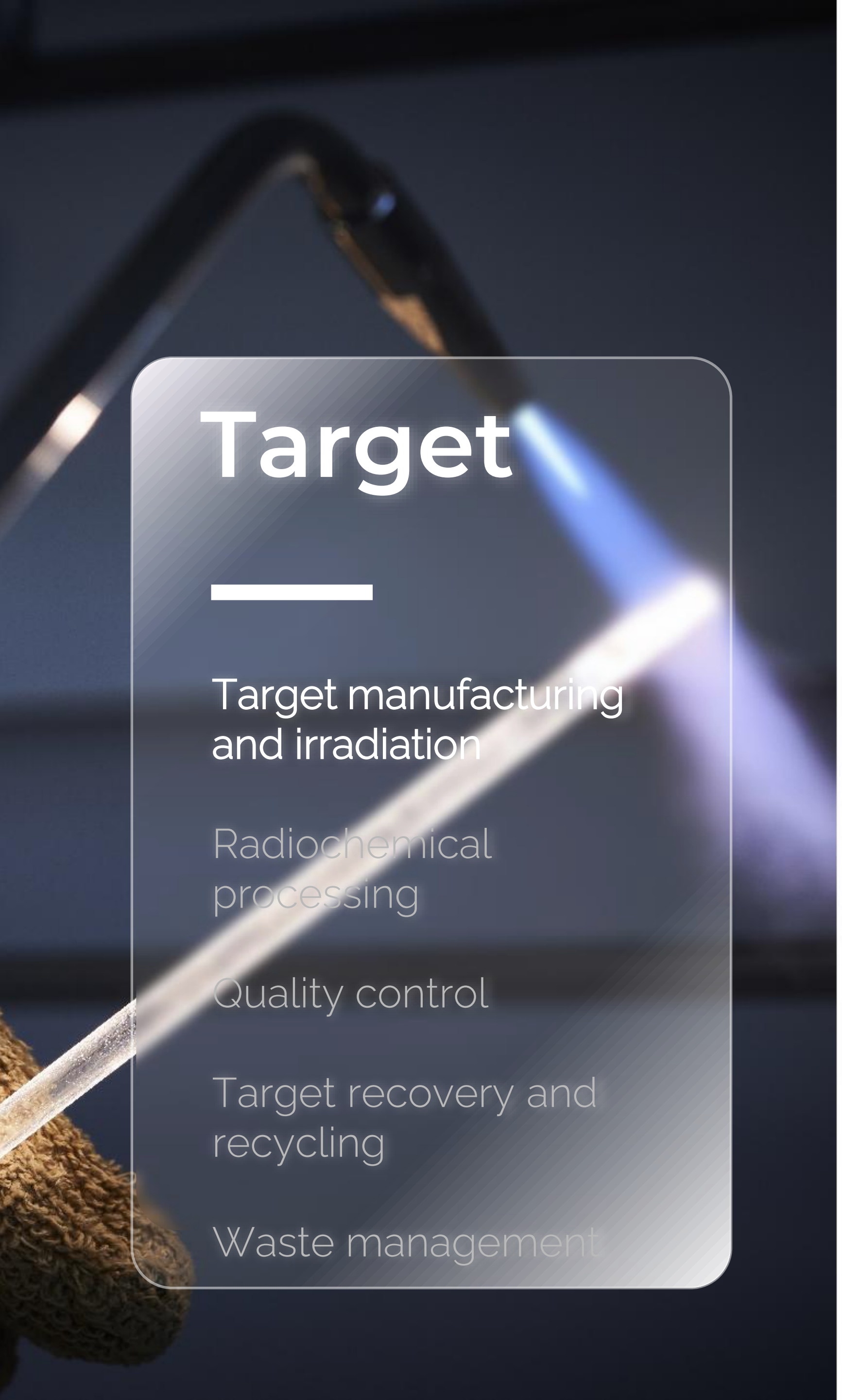


Stable isotope enrichment



Stable isotope enrichment





Target material scarcity

Scarcity of highly enriched target material

- High enrichment factor and high chemical purity needed
- Very high dependency on Russian calutrons (WWII era technology)

→ Can separate almost every stable isotope, but costly to operate and relatively small quantities only

→ Market dominated by Russia

→ Situation is slowly changing – but new initiatives are expensive and time-consuming

→ Most initiatives focused on ^{176}Yb supply for ^{177}Lu production

Source: Co-ordinated Approach to the Development and Supply of Radionuclides in the EU - N°ENER/D3/2019-231 - Final Report

Neutron activation

Target manufacturing and irradiation

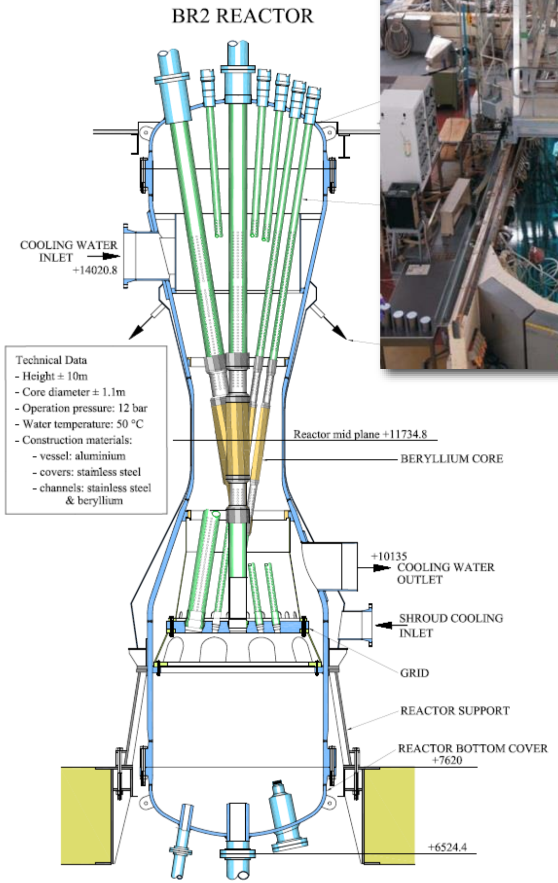
Radiochemical processing

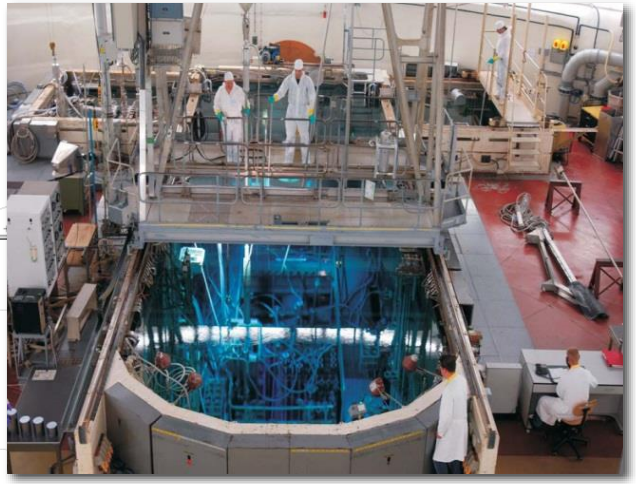
Quality control

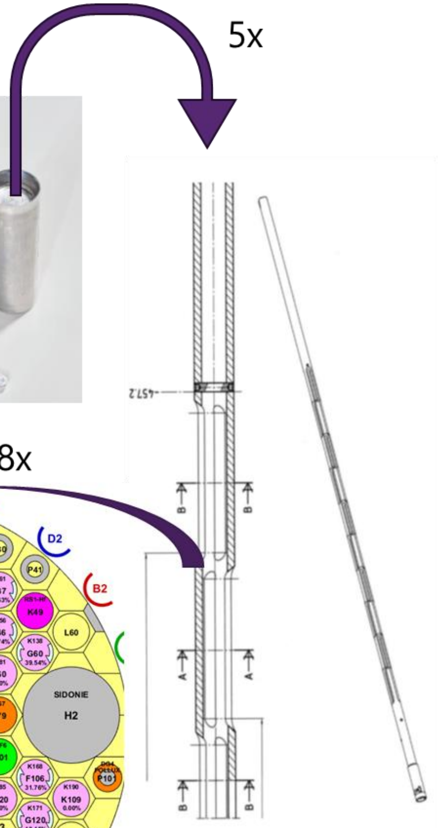
Target recovery and recycling

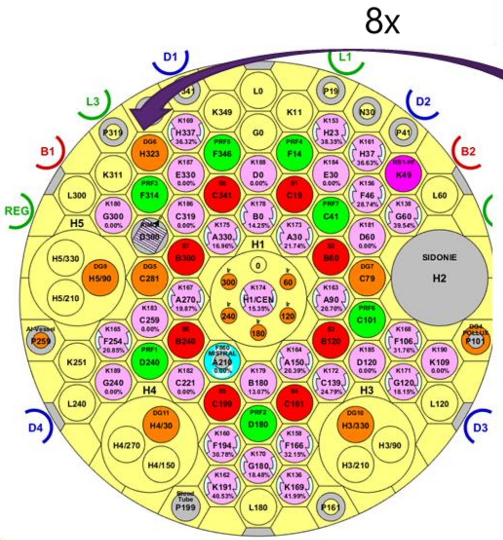
Waste management

xxxXx → Target → **Irradiation** → Separation / Target Recycling → Quality control → Sales Distribution → yyyYy









Neutron activation

Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management

^{xxx}Xx → Target → **Irradiation** → Separation / Target Recycling → Quality control → Sales Distribution → ^{yyy}Yy

Transfer of irradiated targets to hotcell for decanning

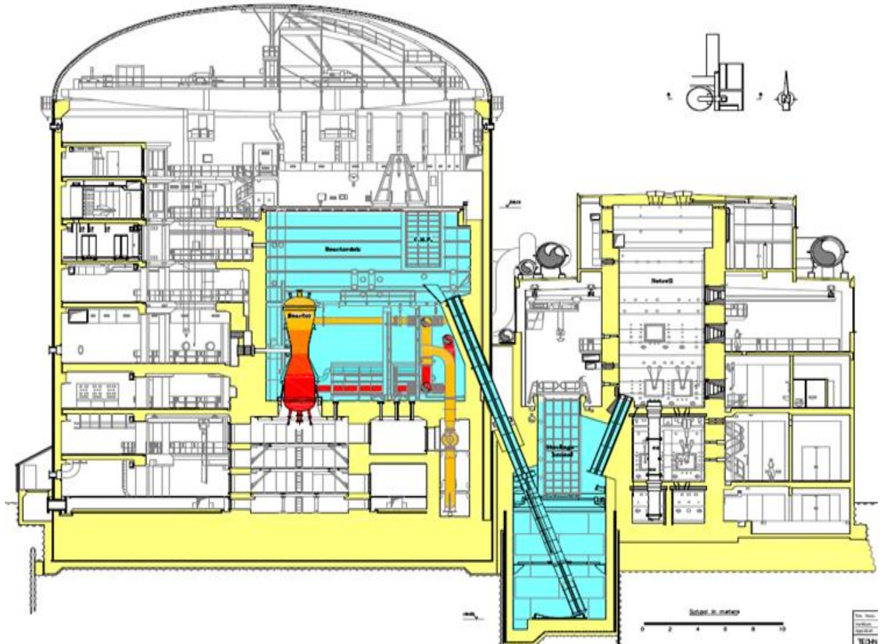
→ Cooling of irradiated targets → *decay of short-lived radio-contaminants*

→ Opening of aluminium irradiation can

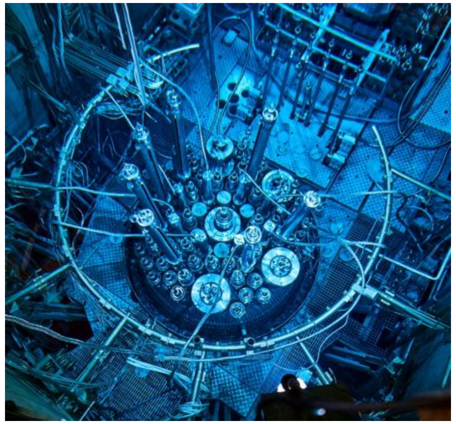
→ Preparation for shipment in dedicated transport containers

Type A (≤700 GBq ^{177}Lu)

Type B (>700 GBq ^{177}Lu)

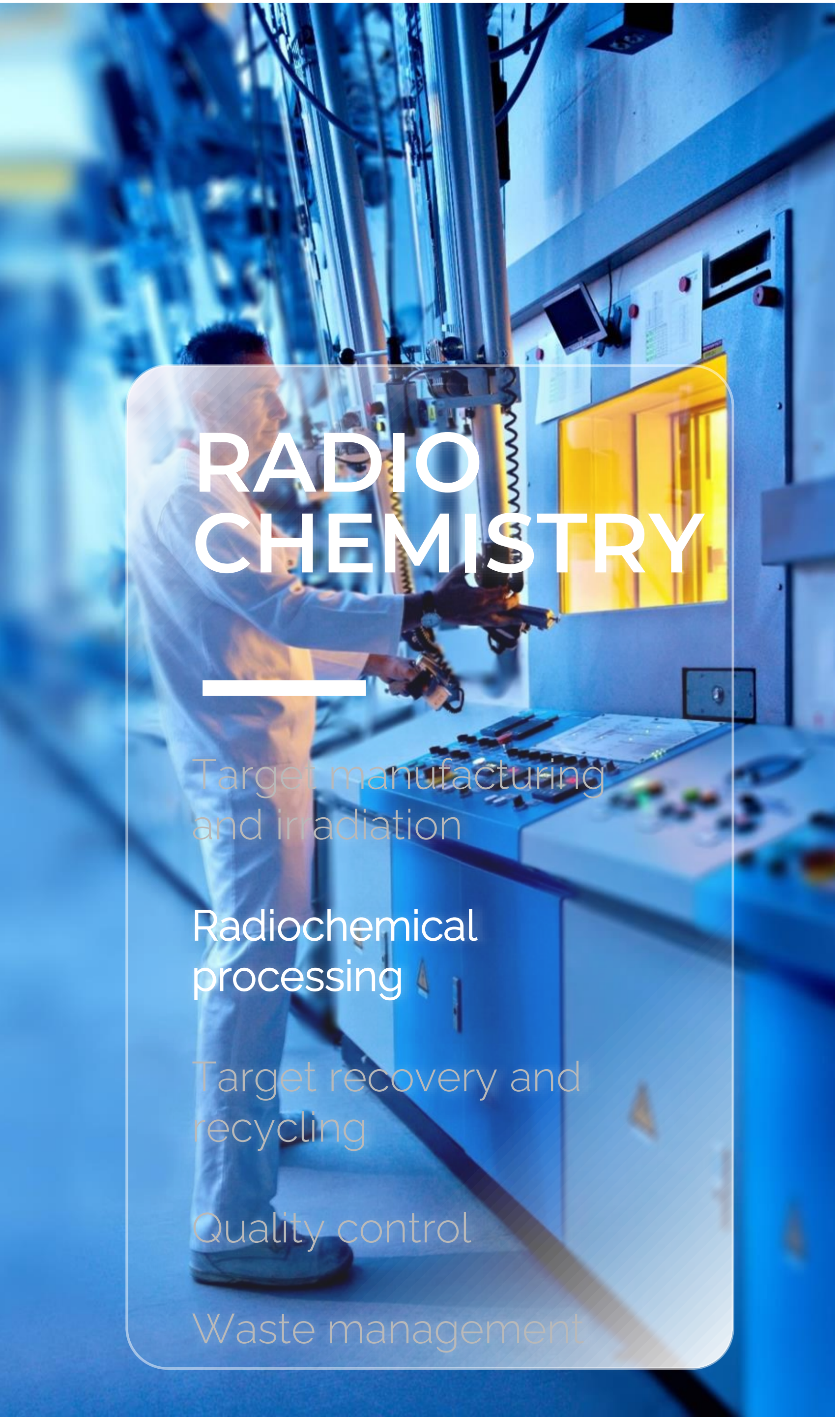


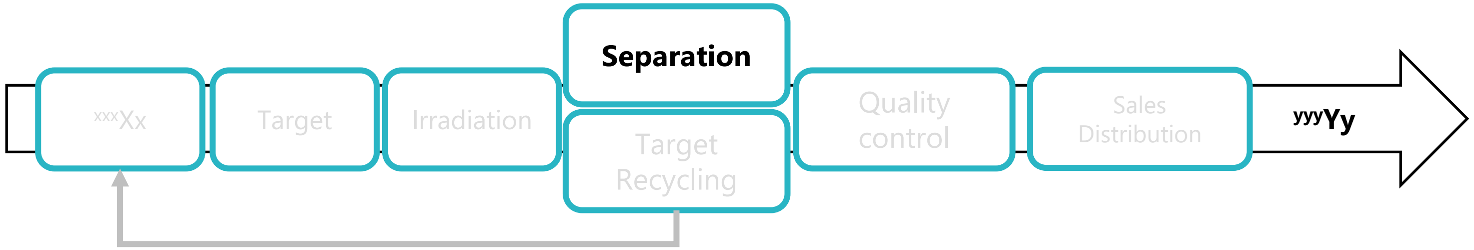
Transport of activated target material



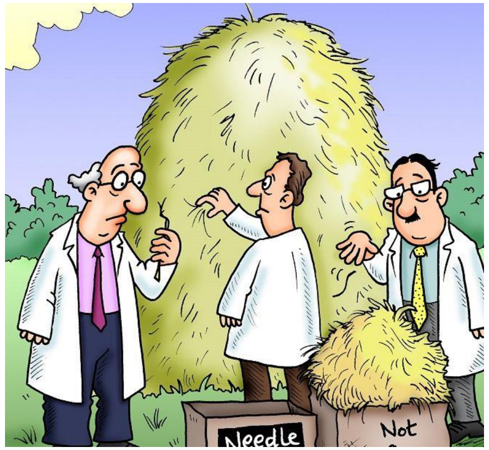
Reactor

Radiochemical processing facility





- Isolate radionuclide from target matrix
- Develop efficient separation methods, guaranteeing
  - High quality end-product
  - High target recovery and regeneration
  - Appropriate waste management
- Easy scale-up and cost-efficient
  - MBq scale → GBq scale
  - GBq scale → TBq scale
  - Simple, robust and fast
  - Automated and remote-controlled
  - Insensitive to target contaminants
  - GMP compliant



Lu:Yb ratio 1:10^4-10^6

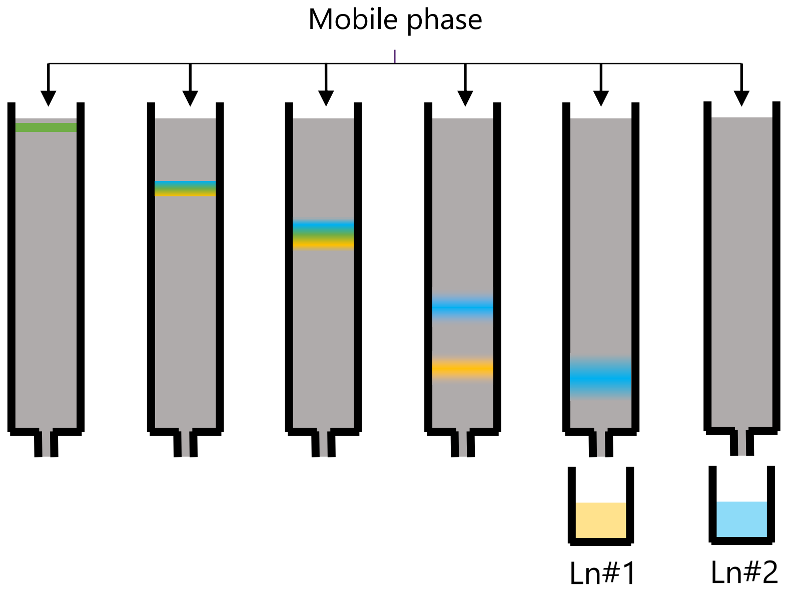
Lanthanides – Separation strategies

Small difference in affinity for coordinating ligands

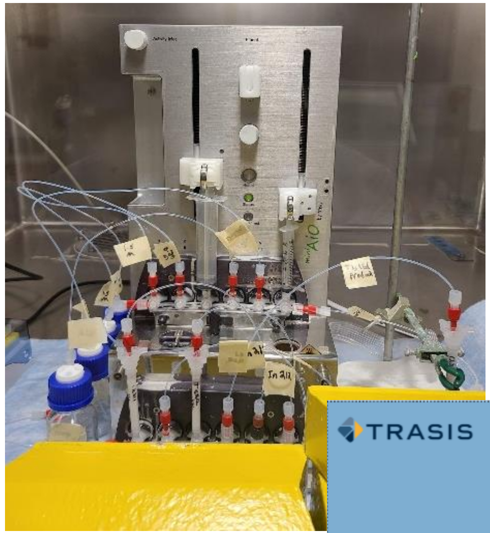
- Extraction chromatography
  - Extractant physically impregnated onto solid support
  - Heavier lanthanide binds stronger to extractant
  - Lighter lanthanide elutes first
- Strong cation exchange
  - Functional groups resin (usually SO_3^-)
  - Chelating ligand in mobile phase
  - Heavier lanthanide binds stronger to chelating ligand
  - Heavier lanthanide elutes first

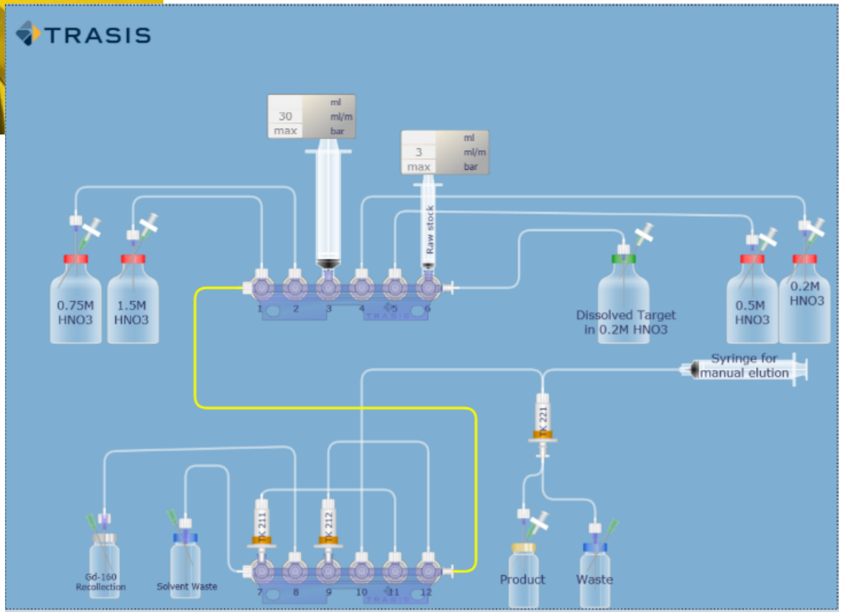
⇒ **Obtain high-purity fractions**

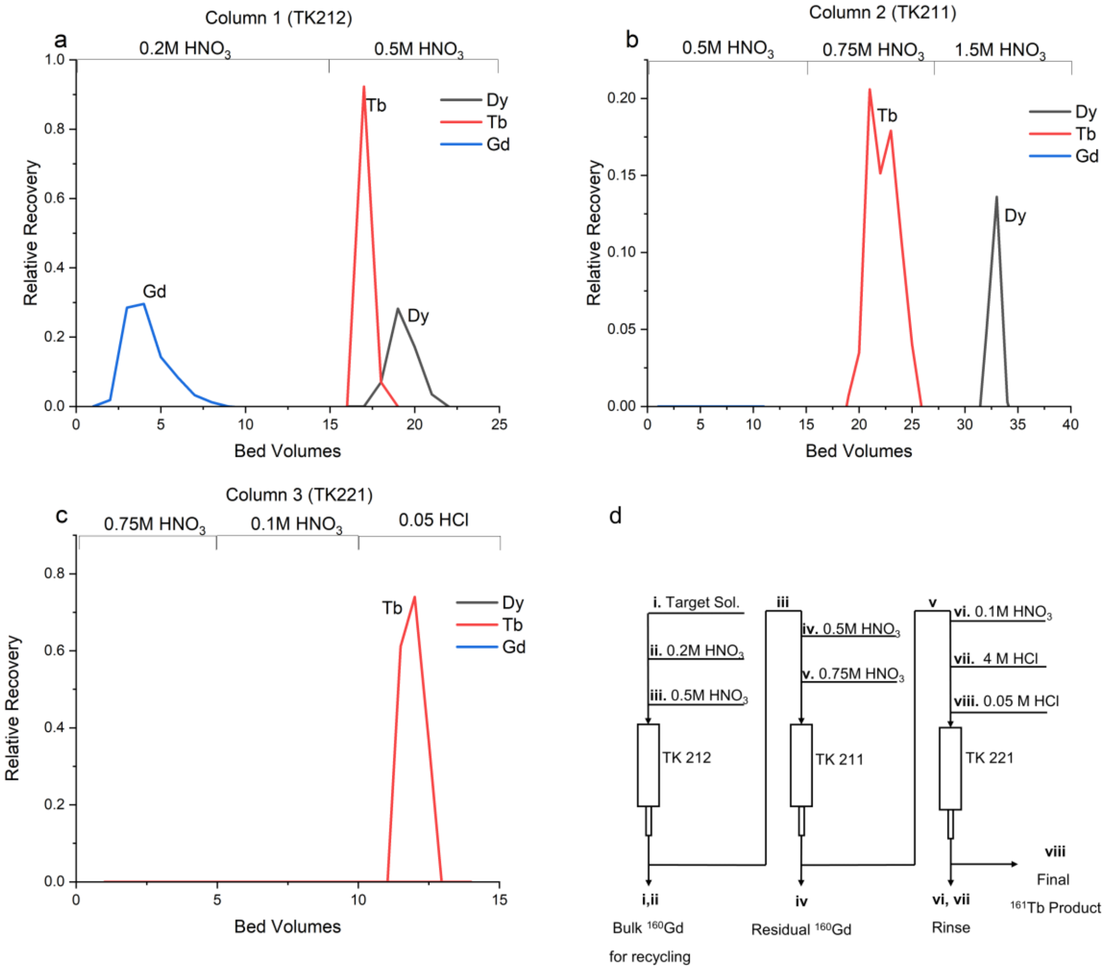
⇒ **Separate micro amounts for macro amounts**



Extraction chromatography method







S. McNeil et al., EJNMMI Radiopharm. and Chem., 2022

Strong cation exchange method

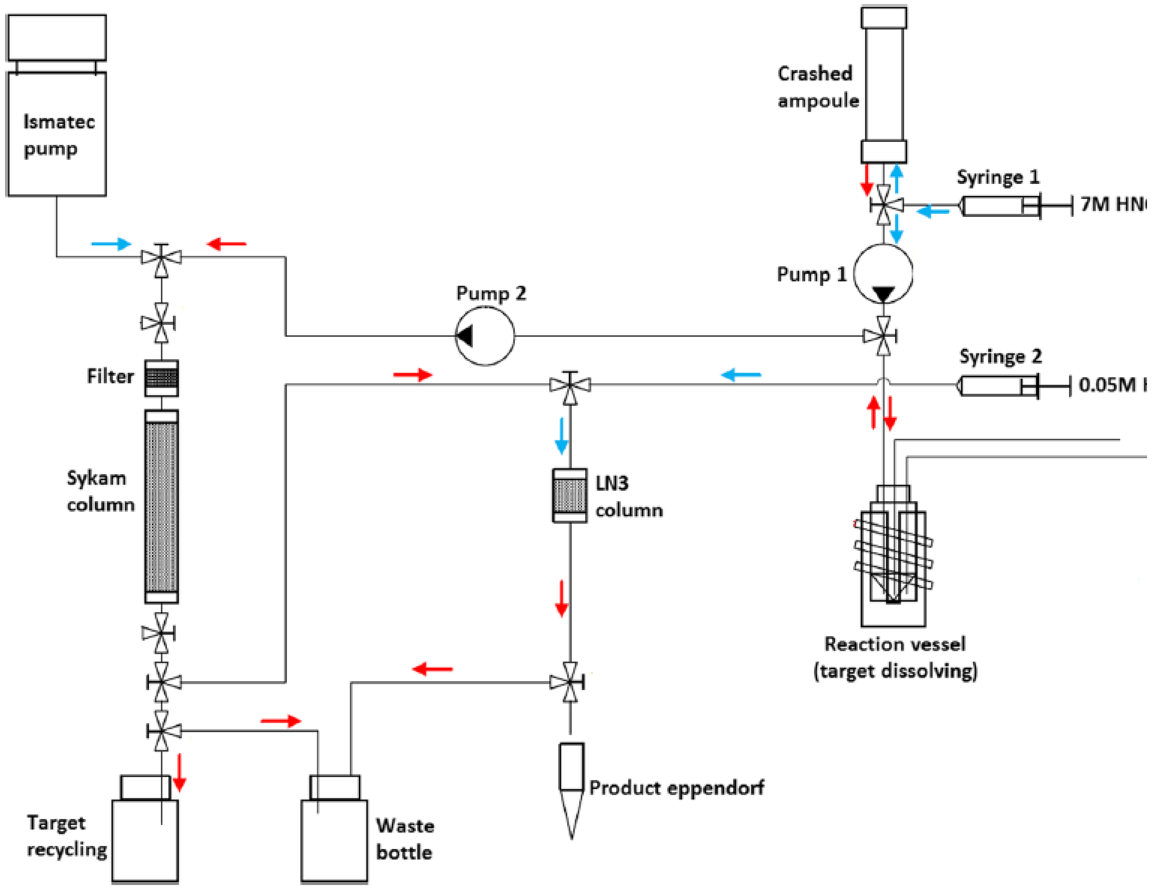


Fig. 2 Schematic diagram of the ^{161}Tb chemical separation system

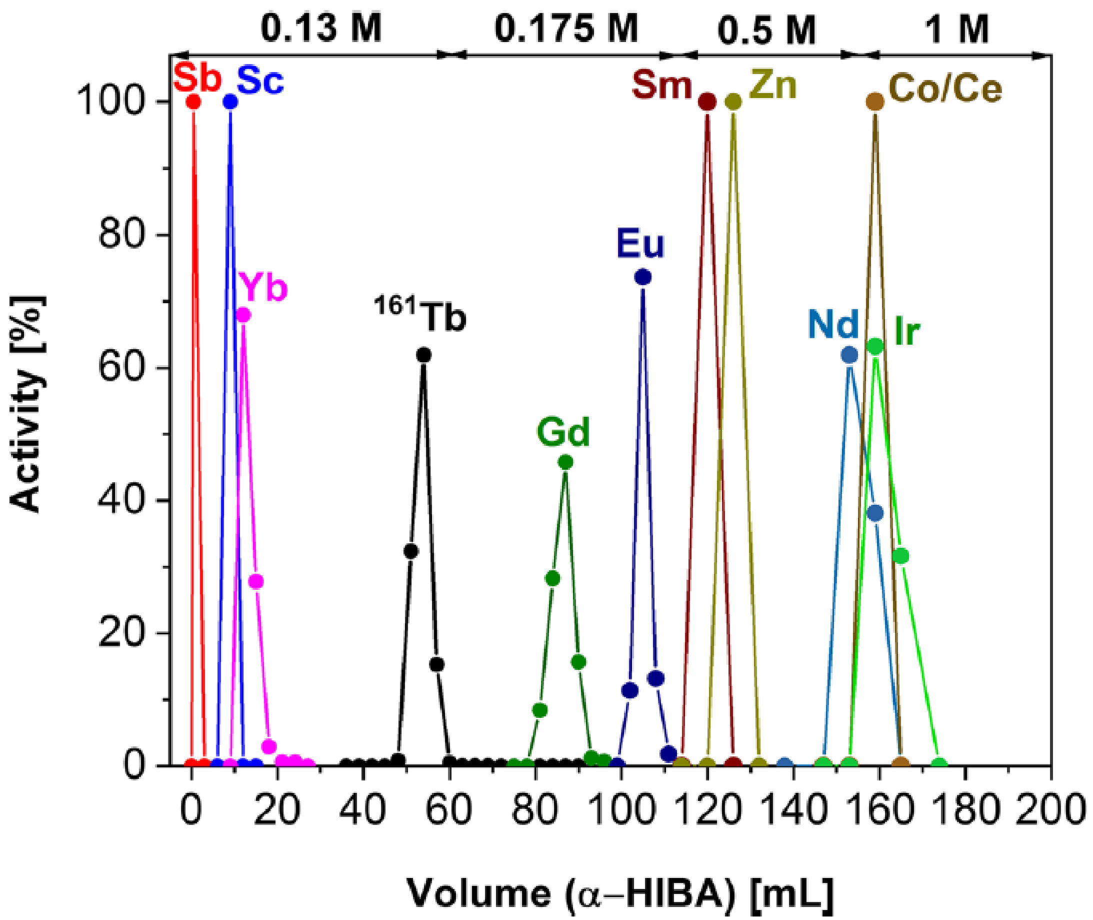
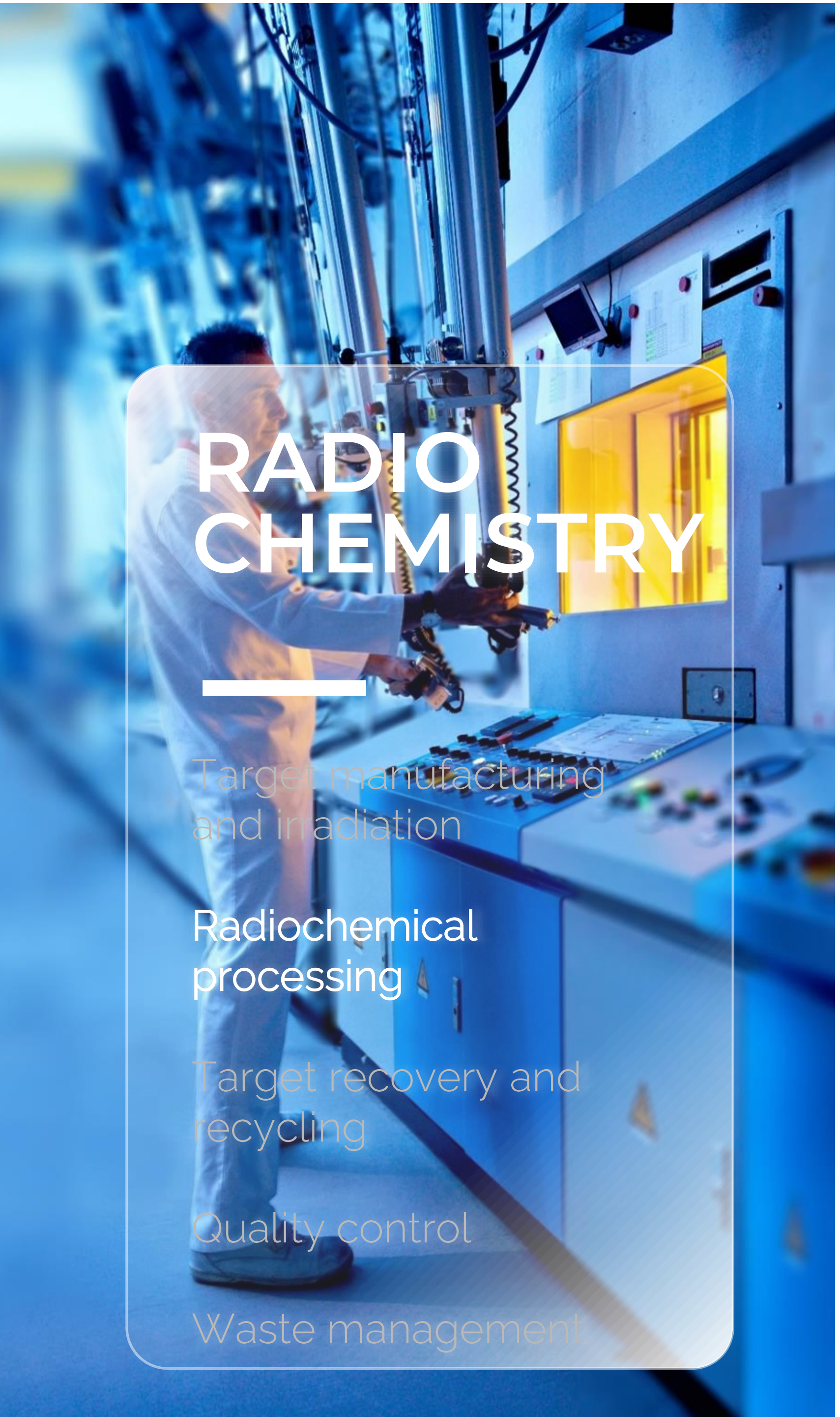
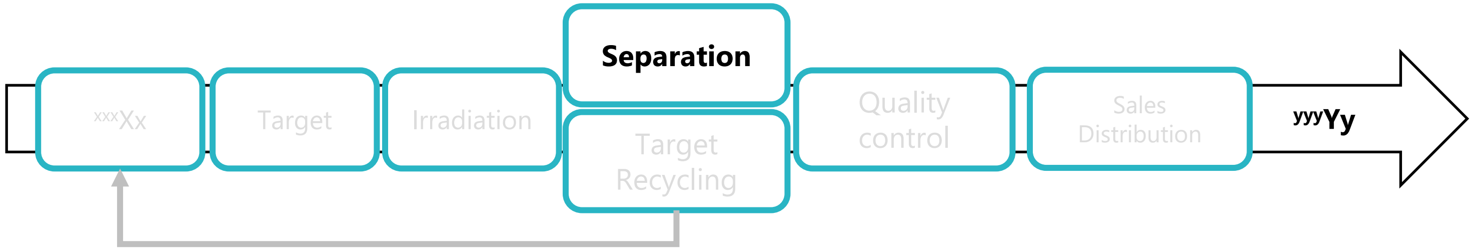


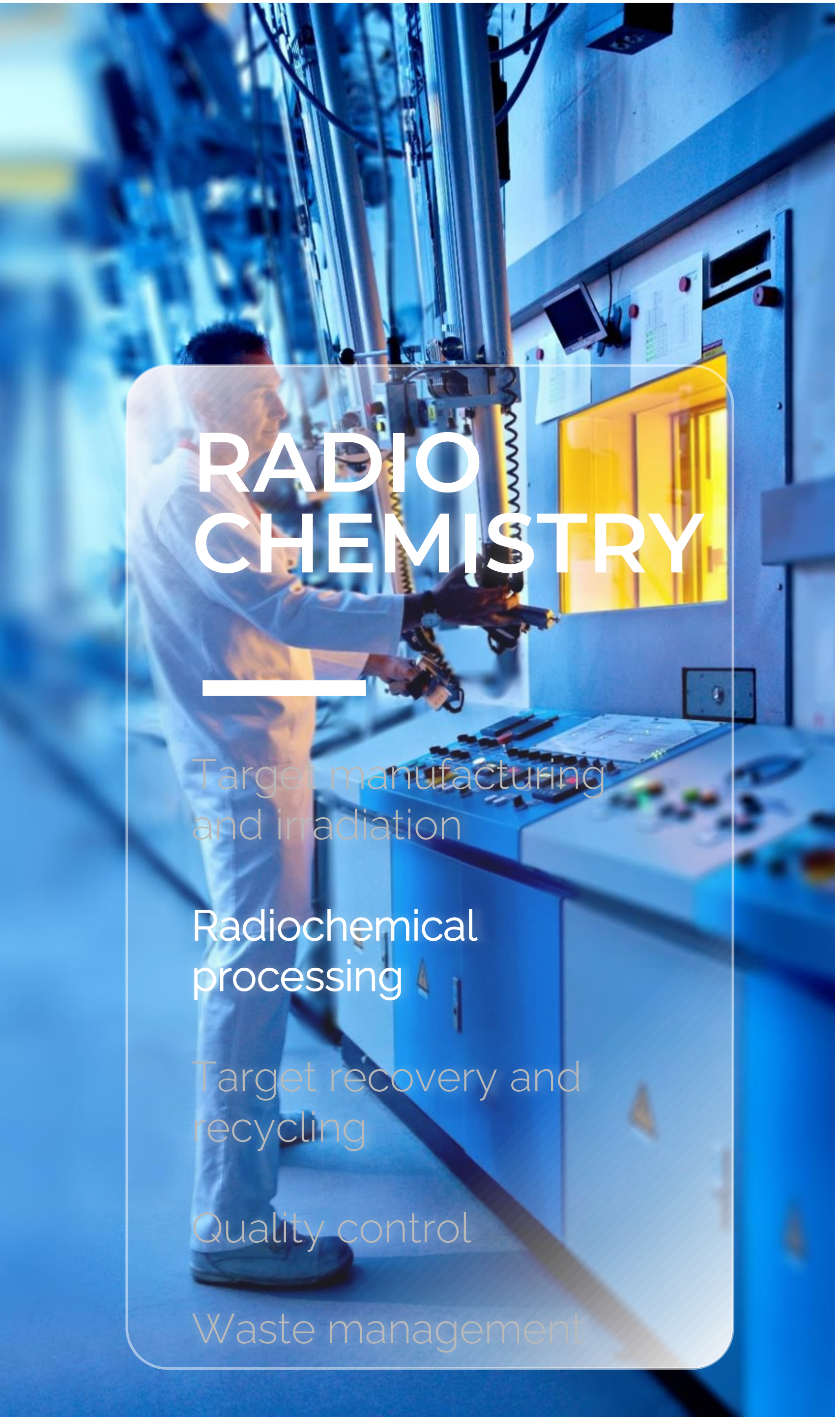
Fig. 1 Elution profile of ^{161}Tb separation from the irradiated target material and side products (10 mm × 170 mm Sykam resin column, 8 mg $^{160}Gd_2O_3$, 0.6 mL/min eluent flow rate)

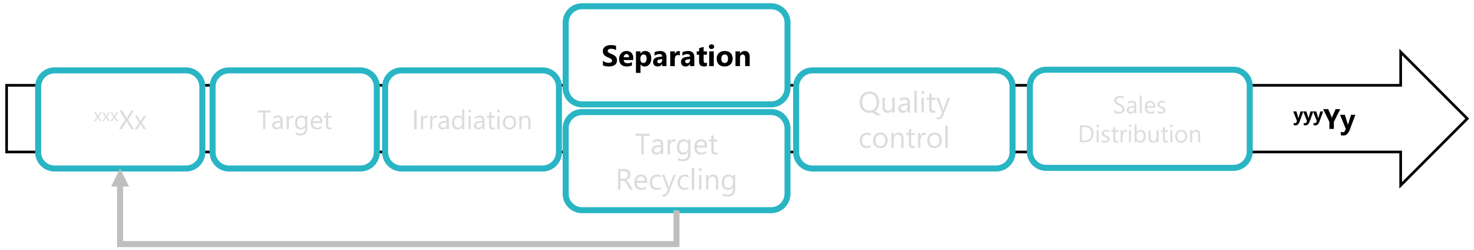




Production environment – typically hot cells in a clean room facility

- Lead shielded hot cells
- Processes (fully) automated
- Hot cells equipped with telemanipulators for remote handling

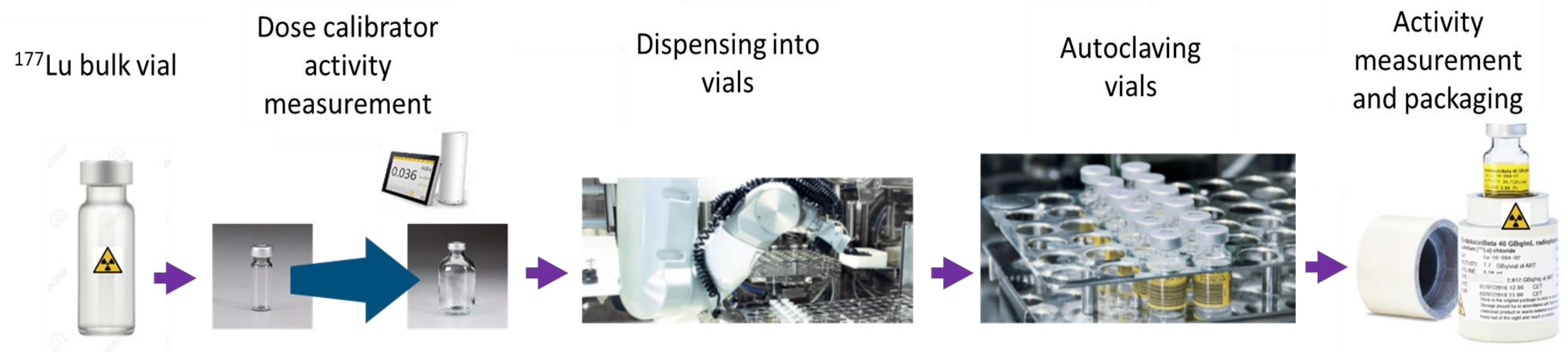


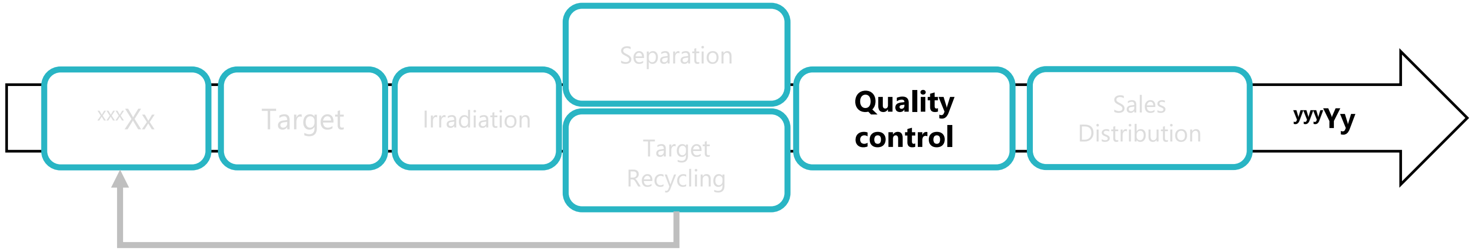


Production environment – typically hot cells in a clean room facility

- Lead shielded hot cells
- Processes (fully) automated
- Hot cells equipped with telemanipulators for remote handling

- Dispensing and sterilization
- Packaging





- High quality product – Tested according to Eur. Phar. guidelines
- Needed to guarantee product quality for medical use
  - Radionuclidic purity *(gamma spectrometry)*
  - Chemical purity *(ICP-MS/ICP-OES)*
  - Radiochemical purity *(radio-TLC)*
  - Activity concentration *(dose calibrator)*
  - Specific activity *(dose calibrator + ICP-MS/ICP-OES)*
  - Radiolabeling (apparent molar activity) *(radio-TLC)*
  - Biocompatible (endotoxin + sterility)
- Certificate of analysis

Quality control

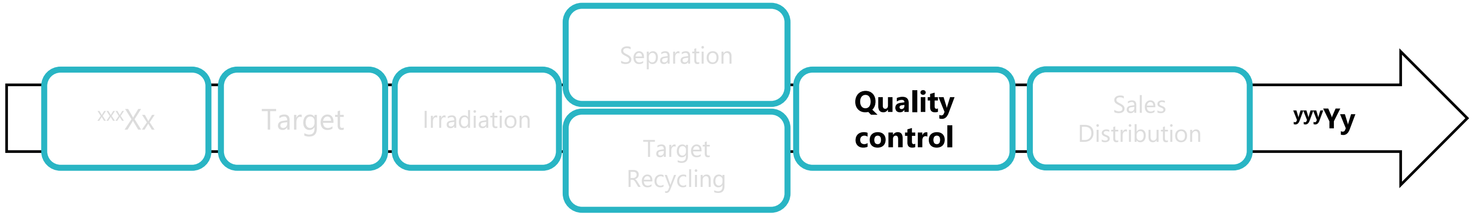
Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management



Certificate of Analysis

EndolucinBeta 40 GBq/ml Radiopharmaceutical precursor solution

Lot No.:	Lu-22-346-01	**Time of Manufacturing [CET]:**	13.06.2022 11:00
Serial No.:	11103081-0-0		
Customer:	SCK-CEN		
Activity [GBq]:	9.3	**ART [CET]:**	20.06.2022 12:00
Volume [µl]:	238	**Expiry Date [CET]:**	22.06.2022 11:00
Chemical Form:	Lu (3+) in aqueous 0.04 M HCl solution		
Packaging:	2 ml type I glass vial, closed with fluorotec coated bromobutyl septum and center hole crimp cap		

Test	Specification	Unit	Result
Activity per Vial [1]	90 - 110 of the activity stated on the label	%	complies
Radioactivity Concentration [1] (Dose Calibrator)	36 - 44	GBq/ml	39
Appearance	Clear and colorless solution	n.a.	complies
Identity Lu-177 (Gamma spectrometry)	113 keV gamma line existing 208 keV gamma line existing	n.a.	complies
Identity Chloride (Ph. Eur.)	White precipitate visible	n.a.	complies
pH value (pH indicator strips)	1 - 2	n.a.	complies
Specific Activity (ICP-MS) [2]	≥ 3000	GBq/mg	3020
Chemical Purity (ICP-MS) corrected to Lu-177 activity at EOS	Fe ≤ 0.25 Cu ≤ 0.5 Zn ≤ 0.5 Pb ≤ 0.5 Yb-176 ≤ 0.14 Sum of impurities ≤ 0.5	µg/GBq µg/GBq µg/GBq µg/GBq µg/GBq µg/GBq	<0.01 <0.1 <0.1 <0.1 <0.01 <0.1
Radionuclidic Purity [3] (Gamma spectrometry) corrected to Lu-177 activity at EOS	Yb-175 ≤ 0.01 Sum of other impurities ≤ 0.01	% %	<0.01 <0.01
Radiochemical Purity (TLC)	≥ 99.0 as 177LuCl3	%	100.0
Radiolabeling Yield (TLC) based on radiolabeling with Lu-177 of DOTA-derivate, molar ratio 1:4	≥ 99.0	%	99.9
Bacterial Endotoxins (Ph. Eur.)	≤ 20	EU/ml	<2
Sterility (Ph. Eur.)	Sterile	n.a.	Sample taken

1 Result taken from In-Process Control, value decay-corrected to ART
2 Result taken from Release / Retest of API, value decay-corrected to ART
3 Result taken from Release / Retest of API, value decay-corrected to EOS

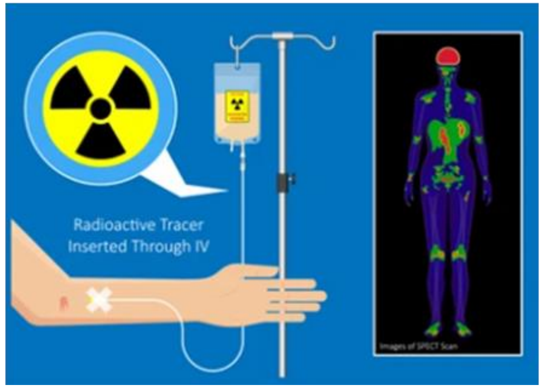
ART: Activity reference time
EOS: End of shelf life
** OOS Result

This batch complies with the specification.

Transport of purified radionuclide

Radiochemical processing facility

Radiopharmaceutical company



Hospital

Target recycling

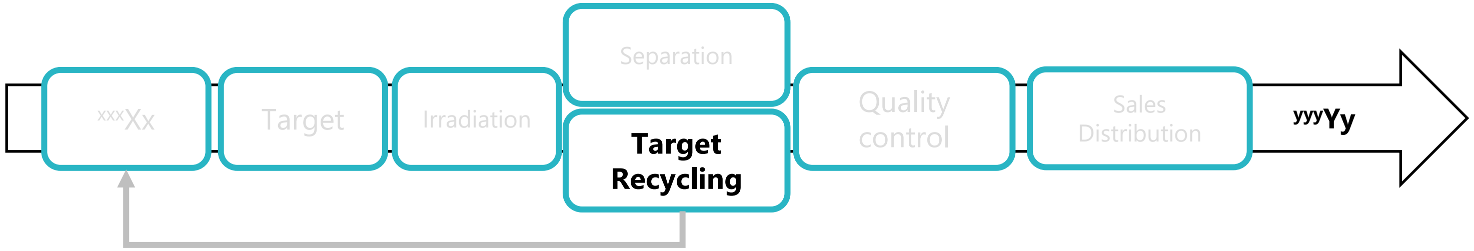
Target manufacturing and irradiation

Radio-chemical processing

Quality control

Target recovery and recycling

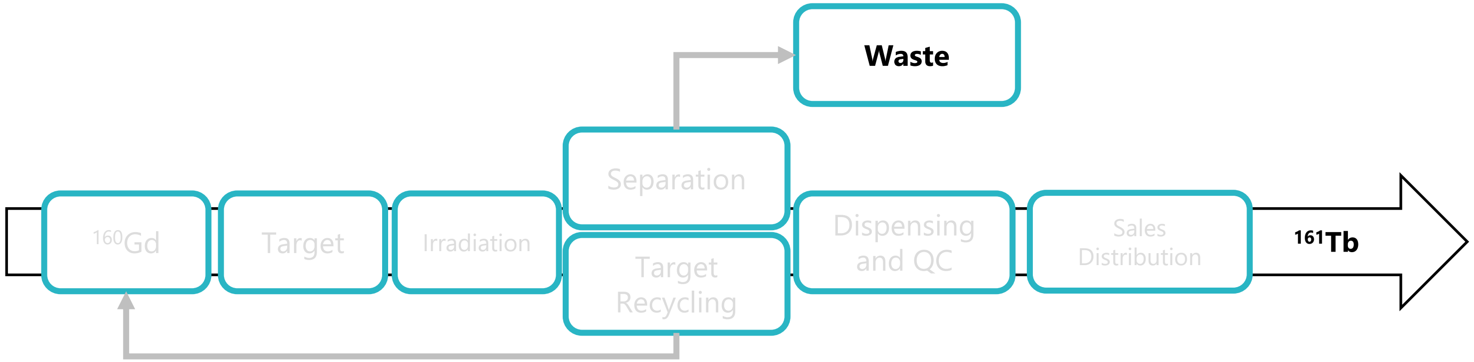
Waste management



- Target material is scarce and highly valuable
- Needs to be recovered from separation process matrix
  → Conversion to the oxide (or other suitable compound)
- Needs to be suitable for re-irradiation, i.e. safe handling by reactor operators (acceptance criteria set by reactor management)
  - Removal of long-lived radio-contaminants
  → Decay strategy
  → Reprocessing strategy
  - Proper characterization and QC

Waste management

- Target manufacturing and irradiation
- Radio-chemical processing
- Quality control
- Target recovery and recycling
- Waste management



- Identification of long-lived radio-contaminants in each fraction
  - Depends on purity of target material
- Appropriate waste collection and treatment strategies
  - Liquid waste
  - Solid waste
- Appropriate selection of materials used for irradiation (e.g. quartz quality)

→ To be considered during design of the radiochemical process and selection of appropriate target material!

Conclusions

- High thermal neutron fluxes are required for efficient production of radionuclides
- Two major production pathways
  - $^{235}U(n,f)$ → Major production route for $^{99}Mo/^{99m}Tc$
  - Neutron activation → Predominantly therapeutic radionuclides
- Supply chain can be complex, and is a race against time
- Simple, robust and scalable radiochemistry steps
- High target quality is key
- Both research reactors and accelerators/cyclotrons are needed for nuclear medicine

Nuclear research reactors are powerfull thermal neutron sources

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Crucial for manufacturing of medical radionuclides

27 EU

PRISMAP

Medical Radionuclides

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PRISMAP PROJECT

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