KU LEUVEN

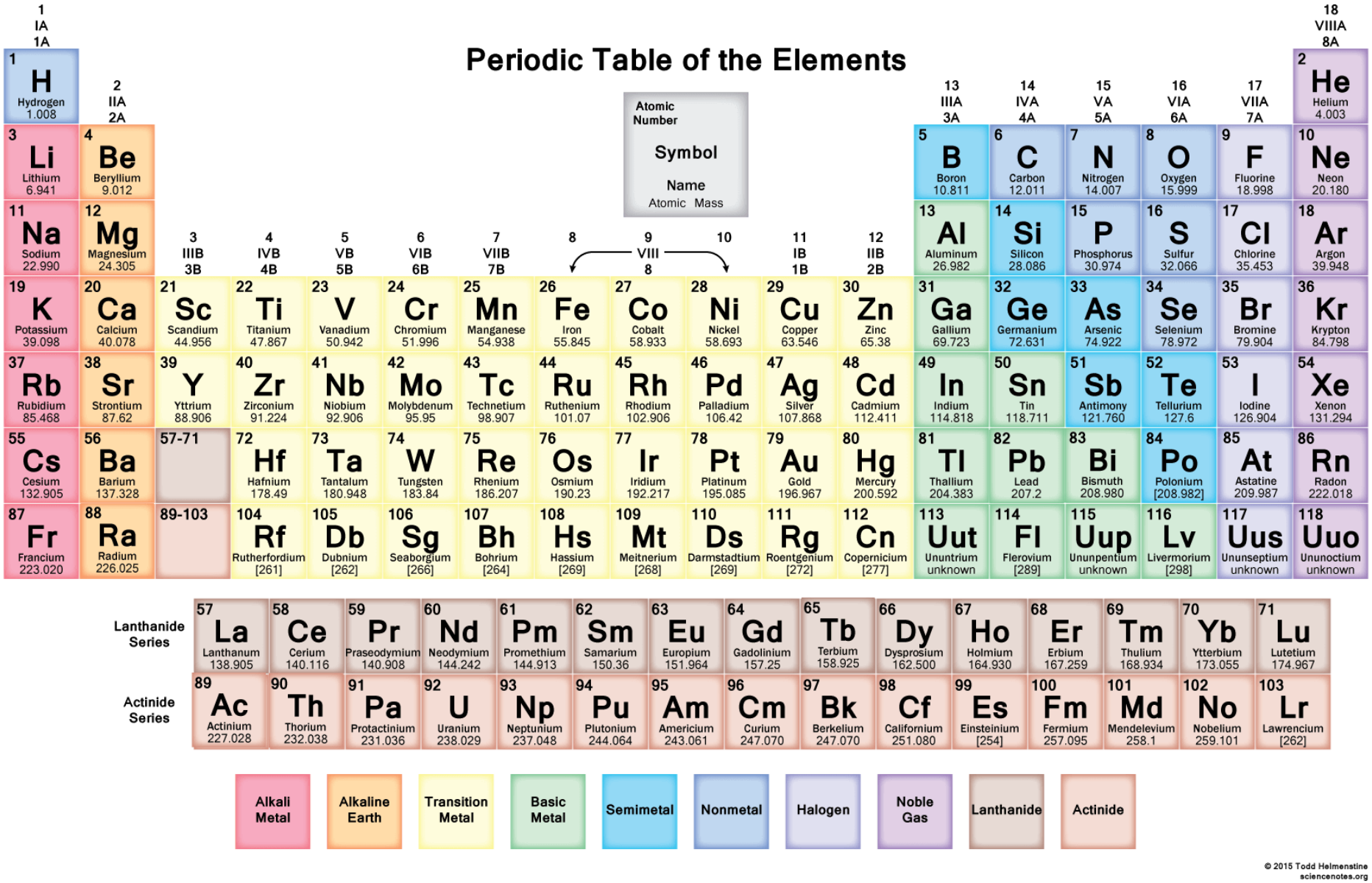
Targeted alpha therapy: when chemistry meets physics in the radiopharmacy

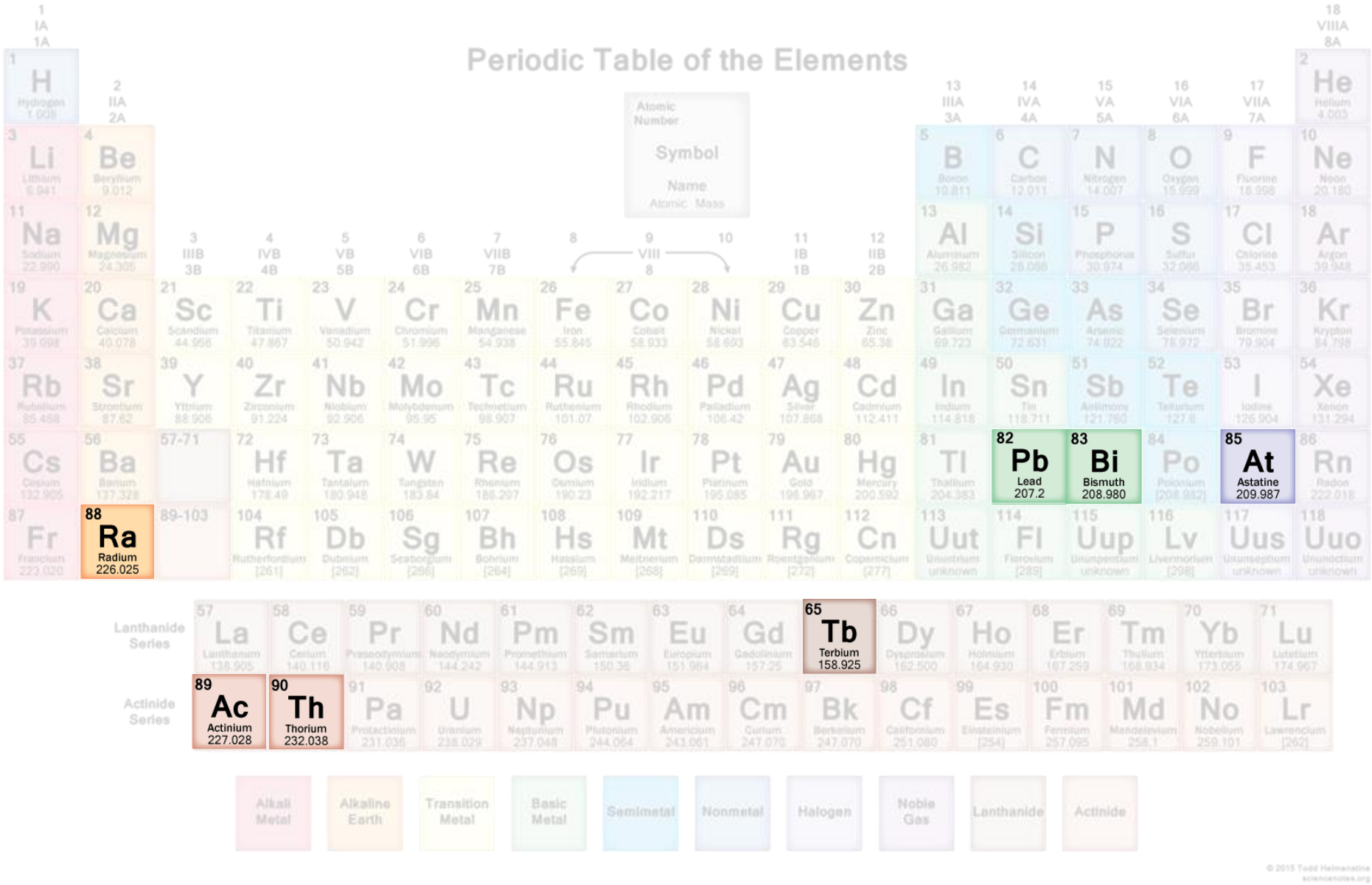
Janke Kleynhans

23 February 2024

Measurement in the Radiopharmacy

- The alpha-emitters considered
- Radioactive concentration/amount
- Radiochemical yield and purity
- Stability of radiopharmaceuticals
- Waste management
- Health physics and safety


Periodic Table of the Elements
Atomic Number
Symbol
Name
Atomic Mass
1 IA 1A
2 IIA 2A
3 IIIB 3B
4 IVB 4B
5 VB 5B
6 VIB 6B
7 VIIB 7B
8 9 VIII 8 10
11 IB 1B
12 IIB 2B
13 IIIA 3A
14 IVA 4A
15 VA 5A
16 VIA 6A
17 VIIA 7A
18 VIIIA 8A
1 H Hydrogen 1.008
2 He Helium 4.003
3 Li Lithium 6.941
4 Be Beryllium 9.012
5 B Boron 10.811
6 C Carbon 12.011
7 N Nitrogen 14.007
8 O Oxygen 15.999
9 F Fluorine 18.998
10 Ne Neon 20.180
11 Na Sodium 22.990
12 Mg Magnesium 24.305
13 Al Aluminum 26.982
14 Si Silicon 28.086
15 P Phosphorus 30.974
16 S Sulfur 32.066
17 Cl Chlorine 35.453
18 Ar Argon 39.948
19 K Potassium 39.098
20 Ca Calcium 40.078
21 Sc Scandium 44.956
22 Ti Titanium 47.867
23 V Vanadium 50.942
24 Cr Chromium 51.996
25 Mn Manganese 54.938
26 Fe Iron 55.845
27 Co Cobalt 58.933
28 Ni Nickel 58.693
29 Cu Copper 63.546
30 Zn Zinc 65.38
31 Ga Gallium 69.723
32 Ge Germanium 72.631
33 As Arsenic 74.922
34 Se Selenium 78.972
35 Br Bromine 79.904
36 Kr Krypton 84.798
37 Rb Rubidium 85.468
38 Sr Strontium 87.62
39 Y Yttrium 88.906
40 Zr Zirconium 91.224
41 Nb Niobium 92.906
42 Mo Molybdenum 95.95
43 Tc Technetium 98.907
44 Ru Ruthenium 101.07
45 Rh Rhodium 102.906
46 Pd Palladium 106.42
47 Ag Silver 107.868
48 Cd Cadmium 112.411
49 In Indium 114.818
50 Sn Tin 118.711
51 Sb Antimony 121.760
52 Te Tellurium 127.6
53 I Iodine 126.904
54 Xe Xenon 131.294
55 Cs Cesium 132.905
56 Ba Barium 137.328
57-71
72 Hf Hafnium 178.49
73 Ta Tantalum 180.948
74 W Tungsten 183.84
75 Re Rhenium 186.207
76 Os Osmium 190.23
77 Ir Iridium 192.217
78 Pt Platinum 195.085
79 Au Gold 196.967
80 Hg Mercury 200.592
81 Tl Thallium 204.383
82 Pb Lead 207.2
83 Bi Bismuth 208.980
84 Po Polonium [208.982]
85 At Astatine 209.987
86 Rn Radon 222.018
87 Fr Francium 223.020
88 Ra Radius 226.025
89-103
104 Rf Rutherfordium [261]
105 Db Dubnium [262]
106 Sg Seaborgium [266]
107 Bh Bohrium [264]
108 Hs Hassium [269]
109 Mt Meitnerium [268]
110 Ds Darmstadtium [269]
111 Rg Roentgenium [272]
112 Cn Copernicium [277]
113 Uut Ununtrium unknown
114 Fl Flerovium [289]
115 Uup Ununpentium unknown
116 Lv Livermorium [298]
117 Uus Ununseptium unknown
118 Uuo Ununoctium unknown
Lanthanide Series
57 La Lanthanum 138.905
58 Ce Cerium 140.116
59 Pr Praseodymium 140.908
60 Nd Neodymium 144.242
61 Pm Promethium 144.913
62 Sm Samarium 150.36
63 Eu Europium 151.964
64 Gd Gadolinium 157.25
65 Tb Terbium 158.925
66 Dy Dysprosium 162.500
67 Ho Holmium 164.930
68 Er Erbium 167.259
69 Tm Thulium 168.934
70 Yb Ytterbium 173.055
71 Lu Lutetium 174.967
Actinide Series
89 Ac Actinium 227.028
90 Th Thorium 232.038
91 Pa Protactinium 231.036
92 U Uranium 238.029
93 Np Neptunium 237.048
94 Pu Plutonium 244.064
95 Am Americium 243.061
96 Cm Curium 247.070
97 Bk Berkelium 247.070
98 Cf Californium 251.080
99 Es Einsteinium [254]
100 Fm Fermium 257.095
101 Md Mendelevium 258.1
102 No Nobelium 259.101
103 Lr Lawrencium [262]
Alkali Metal
Alkaline Earth
Transition Metal
Basic Metal
Semimetal
Nonmetal
Halogen
Noble Gas
Lanthanide
Actinide
© 2015 Todd Helmenstine
sciencenotes.org



Eychenne et al., 2021. DOI: 10.3390/pharmaceutics13060906.

65 Tb Terbium 158.925

82 Pb Lead 207.2

83 Bi Bismuth 208.980

83 Bi Bismuth 208.980

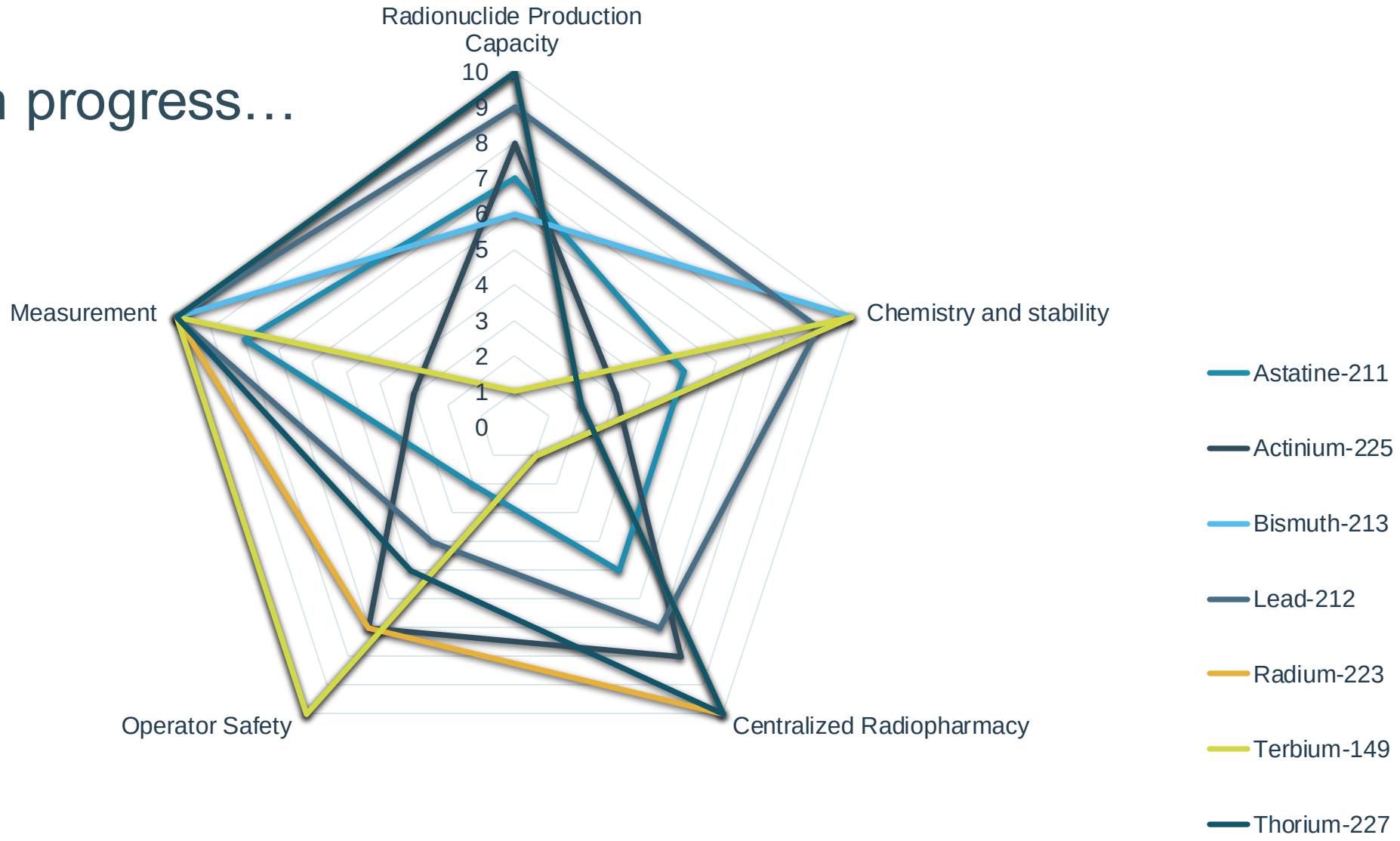
85 At Astatine 209.987

88 Ra Radium 226.025

89 Ac Actinium 227.028

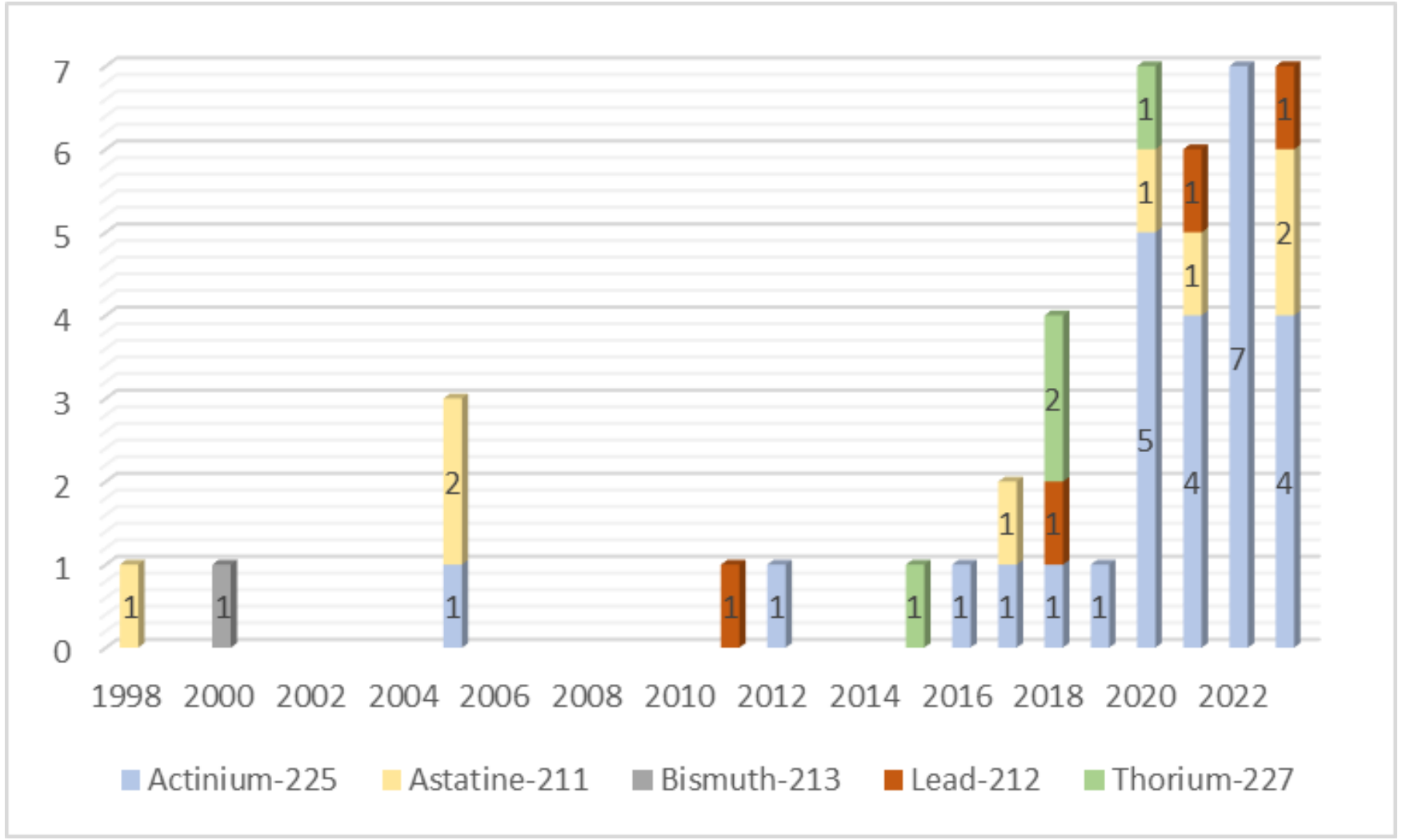
90 Th Thorium 232.038

Theory in progress…



Property & opinion of presenter – do not use information elsewhere.

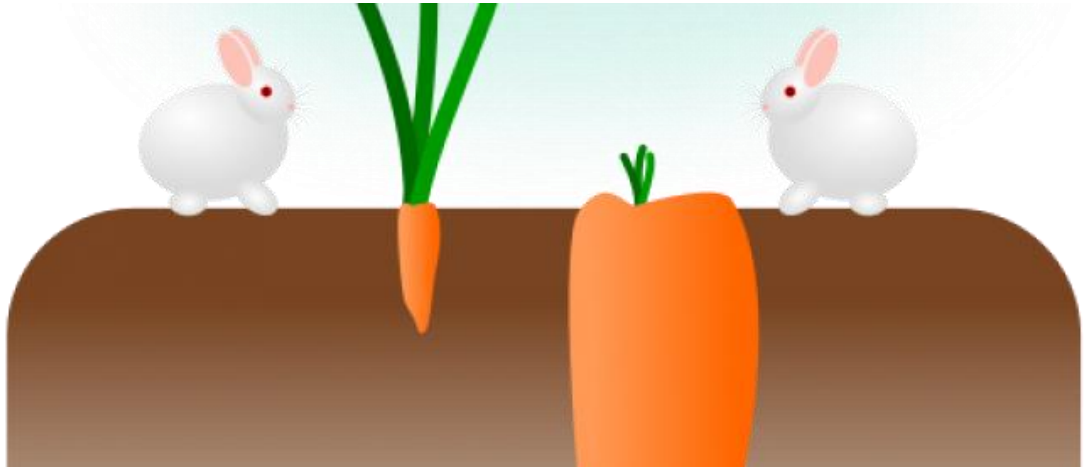
Clinical trials



Trials registered at clinicaltrials.gov as of October 2023
Excluding radium-223.

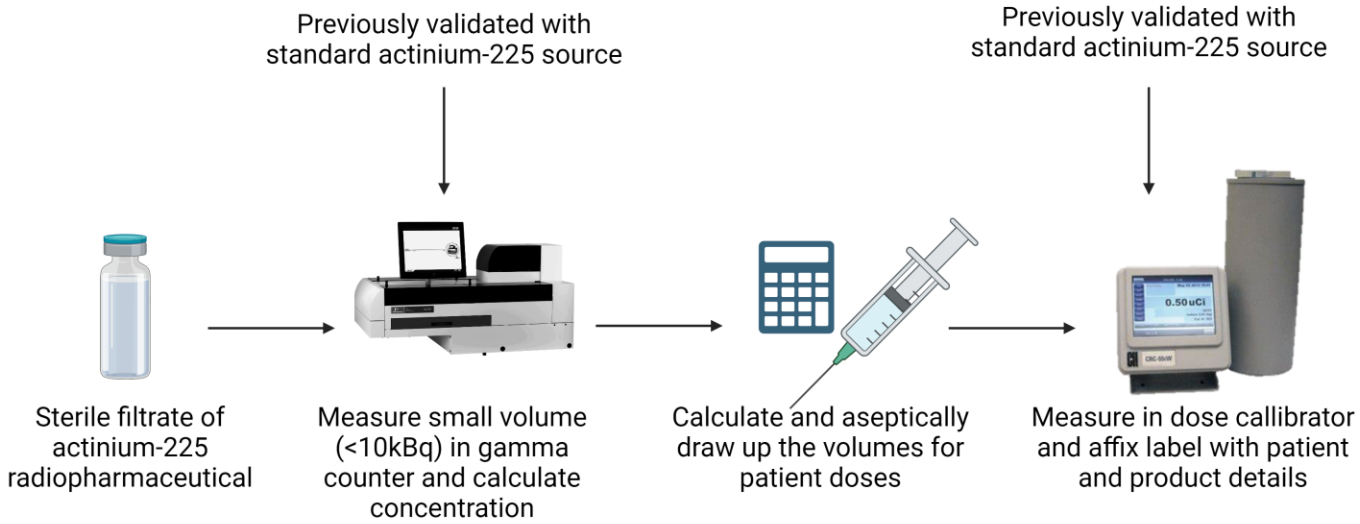
The alpha-radiopharmacy

- Superior radiation detectors and health monitoring of staff
- Superior ventilation protection – isolators/closed systems
- Dedicated workspaces and QC equipment (presence of other emissions disrupt detection)
- Unique detections systems for QC
- Safer production equipment and closed systems
- Specialist staff



Measurement of low activities/indirect measurements

Misadministration
– dose different from prescribed dose by 20%
– e.g. 6 MBq Ac-225 (4.8 – 7.2 MBq)

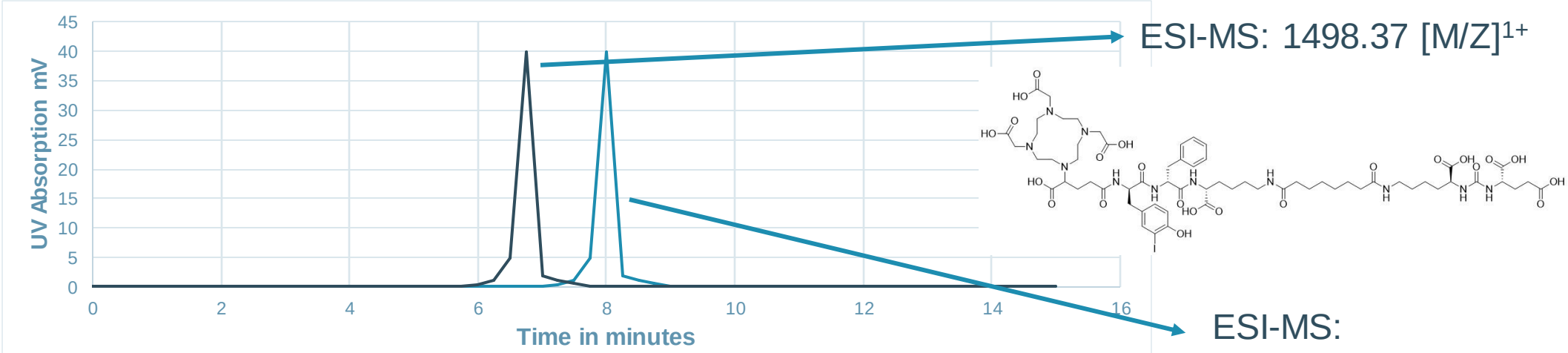


Information courtesy of E de Blois, Erasmus MC.
Figure courtesy of J. Kleynhans, created with Biorender.com

Cold standards for analytical method validation

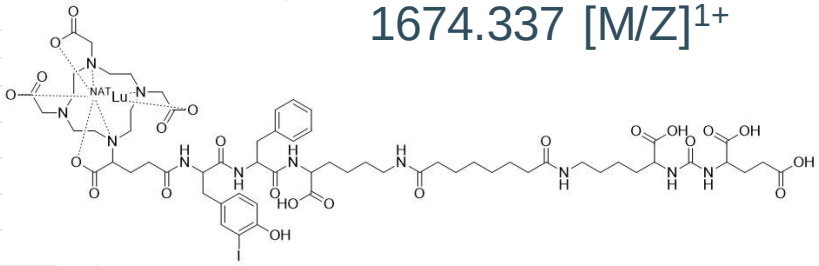
Cold compound reference standard
^{nat}Lu-PSMA-I&T
Fully characterized & GMP Produced

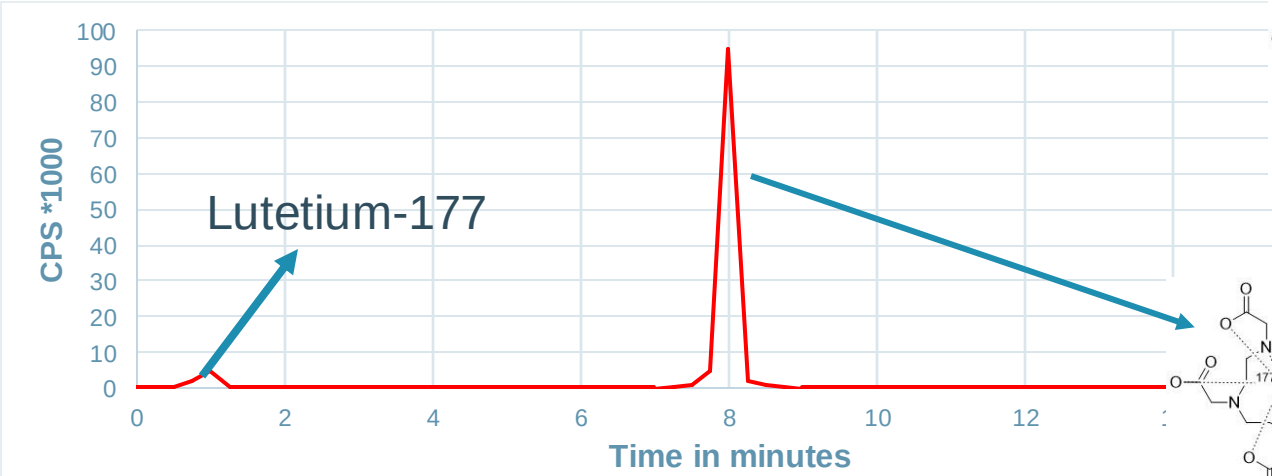
[^{177}Lu]Lu-PSMA-I&T

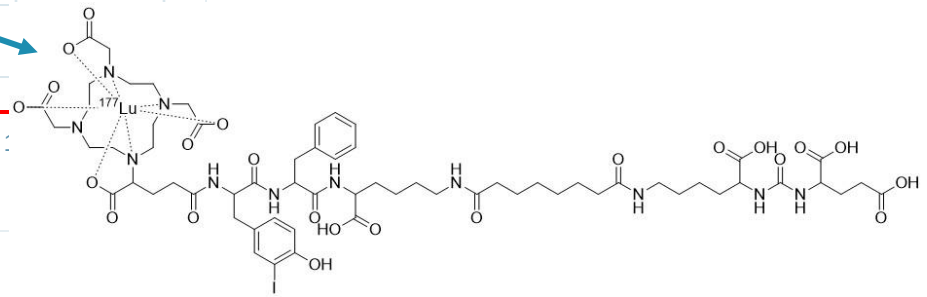


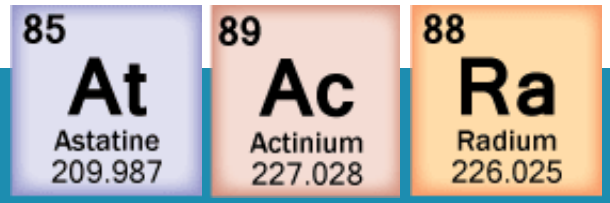
ESI-MS: 1498.37 $[M/Z]^{1+}$

ESI-MS:
1674.337 $[M/Z]^{1+}$

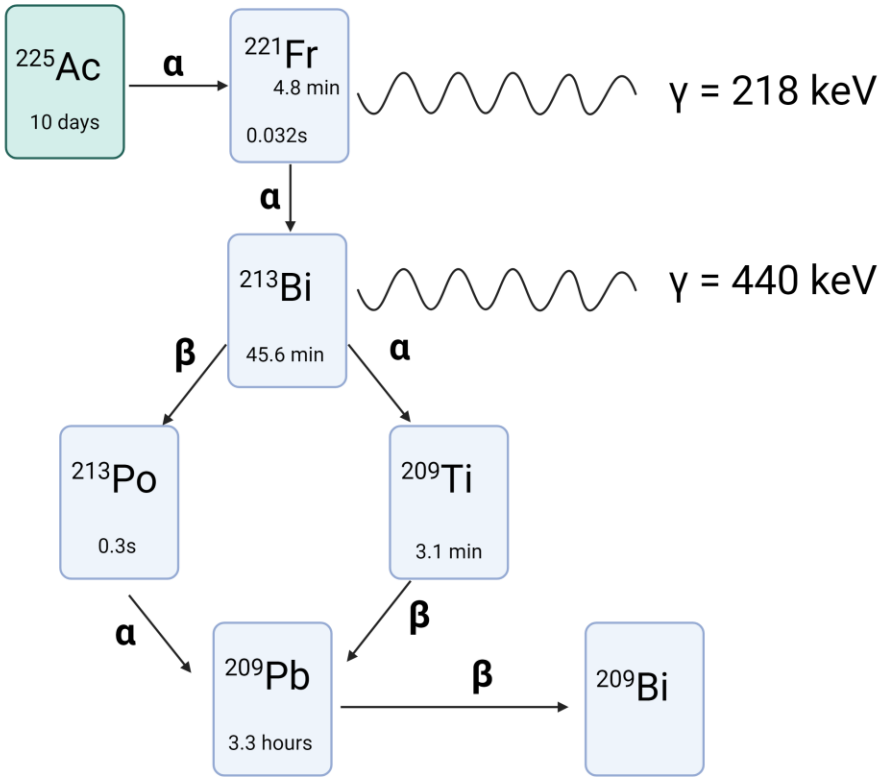


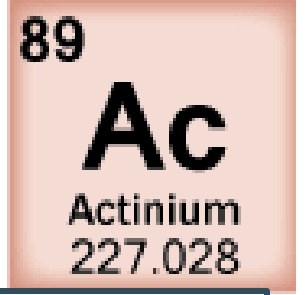


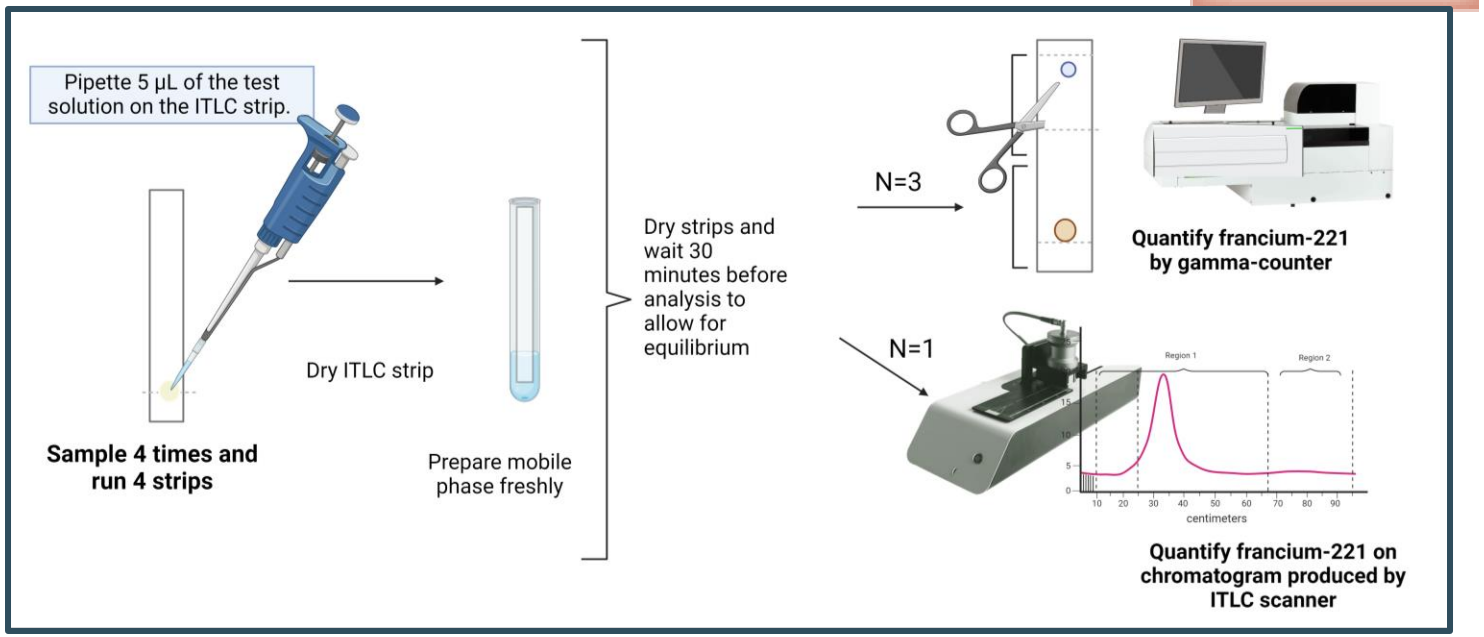


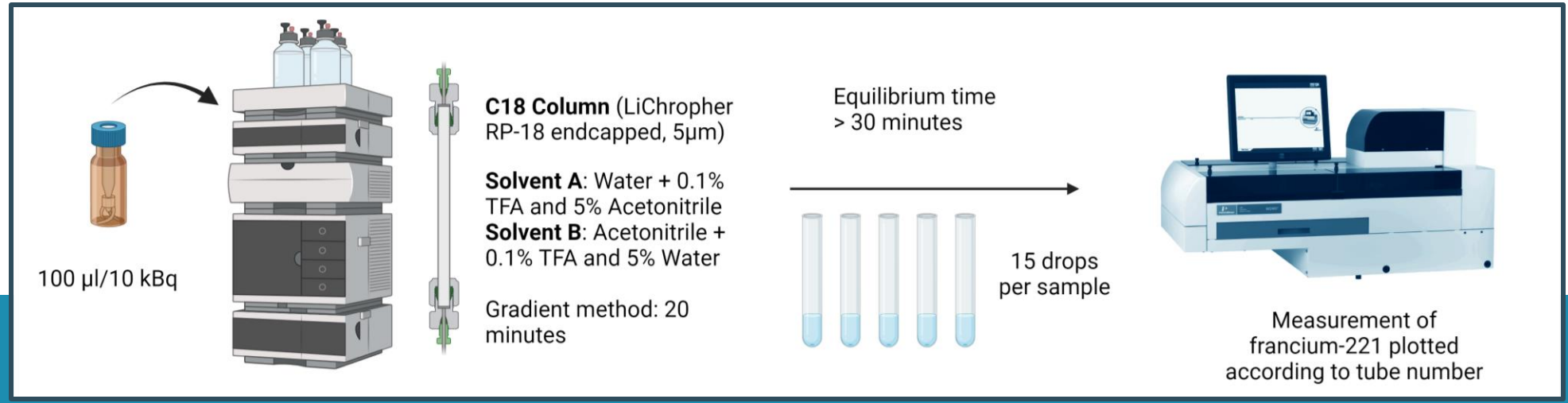


Lack of useful gamma-emissions

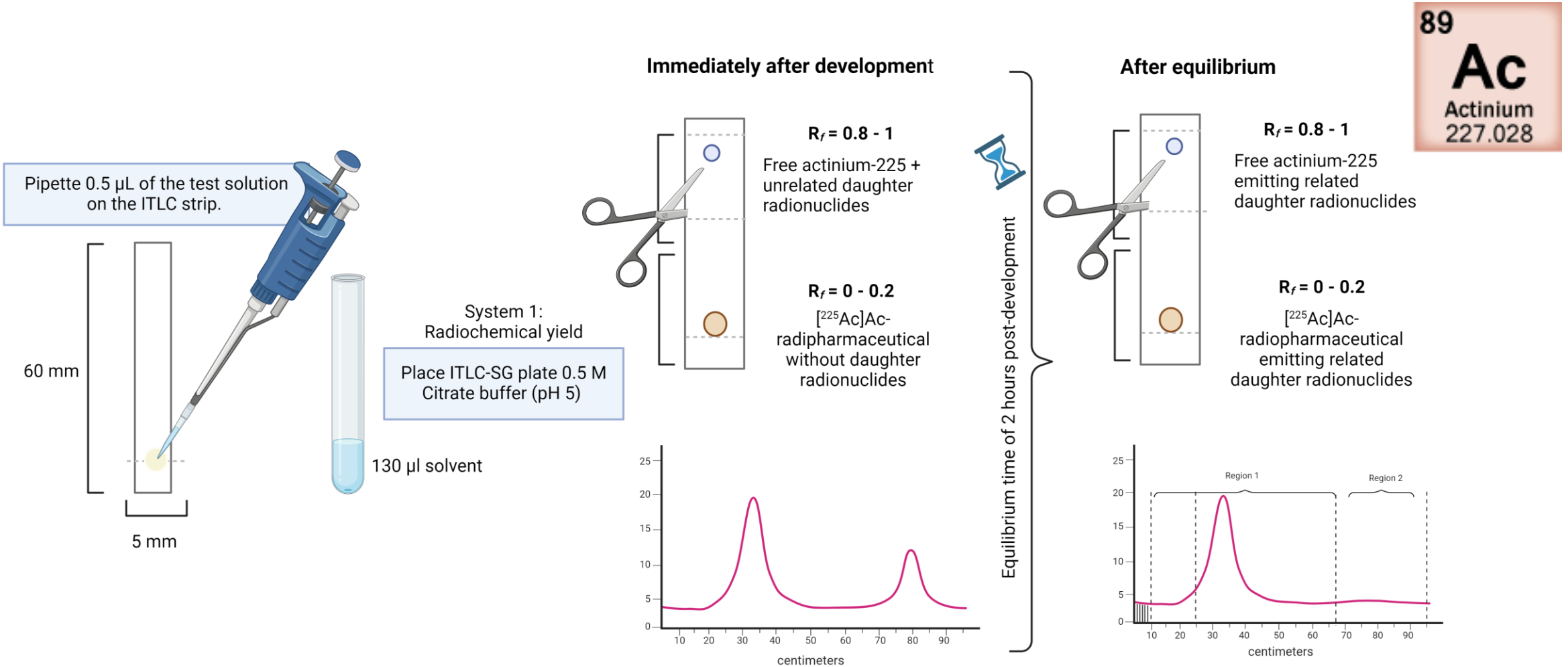




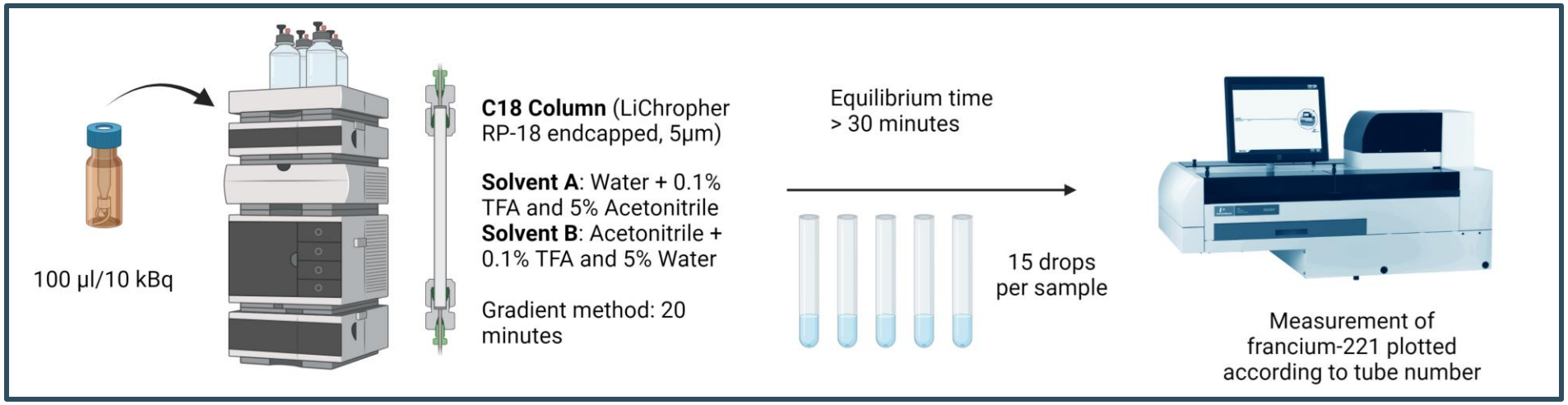




KU LEUVEN


89
Ac
Actinium
227.028
Pipette 0.5 µL of the test solution on the ITLC strip.
60 mm
5 mm
130 µl solvent
System 1:
Radiochemical yield
Place ITLC-SG plate 0.5 M Citrate buffer (pH 5)
Immediately after development
R_f = 0.8 - 1
Free actinium-225 + unrelated daughter radionuclides
R_f = 0 - 0.2
[225Ac]Ac-radipharmaceutical without daughter radionuclides
Equilibrium time of 2 hours post-development
After equilibrium
R_f = 0.8 - 1
Free actinium-225 emitting related daughter radionuclides
R_f = 0 - 0.2
[225Ac]Ac-radiopharmaceutical emitting related daughter radionuclides
Region 1
Region 2
centimeters
Inaccurate measurement of purity
Purity < 92% at 2 hours post incubation indicates a real purity of <95%

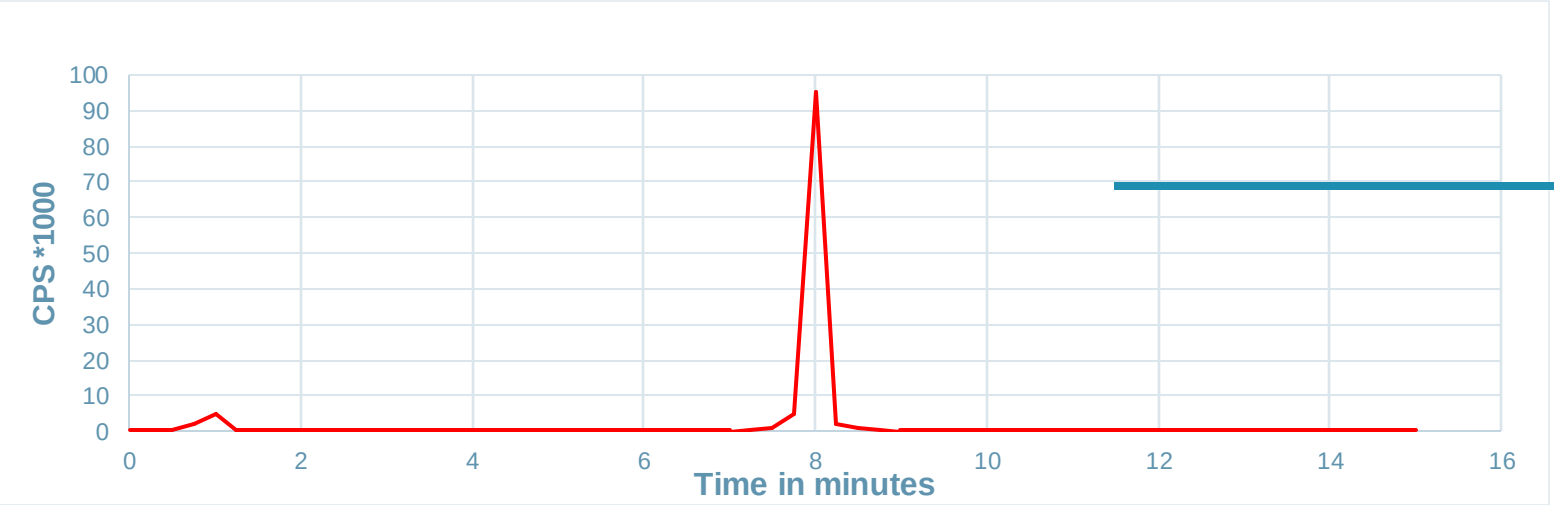
LOQ & LOD



EANM Guidelines: Validation of LOQ should determine the amount of radioactivity (kBq/volume) tested assure the quantification of small amounts of radioactive impurities (0.5%).

Information courtesy of E de Blois, Erasmus MC.
Figure courtesy of J. Kleynhans, created with Biorender.com

HPLC method recovery



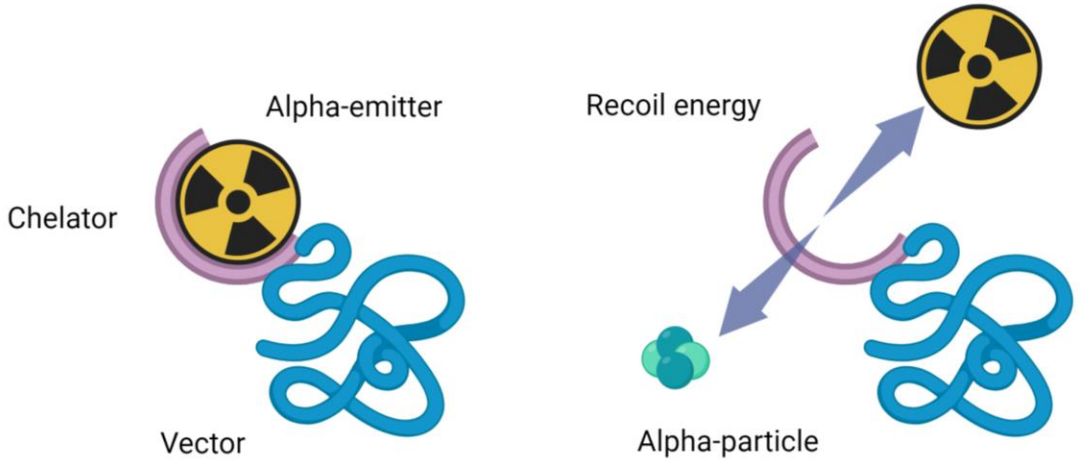
Radiochemical species can be retained on the column.

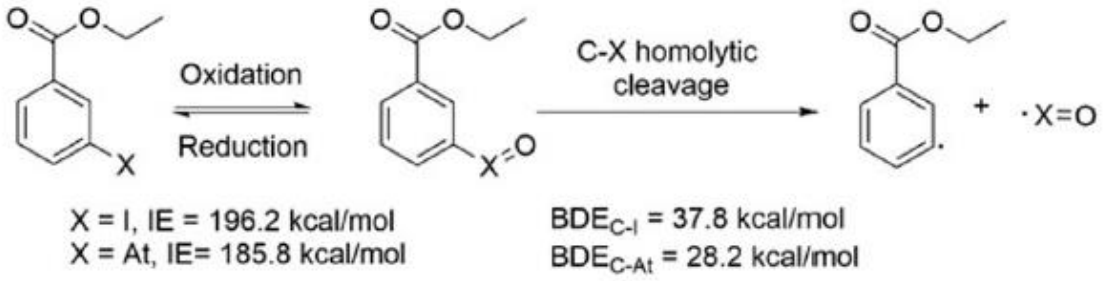
Tested

- Total activity injected – vs activity measured/activity eluted
- Injecting spiked known mixtures of radiochemical species – identify compounds that is retained.

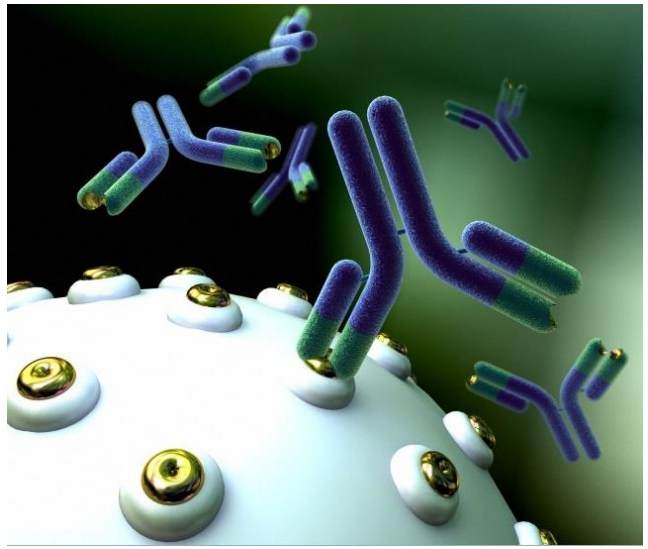
For alpha-emitters the LOD & LOQ or lack of useful gamma emissions results in complications.

Radiopharmaceutical stability



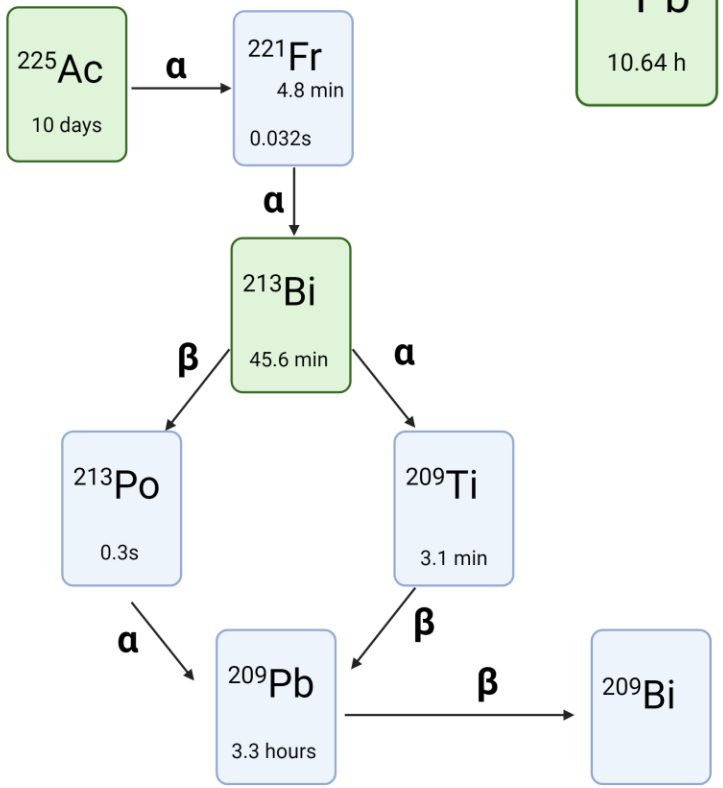


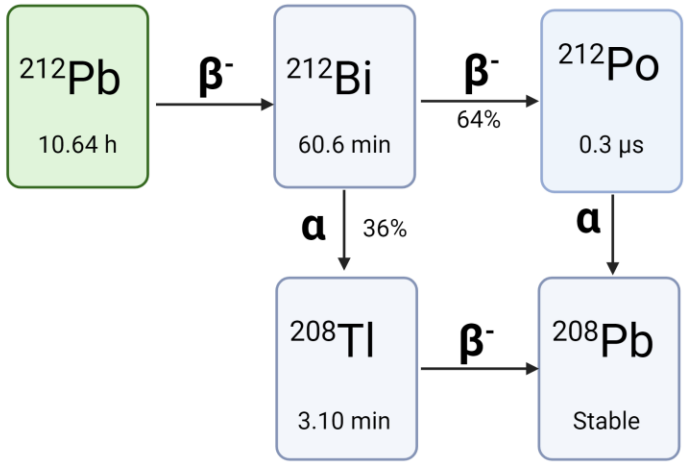
Radionuclide	Physical half-life
Thorium-227	18.7 days
Radium-223	11.4 days
Actinium-225	9.9 days
Lead-212	10.64 hours
Astatine-211	7.21 hours
Terbium-149	4.1 hours
Bismuth-213	46 minutes

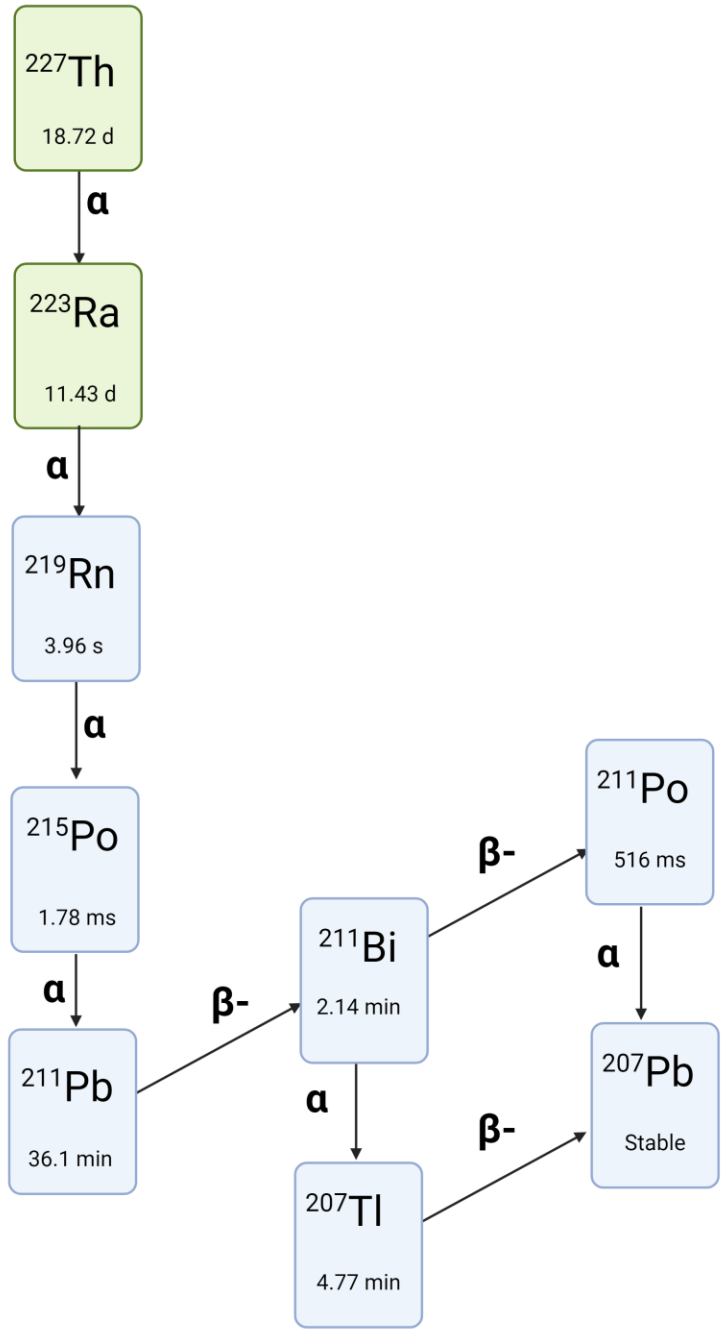


Guérard et al., 2021. DOI: 10.1021/acs.accounts.1c00327

Chemistry of the daughters



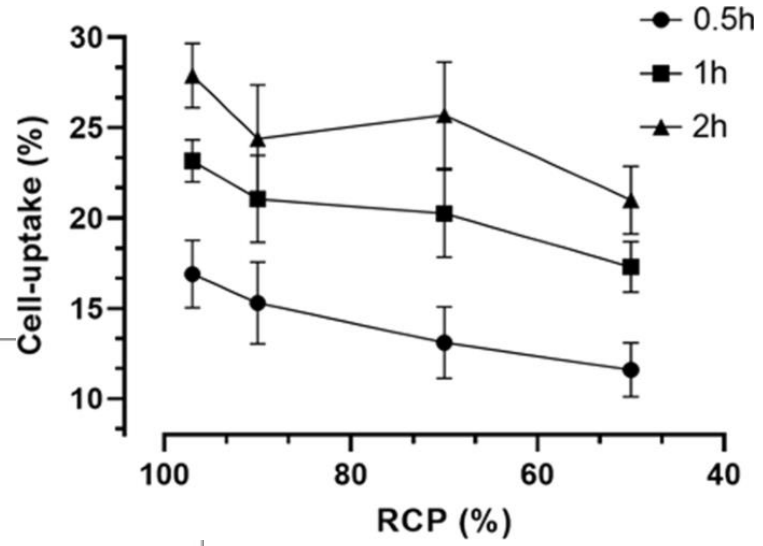


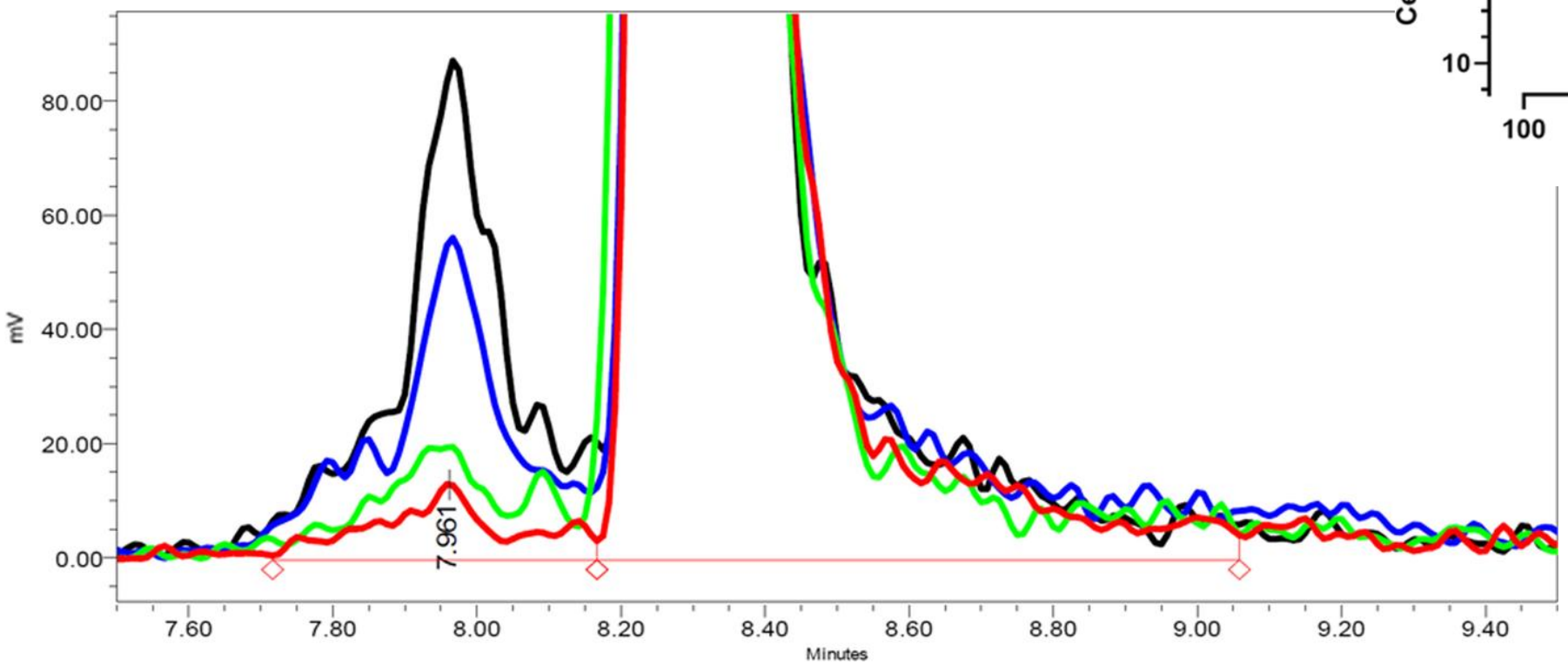


KU LEUVEN

Detection of radiolytic products

Only radioHPLC anslysis is suitable for identification of radiolysis.

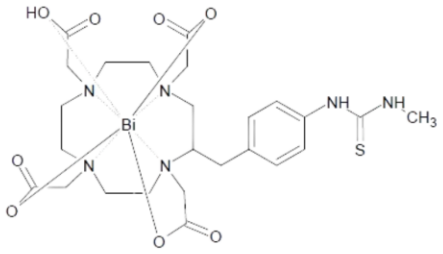




Hooijman et al. 2022. EJNMMI Radiopharmacy and Chemistry, 7:29
DOI: 10,1186/s41181-022-00181-0.

Shipment and shelf-life

Radionuclide shelf-life

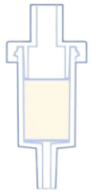


Radiolabelling

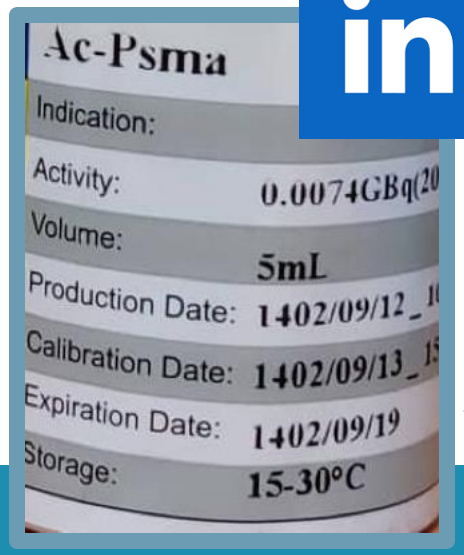
Product shelf-life

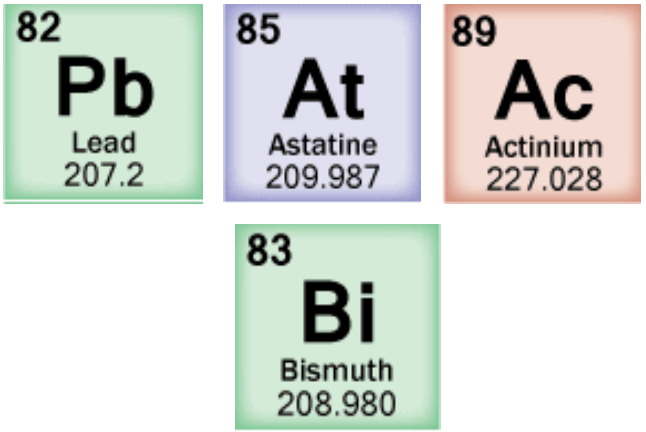
Vector stability
Radionuclide complex stability
Radiolysis products
Physical half-life

Impurity built-up
Radiolysis products
Physical half-life



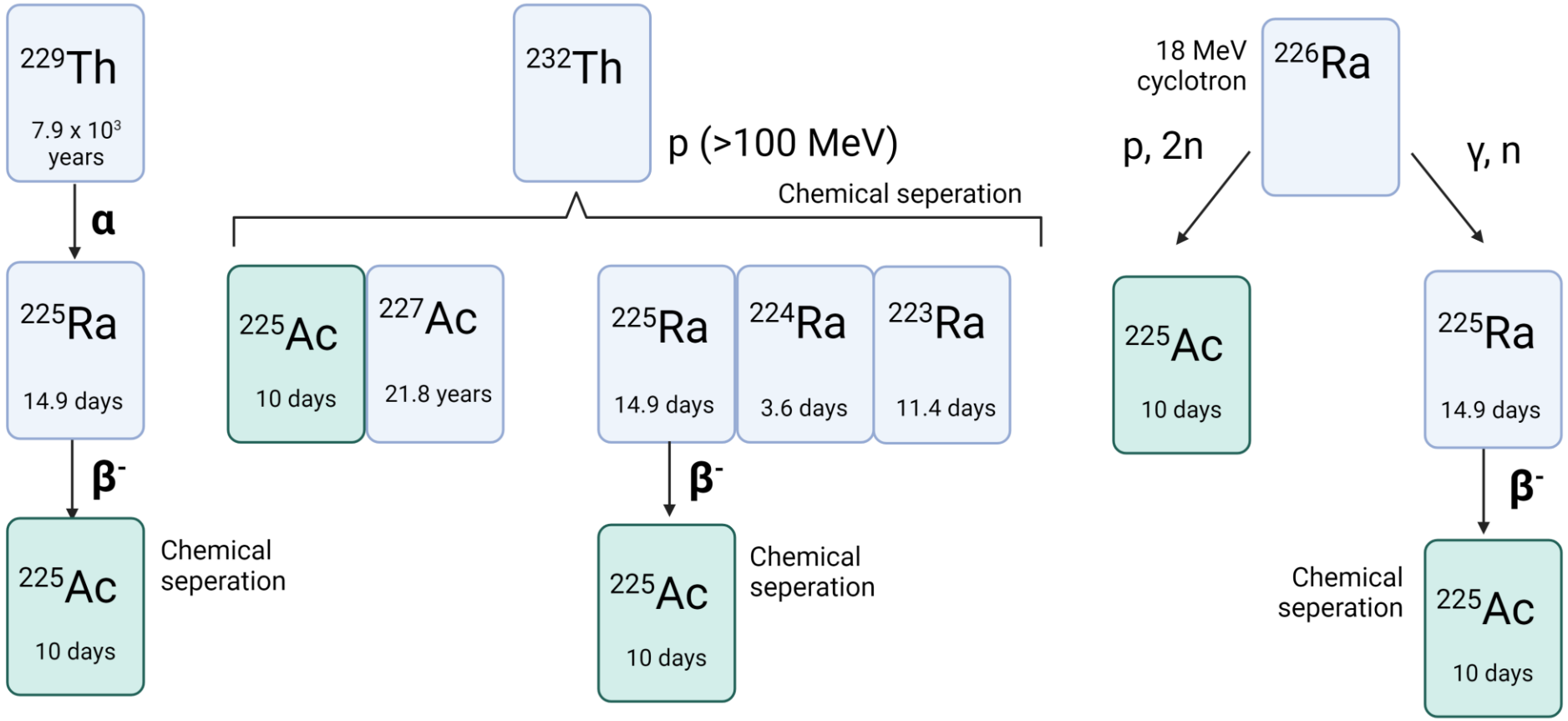
Generator system





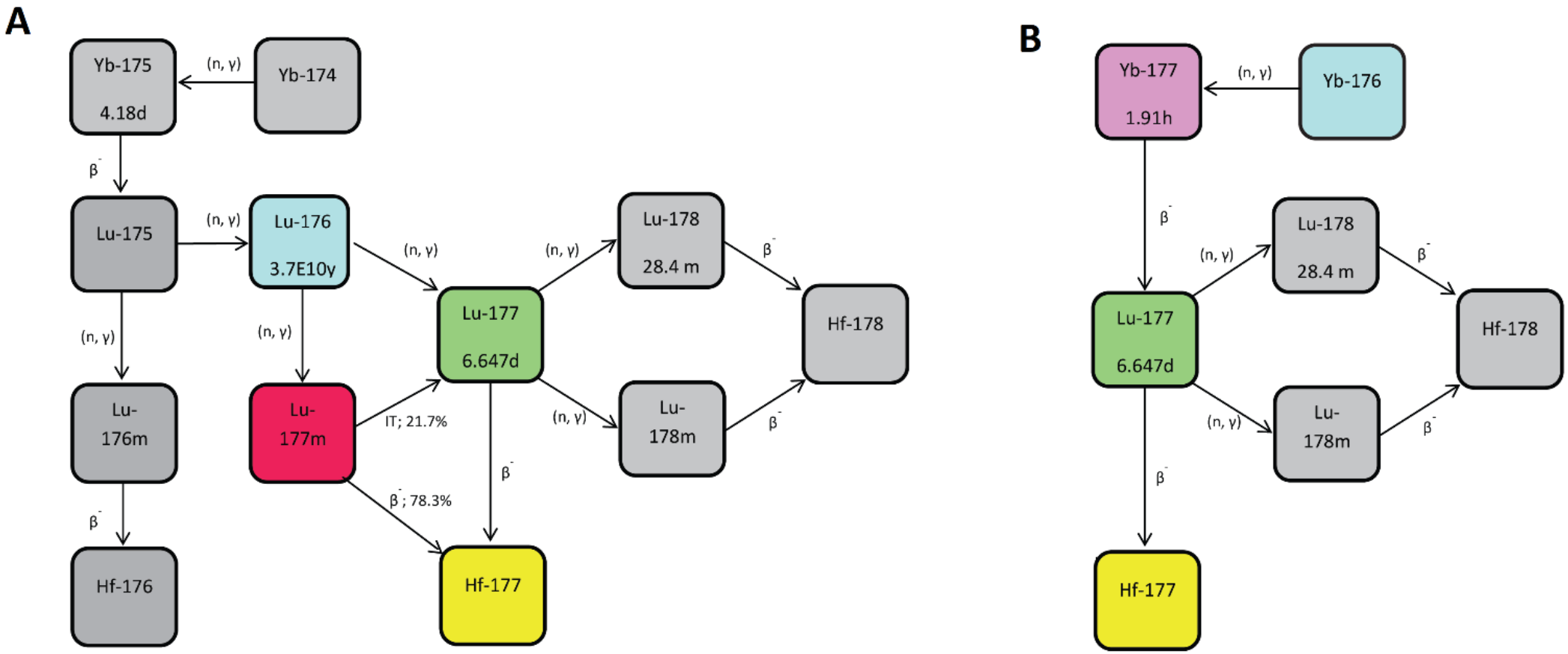
Radionuclide	Physical half-life
Thorium-227	18.7 days
Radium-223	11.4 days
Actinium-225	9.9 days
Lead-212	10.64 hours
Astatine-211	7.21 hours
Terbium-149	4.1 hours
Bismuth-213	46 minutes

Waste management



Information courtesy of Radchenko, V. TRIUMF, figure courtesy of J. Kleynhans, created with Biorender.com

Lutetium-177 example



Information courtesy of O Knoesen, Necsa, figure courtesy of J. Kleynhans, created with Biorender.com

Prevot *et al. EJNMMI Physics* (2023) 10:3
https://doi.org/10.1186/s40658-023-00524-z

EJNMMI Physics

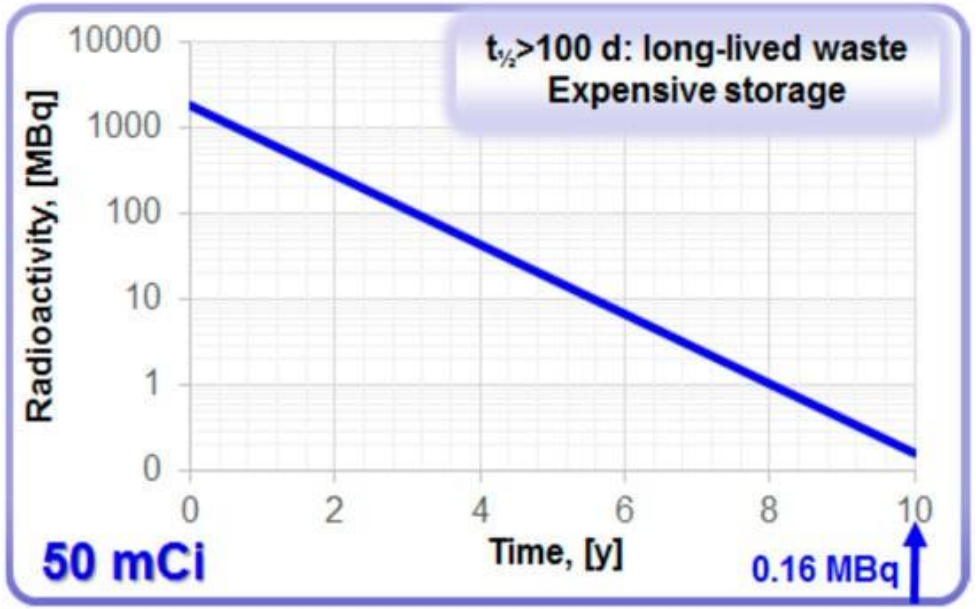
SHORT COMMUNICATION **Open Access**

Dealing with dry waste disposal issues associated with ^{177m}Lu impurities: a long-term challenge for nuclear medicine departments

Sylviane Prevot[1*], Inna Dygaï-Cochet[1], Jean-Marc Riedinger[1], Jean-Marc Vrigneaud[1,2], Myriam Quermonne[1], Matthieu Gallet[1] and Alexandre Cochet[1,2]

Waste management problems:

- Long lived impurities from production methods
- Parent radionuclides from generator systems



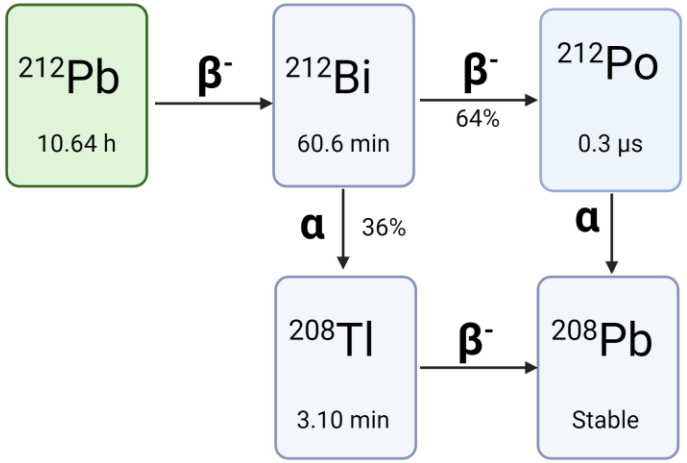
Velikyan. DOI: 2015. 10.3390/molecules200712913.

Health physics and safety

An Experimental Generator for Production of High-Purity ^{212}Pb for Use in Radiopharmaceuticals

Ruth Gong Li, Vilde Yuli Stenberg and Roy Hartvig Larsen

Journal of Nuclear Medicine January 2023, 64 (1) 173-176; DOI: https://doi.org/10.2967/jnumed.122.264009



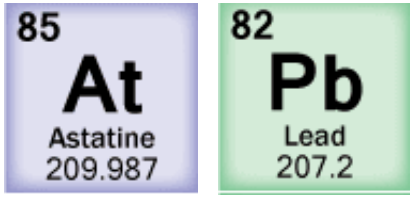
In experimental setup no radiation concerns – Upscaling to Hospital Radiopharmacy:

Potential safety concerns is radion-220 exposure when the generator is opened.

With a 7cm lead shield dose rate 0.7 µSv per MBq.

Personal experience with manual gallium-68 generator-based labelling 0.02 µSv per MBq.

Isolators!



Useful reads

Hooijman *et al.*
EJNMMI Radiopharmacy and Chemistry (2024) 9:9
https://doi.org/10.1186/s41181-024-00239-1

EJNMMI Radiopharmacy and Chemistry

REVIEW **Open Access**

Implementing Ac-225 labelled radiopharmaceuticals: practical considerations and (pre-)clinical perspectives

Eline L. Hooijman[1,2], Valery Radchenko[3,4], Sui Wai Ling[1], Mark Konijnenberg[1], Tessa Brabander[1], Stijn L. W. Koolen[1,2,5] and Erik de Blois[1*]

Useful reads

Kleynhans *et al.*
EJNMMI Radiopharmacy and Chemistry (2022) 7:23
https://doi.org/10.1186/s41181-022-00175-y

EJNMMI Radiopharmacy and Chemistry

LETTER TO THE EDITOR Open Access

The determination of the radiochemical purity of Actinium-225 radiopharmaceuticals: a conundrum

Janke Kleynhans[1] and Adriano Duatti[2*]

Useful reads

Journal of Nuclear Medicine, published on January 4, 2024 as doi:10.2967/jnumed.123.266774

EDITORIAL

Is ^{212}Pb Really Happening? The Post-^{177}Lu/^{225}Ac Blockbuster?

Richard Zimmermann

Chrysalium Consulting, Lalaye, France; MEDraysintell, Lou Belgium

Journal of Nuclear Medicine, published on August 17, 2023 as doi:10.2967/jnumed.123.265907

EDITORIAL

Is Actinium Really Happening?

Richard Zimmermann

Chrysalium Consulting, Lalaye, France; MEDraysintell, Louvain-la-Neuve, Belgium; and Oncidium Foundation, Mont-Saint-Guibert, Belgium

THE STATE OF THE ART

Production and Supply of α-Particle–Emitting Radionuclides for Targeted α-Therapy

Valery Radchenko[1,2], Alfred Morgenstern[3], Amir R. Jalilian[4], Caterina F. Ramogida[1,5], Cathy Cutler[6], Charlotte Duchemin[7,8], Cornelia Hoehr[1], Ferrid Haddad[9], Frank Bruchertseifer[3], Haavar Gausemel[10], Hua Yang[1], Joao Alberto Osso[4], Kohshin Washiyama[11], Kenneth Czerwinski[12], Kirsten Leufgen[13], Marek Pruszyński[14,15], Olga Valzdorf[16], Patrick Causey[17], Paul Schaffer[1], Randy Perron[18], Samsonov Maxim[19], D. Scott Wilbur[20], Thierry Stora[7], and Yawen Li[20]

ESRR'24

21st European Symposium on Radiopharmacy & Radiopharmaceuticals

April, 18 – 21 2024 in Coimbra, Portugal

Sunday, April 21, 2024

08:30 – 09:15	Back-to-basics III: **Alpha emitters, from basic physics to labeling and measuring** *Janke Kleynhans, Leuven, BE*

KU LEUVEN

Thanks to mentors who spend time to discuss science and shape my understanding:

Adriano Duatti, Erik de Blois, Amir Jalilian, Valery Radchenko, Mike Sathekge, Mariza Vorster, Otto Knoesen, Jan Rijn Zeevaart, Thomas Ebenhan, Eline Hooijman, Frank Bruchertseifer, Emilliano Cazzola, Richard Zimmerman

The Laboratory for Radiopharmaceutical Research at KU Leuven

and many many more…

bio RENDER

Images created with licenced version of BioRender

fwo Research Foundation Flanders Opening new horizons

Dr Janke Kleynhans is supported by the Fonds Wetenschappelijk Onderzoek - Vlaanderen through a senior postdoctoral grant [1226524N-7029].