Activity standards for alpha-emitters in support of precision cancer therapy

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National Institute of Standards and Technology
U.S. Department of Commerce

PHYSICAL MEASUREMENT LABORATORY

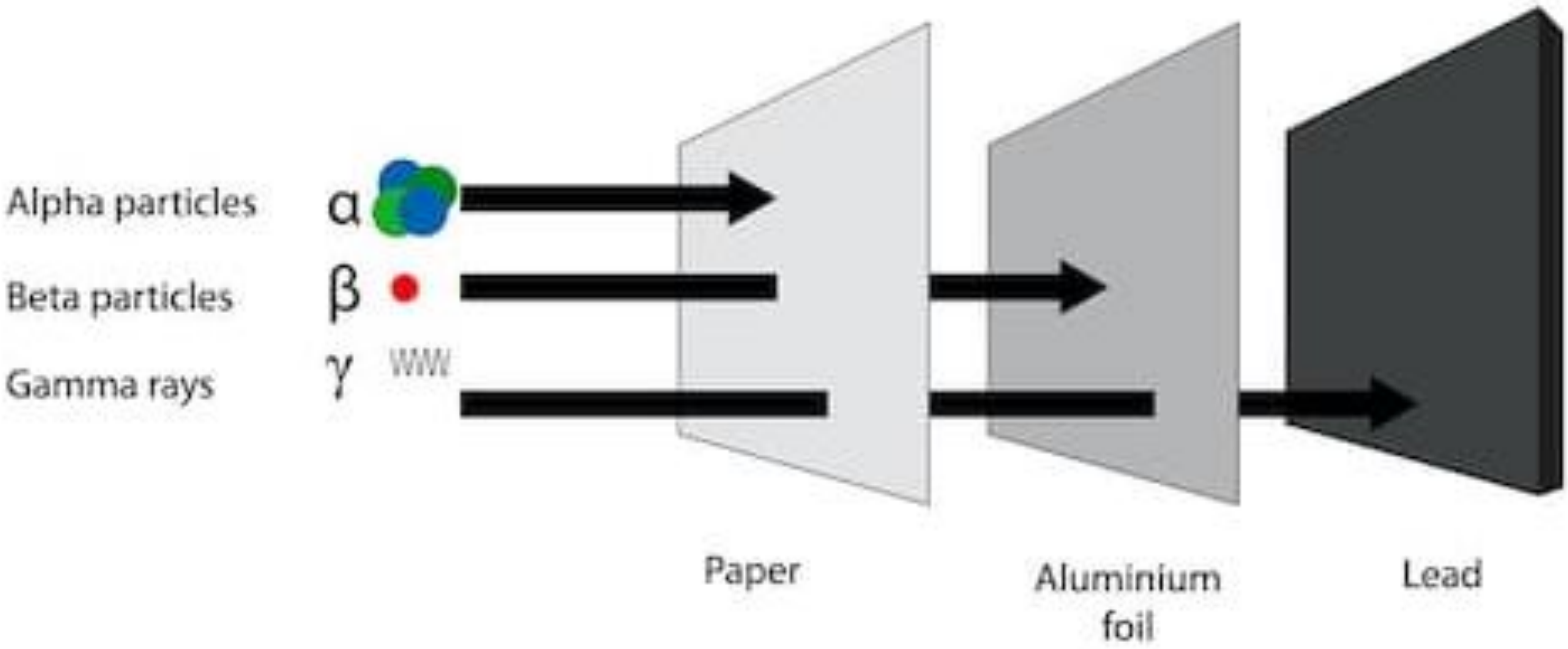
Consider two trends in cancer therapy:

- **Targeted alpha therapy**

- **Theranostics**

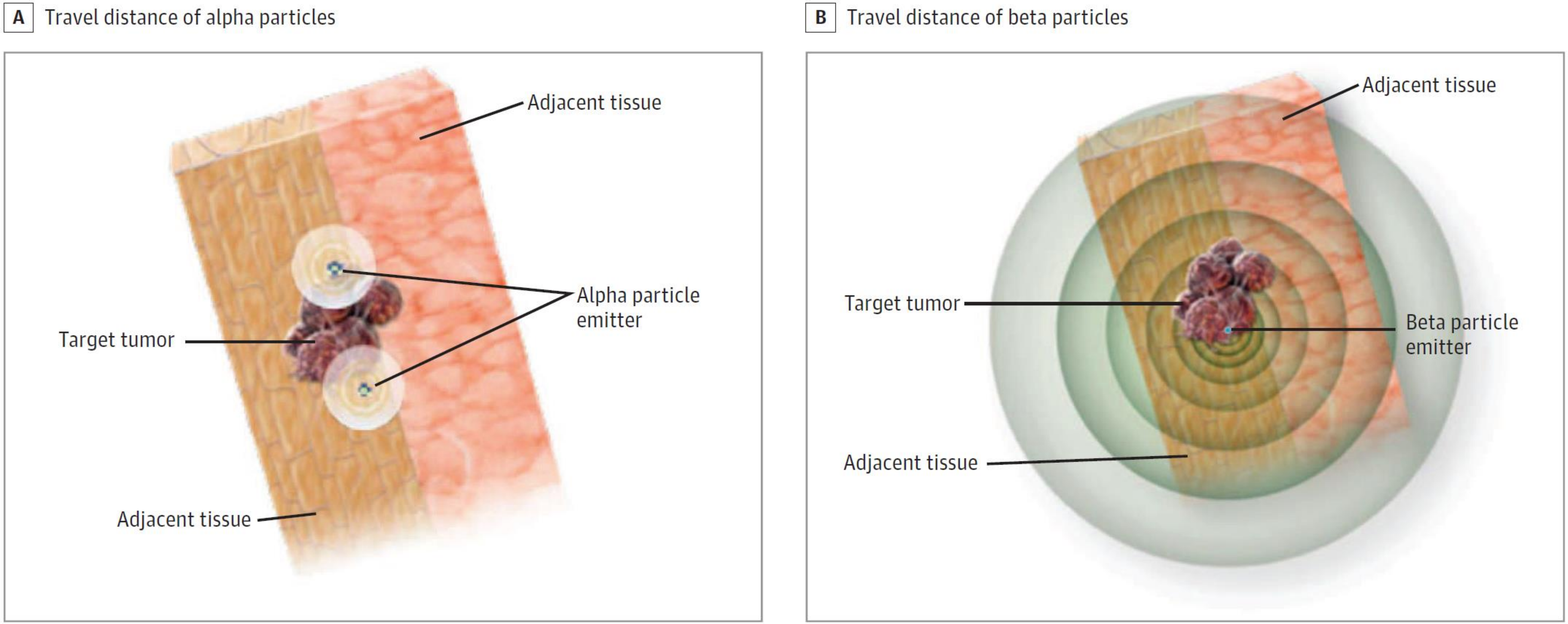
  (**Thera**py + Diag**nostics** = **Theranostics**)

Alphas have short range



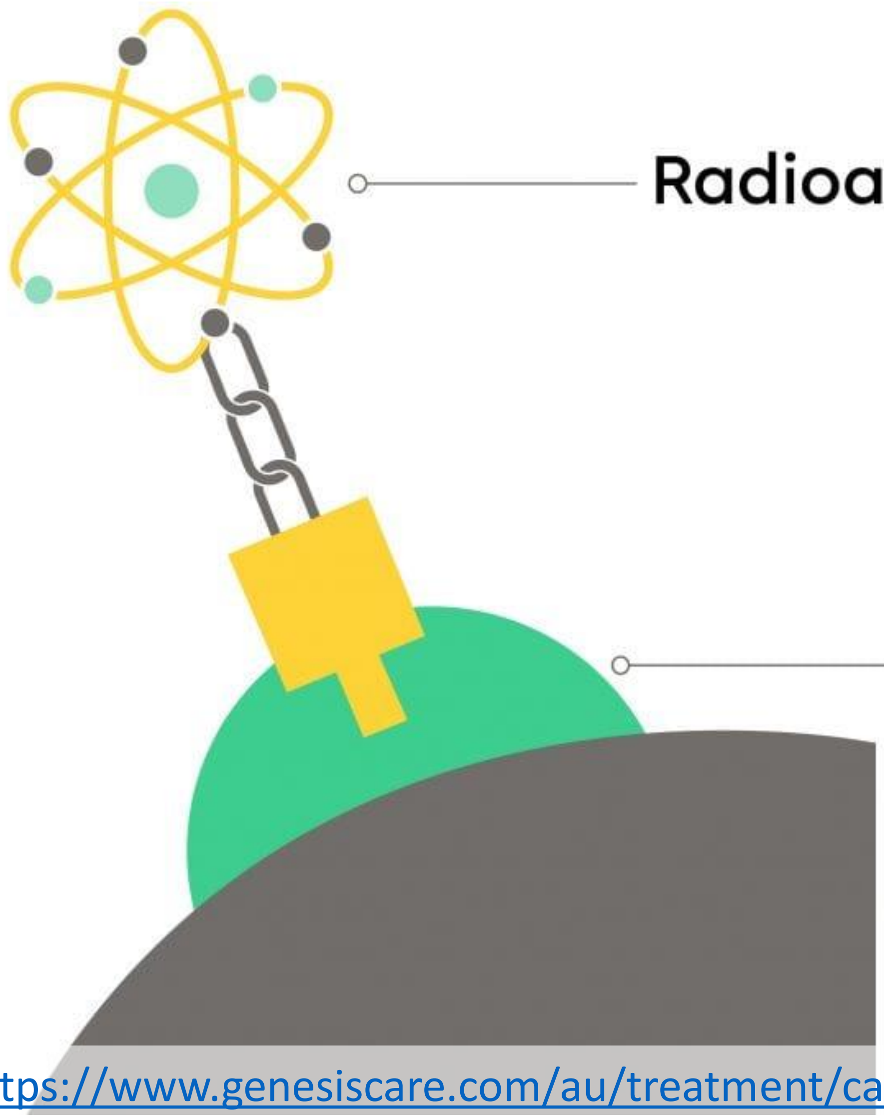
https://www.shutterstock.com/image-vector/penetration-range-alpha-beta-gamma-radiation-218762140

Targeted alpha therapy



JAMA Oncology, 4(12), 1765, 2018.

Theranostics means precision medicine



Imaging nuclide and therapeutic nuclide delivered with same targeting system for:

- Biodistribution
- Dose planning
- Dosimetry

https://www.genesiscare.com/au/treatment/cancer/theranostics/

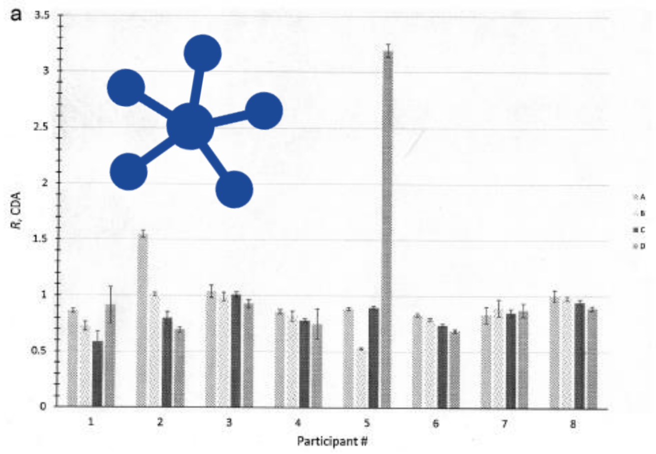
The becquerel in nuclear medicine

NIST

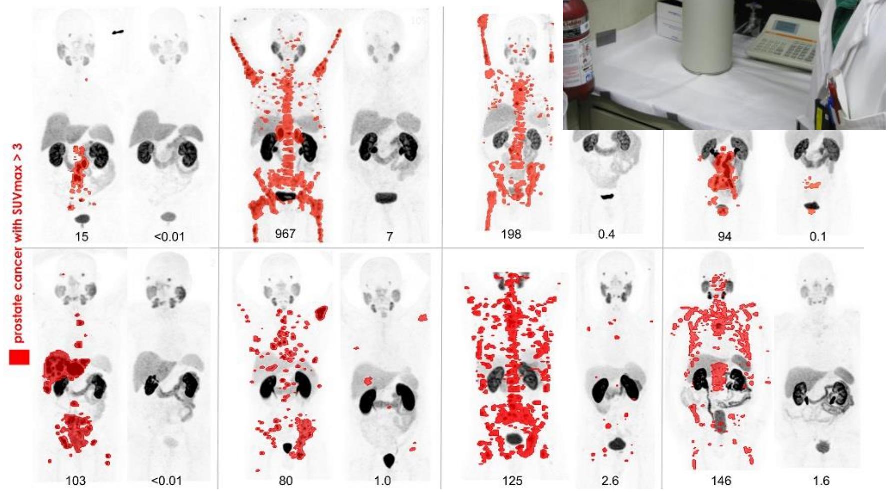
Precision measurements of activity are the foundation for:

- Reliable administration of patient dosages
- Quantitative molecular imaging
- Personalized dosimetry
- Multicenter trials


https://images.app.goo.gl/DEytSwNtUHjsYsov6



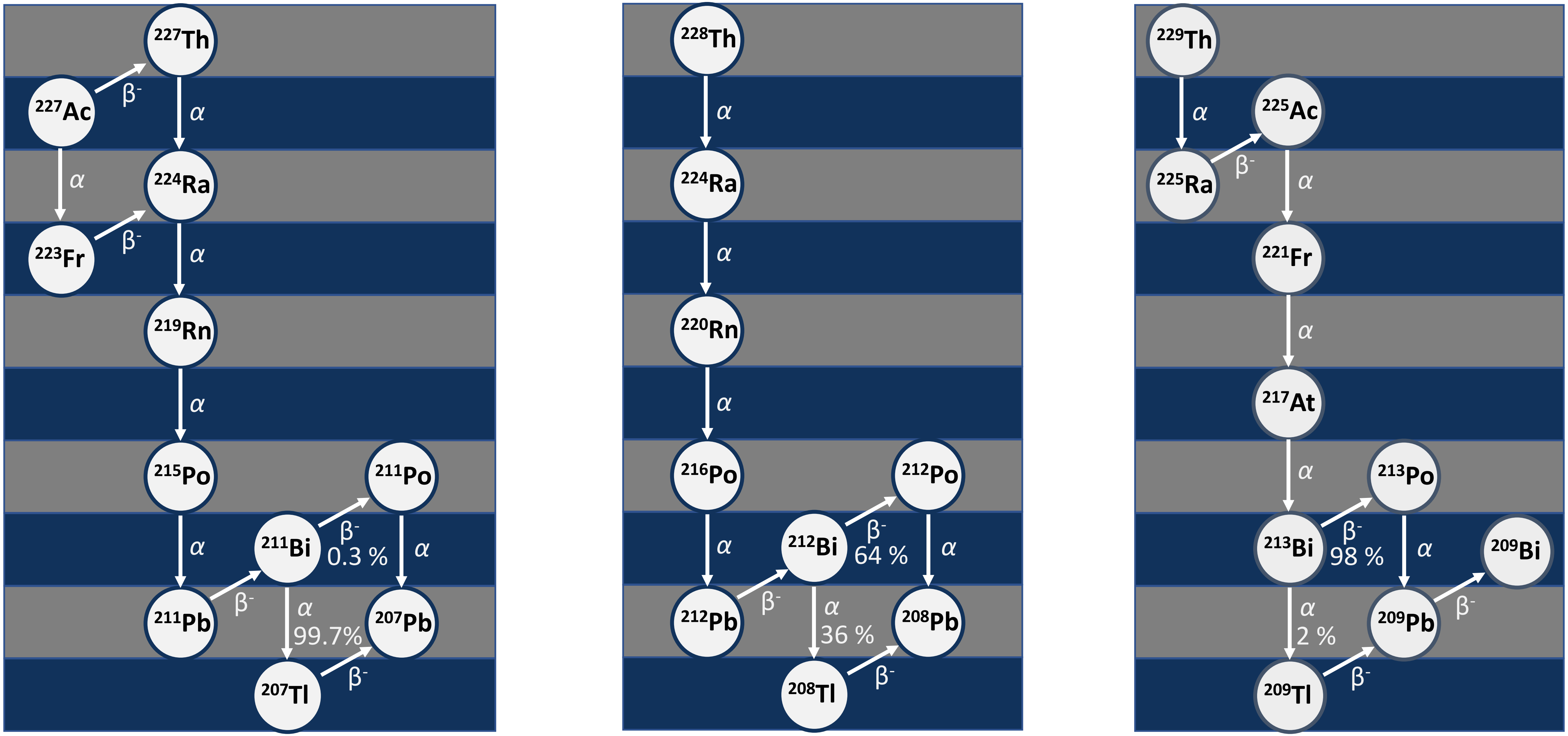
Zimmerman et al., Z. Med. Phys. 27 (2017) 98.



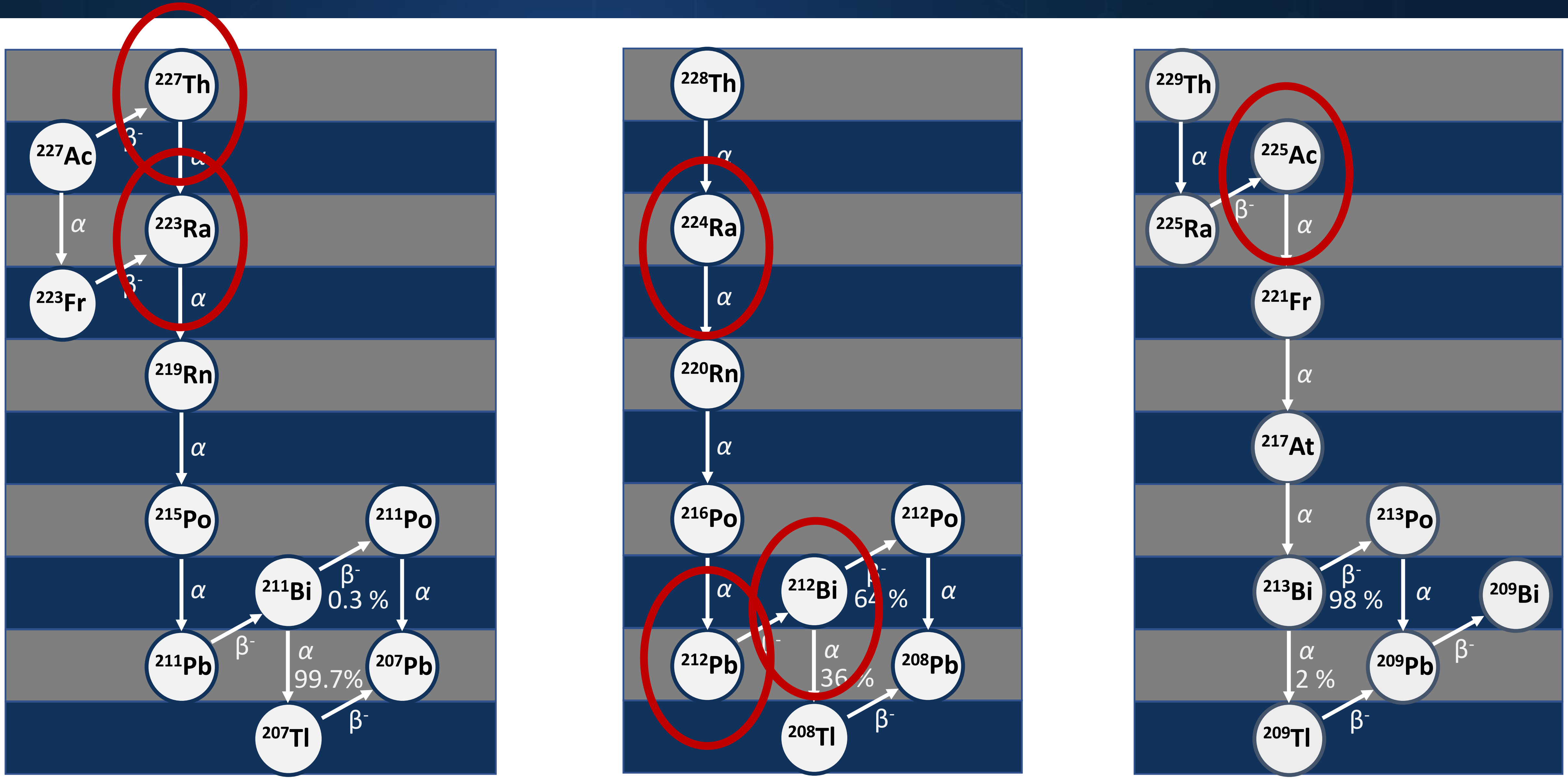
https://www.snmmi.org/NewsPublications/NewsDetail.aspx?ItemNumber=29483

Medically important alpha emitters

NIST



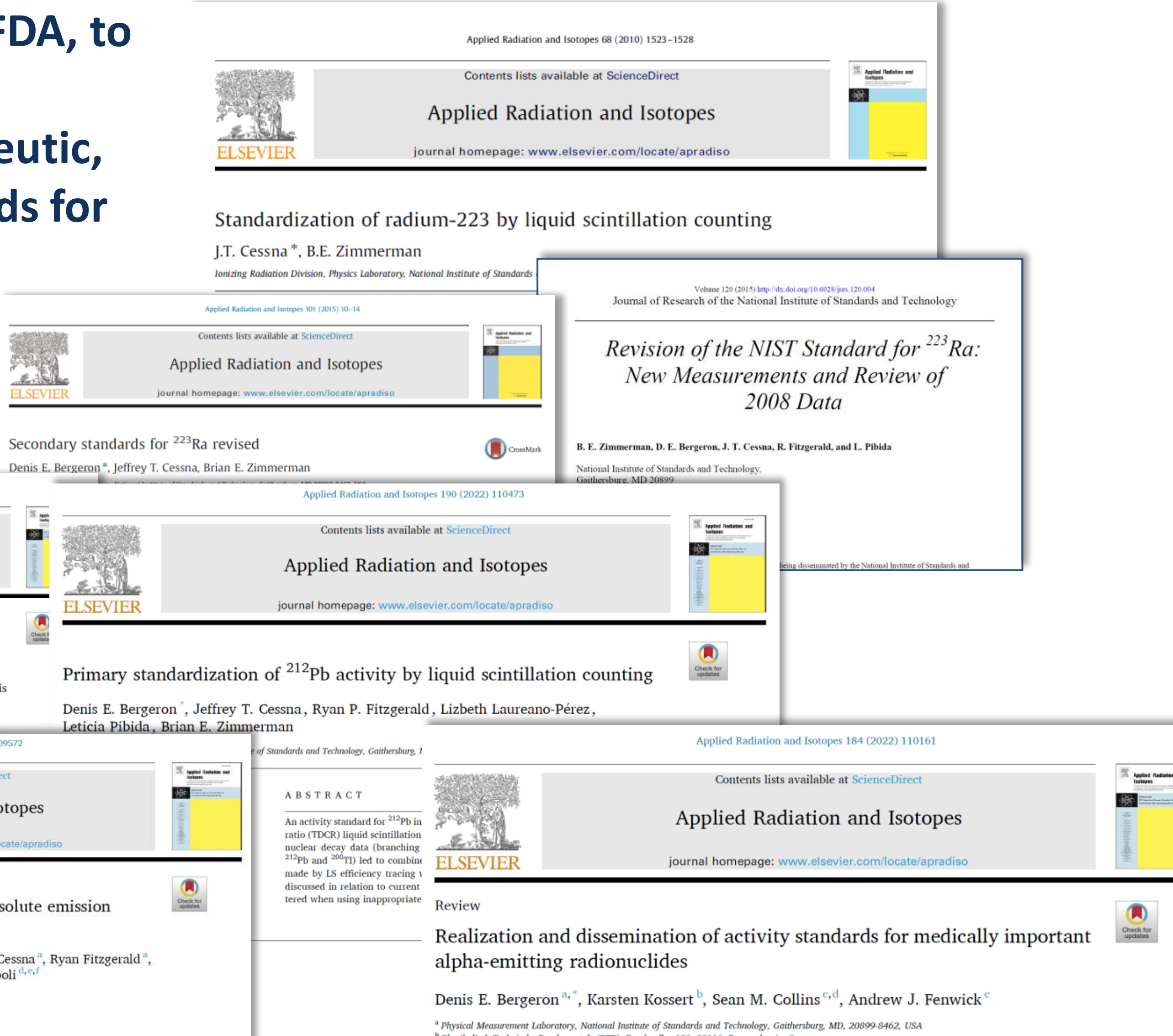
(Some) Medically important alpha emitters

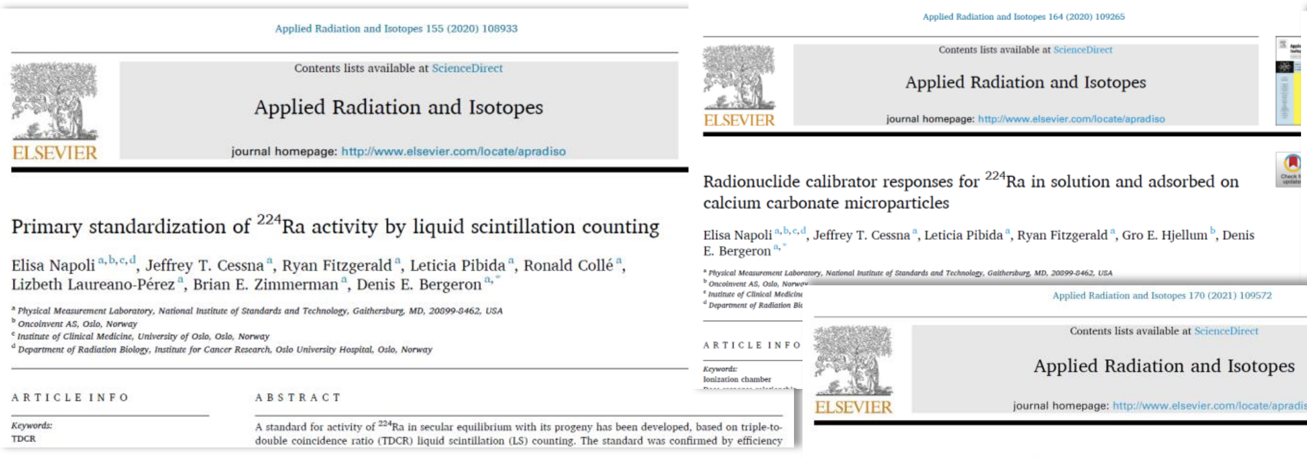


Recently standardized alpha-emitters

Algeta approached NIST in 2005, at the direction of FDA, to develop measurement standards for $^{223}RaCl_2$.
With the success of this “first-in-class” alpha-therapeutic, we have seen increased demand for activity standards for other alpha-emitters with therapeutic potential.

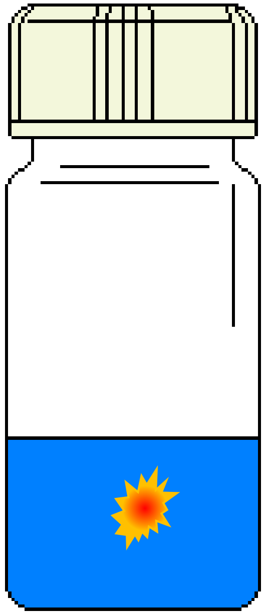
Bayer works with NIST to maintain traceability and shipments of Xofigo to new sites include a NIST-traceable calibration source*





**NIST does not endorse commercial products.*

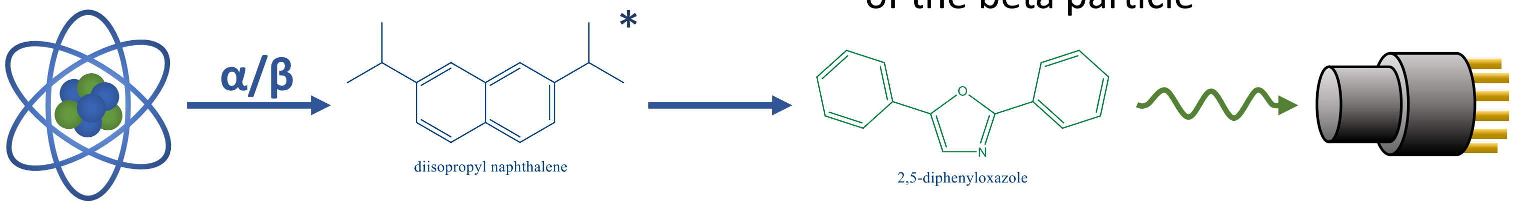
Liquid-scintillation based primary methods



Radionuclide decays, emitting alpha or beta particle

Energy is delivered to the solvent molecule and transferred to the fluor

Fluor molecules relax via photon emission, with the number of photons being proportional to the energy of the beta particle

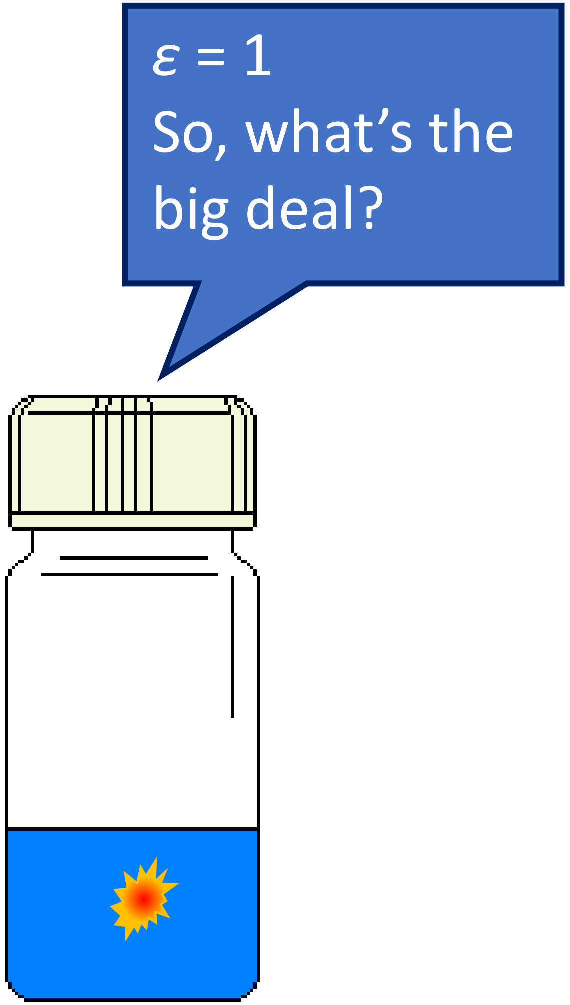


Some quenching mechanisms prevent beta particle energy from exciting solvent molecules

Some quenching mechanisms inhibit energy transfer to fluor molecules

Color quenching and scattering inhibit PMT detection of optical photons

Measurement challenges

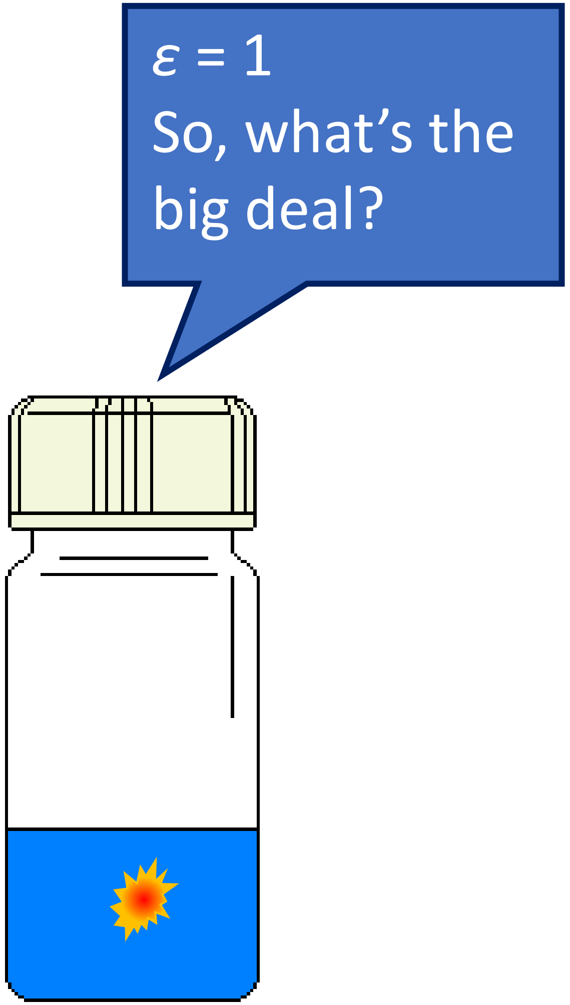


Challenges? Really?

- **Decay chains**
  - Progeny include beta-emitters ($\varepsilon < 1$)
  - Pre-equilibrium measurements
- **Impurities**
  - Breakthrough
  - Co-produced isotopes

Measurement challenges

NIST



Challenges? Really?

- **Decay chains**
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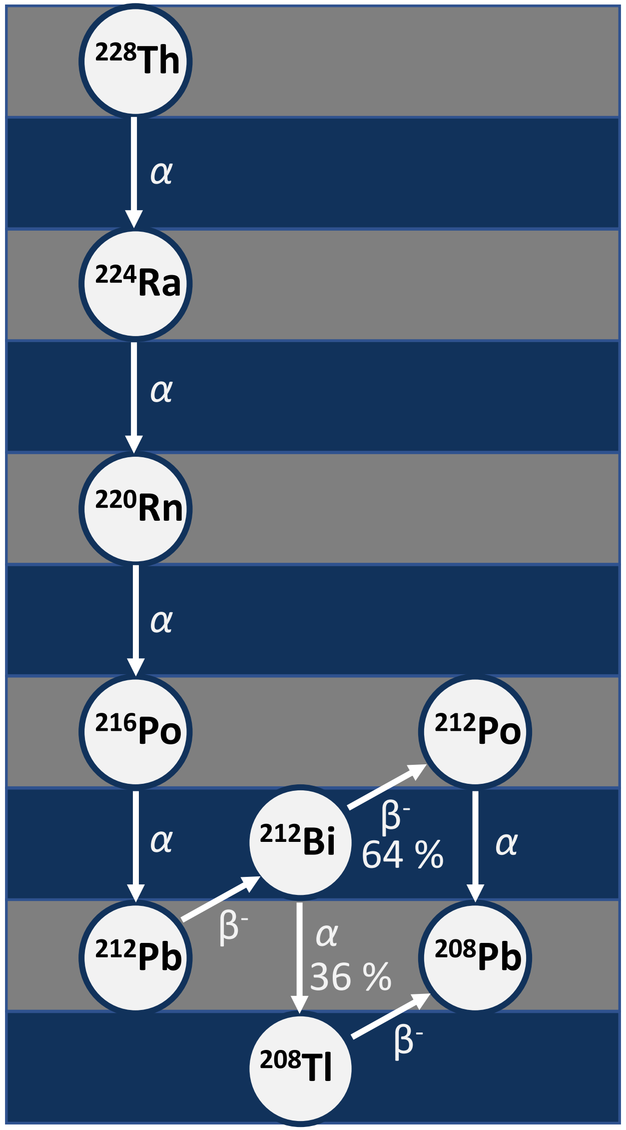
^{224}Ra decays by four α-emissions



Following Bateman (1908), concentrations of isotopes in a decay chain are calculable from initial concentrations and decay constants (λ)

$$\frac{dN_1}{dt} = -\lambda_1 N_1$$

$$\frac{dN_i}{dt} = \lambda_{i-1} N_{i-1} - \lambda_i N_i \ \ (i = 2, n)$$

^{224}Ra reaches equilibrium 6 d after t_{sep}

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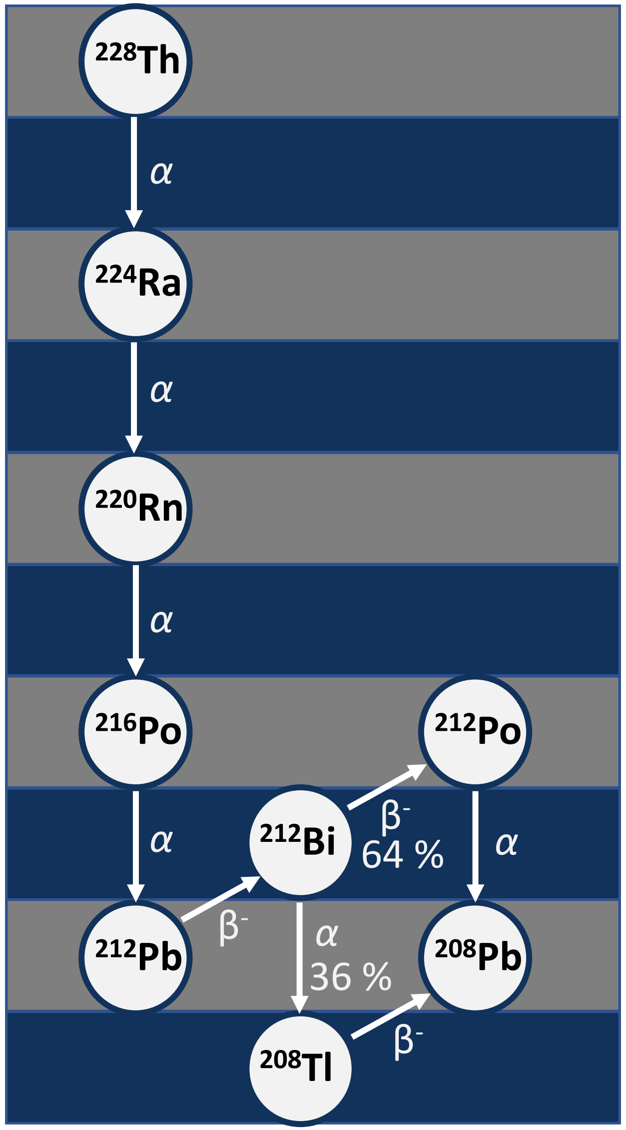
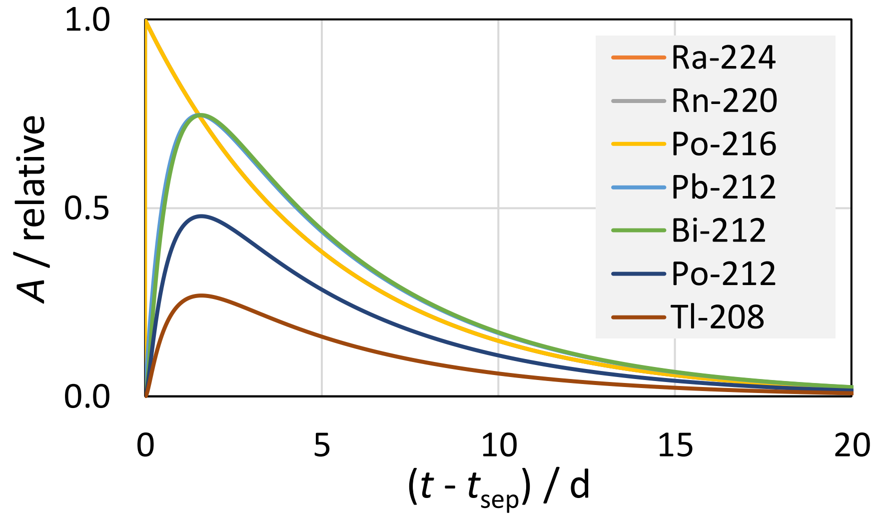
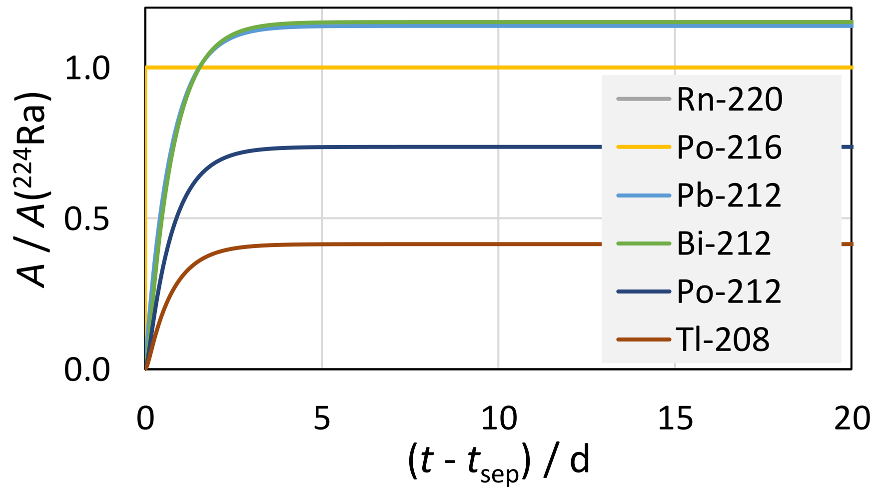


	$T_{1/2}$	$A/A_{Ra\text{-}224}$
^{224}Ra	3.631(2) d	1
^{220}Rn	55.8(3) s	1.000178(1)
^{216}Po	0.148(4) s	1.000178(1)
^{212}Pb	10.64(1) h	1.13928(15)
^{212}Bi	60.54(6) min	1.15263(15)
^{212}Po	300(2) ns	0.7385(11)
^{208}Tl	3.058(6) min	0.4144(20)

Most γ-rays in the decay chain come from ^{212}Pb and ^{208}Tl

Pre-equilibrium activity assays are tricky





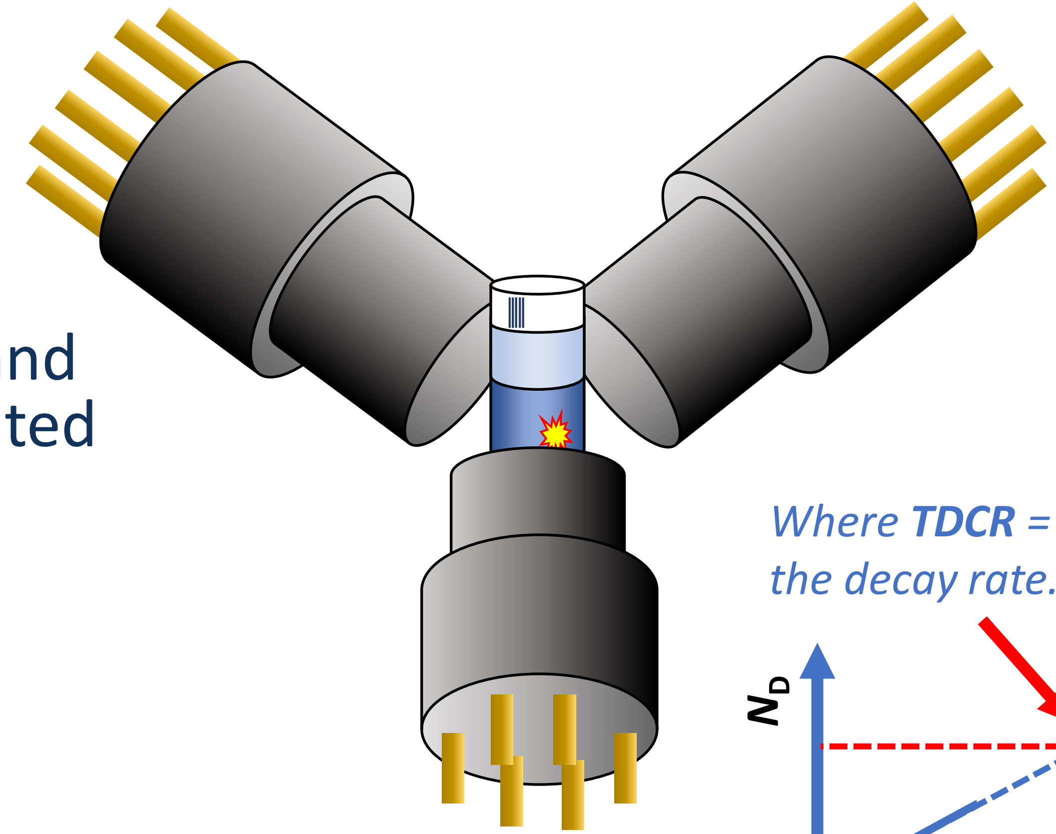
TDCR is well-suited for alpha-emitters

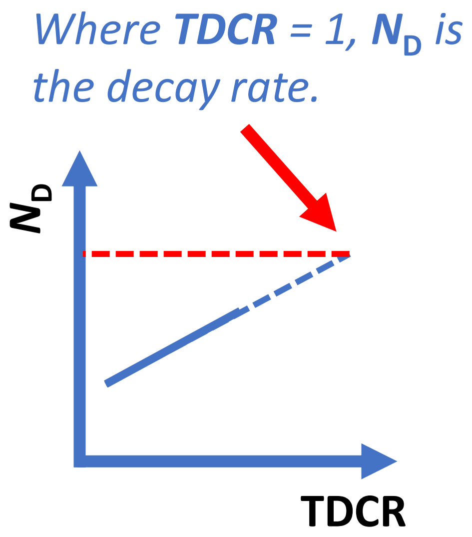
Triple-to-double Coincidence Ratio (TDCR) counting

- Liquid scintillation counting
- 3-detector system where double and triple coincidence events are counted

$$TDCR = N_T/N_D = \varepsilon_T/\varepsilon_D$$

- Vary efficiency
- **As $\varepsilon_T/\varepsilon_D \rightarrow 1$, N_D (and N_T) $\rightarrow N$**
  - In practice, a bit more complicated, but we have good models!





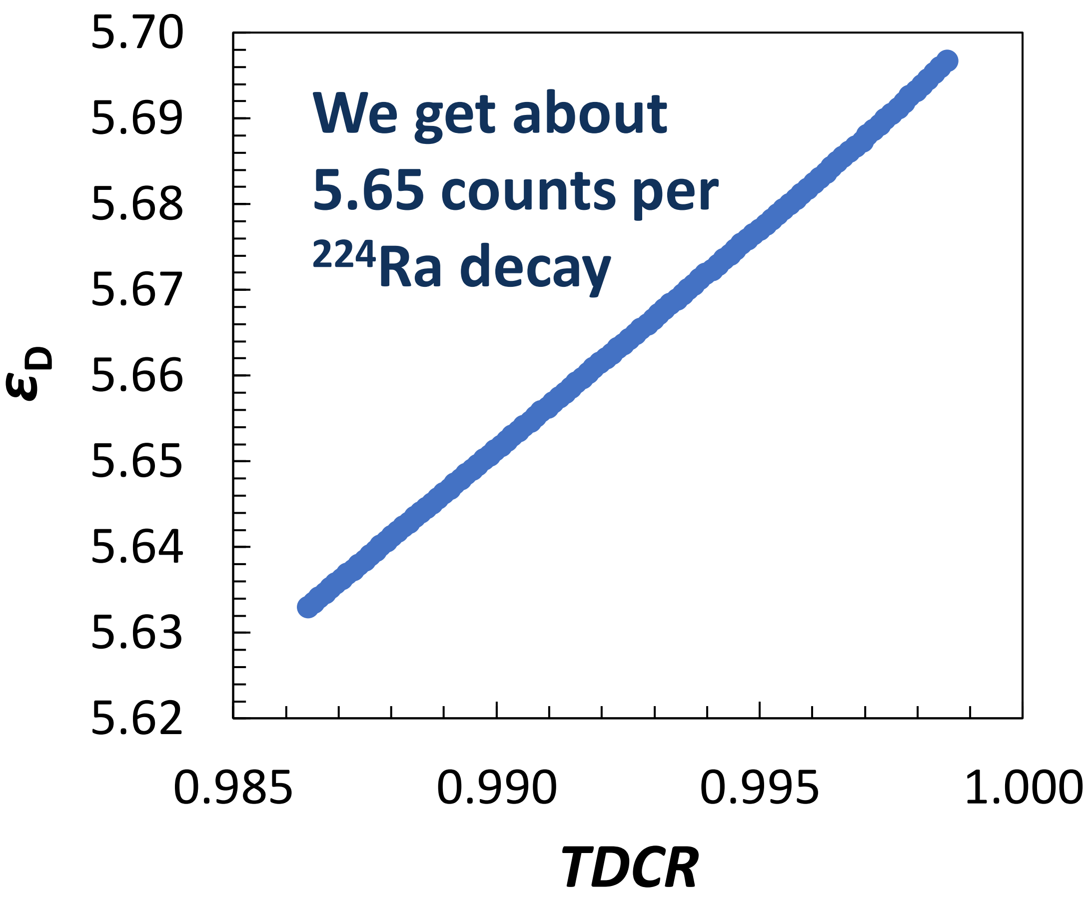
LS counting efficiencies are high

NIST

Triple-to-double Coincidence Ratio (TDCR) counting

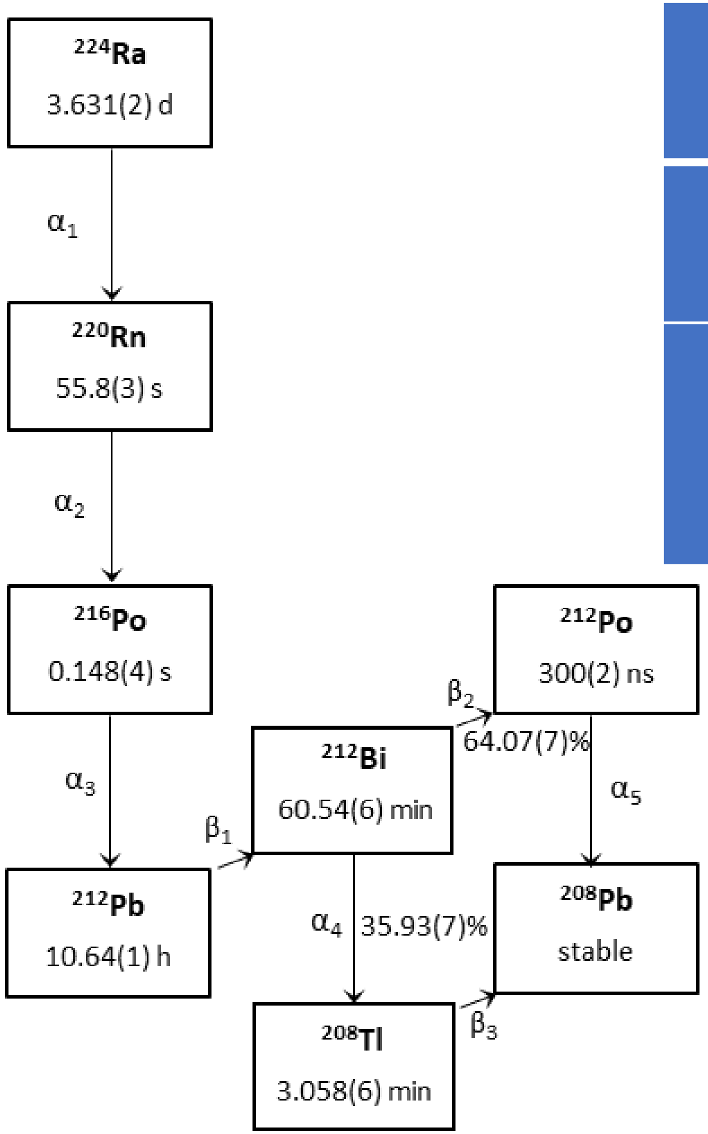
$$\boldsymbol{TDCR = N_T/N_D = \varepsilon_T/\varepsilon_D}$$

The MICELLE2 model* uses a Monte Carlo approach to calculate ε_T and ε_D for β^- decay branches



*Kossert & Grau Carles, Appl. Radiat. Isotop. 68, 1482-1488 (2010).

The model: assumptions & decay data



Daughter nuclide	beta-gamma transitions					
	A	P_{br}	B	P_{br}	C	P_{br}
^{212}Pb	$\beta_{0,3}\ \gamma_{3,1}\ \gamma_{1,0}$	0.0499	$\beta_{0,2}\ \gamma_{2,0}$	0.817	$\beta_{0,0}$	0.1331
^{208}Tl	$\beta_{0,2}\ \gamma_{2,1}\ \gamma_{1,0}$	0.492	$\beta_{0,3}\ \gamma_{3,1}\ \gamma_{1,0}$	0.221	$\beta_{0,4}\ \gamma_{4,2}\ \gamma_{2,1}$	0.287

- **Assume 100 % detection for α decays**
- **Assume 100 % detection for ^{212}Bi+^{212}Po**

Napoli et al., Appl. Radiat. Isotop. 155, 108933 (2020).

NIST ^{224}Ra and ^{212}Pb activity standards

Applied Radiation and Isotopes 155 (2020) 108933

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso

Primary standardization of ^{224}Ra activity by liquid scintillation counting

Elisa Napoli[a,b,c,d], Jeffrey T. Cessna[a], Ryan Fitzgerald[a], Leticia Pibida[a], Ronald Collé[a], Lizbeth Laureano-Pérez[a], Brian E. Zimmerman[a], Denis E. Bergeron[a,*]

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[b] Oncoinvent AS, Oslo, Norway
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ARTICLE INFO

Keywords:
TDCR

ABSTRACT

A standard for activity of ^{224}Ra in secular equilibrium with its progeny has been developed, based on triple-to-double coincidence ratio (TDCR) liquid scintillation (LS) counting. The standard was confirmed by efficiency

u_c = 0.23 %

Applied Radiation and Isotopes 190 (2022) 110473

Contents lists available at ScienceDirect

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Primary standardization of ^{212}Pb activity by liquid scintillation counting

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ARTICLE INFO

Keywords:
Pb-212
TDCR
Anticoincidence counting
Efficiency tracing
Radionuclide calibrator
Dose calibrator
Well counter
Activity calibration
Decay chain

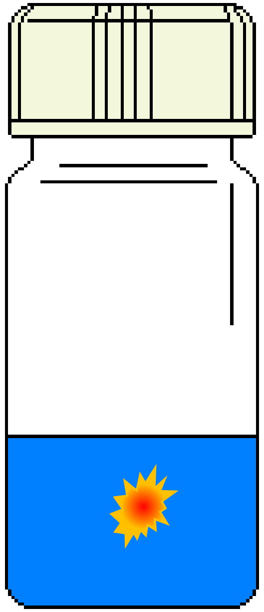
ABSTRACT

An activity standard for ^{212}Pb in equilibrium with its progeny was realized, based on triple-to-double coincidence ratio (TDCR) liquid scintillation (LS) counting. A Monte Carlo-based approach to estimating uncertainties due to nuclear decay data (branching ratios, beta endpoint energies, γ-ray energies, and conversion coefficients for ^{212}Pb and ^{208}Tl) led to combined standard uncertainties ≤ 0.20 %. Confirmatory primary measurements were made by LS efficiency tracing with tritium and 4παβ(LS)-γ(NaI(Tl)) anticoincidence counting. The standard is discussed in relation to current approaches to ^{212}Pb activity calibration. In particular, potential biases encountered when using inappropriate radionuclide calibrator settings are discussed.

u_c = 0.20 %

Measurement challenges

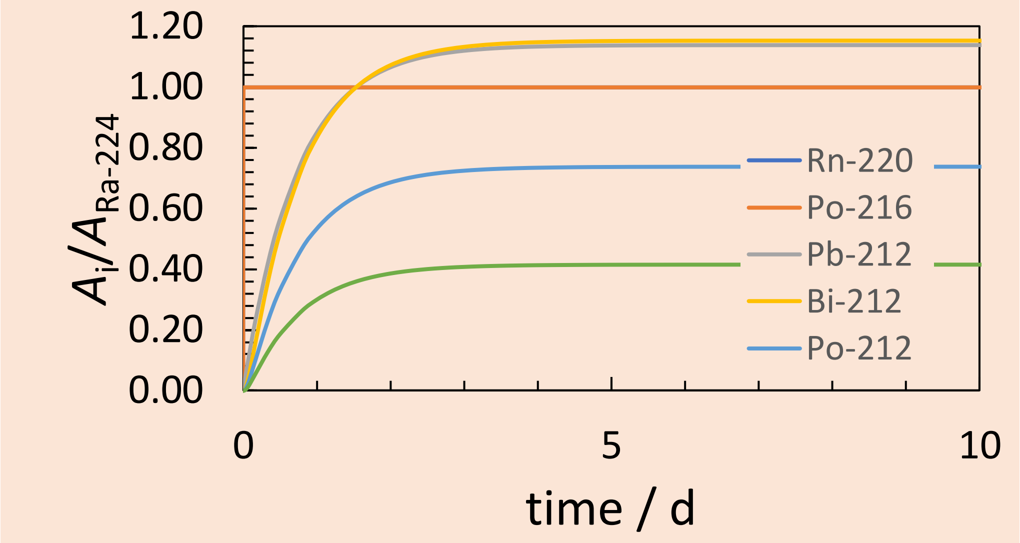
ε = 1
So, what's the big deal?

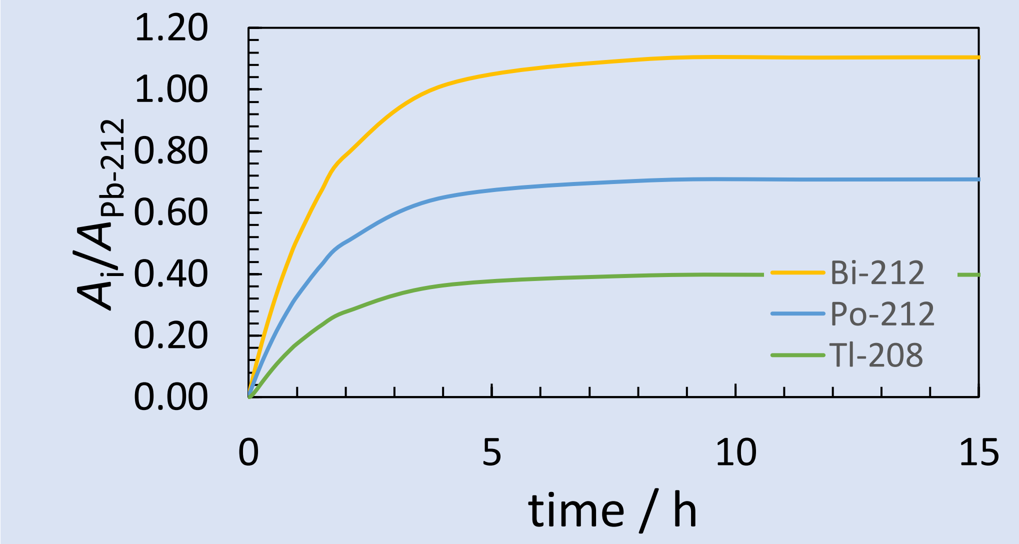


Challenges? Really?

- **Decay chains**
  - Progeny include beta-emitters (ε < 1)
  - Pre-equilibrium measurements
- **Impurities**
  - Breakthrough
  - Co-produced isotopes

Equilibration considerations



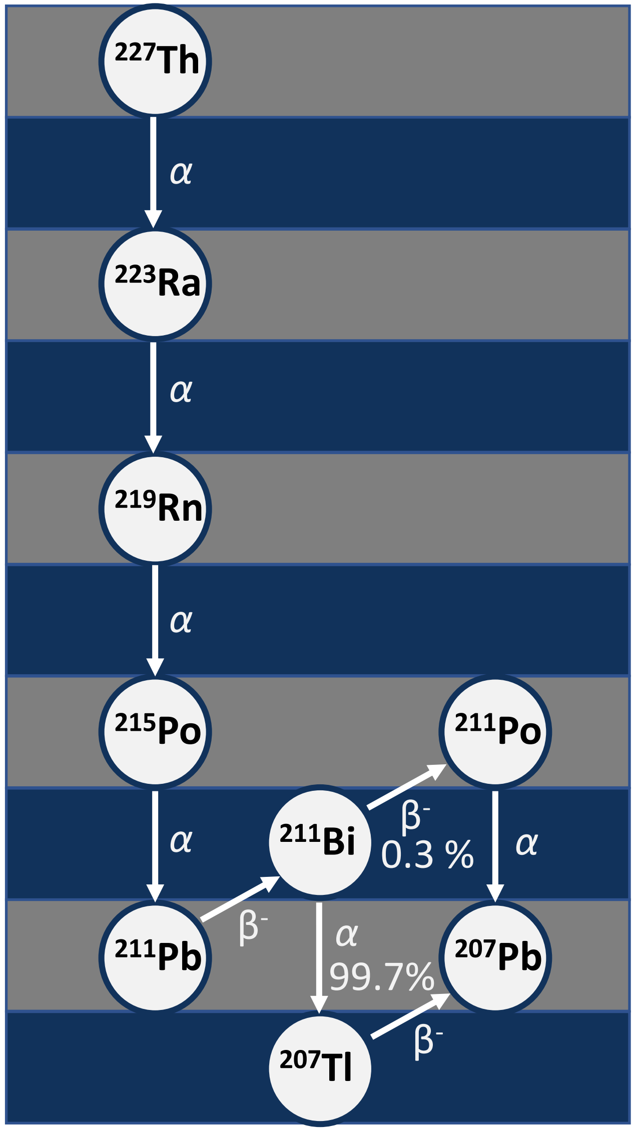


^{224}Ra (longest-lived progeny is ^{212}Pb, $T_{1/2}$ = 10.6 h) takes > 6 d to reach equilibrium

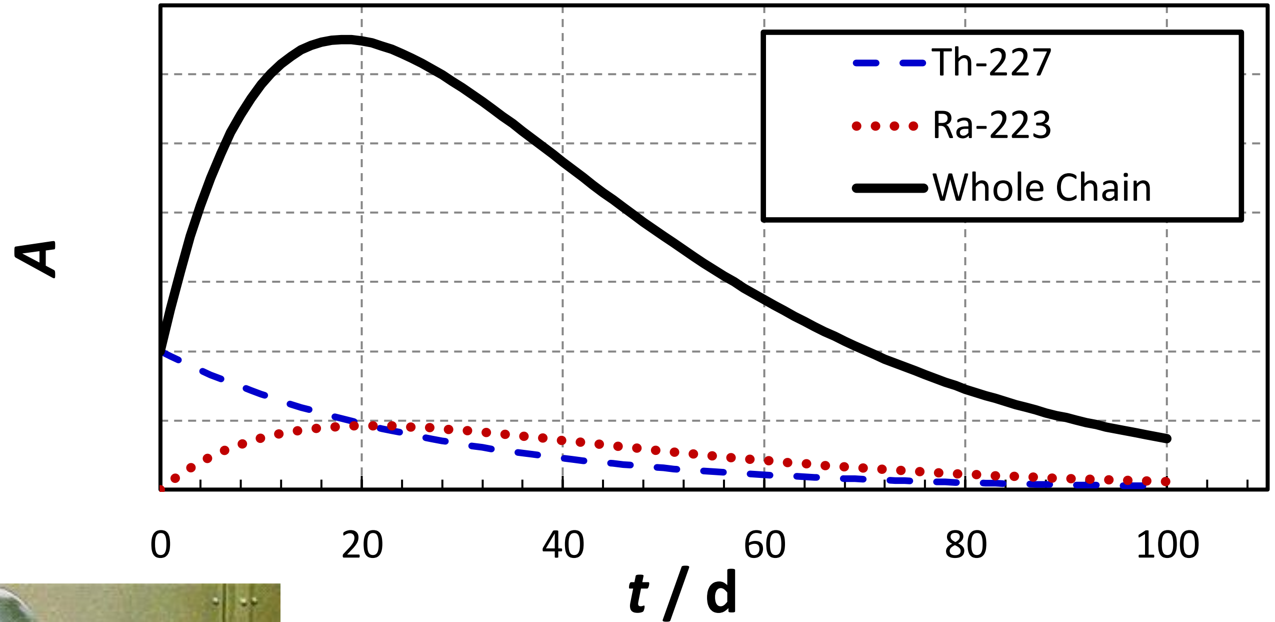
Separated from its parent, ^{212}Pb (longest-lived progeny is ^{212}Bi, $T_{1/2}$ = 60.55 min) reaches equilibrium in ~ 12 h.

Breakthrough of the parent leads to "supported" ^{212}Pb

Measuring during ingrowth



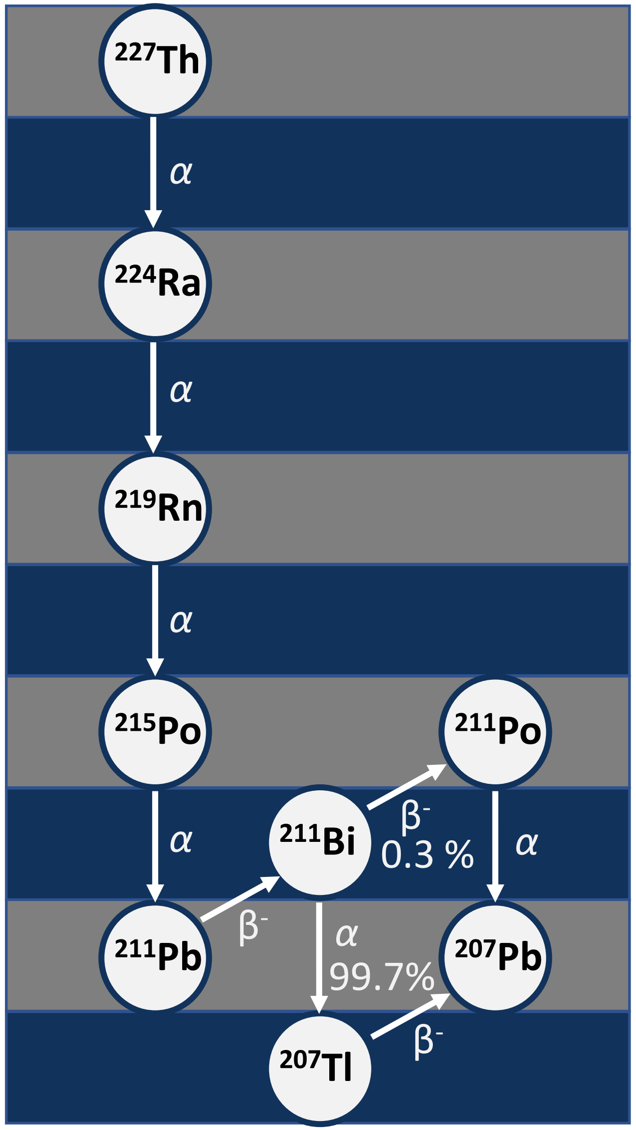
Th-227 differs from previously considered decay chain nuclides because we cannot wait for equilibrium.



"If there's one thing that I detest, it is a fair fight. But if I must, then I must…"
--Dark Helmet

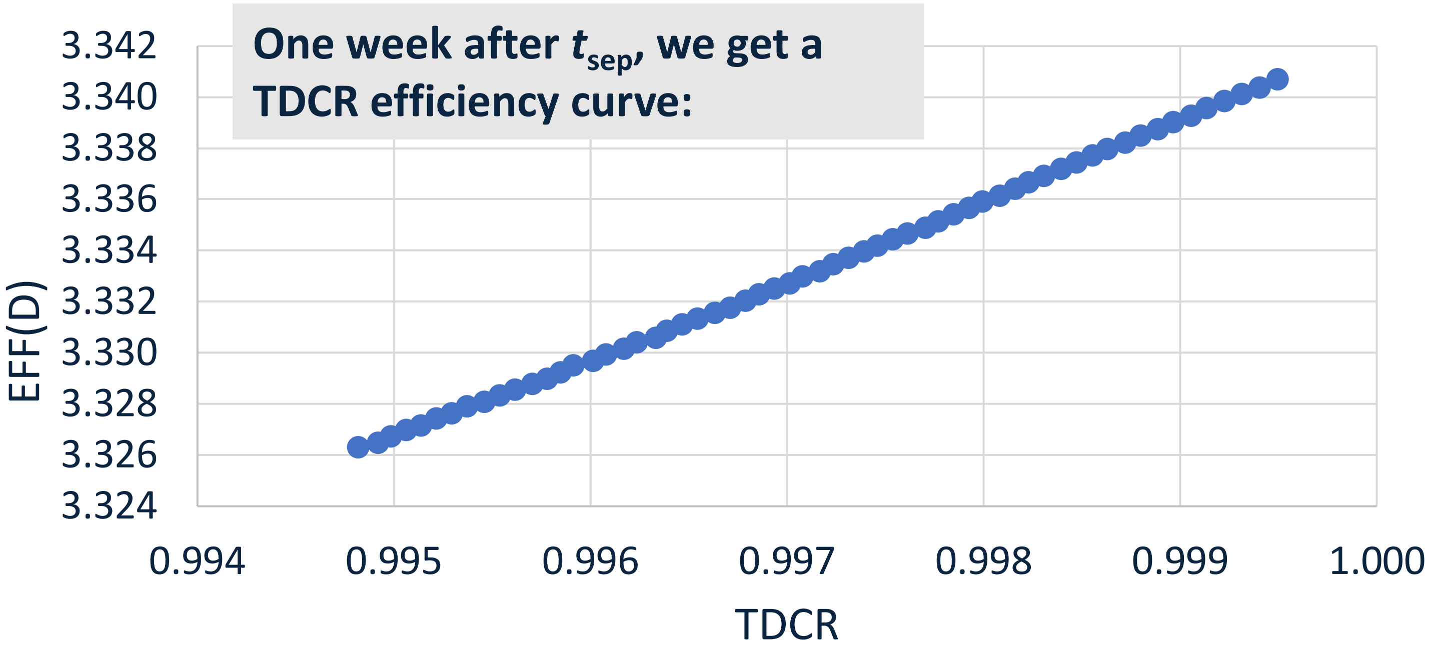
https://rickmoranisgifs.tumblr.com/post/65998603558

Preliminary LS efficiency calculations

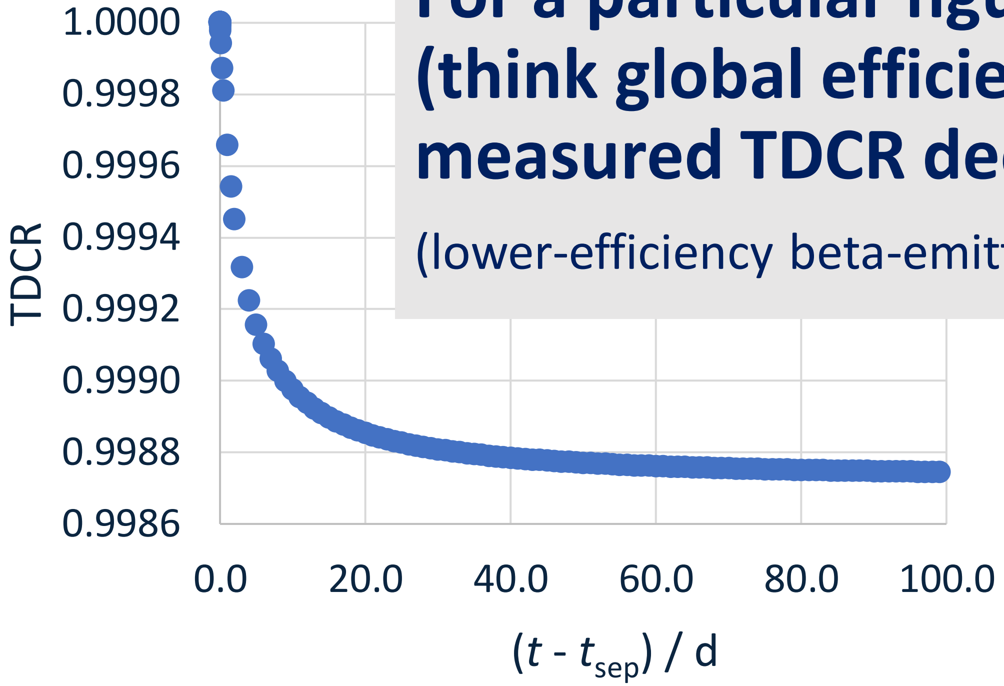


Estimate 100 % LS counting efficiency for alpha emissions

Calculate efficiencies for beta emissions with MICELLE2

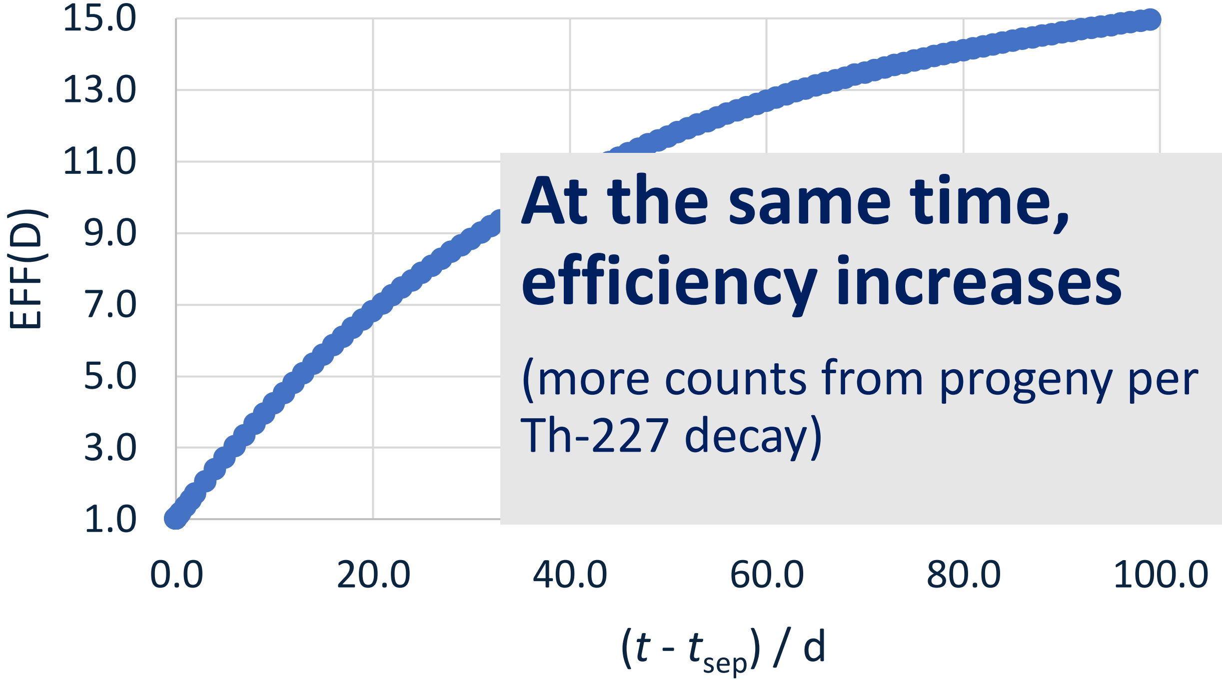


Time evolution of LS efficiencies



For a particular figure-of-merit (think global efficiency), the measured TDCR decreases with time

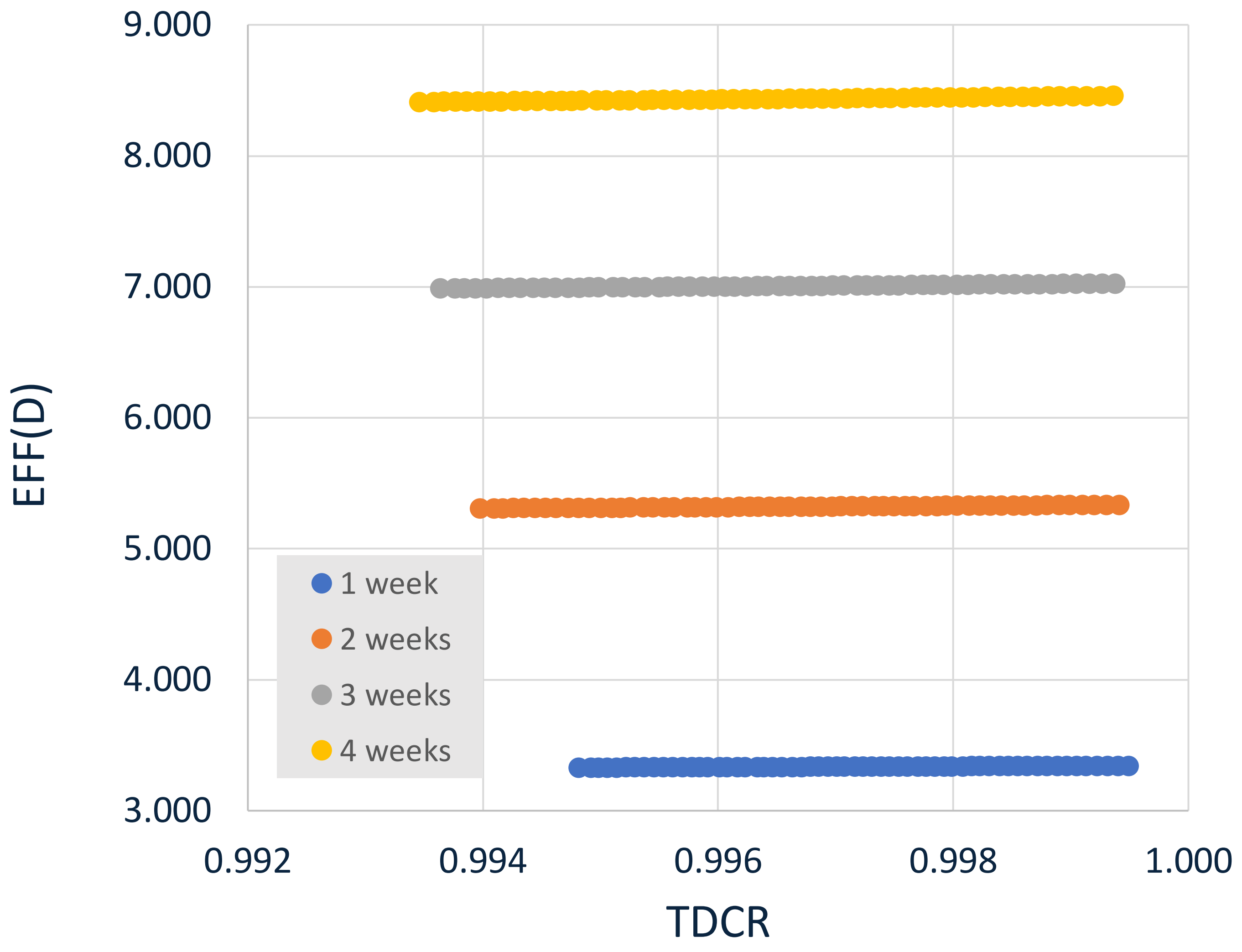
(lower-efficiency beta-emitting progeny grow in)



At the same time, efficiency increases

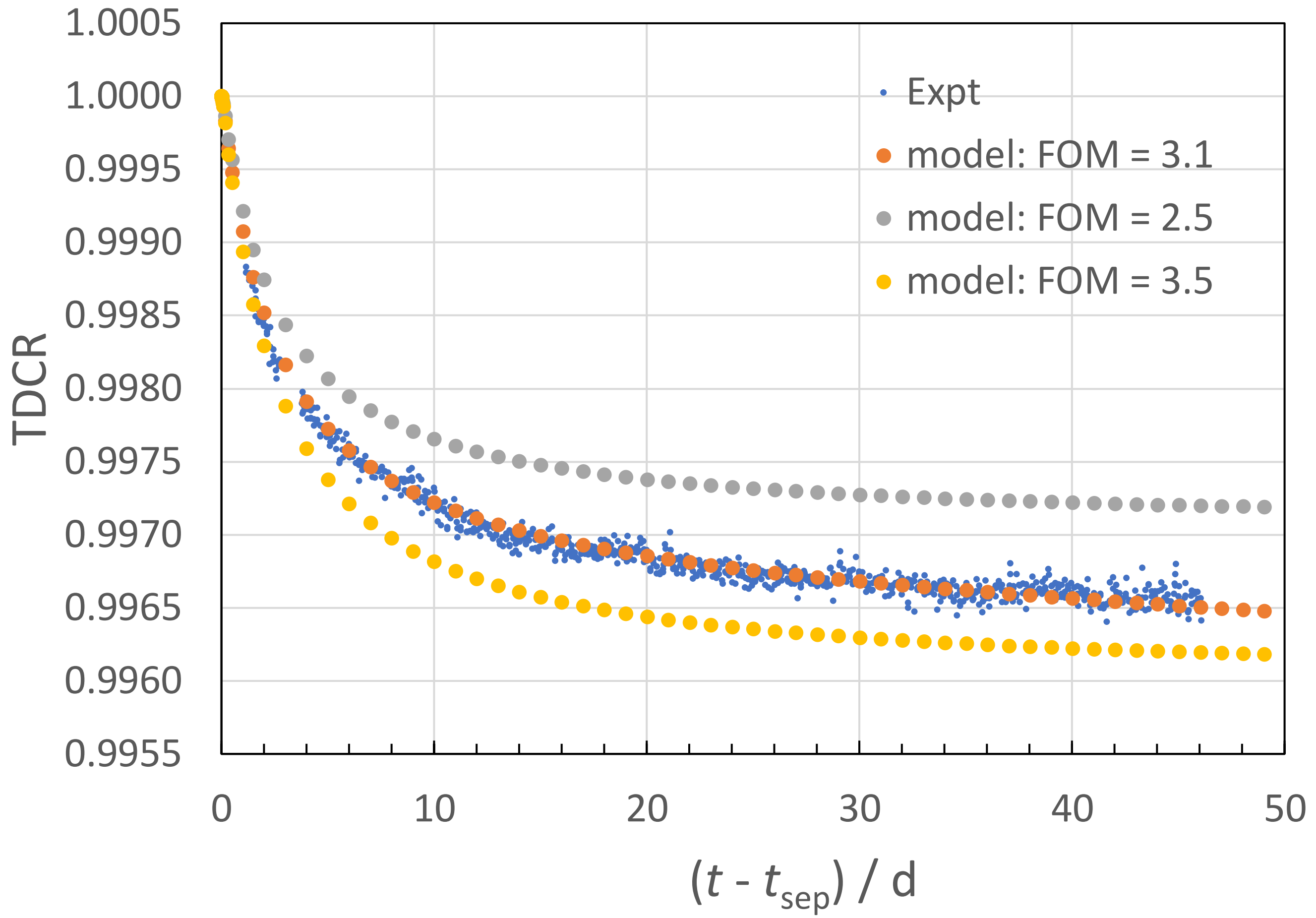
(more counts from progeny per Th-227 decay)

Time-dependent efficiency curves



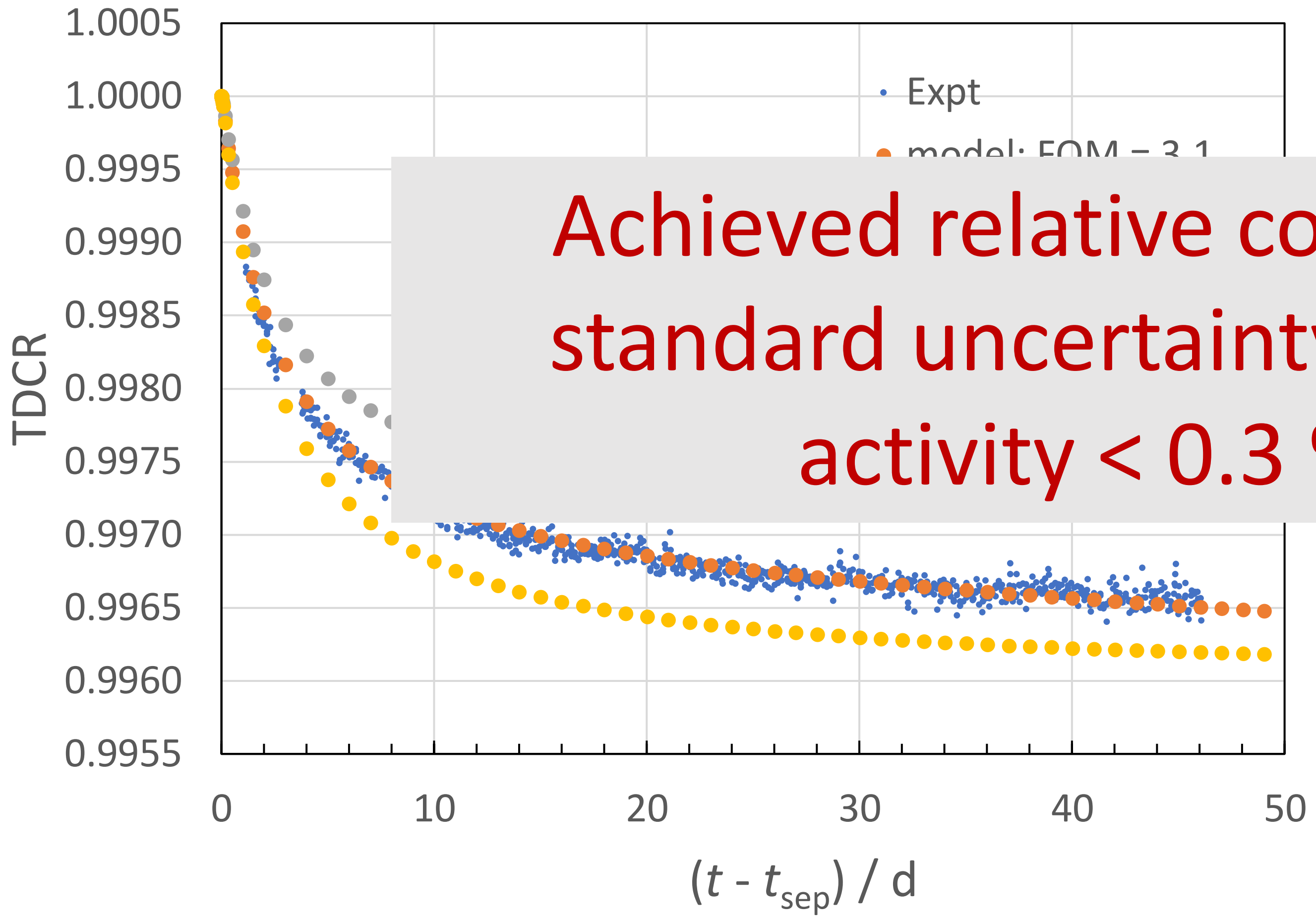
So, for a given LS source, we predict the decrease in experimental TDCR and an increase in efficiency over time.

The single Figure-of-Merit model



- **If we assume the LS source is stable, then the observed triple-to-double coincidence ratio is expected to change as the beta-emitting progeny grow in**
- **Our efficiency model tracks the ingrowth**
- **The slope of the curve is predicted by the counting efficiencies for the beta-emitters, so the free parameter (figure-of-merit) can be adjusted fit the experimental data to the model**
- **Modeled efficiencies are then used to calculate activity**

The single Figure-of-Merit model



Achieved relative combined standard uncertainty on the activity < 0.3 %

- If we assume the LS source is stable, then the observed triple-to-double coincidence ratio is expected to … beta-emitting progeny
- … model tracks the
- …he curve is predicted …g efficiencies for the beta-emitters, so the free parameter (figure-of-merit) can be adjusted fit the experimental data to the model
- Modeled efficiencies are then used to calculate activity

Measurement challenges

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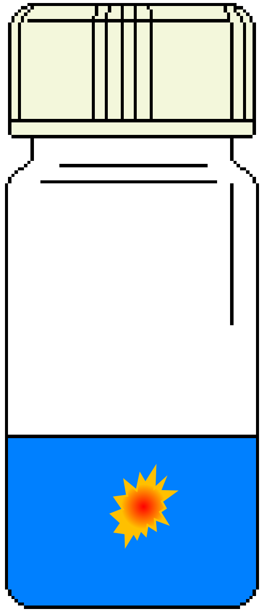
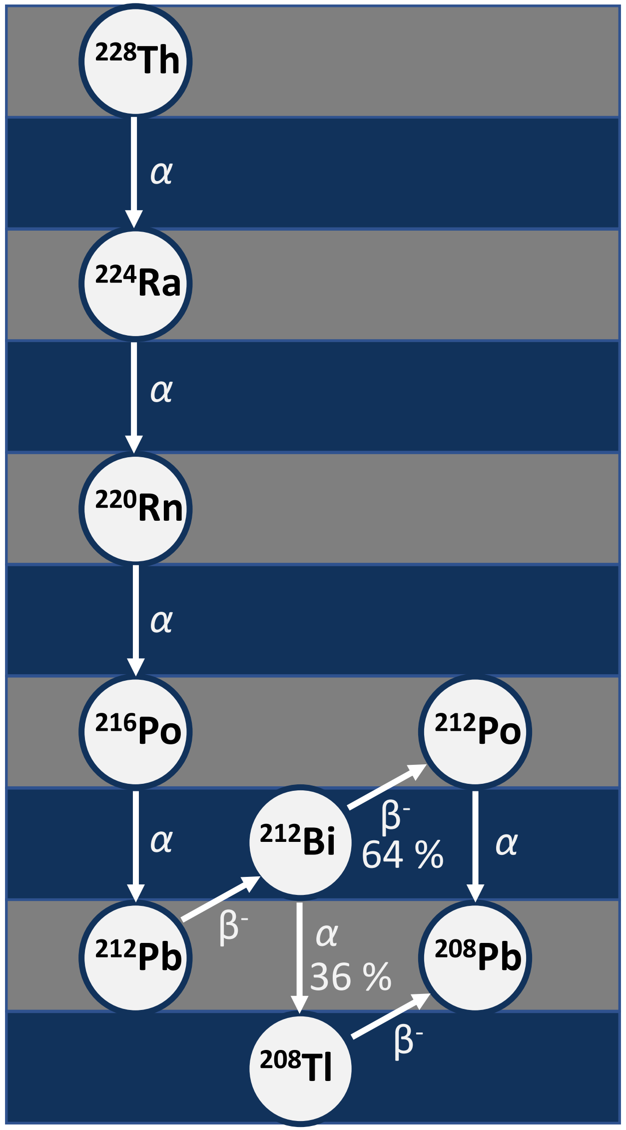
$\varepsilon = 1$
So, what's the big deal?



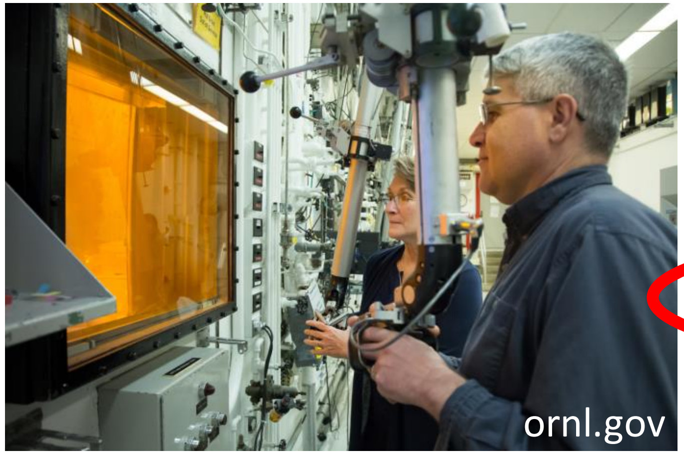
Challenges? Really?

- **Decay chains**
  - Progeny include beta-emitters ($\varepsilon < 1$)
  - Pre-equilibrium measurements
- **Impurities**
  - Breakthrough
  - Co-produced isotopes

The problem of breakthrough



In our ^{224}Ra standardization campaigns, ^{228}Th breakthrough was mostly insignificant. Except for the one time it wasn't.



t_{sep}	$f_{Th\text{-}228}$ at t_{sep}
9/14/2018	$(3.3 \pm 0.4) \times 10^{-6}$
11/2/2018	$(5.0 \pm 1.6) \times 10^{-6}$
2/8/2019	$(4.2 \pm 0.6) \times 10^{-6}$
4/22/2019	$(9.7 \pm 0.1) \times$ **10^{-4}**

See: https://doi.org/10.1021/scimeetings.0c01048

Bergeron et al., ARI 155, 108933 (2020).

'Negligible' breakthrough in the literature

NIST

Appl. Radiat. Isot. Vol. 39, No. 4, pp. 283–286, 1988
Int. J. Radiat. Appl. Instrum. Part A
Printed in Great Britain

0883-2889/88 $3.00 + 0.00
Pergamon Press plc

An Improved Generator for the Production of ^{212}Pb and ^{212}Bi from ^{224}Ra

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(*Received 7 October 1987*)

We have developed an improved generator for the production of the alpha emitting radionuclide ^{212}Bi and its parent, ^{212}Pb. These radionuclides are well suited to use as radiotherapeutic agents due to their relatively

the activity remains on the anion exchange resin. Breakthrough of the thorium in the radium solution is negligible, less than 1 ppm. Generators which have been returned to ANL decay with the half life of ^{224}Ra.

The yield of the generator as a function of HI

Received: 8 November 2017 | Revised: 16 December 2017 | Accepted: 17 January 2018
DOI: 10.1002/jlcr.3610

RESEARCH ARTICLE

WILEY Journal of Labelled Compounds and Radiopharmaceuticals

Ra-224 labeling of calcium carbonate microparticles for internal α-therapy: Preparation, stability, and biodistribution in mice

Sara Westrøm[1,2,3] | Marion Malenge[1] | Ida Sofie Jorstad[1] | Elisa Napoli[1,3,4] | Øyvind S. Bruland[1,3,5] | Tina B. Bønsdorff[1] | Roy H. Larsen[1]

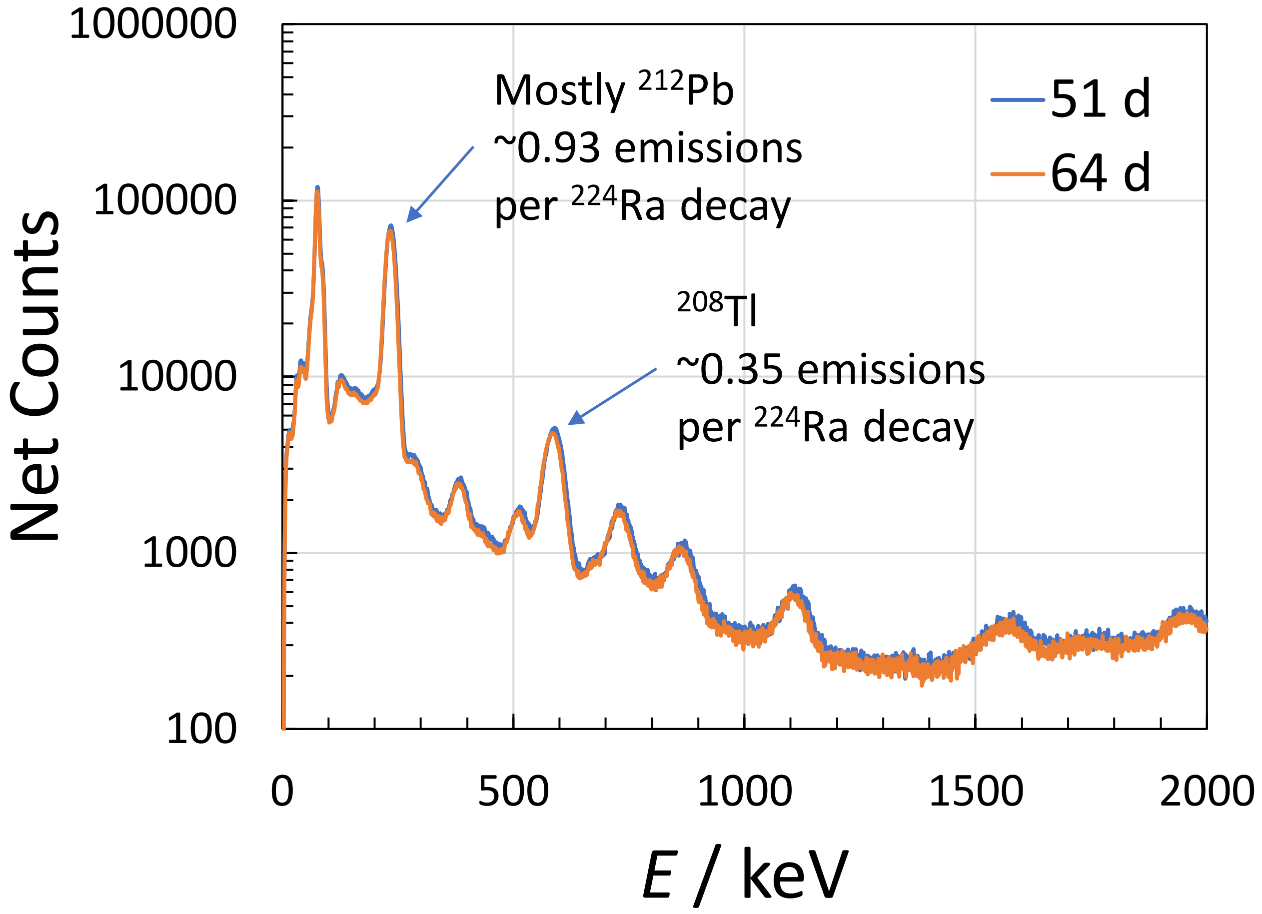
3.2 | Ra-224 generator performance

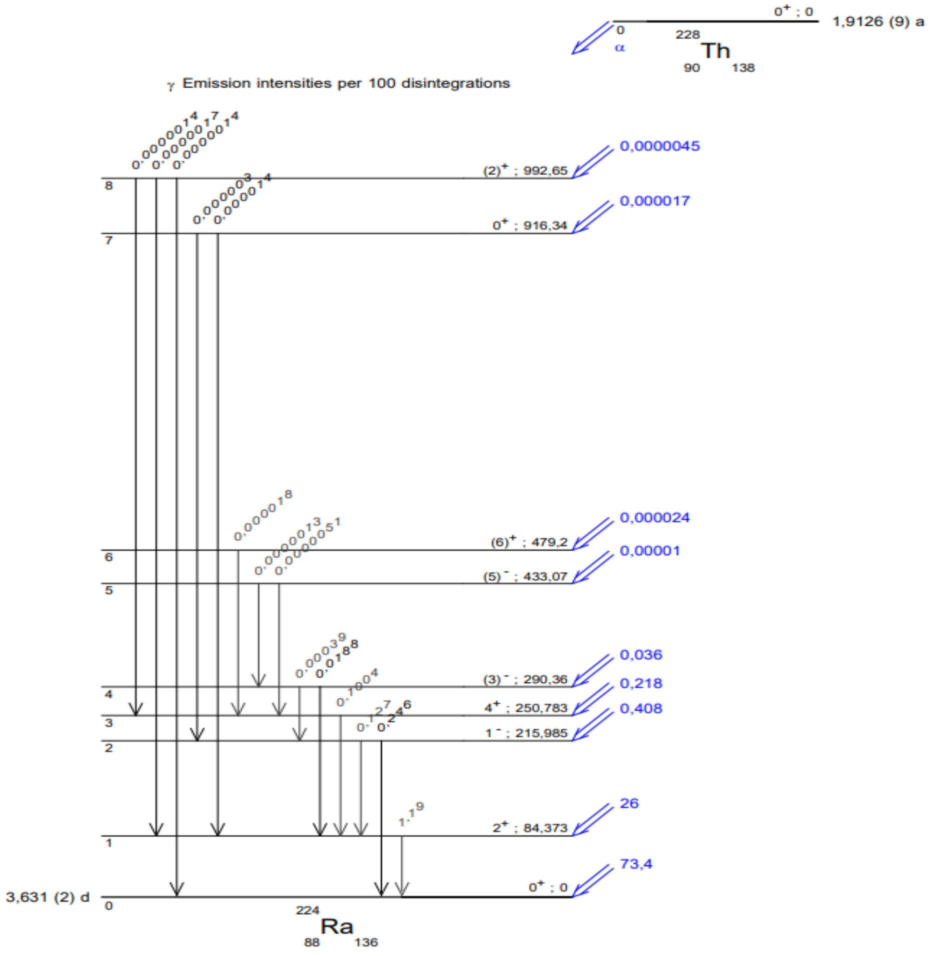
Breakthrough of the ^{228}Th parent was determined with α-spectroscopy to be less than or equal to 1.5×10^{-3} Bq/mL. This amount corresponds to less than 3×10^{-7} of the original ^{224}Ra activity. No ingrowth of ^{224}Ra from ^{228}Th was detected when half-life measurements with liquid scintillation were performed. Altogether, the results from these 2 analyses suggest that the quality of the prepared ^{224}Ra solution was satisfactory.

NaI(Tl) won't see ^{228}Th in spectrum

NIST

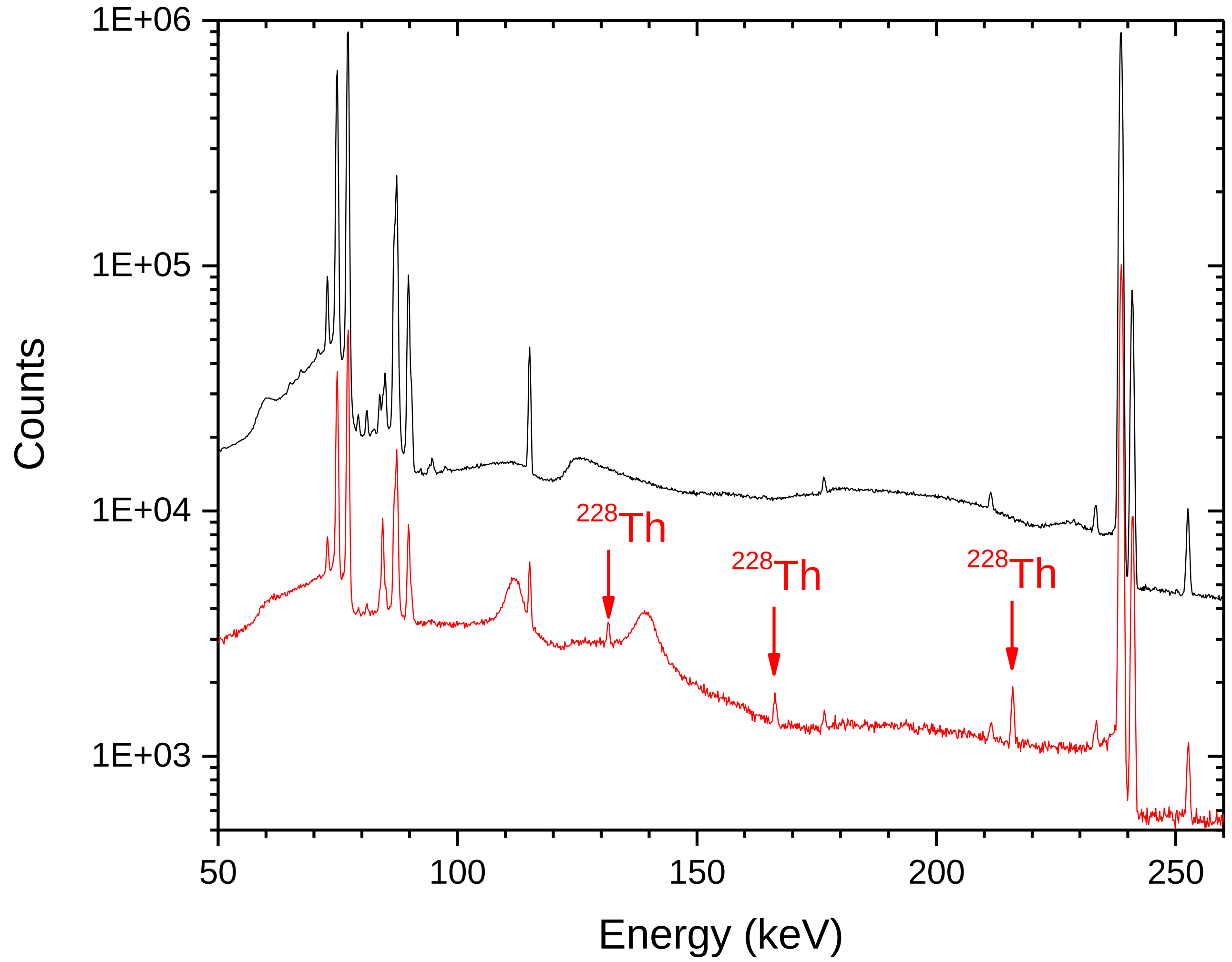
^{228}Th decays mostly to the ground state of ^{224}Ra





http://www.lnhb.fr/nuclides/Th-228_tables.pdf

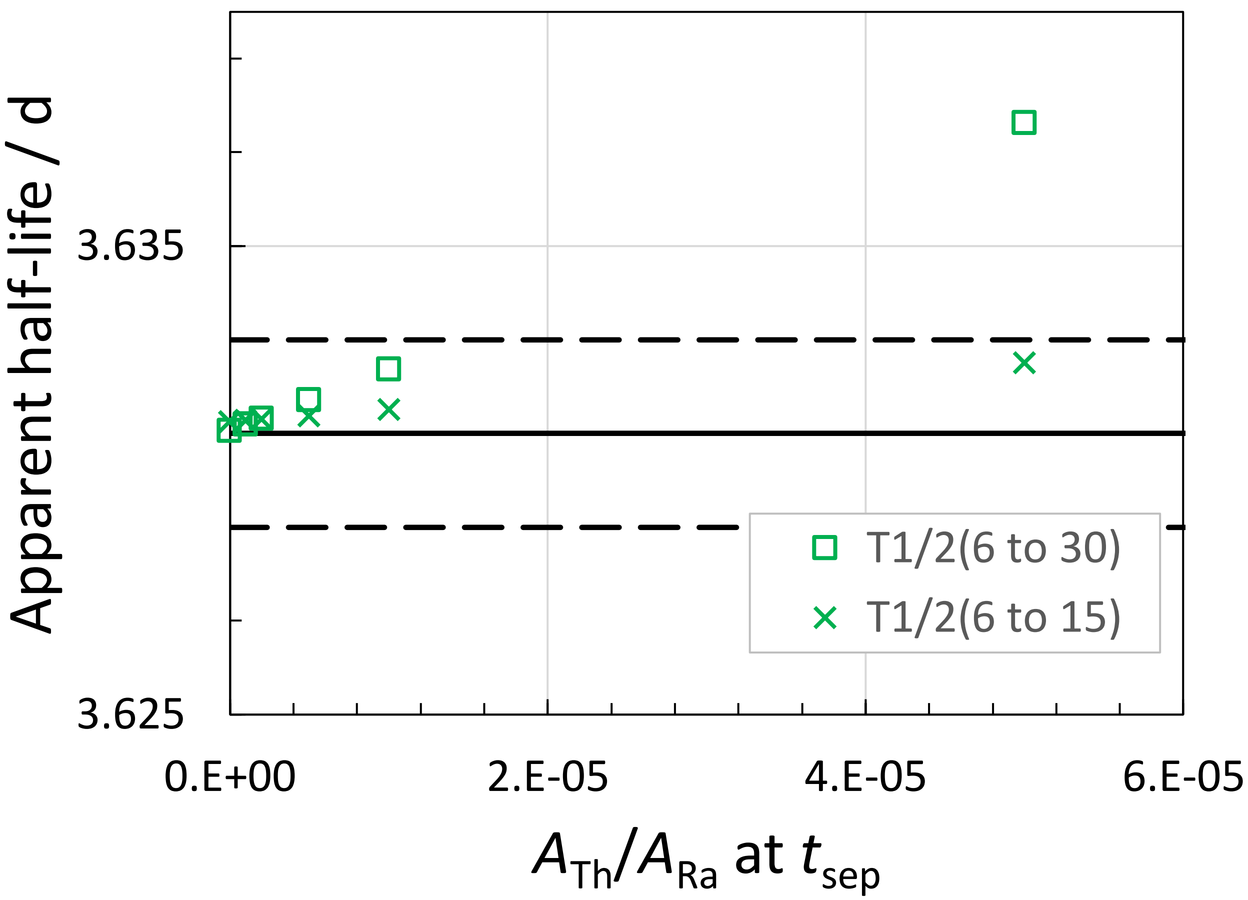
HPGe detection of ^{228}Th faces challenges



The resolution of HPGe allows identification of the weak γ-ray peaks from ^{228}Th decay

Minimum detectable activities at early times are high, due to the Compton background from ^{224}Ra and its progeny

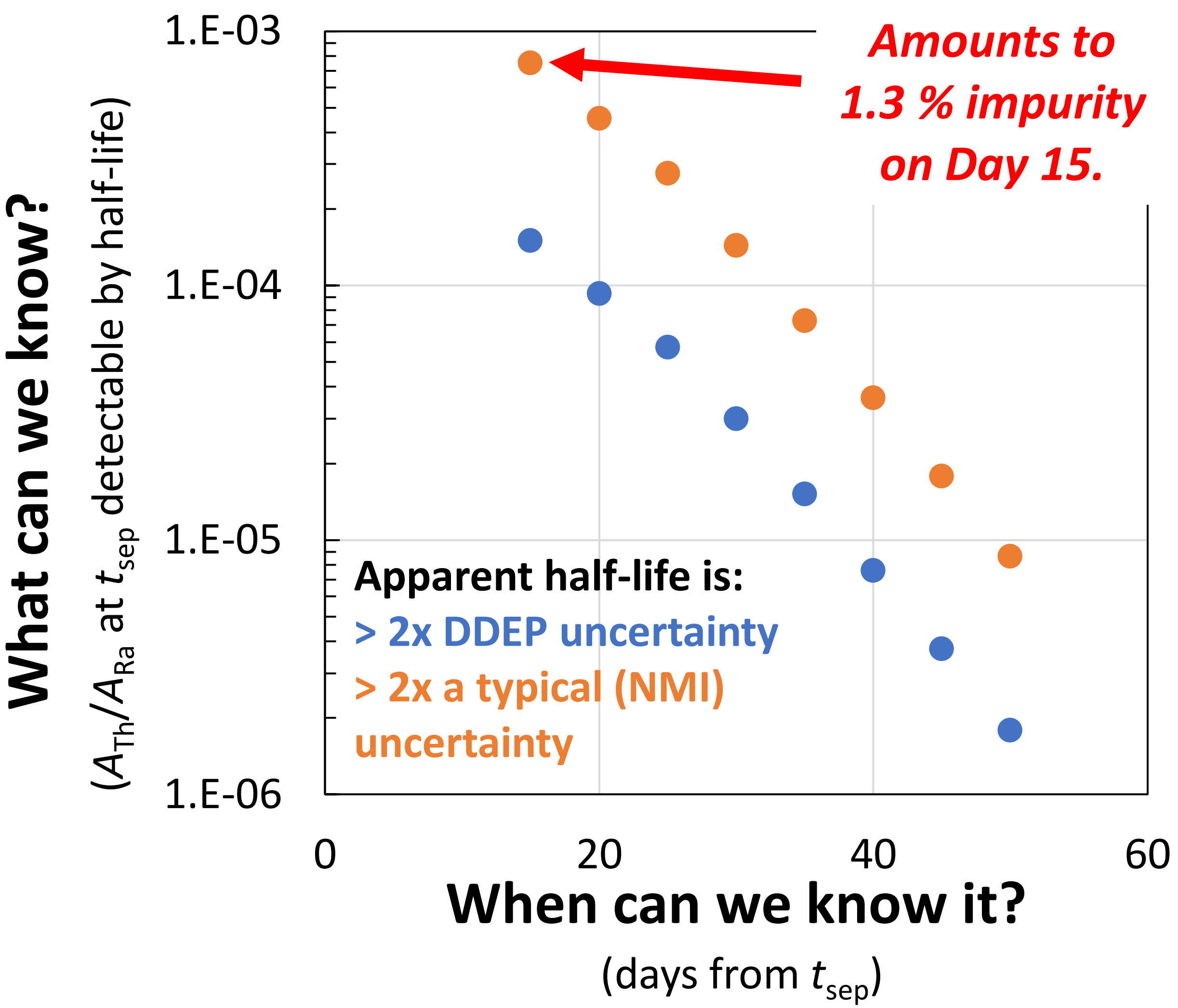
Can half-life detect < 1 ppm ^{228}Th?



Half-lives determined with pre-equilibration data require more complicated fitting

Half-lives determined with post-equilibration (> 6 d past t_{sep}) data are fairly robust against ^{228}Th breakthrough

Plotting what v. when

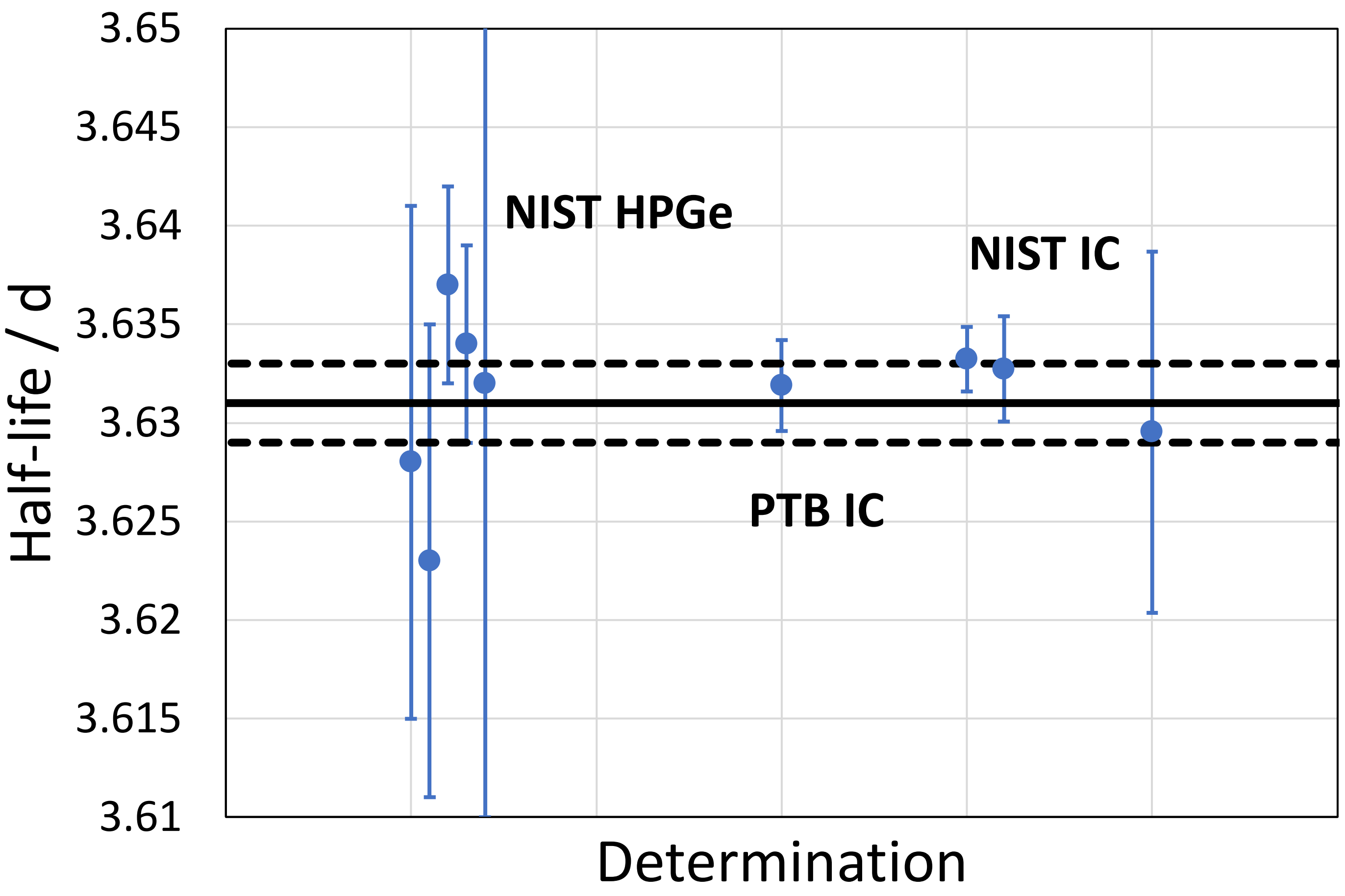


Monitoring half-life can provide sensitivity to ppm-level ^{228}Th breakthrough…

….if you can distinguish a deviation of 2σ from the evaluated half-life (i.e., you're the ***best in the world*** *at measuring half-lives)*

…and you measure until 50 days post-separation

Nobody's that good!



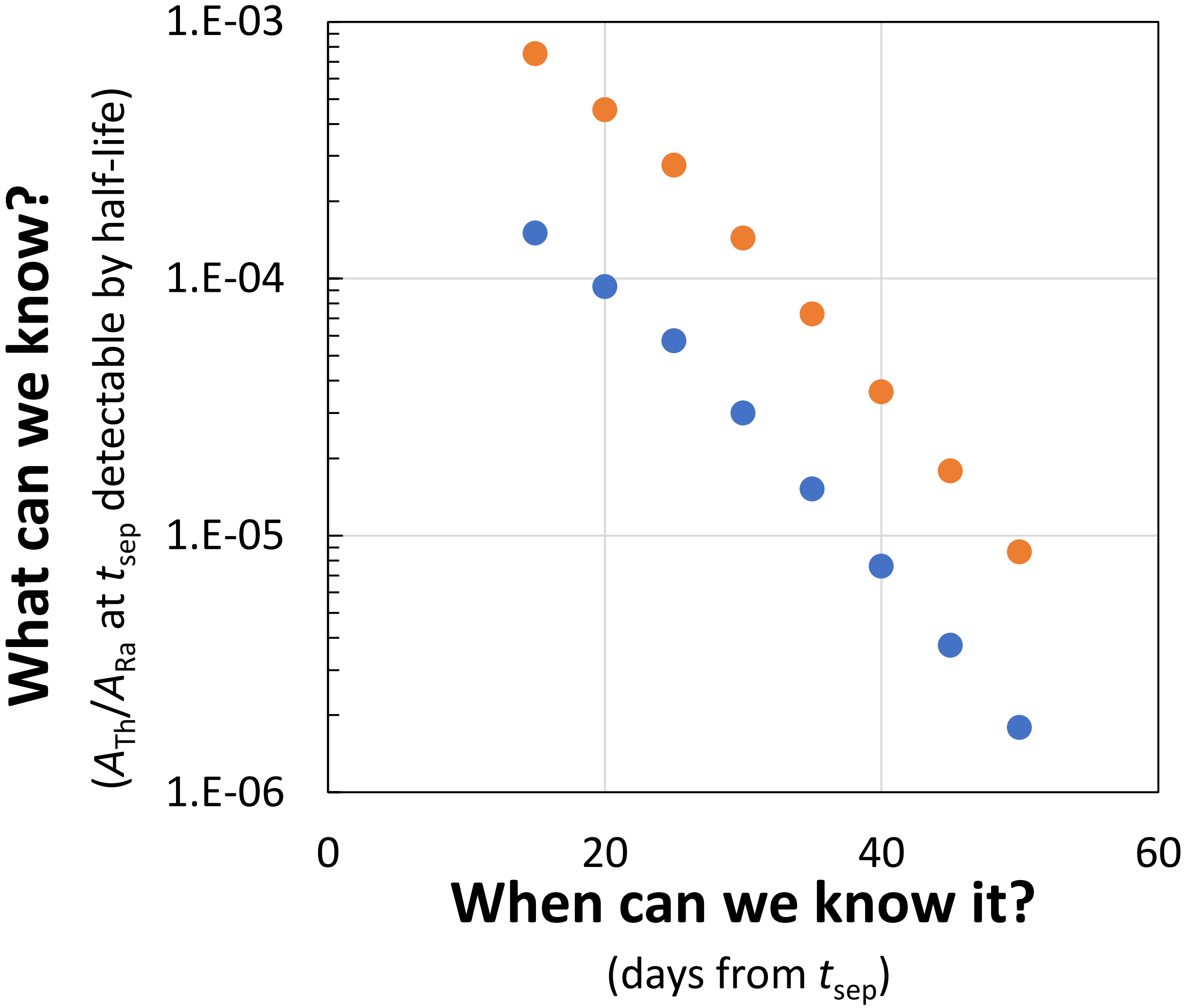
Data are being considered for a new half-life evaluation (DDEP*)

There is spread in the dataset, and estimated uncertainties vary

*http://www.lnhb.fr/nuclear-data/nuclear-data-table/
Bergeron et al., ARI 170, 109572 (2021).

So, catching breakthrough is a challenge

NIST



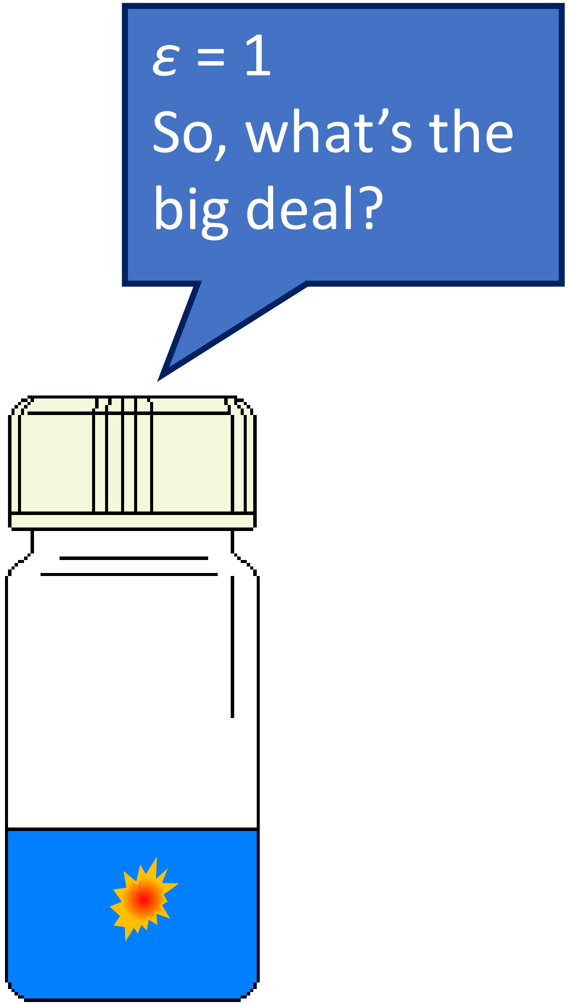
- **Gamma-ray spectrometry and half-life cannot provide an early measure of ^{228}Th breakthrough in ^{224}Ra**
- **Mass spectrometry could provide a sensitive alternative**

$$A_{Th}/A_{Ra} = 5 \times 10^{-6}$$

corresponds to

$$N_{Th}/N_{Ra} = 1 \times 10^{-3}$$

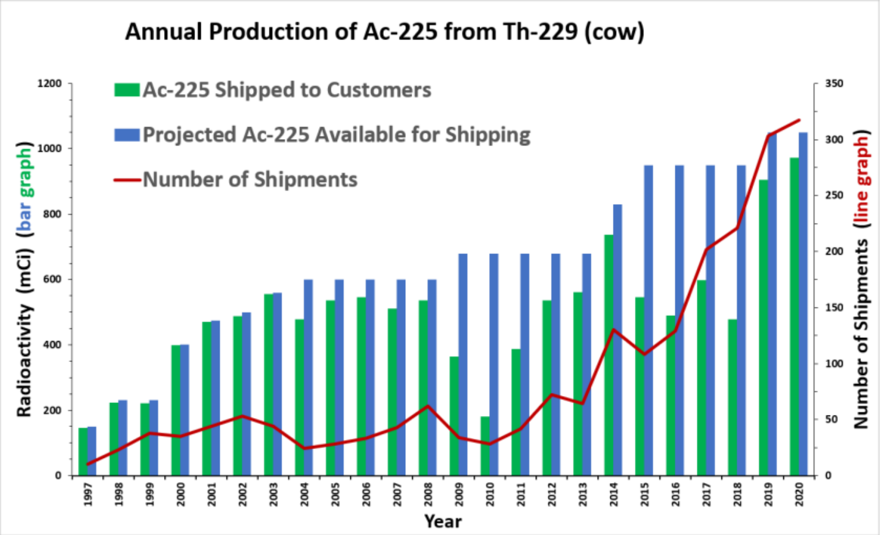
Measurement challenges



Challenges? Really?

- **Decay chains**
  - Progeny include beta-emitters (ε < 1)
  - Pre-equilibrium measurements
- **Impurities**
  - Breakthrough
  - Co-produced isotopes

Other impurities are tricky, too



https://www.fda.gov/media/152472/download
From the 2021 FDA-NRC Workshop on Ac-225.

Along with breakthrough for column-produced materials, there is serious concern right now about co-produced isotopes that cannot be easily separated

The ^{227}Ac impurity in accelerator-produced ^{225}Ac has the NRC considering licensing an impurity for the first time

It's not the dose to patients that's the concern; it's the occupational exposure to workers and the disposal questions. (Similar issues have come up with ^{177m}Lu impurities in ^{177}Lu radiopharmaceuticals.)

TES resolves ^{227}Ac contributions

NIST

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Check for updates

Measurement of ^{227}Ac impurity in ^{225}Ac using decay energy spectroscopy

A.D. Tollefson [a], C.M. Smith [a,*], M.H. Carpenter [a], M.P. Croce [a], M.E. Fassbender [a], K.E. Koehler [a], L.M. Lilley [a], E.M. O'Brien [a], D.R. Schmidt [b], B.W. Stein [a], J.N. Ullom [b,c], M.D. Yoho [a], D.J. Mercer [a]

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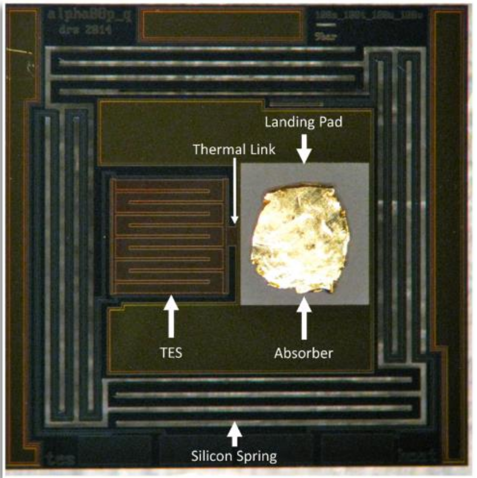


favorable candidates for early measurements.

We deduce from our data that the a priori detection limit is 0.0026 Bq of ^{227}Th per Bq of ^{225}Ac, assuming a 24-h measurement using a single DES channel and 1 Bq of sample. Assuming the realistic conditions of chemical purification 15 days post-irradiation followed by measurement five days later, this corresponds to an EOB limit of detection ^{227}Ac/^{225}Ac activity ratio of 0.38%. In order to meet our sensitivity goal of 0.15%, we must engage seven of our eight DES channels in a simultaneous measurement, giving a detection limit of 0.14%. Substantial improvements may be possible with better understanding and reduction of the background, and with faster DES sensors to allow for higher activity samples.

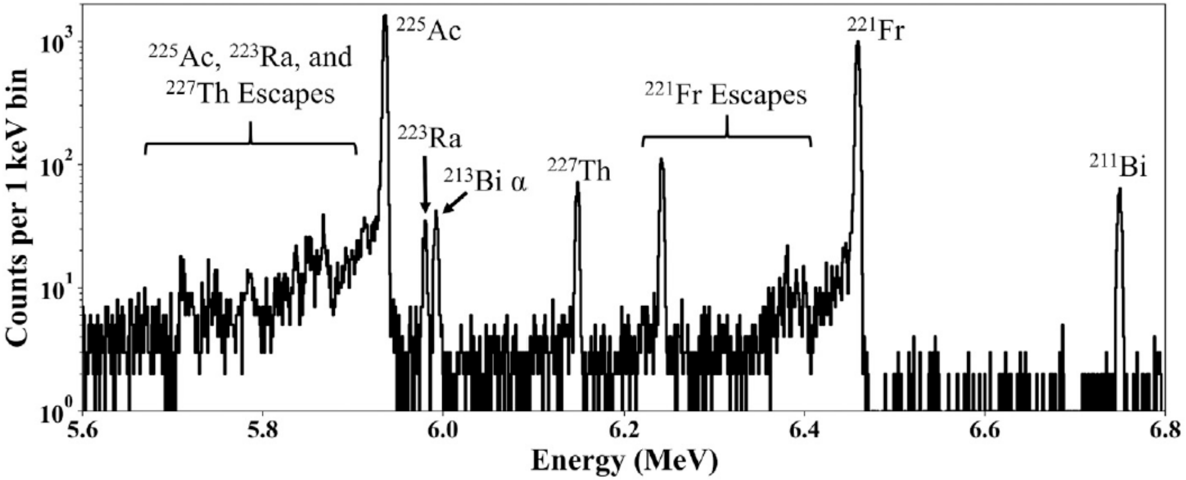
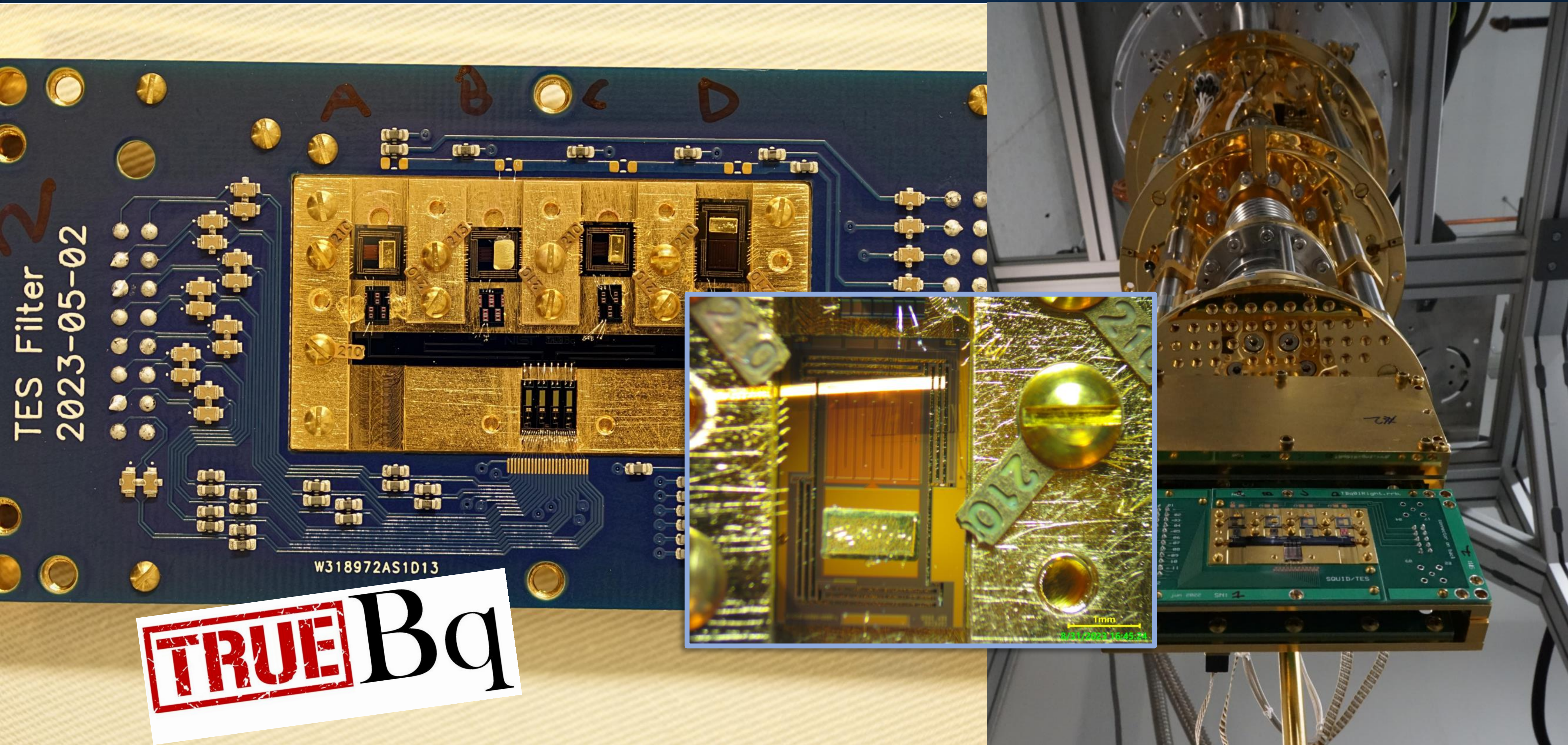


Fig. 8. ^{225}Ac production sample spectrum, processed with optimal filtering, with clear indication of ^{227}Ac impurity visible from ^{223}Ra, ^{227}Th, and ^{211}Bi daughters. The ^{221}Fr m peak at 6.46 MeV has a full-width at half-maximum of 4.7 keV when fit with a single-tailed Bortels function.

DES at NIST


TES Filter
2023-05-02
A
B
C
D
W318972AS1D13
TRUE Bq
1mm
SQUID/TES

Conclusions/Summary

- **Targeted alpha therapy and theranostics drive demand for activity standards for alpha-emitting radionuclides**
- **Our primary methods are well-suited for alpha-emitters, but real challenges arise in every case**
  - Decay chain (pre)equilibrium
  - Decay data
  - Impurities
- **Opportunities for complementary/supplemental measurements by DES, mass spectrometry… maybe even atomic spectroscopy? Let's talk!**

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Collaborators: Elisa Napoli, Gro Hjellum (Oncoinvent, AS); Seán Collins, Andy Fenwick (NPL)

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