^{228}Th breakthrough in ^{224}Ra samples: what can we know and when can we know it?

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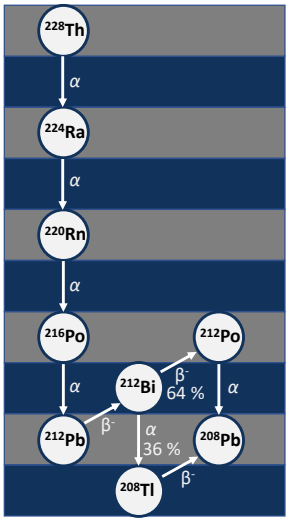
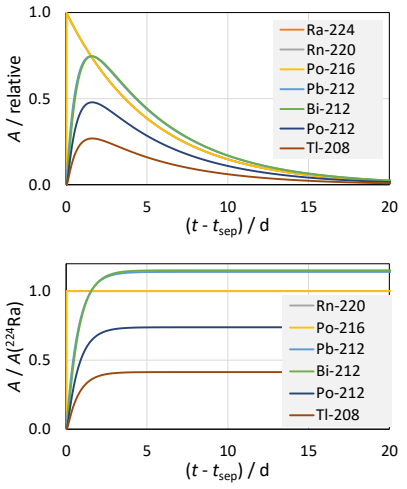
^{224}Ra decays by four α-emissions



	$T_{1/2}$	$A/A_{Ra\text{-}224}$
^{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)

Complex decay chain requires about 6 d to reach secular equilibrium.



From the medical perspective, the four alphas emitted in the Ra-224 decay represent a potent candidate for applications in targeted alpha therapy.

From the measurement perspective, the complex decay scheme makes for an interesting case; we must account for the relative detection efficiencies of all progeny and carefully account for their ingrowth.

The table shows the activity ratios predicted by the Bateman equation for a Ra-224 sample at secular equilibrium with its progeny.

The plots to the right show how progeny ingrowth proceeds over time (as calculated by the Bateman equation). In the top plot, the activities are plotted relative to the initial activity of Ra-224 at the separation time. In the bottom plot, the activities are plotted relative to the Ra-224 activity over time. In this plot we watch the relative activities converge on the values shown in the table as secular equilibrium is achieved about 6 d after separation from Th-228.

Half-lives and their (k = 1) uncertainties are taken from the decay data evaluation project (DDEP):
http://www.lnhb.fr/nuclear-data/nuclear-data-table/

Uncertainties on the activity ratios are estimated by propagating nuclear data uncertainties (from DDEP) through the Bateman calculations.

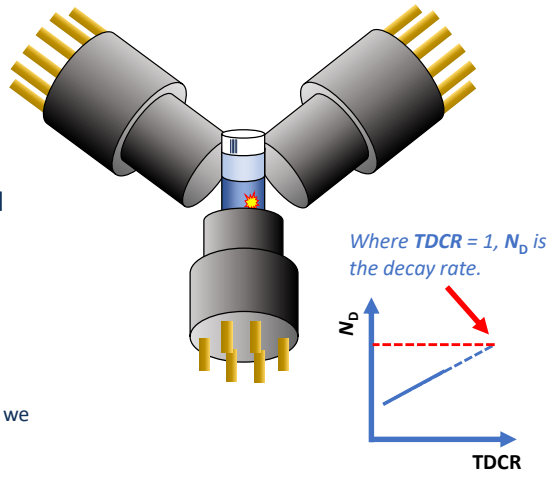
TDCR is suited for assay of ^{224}Ra activity

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!



The ^{224}Ra activity standard developed by NIST is based on TDCR counting. This is a self-calibrating, "primary", liquid scintillation counting method. Measuring the number of triple- and double-coincidence events gives a measure of the counting efficiency. The source activity (A) can then be calculated from the efficiency (ε) and count rate (N): $A = N/\varepsilon$

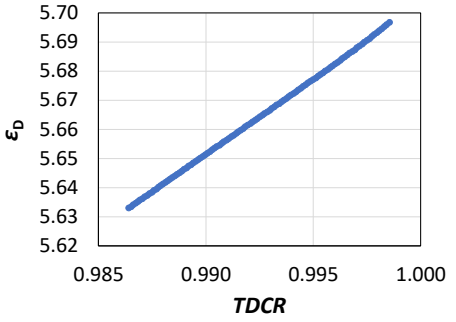
LS counting efficiencies are high

Triple-to-double Coincidence Ratio (TDCR) counting

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

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

We get about 5.65 counts per ^{224}Ra decay

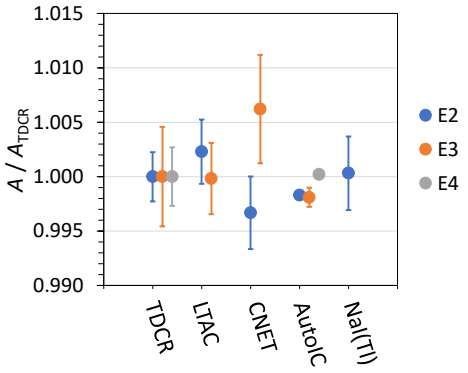


*Kossert & Grau Carles, Appl. Radiat. Isotop. 68, 1482-1488 (2010).

For alpha-decays, the LS counting efficiency is assumed to be 1 (see, e.g., Fitzgerald and Forney, 2011**). For the high-energy beta-decays, the LS counting efficiency is calculated using the MICELLE2 model developed by Kossert and Grau Carles (2010). For the ^{224}Ra calculations, their code was modified as described in Napoli et al., Appl. Radiat. Isotop. 155, 108933 (2020). The model provides a relationship between the TDCR and the absolute counting efficiency, which is used to calculate the sample activity.

**https://tsapps.nist.gov/publication/get_pdf.cfm?pub_id=906829

The ^{224}Ra activity standard



HPGe measurements showed a consistent bias of -4 %. It appears the $\gamma_{1,0}$(Rn) emission probability requires revision.

The activity standard* carries a relative combined standard uncertainty < 0.5 %.

Dissemination via ionization chamber factors & nuclear data (coming soon)

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

The standard is based on three measurement campaigns (labeled “E2”, “E3”, and “E4”). In addition to TDCR, confirmatory activity measurements were performed with live-timed anticoincidence counting (LTAC), CIEMAT-NIST efficiency tracing with tritium (CNET), and 4π-γ measurements with an ionization chamber (AutoIC) and a well-type NaI(Tl) counter. The plot shows that between-method and between-experiment agreement on the determined activity was very good.**

Activities determined with high purity germanium (HPGe) detector measurements and the DDEP gamma-ray emission probability (not shown in the plot) gave a consistent 4 % bias. This bias suggests that the evaluated emission probability requires revision.

The activity standard was translated into calibration factors for radionuclide calibrators (ionization chambers) of the type found in many radiopharmacies and clinics (Napoli et al., 2020).

**In this plot, the uncertainty bars for the AutoIC and NaI(Tl) points are based on the statistical counting uncertainties only. These activities were calculated with benchmarked efficiency models, which carry much larger uncertainties. The TDCR, LTAC, and CNET uncertainty bars represent combined standard uncertainties (k = 1).

Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

Impurities matter in our measurements

- **We look for photon-emitting radionuclidic impurities with HPGe spectrometry**
  - ^{228}Th-breakthrough is detected after several half-lives of decay
- **Dr. Copping (ORNL) was responsive in addressing the batch-to-batch variation we found**

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	$(9.7 \pm 0.1) \times 10^{-4}$

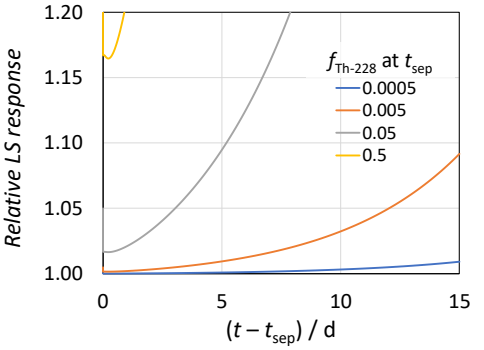
In most experiments, we found consistent ^{228}Th breakthrough with a few Bq/MBq at the separation time. In one experiment, in April 2019, much higher levels of ^{228}Th were observed ($f_{Th\text{-}228} = A_{Th\text{-}228}/A_{Ra\text{-}224}$). Dr. Roy Copping at Oak Ridge National Laboratory investigated and found that a different column type was used for that separation. The high breakthrough was considered anomalous.

The uncertainties on the impurity fractions are combined standard uncertainties ($k = 1$).

Impurities matter in our measurements

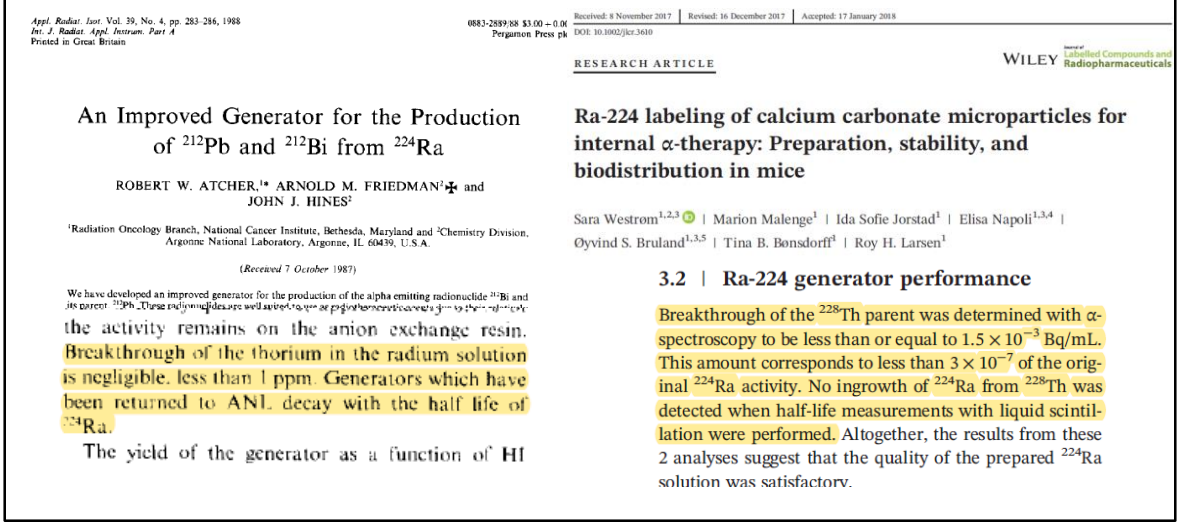
- **Most measurements are relatively insensitive to a small ^{228}Th impurity, with corrections < 0.5 %**
- **Main contribution is delayed equilibrium**
- **Becomes important for precision comparisons or half-life determinations**

Liquid scintillation counting will be most sensitive to the presence of ^{228}Th.



Since most measurements rely on γ-rays, they will be relatively insensitive to ^{228}Th (most abundant γ-ray, at 84 keV, is emitted in just 1.19 % of decays).
Liquid scintillation counting is sensitive to the alpha-emissions, but the very high counting efficiency of ^{224}Ra and progeny will tend to swamp the ^{228}Th signal. The plot shows the LS response of a sample with initial ^{228}Th impurity relative to a sample with no impurity. So, for example, 5 days after separation, a sample with $f_{\text{Th-228}} = 0.05$ at t_{sep} will give about 1.1x as many LS counts as a pure Ra-224 sample. Over time, the gradual ingrowth of ^{228}Th progeny (you can think of it as 'delayed equilibration' relative to a pure ^{224}Ra source) leads to a larger effect.

‘Negligible’ breakthrough in the literature



Appl. Radiat. Isot. Vol. 39, No. 4, pp. 283–286, 1988
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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 [illegible] 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

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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

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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.

Literature reports on separation of ^{224}Ra claim ‘negligible’ breakthrough. The Atcher (1988) paper uses apparent half-life to support this claim. The more recent Westrøm (2018) paper uses alpha spectrometry in addition to half-life.
We ask the question, “What can we know and when can we know it?”

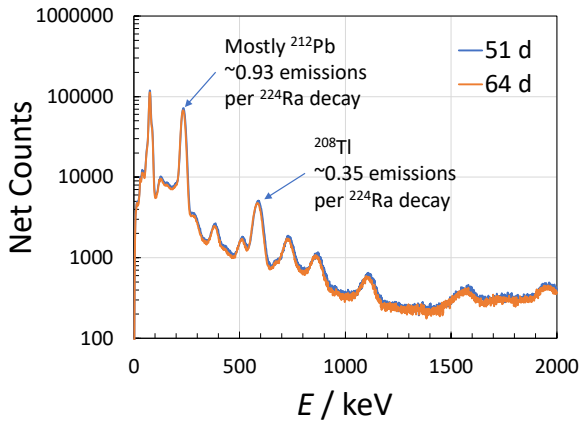
What can we know and when can we know it?

We analyzed real and simulated data for a NaI(Tl) well-type detector, HPGe, liquid scintillation, and ionization chambers

We asked how the different detection methods performed at identifying ^{228}Th breakthrough

Simulated data were generated from validated GEANT4 models of our instruments. Responses were calculated for each nuclide. Total responses at different time points were calculated by combining the individual-nuclide-responses according to the activity ratios predicted by the Bateman Equation. In this way, we could isolate the ^{228}Th contributions and discern when they might be detectable in real-world measurements.

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

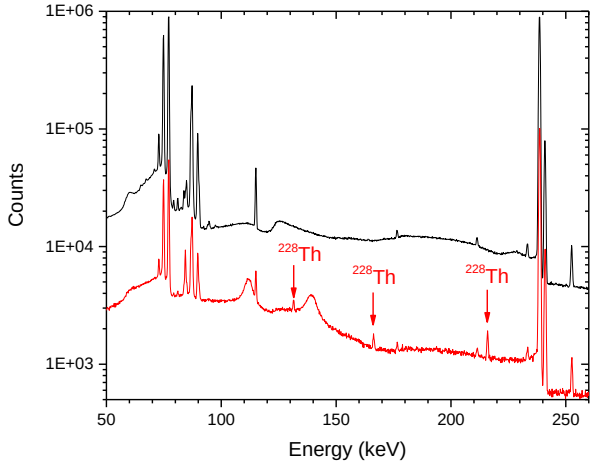


- **^{228}Th decays mostly (73.4 %) to the ground state of ^{224}Ra**
- **The 26 % branch to the first excited state of ^{224}Ra results in very few 84.4 keV γ-ray emissions (1.2 %)**
- **The presence of ^{228}Th in the sample is evident in the half-life, not the spectrum**

Decay data from DDEP:
http://www.lnhb.fr/nuclides/Th-228_tables.pdf

The plot shows real data measured on a NaI(Tl) well-type counter with a "decayed" (i.e., $(t - t_{sep})$ = 51 d and 64 d) ^{224}Ra source. The resolution of a NaI(Tl) detector is insufficient to allow observation of the weak gamma-ray emissions from ^{228}Th. After > 10 ^{224}Ra half-lives, the spectrum appears unchanged as the contributions from ^{228}Th progeny (including, of course, ^{224}Ra and progeny) swamp the weak 84 keV gamma ray. The spectra in the figure are not normalized or decay corrected. The spectrum collected at 64 d is slightly weaker than the one collected at 51 d; the source is decaying with the ^{228}Th half-life.

HPGe detection of ^{228}Th faces challenges

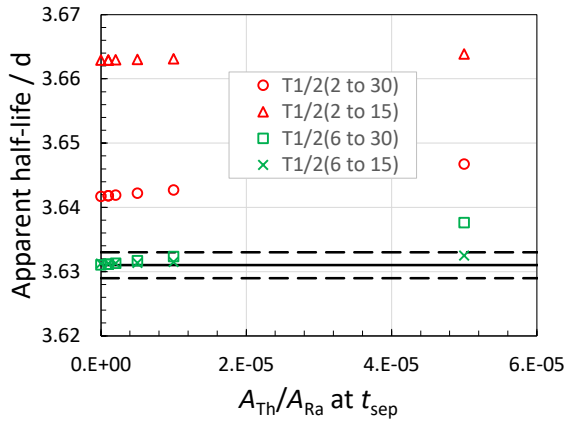


The resolution of HPGe allows identification of the weak γ-ray peaks from ^{228}Th decay

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

The plot shows real data measured on a high purity germanium (HPGe) detector. The initial ^{224}Ra spectrum, acquired at $(t - t_{sep}) \approx 7$ d, is shown in the black trace. After > 10 ^{224}Ra half-lives (red trace), the spectrum is preserved by ^{228}Th progeny; however, the weak gamma-ray contributions from ^{228}Th decay are resolvable.

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



Half-lives determined with pre-equilibration data give biased results with obvious trends in fit residuals

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

We're defining "ppm" here, according to convention in the literature, as $A_{Th}/A_{Ra} = f_{Th\text{-}228} = 10^{-6}$

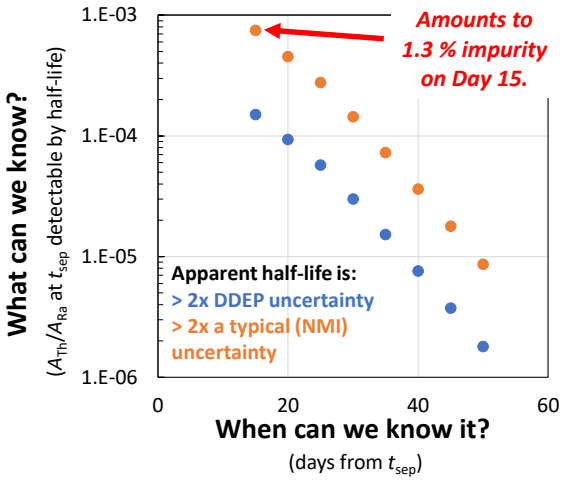
Decay consistent with the ^{224}Ra half-life has been taken as the best evidence against ^{228}Th breakthrough. How useful is this metric?

Half-life measurements cannot start until the source reaches equilibrium (about 6 d after separation). Fitting datasets that include earlier points will give a biased half-life, with the magnitude of bias depending on how long you measure. Examination of the residuals of fits to datasets with early points will show obvious trends from the progeny ingrowth. It would be difficult to miss.

Fits to data acquired after equilibrium will give the correct ^{224}Ra half-life, even with $A_{Th}/A_{Ra} > 10^{-5}$ at t_{sep}. The longer you collect data, the better your chance at detecting breakthrough.

In this plot, the DDEP-evaluated half-life is shown as a solid black line, with its (k = 1) uncertainty depicted as dashed black lines. These will appear in later plots for reference.

Plotting what v. when



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

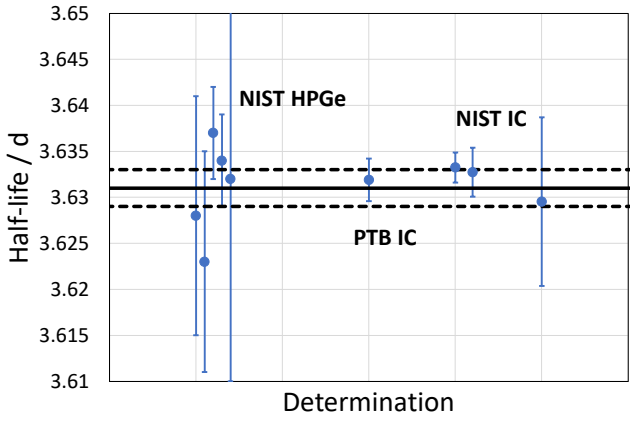
*….if you can distinguish a deviation of 2σ from the evaluated half-life (i.e., you're the **best in the world** at measuring half-lives)*

…and you measure until 50 days post-separation

To answer "What can we know and when can we know it?", we can plot the amount of impurity that would result in a certain deviation from the ^{224}Ra half-life against the time of counting. For example, if a researcher was capable of distinguishing a deviation of just 2x the uncertainty given in the Decay Data Evaluation Project (DDEP) evaluation, and could count for 20 days after separation, a ^{228}Th impurity corresponding to 10^{-4} at t_{sep} could be detected. These estimates are from Monte Carlo simulations of an ionization chamber, but the results would be similar for other detectors.

To give another example, if you are NOT capable of distinguishing a deviation of just 2x the DDEP uncertainty, but instead "only" capable of distinguishing a deviation at 2x the uncertainty typically achieved in a half-life determination at a national metrology institute (NMI; e.g., NIST, PTB, NPL…), then on day 20 you could detect a ^{228}Th impurity > 3×10^{-4}.

Nobody's that good!



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

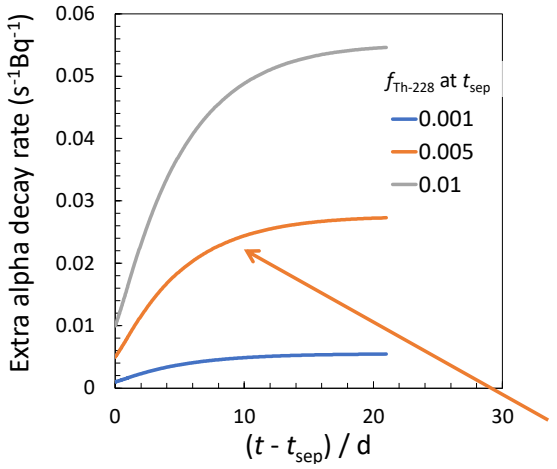
There is spread in the dataset, and estimated uncertainties vary

*http://www.lnhb.fr/nuclear-data/nuclear-data-table/

To reinforce the examples from the "What can we know and when can we know it?" plot, here are a few examples of recent half-life determinations at NIST. Also shown is the ionization chamber determination by Schrader (Appl. Radiat. Isotop. 60, 317-323 (2004)) that is the main contributor to the adopted DDEP value (the black line). The uncertainties on the determined half-life depend on the measurement conditions (initial activity, time window, etc.) and the method. It should be clear that small deviations from the ^{224}Ra half-life due to impurities would be hard to detect under any but the very best conditions.

The uncertainty bars represent combined standard uncertainties (k = 1).

Does missed ^{228}Th breakthrough matter?



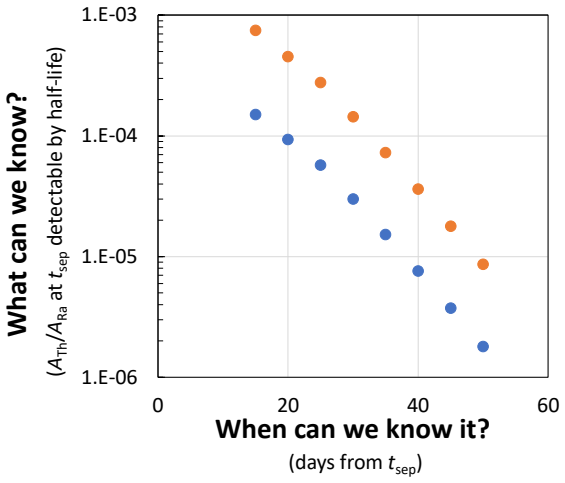
If the precision measurements at NMIs are barely impacted by breakthrough, should anyone outside care?

In medicine, total "extra" dose from breakthrough depends sensitively on administration time (relative to t_{sep}) and clearance rate

On day 10, a 0.5 % ^{228}Th impurity at t_{sep} is contributing about 25000 extra α- particles per second per MBq of ^{224}Ra.

The plot shows the alpha decay rate from ^{228}Th and progeny above what would be expected for a pure ^{224}Ra source. The "extra" dose is predictable if the impurity fraction, administration time, and clearance time are known.

Summary & Conclusions



- **Gamma-ray spectrometry and half-life cannot provide an early measure of ^{228}Th breakthrough in ^{224}Ra**
  - *Mass spectrometry provides a sensitive alternative*
- **With caveats on administration time and clearance biology, unplanned dose is unlikely to be a concern**

With the methods considered here, early detection of breakthrough is not possible. If the "extra" dose from alpha particle emission from ^{228}Th and its progeny is always less than a few percent, then it may not be a concern from the medical/regulatory perspective.

Thanks to

Ryan Fitzgerald, Leticia Pibida, Jeffrey Cessna, and Brian Zimmerman (NIST)
Elisa Napoli (Oncoinvent, AS; University of Oslo)
Sean Collins (NPL)
Roy Copping (ORNL)

Looking for post-doc opportunities?
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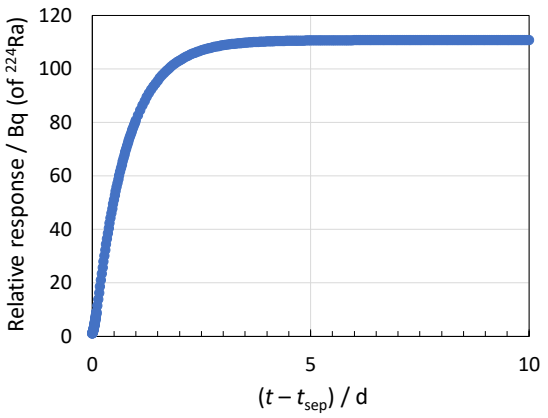
Backup slides

Measuring before equilibrium is tricky



Ionization chamber response increases rapidly after separation as progeny grow in, meaning that any uncertainty on difference between t_{sep} and t_{meas} results in a very large uncertainty on the activity