National Physical Laboratory

Primary standardisation of ^{227}Th – developing traceability and nuclear data for a novel α-emitting radiopharmaceutical

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lockdown seminar - 2020-09-03

Overview

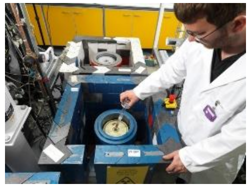
- Traceability and why it’s needed
- What is a primary standardisation
- Thorium-227 and its challenges
- Half-lives determinations of ^{227}Th and ^{223}Ra
- Radiochemistry and time zero
- Standardisation of Thorium-227
- Absolute gamma-ray emissions

Traceability for Pre-clinical & Clinical Use

The absolute primary standardisation of radioactivity is a key mission of NMIs (e.g. NPL) to provide the international radioactivity community traceability to the SI unit of the becquerel.

Primary Radioactivity Standards

↓



Secondary Radioactivity Standards

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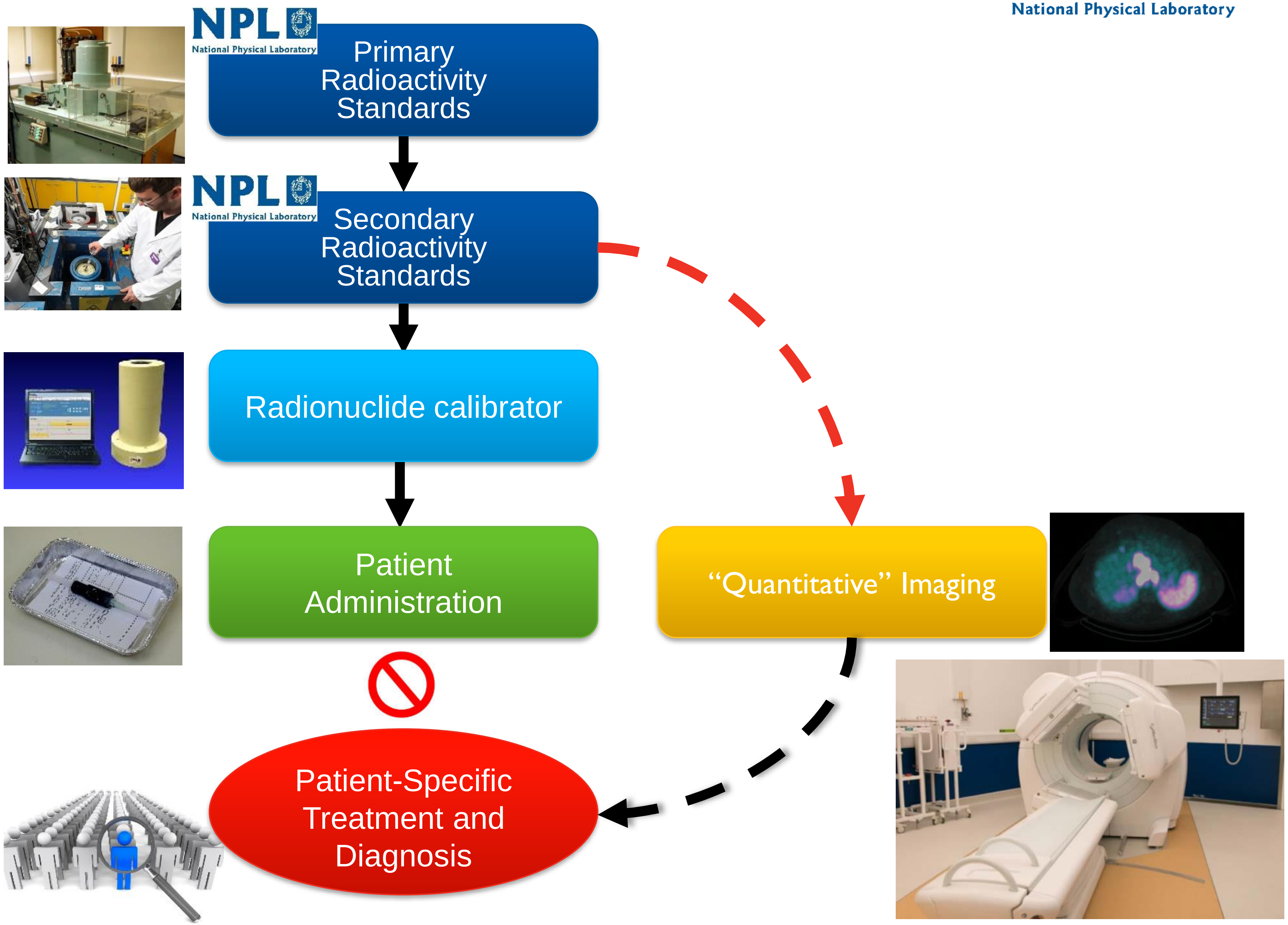
Radionuclide calibrator

↓

Patient Administration

Patient-Specific Treatment and Diagnosis

Traceability for Pre-clinical & Clinical Use



Importance of traceability– View of a Pharmaceutical Manufacturer

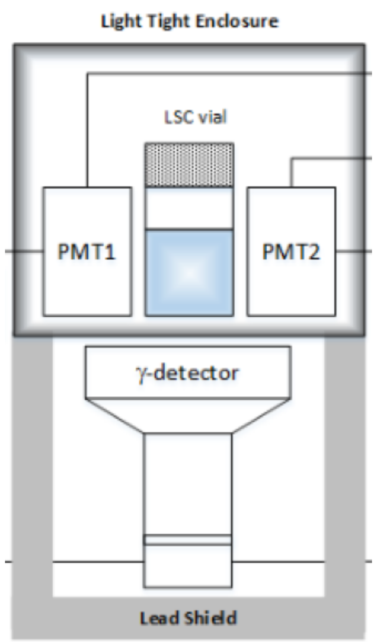
- Accurate radioactivity measurements, in order to demonstrate compliance with regulators, is vital for the business.

- Important to ensure the correct dose administered to the patient.

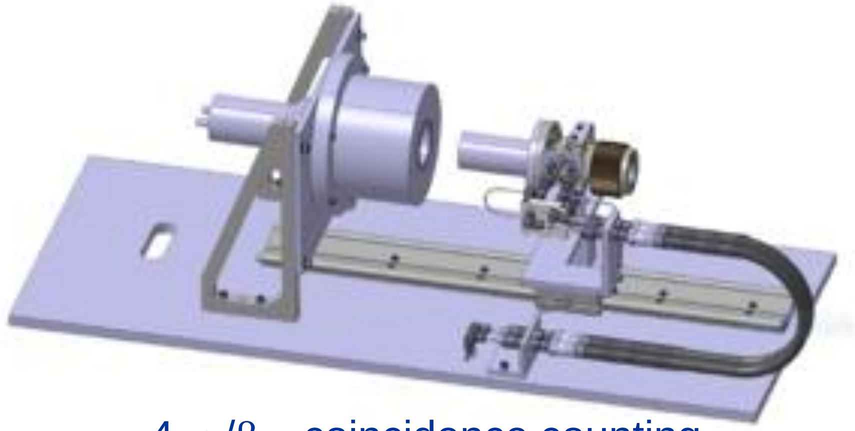
- Accurate radioactivity measurements of Radiopharmaceuticals, is only obtained by using high quality measurement equipment calibrated with a Certified Standard Reference Source.

- Accurate nuclear decay data needed for release of product
  - γ-ray emission intensities
  - Half-lives

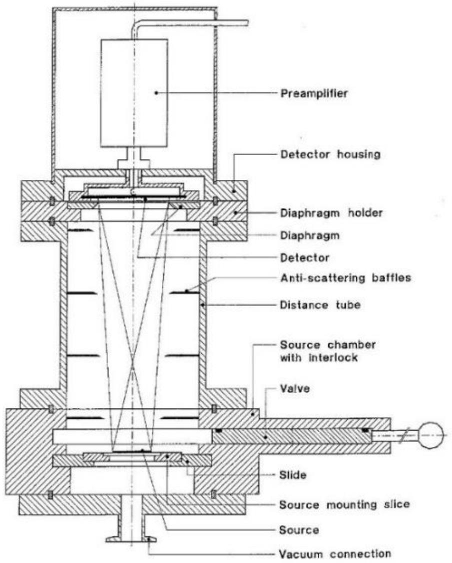
Primary standardisation: Techniques



4π(LS)-γ coincidence counting



$4\pi\alpha/\beta$-γ coincidence counting



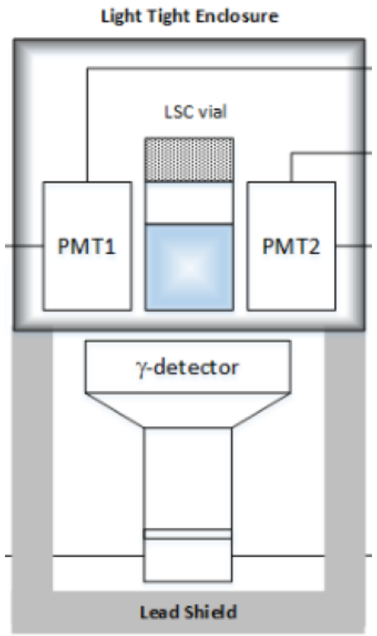
Defined Solid Angle (DSA) α-counting

- Defined by capability to measure simultaneously:
  - (1) The disintegration rate
  - (2) The detection efficiency
- No prior knowledge of detector efficiencies or nuclear data required

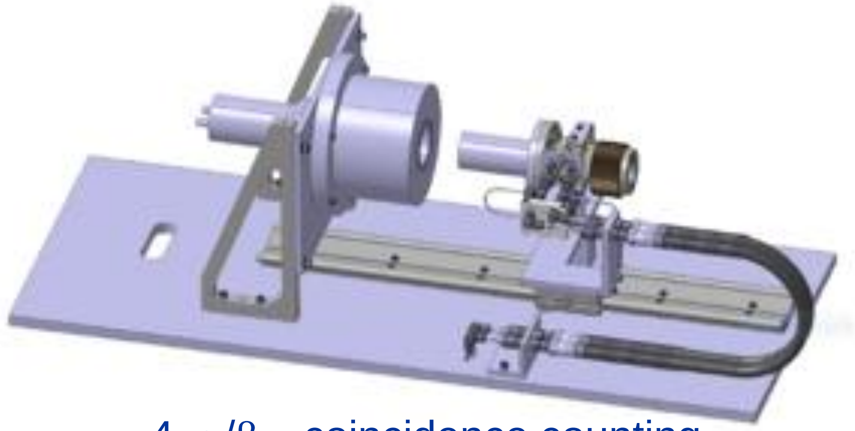
Triple-to-Double Coincidence Ratio (TDCR) counting

γ-γ coincidence counting

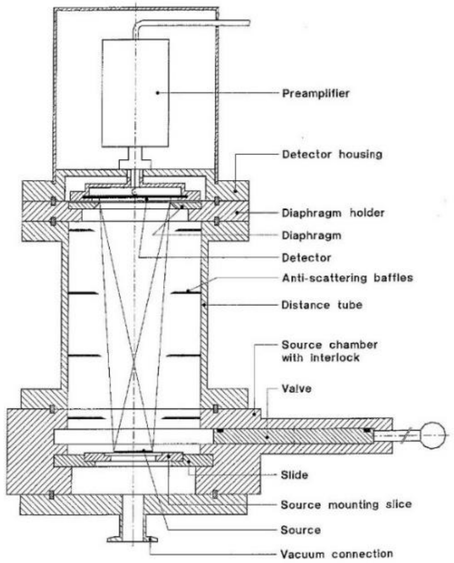
Primary standardisation: Techniques



4π(LS)-γ coincidence counting



4πα/β-γ coincidence counting



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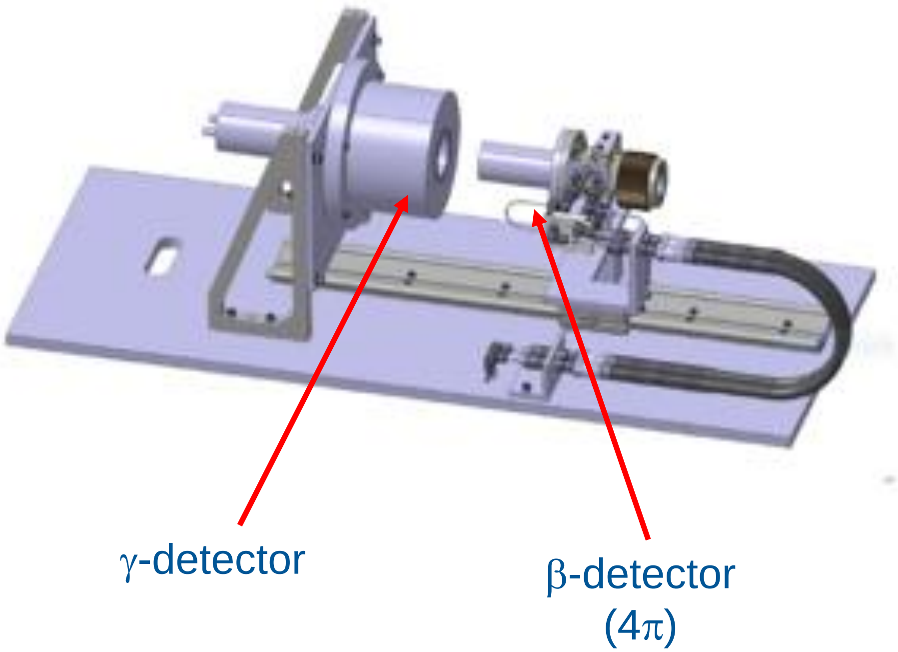
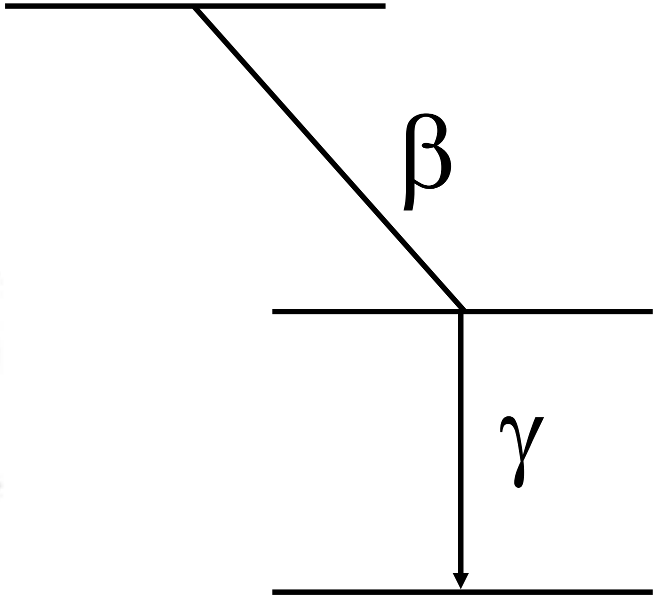
Triple-to-Double Coincidence Ratio (TDCR) counting

A few caveats…

γ-γ coincidence counting

4πβ-γ coincidence counting (idealised decay scheme and detectors)





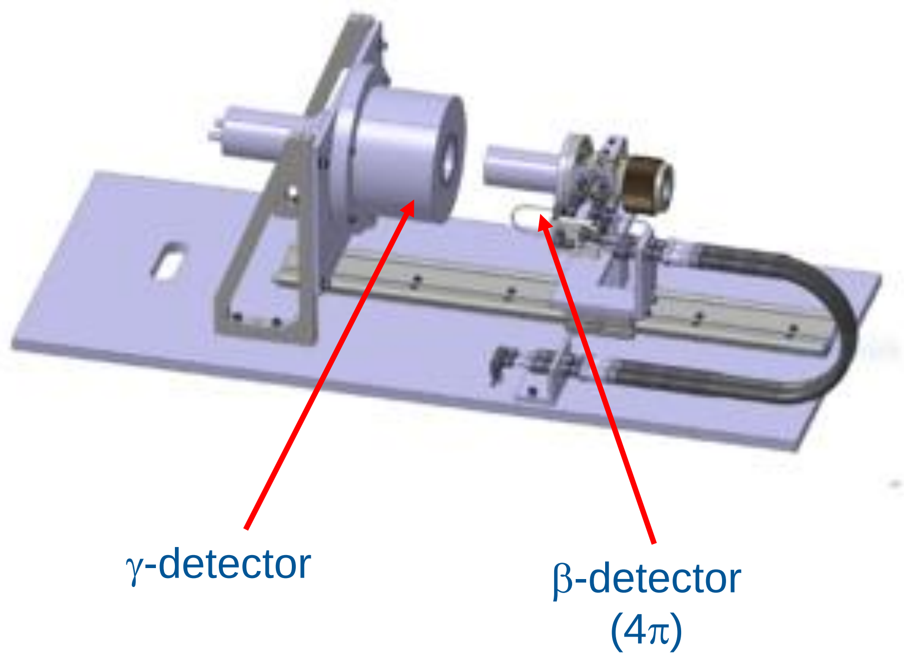
Count rates:

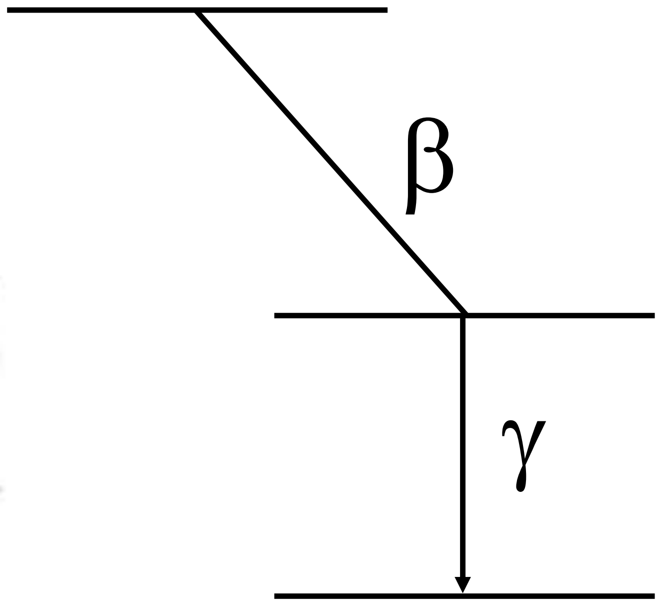
$N_\beta = N_0.\varepsilon_\beta$

$N_\gamma = N_0.\varepsilon_\gamma$

$N_c = N_0.\varepsilon_\beta.\varepsilon_\gamma$

$4\pi\beta$-γ coincidence counting (idealised decay scheme and detectors)





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Efficiencies:

$\varepsilon_\beta = N_c / N_\gamma$

$\varepsilon_\gamma = N_c / N_\beta$

$4\pi\beta$-γ coincidence counting (idealised decay scheme and detectors)

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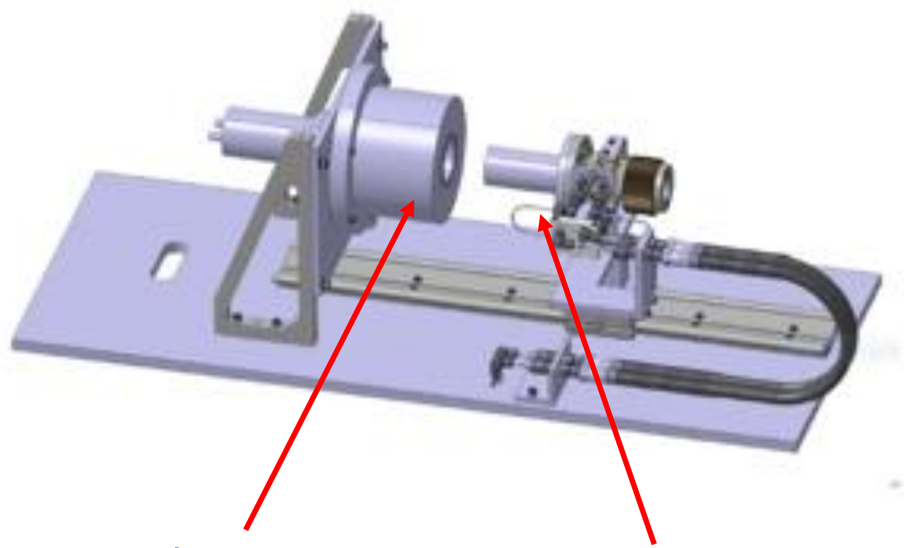
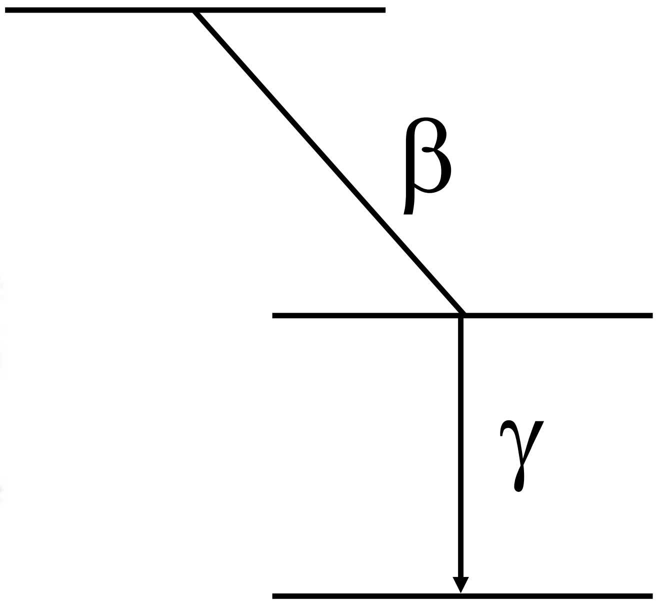


γ-detector

β-detector (4π)



Count rates:

$N_\beta = N_0.\varepsilon_\beta$

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$N_c = N_0.\varepsilon_\beta.\varepsilon_\gamma$

→

Efficiencies:

$\varepsilon_\beta = N_c / N_\gamma$

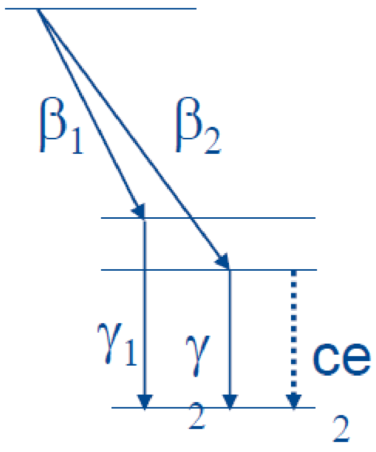
$\varepsilon_\gamma = N_c / N_\beta$

→

Activity:

$N_0 = N_\beta.N_\gamma / N_c$

4πβ-γ coincidence counting (real world…)



for multiple beta branches :

$$N_\beta = N_0 \sum_r a_r \left[\varepsilon_{\beta_r} + \left(1 - \varepsilon_{\beta_r}\right) \left[\left(\frac{\alpha_r}{1+\alpha_r} \right) \varepsilon_{\beta ce_r} + \left(\frac{1}{1+\alpha_r} \right) \varepsilon_{\beta\gamma_r} \right] \right]$$

$$N_\gamma = N_0 \sum_r a_r \left[\left(\frac{1}{1+\alpha_r} \right) \varepsilon_{\gamma_r} \right]$$

$$N_c = N_0 \sum_r a_r \left[\left(\frac{1}{1+\alpha_r} \right) \varepsilon_{\beta_r} \varepsilon_{\gamma_r} + \left(1 - \varepsilon_{\beta_r}\right) \varepsilon_{c_r} \right]$$

$4\pi\beta$-γ coincidence counting (real world…)

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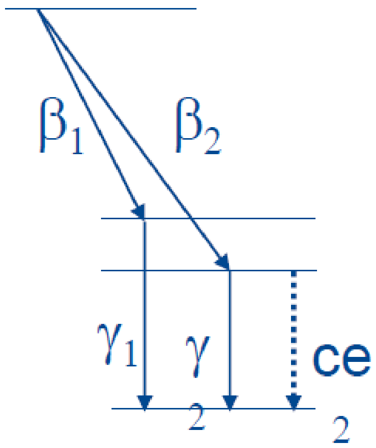

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$$N_\gamma = N_0 \sum_r a_r \left[\left(\frac{1}{1+\alpha_r}\right) \varepsilon_{\gamma_r} \right]$$

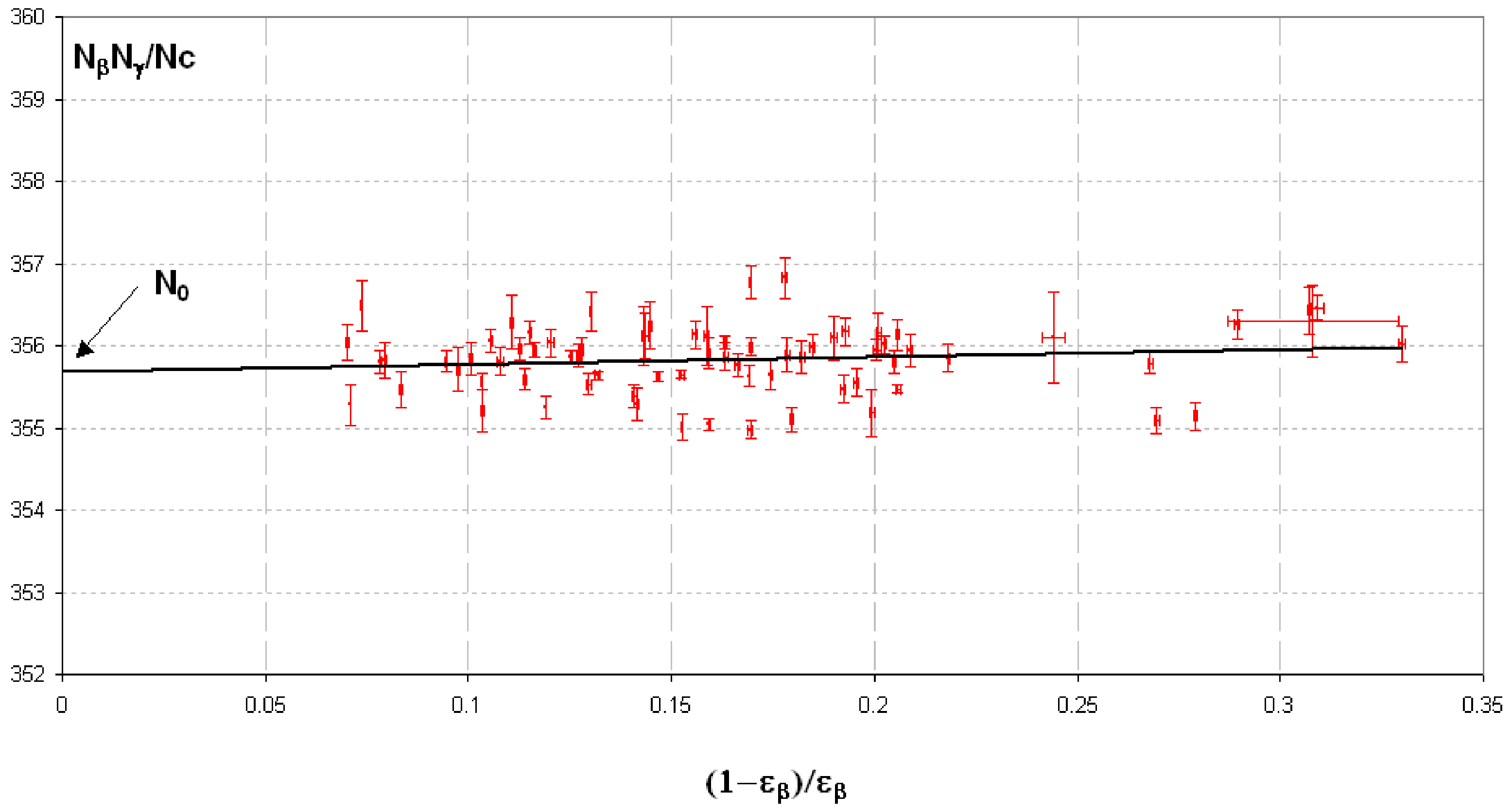
$$N_c = N_0 \sum_r a_r \left[\left(\frac{1}{1+\alpha_r}\right) \varepsilon_{\beta_r} \varepsilon_{\gamma_r} + \left(1-\varepsilon_{\beta_r}\right) \varepsilon_{c_r} \right]$$

- Modifying detection efficiency of one channel (typically beta channel) to change ε_β
  - Multiple methods available

- Extrapolating to $\varepsilon_\beta = 1$ (or $(1-\varepsilon_\beta)/\varepsilon_\beta = 0$)

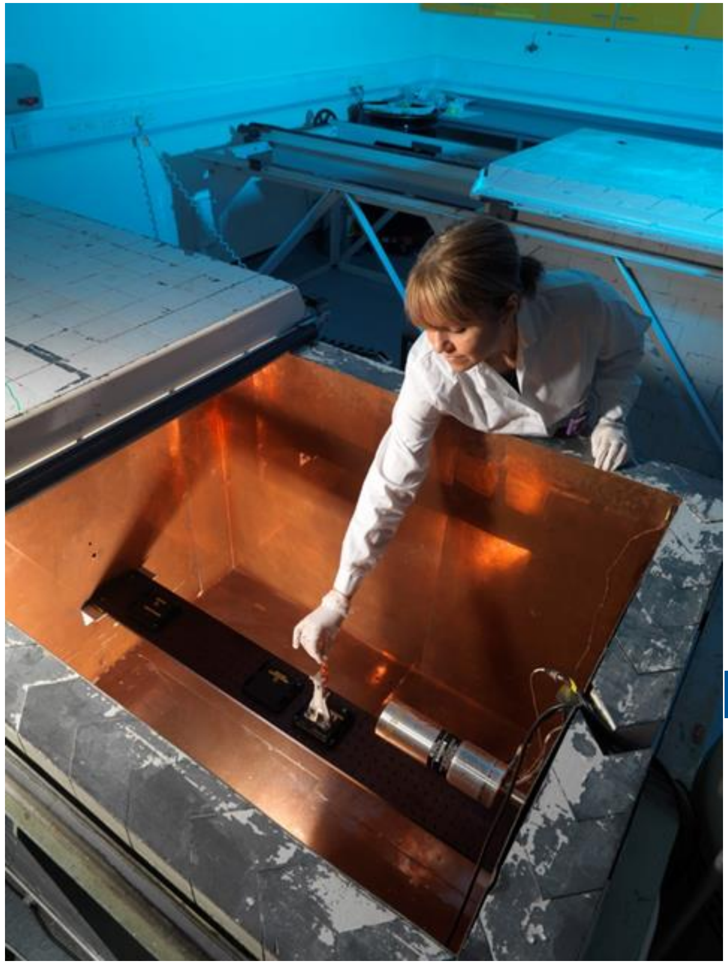
Efficiency Extrapolation

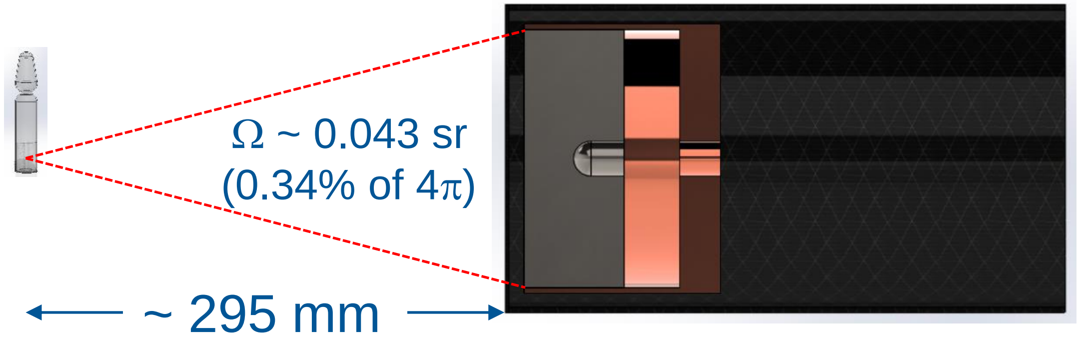
$$\frac{N_\beta \, N_\gamma}{N_c} = N_o \left[1 + f \left(\frac{1 - \varepsilon_\beta}{\varepsilon\beta} \right) \right]$$

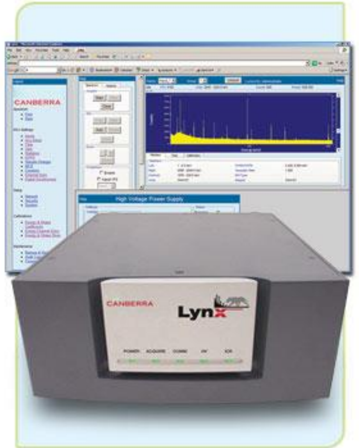


May not always be a linear extrapolation or this flat!

HPGe gamma-ray spectrometry at NPL







- Calibrated using suite of primary and secondary standards

HPGe gamma-ray spectrometry at NPL

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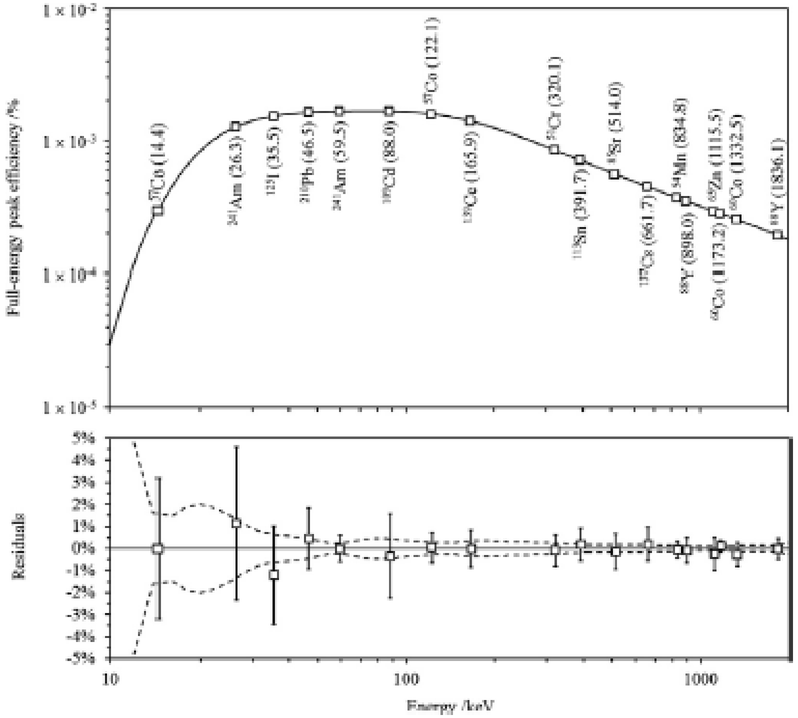
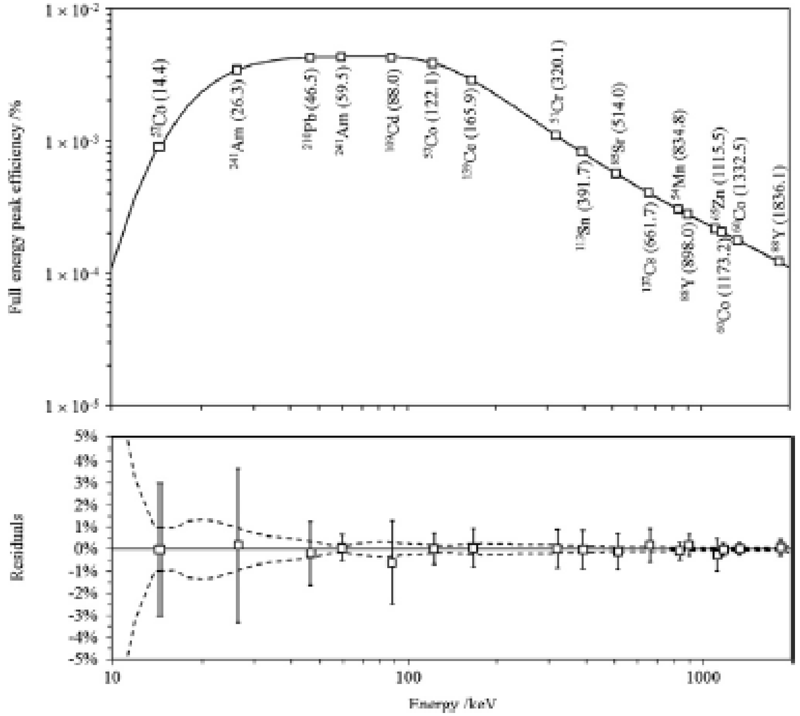
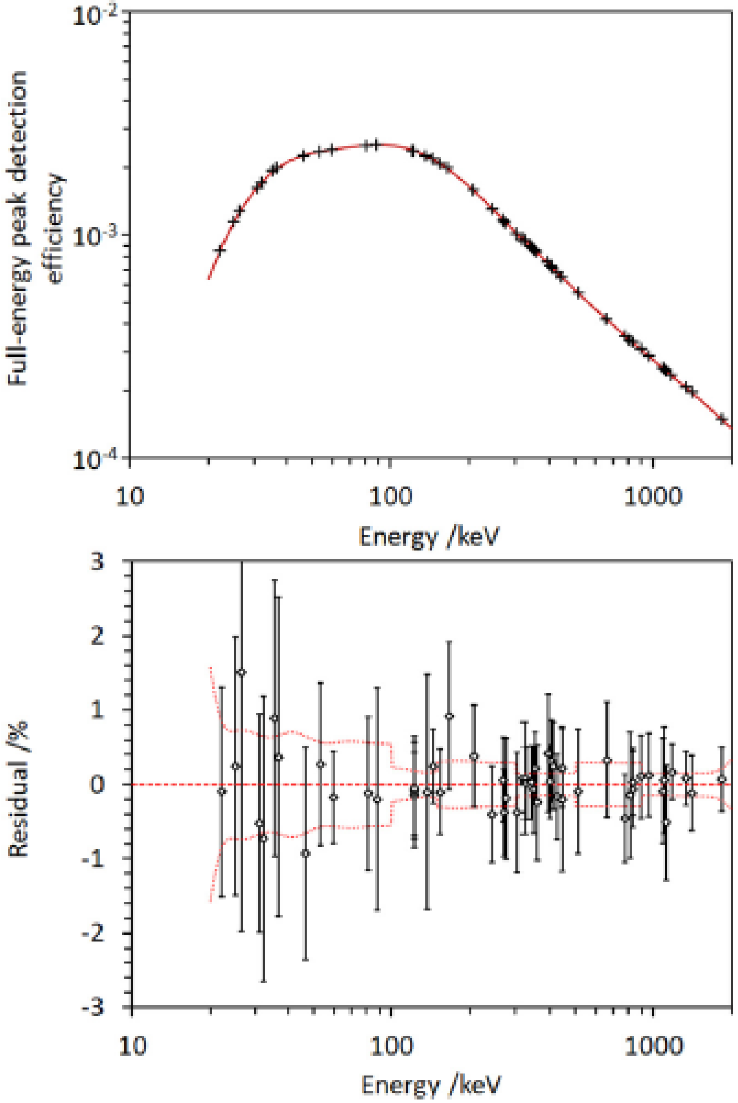
BART



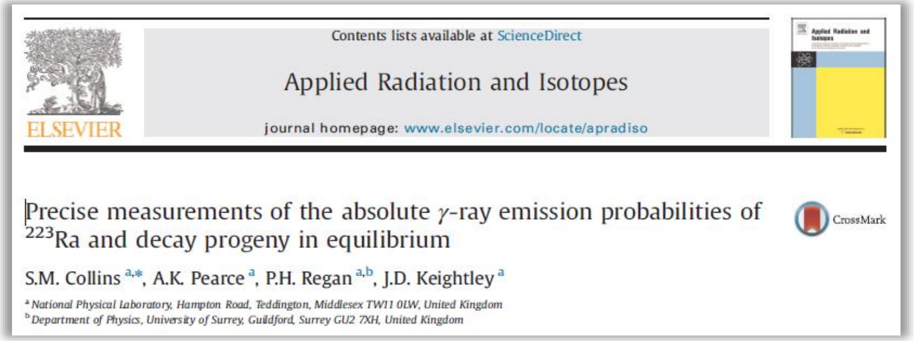
LISA



LOKI



- Efficiency curve fit with a b-spline
- Covariances in calibration accounted for



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Applied Radiation and Isotopes

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

Precise measurements of the absolute γ-ray emission probabilities of ^{223}Ra and decay progeny in equilibrium

S.M. Collins [a,*], A.K. Pearce [a], P.H. Regan [a,b], J.D. Keightley [a]

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[b] Department of Physics, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom

https://doi.org/10.1016/j.apradiso.2015.04.008

Thorium-227

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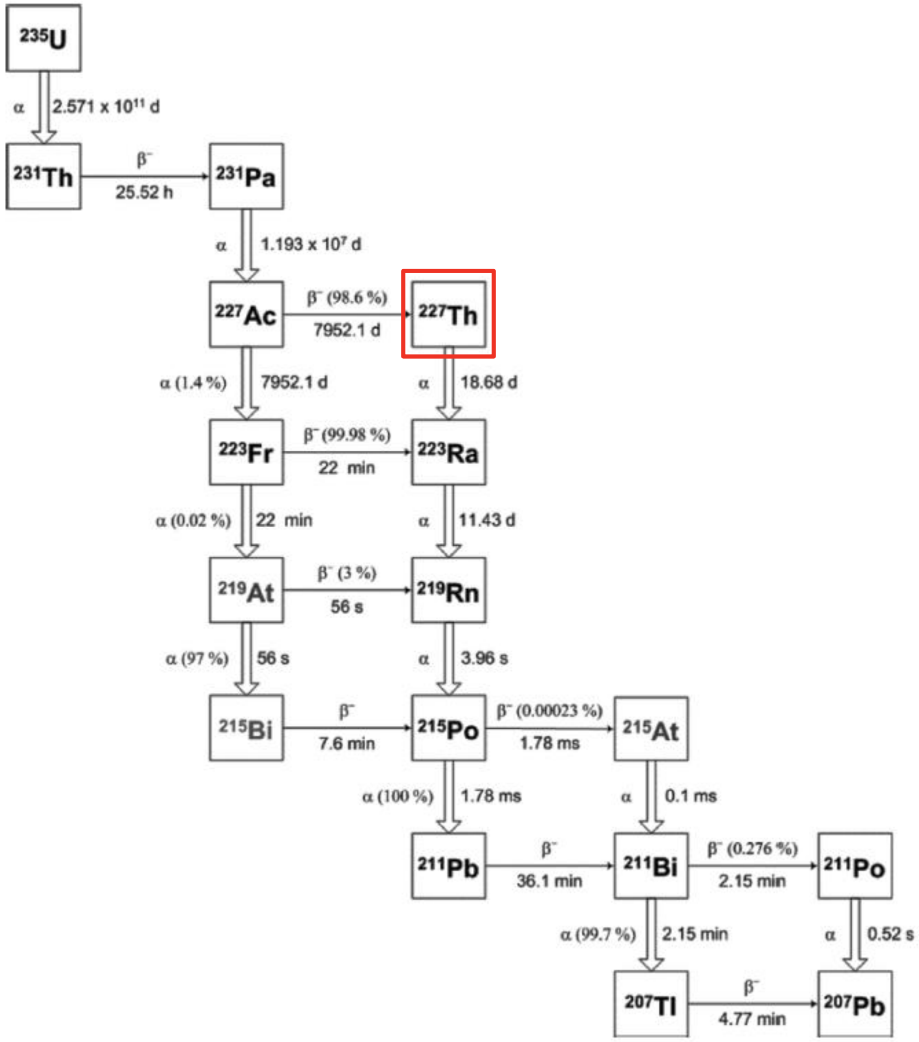
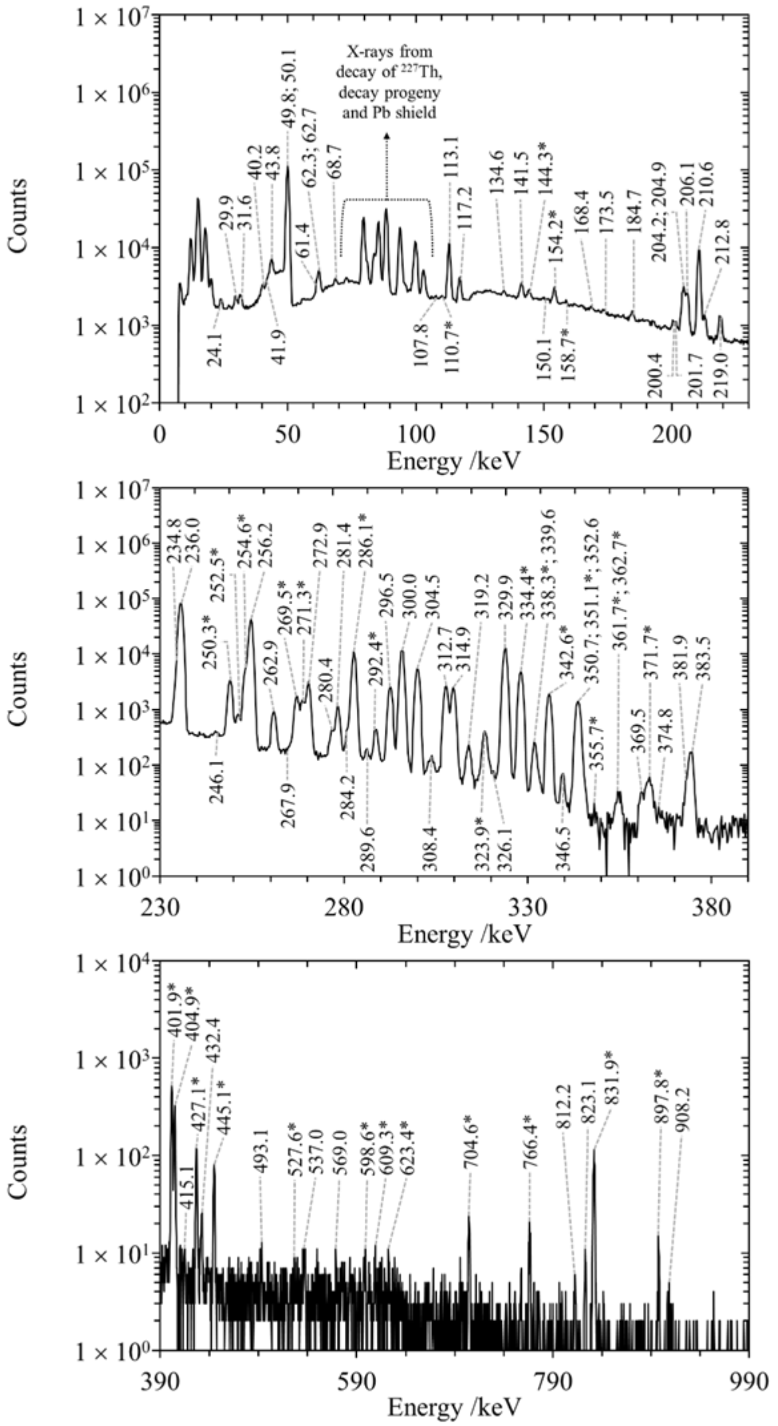




100% α-decay

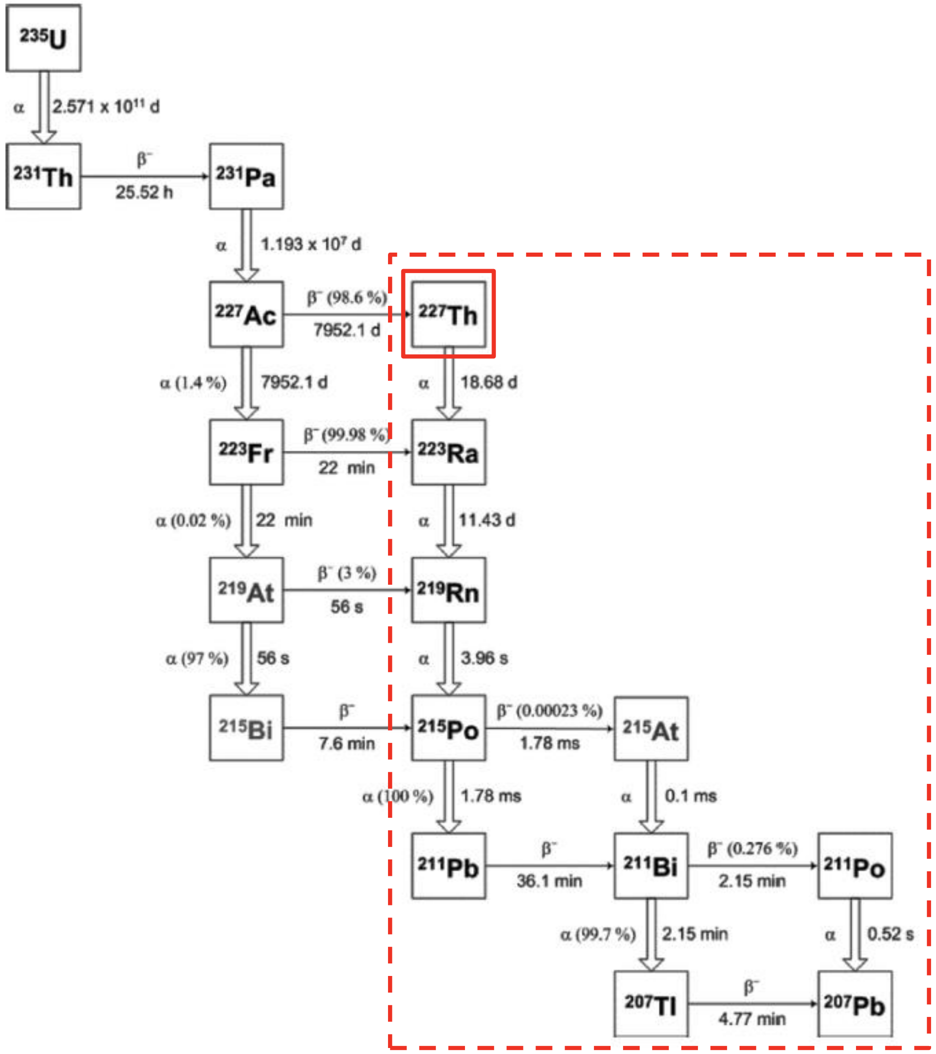
$T_{1/2}$ = 18.697d

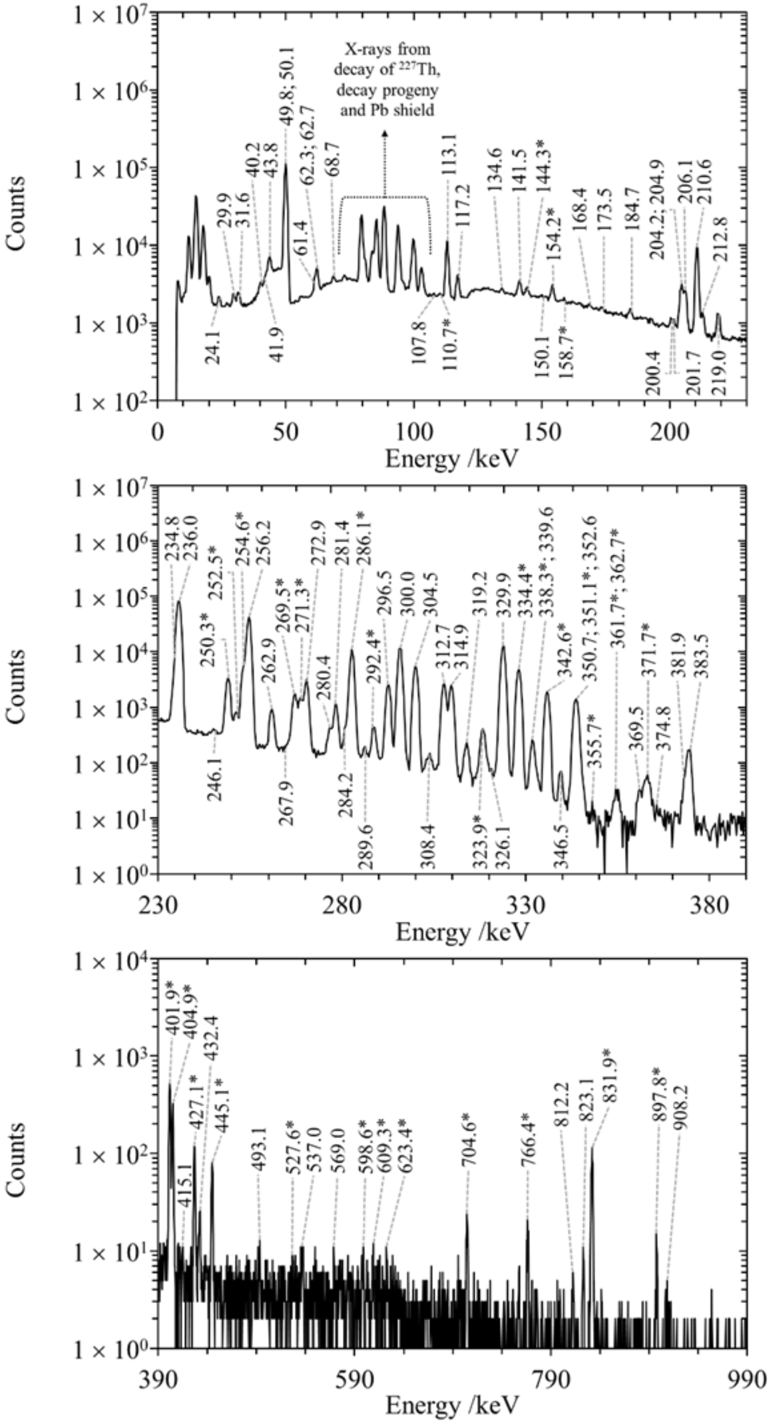
46 α-transitions

240 γ transitions

Low γ-ray emission intensities

Thorium-227





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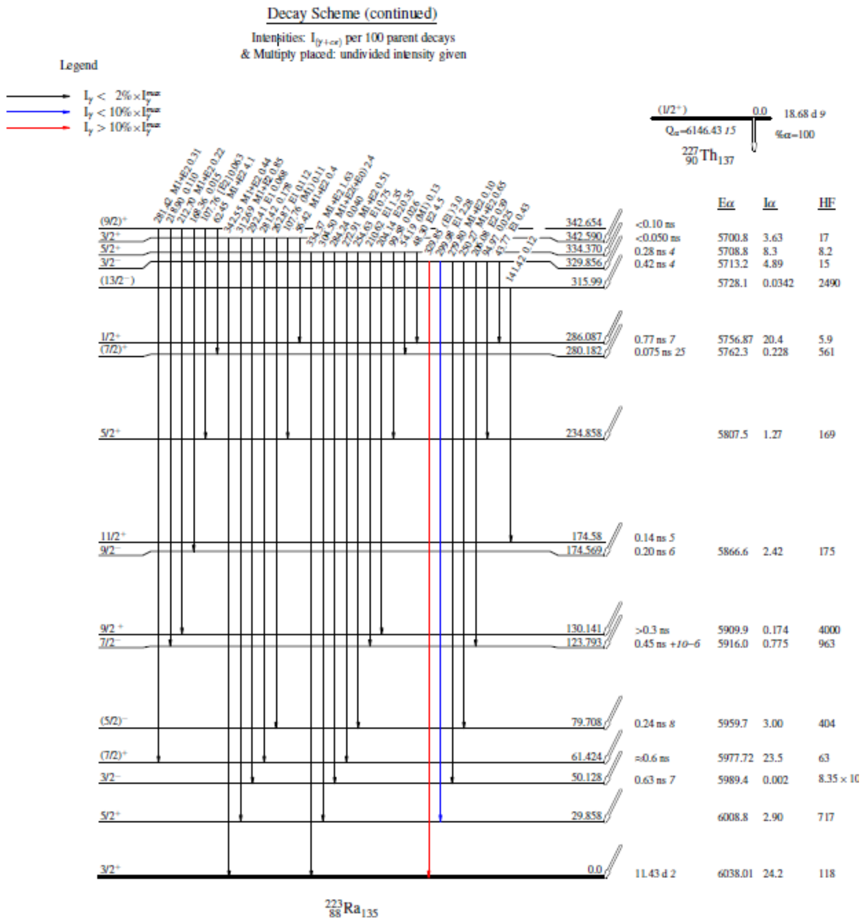
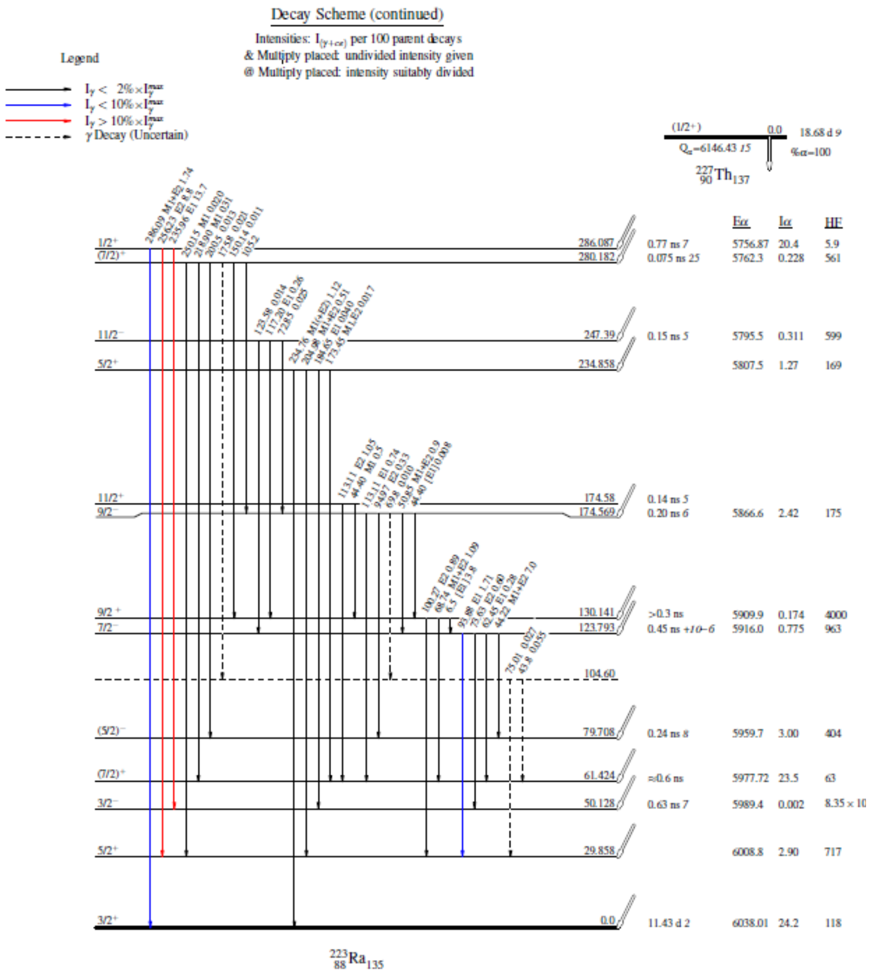
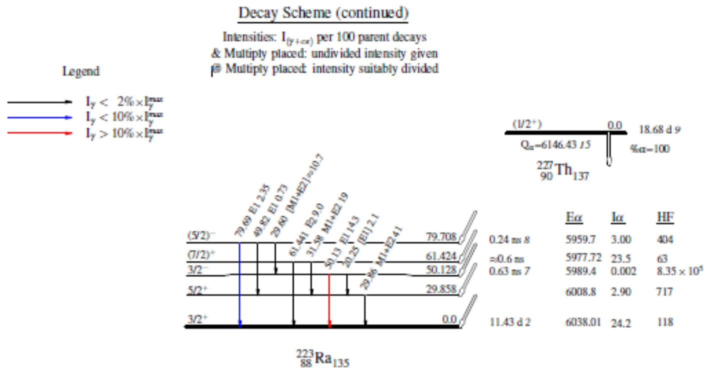
Decay Scheme (Partial…it's complex)







Temporal relationship of ^{227}Th → progeny

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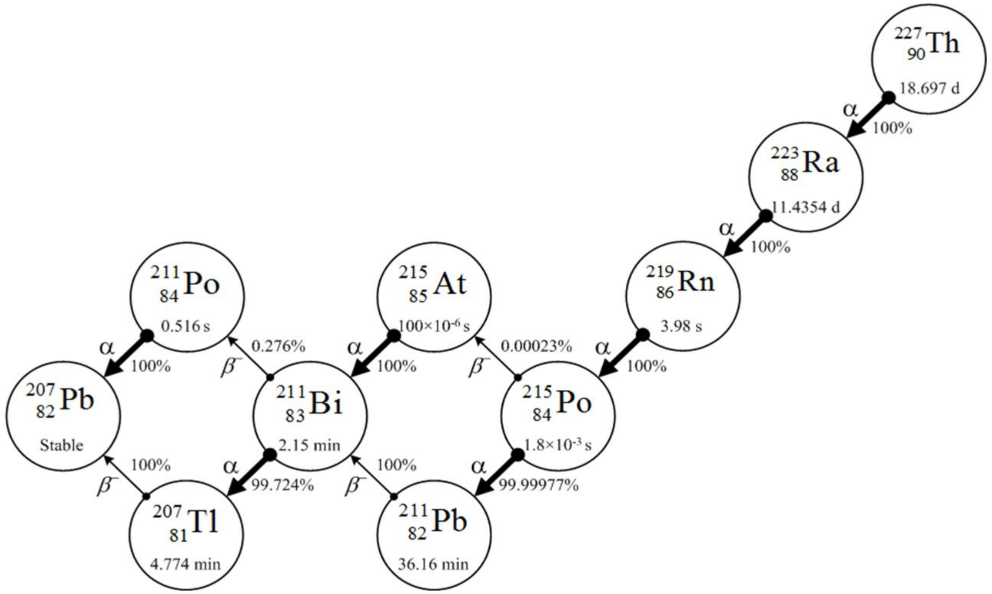


Bateman equations:

$$N_1(t) = N_1(0)e^{-\lambda_1 t} \quad (j = 1; 227Th)$$

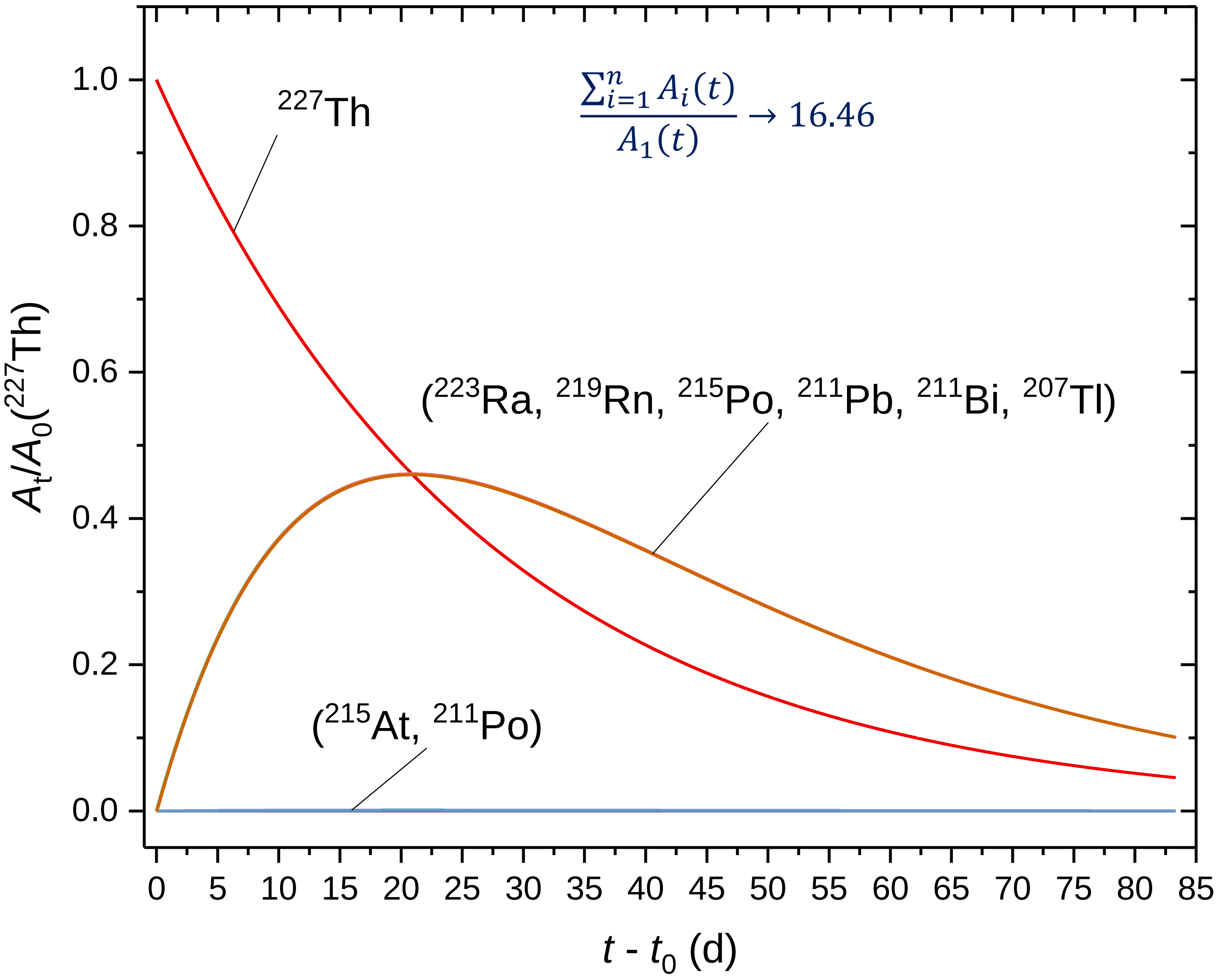
$$N_j(t) \approx N_1(0)\left(\prod_{i=1}^{j-1} b_{i+1}\lambda_i\right)\sum_{k=1}^{j}\left(\frac{e^{-\lambda_k t}}{\prod_{\substack{i=1 \\ (i\neq k)}}^{j} (\lambda_i - \lambda_k)}\right)$$

$$A_j(t) = \lambda_j N_j(t)$$

$N_j(t)$ = number of atoms of nuclide j at time t

λ_j = decay constant for nuclide j (s^{-1})

$A_j(t)$ = Activity of nuclide j at time t



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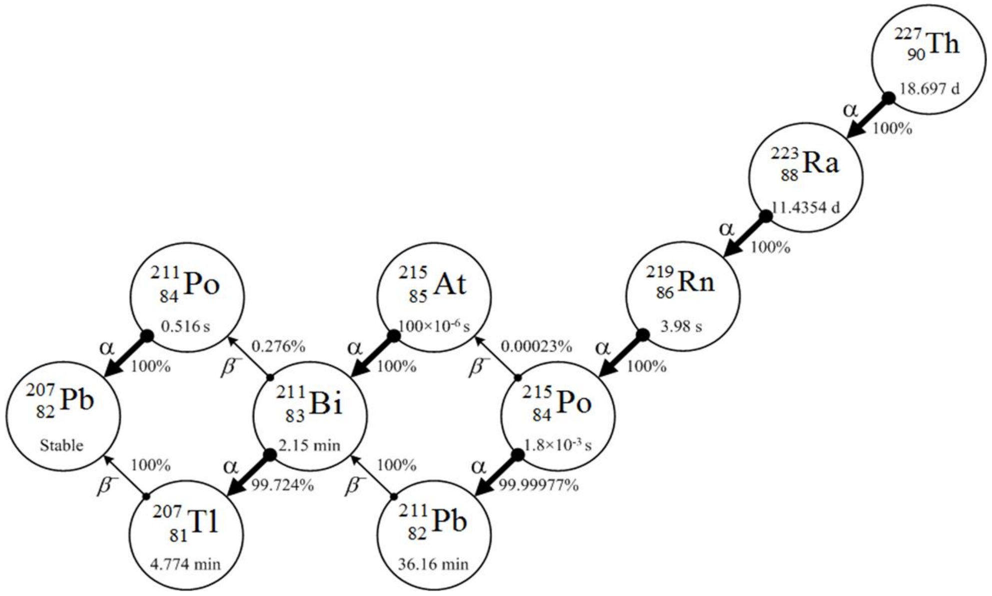

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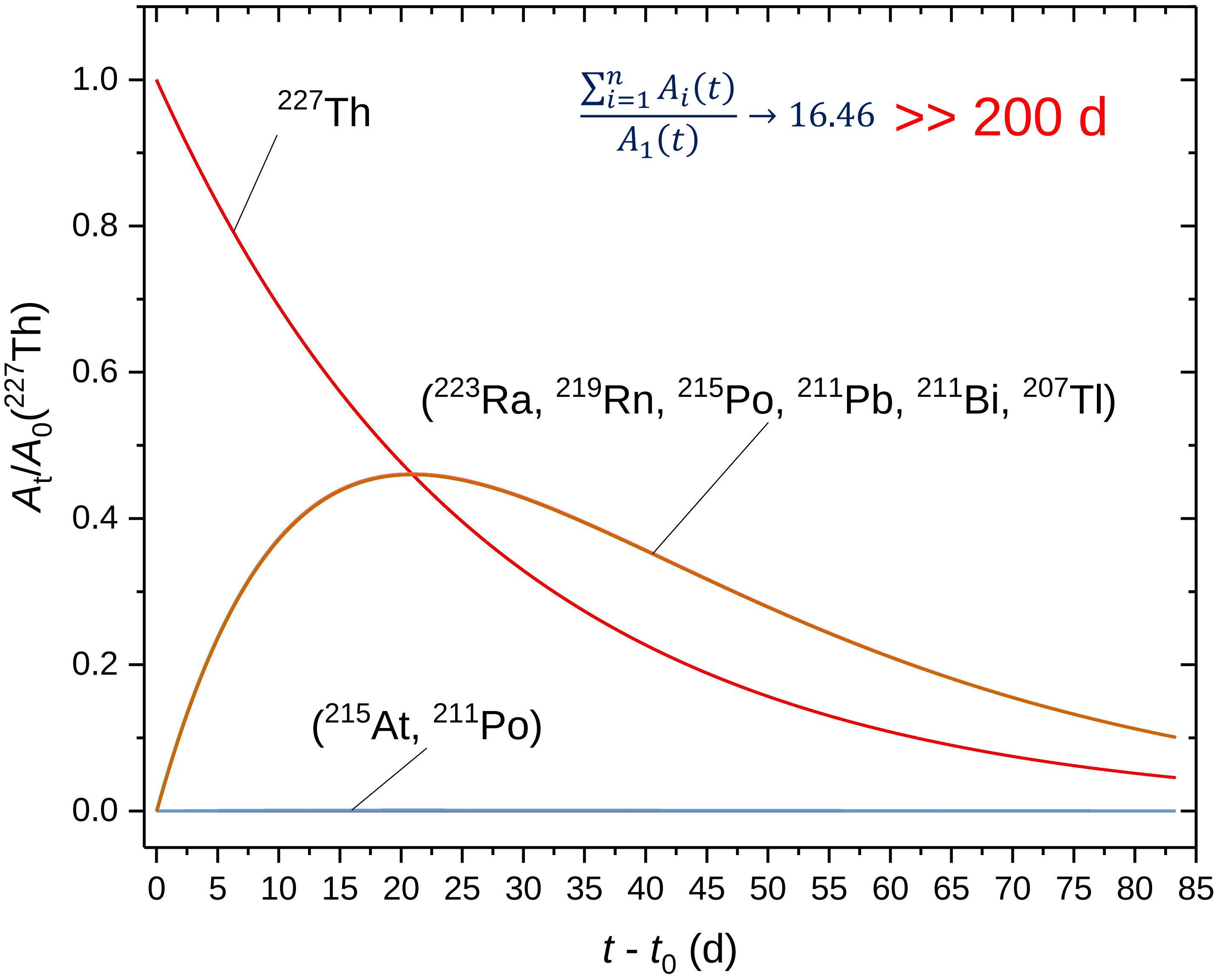
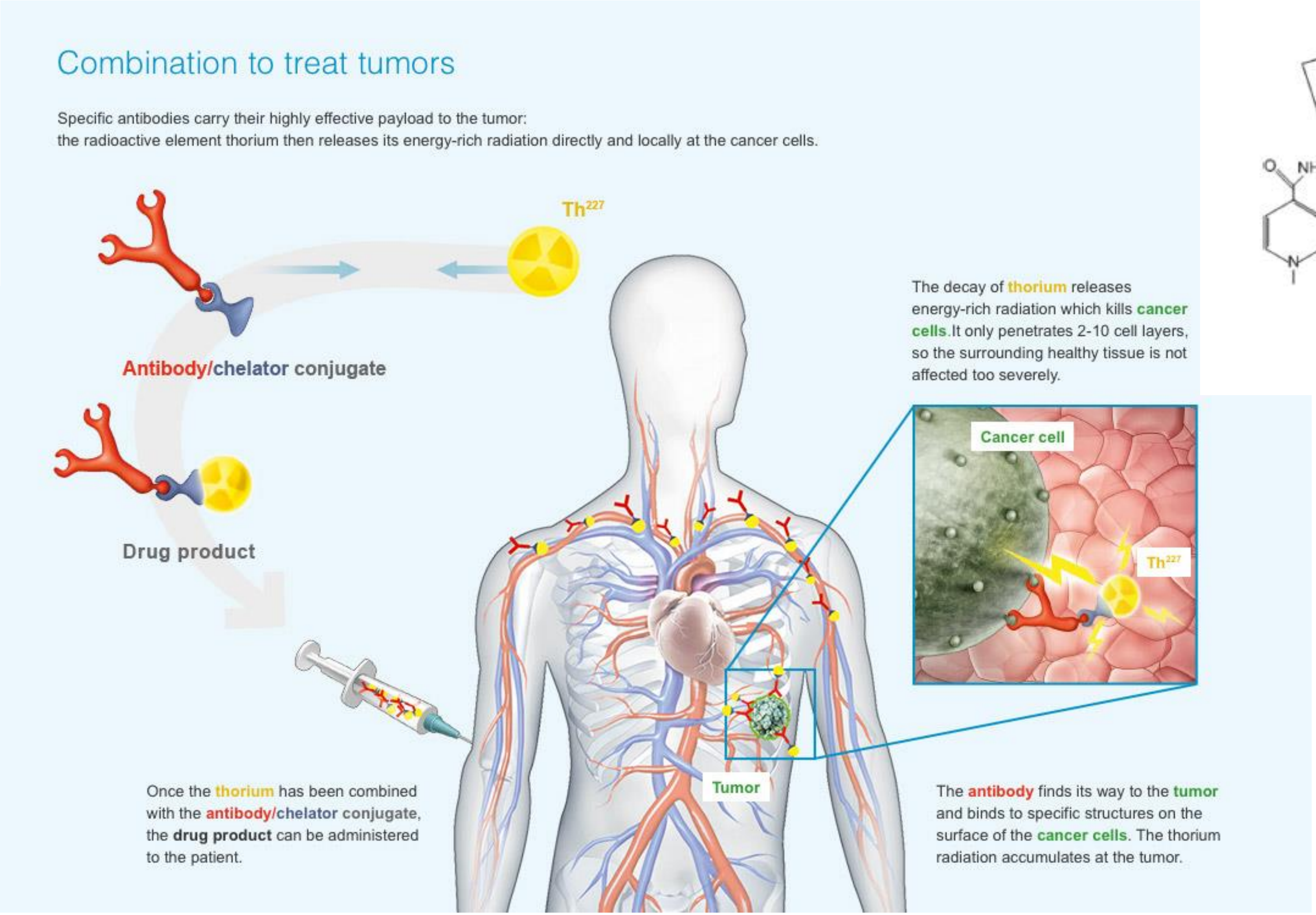
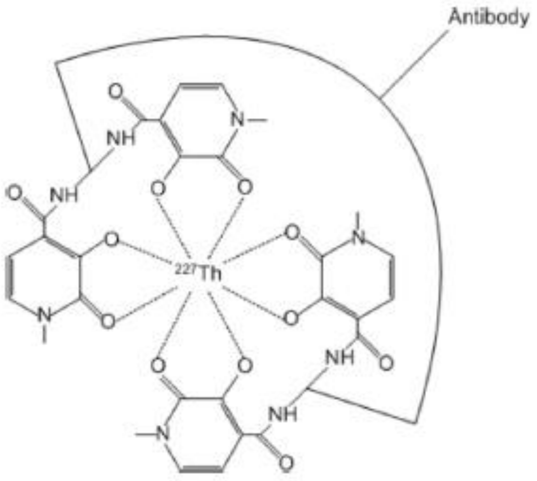


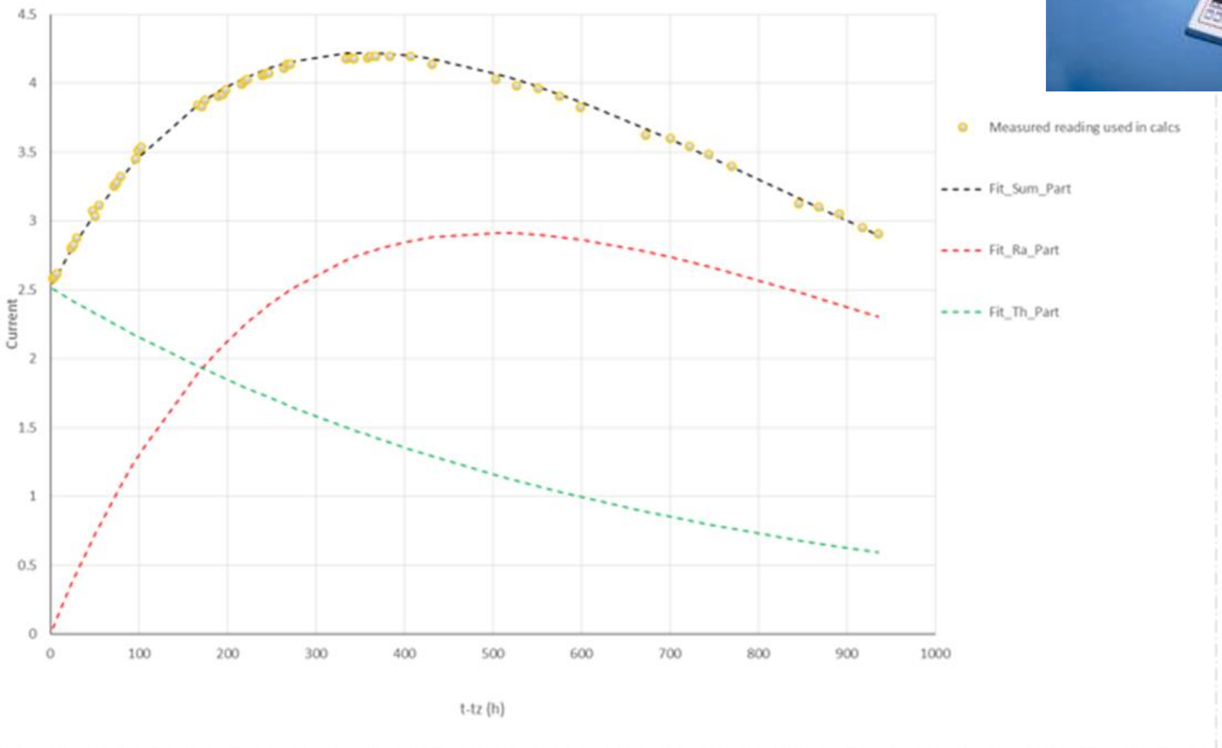
Thorium-227 for targeted alpha radiotherapy



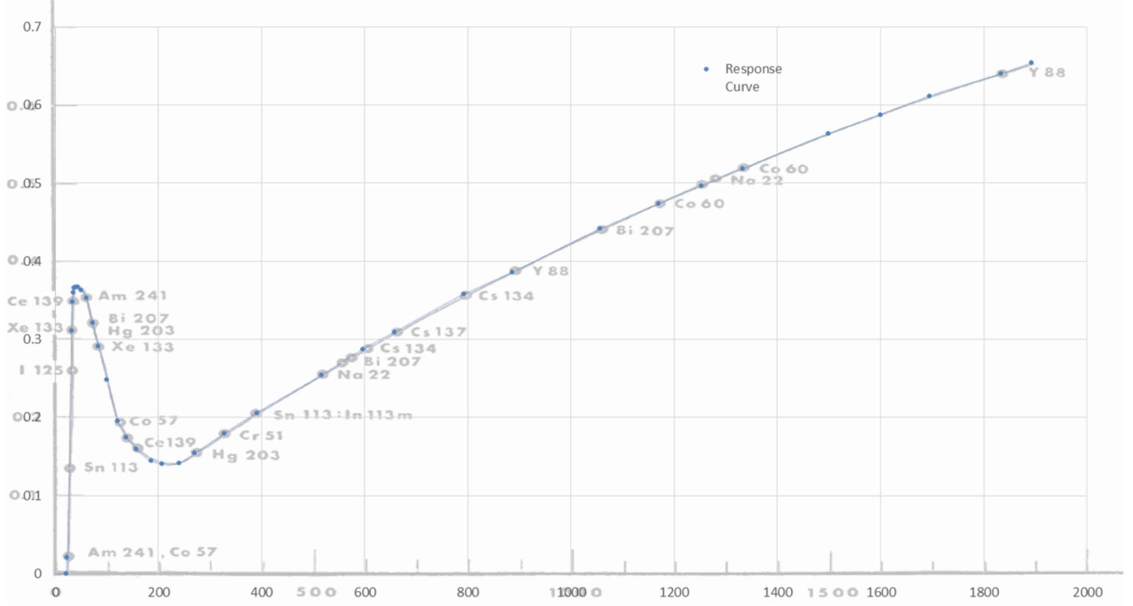


https://www.research.bayer.com/en/fighting-cancer-with-radio-immunotherapy.aspx

Dial factors for radionuclide calibrators for ^{227}Th



Photon response curve for Capintec

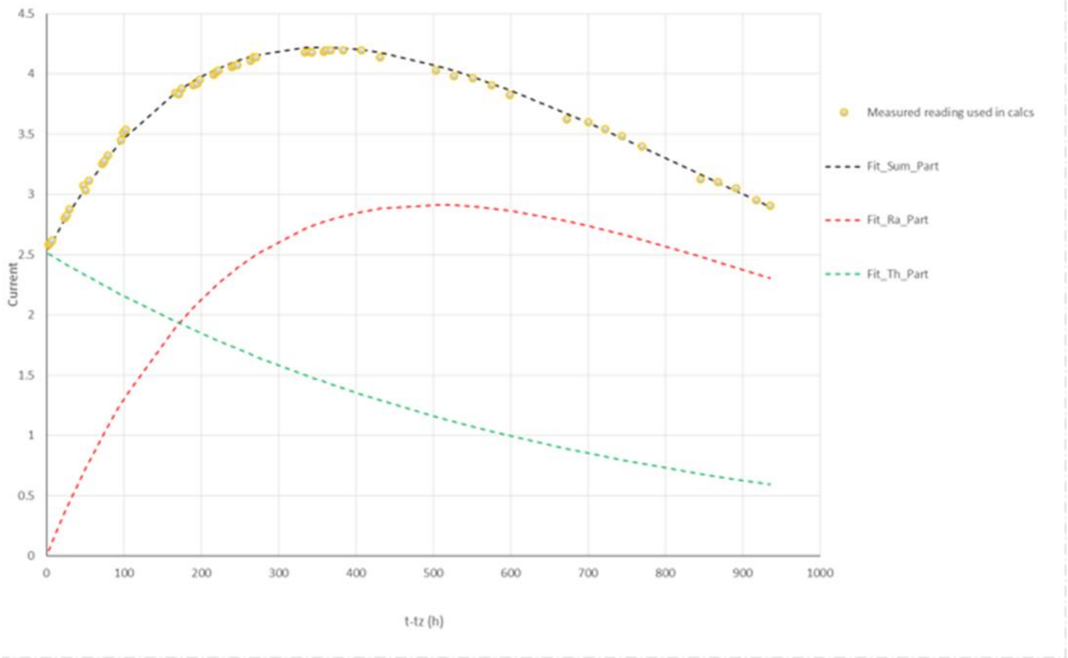


- For Ionisation Chamber measurements (SIR) it is not just the activities of the progeny that are important.
- Must consider the convolution of the activities and their relative responses.

Primary standardisation of ^{227}Th: Challenges

- Ingrowth
  - Radium-223 and other progeny removed prior to administration.
  - Total count rate changing with time…including during measurement
  - Need to divide observed total rate by the calculated sum of progeny at time of measurement
  - Need to know time elapsed since separation

    (time zero, where $A_t(^{227}\text{Th}) = 100\%$)



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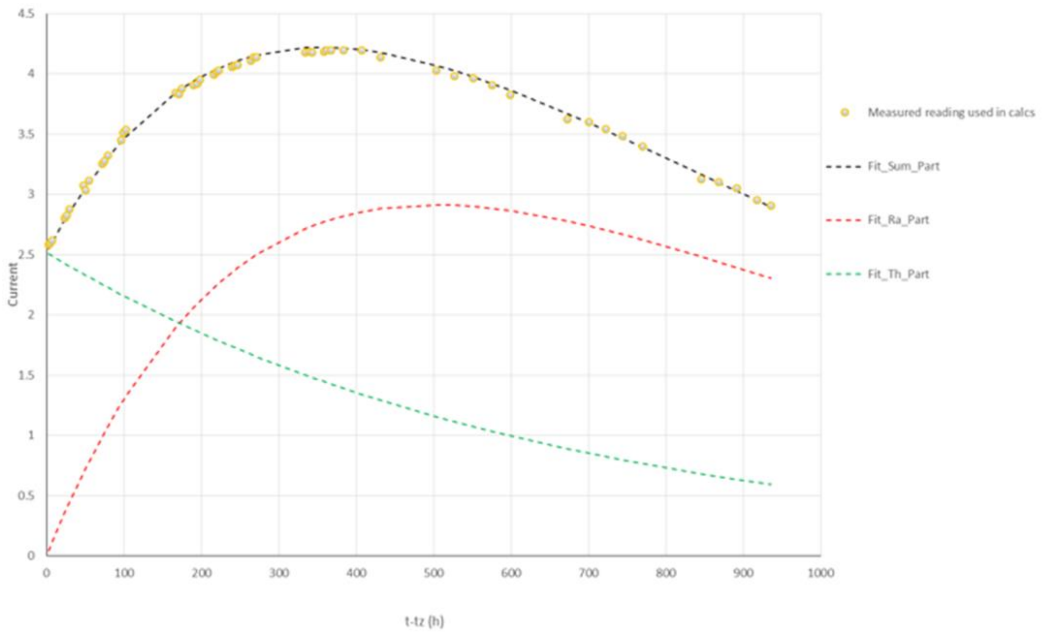
- Radiochemistry
  - Need an efficient method to remove progeny



Primary standardisation of ^{227}Th: Challenges

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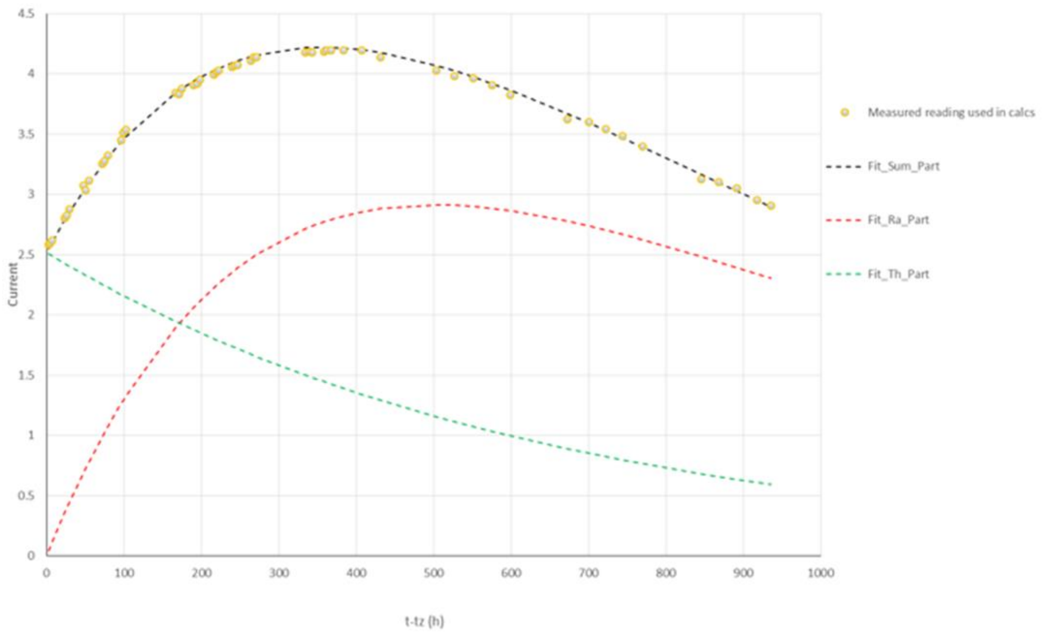
  - Temporal dependence makes half-lives critical for accuracy and precision
  - Poor precision of gamma-ray emission intensities



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- Radiochemistry
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- Nuclear decay data
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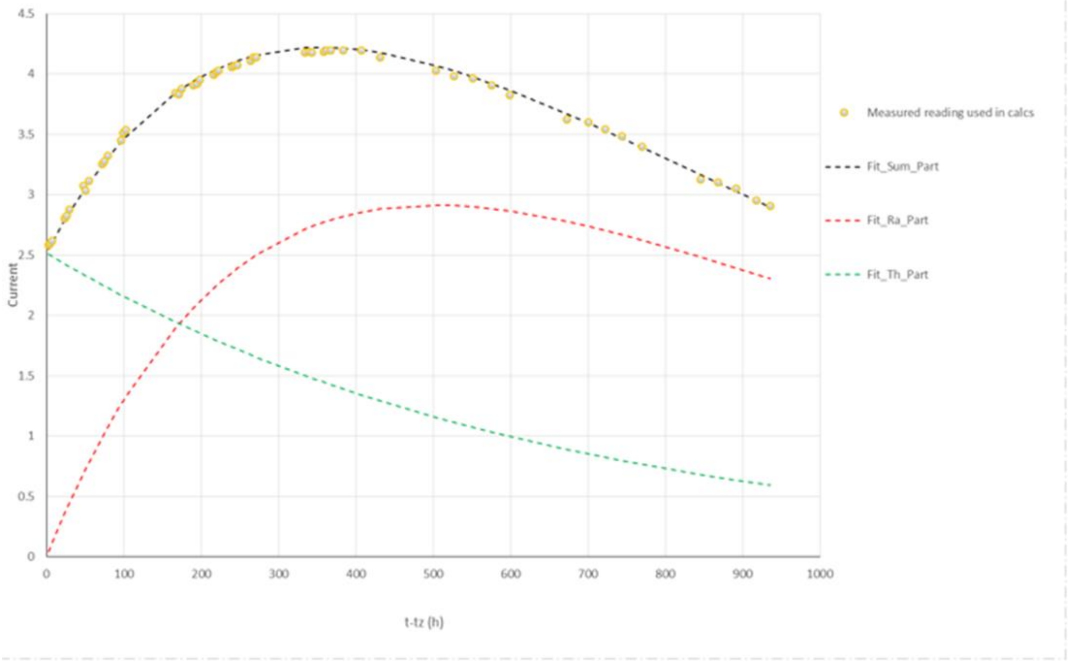
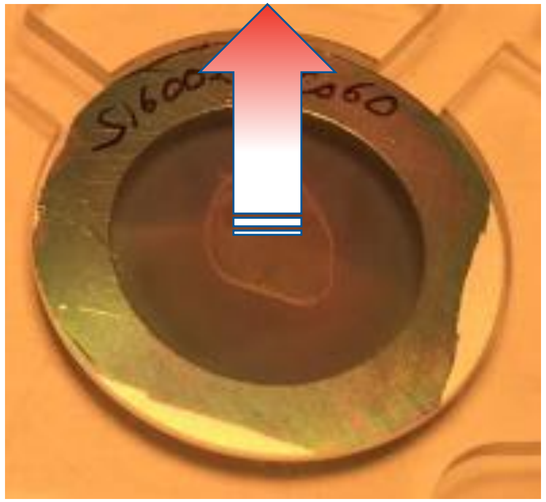
  - Poor precision of gamma-ray emission intensities
- Rn-219
- Po-215
  - Temporal relationship with Rn-219 can lead to losses of counts





Where to start?

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Direct measurement of the half-life of ^{223}Ra

S.M. Collins [a,*], A.K. Pearce [a], K.M. Ferreira [a], A.J. Fenwick [a], P.H. Regan [a,b], J.D. Keightley [a]
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[b] Department of Physics, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom

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Standardisation of ^{223}Ra by liquid scintillation counting techniques and comparison with secondary measurements

John Keightley *, Andy Pearce, Andrew Fenwick, Sean Collins, Kelley Ferreira, Lena Johansson
National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, UK

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The half-life of ^{227}Th by direct and indirect measurements

S.M. Collins [a,*], S. Pommé [b], S.M. Jerome [a], K.M. Ferreira [a], P.H. Regan [a,c], A.K. Pearce [a]
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Precise measurements of the absolute γ-ray emission probabilities of ^{223}Ra and decay progeny in equilibrium

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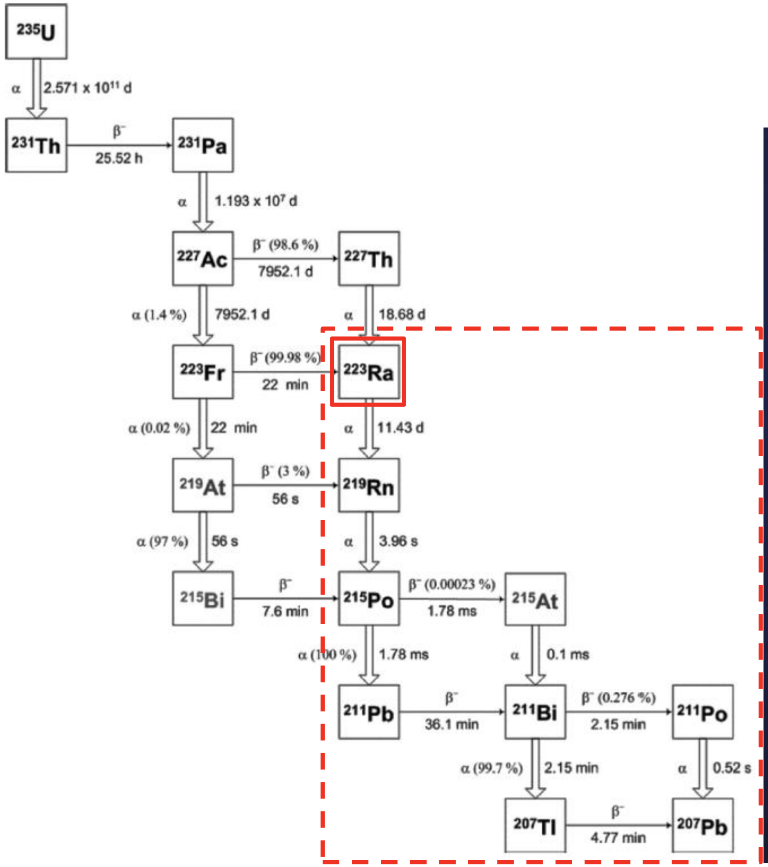
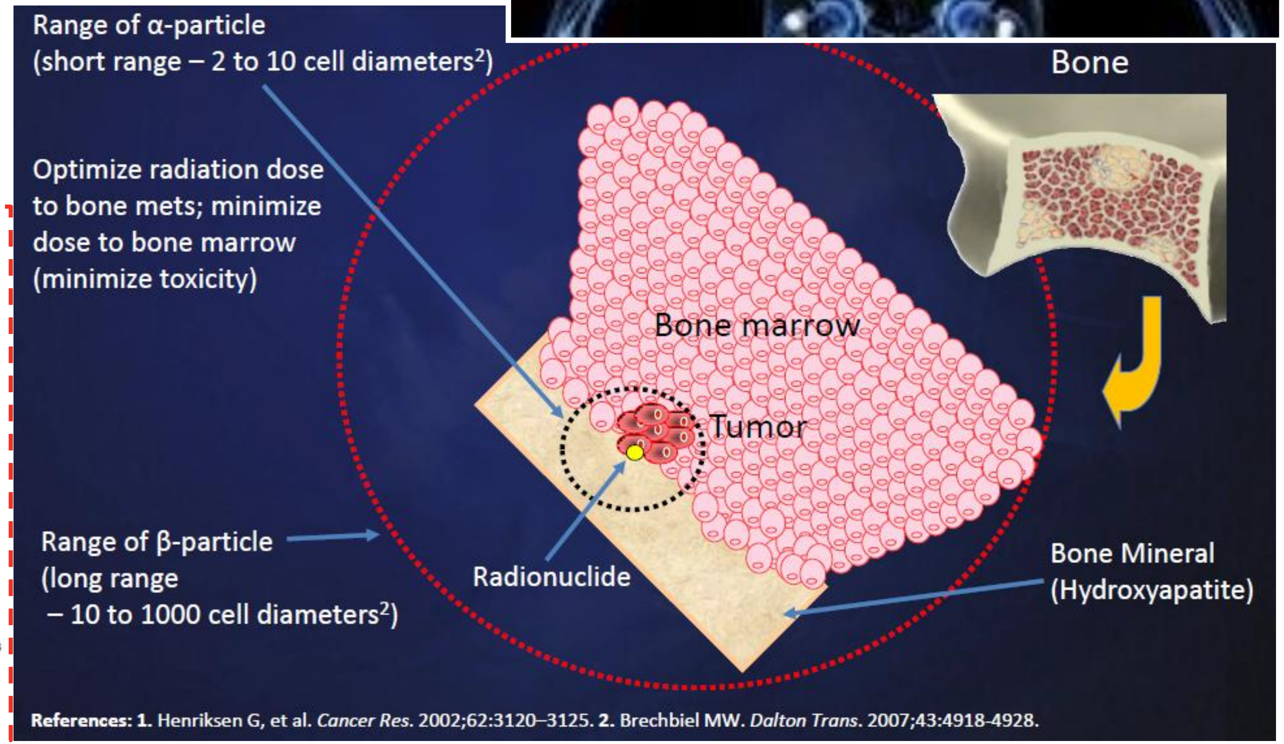
Ra-223 radiopharmaceutical: Xofigo™

- Used to treat men with advanced prostate cancer when the disease has spread to the bones and is causing symptoms (pain).



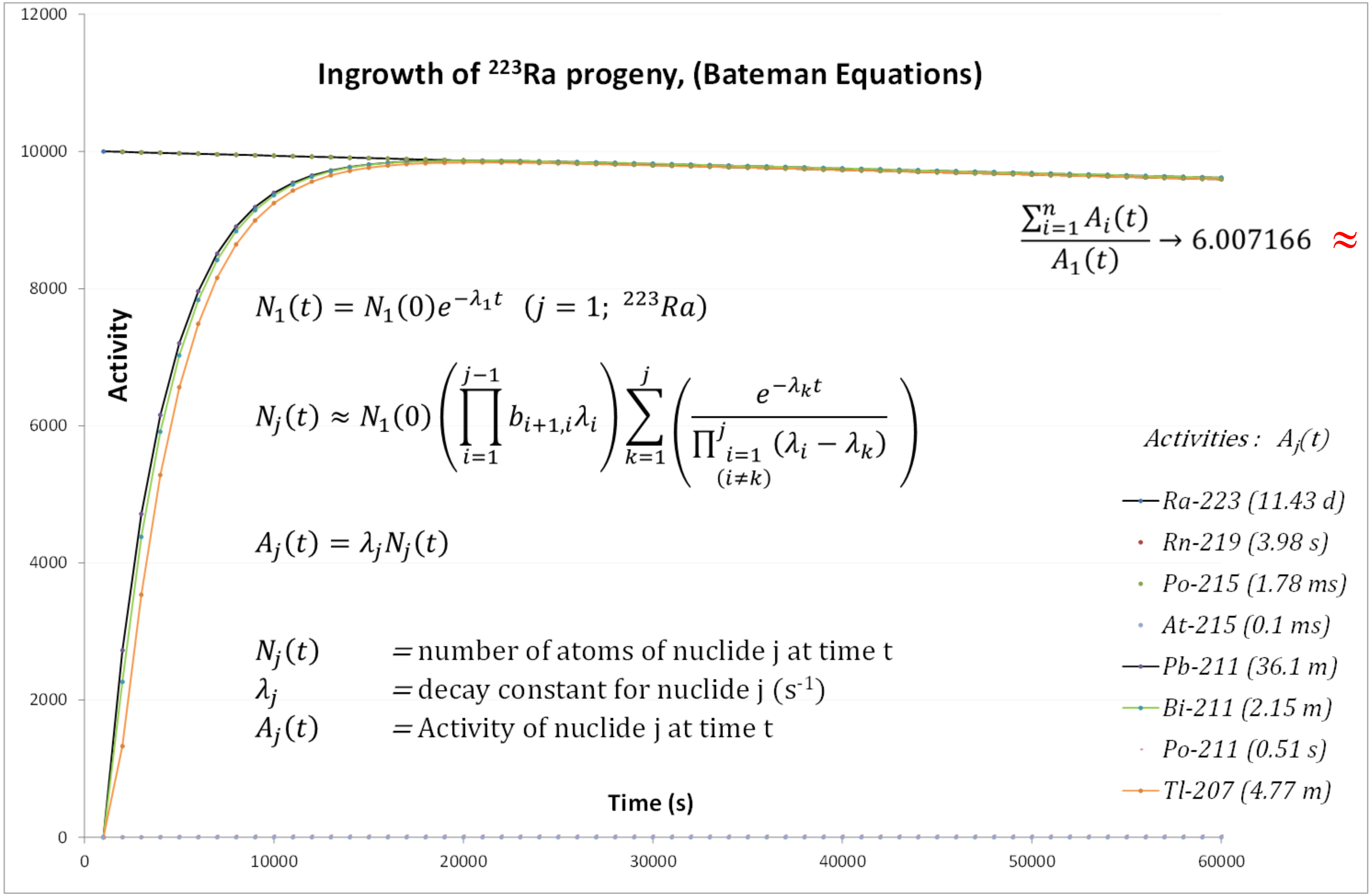


Why is it useful to start here for ^{227}Th?

- Absolute gamma-ray emission intensities
  - Needed for determining time zero
  - For determining activity by ingrowth rate measurements (HPGe)
  - Th227 and decay progeny share gamma-ray emissions with same energy, needed for corrections.

- ^{223}Ra calibration factors for IC

Temporal relationship of ^{223}Ra → progeny



≈ 10 h

Standardisation of ^{223}Ra at NIST

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Standardization of radium-223 by liquid scintillation counting

J.T. Cessna *, B.E. Zimmerman

Ionizing Radiation Division, Physics Laboratory, National Institute of Standards and Technology, 100 Bureau Drive MS 8462, Gaithersburg, MD 20899-8462, USA

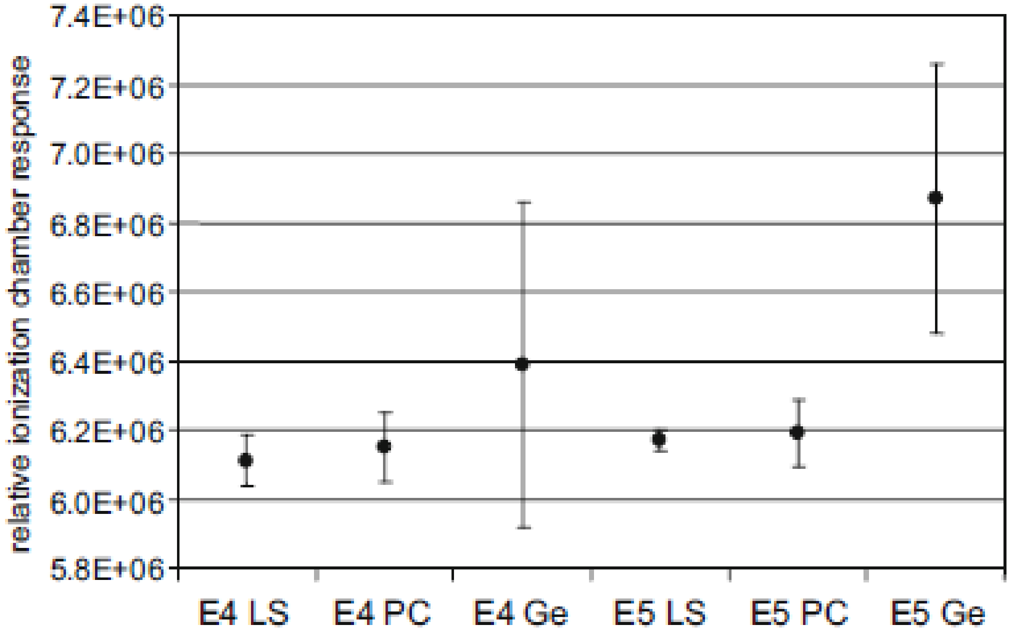

Fig. 3. Results of activity determinations by the CIEMAT/NIST method of ^{3}H efficiency tracing liquid scintillation counting (LS), $2\pi\alpha$ proportional counting (PC), and germanium spectroscopy (Ge) expressed relative to measurements of a radium (^{226}Ra) reference source on the NIST $4\pi-\gamma$ secondary ionization chamber. Uncertainty bars represent expanded uncertainties, $k=2$.

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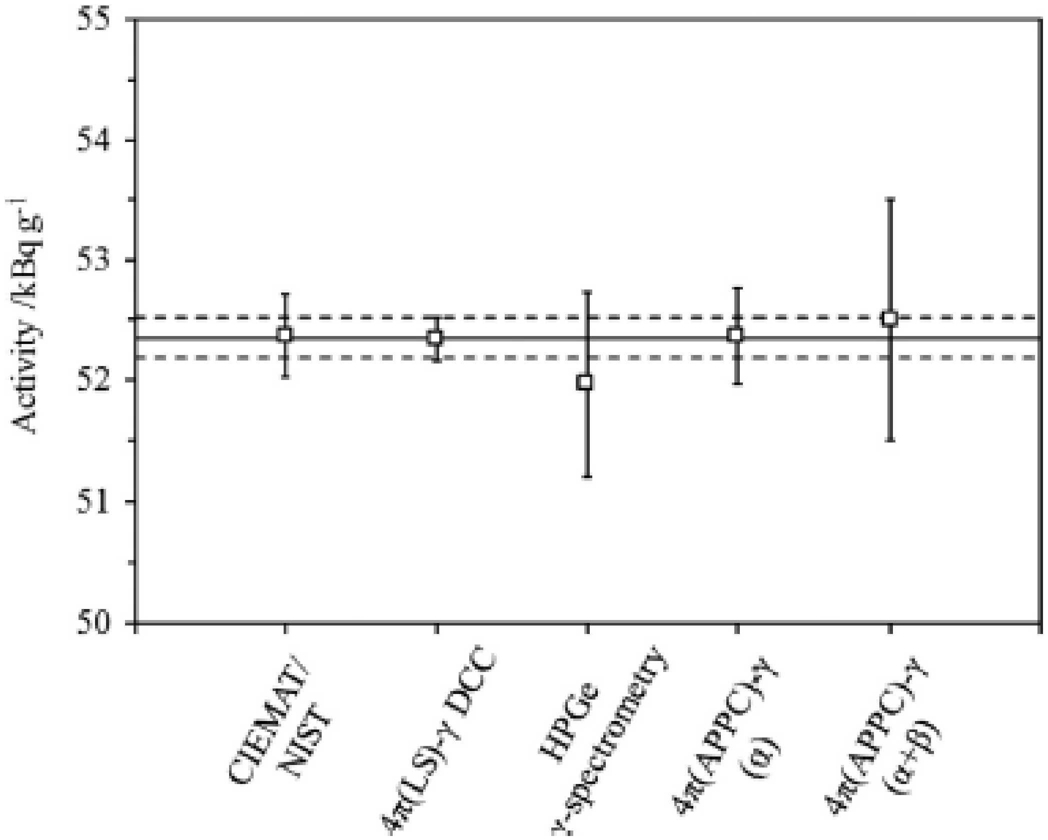

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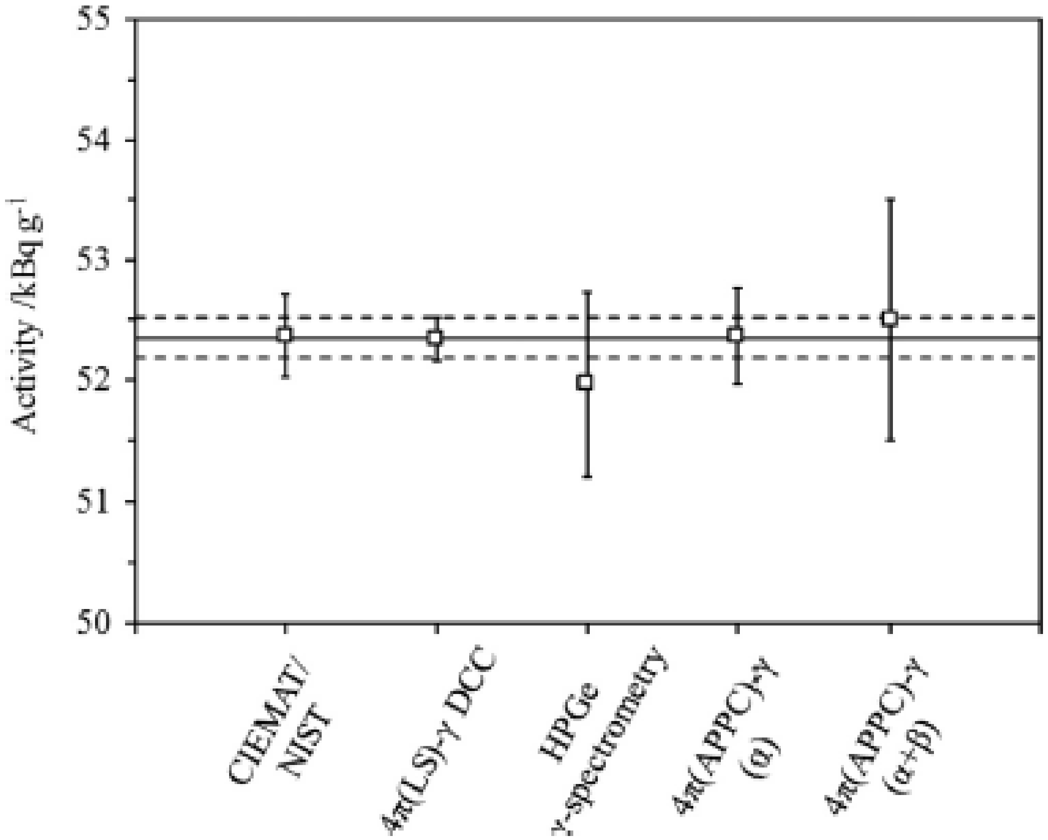
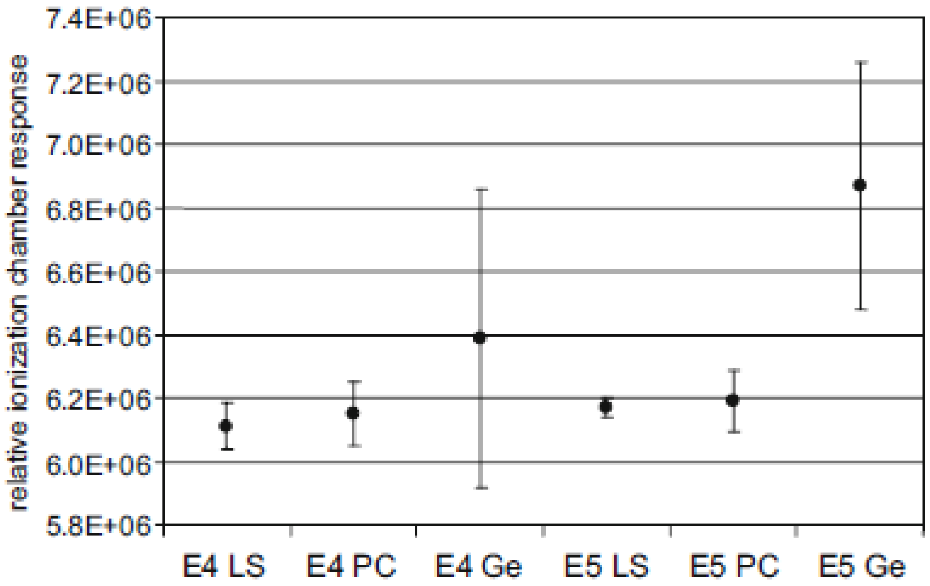


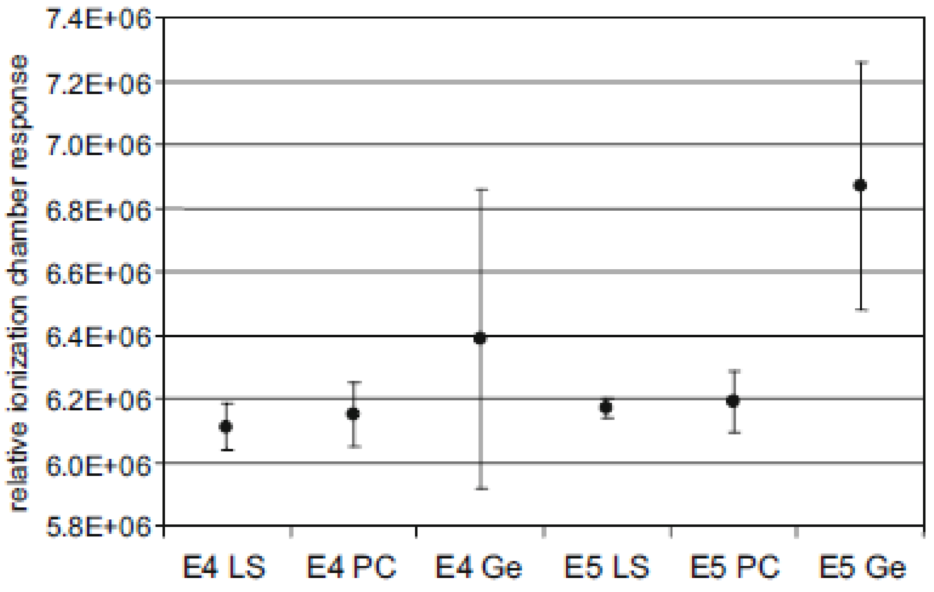
Comparison of NPL and NIST ionisation chamber calibration factors

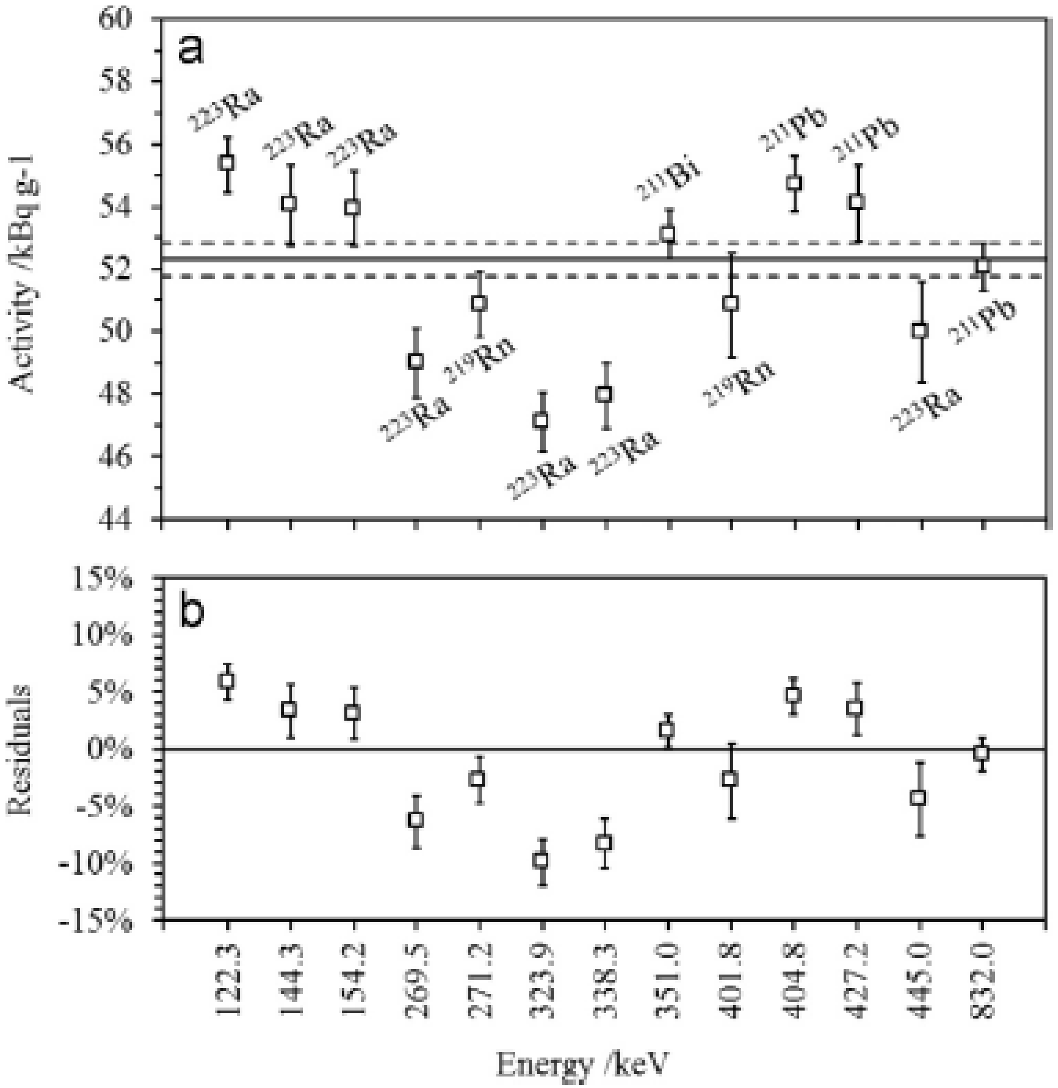
~ 10% difference

Discrepancy between NIST and NPL



Discrepancy between NIST and NPL





Discrepancy between NIST and NPL

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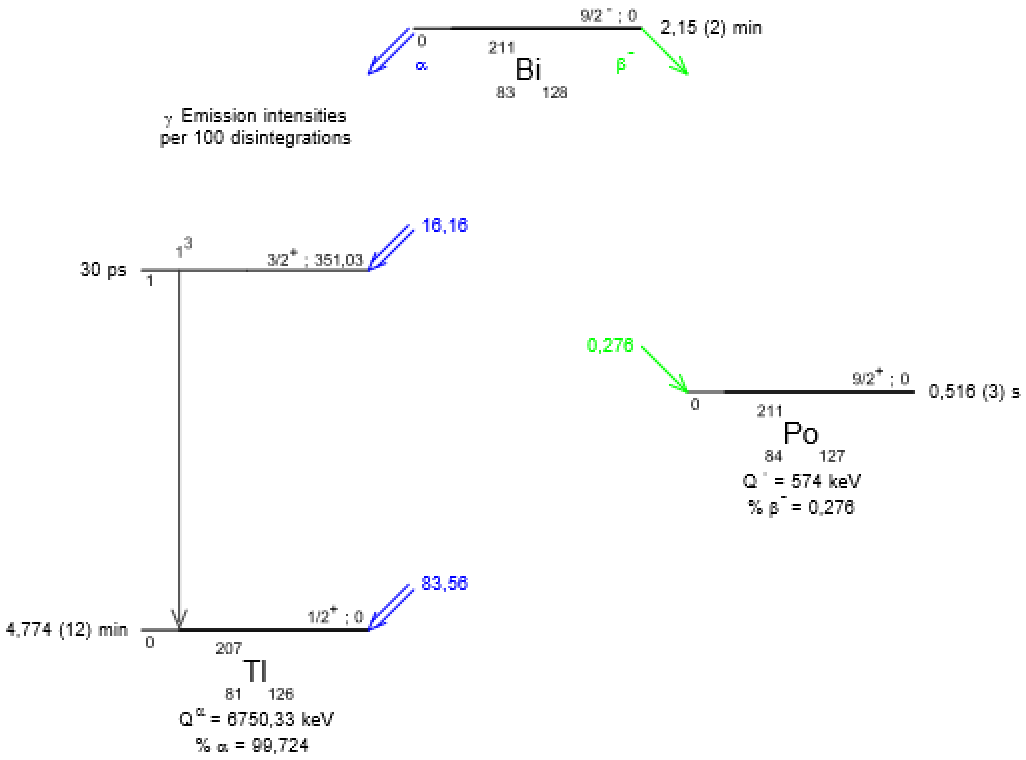

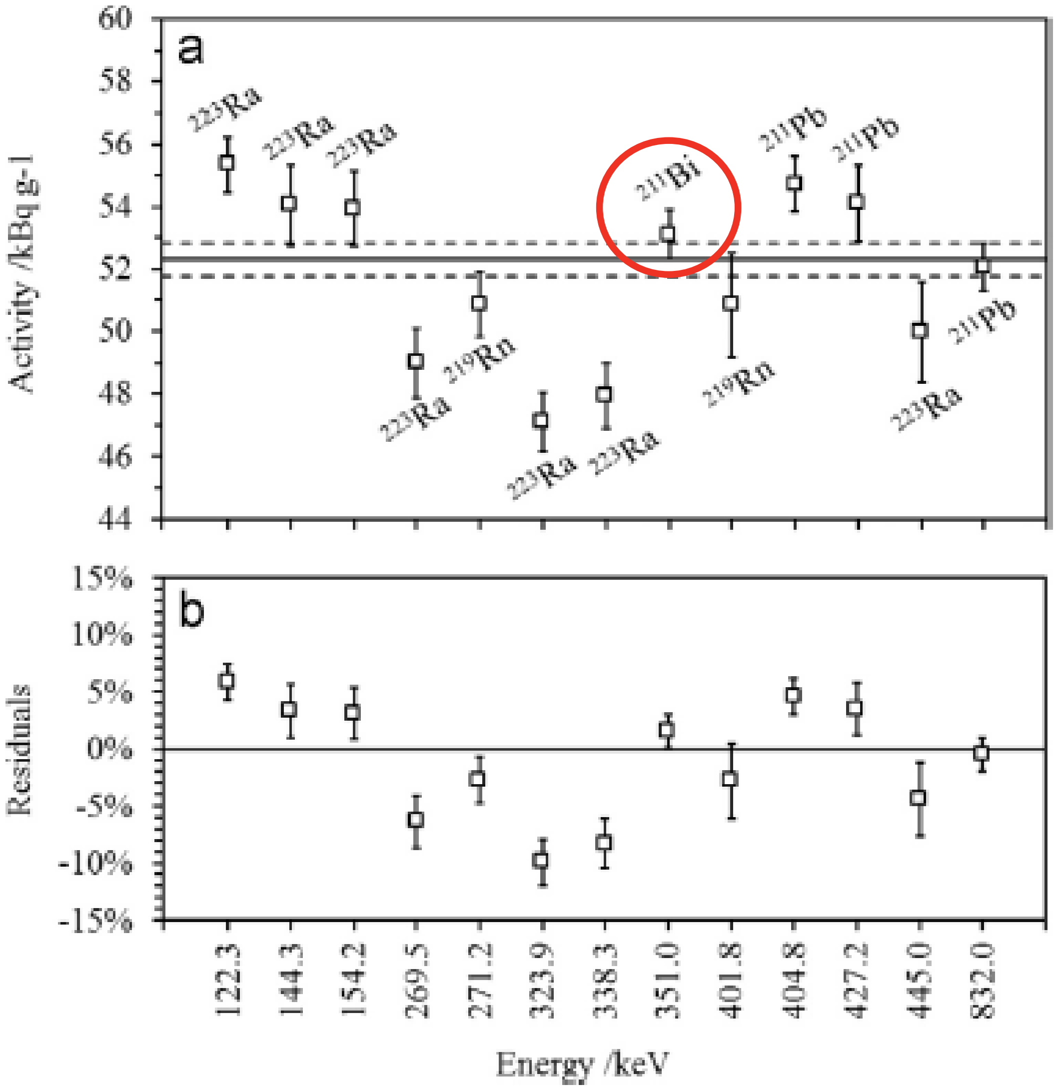

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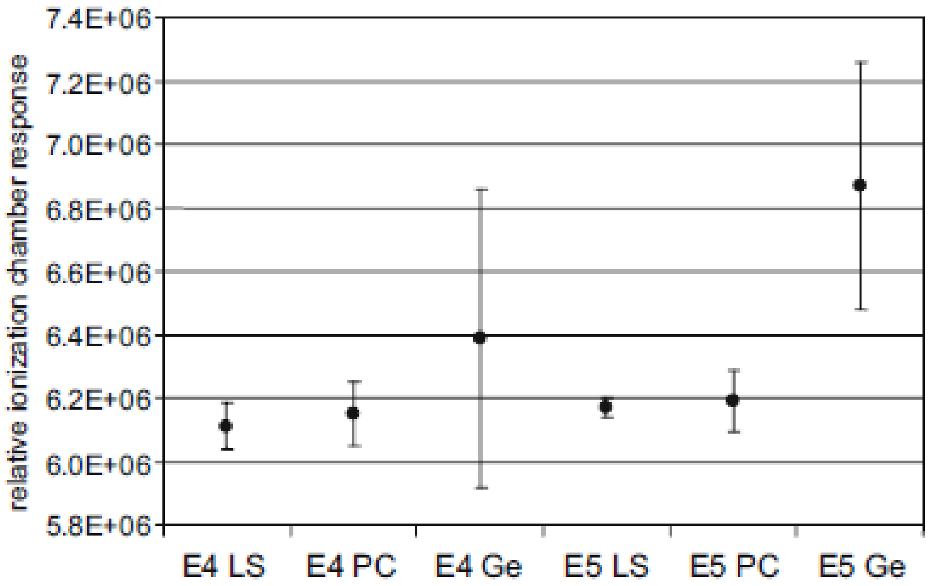

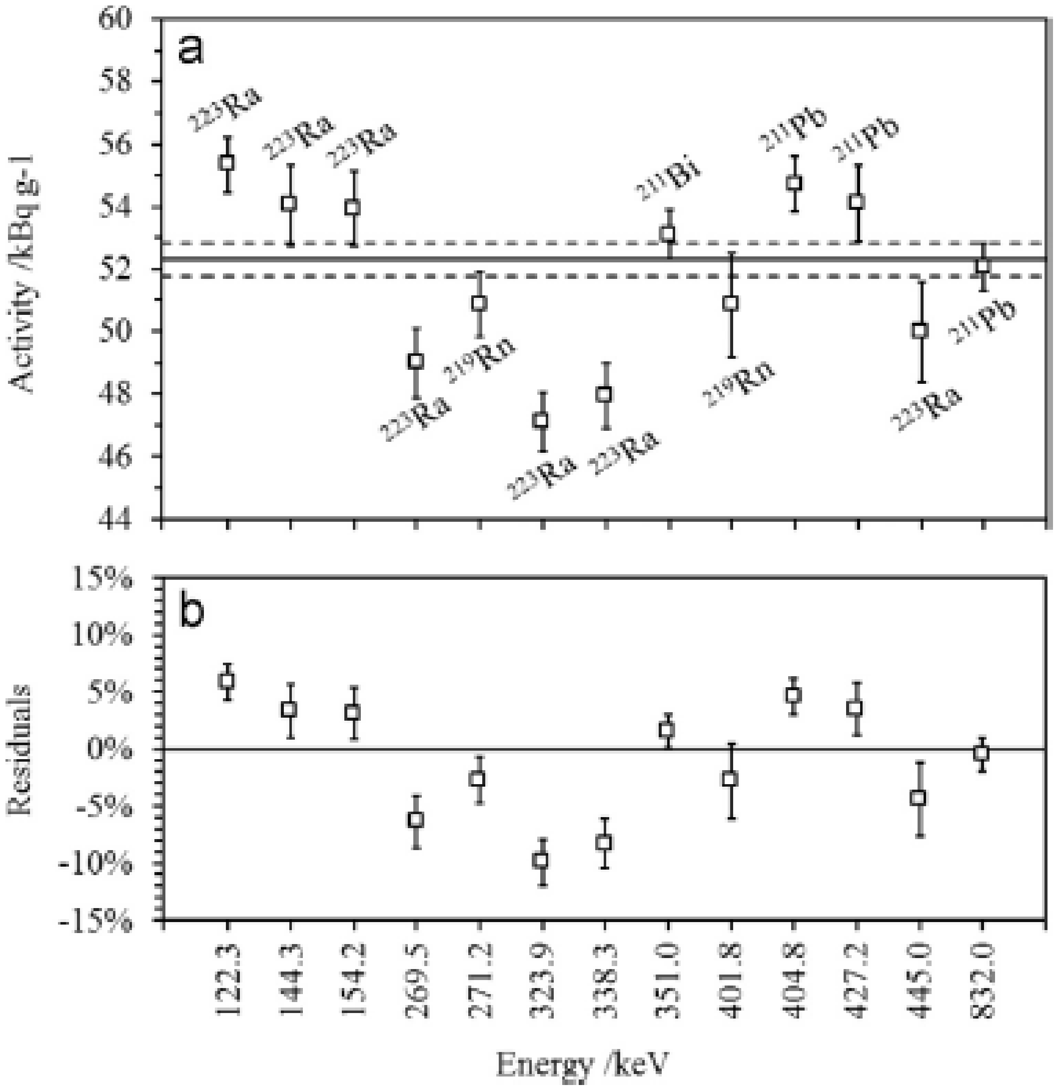

RaCl$_2$ unstable in NIST solution

Volume 120 (2015) http://dx.doi.org/10.6028/jres.120.004
Journal of Research of the National Institute of Standards and Technology

Revision of the NIST Standard for ^{223}Ra: New Measurements and Review of 2008 Data

B. E. Zimmerman, D. E. Bergeron, J. T. Cessna, R. Fitzgerald, and L. Pibida

National Institute of Standards and Technology,
Gaithersburg, MD 20899

Updated absolute emission intensities

- Derive absolute values from primary standard – don't need to know internal conversion coefficients

Radionuclide	Energy /keV	I_γ(This work) %	I_γ(DDEP) %	z-score	Difference %
^{223}Ra	269.5	13.37 (7)	14.23 (32)	-2.6	-6.0
^{219}Rn	271.2	10.75 (6)	11.07 (22)	-1.4	-2.9
^{215}Po	438.8	0.0533 (7)	0.058 (19)	-0.3	-8.1
^{211}Pb	404.8	4.011 (9)	3.83 (6)	3.0	4.7
^{211}Bi	351.0	13.17 (7)	13.00 (19)	0.8	1.3
^{207}Tl	897.7	0.2725 (15)	0.263 (9)	1.0	3.6

Radionuclide	Energy /keV	I_γ(NPL) %	I_γ(NIST) %	I_γ(PTB) %	$\chi^2/(n-1)$
^{223}Ra	122.3	1.312 (6)	1.30 (1)	1.304 (12)	0.3
^{223}Ra	144.3	3.481 (16)	3.51 (3)	3.469 (20)	0.3
^{223}Ra	154.2	6.02 (3)	6.08 (6)	6.03 (5)	0.2
^{223}Ra	269.5	13.37 (7)	13.24 (12)	13.16 (15)	0.5
^{223}Ra	323.9	3.655 (18)	3.63 (2)	3.661 (21)	0.3
^{223}Ra	338.3	2.605 (13)	2.59 (2)	2.614 (13)	0.3
^{223}Ra	445.0	1.218 (6)	1.217 (8)	1.222 (6)	0.1
^{219}Rn	271.2	10.75 (6)	10.69 (10)	10.87 (12)	0.3
^{219}Rn	401.8	6.57 (3)	6.56 (4)	6.62 (4)	0.3
^{211}Pb	404.8	4.011 (19)	4.01 (3)	4.05 (5)	0.1
^{211}Pb	427.2	1.890 (9)	1.89 (1)	1.912 (10)	0.8
^{211}Pb	832.0	3.448 (16)	3.48 (3)	3.430 (17)	0.5
^{211}Bi	351.0	13.17 (7)	13.11 (9)	13.24 (6)	0.4
No. of γ-rays reported		83	15	43	

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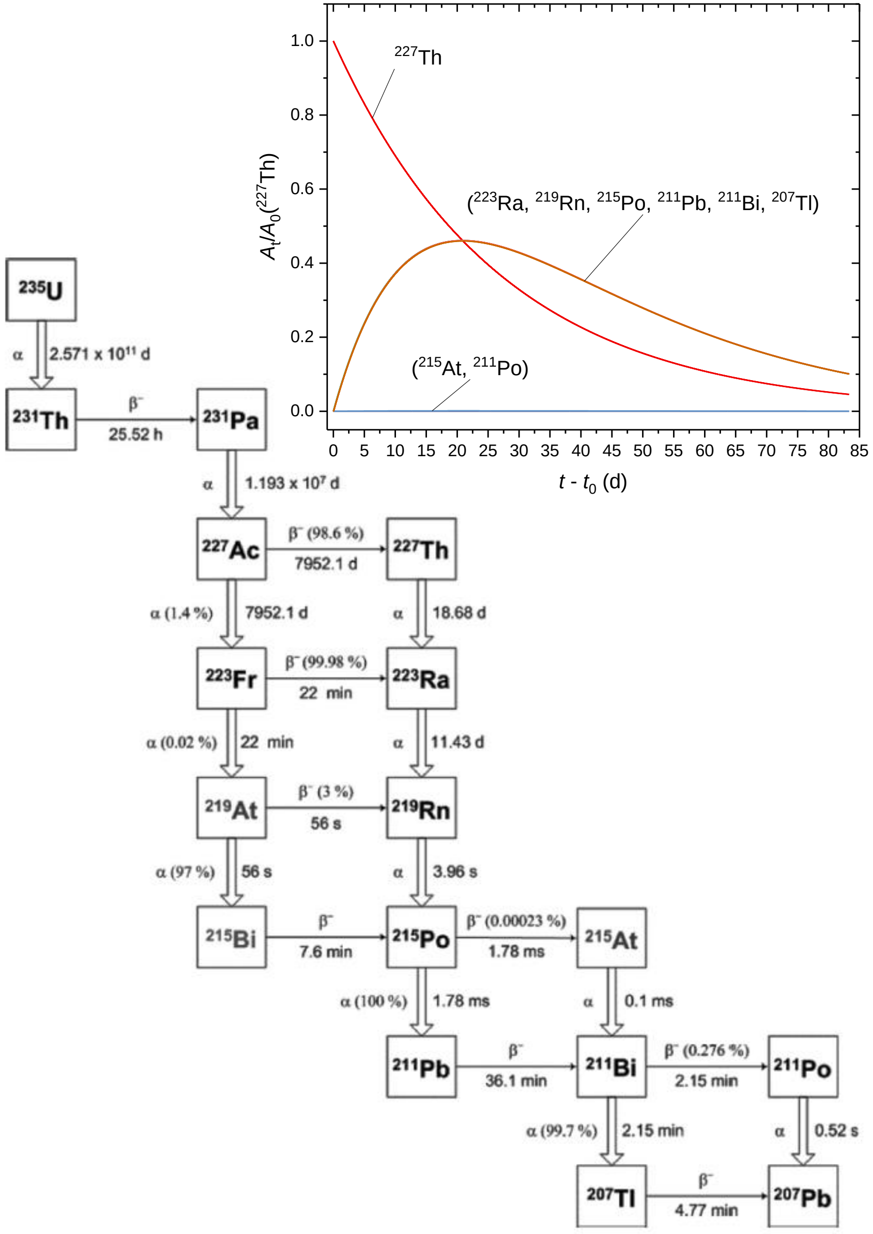
Summary of half-lives

- Critical for calculating corrections for ingrowth
- Recommended values (DDEP) for critical radionuclides

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

	Evaluated $T_{1/2}$	'New' $T_{1/2}$
^{227}Th	18.718(5) d	
^{223}Ra	11.43(3) d	



Uncertainties in half-lives

- Underestimation of uncertainties a significant problem
  - Inconsistent evaluation datasets

- Many studies only quote uncertainty of the fit

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Half-life data—a critical review of TECDOC-619 update

M.J. Woods[a,*], S.M. Collins[b]

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Metrologia 52 (2015) S51–S65 doi:10.1088/0026-1394/52/3/S51

The uncertainty of the half-life

S Pommé

European Commission, Joint Research Centre, Institute for Reference Materials and Measurements, Retieseweg 111, B-2440 Geel, Belgium

$$\frac{u\left(T_{1/2}\right)}{T_{1/2}} \approx \frac{2}{\lambda t}\sqrt{\frac{2}{n+1}}\,\frac{u(A)}{A}$$

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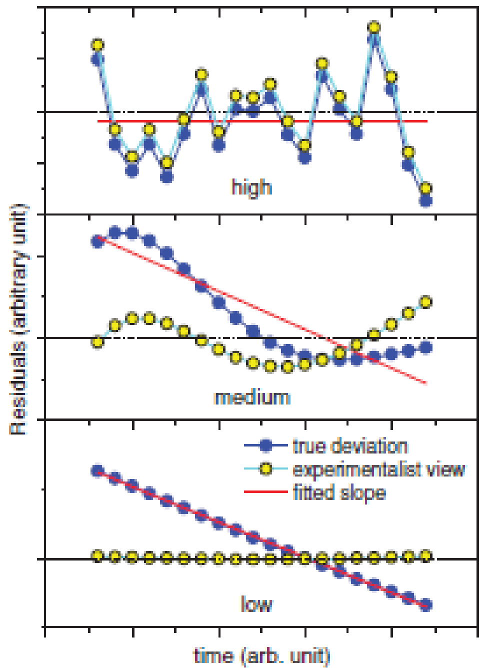

Figure 1. True (dark dots) and perceived (light dots) residuals from a fit of a decay curve through hypothetical data affected by high (top), medium (middle) and low (bottom) frequency instabilities. Systematic deviations are not fully observed by the experimentalist, as the fit tends to minimise them.

Uncertainties in half-lives

National Physical Laboratory

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The uncertainty of the half-life

S Pommé

European Commission, Joint Research Centre, Institute for Reference Materials and Measurements, Retieseweg 111, B-2440 Geel, Belgium

$$\frac{u\left(T_{1/2}\right)}{T_{1/2}} \approx \frac{2}{\lambda t}\sqrt{\frac{2}{n+1}}\frac{u(A)}{A}$$

Analysis of residuals of fit key

Available online at www.sciencedirect.com

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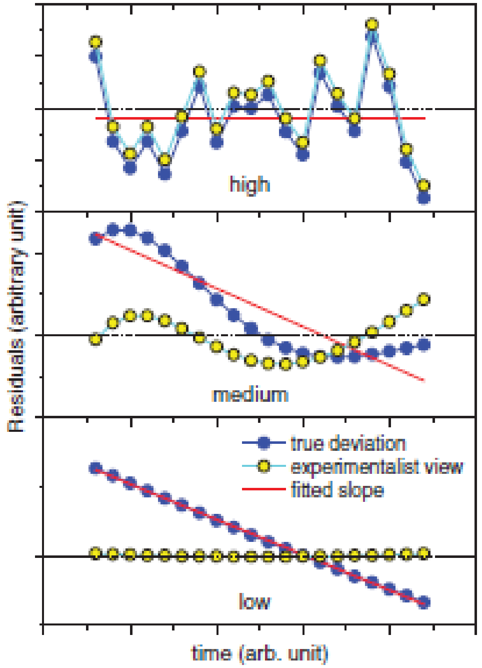

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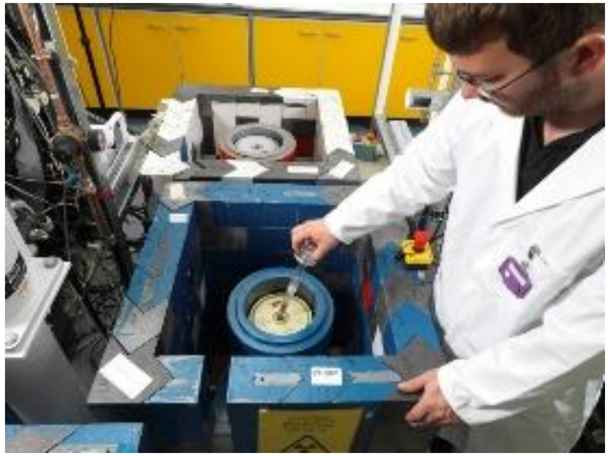
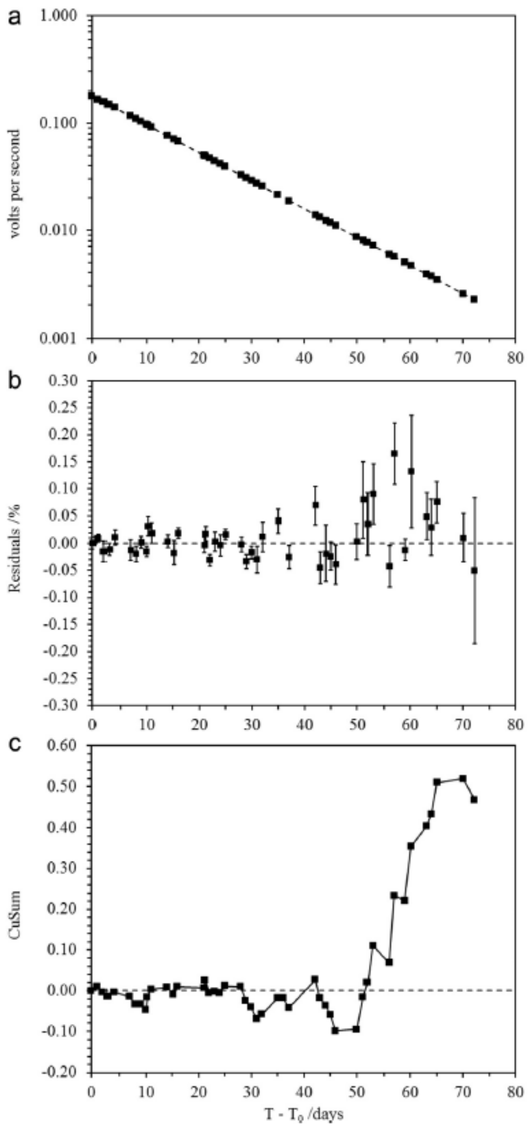


- Excellent long-term stability
- Back-to-back system – reduces background significantly
- Good linearity of response

$T_{1/2}(^{223}\text{Ra}) = 11.4363 \pm 0.0027$ d



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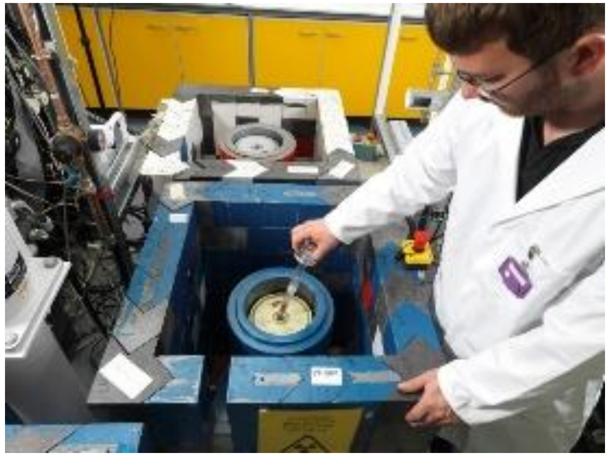
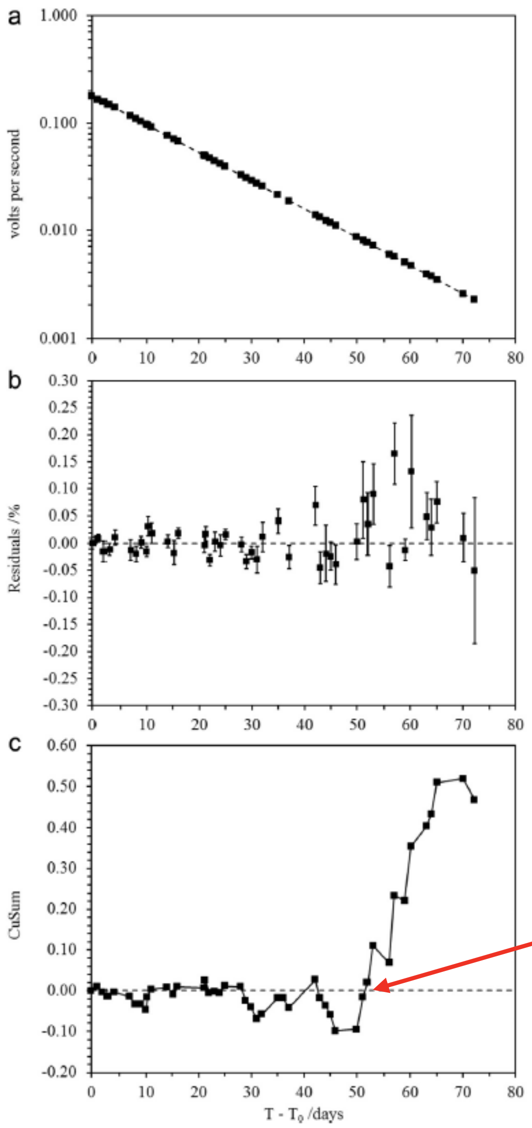




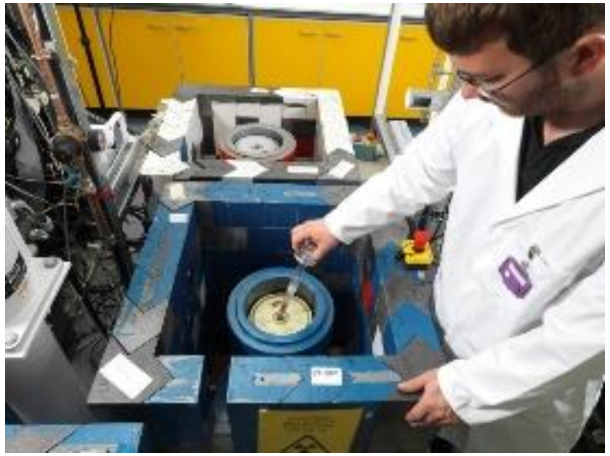
- Excellent long-term stability

- Back-to-back system – reduces background significantly

- Good linearity of response

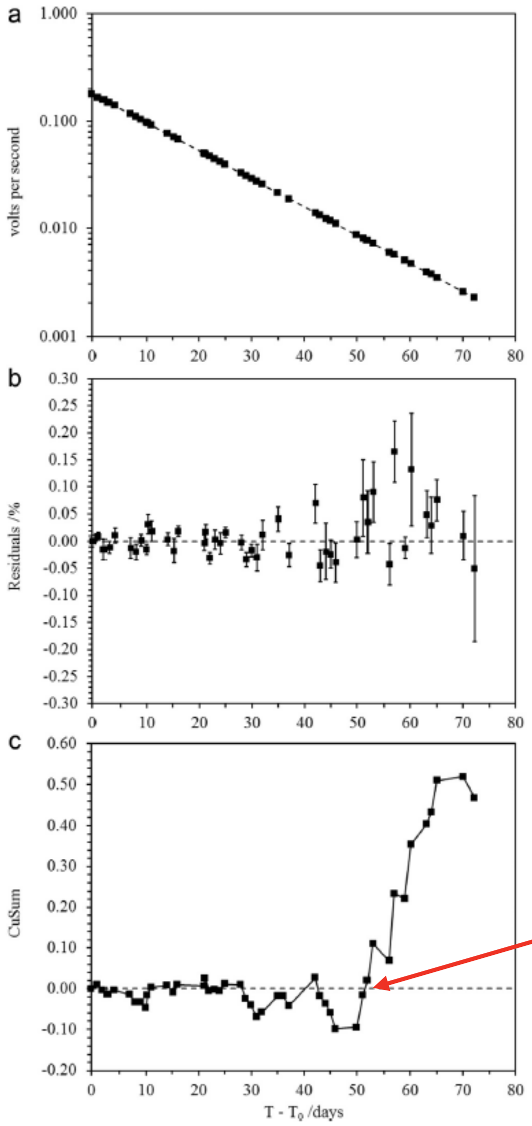
Range change in DVM (non-linearity)

Half-life of ^{223}Ra



- Excellent long-term stability
- Back-to-back system – reduces background significantly
- Good linearity of response over the same voltage range

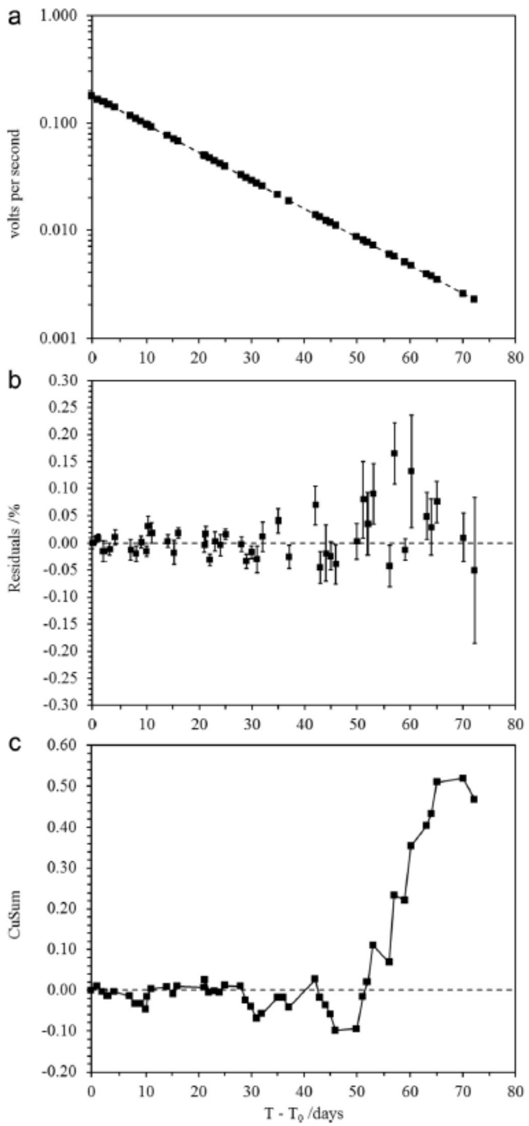
$T_{1/2}(^{223}\text{Ra}) = 11.4363 \pm 0.0027$ d



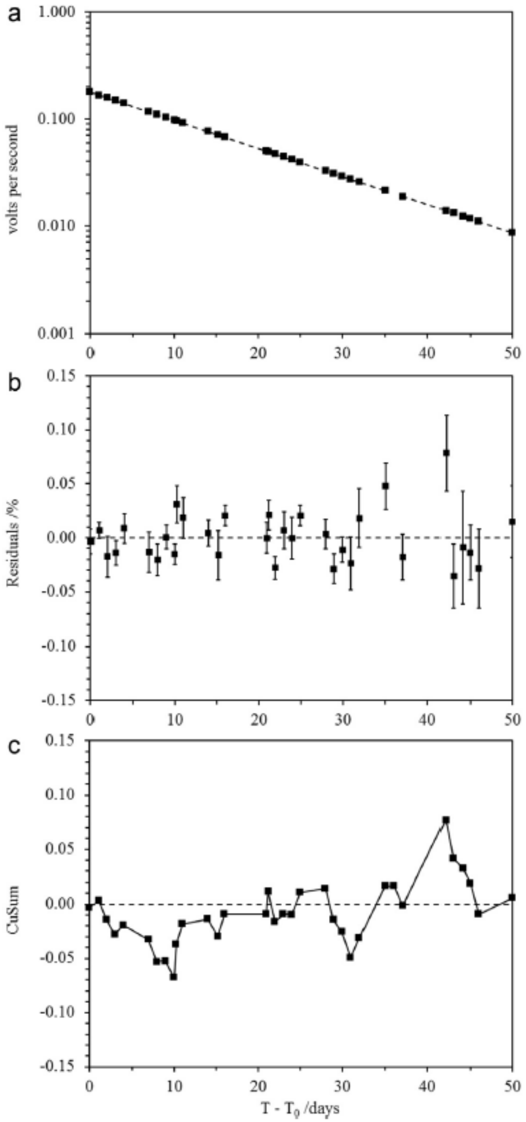
Range change in DVM (non-linearity)

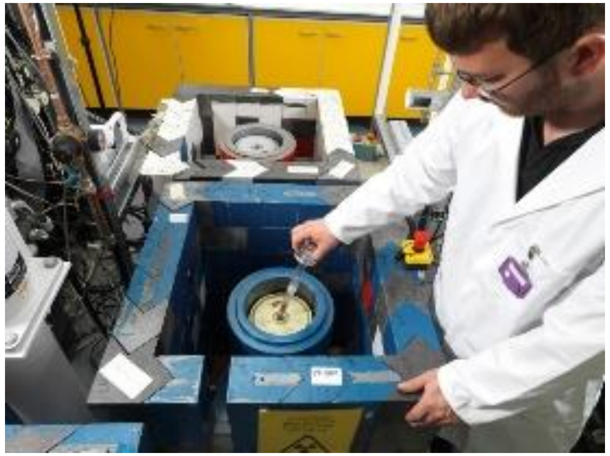
Half-life of ^{223}Ra

$T_{1/2}(^{223}Ra) = 11.4363 \pm 0.0027$ d



$T_{1/2}(^{223}Ra) = 11.4358 \pm 0.0028$ d





- Excellent long-term stability
- Back-to-back system – reduces background significantly
- Good linearity of response over the same voltage range

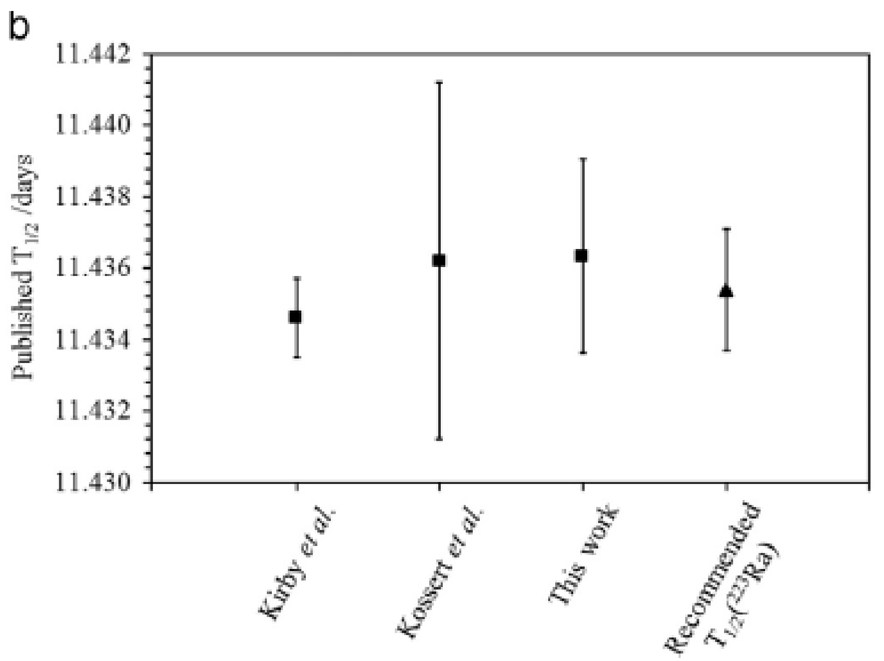
Half-life of ^{223}Ra

The determined ^{223}Ra half-life and uncertainty budget. The uncertainty values are quoted at $k = 1$.

Uncertainty components	$\sigma(A)/A$ (%)	n	Factor	$\sigma(T_{1/2})/T_{1/2}$ (%)
High frequency				
Standard deviation of residuals	0.024	33	0.16	0.0038
Medium frequency				
Trends in residuals	0.024	1	0.66	0.016
Geometric repeatability	0.070	33	0.16	0.011
Low frequency				
Background	0.00016	1	0.66	0.00010
Impurities	0.010	1	0.66	0.0070
Efficiency stability	0.016	1	0.66	0.011
Linearity	0.010	1	0.66	0.0066
Final half-life result	**11.4358 (28) days**			**0.024**

Half-life of ^{223}Ra – Comparison to literature

Authors	Year	Value (days)	Method	Comment
Hagee et al.	1954	11.685 (56)	Abstracted from proportional alpha counting of ingrowth ^{223}Ra from ^{227}Ac	Superseded by Kirby et al. (1965)
Robert*	1959	11.22 (5)	Microcalorimetry	
Kirby et al.*	1965	11.4346 (11)	Weighted mean of direct measurement of ^{223}Ra by microcalorimetry and proportional alpha counting.	
Jordan et al.	1967	11.372 (45)	Abstracted from calorimetry measurements of ingrowth of ^{223}Ra from ^{227}Ac.	Superseded by Kirby et al. (1965)
Miller et al.*	1987	11.444 (46)	Abstracted from alpha spectrometry of ingrowth of ^{215}Po from ^{227}Th decay	
Kossert et al.*	2015	11.4362 (50)	Direct measurement of ^{223}Ra in equilibrium by liquid scintillation techniques	
This work*	2015	11.4358 (28)	Direct measurement of ^{223}Ra in equilibrium by Ionisation chamber	



$T_{1/2}$(DDEP) = 11.43(3) d

$T_{1/2}$(This work) = 11.4354(17) d

Half-life of ^{227}Th

National Physical Laboratory

Reference	$T_{1/2}$ (^{227}Th)/days	Method	Comment
Peterson and Ghiorso (1949)	18.68 (1)	α activity ratio measurements of ^{227}Th/^{230}Th	
Hagee et al. (1954)	18.169 (84)	Determined indirectly by ingrowth decay progeny of ^{227}Ac using microcalorimetry.	Superseded by Jordan and Blanke (1967)
Eichelberger et al. (1963)	18.729 (48)	Determined indirectly by ingrowth decay progeny of ^{227}Ac using microcalorimetry.	Superseded by Jordan and Blanke (1967)
Jordan and Blanke (1967)*	18.7176 (52)	Determined indirectly by ingrowth decay progeny of ^{227}Ac using microcalorimetry.	
Miller et al. (1987)	18.738 (54)	Determined indirectly by ingrowth of ^{215}Po using α-spectrometry.	

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The half-life of ^{227}Th by direct and indirect measurements

CrossMark

S.M. Collins [a,*], S. Pommé [b], S.M. Jerome [a], K.M. Ferreira [a], P.H. Regan [a,c], A.K. Pearce [a]

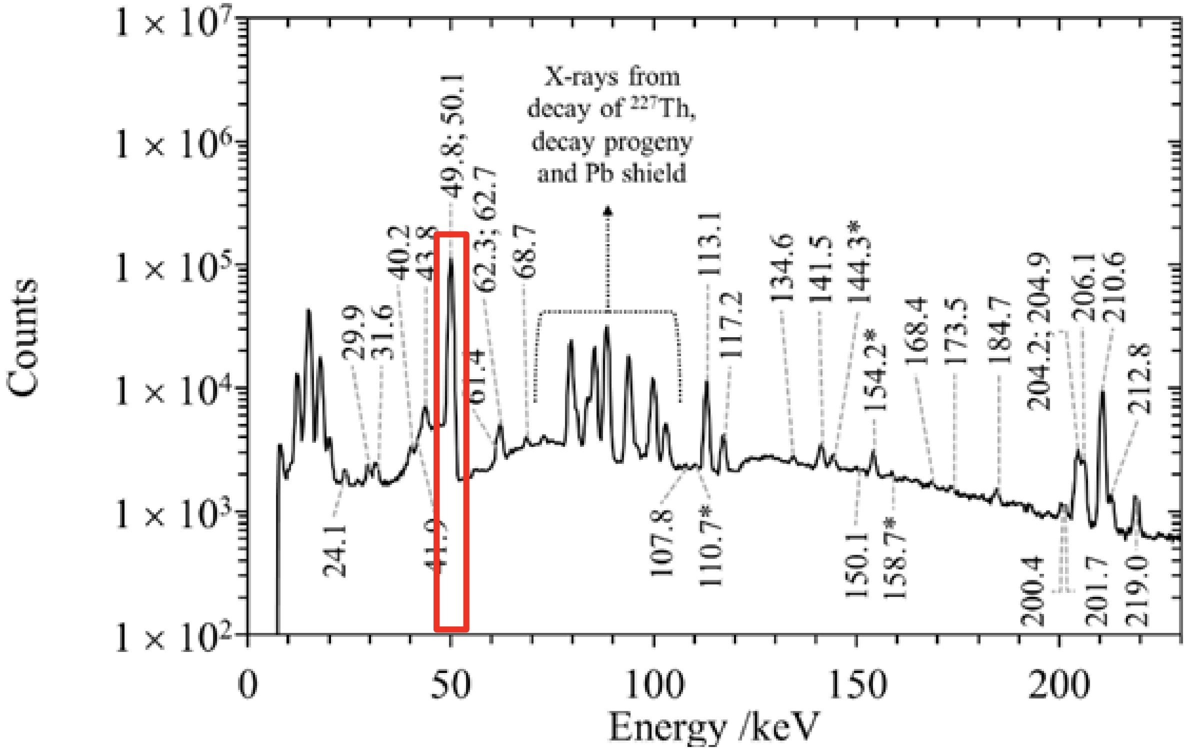
[a] National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, UK
[b] European Commission, Joint Research Centre, Institute for Reference Materials and Measurements, Retieseweg 111, B-2440 Geel, Belgium
[c] Department of Physics, University of Surrey, Guildford, Surrey GU2 7XH, UK

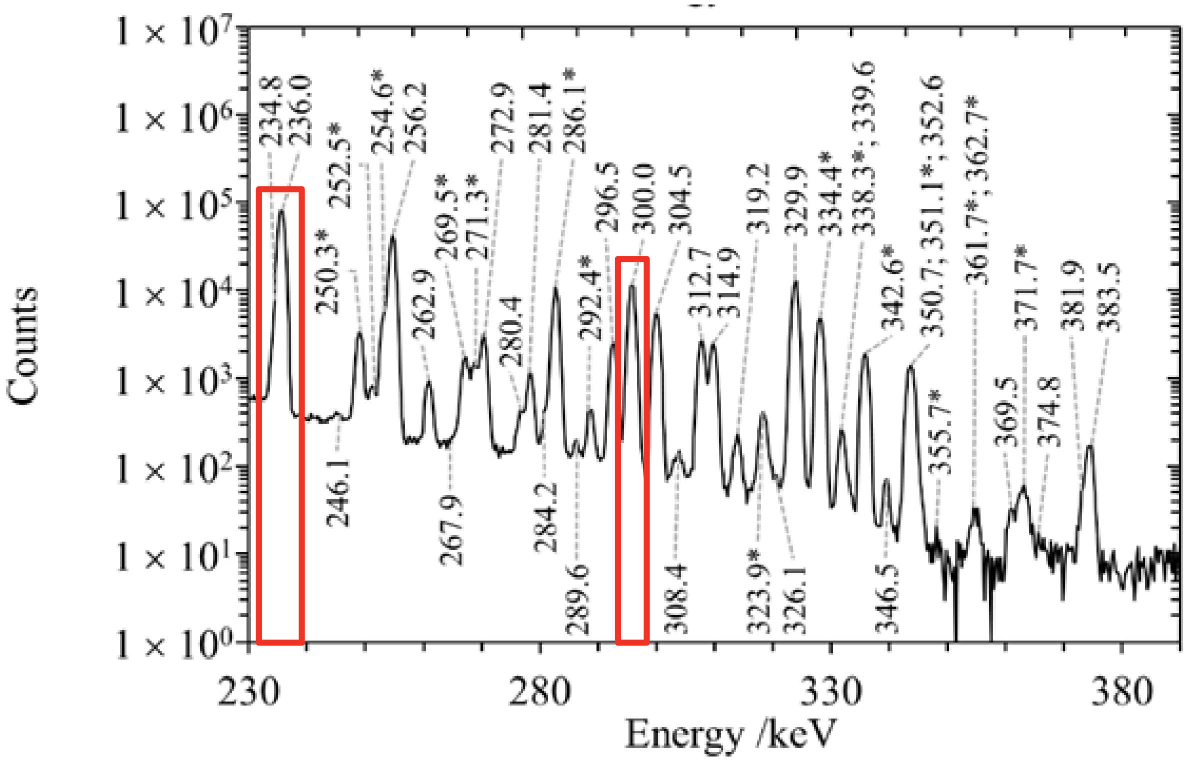
HPGe gamma-ray spectrometry (direct) & Ionisation Chamber (indirect)

Decay progeny removed before starting measurements

Half-life of ^{227}Th – HPGe gamma-ray spectrometry (direct)

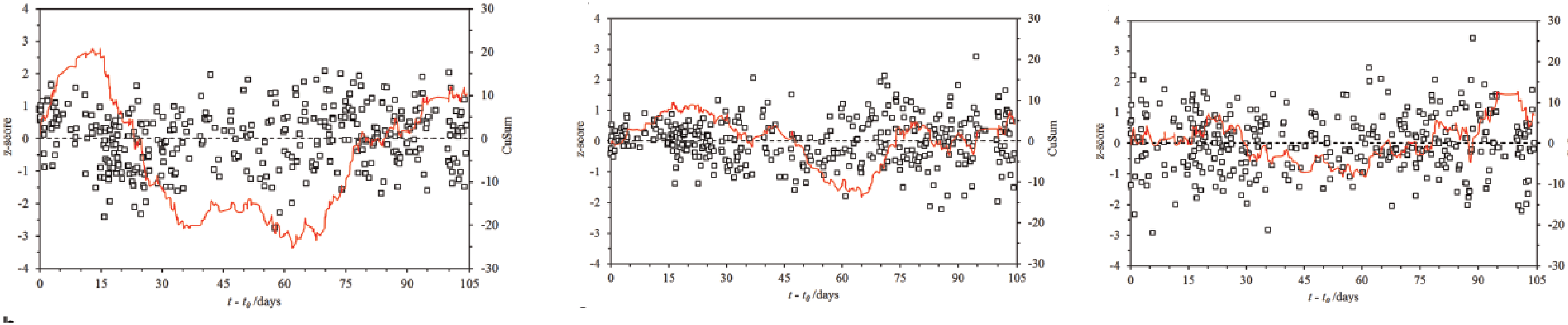
National Physical Laboratory





Half-life of ^{227}Th – HPGe gamma-ray spectrometry (direct)

$$A_t = A_0 e^{-\lambda t} \frac{1 - e^{\lambda \Delta t}}{\lambda \Delta t}$$



50.1 keV

236 keV

300 keV

Half-life of ^{227}Th – HPGe gamma-ray spectrometry (direct)

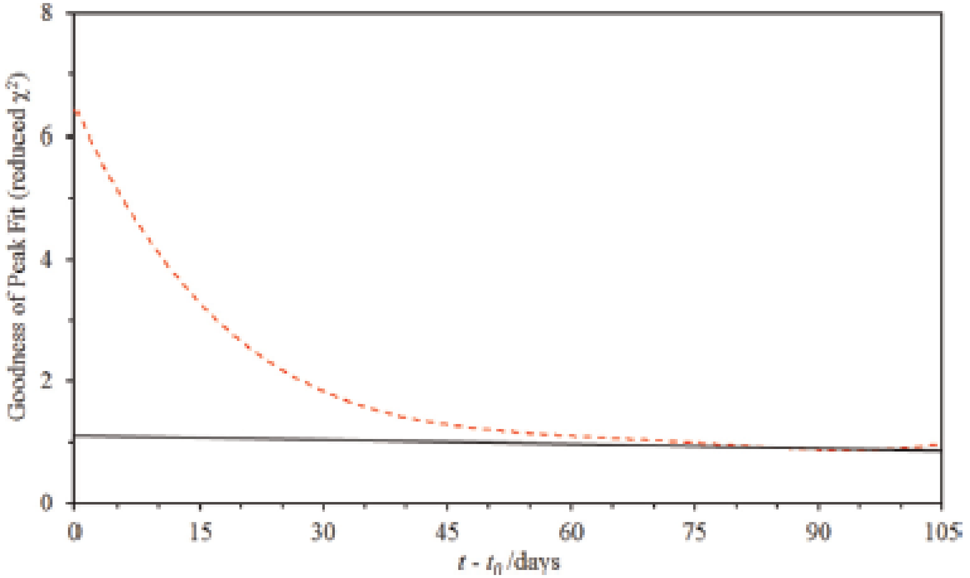


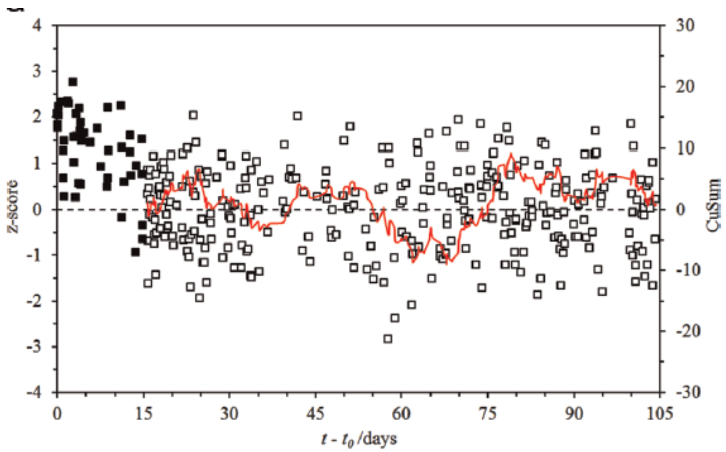
Fig. 4. Goodness of the peak fit of the 50.1 keV (dashed line) and the 236.0 keV doublet (solid line) as calculated by the peak fitting software.

Compton continuum evolving as progeny grow in.

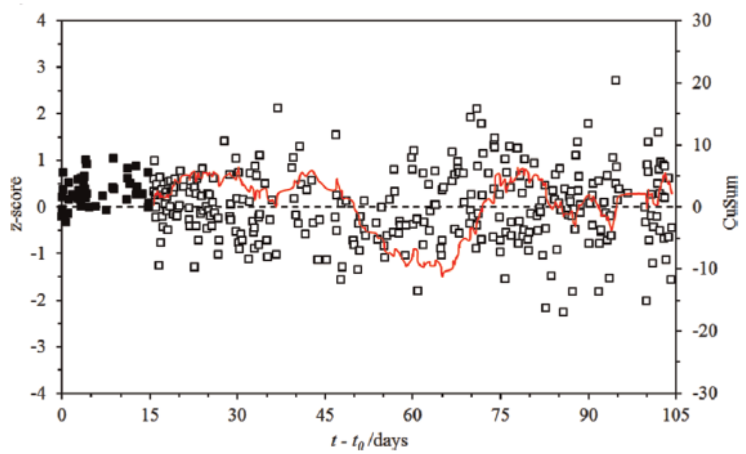
.

Half-life of ^{227}Th – HPGe gamma-ray spectrometry (direct)

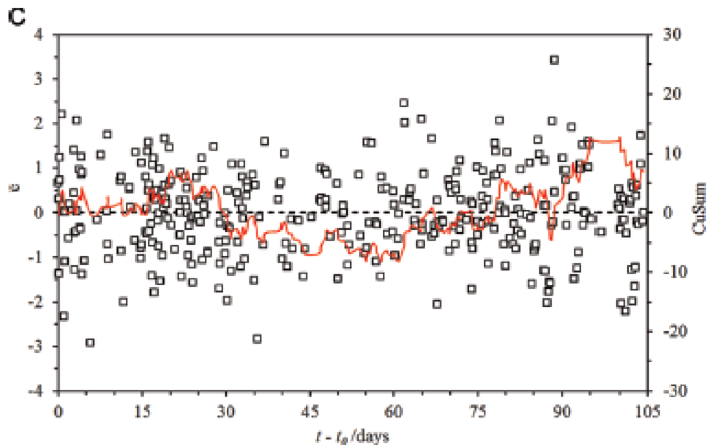
$$A_t = A_0 e^{-\lambda t} \frac{1 - e^{\lambda \Delta t}}{\lambda \Delta t}$$



50.1 keV



236 keV



300 keV

Half-life of ^{227}Th – Ionisation chamber (indirect)

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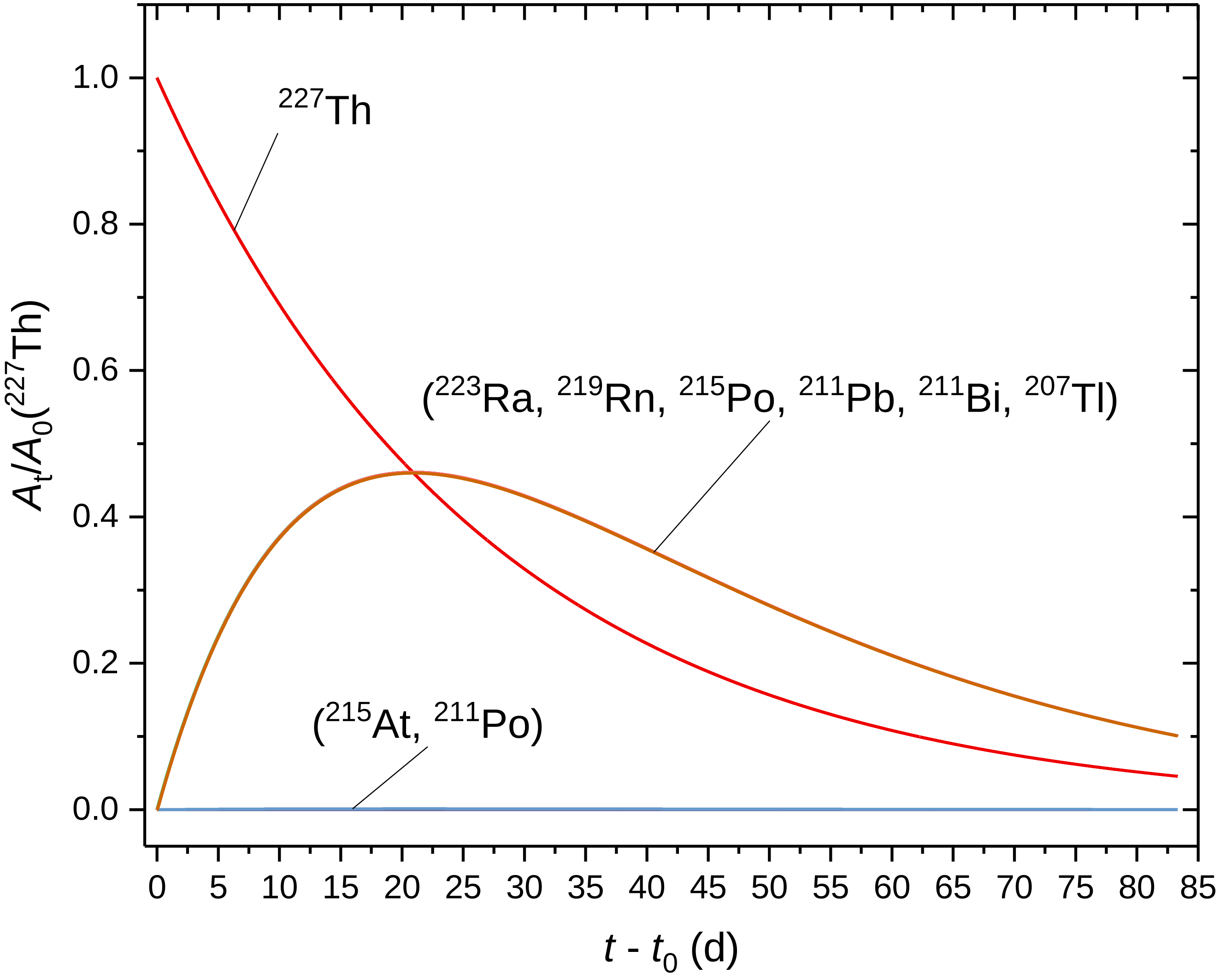
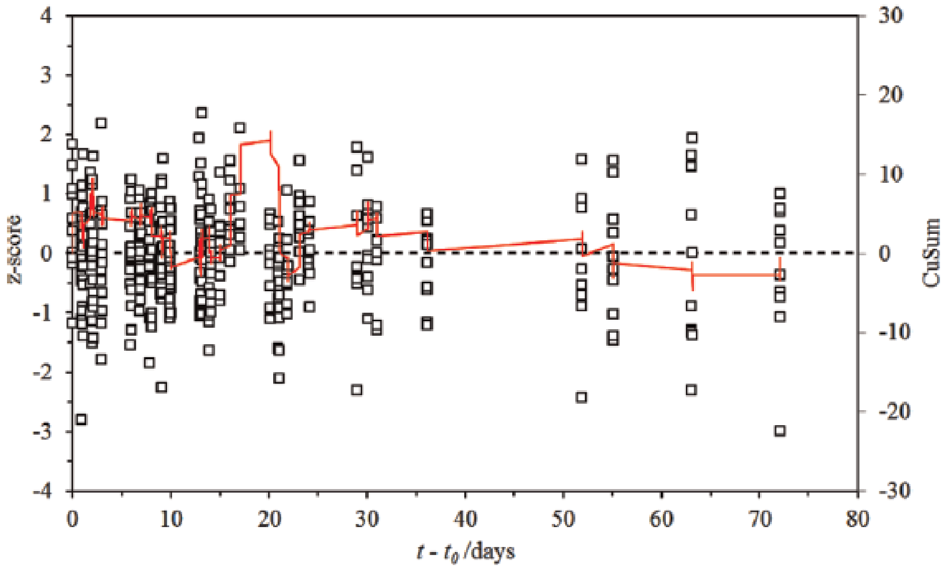


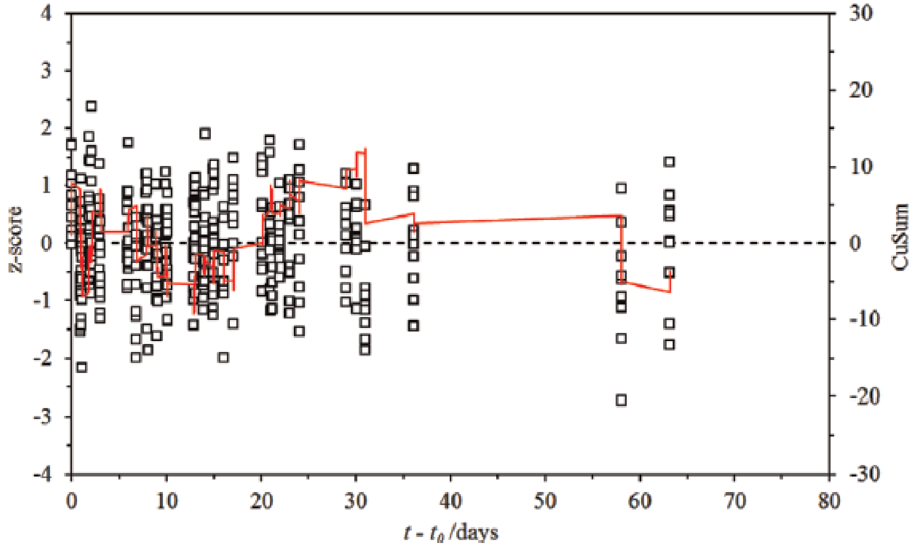
- Measuring the sum of the response
- Each radionuclide has a different response
- Fitting was performed assuming just a two-body system i.e. All progeny share the ^{223}Ra half-life

Half-life of ^{227}Th – Ionisation chamber (indirect)

$$A_t = B_{Th,0} e^{-\lambda_{Th} t} \frac{1 - e^{-\lambda_{Th} \Delta t}}{\lambda_{Th} \Delta t} + B_{Ra,0} e^{-\lambda_{Ra} t} \frac{1 - e^{-\lambda_{Ra} \Delta t}}{\lambda_{Ra} \Delta t}$$

λ_{Ra} was fixed to (ln(2)/11.4354)





Half-life of ^{227}Th – Ionisation chamber (indirect)

- Linear relationship between ^{227}Th and ^{223}Ra half-lives

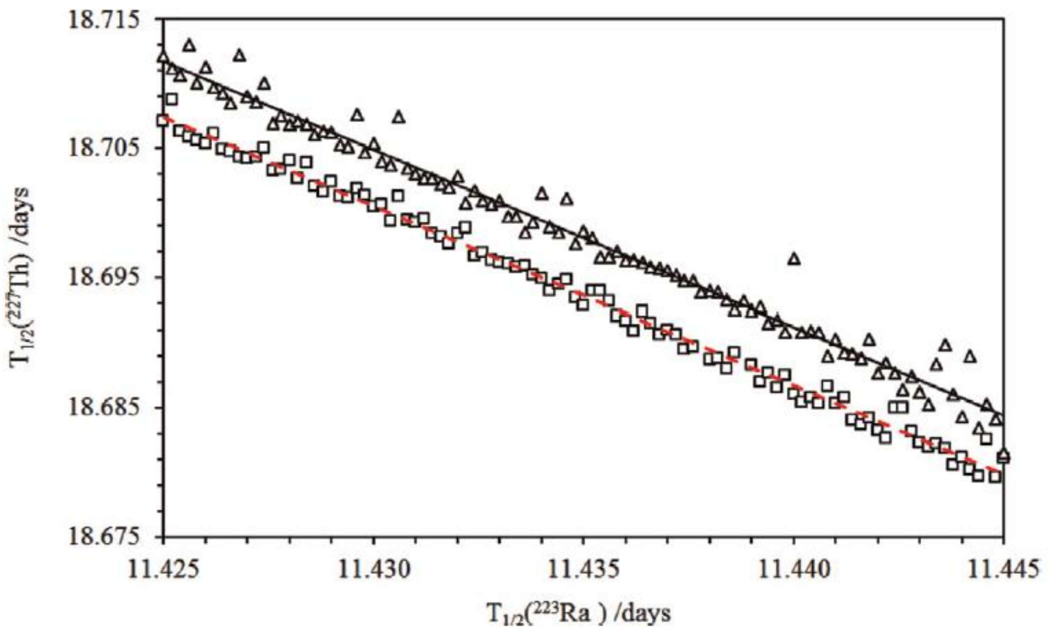


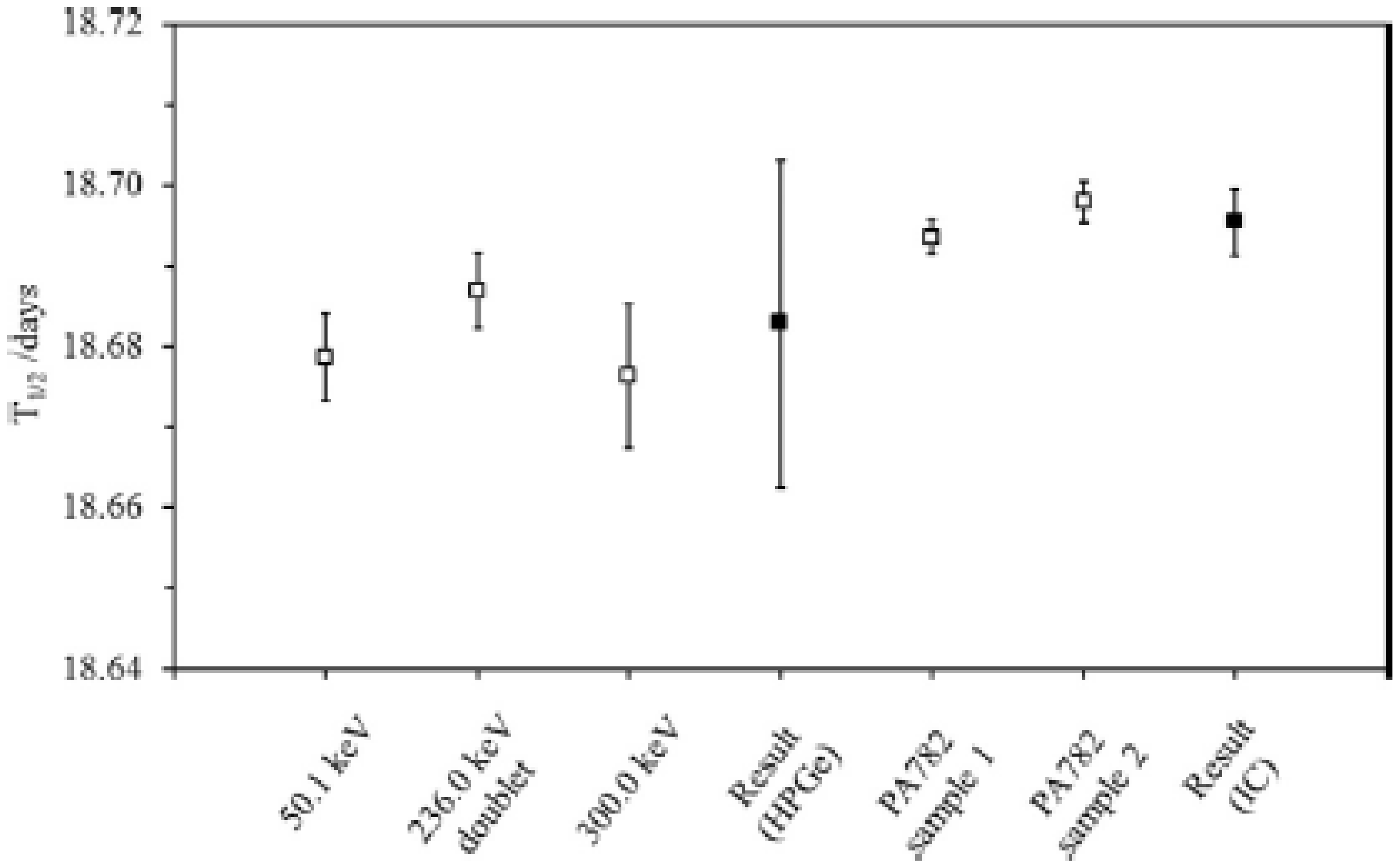
Fig. 8. Dependence of the fitted ^{227}Th half-life on the half-life of ^{223}Ra. The two datasets refer to sample 1 (squares) and sample 2 (triangle) measured by the ionisation chamber.

$$T_{1/2}(^{227}\mathrm{Th}) \approx -\,1.3802 \times T_{1/2}(^{223}\mathrm{Ra}) + 34.4766$$

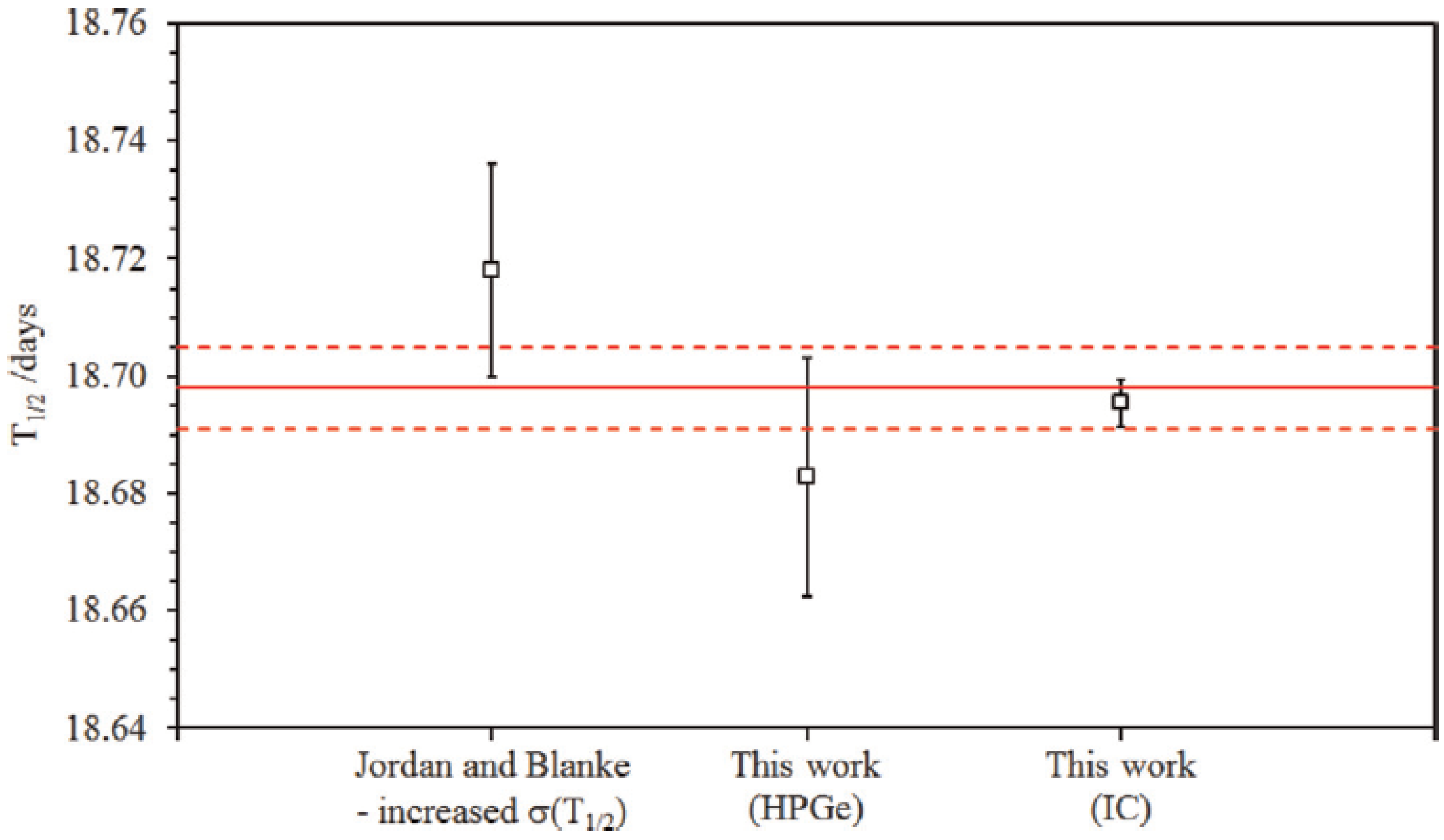
$$T_{1/2}(^{227}\mathrm{Th}) \approx -\,1.3662 \times T_{1/2}(^{223}\mathrm{Ra}) + 34.3214$$

- Half-life can be re-evaluated in future If ^{223}Ra half-life changes.

Half-life of ^{227}Th – Results



Half-life of ^{227}Th – Results

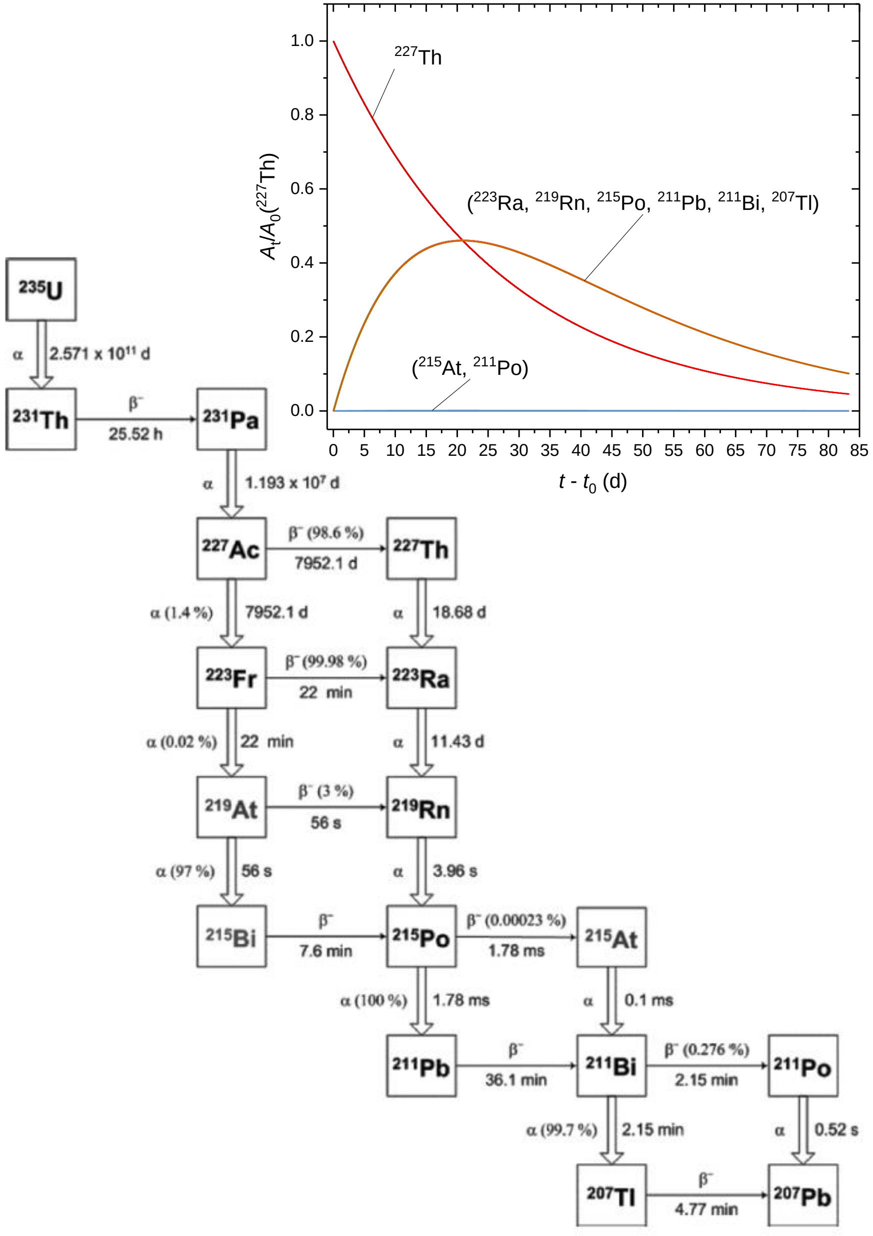


$$T_{1/2}(^{227}\text{Th}) = 18.697(7)\ \text{d}$$

Summary of half-lives

- Critical for calculating corrections for ingrowth
- Recommended values (DDEP) for critical radionuclides
  http://www.lnhb.fr/nuclear-data/nuclear-data-table/

	Evaluated $T_{1/2}$	'New' $T_{1/2}$
^{227}Th	18.718(5) d	18.697(7)
^{223}Ra	11.43(3) d	11.4354(17) d



Where to start?

NPL National Physical Laboratory

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Direct measurement of the half-life of ^{223}Ra

S.M. Collins [a,*], A.K. Pearce [a], K.M. Ferreira [a], A.J. Fenwick [a], P.H. Regan [a,b], J.D. Keightley [a]
[a] National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, United Kingdom
[b] Department of Physics, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom

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Precise measurements of the absolute γ-ray emission probabilities of ^{223}Ra and decay progeny in equilibrium

S.M. Collins [a,*], A.K. Pearce [a], P.H. Regan [a,b], J.D. Keightley [a]
[a] National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, United Kingdom
[b] Department of Physics, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom

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Measurement of the ^{211}Pb half-life using recoil atoms from ^{219}Rn decay

P.M. Aitken-Smith *, S.M. Collins
National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, UK

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Standardisation of ^{223}Ra by liquid scintillation counting techniques and comparison with secondary measurements

John Keightley *, Andy Pearce, Andrew Fenwick, Sean Collins, Kelley Ferreira, Lena Johansson
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The potential radio-immunotherapeutic α-emitter ^{227}Th – part II: Absolute γ-ray emission intensities from the excited levels of ^{223}Ra

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The half-life of ^{227}Th by direct and indirect measurements

S.M. Collins [a,*], S. Pommé [b], S.M. Jerome [a], K.M. Ferreira [a], P.H. Regan [a,c], A.K. Pearce [a]
[a] National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, UK
[b] European Commission, Joint Research Centre, Institute for Reference Materials and Measurements, Retieseweg 111, B-2440 Geel, Belgium
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Evaluation of the separation and purification of ^{227}Th from its decay progeny by anion exchange and extraction chromatography

P.I. Ivanov [a,*], S.M. Collins [a], E.M. van Es [a,b], M. García-Miranda [a], S.M. Jerome [a], B.C. Russell [a]
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[b] Chemistry Department, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom

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Fundamental uncertainty equations for nuclear dating applied to the ^{140}Ba-^{140}La and ^{227}Th-^{223}Ra chronometers

S. Pommé [a,*], S.M. Collins [b], A. Harms [b,1], S.M. Jerome [b]
[a] European Commission, Joint Research Centre, Retieseweg 111, B-2440 Geel, Belgium
[b] National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, UK

Radiochemistry for ^{227}Th & Time zero

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- Good radiochemical separation of decay progeny essential
- Needs to provide a time zero close to the time of separation
  - Not always possible to determine experimentally i.e. nuclear medicine departments
- Accurate time zero needed for precise standardisation

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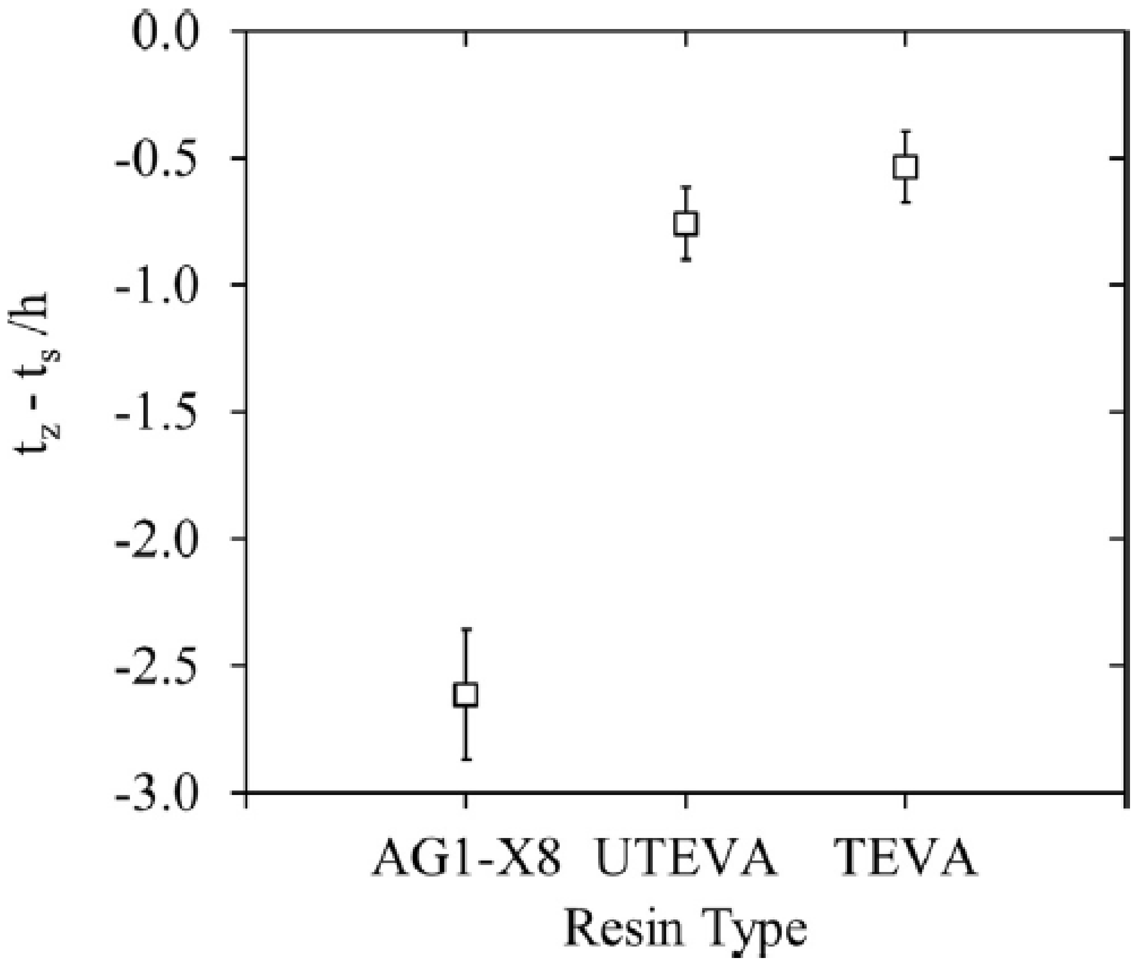
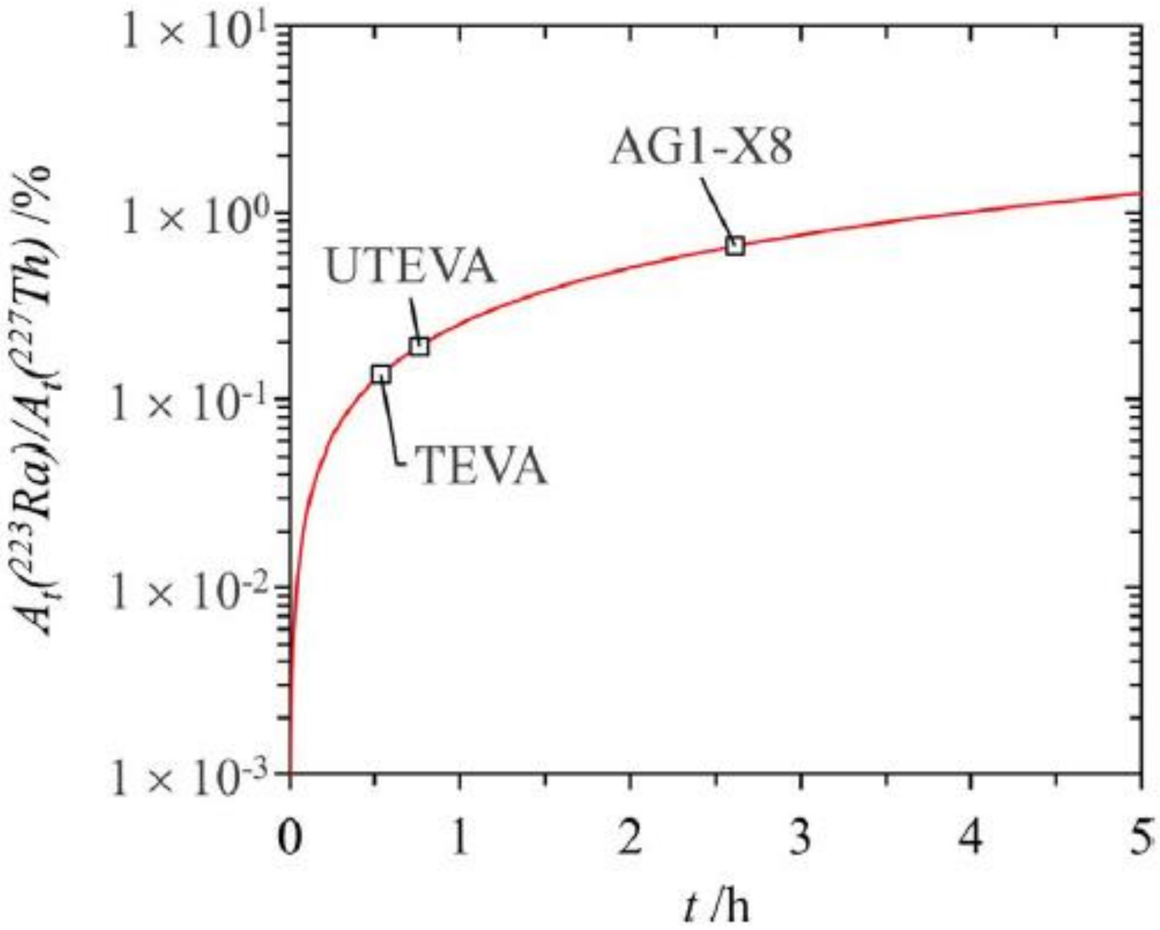
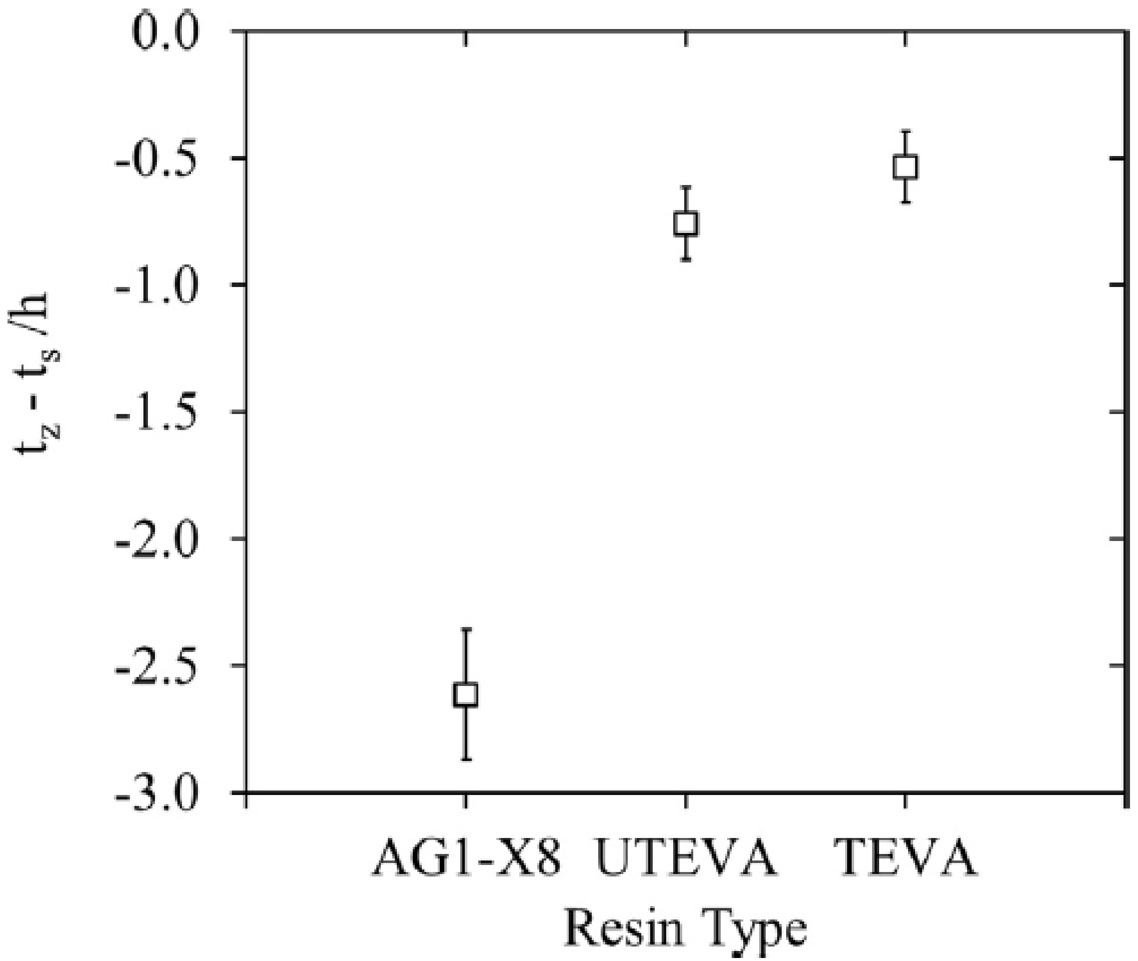
[b] National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, UK

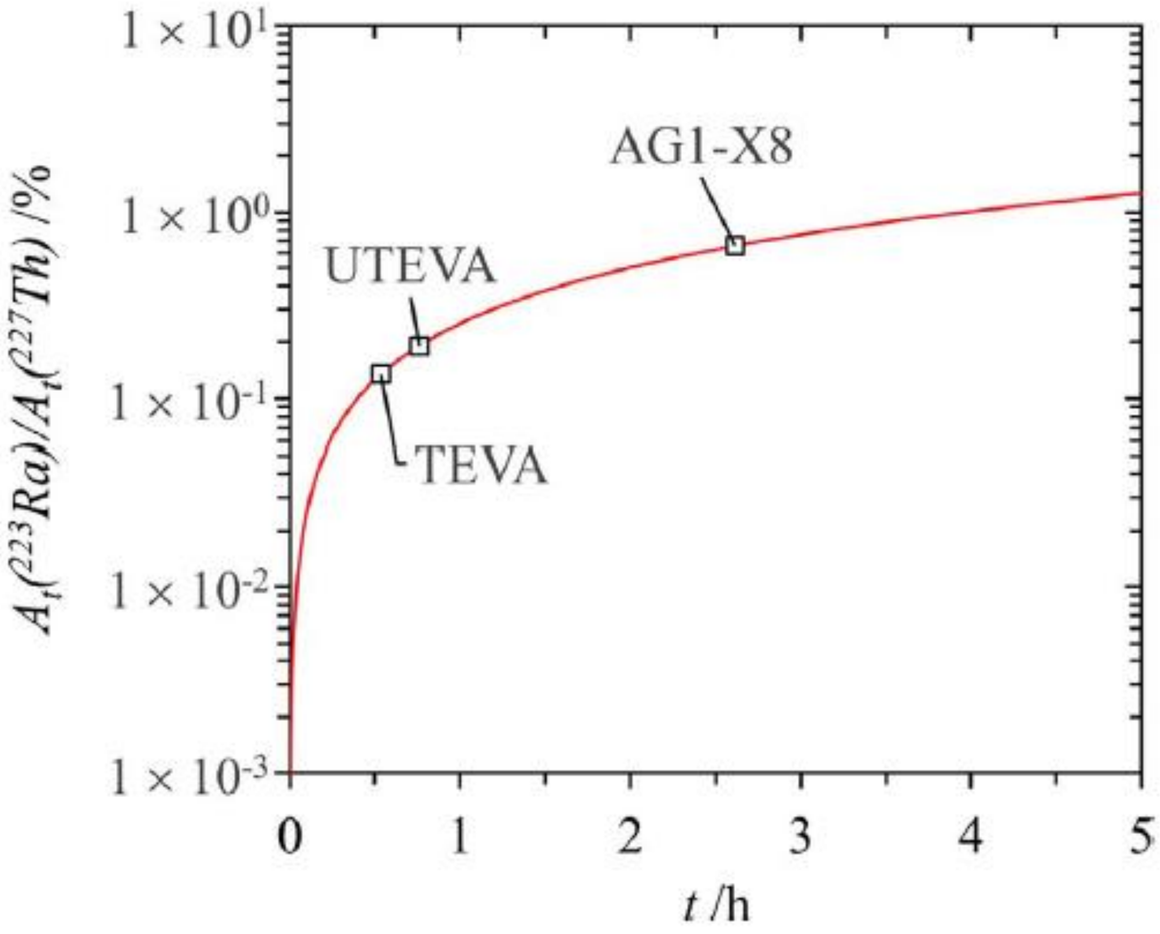
Assessing efficacy of radiochemistry for ^{227}Th





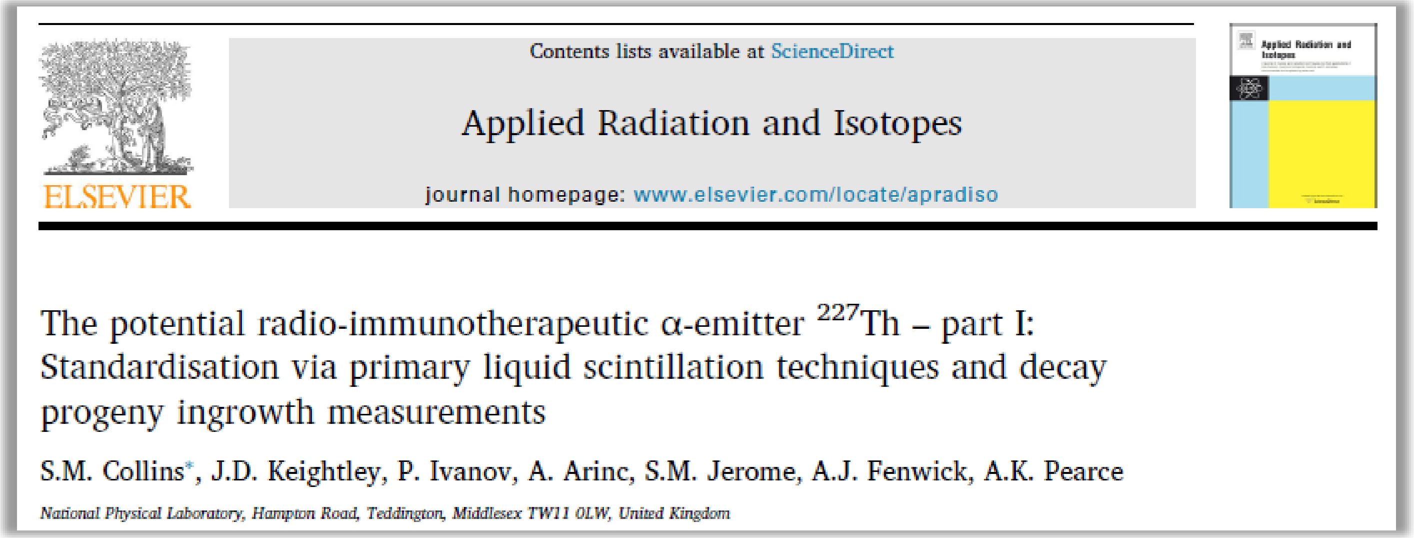
Assessing efficacy of radiochemistry for ^{227}Th





But….

Assessing efficacy of radiochemistry for ^{227}Th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The potential radio-immunotherapeutic α-emitter ^{227}Th – part I: Standardisation via primary liquid scintillation techniques and decay progeny ingrowth measurements

S.M. Collins*, J.D. Keightley, P. Ivanov, A. Arinc, S.M. Jerome, A.J. Fenwick, A.K. Pearce

National Physical Laboratory, Hampton Road, Teddington, Middlesex TW11 0LW, United Kingdom

- Vacuum box was added to the method.
- End of separation = 09:00 UTC
- Measured time zero = 08:57:20 UTC ± 00:01:19

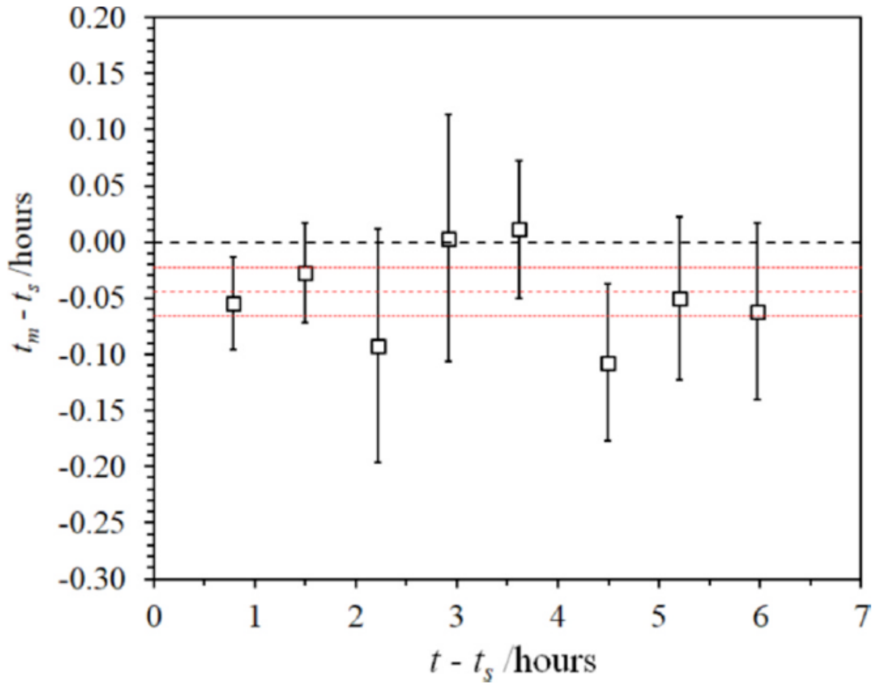


Fig. 4. Difference in the measured time zero from the chemical separation endpoint for each measurement using the γ-ray emission probabilities for the sum of the 234.8 keV and 236.0 keV doublet emissions of ^{227}Th determined in this work. The solid and dashed lines indicate the weighted mean time zero and its standard uncertainty.

Standardisation of ^{227}Th

National Physical Laboratory

- Two primary methods used

  4π(LS)-γ coincidence counting

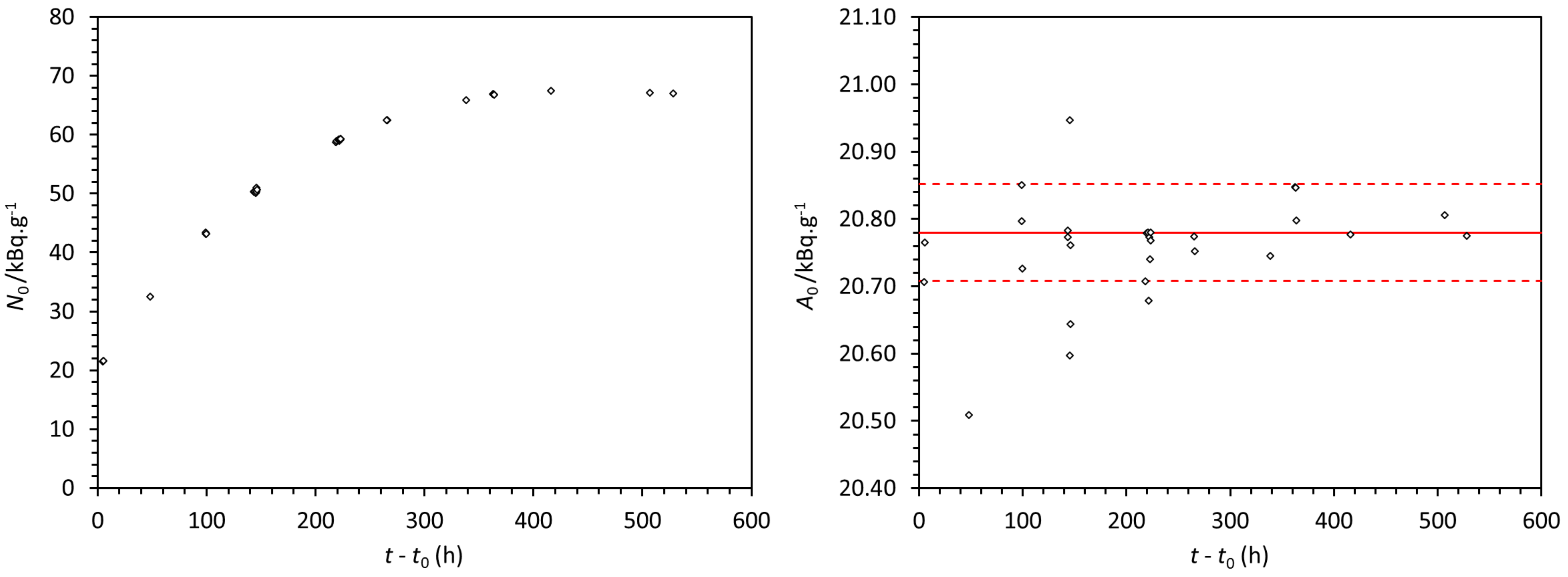
  $4\pi\alpha$(LS) counting

- Two confirmatory ingrowth techniques used

  HPGe gamma-ray spectrometry

  Ionisation chamber

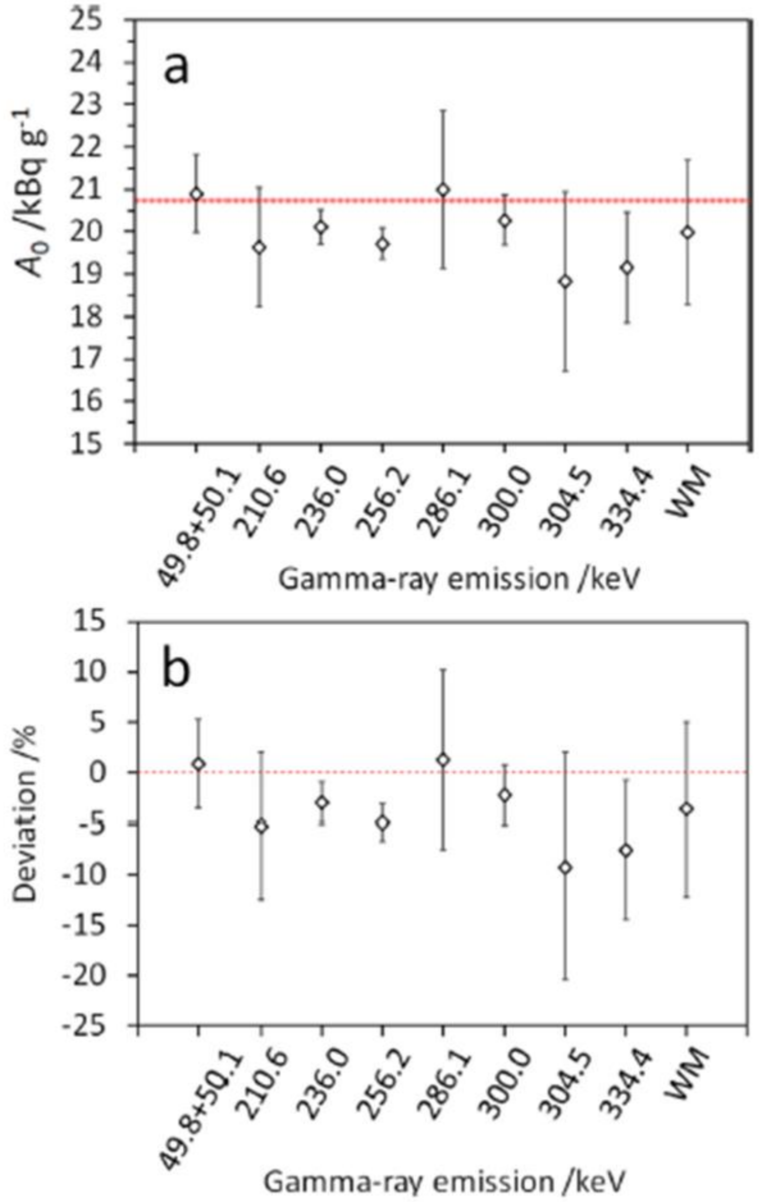
Standardisation of ^{227}Th - 4π(LS)-γ coincidence counting



Absolute gamma-ray emission intensities

National Physical Laboratory

- 11% spread in activities determined by main gamma-ray emissions
- -3.4% difference to primary standard
- 8.5 % uncertainty on normalisation scaling factor
- Significant improvements using primary standard can be made



Standardisation of ^{227}Th – HPGe ingrowth measurements

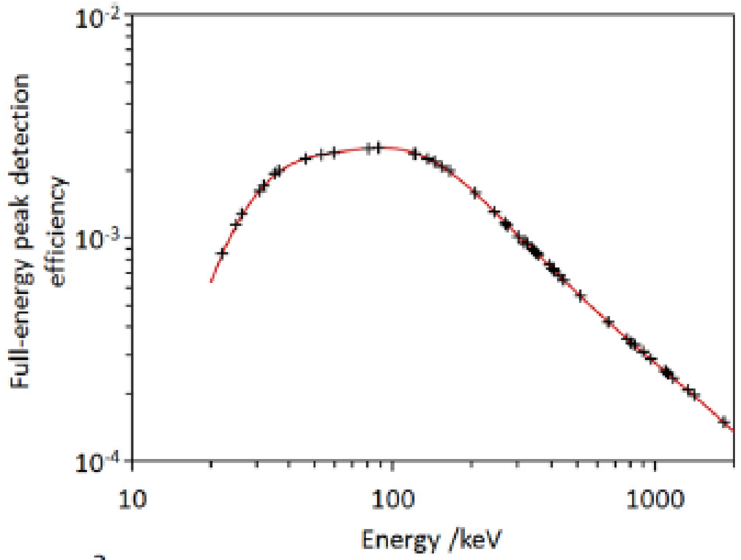
- Using gamma-rays from ^{223}Ra and ^{219}Rn
  - 154.2 keV; 269.5 keV; 271.2 keV; 401.8 keV
  - I_γ from weighted mean of NPL, NIST and PTB

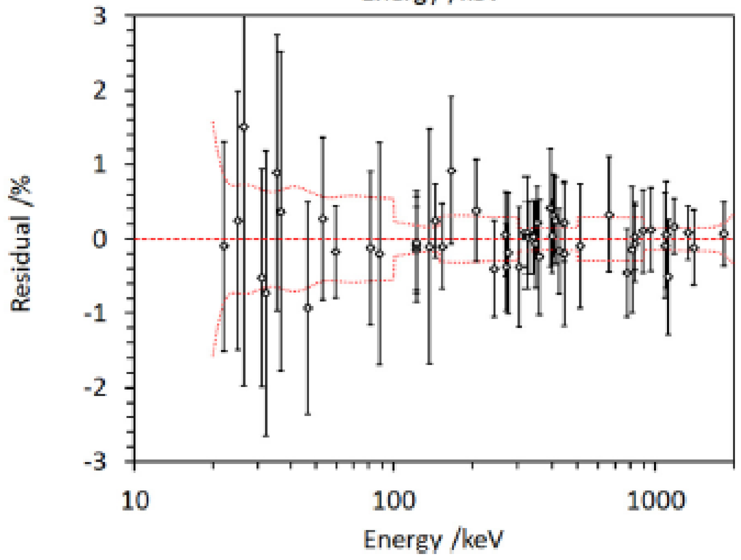
- Activity at start of measurement determined by:

$$A_t(D) = \frac{\left(\frac{N(E)}{I_\gamma(E)\cdot\varepsilon(E)\cdot m}\cdot k_\mu \cdot k_\rho(E)\right) - \Delta N_D}{\Delta t}\cdot k_\lambda$$

where,

$$\Delta N_D = \left(A_z(^{227}Th)\cdot e^{-\lambda_{Th}t}\cdot\frac{\lambda_{Ra}}{(\lambda_{Ra}-\lambda_{Th})\cdot\ln(2)}\right)\cdot\left(\frac{\ln(2)\cdot(1-e^{-\lambda_{Th}\Delta t})}{\lambda_{Th}} - \frac{\ln(2)\cdot(1-e^{-\lambda_{Ra}\Delta t})}{\lambda_{Ra}}\right)$$



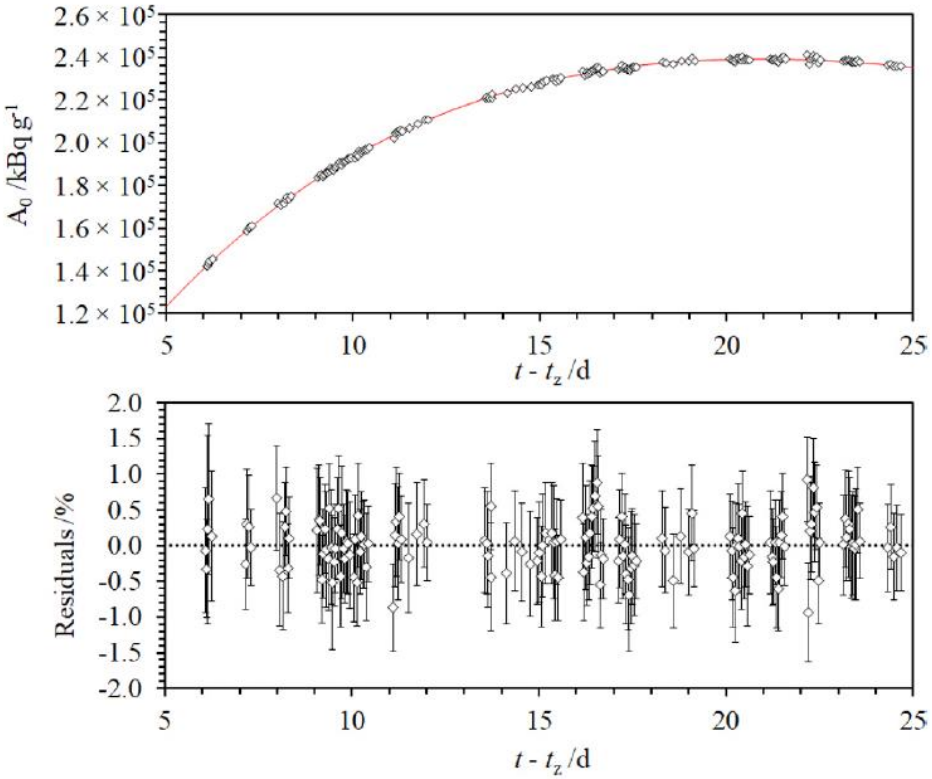


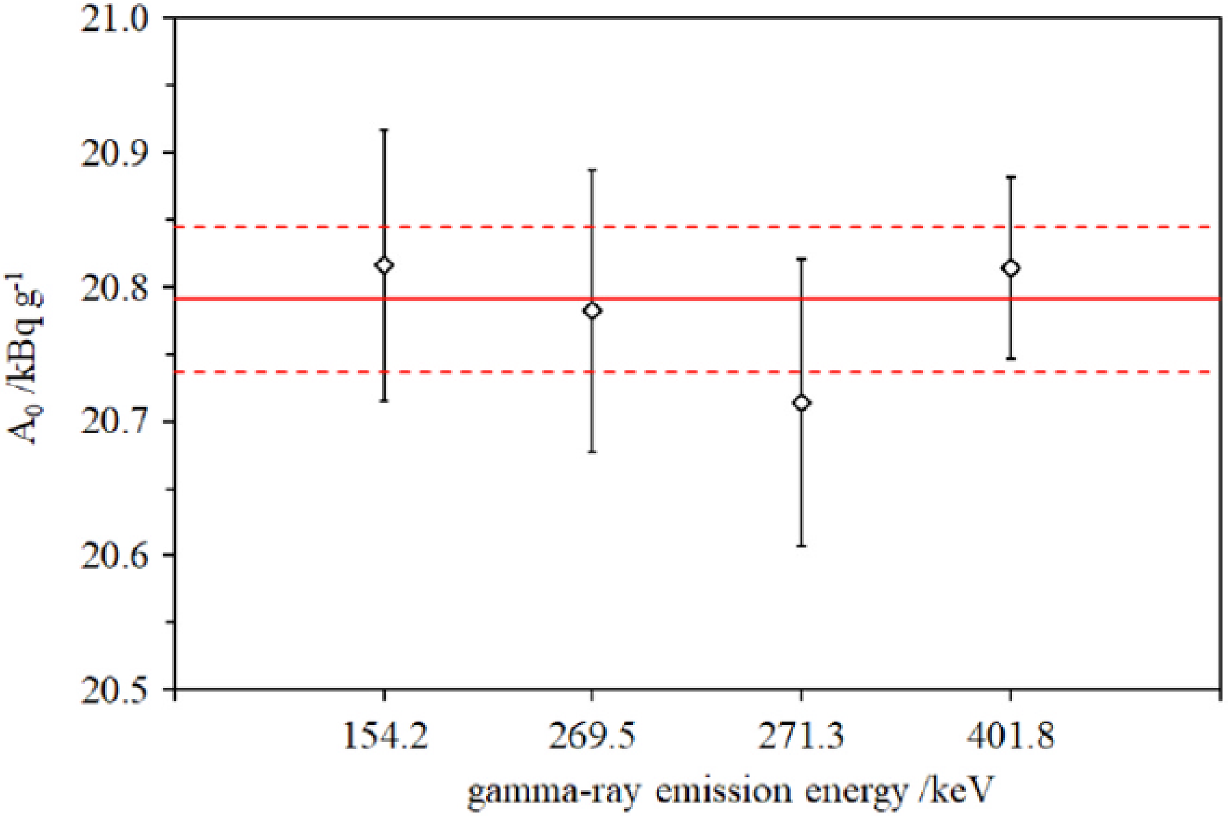
Standardisation of ^{227}Th – HPGe ingrowth measurements

- Weighted least-squares fit:

$$A_t(D) = \left(A_z(^{227}Th) \cdot \frac{\lambda_{Th}}{\lambda_{Ra} - \lambda_{Th}} \right) \cdot \left(e^{-\lambda_{Th} t} - e^{-\lambda_{Ra} t} \right)$$

- Vary $A_z(^{227}Th)$

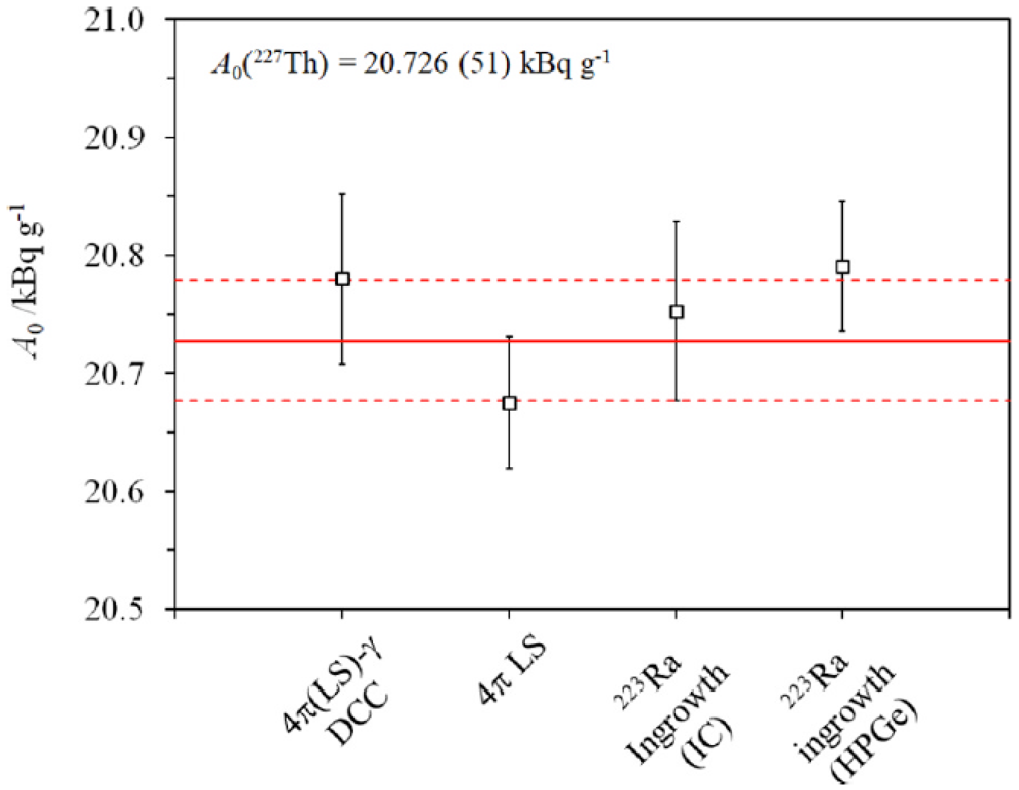




Standardisation of ^{227}Th – Results

Results of the absolute standardisation and ^{223}Ra ingrowth techniques for the determination of activity of ^{227}Th at the reference time 2016–12-13 09:00 UTC. The final activity per unit mass and its standard uncertainty have been determined from the 4π(LS)-γ DCC and the 4π LS counting measurement techniques.

Measurement technique	Activity /kBq g^{-1}
4π(LS)-γ DCC	20.780 (72)
4π LS	20.675 (56)
4π LS (Tricarb)	*20.676 (56)*
4π LS (Beckman)	*20.674 (56)*
^{223}Ra ingrowth technique	
IC-PA782-5mL	*20.754 (76)*
IC-VINTEN-NBS	*20.743 (93)*
IC-VINTEN-10R	*20.759 (87)*
HPGe	20.791 (55)
HPGe (Browne, 2001)	20.0 (17)
Final Result	20.726 (51)

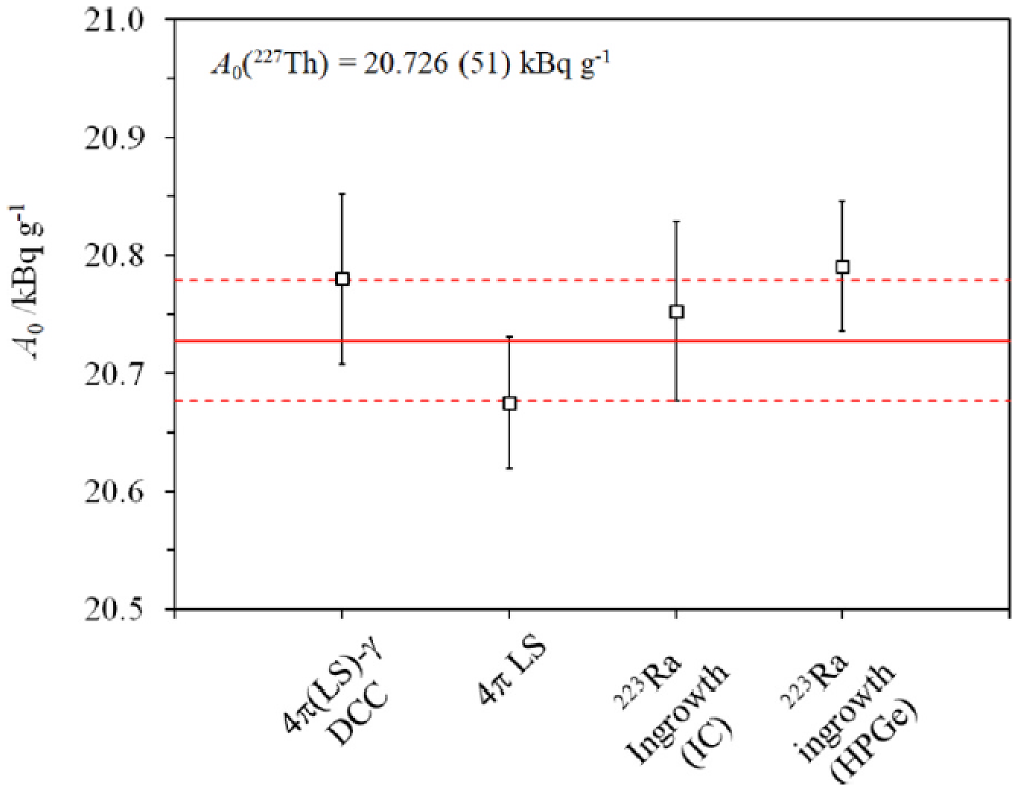


Standardisation of ^{227}Th – Results

NPL National Physical Laboratory

Results of the absolute standardisation and ^{223}Ra ingrowth techniques for the determination of activity of ^{227}Th at the reference time 2016–12-13 09:00 UTC. The final activity per unit mass and its standard uncertainty have been determined from the 4π(LS)-γ DCC and the 4π LS counting measurement techniques.

Measurement technique	**Activity /kBq g^{-1}**
4π(LS)-γ DCC	20.780 (72)
4π LS	20.675 (56)
4π LS (Tricarb)	*20.676 (56)*
4π LS (Beckman)	*20.674 (56)*
^{223}Ra ingrowth technique	
IC-PA782-5mL	*20.754 (76)*
IC-VINTEN-NBS	*20.743 (93)*
IC-VINTEN-10R	*20.759 (87)*
HPGe	20.791 (55)
HPGe (Browne, 2001)	20.0 (17)
Final Result	20.726 (51)



The HPGe result isn't really the 'best' – issue of unpicking the correlations between NPL, NIST and PTB absolute gamma-ray emissions for ^{223}Ra

Absolute gamma-ray emission intensities

NPL National Physical Laboratory

- Rate calculated using

$$R_0(E) = \frac{(N(E) - k_{In}(E) - B(E))}{\Delta t \cdot m} \cdot k_\lambda \cdot k_\mu \cdot k_\rho(E)$$

where,

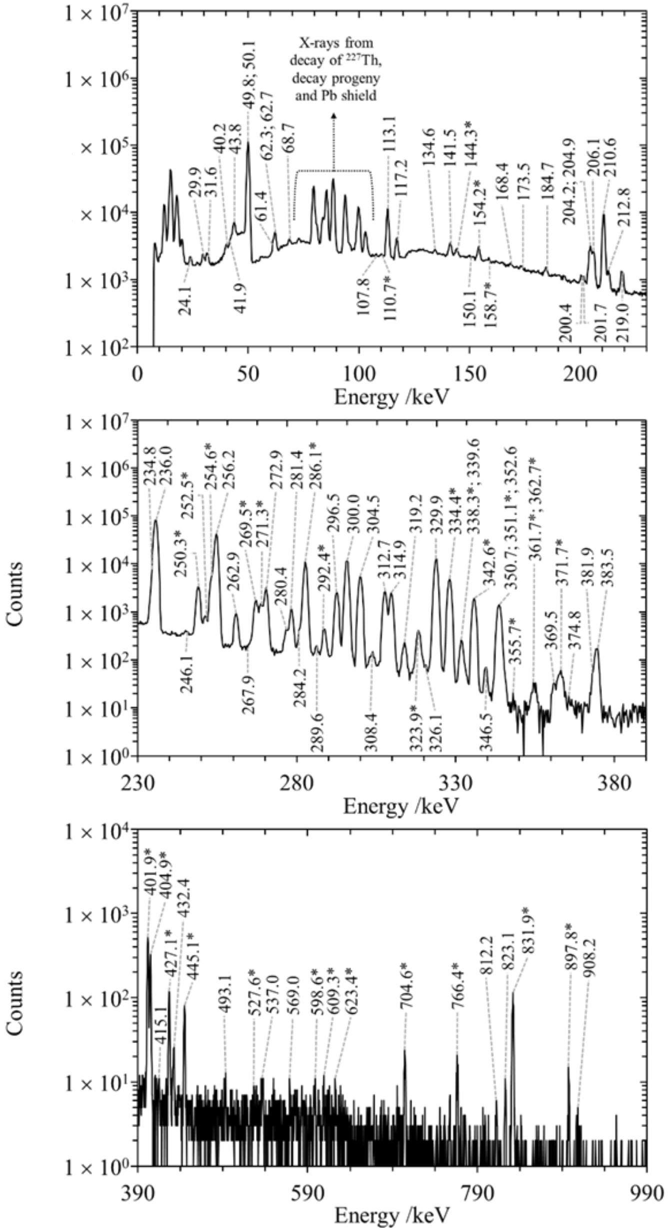
$$k_{In}(E) = N_D \cdot \varepsilon(E) \cdot I_\gamma(E)$$

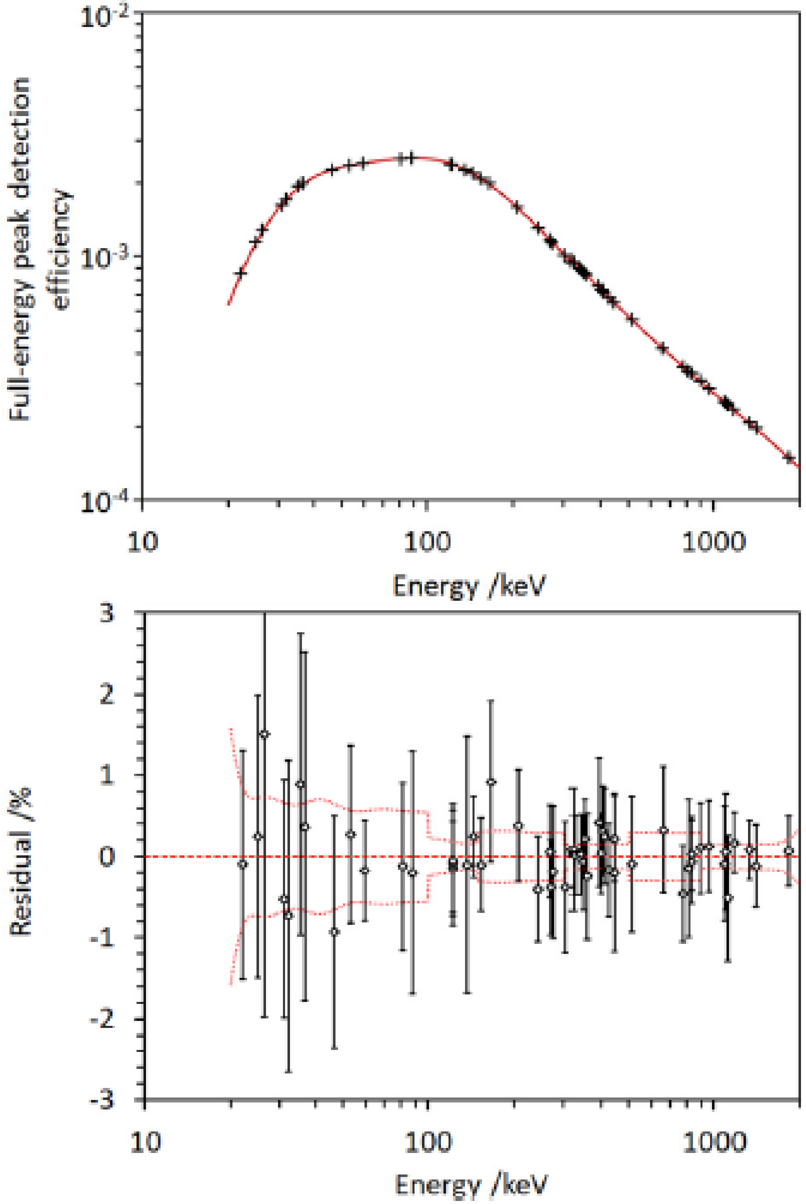
where,

$$N_D = \left(\left(A_z(^{227}Th) \cdot \frac{\lambda_{Ra}}{\lambda_{Ra} - \lambda_{Th}}\right) \cdot \left(e^{-\lambda_{Th} t} - e^{-\lambda_{Ra} t}\right)\right) \cdot \frac{(1 - e^{-\lambda_{Ra}\Delta t})}{\lambda_{Ra}} + \left(A_z(^{227}Th) \cdot \frac{\lambda_{Ra}}{(\lambda_{Ra} - \lambda_{Th}) \cdot \ln(2)}\right) \cdot \left(\frac{\ln(2) \cdot (1 - e^{-\lambda_{Th}\Delta t})}{\lambda_{Th}} - \frac{\ln(2) \cdot (1 - e^{-\lambda_{Ra}\Delta t})}{\lambda_{Ra}}\right)$$

- Emission intensity using

$$I_\gamma(E) = \frac{\overline{R}_0(E)}{A_0(^{227}Th) \cdot \varepsilon(E)}$$





Absolute gamma-ray emission intensities

National Physical Laboratory

Absolute γ ray emission intensities per 100 decays (I_γ) and intensities normalised to the 236.0 keV γ ray emission ($I_\gamma/I_{\gamma(236)}$). Multiply the normalised intensities by 0.12470 ± 0.00034 to determine the absolute emission intensities. The γ-ray energies marked with an asterisk (*) have been corrected for the ingrowth of interfering decay progeny.

Energy/keV	I_γ/per 100 decays	$I_\gamma/I_{\gamma(236)}$%	Energy/keV	I_γ/per 100 decays	$I_\gamma/I_{\gamma(236)}$%
29.9	0.0703 (19)	0.564 (15)	249.6*	0.0036 (22)	0.029 (18)
31.6*	0.0685 (38)	0.549 (31)	250.2 & 250.3	0.4884 (22)	3.916 (14)
43.8	0.2320 (91)	1.860 (73)	252.5	0.0917 (22)	0.736 (18)
49.8 & 50.1	8.879 (62)	71.20 (46)	254.6	0.7178 (33)	5.756 (21)
62.3	0.1381 (11)	1.1071 (86)	256.2	6.642 (30)	53.26 (19)
68.7*	0.04720 (88)	0.3785 (70)	262.9	0.12111 (73)	0.9712 (52)
99.5	0.3154 (94)	2.529 (75)	267.7	0.0109 (18)	0.087 (14)
100.2	0.7193 (34)	5.768 (22)	272.9	0.5059 (23)	4.057 (15)
102.5*	0.2473 (17)	1.983 (12)	279.7	0.05018 (45)	0.4024 (34)
103.7*	0.06003 (85)	0.4814 (67)	281.4	0.1731 (19)	1.388 (15)
108.0	0.0114 (18)	0.091 (15)	284.2	0.04102 (48)	0.3289 (37)
110.7*	0.0110 (14)	0.088 (11)	286.1	1.7537 (79)	14.063 (51)
113.1	0.8026 (38)	6.435 (25)	289.8	0.0164 (12)	0.1315 (94)
117.2	0.2000 (20)	1.604 (15)	292.4	0.0604 (12)	0.4846 (97)
134.6	0.0358 (38)	0.287 (30)	296.5	0.4565 (36)	3.660 (27)
141.5	0.1216 (16)	0.975 (13)	300.0 & 300.5	2.1522 (80)	17.258 (44)
150.1	0.0070 (15)	0.056 (12)	304.5	1.0404 (39)	8.343 (22)
162.2	0.0110 (25)	0.088 (20)	308.4	0.0192 (14)	0.154 (11)
164.8	0.0153 (17)	0.122 (13)	312.7	0.5057 (31)	4.055 (23)
168.4	0.0115 (25)	0.092 (20)	314.9	0.4754 (19)	3.812 (11)
169.7	0.0061 (17)	0.049 (14)	319.2	0.03682 (94)	0.2953 (75)
173.5	0.0166 (13)	0.133 (11)	326.1	0.00514 (62)	0.0412 (49)
184.7	0.03764 (51)	0.3018 (40)	329.9	2.696 (10)	21.615 (55)
197.5	0.01062 (74)	0.0852 (59)	334.4*	1.0100 (52)	8.099 (35)
200.5	0.0257 (21)	0.206 (17)	339.6	0.0032 (15)	0.026 (12)
201.7	0.0250 (30)	0.200 (24)	342.6*	0.4146 (20)	3.324 (13)
204.2	0.1901 (18)	1.525 (14)	346.5	0.01187 (30)	0.0952 (24)
204.9	0.1510 (16)	1.211 (13)	362.7*	0.00279 (62)	0.0224 (50)
206.1	0.2378 (22)	1.907 (17)	381.9	0.00605 (25)	0.0485 (20)
210.6	1.1843 (54)	9.497 (35)	383.5*	0.04459 (40)	0.3576 (30)
212.8	0.0864 (25)	0.693 (20)	398.2	0.0043 (18)	0.035 (15)
218.9	0.10588 (68)	0.8490 (49)	447.2	0.00249 (71)	0.0200 (57)
234.8	0.4417 (91)	3.542 (73)	812.2	0.00280 (45)	0.0224 (36)
236.0	12.470 (57)	100.00 (36)	823.1	0.00340 (15)	0.0273 (12)
246.1	0.0141 (23)	0.113 (19)	908.2	0.00195 (13)	0.0156 (11)

Uncertainty budget for the 236.0 keV γ-ray emission intensity.

Component	$u(I_\gamma)/I_\gamma$ /%
Standard uncertainty of the weighted mean (12 measurements)	0.044
Activity per unit mass	0.25
FEP detection efficiency	0.28
Decay progeny interference correction	–
Peak & Continuum fitting	0.20
True-coincidence summing	0.10
Gravimetric	0.020
Gravimetric dilution	0.042
Self-absorption correction	0.0026
Dead time/ pulse pile-up	0.12
Decay correction	0.025
Combined uncertainty	0.45

70 gamma-rays

Absolute gamma-ray emission intensities

Absolute γ ray emission intensities per 100 decays (I_γ) and intensities normalised to the 236.0 keV γ ray emission ($I_\gamma/I_{\gamma(236)}$). Multiply the normalised intensities by 0.12470 ± 0.00034 to determine the absolute emission intensities. The γ-ray energies marked with an asterisk (*) have been corrected for the ingrowth of interfering decay progeny.

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141.5	0.1216 (16)	0.975 (13)	300.0 & 300.5	2.1522 (80)	17.258 (44)
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218.9	0.10588 (68)	0.8490 (49)	447.2	0.00249 (71)	0.0200 (57)
234.8	0.4417 (91)	3.542 (73)	812.2	0.00280 (45)	0.0224 (36)
236.0	12.470 (57)	100.00 (36)	823.1	0.00340 (15)	0.0273 (12)
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70 gamma-rays

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Gravimetric dilution	0.042
Self-absorption correction	0.0026
Dead time/ pulse pile-up	0.12
Decay correction	0.025
Combined uncertainty	0.45

236 keV intensity

- I_γ(ENSDF) = 12.9(11)
- I_γ(NPL) = 12.470(57)
- 3.3% lower than ENSDF
- ~ 20 times more precise

Gamma-ray emission intensities – comparison to literature

National Physical Laboratory

Comparison of the normalised γ-ray emissions with absolute intensities > 0.1% determined in this work and previous literature. Only those γ-ray emissions detected in this work have been listed.

Energy/keV	This work	Abdul-Hadi et al. (1992)	Hesselink et al.(1972)	Briançon et al.(1969)	χ^2/(n-1)
49.8	71.20 (46)	3.5 (5)	1.7 (13)	4.6 (14)	1.2
50.1		63 (2)	75.7 (52)	65 (3)	
113.1	6.435 (25)	6.6 (3)	4.70 (63)	5.50 (74)	1.8
117.2	1.604 (15)	1.7 (1)	1.50 (31)	1.38 (18)	0.9
204.2	1.525 (14)	1.7 (2)	2.0 (4)	1.6 (4)	0.9
204.9	1.211 (13)	1.2 (2)	1.5 (3)	1.2 (3)	0.6
206.1	1.907 (17)	1.9 (2)	2.32 (41)	1.70 (42)	0.6
210.6	9.497 (35)	9.4 (3)	11.00 (91)	8.5 (11)	1.1
234.8	3.542 (73)	3.4 (3)	5.0 (10)	3.10 (65)	1.0
236.0	100.00 (36)	100 (-)	100 (-)	100 (-)	–
254.6	5.756 (21)	5.3 (3)	7.9 (10)	3.90 (86)	1.9
256.2	53.26 (19)	54 (1)	55.0 (46)	57.0 (55)	2.8
272.9	4.057 (15)	3.9 (2)	4.30 (62)	3.90 (68)	0.5
281.4	1.388 (15)	1.4 (1)	1.30 (30)	1.30 (32)	0.2
286.1	14.063 (51)	15.0 (1)	14.30 (90)	12.3 (11)	4.9
296.5	3.660 (27)	3.3 (3)	3.40 (62)	3.70 (58)	0.7
300.0	17.258 (44)	17.3 (5)	18.8 (15)	16.9 (22)	0.6
304.5	8.343 (22)	8.6 (5)	12.0 (11)	7.7 (10)	2.0
312.7	4.055 (23)	4.0 (3)	4.50 (92)	3.90 (68)	0.3
314.9	3.812 (11)	3.7 (3)	4.70 (92)	3.60 (58)	0.6
329.9	21.615 (55)	21.7 (5)	25.2 (17)	21.5 (26)	1.2
334.4	8.099 (35)	8.2 (3)	10.00 (99)	8.5 (13)	1.1
342.6	3.324 (13)	3.4 (1)	1.70 (41)	3.20 (65)	2.4

Outcomes

- FDA in US have approved traceability for clinical studies of ^{227}Th to NPL – a first

- Phase I clinical trials now in proceeding (https://clinicaltrials.gov/ct2/show/NCT03507452)

- Investigations of quantitative medical imaging using ^{227}Th

Cancer Biotherapy & Radiopharmaceuticals, Vol. 35, No. 7 | Open Access |

Quantitative Dual-Isotope Planar Imaging of Thorium-227 and Radium-223 Using Defined Energy Windows

Iain Murray, Bruno Rojas, Jonathan Gear, Ruby Callister, Adriaan Cleton, and Glenn D. Flux

JNM
The Journal of Nuclear Medicine

Quantitative Dual Isotope SPECT Imaging of the alpha-emitters Th-227 and Ra-223

Michael Ghaly[1,2,3], George Sgouros[1,2,3] and Eric Frey[1,2,3]

Summary

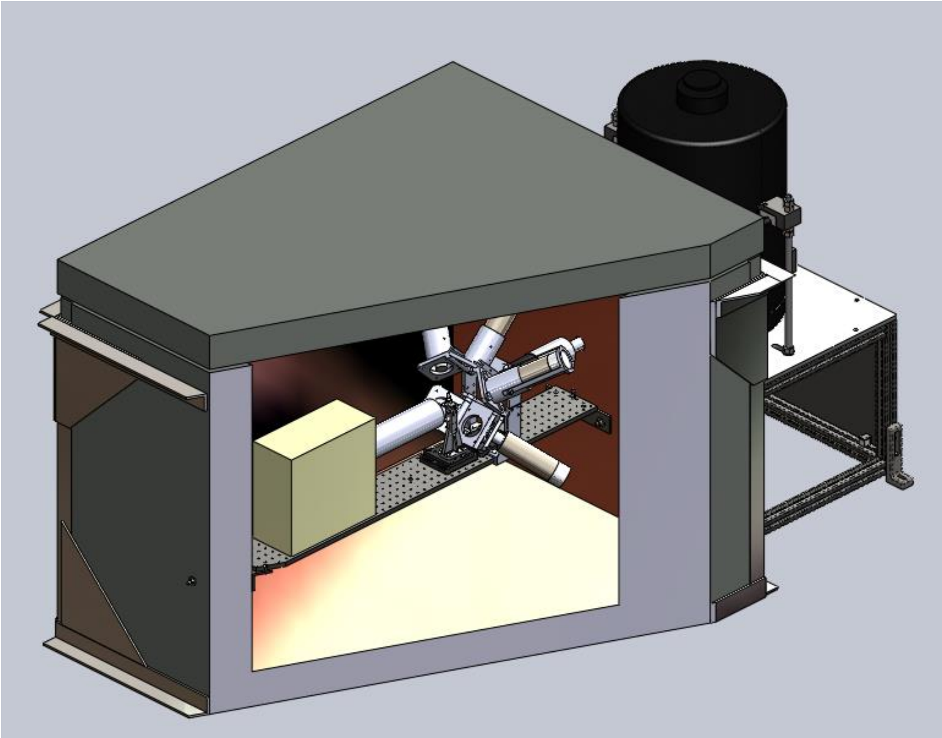
- Developed traceability for ^{227}Th through two liquid scintillation techniques

- Effective radiochemistry technique developed

- New precise measurements of the half-lives made for ^{227}Th, ^{223}Ra and ^{211}Pb

- New precise absolute emission intensities for ^{227}Th and progeny derived from primary standard

- Still work to do be done on the decay scheme



Credits


Dr John Keightley


Arzu Arinc


Dr Peter Ivanov


Andrew Fenwick


Paris Aitken-Smith


Maria Garcia-Miranda


Andy Pearce


Dr Ben Russell


Prof Paddy Regan


Dr Elsje van Es


Kelley Ferriera


Dr Dr Stefaan Pommé


Simon Jerome


Dr Lena Johannson

Many thanks also to BAYER AS

Thank you for your time

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