Realization and dissemination of activity standards for medically important alpha-emitting radionuclides

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Abstract

Interest in targeted cancer therapy with alpha-emitting radionuclides is growing. To evaluate emerging radiotherapeutic agents requires precise activity measurements for consistent dose-response relationships and patient-specific dosimetry. National metrology institutes around the world have reported on the development and comparison of activity standards for medically important alpha emitters. This review describes the relevant methods and models underpinning these standards, the generation of new nuclear decay data, and the impacts on preclinical and clinical activity assays using radionuclide calibrators and γ-ray spectrometry.

Keywords: liquid scintillation counting; coincidence counting; gamma-ray spectrometry; Ra-223; Ra-224; Ac-225; Th-227; decay chain; activity calibration; HPGe; dose calibrator

1. Introduction

A rapidly growing literature is establishing the efficacy of cancer therapies using alpha emitter-based radiopharmaceuticals. With various approaches to targeted alpha therapy, researchers have established a paradigm for delivering high doses of radiation selectively to the tumor microenvironment, largely sparing neighboring healthy tissue and avoiding systemic toxicity (Brechibiel, 2007; Parker et al., 2018; Poty et al., 2018a; 2018b; Hatcher-Lamarre et al., 2021). The promise of such efficient therapy emboldens metrologists to aim for accompanying precision in patient-specific dosimetry based on quantitative medical imaging of the therapeutic radiopharmaceutical itself or a theranostic complement. The first step towards precision radiopharmaceutical therapy, dosimetry, and quantitative imaging is the activity assay.

Regulators look to national metrology institutes (NMIs) to define standards for the SI unit of activity, the becquerel (Bq). Since the mid-2000s, as interest in alpha emitter-based radiopharmaceuticals has exploded, NMIs around the world have honed techniques, developed approaches, and overcome challenges to deliver activity standards for a host of radionuclides including ^{223}Ra, ^{224}Ra, ^{225}Ac, and ^{227}Th. In the course of this work, radionuclide metrologists work to compare activity standards and establish equivalency. Results are disseminated to end users through calibration programs and through the publication of nuclear decay data and benchmark calibration settings for clinical activity calibrators.

In this review, we summarize the primary methods that have been brought to bear in activity standardizations of medically important alpha-emitting radionuclides, focusing on liquid-scintillation based methods. We discuss the complex decay chains common for alpha emitters and how they can present measurement challenges. We raise examples where NMIs have established equivalency of activity standards through both indirect and direct comparison exercises. We address the determination of calibration settings for commercial radionuclide calibrators and gather some relevant published settings. Finally, we describe recent efforts to determine nuclear decay data for medically important alpha emitters, stressing how these data are critical to primary activity measurements and, crucially, how primary activity measurement campaigns yield key half-lives and absolute photon emission intensities. In all cases, these efforts are directed towards enabling the highest possible precision in preclinical and clinical measurements of activity administered to patients.

2. Primary methods for activity standards

Primary methods are those that do not rely on calibrations using a standard for the quantity being measured (Pommé, 2007; Collé, 2009). These methods require a means of determining the absolute counting efficiency of the system with only the nuclear decay data and experimental arrangement as inputs. For alpha emitters, a classic example is defined solid angle (DSA) counting, where an alpha particle detector with 100 % quantum efficiency is placed at a precisely known distance from a discreet source such that the detector subtends a known solid angle (Pommé, 2007). The flux of alpha particles sampled over this solid angle can then be used to calculate the total emission rate for an isotropic source, which is combined with the decay data to calculate the source activity. While to date there are no examples of DSA being used to measure the activity of a

medically important alpha emitting radionuclide, Marouli et al. (2019) discuss measurements of ^{227}Ac in equilibrium with its progeny, including ^{227}Th and ^{223}Ra. The contamination risks posed by diffusion of radon progeny and high energy recoils that Marouli et al. address will be common to the decay chains of interest for medical applications. For activity measurements "contamination" means lost counts, as do the common measures taken to avoid contamination, e.g., covering dried sources with thin protective films. Fortunately, liquid scintillation-based methods offer a 4π detection scheme with very high counting efficiencies and, in various forms, account for all primary activity standardizations of medically important alpha-emitting radionuclides to date.

2.1. Liquid scintillation

Liquid scintillation (LS) counting is a very powerful method for the activity determination of a number of radionuclides and plays a key role in radionuclide metrology. Usually, weighed aliquots of a radioactive solution are added to an LS vial that contains the liquid scintillator and – in some cases – additional ingredients to ensure sample stability and/or to vary counting efficiencies. The LS sources are then measured in special counters with two or three photomultiplier tubes (PMT) and coincidences, i.e., events which are detected at the same time in at least two PMTs, are counted. Since alpha particles that are emitted as a consequence of an alpha decay have high energies of a few MeV, a considerable number of scintillation photons is created and, as a consequence, it becomes possible to achieve counting efficiencies of virtually 100 %, which was confirmed by several experimental studies (see, e.g., Cassette et al., 2002; Kossert et al., 2009; Fitzgerald and Forney, 2011).

The alpha emitters of interest for medical applications often have complex decay schemes and/or give rise to short-lived progeny that decay by various modes. For these other decay modes, namely beta minus, beta plus, electron capture, as well as for potential additional gamma and isomeric transitions, the counting efficiency is usually lower than 100 % and must be determined with high accuracy. This task can be completed by using the triple-to-double coincidence ratio (TDCR) method and/or the CIEMAT/NIST efficiency tracing technique (CNET) which are well established methods in radionuclide metrology. Both methods are based on the same free parameter model (Grau Malonda, 1999) and require accurate calculations of the respective electron energy spectra. These spectra include contributions from electrons which are emitted directly due to the radioactive decay, as well as secondary electrons produced from interactions between the components of the liquid scintillation cocktail and emitted photons.

The ultimate goal of the measurements is to determine the massic activity A_m of a radioactive solution, which is given by

$$A_m = \frac{A}{m} = \frac{R_{net}}{m \cdot \varepsilon} \quad (1)$$

where A is the sample activity, m the mass of solution in the LS sample, R_{net} the net counting rate of the sample and ε the counting efficiency.

In a liquid scintillation counter with two photomultiplier tubes with equal quantum efficiencies, the counting efficiency of a pure beta emitter is given by

$$\varepsilon_2 = \int_0^{E_{max}} S(E)(1-e^{\frac{-E\cdot Q(E)}{2\cdot M}})^2 dE, \quad (2)$$

where $S(E)$ is the normalized electron spectrum resulting from the decay, $Q(E)$ is the ionization quenching function that takes into account the fact that the number of created scintillation photons is not proportional to the deposited electron energy, and M is a free parameter (Garcia-Toraño and Grau Malonda, 1985).

The free parameter M can be determined by means of the CNET method (Coursey et al., 1986). To this end, a second measurement is carried out using an activity standard of the tracer nuclide, which is ^{3}H in most cases. Since the activity of the tracer is known, Eq. 2 can be calculated a second time with the normalized spectrum $S(E)$ of the tracer to find the free parameter M. This parameter can then be used to compute the counting efficiency of the nuclide under study, provided that the samples with the tracer nuclide were measured under the same experimental conditions.

In a system with three photomultiplier tubes having equal quantum detection efficiencies, the counting efficiency for triple coincidences can be calculated applying

$$\varepsilon_T = \int_0^{E_{max}} S(E)(1-e^{\frac{-E\cdot Q(E)}{3\cdot M}})^3 dE, \quad (3)$$

and the counting efficiency for the logical sum of double coincidences is given by

$$\varepsilon_D = \int_0^{E_{max}} S(E)(3(1-e^{-EQ(E)/3M})^2 - 2(1-e^{-EQ(E)/3M})^3) dE\,. \quad (4)$$

Here also, the counting efficiencies depend on the free parameter M. The free parameter of a given LS sample is defined by the condition

$$\frac{\varepsilon_T(M)}{\varepsilon_D(M)} = \frac{R_T}{R_D}\,, \quad (5)$$

where R_T and R_D are the experimentally determined net counting rates in the triple and the double coincidence channels, respectively. After determination of the free parameter, the counting efficiency ε_D can be computed and subsequently the sample activity is obtained from Eq. 1 with $\varepsilon = \varepsilon_D$ and $R_{net} = R_D$. In the same manner, the activity can be calculated using ε_T and R_T.

In recent studies, it was shown that the computation of the β^- spectrum $S(E)$ requires advanced methods that take the atomic exchange effect and further radiative corrections into account (Mougeot, 2015). This plays a significant role for beta emitters with low maximum energies (Kossert and Mougeot, 2015; Kossert et al., 2018) and can also be relevant for high energy beta emitters (Kossert and Mougeot, 2021). For electron capture and other complex decays, the above-mentioned approach is often replaced with a stochastic approach (see. e.g., Grau Carles, A., 2007; Kossert and Grau Carles, 2010; Kossert et al., 2014a) since the computation by means of analytical methods becomes too complex.

It should be noted that the above-stated equations for the counting efficiencies are only valid if the same free parameter can be assigned to each of the two or three PMTs. If the PMT responses are different, which is the usual case, other approaches are needed that account for the PMT asymmetry (Broda et al., 2007, Kossert et al., 2020b, Kossert, 2021).

Further valuable information on the methods, the related models, relevant corrections, and related uncertainties were summarized by Broda et al. (2007) and Kossert et al. (2015a). In the following, we will discuss selected applications of the methods to standardize medically important alpha-emitting radionuclides.

The application of the TDCR method and the CNET method for the above-mentioned decay chains of ^{223}Ra, ^{224}Ra, ^{225}Ac, and ^{227}Th can be quite laborious. However, despite the complexity of the efficiency computation the relative uncertainties of the massic activity can be quite low and, consequently, the LS methods are very appealing for activity standardizations. The small uncertainties result from the fact that the decay chains comprise several alpha transitions with counting efficiency of 100 %; and the counting efficiencies of most beta transitions are very high, too. Thus, uncertainty components assigned to the efficiency model and to nuclear and atomic input data can be rather small. In the case of ^{223}Ra and ^{224}Ra, several authors evaluated their overall relative standard uncertainty of the massic activity to be lower than 0.4 % (see, e.g., Kossert et al., 2015b; Napoli et al., 2020a; Nedjadi et al., 2021). Model uncertainties can be further mitigated by comparing the results from the TDCR method and the CNET method, which are often anti-correlated. Kossert and co-workers have demonstrated that propagating model uncertainties to both methods can yield an average that is much more robust than either method independently (Nähle and Kossert, 2011; Kossert and Mougeot, 2015).

2.2. Coincidence counting methods

In addition to the TDCR and CNET methods, some groups have used 4π(LS)-γ coincidence counting methods for primary activity measurements of medically important alpha-emitting radionuclides (Zimmerman et al., 2015; Keightley et al., 2015; Collins et al., 2019a; Napoli et al., 2020a; Bergeron et al., 2021; Simões et al., 2021). There have been numerous excellent reviews on coincidence counting techniques and applications (Bobin, 2007; Keightley and Park, 2007; Fitzgerald et al., 2015).

Coincidence counting methods are often considered “model-independent” since they do not require the type of data-dependent efficiency model common to the free-parameter methods (Section 2.1). For alpha emitters and their high-energy beta-emitting progeny, the model-independence is clear from the expression for calculating activity (A):

$$A = N_\beta \times N_\gamma / N_\mathrm{c} \tag{6}$$

where N_β, N_γ, and N_c refer to the experimental counting rates in the β- and γ-channels and coincidence channels, respectively. In the efficiency extrapolation approach to coincidence counting, LS counting efficiency is varied by, e.g., adjusting the lower-level discriminator

threshold to establish a curve that can be extrapolated to perfect counting efficiency ($N_c/N_\gamma = 1$). With high LS efficiency, these curves are relatively flat and extrapolation ranges are short, so that associated uncertainties—often the largest contributor to the overall uncertainty on the activity—are typically ≤ 0.2 %. With coincidence gates set to monitor the counting efficiency for all alpha and beta decays, convergent or multidimensional extrapolations can assure robust activity estimates. The descriptions of ^{223}Ra activity standardization by digital coincidence counting (Keightley et al., 2015) and live-timed anticoincidence counting (Zimmerman et al., 2015) provide an excellent introduction to the considerations and corrections required for a thorough treatment of a typical medically important alpha emitter.

2.3. 4πγ methods

Well-type detectors with near 4π geometric efficiency have been used in several cases for confirmatory activity measurements. With 4πγ counting, small uncertainties can be obtained for some radionuclides with suitable simultaneous gamma emission (see, e.g., Winkler and Pavlik, 1983); however, for the alpha decay series discussed here, the uncertainties obtained with the method are generally larger than with the methods mentioned above. For ^{223}Ra, Nedjadi et al. (2021) reported integral counting results with a well-type NaI(Tl) detector. Monte Carlo simulations with the GEANT4 package (Allison et al., 2006; 2016) provided counting efficiencies and the uncertainty on the activity (1.06 %) was limited by the input decay data. For ^{224}Ra, Napoli et al. (2020a) report excellent agreement between the activity determined with a well-type NaI(Tl) detector and GEANT4-based efficiencies and other primary methods, but estimate 3 % uncertainties.

4πγ measurements are also possible with ionization chambers, where an ionization current is measured instead of a counting rate. Several groups report on 4πγ measurements with ionization chambers with well-characterized and/or simulated response curves (Keightley et al., 2015; Zimmerman et al., 2015; Napoli et al., 2020a; Nedjadi, 2021). Whether the response curves have been established analytically or calculated with benchmarked Monte Carlo simulations, the predicted response to a new nuclide (and its progeny, see Section 2.4) will depend on the quality of the input decay data. In addition, analytically establishing an energy-dependent response curve or benchmarking any model requires a number of measurements with other reliably calibrated radionuclides. Changes to source geometry or composition can result in significant biases, especially for radionuclides emitting β particles and/or low-energy photons. Finally, Monte Carlo simulations can be limited by knowledge of the ionization chamber geometry and gas pressure, with response to β particles and low-energy photons being particularly sensitive. All of these considerations will contribute uncertainty to activities estimated from 4πγ methods.

2.4. Accounting for complex decay chains

2.4.1. Radionuclides at equilibrium with progeny

Often, the alpha radionuclide of interest can be measured in radioactive equilibrium with its progeny. The Bateman equations (Bateman, 1910) describe the time-evolution of the activities of a nuclide and its progeny. The time when equilibrium is reached depends on the half-life of the longest-lived progeny. For ^{223}Ra, with ^{211}Pb ($T_{1/2}$ = 36.1(2) min; DDEP, 2021) being its longest-

lived progeny, < 99.999 % equilibrium is reached approximately 0.5 d after purification (i.e., separation from the ^{227}Th parent and progeny). The time of separation is denoted herein as T_0. Tor ^{225}Ac, with its progeny ^{209}Pb ($T_{1/2}$ = 3.277(15) h; DDEP, 2021), equilibrium is reached approximately 3 d after T_0 (Figure 1).

For ^{224}Ra, with ^{212}Pb ($T_{1/2}$ = 10.64(1) h; DDEP, 2021) as one progeny, it takes approximately 8 d to reach > 99.999 % equilibrium (Figure 2). This corresponds to about 2.2 ^{224}Ra half-lives which means that less than 22 % of the initial ^{224}Ra activity remains when approaching equilibrium.

Where ^{212}Pb plays the determining role in the 8 d equilibration time of a ^{224}Ra source, when ^{212}Pb is separated from its progenitors (see example in Section 4), we expect > 99.999 % equilibration of ^{212}Pb with its longest lived progeny ^{212}Bi ($T_{1/2}$ = 60.54(6) min; DDEP, 2021) within approximately 12 h. Chemical separations, however, are not perfect; in chromatographic separations, "breakthrough" occurs when an adsorbate reaches the end of the column and leaves with the effluent. In the case where ^{212}Pb is being isolated from its progenitors, a small breakthrough impurity of the ^{224}Ra parent results in delayed equilibration since more ^{212}Pb atoms are being formed as ^{224}Ra decays (i.e., this is a "supported" ^{212}Pb source). Thus, ^{212}Pb and its progeny may be found long after an unsupported source would have been expected to decay. Section 2.4.3 discusses breakthrough in more detail.

Once equilibrium has been reached, the activity ratios for decay progeny to the parent (A_i/A_{parent}) are constant. With knowledge of these ratios, the total counting efficiency in any experiment can be calculated from the appropriately weighted sum of the individual counting efficiencies for all nuclides. This approach was applied to ^{223}Ra (Cessna and Zimmerman, 2010, Kossert et al., 2015b, Keightley et al., 2015, Nedjadi, 2021), ^{225}Ac (Kossert et al., 2020a) and ^{224}Ra (Napoli et al., 2020a; Bergeron et al., 2021) when using the LS methods (Section 2.1). However, as we will discuss in the following, a few complications may arise and require careful investigation.

Several decay chains contain Rn isotopes which could lead to a reduced counting efficiency if parts of this radioactive noble gas would escape from the LS volume before its decay. However, the solubility of Rn (and other noble gases) in organic liquids like diisopropyl naphthalene-based liquid scintillators is very high and experimental studies confirm that losses of ^{219}Rn in the decay chain of ^{223}Ra or ^{227}Th as well as losses of ^{220}Rn in the decay chains of ^{228}Th/^{224}Ra are negligible (Cessna and Zimmerman, 2010; Kossert and Nähle, 2011; Kossert et al., 2015b).

A second problem may arise if the decay chain comprises very short-lived progeny that may decay during the deadtime triggered by the detection of the previous decay. In such a case, a correction must be applied. For the analysis of ^{223}Ra LS measurement data, Kossert et al. (2015b) proposed a simple approximation to allow for ^{215}Po decays that may occur during the deadtime triggered by detected ^{219}Rn decays. The portion of ^{215}Po decay events that is not lost due to this effect can be estimated by the correction factor

$$k_{^{215}\mathrm{Po,\ survival}} = e^{-\ln 2 \frac{t_{\mathrm{dead}}}{T_{1/2}\left(^{215}\mathrm{Po}\right)}}. \qquad (7)$$

For a dead time t_{dead} = 50 µs the correction factor is 0.9807, i.e., about 2 % of ^{215}Po decay events would not be counted. Zimmerman et al. (2015) described the same correction in coincidence counting and demonstrated the validity of their model by experimentally varying their imposed extending deadtime. Since ^{219}Rn is an alpha emitter it can be assumed that all its decays are detected.

The situation is a bit more complex if the parent is a beta emitter with lower counting efficiency. In such a case, the parent radionuclide could be detected in only one PMT. Such an event would not be counted but it would trigger a deadtime. Treatment of this effect has been considered for the case of ^{229}Th by Fitzgerald et al. (2010) and Kossert et al. (2014b) to account for the combined contributions of the beta emitter ^{213}Bi and the short-lived alpha emitter ^{213}Po ($T_{1/2}$ = 3.70(5) µs; DDEP, 2021). A corresponding correction is also required when measuring ^{225}Ac, which is part of the same decay chain. In this case, Kossert et al. (2020a) demonstrated the importance of the correction by variation of the experimental deadtime.

The presence of very short-lived progeny can also lead to complications when using commercial LS counters, but in these cases, insufficient knowledge and control of system parameters (e.g., deadtime) makes it impossible to apply corrections. Fitzgerald et al. (2010) attributed systematic biases in measured ^{229}Th activities of up to 2.8 % to differences in the extending deadtime imposed by different commercial counters. When studying ^{228}Th in equilibrium with progeny, Kossert and Nähle (2011) observed systematic discrepancies between 1.3 % and about 5 % when comparing the results of TriCarb LS counters (PerkinElmer, Waltham, MA, USA)[1] with those of other LS instruments, including a custom-built TDCR counter. Their vague suspicion is that the TriCarb's time-resolved analysis method might be causing these differences. These findings are also relevant for ^{224}Ra which is part of the ^{228}Th decay chain; while Napoli et al. (2020a) reported consistent results for ^{224}Ra activity using two different commercial counters, it can be noted that the TriCarb model used in this work was different from the one discussed by Fitzgerald et al. (2010) or Kossert and Nähle (2011).

2.4.2. Radionuclides not at equilibrium with progeny

In some cases (e.g., ^{227}Th, ^{225}Ra), the activity determination must be completed before radioactive equilibrium has been reached. A recent prominent example is ^{227}Th ($T_{1/2}$ = 18.68(9) d; NNDC, 2021) with its rather long-lived daughter ^{223}Ra ($T_{1/2}$ = 11.43(3) d; DDEP, 2021). When starting the measurement near T_0 with (almost) pure ^{227}Th, the instrument response (i.e., count rate for LS, current for ionization chamber) will initially increase. The activity standardization can be very challenging, in particular if one also accounts for the fact that the chemical separation (see, e.g., Ivanov et al., 2017) might be imperfect. In this case, the ratios A_i/A_{parent} change with time, so efficiency calculations must incorporate time-dependent weighting factors to sum the efficiencies of the individual nuclides. Collins et al. (2019) adopted such an approach in their treatment of ^{227}Th, generating a large look-up table with 1 min granularity to calculate time-dependent counting

[1] Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the authors' institutions, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

efficiencies. A comprehensive and complex analysis was carried out by Kossert et al. (2019) in the computation of counting efficiencies for ^{227}Th and its progeny. As in the previous section, corrections are required to allow for very short-lived members of the decay chain (in particular, ^{215}Po) and Kossert et al. (2019) proposed a time-dependent correction for decays during the measurement. The overall consideration can be simplified once ^{211}Pb reaches quasi-equilibrium with ^{223}Ra. Then, ^{223}Ra and its progeny can be considered as one radionuclide (with the counting efficiency as discussed in the previous section) and the overall analysis becomes much simpler.

2.4.3. Breakthrough and impurities

The alpha-emitting radionuclides currently in widespread medical use are typically produced via radiochemical means, e.g., column separation of ^{223}Ra from ^{227}Ac. A key advantage of this approach is that high radiochemical purity is usually achieved. The main impurities for column-produced material are from breakthrough of the long-lived parent or short-lived progeny. While breakthrough can be a concern from the perspective of patient toxicity and/or waste handling, we focus here on the impacts on activity measurements. The breakthrough of a long-lived parent can be very difficult to detect at early times, but becomes clear after multiple half-lives of the principal radionuclide. In cases like ^{224}Ra, where the ^{228}Th parent decays without any intense γ-ray emissions, γ-ray spectrometry can only infer breakthrough from the persistence of emissions from progeny after the short-lived species would have been expected to completely decay. In other words, the apparent half-life would be considerably longer than the true half-life (although it may be necessary to monitor the decay for an impractically long time to detect breakthrough in this way). The decaying progeny will, of course, contribute counts to any method applied for primary activity measurements since the method will have been designed specifically to count those progeny; therefore, careful corrections are required. Similarly, incomplete separation of a radionuclide from its progeny will result in unwanted counts in an activity measurement. In addition, breakthrough can make it more difficult to confidently determine T_0, confusing time-dependent efficiency calculations or calibrations.

While breakthrough is a concern, the appeal of column-produced material can be illustrated by considering impurities in ^{225}Ac. Despite extensive medical research with ^{225}Ac, widespread clinical use has been hampered by the limited supply of ^{229}Th, with just three sources available worldwide according to Morgenstern et al. (2020). Accelerator-produced ^{225}Ac offers an exciting solution to this supply problem, but the coproduction of ^{227}Ac ($T_{1/2}$ = 21.772(3) a; DDEP, 2021) during spallation of ^{232}Th raises regulatory concerns and measurement challenges. The low emission intensities of γ-rays from ^{227}Ac make detection and quantification difficult, especially at early times when ^{225}Ac and its progeny are still prominent. Tollefson et al. (2021) demonstrated how the extremely high resolution and quantum efficiency of decay energy spectroscopy with cryogenic transition edge sensors can give a precise early quantification of ^{227}Ac impurity in an ^{225}Ac sample. To date, the only primary activity standardization for ^{225}Ac (Kossert et al., 2020a) used column-produced material. Correcting for ^{227}Ac impurities in a LS-based activity measurement will require careful consideration of the time-evolution of the activity ratios for the decay progeny (Section 2.4.2) and good estimates for the LS efficiencies (^{227}Th and ^{223}Ra are ^{227}Ac progeny and their LS efficiencies have been discussed above).

3. Comparison and dissemination of activity standards

3.1. International comparison

A sound international metrological basis is usually obtained when National Metrology Institutes participate in international comparison (Zimmerman and Judge, 2007).

One very simple and well-established comparison method is for a pilot lab to distribute aliquots of a stock solution to participating metrology institutes. The participants then use their various measurement techniques to determine the massic activity and return their results to the pilot lab. If the pilot lab itself is taking part in the comparison, it will have previously deposited its results to another trusted institute. Once all results have been received, a comparison and assessment of all the values can be undertaken. This type of comparison is, however, attended by a great deal of logistical cost and effort, seeing as the aliquots often need to be shipped to many countries around the world. To date, the Consultative Committee for Ionizing Radiation (CCRI, Section II) at the Bureau International des Poids et Mesures (BIPM) in Paris has not yet organized any key comparison on the above-mentioned alpha-emitting radionuclides, but NMIs can also organize bi- and multilateral comparisons. For example, NIST and NPL recently carried out a direct bilateral comparison of ^{224}Ra activity standards, reporting excellent accord, with a ratio between the activities of A_{NIST}/A_{NPL} = 1.0012(57) (Bergeron et al., 2021).

Another well-established comparison procedure is known as the International Reference System (Système International de Référence, or SIR) based at the BIPM (Ratel, 2007). The SIR relies on ionization chambers in which most photon-emitting radionuclides can be measured. A participating institute can at practically any time send in a solution of a radionuclide in a sealed ampoule of well-defined geometry while also reporting the activity determined at that institute. BIPM staff then determine the relationship between the measured ionization current and the reported activity and ensure the long-term stability of the SIR by means of long-lived ^{226}Ra reference sources. If at least two institutes make submissions to the SIR, comparisons between these measurement results can be carried out as well. In particular, for NMIs looking to demonstrate their calibration capabilities for large numbers of radionuclides, the SIR allows the required comparison measurements to be performed. Since the establishment of the SIR in 1976, over 1000 ampoules of 70 radionuclides have been submitted, underscoring the enormous significance of this system (BIPM, 2021).

In the case of ^{223}Ra, the results of three metrology institutes are considered in a recent SIR comparison (Michotte et al., 2021) indicating good agreement of the results. Further submissions of this particular radionuclide are expected.

For very short-lived radionuclides, it is often impractical to ship sources for direct or SIR comparisons. In such cases, the transfer instrument of the international reference system (SIRTI) can provide an alternative means of comparison (Michotte and Fitzgerald, 2010; Michotte et al., 2013).

International equivalence has also sometimes been estimated by using the network of Vinten 671 ionization chambers (Woods et al., 1983) located in several NMIs around the world. The construction of these chambers to a common design was overseen by NPL researchers and the current response of each chamber has been directly compared to the reference chamber (located at the UK's National Physical Laboratory) using radionuclides with γ-ray emissions between 30 keV and 1300 keV. Calibration coefficients (with units pA/MBq) determined when performing primary standardizations can be compared to give an indication of equivalence between laboratories, as has been done for, e.g., ^{223}Ra (Keightley et al., 2015) and ^{224}Ra (Bergeron et al., 2021).

3.2. Radionuclide Calibrators

Most clinical measurements of activity rely on well-type re-entrant pressurized ionization chambers combined with an electrometer and the electronics to display in activity units. These are commonly referred to as radionuclide calibrators (or 'dose calibrators'). Proper calibration, quality control, and maintenance of these instruments has been the subject of numerous reviews and guidance documents (e.g., ANSI, 2004; Gadd et al., 2006; Zanzonico, 2008; Carey et al., 2012). With an activity standard established using primary methods (Section 2) it is possible to determine a calibration setting that will return the correct activity either by 'dialing in' or by establishing a calibration curve (Zimmerman and Cessna, 2000). The calibration curve method has the advantage that the uncertainty of the fit (calculated from the residuals) to the curve can be used in an uncertainty budget as a surrogate for the standard deviation on the readings.

Table 1 complies recently determined calibration settings for some medically important alpha emitters. The determined settings are reported with an uncertainty (given in parentheses) which is additionally translated to a value, u_A, which represents the relative uncertainty on the activity reading at that setting.

Table 1 includes reported results from three laboratories for ^{223}Ra. The agreement between the NIST and NPL settings for Capintec R series calibrators in fact reflects a revision (Bergeron et al., 2015) of the originally reported settings (Bergeron et al., 2010) in light of the original discrepancy pointed out in (Keightley et al., 2015). The settings from Simões et al. (2021) are not consistent; this is attributed to differences in software releases, but consultation with the manufacturer confirms that software updates do not affect the relationship between numerical dial settings and chamber response.

NMIs determine and report calibration settings in standard geometries, most often acid solutions in flame-sealed ampoules or crimp-sealed glass vials. The diversity of chemical forms and source geometries encountered in clinical settings can create measurement challenges. Reduced geometric efficiency for syringes hanging from a dipper and increased attenuation due to scattering from high-*Z* microparticles have been shown to affect radionuclide calibrator measurements of drug substances based on alpha emitters (Bergeron et al., 2010; 2015; Napoli et al., 2020b). The calibration settings appropriate for a clinical product may thus differ significantly from those reported by NMIs for solutions in flame-sealed ampoules and this problem can be expected to arise frequently as nanoparticle-based formulations (see, e.g., Pallares and Abergel, 2020) become more common. End-users should always follow manufacturers' instructions.

There is potential for confusion when referring to tables of calibration settings found in radionuclide calibrator manuals. In many cases, the settings provided are based on theoretical calculations based on the adopted γ-ray energies and intensities and the instrument response curve. An example discussed recently by Napoli et al. (2020c) concerns the several settings for ^{212}Pb recommended in the Capintec user's manual (Capintec, 1986). A setting for ^{212}Pb in isolation is given near a setting recommended for ^{212}Pb in equilibrium with ^{212}Bi and another recommended to give the "*Total Act. Of Pb & Bi in eqb. Sample*." It appears that none of these recommended settings include an accounting for the contributions of progeny beyond ^{212}Bi; the 2.6 MeV γ-ray emitted in the decay of ^{208}Tl is expected to account for much of the overall ionization chamber response to ^{212}Pb and its progeny, explaining the large differences between the settings found experimentally by Napoli et al. and settings found in the instrument manual. For decay chain nuclides especially, users should be wary of similar cases that might be encountered when referencing theoretically-determined radionuclide calibrator settings.

For radionuclides that are not in equilibrium with decay progeny at the time of measurement, it is necessary to perform a correction which is typically dependent on T_0. This is challenging when considering complex decay schemes where there may be multiple decay progeny to consider. Capintec provide an equation to calculate 'multiplication factors' and include some common examples of these which are derived using the published factors provided by Capintec. To calculate these corrections, it is necessary to know the response function (dial setting) for each of the progeny and these are often predicted using instrument response curves. An alternative to calculating the correction is to measure an ingrowth curve using a representative sample from a time close to T_0. From this, a time-dependent look-up table can be created and used to perform corrections to measurements when using a fixed calibration setting. The advantage of this technique is that both chamber and geometry are considered, and it does not require knowledge of the decay characteristics of all progeny.

3.3. **Gamma-ray Spectrometry**

Gamma-ray spectrometry is ubiquitous across all fields that are involved in the measurement of ionizing radiation, providing a relatively simple non-destructive method for identification and quantification of γ-ray and/or x-ray emitting radionuclides in a given matrix. There are a wide range of different spectrometers utilizing different technology: ranging from the relatively cheap high-efficiency but low resolution NaI(Tl) scintillation detector, to the expensive lower efficiency and high resolution high-purity germanium (HPGe) semiconductor detectors. These detectors are employed within NMIs, pre-clinical, and clinical facilities bringing their specific advantages to bear upon different research activities.

Spectrometers are used extensively within NMIs, either as part of a primary standardization counting system providing the gamma-channel (e.g., NaI(Tl); $CeBr_3$; HPGe) or as standalone systems (HPGe; Si(Li)). They are of particular importance in supporting primary activity assays, providing confirmatory measurements based on the accepted nuclear decay data at the time and assessing the radionuclidic purity of the sample being measured (Section 2.4.3). The latter application is of utmost importance as activity standards are based on non-spectroscopic counting techniques that cannot by themselves differentiate between the decays of different radionuclides

that may be present in a sample. A HPGe γ-ray spectrometer, calibrated for its full-energy peak detection efficiency in a traceable manner, can be used to identify and quantify any γ-ray emitting radionuclides present. From this information, corrections can be made to observed activity in the primary and secondary techniques. This can be of particular importance when applied to alpha-emitting radionuclide progeny that are separated from a parent radionuclide, e.g., ^{227}Ac-^{227}Th, ^{228}Th-^{224}Ra, ^{228}Th/^{224}Ra-^{212}Pb. As discussed previously, breakthrough of these parent radionuclides is unavoidable in imperfect radiochemical separations. The parent nuclides must therefore be treated as radionuclidic impurities and their contributions accounted in an activity standardization (e.g., Bergeron et al., 2021). This is also true where progeny are not in equilibrium with the parent during the standardization, such as is the case for ^{227}Th separated from its decay progeny. In this case, HPGe γ-ray spectrometry can be used to determine the effective T_0 (Pommé et al., 2016).

Many of these alpha emitters are accompanied by x-ray and γ-ray emissions that typically have low emission intensities and, in cases where the parent is at the head of a long decay series, there can be a large number of γ-ray emissions detected from the progeny. Analysis of the spectrum and identification of the single photons using HPGe γ-ray spectrometry is relatively simple due to the high resolution, though complications due to low- or high-energy tailing in ^{224}Ra have been observed (Collins et al., 2020). However, in pre-clinical and clinical studies which primarily use low resolution scintillation detectors in single photon emission computed tomography (SPECT) and positron emission tomography (PET) this analysis becomes far more complicated due to extensive crosstalk between neighboring full-energy peaks as well as scattered photons. An extensive literature on the use of SPECT and PET techniques for imaging of alpha-emitting radionuclides has grown over the last decade as the range of treatments expands (Hindorf et al., 2012; Benabdallah et al., 2019; Larson et al., 2020, Murray et al., 2020).

Considering that these radionuclides are typically present in naturally occurring decay series, e.g. ^{235}U, it might have been expected that the nuclear decay data for these radionuclides would be well characterized. In recent years, however, it has been observed that in many of these radionuclides the decay data in the literature have been of dubious accuracy (Pibida et al., 2015; Kossert et al., 2015b; Collins et al., 2015a; Collins et al., 2019b). This has led to a lack of confidence in the data to derive activities by γ-ray spectrometry as has been identified in the work of NIST in their initial standardization of ^{223}Ra (Cessna and Zimmerman, 2010). It was identified by Keightley et al. (2015) that the activity determined from the major γ-ray emissions of the ^{223}Ra and decay progeny resulted in a spread of 18.3 %. However, the weighted mean of all of these γ-ray emissions resulted in an activity that was in agreement with the primary standardization; these deviations were confirmed in Kossert et al. (2015) and Pibida et al. (2015). Collins et al. (2015a) investigated the role of decay data used for HPGe calibrations in the discrepant γ-ray emission intensities for ^{223}Ra and its progeny. In the one report that provided a detailed description of the HPGe calibration (Krien et al., 1970), it was noted that the ^{75}Se data cited differed significantly from a more recent evaluation (Negret and Singh, 2013). Collins et al. compared these two sets of the γ-ray emission intensities data using a standard of ^{75}Se measured on a HPGe. The resulting full-energy peak detection efficiency curves had vastly different shapes, with the Krien et al. emission data resulting in an unexpected detection efficiency curve

shape (Figure 3a). The ^{223}Ra γ-ray emission intensities derived from the revised efficiency curve and normalized to the 154.2 keV peak were much more consistent with Collins' results (Figure 3b & 3c). Moreover, agreement for γ-rays at higher energies (> 250 keV) could be further improved by normalizing to the 269.5 keV peak, supporting the assertion that differences in HPGe calibration curves account for the discrepant absolute γ-ray emission intensities. This case illustrates not only the persistent need for accurate decay data, but also the importance of citing the source of decay data used for spectrometer calibrations.

Where relatively long-lived progeny are separated initially from the parent radionuclide of interest, e.g. ^{227}Th-^{223}Ra, there may be significant uncertainty on the value of T_0. Where this time differs significantly from the true T_0 in the chemical separation (typically either the mid- or end-point), this can result in significant errors in activity assays as the corrections for ingrowth will be incorrect. A useful application of HPGe γ-ray spectrometry, where both the parent and at least one progeny emit γ rays, is to determine T_0 via the ratio of the activity of both at a point in time (i.e., the start of the measurement, T_s). This technique can accurately estimate T_0 based on a single measurement, and the closer that measurement is made to the true T_0, the more precisely it can be determined (though, counter-intuitively, the relative uncertainty may be very large due to the statistical uncertainty of the low activity of the progeny). In fact, in Collins et al. (2019), T_0 for ^{227}Th-^{223}Ra was measured with a standard uncertainty of approximately 1 minute from a series of eight measurements made within 6 hours of the end of the chemical separation. For this technique, reliable nuclear decay data is necessary to have confidence in the T_0 determined. In Pommé et al (2016) it was observed that the accuracy and precision of the ^{227}Th-^{223}Ra chronometer was drastically improved using the γ-ray decay data and half-lives for ^{227}Th and ^{223}Ra from Collins et al. (2015a,b,c) over using values as recommended in DDEP and ENSDF where a bias had initially been seen. The uncertainty of the T_0 determinations was also significantly improved. Figure 4 illustrates the improvements with a reanalysis of the first six days of data from Pommé et al. (2016). Figure 4a and 4c use recommended γ-ray emission intensities for the 50 keV and 236 keV from ^{227}Th and the 154.2 keV of ^{223}Ra prior to the publication of new γ-ray emission intensities by NIST, NPL, and PTB for ^{223}Ra in 2015 and ^{227}Th in 2019 (Browne, 2001; Pibida et al., 2015; Kossert et al., 2015b; Collins et al., 2015a; Collins et al., 2019b). The effect of adopting the new emission intensities is shown in Figure 4b and 4d.

As absolute γ-ray emission intensities are directly linked to an NMI's primary standard, the use of this absolute γ-ray emission intensity can join the comparison methods enumerated in Section 3.1, especially where the half-life is considered too short or the activity of the radionuclide available is insufficient to provide a submission to the SIR. This approach was adopted as part of the bilateral comparison between NIST and NPL for ^{224}Ra activity, complementing the direct comparison and giving a ratio of activities, A_{NIST}/A_{NPL} = 1.000(9) (Bergeron et al., 2021). There are some provisos to this type of comparison, as the absolute emission intensity is dependent on the individual NMIs capabilities for the analysis of the γ-ray spectra (see also section 4.2).

As discussed further in the next section, one product of the primary standardizations carried out by NMIs around the world is the generation of new absolute γ-ray emission intensities which are resolving many of the discrepancies seen in the current literature.

4. Nuclear decay data

The above-mentioned methods for the activity determination usually require several nuclear and atomic input data. Photon emission intensities are needed for γ-ray spectrometry and for the computation of ionization chamber efficiencies. The LS methods require some nuclear and atomic input data, such as energies, decay probabilities of various branches and half-lives to compute equilibrium factors and decay corrections. And, half-lives are of course also required for decay corrections for all methods. Usually, such data are taken from evaluated databases like the Decay Data Evaluation project (DDEP) which is maintained by radionuclide metrologists (DDEP, 2021). A sound data evaluation, however, requires reliable experimental input data with high precision.

4.1. Half-lives

The determination of rather short half-lives is often carried out by means of repeat measurements of a radioactive source. When the source does not contain any radioactive impurity the net instrument readings (i.e., after background subtraction) can be fitted with an exponential function to determine the half-life. This method, which is often done using 4π ionization chambers is, however, based on the assumption that the source-detector system is stable. While the detection efficiency of the instrument can be monitored by means of long-lived reference sources, potential variations of the overall detection efficiency due to possible changes of the radioactive source (e.g. precipitation, sorption phenomena on vial walls etc.) could remain undiscovered. Measurements with a TDCR LS counter can provide a remedy here. When using a TDCR counter, the measurements yield counting rates for triple (T) as well as for double coincidences (D). A stable source-detector system with stable counting efficiency over time should lead to a stable TDCR parameter, and consequently, one expects that the fit results must be consistent regardless of whether triple or double coincidence counting rates are used. An impressive long-term measurement was presented by Kossert et al. (2020) who measured an ^{225}Ac source over 111 d, which corresponds to more than 11 half-lives. The source-detector system was found to be very stable leading to consistent results when fitting the counting rates R_T and R_D, respectively. In addition, ionization chamber measurements were used to get a second result and the combined result ($T_{1/2}$ = 9.9179(30) d) is in very good agreement with a recent determination from Pommé et al. (2012) who made long-term counting experiments using silicon alpha detectors with different geometries, two inorganic scintillation detectors, a proportional counter, and a high-purity germanium detector and obtained a combined result $T_{1/2}$ = 9.920(3) d.

A TDCR system was also used to determine the half-life of ^{223}Ra which was found to be 11.4362(50) d (Kossert et al., 2015). Again, the result is in good agreement with results obtained from other groups that used ionization chamber measurements (Collins et al., 2015) or ionization chamber measurements plus measurements with a Na(Tl) well type detector (Bergeron and Fitzgerald, 2015). Prior to these new determinations, the adopted half-life, from the DDEP, was 11.43(3) d (Bé et al., 2011). In 2021, a new evaluation included the recent measurements, giving a much more precise value of 11.4366(28) d (Singh et al. 2021).

When standardizing ^{227}Th, Kossert and Nähle (2019) combined results from a CNET counter and from an ionization chamber to obtain the half-life which was found to be 18.681(9) d – still in agreement with the outcome from Collins et al. (2015c) who obtained $T_{1/2}$ =18.695(4) d as a combined result from ionization chamber measurements and γ-ray spectrometry. It should be noted that the $T_{1/2}$(^{227}Th) obtained from long-term measurements using LS counting or ionization chamber measurements has a linear relationship with the ^{223}Ra half-life adopted for the analysis, whereas the half-life determination by means of repeat spectrometry of ^{227}Th γ rays can be realized without *a priori* knowledge of $T_{1/2}$(^{223}Ra). Knowing that this was the case, Collins et al. (2015c) provided a novel means to correct the half-life determined via the ionization chamber where a different half-life of ^{223}Ra was available.

Half-life measurements become more challenging when aiming at determinations of short-lived progeny. A direct measurement may require chemical separations with the risk of limited separation yields. An elegant preparation of a ^{211}Pb LS source was presented by Kossert (2015) who collected the ^{219}Rn emanation of a ^{223}Ra source in a mineral-oil based LS cocktail and also in water. In this way it became possible to prepare LS samples as well as Cherenkov samples which were then measured in a TDCR counter. With this technique it was possible to determine the ^{211}Pb half-life ($T_{1/2}$ = 36.165(37) min) with high accuracy. Interestingly, the liquid scintillation samples were found to be stable when using polyethylene vials but unstable when using glass vials.

The experiment using a Rn LS trap was modified by Kossert (2017). When using ^{228}Th sources it was possible to collect ^{220}Rn and, as a result, to obtain ^{212}Pb LS samples with high purity. Such samples were measured in a TDCR counter and the half-life was determined to be 10.622(7) h.

Aitken-Smith and Collins (2016) nicely demonstrated an alternative approach to the preparation of pure ^{211}Pb sources for half-life measurements. They started with a dried ^{223}Ra source and collected alpha recoils from the ^{219}Rn emanations to prepare a series of pure solid ^{211}Pb sources. The sources were measured in a 2π proportional counter operated in alpha mode to reduce backgrounds to < 0.1 s^{-1}. This low background afforded an extended measurement campaign with 12 measurements spanning more than 10 half-lives. Following the decay of ^{211}Bi and ^{211}Po over that time, the ^{211}Pb half-life was found to be $T_{1/2}$ = 36.161(17) min, in agreement with Kossert (2015) and with improved precision.

Takács and Kossert (2021) used a similar approach with ^{225}Ac to collect alpha recoil atoms on an acrylic glass backing. The backing had the geometry of a half-cylinder and after combining it with the second half it has the outer dimension of a standard LS vial. This cylinder was then measured in a TDCR counter as a Cherenkov source to determine the half-lives of ^{213}Bi and ^{209}Pb. In addition, polyethylene films were used as a backing for the collection of recoil atoms. These films were then measured in a well-type NaI detector to detect γ rays. The subsequent analysis of the data yielded an independent result for the half-life of ^{213}Bi. When combining the results of both measurement techniques, Takács and Kossert (2021) determined a ^{213}Bi half-life of 45.60(9) min and a ^{209}Pb half-life of 195.1(26) min. The results agree with those of Marouli et al. (2013) and

Suliman et al. (2013), who used ion-implanted planar silicon (PIPS) detectors. It seems possible that the experiment from Takács and Kossert (2021) could be improved when using a plastic scintillator rather than acrylic glass as backing; but even the first experiment already shows the high potential of LS and Cherenkov counting techniques for the determination of half-lives.

The determination of very short half-lives is also possible when combining an LS-γ counter with a full digital data acquisition (Dutsov et al., 2021; Takács and Kossert, 2021). In this case, the pulse-heights in the LS channels and in the γ-ray detector are recorded with time stamps and an off-line analysis can then be used to obtain time-difference spectra.

Kossert et al. (2020) measured ^{229}Th and ^{225}Ac LS source with such a system that was equipped with a $CeBr_3$ solid scintillator as external γ-ray detector. Detected ^{213}Po γ-rays at about 440 keV in the γ channel in coincidence with the preceding beta decay were defined as the start signal and the detection of the subsequent (delayed) ^{213}Po alpha decays in the LS detector were defined as the stop signal. In this way, the half-life of the short-lived ^{213}Po was determined to be 3.709(12) μs which is in agreement with the result of Suliman et al. (2013) who combined a PIPS alpha detector with a digitizer data acquisition system.

4.2. Gamma-ray emission intensities

As discussed in Section 3.3, there have been a number of publications since 2015 that have identified a large spread in the activities determined by HPGe using the absolute γ-ray emission intensities for ^{223}Ra and its progeny. Through the use of primary standardized sources of ^{223}Ra (or ^{227}Ac in the case of Marouli et al. (2019)) and well-characterized HPGe γ-ray spectrometers, the determination of new absolute γ-ray emission intensities was possible. The main γ rays and the deviation from the evaluated intensities from the DDEP are listed in Table 2.

In Table 2 the main γ-ray emissions of the ^{223}Ra and progeny are shown with the relative deviations (I_{ref}/I_{DDEP}) of the published absolute intensity values since 2015 against those of the DDEP evaluation. It is clear that those of Pibida et al. (2015), Collins et al. (2015a), and Kossert et al. (2015b) are consistent in the direction and magnitude of their deviations; however the more recent determinations by Marouli et al. (2019) and Simões et al. (2021) differ by some margin and in some cases much more closely align with the DDEP values. The reduced χ^2 of these new determinations (Table 2) show significant discrepancies between them, predominantly as a result of the Simões et al. (2021) values. It is interesting to note that while Pibida et al. (2015), Collins et al. (2015a), and Kossert et al. (2015) agree, Marouli et al. (2019) and Simões et al. (2021) do not.

However, when these same literature values are normalized to the 154.2 keV intensity and compared, as recommended in Collins et al. (2015a), a slightly different picture evolves. This method of analysis removes the effect of the primary standardization, allowing, to some degree, a direct comparison of the HPGe measurements. In Table 3, the normalized values of the five determinations are presented. This comparison shows the data to be generally more consistent,

with the remaining unresolved discrepancies resulting from the inclusion of the Simões et al. (2021) values.

The recent evaluation of the emission intensities from the decay of ^{223}Ra by Singh et al. (2021), which incorporated these new determinations, has resulted in γ-ray emission intensities that are significantly changed from those of the DDEP evaluation (Bé et al., 2011) and with precision improved by factor of between two to five (Table 4). This improvement would have been difficult to achieve without the availability of standardized sources and the high levels of precision in the HPGe γ-ray spectrometry calibrations achieved at NMIs.

As discussed in Section 3.3, absolute γ-ray emission intensities can provide a means of comparison of primary standardizations between NMIs. Based on the data in Tables 2 and 3, we can assert that the NIST, NPL and PTB activity standards for ^{223}Ra are in agreement. This assertion was recently confirmed for the NPL and PTB standards via the SIR (Michotte et al., 2021). Interestingly, while the normalized intensities of Marouli et al. (2019) are consistent with NIST, NPL, and PTB (see Table 3), the consistently higher absolute intensities (see Table 2) may indicate that the primary standardization of the ^{227}Ac is not in agreement. The same could be said for Simões et al. (2021), though there are discrepancies in the relative intensities that makes the picture less clear. In another recent standardization at the Insitut de Radiophysique (Switzerland), they compared the activities determined by HPGe γ-ray spectrometry using the intensities determined by Kossert et al. (2015b) and Collins et al. (2015a) to their primary standardization through LS techniques. The ratio of activities determined by HPGe and LS, $A_{\mathrm{HPGe}}/A_{\mathrm{LS}} = 1.029(6)$ (where the stated uncertainty is from the HPGe activity only), indicates a discrepancy.

5. Summary and outlook

To support the needs of medical researchers, pharmaceutical enterprises, and clinicians, national metrology institutes (NMIs) have developed activity standards for alpha-emitting nuclides including ^{223}Ra, ^{224}Ra, ^{225}Ac, and ^{227}Th. The primary methods used to develop these standards are based on liquid scintillation (LS) counting, which affords very high efficiencies. Confirmatory measurements are often achieved with 4πγ methods, including ionization chambers and well-type NaI(Tl) detectors. All of these measurements require γ-ray spectrometry for impurity assays and traceably calibrated detectors can additionally provide confirmatory activity measurements (based on evaluated γ-ray emission intensities).

The medically important alpha emitters we have discussed belong to complex decay chains. In most cases, activity measurements can be made after the nuclide of interest has reached equilibrium with its progeny. Cases like ^{227}Th, where activity measurements must be made during the period of progeny ingrowth, require careful time-dependent corrections to efficiency calculations, making precise assays challenging. Additional measurement challenges common to decay chain nuclides include detecting and correcting for imperfect radiochemical separations (including parent breakthrough) and accounting for very short-lived progeny that may decay during the deadtime triggered by the preceding decay.

Activity standardizations routinely yield improved nuclear decay data. Improved γ-ray emission intensities directly impact spectrometry-based activity calibrations in research and clinical settings and theoretical calibration factors for 4πγ detectors including radionuclide calibrators. Revised and precise half-lives not only impact everyday decay corrections, but enable improved calculations of equilibrium activity ratios for decay chain nuclides.

In recent years, metrologists have overcome challenges and developed new approaches to standardize a small set of alpha-emitting radionuclides. Research advances in targeted alpha therapy are fueling interest in and availability of an expanding list of candidate radionuclides. For the most part, the decay chains are familiar and so the nuclide-specific detection efficiencies have been considered and must only be combined to describe new equilibria. We expect to improve agreement between LS-based and photon-based activity assays as the decay data (especially γ-ray emission intensities) continue to improve. Additional measurement challenges will arise with nuclides requiring timely separations and having time-dependent instrument responses. Drug products taking new and exotic physical and chemical forms will complicate the broad dissemination of activity standards. As these challenges are met by meticulous application of and continued innovation on the techniques of radionuclide metrology, precise activity measurements will help to make good on the promises of targeted alpha therapy. Delivering reliable and accurate administrations of radiopharmaceuticals assures maximum damage to targeted cells, sparing healthy tissue and making life better for cancer patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1 Radionuclide calibrator factors recently reported for some medically important alpha emitters. All settings are for 5 mL of solution in a 5 mL flame sealed glass ampoule—see references for details. Uncertainties (with expansion factors, *k*, given) on the calibration settings are given in parentheses and the resulting relative uncertainty on the activity reading is given as U_A.

Radionuclide	Chamber	Setting	U_A / %	*k*	Reference
^{223}Ra	CRC-25R	231(3)	1.0	1	Keightley et al., 2015
^{223}Ra	CRC-12	231(5)	1.6	2	Bergeron et al., 2015
^{223}Ra	CRC-15R	233(2)	0.65	2	Bergeron et al., 2015
^{223}Ra	CRC-35R	234(4)	1.1	2	Bergeron et al., 2015
^{223}Ra	CRC-25PET	234(2)	0.75	2	Bergeron et al., 2015
^{223}Ra	AtomLab-100	18.6(3)	1.6	2	Bergeron et al., 2015
^{223}Ra	AtomLab-500	18.7(2)	0.87	2	Bergeron et al., 2015
^{223}Ra	CRC-15R	243(2)		1	Simões et al., 2021
^{223}Ra	CRC-25R	249(1)		1	Simões et al., 2021
^{223}Ra	CRC-25R	231(1)		1	Simões et al., 2021
^{223}Ra	CRC-25R	247(1)		1	Simões et al., 2021
^{224}Ra	CRC-15R	739(9)	1.1	2	Napoli et al., 2020b
^{224}Ra	CRC-35R	745(15)	1.4	2	Napoli et al., 2020b
^{224}Ra	CRC-55tR	736(8)	0.9	2	Napoli et al., 2020b
^{224}Ra	CRC-25PET	737(9)	0.8	2	Napoli et al., 2020b
^{224}Ra	CRC-55tPET	732(7)	0.7	2	Napoli et al., 2020b

Table 2 Relative deviation of the absolute gamma-ray emission intensities determined by Pibida et al. (2015), Collins et al. (2015a), Kossert et al. (2015b), Marouli et al. (2019) and Simões et al. (2021) to the evaluated intensities by the DDEP for the main gamma rays of ^{223}Ra and progeny. The reduced χ^2 for these new determinations is also shown.

Energy /keV	Radionuclide	DDEP (Bé at al., 2011) /I_γ	Pibida et al. (2015)	Collins et al. (2015a)	Kossert et al. (2015b)	Marouli et al. (2019)	Simões et al. (2021)	$\chi^2/(\nu-1)$
			(I_{ref}/I_{DDEP}) /%					
122.3	^{223}Ra	1.238(19)	5.0	6.0	5.3	12.3	-1.0	2.1
144.3	^{223}Ra	3.36(8)	4.5	3.6	3.2	10.4	-1.2	2.7
154.2	^{223}Ra	5.84(13)	4.1	3.1	3.3	10.1	-0.2	2.5
269.5	^{223}Ra	14.23(32)	-7.0	-6.0	-7.5	-0.9	-1.5	5.9
271.2	^{219}Rn	11.07(22)	-3.4	-2.9	-1.8	2.1	-4.0	1.1
323.9	^{223}Ra	4.06(8)	-10.6	-10.0	-9.8	-5.2	-6.2	2.4
338.3	^{223}Ra	2.85(6)	-9.1	-8.6	-8.3	-3.2	0.0	6.6
351.0	^{211}Bi	13.00(19)	0.9	1.3	1.9	6.9	3.62	1.2
401.8	^{219}Rn	6.75(22)	-2.8	-2.7	-1.9	3.4	-2.1	0.9
404.8	^{211}Pb	3.83(6)	4.7	4.7	5.7	9.7	10.2	0.9
427.2	^{211}Pb	1.81(4)	4.4	4.4	5.6	8.3	0.0	1.8
445.0	^{223}Ra	1.28(4)	-4.9	-4.8	-4.5	0.0	0.8	0.6
832.0	^{211}Pb	3.5(5)	-0.6	-1.5	-2.0	6.3	0.6	1.8

Table 3 Gamma-ray emission intensities normalized to the 154.2 keV gamma ray from ^{223}Ra for Pibida et al. (2015), Collins et al. (2015a), Kossert et al. (2015b), Marouli et al. (2019), and Simões et al. (2021). The reduced χ^2 for the dataset for each gamma ray is given.

Energy /keV	Radionuclide	Pibida et al. (2015)	Collins et al. (2015)	Kossert et al. (2015)	Marouli et al. (2019)	Simões et al. (2021)	$\chi^2/(\nu\text{-}1)$
		($I_\gamma/I_{\gamma,154\ keV}$) /100 decays					
122.3	^{223}Ra	21.38(27)	21.79(15)	21.63(27)	21.6(12)	21.03(68)	0.7
144.3	^{223}Ra	57.73(75)	57.82(39)	57.53(58)	57.7(31)	56.95(13)	0.1
269.5	^{223}Ra	217.8(29)	222.1(16)	218.2(31)	219(11)	240.5(42)	5.8
271.2	^{219}Rn	175.8(24)	178.6(13)	180.3(25)	175.7(88)	182.3(32)	0.8
323.9	^{223}Ra	59.70(67)	60.71(43)	60.71(61)	59.9(34)	65.4(14)	3.5
338.3	^{223}Ra	42.60(53)	43.27(31)	43.35(42)	42.9(22)	48.9(11)	7.0
351.0	^{211}Bi	215.6(26)	218.8(16)	219.6(21)	216(11)	231.1(51)	1.9
401.8	^{219}Rn	107.9(13)	109.14(74)	109.8(11)	108.6(56)	113.4(29)	0.9
404.8	^{211}Pb	65.95(82)	66.63(46)	67.2(10)	65.3(33)	72.4(29)	1.3
427.2	^{211}Pb	31.09(35)	31.40(22)	31.71(31)	30.5(15)	31.05(96)	0.6
445.0	^{223}Ra	20.02(24)	20.23(14)	20.27(20)	19.9(11)	22.1(14)	0.7
832.0	^{211}Pb	57.24(75)	57.28(39)	56.88(55)	57.9(30)	60.4(15)	1.3

Table 4 Comparison of the evaluated absolute gamma-ray emission intensities for ^{223}Ra from the DDEP in 2011 and ENSDF in 2021 after inclusion of the new determinations.

Energy	DDEP (Bé et al., 2011)	ENSDF (Singh et al., 2021)	I_{DDEP}/I_{ENSDF}	Precision improvement factor ($u(I_{DDEP})/u(I_{ENSDF})$)
/keV	I_γ /per 100 decay	I_γ /per 100 decay	/%	
122.3	1.238(19)	1.3045(93)	5.4	2.1
144.3	3.36(8)	3.474(25)	3.4	3.2
154.2	5.84(13)	6.020(57)	3.1	2.3
269.5	14.23(32)	13.304(94)	-6.5	3.4
323.9	4.06(8)	3.642(26)	-10.3	3.1
338.3	2.85(6)	2.601(18)	-8.7	3.3
445.0	1.28(4)	1.2184(86)	-4.8	4.7

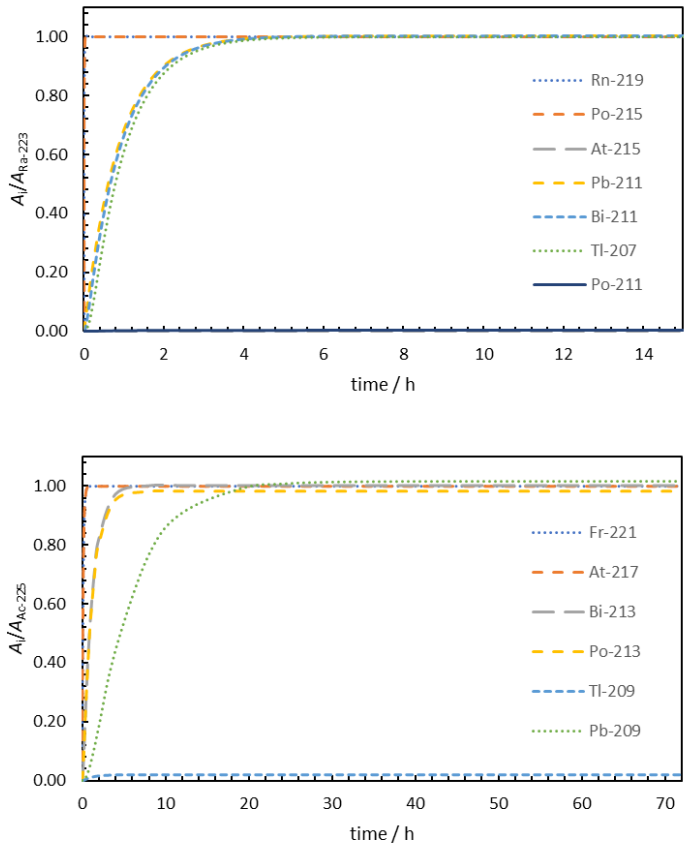

Figure 1. Solving the Bateman equations illustrates that equilibrium is achieved more rapidly for ^{223}Ra (longest-lived progeny is ^{211}Pb, $T_{1/2}$ = 36.1(2) min) than for ^{225}Ac (longest-lived progeny is ^{209}Pb, $T_{1/2}$ = 3.277(15) h). Activities for the progeny are shown relative to the parent activity at the same time.

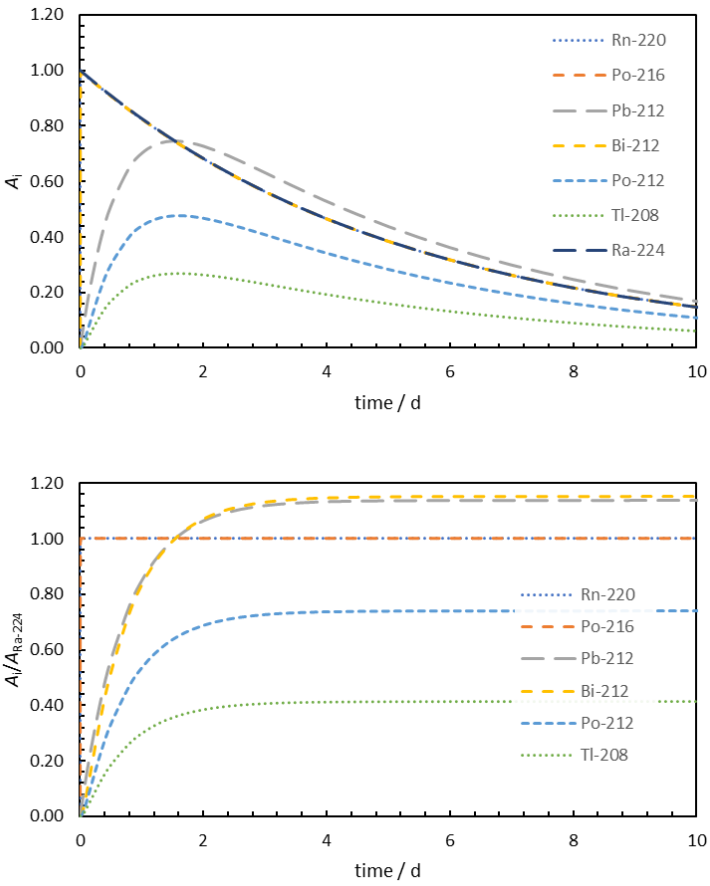

Figure 2. Solving the Bateman equations illustrates that the relatively long-lived ^{224}Ra progeny, ^{212}Pb ($T_{1/2}$ = 10.64(1) h), leads to a long equilibration period. In the top panel, activities are given relative to the initial ^{224}Ra activity, showing that, by the time equilibrium is reached, the ^{224}Ra activity is less than 22 % of its initial value. In the bottom panel, activities for the progeny are shown relative to the ^{224}Ra activity at the same time, as in Figure 1.

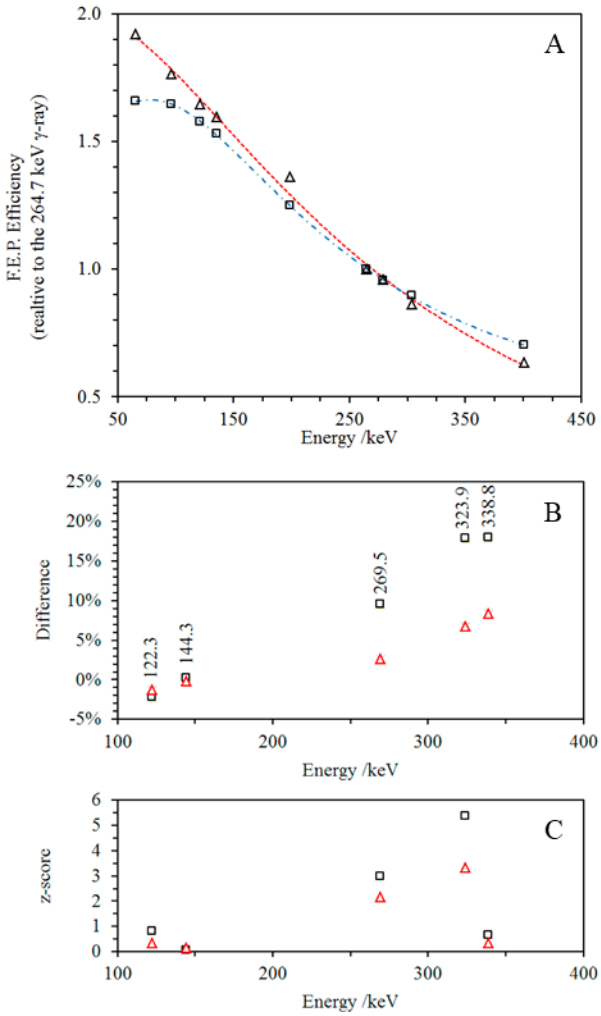

Figure 3. In (A), the comparison of the full-energy peak detection efficiency curves determined using the relative γ-ray emission intensities of ^{75}Se quoted in Krien et al. (1970) (hollow triangles) and the evaluation by Negret and Singh (2013) (hollow squares) is shown. In (B) and (C), the improvement in the consistency of ^{223}Ra γ-ray emission intensities derived from these efficiency curves is illustrated. The difference and z-score of the emission probabilities (normalized to the 154.2 keV γ-ray) of Krien et al. (1970) and this work before (hollow squares) and after (hollow triangles) adjustment for the ^{75}Se nuclear data. These figures have been reproduced from Collins et al. (2015).

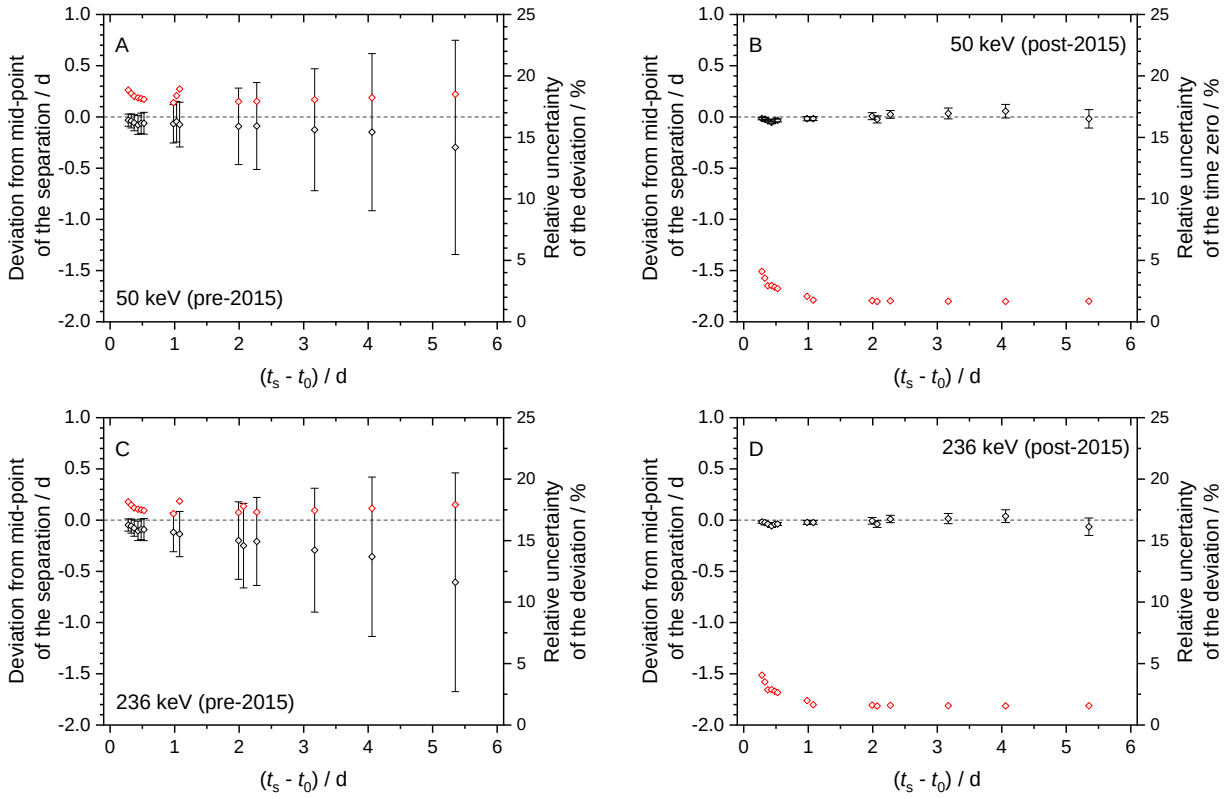

Figure 4. The deviation (hollow black diamonds) from the mid-point of the chemical separation of the ^{227}Th from its progeny is shown for a series of measurements over six days as determined by the measured T_0 using the activity ratio from the 50 keV and 236 keV of ^{227}Th to the 154.2 keV of ^{223}Ra. The relative standard uncertainty is shown on the right axis (hollow red diamonds). (A) and (C) show these deviations using the evaluated γ-ray emission intensities for the 50 keV and 236 keV published in Browne (2001). (B) and (D) show these deviations using the intensities of the 50 keV and 236 keV determined in Collins et al. (2019b) and the evaluated γ-ray emission intensity for the 154.2 keV emission in Singh et al. (2021).