Applied Radiation and Isotopes 224 (2025) 111827

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

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

Letter to the Editor

Needs for radionuclide metrology in the use of alpha-emitters for radionuclide-based therapy: Summary of an International Workshop

Brian E. Zimmerman [a,*], Ana M. Denis-Bacelar [b], Jan Rušnák [c]

[a] Radiation Physics Division, National Institute of Standards and Technology, Gaithersburg, MD, 20899, USA
[b] National Physical Laboratory, Hampton Road, Teddington, UK
[c] Czech Metrology Institute, Okružní 31, 638 00, Brno, Czech Republic

A B S T R A C T

An International Workshop on Standards and Measurements for Alpha-Emitting Radionuclides in Therapeutic Nuclear Medicine was held on 22–23 February 2024 at the Bureau International des Poids et Mesures (BIPM) and online. The workshop brought together members of the medical and metrology communities who play crucial roles in developing Targeted Alpha Therapy (TAT) radiopharmaceuticals. The workshop aimed to discuss ways to improve radioactivity measurements of alpha-emitting radionuclides for TAT. Through the presentations and discussions that took place over the two days of the workshop, information was exchanged, and recommendations for improvements that could lead to improved safety and effectiveness in TAT were proposed. This paper summarizes the topics and important ideas that were discussed at the workshop and presents recommendations for all the communities involved in the development of TAT radiopharmaceuticals to consider.

1. Introduction

The use of alpha-emitting radionuclides in targeted therapy is an active area of research in radiation oncology and is demonstrating great promise as an effective treatment regime for many clinical indications (Miederer et al., 2024). The high linear energy transfer properties of alpha particles as they pass through matter allow for large amounts of energy to be deposited in a smaller volume (i.e., several cell diameters) compared to beta particles (up to a few mm). When combined with a chemical label (targeting molecule) that can precisely deliver the radionuclide to the tumor, they present a highly localized absorbed dose that minimizes damage to surrounding tissue.

With the increased therapeutic potential of alpha-emitting radionuclides, there is an urgent need for improvements in treatment planning. This requires, at a minimum, accurate measurement of the administered activity, reproducible and accurate image-based activity quantitation, and realistic dosimetry models (Stokke et al., 2024). Improvements in radioactivity measurement for alpha-emitting radiopharmaceuticals during preclinical development are crucial to the successful implementation of new treatment candidates before clinical acceptance.

Recognizing the importance of radioactivity measurement, quantitative imaging and dosimetry to this burgeoning field, the Consultative Committee on Ionizing Radiation (CCRI) of the International Bureau of Weights and Measures (BIPM), through its Radionuclide Therapy and Quantitative Imaging (RTQI) Working Group and the EURAMET AlphaMet Project, organized a two-day workshop at the BIPM's headquarters in Sèvres, France on 22–23 February 2024 to bring together members of the metrology, clinical, and industrial communities to discuss measurement issues related to the development and clinical applications of targeted alpha therapy (TAT). This paper aims to summarize the workshop's main discussion topics and discuss the radioactivity measurement needs identified by the attendees.

2. Organization of the workshop

The workshop was hosted at the Pavillon du Mail at the BIPM headquarters in Sèvres by the CCRI, of which the RTQI Working Group is a part. Because of the topic's recognized importance and interest in the larger ionizing radiation community, it was decided to conduct the workshop as a hybrid event, combining it with the CCRI's regular webinar series, with the requirement that all the speakers attend in person. There were 60 in-person attendees and over 230 online participants, making it one of the most widely attended CCRI workshops.

The workshop agenda, a summary of which is included in Appendix A, consisted of 21 speakers representing the following general topic areas: clinical applications, radiopharmaceutical development from the industrial perspective, clinical medical physics, radionuclide production, radiopharmacy practice, radiation safety, infrastructure for

* Corresponding author.
E-mail address: bez@nist.gov (B.E. Zimmerman).

https://doi.org/10.1016/j.apradiso.2025.111827
Received 7 April 2025; Accepted 9 April 2025
Available online 10 April 2025

international metrology, primary standards for radioactivity, nuclear data, dissemination of standards, preclinical dosimetry and imaging, and international efforts involving TAT. Sufficient time was allotted during the workshop for questions from and discussions with the in-person participants and those submitting questions online. The final session of the workshop was dedicated to discussions leading to the development of statements of needs that the radionuclide metrology community could potentially address.

The presentations and recorded videos of the talks have been posted to the conference website and are freely available at https://www.bipm.org/en/committees/cc/ccri/wg/ccri-rtwg/2024-02-22.

3. Summary of key presentation topics

The following sections present some of the key points raised during the talks and discussions. They are not meant to be exhaustive but are provided here to document those topics and critical points that the audience and the organizers felt were important to highlight. In some cases, additional information from the literature (with references) is provided to supplement what was presented during the workshop. In other cases, the reader is referred to specific presentations given at the workshop.

3.1. Current status of clinical TAT and radiopharmaceutical development

Many thorough reviews on the status of clinical practice with a view toward near-term future developments have been presented in the literature (e.g., (Miederer et al., 2024; Jang et al., 2023; Poty et al., 2018). Although research into the use of alpha-emitters has been conducted for a long time (indeed, medical uses for radium were being investigated shortly after its discovery by Marie and Pierre Curie in 1898), there has been a nearly exponential increase in the number of publications appearing since 2010, with the expectation of about 1200 articles published around the time of the workshop (see presentation given at the Workshop by M. Vorster).

To date, the only alpha-emitting radiopharmaceutical that has received widespread approval by regulatory authorities in both Europe and North America is one based on ^{223}Ra. Regarding additional alpha-particle emitting radiopharmaceuticals, there were about 20 commercially sponsored clinical trials being conducted or actively recruited, with an additional 8 being investigator-initiated by mid-2023 (Jang et al., 2023). At the current time, the primary diseases being targeted in those trials discussed during both the workshop and in Jang et al. (Jang et al., 2023) were metastatic prostate cancer and certain neuroendocrine tumors. The main radionuclides under investigation in these trials are ^{225}Ac, ^{227}Th, ^{212}Pb, and ^{211}At. Other radionuclides under consideration are ^{149}Tb, ^{224}Ra, ^{212}Bi, and ^{213}Bi, but these have not received as much attention due to factors such as availability.

The presentations offered by the industrial partners provided insights into what diseases are being targeted, which radionuclides are being incorporated into their products, and what different approaches to preclinical and clinical studies are being applied. These talks provided more detailed information about radiopharmaceuticals and trials aimed at treating prostate (^{212}Pb, ^{223}Ra, ^{225}Ac) or breast (^{212}Pb) cancer, melanoma (^{212}Pb), neuroendocrine tumors (^{212}Pb and ^{225}Ac), and intraperitoneal metastatic disease and ovarian cancer (^{211}At, ^{224}Ra). Although these presentations represented only a fraction of the number of companies working on TAT radiopharmaceuticals around the world, they demonstrate consistency with the same trends that were presented in the clinical overviews during the workshop.

While it would be highlighted several times by the clinical practitioners during the workshop, the need for accurate and reproducible image-based biodistribution data at both the preclinical and clinical levels was also expressed by several of the industrial partners. In some cases, the therapeutic radionuclides under consideration emit gamma rays with sufficient intensity and in the appropriate energy range that can provide the necessary image-derived biodistribution data to enable patient-specific dosimetry calculations to be performed. Most of these cases use Single Photon Emission Computed Tomography (SPECT) and include ^{211}At, ^{212}Pb/^{212}Bi, ^{223}Ra, ^{224}Ra, ^{225}Ac, and ^{227}Th. One of the radionuclides that has been getting more attention recently is ^{149}Tb, which is one of the few alpha emitters that also decay by positron emission, making it potentially suitable for imaging using Positron Emission Tomography (PET).

Using a therapeutic radionuclide to perform imaging studies for dosimetry sometimes provides inferior data because of a combination of low gamma-ray (or positron) emission intensity and/or low administered activity. A potential solution lies in the further development of "theranostic pairs" of radionuclides, that is, pairs of radionuclides that are chemically similar but in which one of the members has decay properties that make it appropriate for imaging and the other has decay properties that make it suitable for therapy (i.e., decaying by β or α particles or Auger electrons). Examples of these that were discussed during the workshop are ^{131}Ba/(^{223}Ra or ^{224}Ra), ^{203}Pb/^{210}Pb, (^{131}I, ^{123}I, ^{131}I, or ^{209}At)/^{211}At, (^{134}Ce or ^{134}La)/^{227}Th, and (^{152}Gd or ^{155}Gd)/^{149}Tb. In this approach, the same labeling procedures are applied to the imaging surrogate as to the therapeutic radionuclide and is expected, therefore, to provide the same biodistribution for both radionuclides. However, the decay characteristics of the imaging surrogate, particularly the shorter half-life and the lack of high energy electrons or alpha particles, enable a higher administered activity prior to therapy, thereby providing better quantification of the temporal and spatial distribution.

The topic of radionuclide production and availability was addressed in two presentations discussing the topic from the perspectives of a collaboration of European institutions and the United States government. In the United States, the US Department of Energy (DoE) leverages accelerators, reactors, and other facilities located at universities and National Laboratories to provide infrastructure for the development and production of radionuclides needed by multiple communities, including in medicine. Priority radionuclides are set in consultation with stakeholders. For TAT, alpha emitters have been a high priority for DoE for at least 10 years and consist of ^{225}Ac, ^{211}At, ^{212,213}Bi, ^{212}Pb/^{212}Bi, ^{223}Ra, and ^{226,227,228}Th, with ^{225}Ac, ^{211}At, and ^{212}Pb/^{212}Bi being the most prevalent in terms of demand.

In Europe, the PRISMAP Horizon Europe collaboration leverages the facilities and experience of more than 30 research groups in 12 countries to develop and supply less prevalent radionuclides with both diagnostic and therapeutic applications. This includes multiple isotopes of Sc, Tb, and Er, along with other, mostly accelerator- or spallation-produced, radionuclides. For TAT, efforts are focused on supplies of ^{225}Ac, ^{211}At, and ^{212}Pb (via its ^{224}Ra parent). Of note is the work on the development of ^{149}Tb, the first alpha emitter being investigated that also decays by positron decay.

3.2. Dosimetry and the role of medical physics in TAT

The safe use of any radiation-based technique for medical application requires accurate dosimetry personalized to the patient's individual health status. Such requirements are set forth in international and national guidance (e.g. (European Council, 2014; International Atomic Energy Agency (IAEA), 2018; International Atomic Energy Agency (IAEA), 2014),), but dosimetry for radionuclide therapy, especially in TAT, is not yet routine clinical practice despite being a regulatory requirement for nuclear medicine following the EURATOM directive (European Council, 2014). One of the barriers to implementing image-based dosimetry for TAT lies in the difficulty in obtaining high-quality biokinetic imaging due to the aforementioned low gamma-ray emission probabilities and the relatively low amounts of activity administered. This results in the need for long imaging times, which is both difficult for the patient and expensive for the clinic. This could, in part, be ameliorated by the development of diagnostic surrogates or theranostic pairs of radionuclides, as discussed above, but care

must be taken to ensure that the biokinetic behavior of the diagnostic agent accurately mimics that of the therapeutic agent.

An important consideration in the collection of biokinetic data required for dosimetry assessments is to ensure that all the instruments used to produce those data are cross-calibrated. This includes making sure that the radionuclide calibrators, imaging (PET, SPECT) scanners, and gamma well counters used as input to the dosimetry models are all calibrated against each other. The ideal way to ensure this is to make sure that each calibration is linked to a standard (Gadd et al., 2006; International Atomic Energy Agency (IAEA), 2006).

One area that has seen recent advances in the development of technology is microimaging, which has been shown to be potentially useful in dosimetry, especially for alpha emitters (see presentation by B. Miller). This includes small-scale animal imaging as well as high-resolution autoradiography. The ability to visualize the activity distribution for radiopharmaceuticals, on the organ scale for small animals and on the tumor scale for both animals and humans, can give significant insight into the heterogeneity of uptake and absorbed dose distribution and can lead to better predictions of efficacy. There is also the suggestion that, because of the short range of alpha-emitters, accurate dosimetry requires pharmacokinetic data at the cellular level, which puts even more demands on current imaging technologies. Further refinements to dosimetry models may be possible through improvements in the quantitative capabilities of these techniques.

The presentations and discussions surrounding the use of dosimetry models generally concluded that image-based dosimetry treatment planning, especially for alpha-emitting radiopharmaceuticals, is an important part of patient care, and there is little justification for not implementing it. It is recognized that improving the useability and harmonization of protocols would go a long way toward greater acceptance in clinical practice, which could lead to improved patient outcomes.

3.3. Specific measurement problems in clinical practice

As requested by the organizers, the presentations throughout the workshop attempted to highlight measurement problems that were seen as barriers to the development and clinical use of alpha-emitting radiopharmaceuticals. One general issue that was noted at several points in the workshop is the lack of harmonized approaches to assessing and documenting measurement uncertainty. These practices are well-established in the metrology community but have yet to take hold in the clinic. Presently, only the Guide for Measurement Uncertainty (GUM) and a European Association of Nuclear Medicine (EANM) guidance document on uncertainties for molecular radiotherapy dosimetry are available, but none of the commercial software options for quantitative imaging and dosimetry include uncertainty calculations (Gear et al., 2018; Joint Committee for Guides in Metrology (JCGM), 2008). As with the usual justifications for not performing dosimetry (too difficult, lack of guidance, unclear or undefined need), this can likely be remedied through education and the development of easily implemented tools.

Aside from the well-documented needs for instrument calibration, particularly radionuclide calibrators, several less-obvious measurement issues were presented that could benefit from collaboration with the metrology community. These included the ability to quantify the progeny in decay chains *in vivo* to monitor changes in the pharmacokinetics as the parent radionuclide decays (see presentation by A. Delker). For example, it is known that renal toxicity is an important consideration from the accumulation of ^{225}Ac decay progeny, particularly ^{213}Bi, and that such toxicity could limit the amount of ^{225}Ac that can be administered (Schwartz et al., 2011). The ability to separately measure these radionuclides may make it easier to better quantify the absorbed dose contributions from non-specific accumulation of progeny radionuclides in the target tissue.

In radiopharmacy, the need for improved measurements related to QA/QC and the release for administration of radiopharmaceuticals was identified. This includes the need for improved quantification of low levels of unbound radionuclides measured by high-performance liquid chromatography (HPLC) analysis, which may be made more difficult in cases in which the decay progeny (or even the parent) lack gamma-ray emissions in sufficiently high abundance to be measurable. This, in turn, suggests the need for improved methods to quantify low levels of radionuclides to be able to properly define the Limit of Detection or the Limit of Quantitation. Guidelines published by the EANM call for validation of methods used for analyzing and characterizing radiopharmaceuticals before they are incorporated into routine practice (Gillings et al., 2020). This includes validating the accuracy and precision of the radioactivity content, radionuclide identity, radionuclidic purity, and radiochemical purity (see presentation by J. Kleynhans). While some tests may possibly be performed using analogs, those processes that require quantification of radioactivity should be validated using a standard of the radionuclide(s) being measured (Hooijman et al., 2024). This, of course, requires that the appropriate radioactivity standards of the radionuclides of interest are available.

These same measurements have an influence on determining the shelf-life of radiopharmaceuticals. This requires the ability to monitor the stability of radiopharmaceuticals over time and this is best done in a way as to be monitored against a reference that will ensure the stability of the measurement system so that any changes that are observed are due solely to the effects of stability of the radiopharmaceutical.

Related to this problem is the ability to quantify the amount of radioactivity in hospital waste to determine if it is within release limits and to ensure regulatory compliance with possession quantities limits. This is not only a regulatory problem but also arises in questions of worker safety, where validation for bioassay methods is also needed (see presentation by A. Sarnelli).

All these measurement issues point to the need for radioactivity standards for those radionuclides of interest in the clinic and suggest the need to quantify possible impurities. Standards of radionuclides at different activity levels and in different geometries are also desirable to assist in the necessary validation measurements.

3.4. Status and future needs in radionuclide metrology for TAT

An entire session dedicated to radionuclide metrology discussed topics related to the development of measurement standards (including needs for evaluated nuclear data), the international metrology infrastructure, the mechanisms used by national metrology institutes (NMIs)[1] to demonstrate the equivalence of standards around the world (and why it matters), as well as the technical aspects of standards development and dissemination.

The status of the development of primary and secondary radioactivity standards for TAT was discussed in several presentations. Primary standards for many of the alpha-emitters discussed during the workshop have been developed at NMIs (Bergeron et al., 2022), and several of those have been transferred to the nuclear medicine community as secondary standards in the form of published baseline radionuclide calibrator settings, calibration services, or as calibrated artifact sources. Of the list of radionuclides discussed in Section 3.1 above, ^{149}Tb, ^{212,213}Bi, and ^{211}At remain uncalibrated or have been standardized by only a single NMI. Even among the radionuclides that have been standardized, very few international comparisons between the NMIs have taken place that provide assurance about the equivalence of those standards

[1] In addition to NMIs, there exist several other institutions, called Designated Institutes (DIs), that may not be a part of the country's national metrology institute, but that are legally designated by that country as serving the same function as an NMI. Such a case may exist, for example, if an institution other than the NMI historically has had the expertise and facilities to provide top-level measurement services in a country. In this paper, the term NMI is used throughout to encompass both NMIs and DIs.

(Judge et al., 2023). The AlphaMet project is addressing some of these challenges by organizing EURAMET comparison exercises for ^{225}Ac, ^{212}Pb, and ^{211}At, linked to the International Reference System (SIR) at the BIPM, amongst participating metrology laboratories (Ratel, 2007).

Nuclear and atomic data constitute critical input quantities in TAT for not only dosimetry calculations and model simulations using Monte Carlo techniques but also for multiple methods used in radionuclide metrology. In particular, evaluated half-lives, gamma-ray emission rates, and β^+, β^-, and α branching ratios are needed as they are the major contributors to both the absorbed dose when performing dosimetry calculations and to the measurement signal when performing precision measurements on a radionuclide. Several NMIs have incorporated the measurement of nuclear data into their normal practice when performing primary standardizations. This has resulted in newly published data for ^{212}Pb, ^{223,224}Ra, and ^{227}Th with additional data for ^{225}Ac expected soon (Kossert et al., 2015; Collins et al., 2015, 2019; Bergeron et al., 2021; Pibida et al., 2015, 2024; Marouli et al., 2019; Galea and Moore, 2024). These datasets are important because, in most cases, they constitute absolute (as opposed to relative) emission rate or branching ratio determinations that are based on precise measurements of the activity, leading to direct measurement of the number of emissions per decay. With the production of new data comes the need for new evaluations that lead to recommended values for those quantities. The world of nuclear data evaluation is small, with a limited number of trained evaluators, and it is difficult to keep up with the increased demand for evaluated data. Organizations such as the Decay Data Evaluation Project (Helmer, 1999) or the National Nuclear Data Center and IAEA Nuclear Data programs (Humbert et al., 2004) must balance the needs for updated evaluations for TAT radionuclides with the needs from other fields.

Another topic getting significant attention during the workshop was the dissemination of secondary standards, particularly the availability of geometry-specific standards, and the use of secondary standard calibration laboratories to provide services directly to the nuclear medicine community. It was observed that a small number of manufacturers currently distribute sources with traceable activity values associated with them as part of their initial setup of a clinical site, but details regarding the certification process are generally lacking, and information provided in the documentation accompanying the source is often incomplete in terms of how the activity value was determined, how the uncertainties were assessed, and how the traceability chain was established, often leading to confusion. In this context, a need was expressed for greater clarity in the data presented in the certificates of analysis issued by radionuclide producers, radiopharmacies, and radiopharmaceutical manufacturers. Particularly, more robust and defensible uncertainties need to be placed on an activity value when that value is being used in the treatment of a patient.

The use of gamma-ray spectrometry as a calibration technique was also discussed in several talks. At first glance, gamma-ray spectrometry with calibrated high-purity germanium (HPGe) detectors would seem to have some benefits over radionuclide calibrators such as being able to simultaneously quantify multiple radionuclides (e.g., radionuclidic impurities) in a single measurement, measure sources that are not in equilibrium, and providing flexibility in terms of being able to calibrate the system in different geometries to adjust for differences in activity level. However, to provide the types of measurements required to be considered a secondary standard, care must be taken to ensure consistency in the peak fitting methods (which also need to be validated) and that the necessary corrections for effects such as deadtime, changes in geometry, and background are taken into account. Just as with radionuclide calibrators, these systems require traceable standards to calibrate them for energy and efficiency. While it might be tempting to develop an efficiency curve using several sources covering a wide energy range and think that this will provide an easy path to traceability, in reality, the measurement is less straightforward. The determination of an efficiency curve does fit the definition of calibration (which, in turn, is used to define measurement traceability) when done in a specific geometry using calibrated sources, and the uncertainty is properly propagated. However, the measurement of a radionuclide other than those used to develop the calibration curve relies on a *non*-traceable quantity, namely the photon emission probability, to calculate the activity. Such a measurement cannot, therefore, be considered to be traceable. A traceable measurement can be made, however, if a calibration factor is determined for the specific radionuclide of interest, using a traceable source in a specified geometry, and the subsequent measurements are made in the same geometry for that radionuclide. In other words, using the HPGe detector in a manner similar to a radionuclide calibrator.

3.5. *International initiatives for enhancing TAT through good measurement practice*

There are currently several international efforts underway to address measurement issues associated with the dosimetry workflow used in TAT. Several European-based projects, such as MetroMRT and MRTDosimetry, have sought to improve the metrology infrastructure (including that for image-guided dosimetry) for radionuclide-based therapies. More recently, the EURAMET AlphaMet project is focused on addressing the measurement challenges in TAT by developing new activity measurement capabilities for ^{225}Ac, ^{212}Pb, and ^{211}At, providing guidance on image-based quantification of activity and absorbed doses for alpha-emitters and their associated uncertainties, as well as a multimodality imaging protocol to improve bone marrow dosimetry and the assessment of treatment toxicity. The European Cooperation in Science and Technology program on "Network for Astatine-labeled Radiopharmaceuticals" (COST-NOAR) is focused on developing the infrastructure to promote the adoption of ^{211}At-labeled therapeutics into clinical practice through enhancements in production, distribution, training, and guidance. Long-term goals for the project include expansion of the network beyond Europe to make it a global resource for ^{211}At-based applications.

Similar to the aforementioned PRISMAP project, the European project entitled "Strengthening the European Chain of Supply for Next Generation Medical Radionuclides" (SECURE) aims to contribute to the sustainability of radionuclide production in Europe and promote its safe application. The project focuses on targetry, production pathways, and expansion of clinical trials for a wide range of applications, including beyond those involving alpha-emitters.

Finally, there are efforts underway from the international metrology community to educate and provide support to end users to improve the safety and effectiveness of TAT applications. These include new guidance documents currently being produced by the CCRI's RTQI Working Group on the topics of standards and traceability (particularly with respect to secondary standards), as well as specific guidance on clinical measurements related to TAT that will use input provided by the workshop. Additionally, the International Electrotechnical Commission (IEC) and the International Standards Organization (ISO) are in the final stages of producing a new international standard governing the use of radionuclide calibrators. The International Atomic Energy Agency (IAEA) also has several projects aimed at providing training and specific guidance for radiopharmaceutical dosimetry, and quantitative imaging, as well as promoting the profession of nuclear medicine physicists around the world (e.g. (International Atomic Energy Agency (IAEA), 2024),).

4. Measurement needs for improving clinical use of targeted alpha therapy

The following section outlines some of the specific needs identified during the workshop that, if addressed with the assistance of the radionuclide metrology community, could greatly enhance the practice of TAT. The main points of the recommendations are given in italics,

while explanatory text is presented in roman font.

4.1. Needs for primary standards of clinically relevant alpha-emitting radionuclides

There is a strong need for primary standards to be developed by the NMIs for those alpha-emitting radionuclides for which radiopharmaceutical products are approved for use or for which approval for human use is expected in the very short term. These include ^{212}Pb/^{212}Bi (and its theranostic "twin" ^{203}Pb), ^{223,224}Ra, and ^{225}Ac.

There is a further need for standards for radionuclides that are in an earlier stage of development so that they can also benefit from the availability of tools that will help researchers calibrate their measurement systems and validate their analysis methods. The radionuclides in this list include ^{149}Tb, ^{211}At, and ^{227}Th. At the current time, the development of Tb and At-based radiopharmaceuticals is constrained by limited availability due to difficulty in producing and distributing them. However, both sets of radionuclides show promise as therapeutic agents (and, in the case of ^{149}Tb, as a theranostic agent), and the demand for standards should increase as these problems are resolved.

Concomitant with the need for primary standards for these radionuclides, interlaboratory comparisons amongst the NMIs that have developed standards will also be necessary to provide assurance to the medical and regulatory communities as to their validity and consistency. The NMIs should look for opportunities for small-scale or regional comparisons in cases where comparisons through the BIPM or CCRI are not possible or cannot be conducted within the timescale necessary to satisfy the medical community or regulators. When possible, methods of linking smaller comparisons together should be investigated. This includes conducting regional comparisons using traveling instruments built and operated in the different Regional Metrology Organizations that can be linked to the International Reference System maintained at the BIPM (Judge et al., 2023).

4.2. Needs for nuclear data measurements and evaluations

Nuclear data play an important role in both the clinical applications and radionuclide metrology aspects of TAT. Besides the obvious need for making decay corrections to the activity value, the physical half-life of the radionuclide (and decay progeny, if present) is also important in evaluating residence times in biodistribution studies. The energy released per decay is important for calculating absorbed dose to tissues and is influenced primarily by the branching ratios, decay probabilities, and energies of alpha and beta particles, as well as Auger and internal conversion electrons. Photons, such as x-rays and gamma rays, don't contribute significantly to the absorbed dose, but their emission probabilities and energies play an important role in the ability to do quantitative imaging that is important to a modern dosimetry calculation workflow.

The radionuclide metrology community is not only a potential producer of nuclear data but is also a large user community as well. As in other nuclear applications, the decay half-life of a radionuclide and its progeny are used to perform decay corrections but are also used in chain decays, such as for alpha-emitters being investigated for TAT, to calculate the equilibrium ratios of radionuclides in the chain. Emission probabilities and energies of the radiations emitted in the decay of a radionuclide are important input quantities for model calculations used to calculate detection efficiencies in many of the techniques that are used for primary standardizations, and particularly for liquid scintillation counting (Kossert and Grau Carles, 2010). In addition, recent studies have highlighted the need for improved knowledge of the beta spectrum shape for beta-emitters for liquid scintillation counting and calorimetry applications (Kossert and Mougeot, 2015; Kossert et al., 2018; Mougeot, 2016, 2017). Since the beta spectrum shape can also have an impact on the determination of the mean energy per decay, improvements in beta spectrum calculations can also improve dosimetry calculations for beta-emitters.

With an increasing number of measurements of nuclear data being produced for alpha-emitters for TAT comes a need for expert evaluations of those data from which recommendations for "best values" can be made. There are two main repositories for evaluated data that are used by the nuclear science community: the Decay Data Evaluation Project (DDEP, http://www.lnhb.fr/home/nuclear-data/nuclear-data-table/) and the Evaluated Nuclear Structure Data File (ENSDF, https://www.nndc.bnl.gov/ensdf/). Because of its emphasis on nuclear and atomic data that are specifically relevant for radioactivity measurements, the preferred source of recommended nuclear data for the radionuclide metrology community continues to be DDEP. This is the data source that has been adopted for use in comparisons organized through the CCRI and for activities conducted by the International Committee on Radionuclide Metrology (ICRM), although ENSDF data are used for radionuclides where a DDEP evaluation does not exist.

For the radionuclides discussed above, DDEP and ENSDF evaluations have been conducted and are available for:

^{203}Pb (DDEP:2006, ENSDF:2005).
^{212}Pb (DDEP:2011, new evaluation underway; ESNDF: 2020).
^{223}Ra (DDEP:2012, ENSDF:2021).
^{224}Ra (DDEP:2011, new evaluation underway; ENSDF: 2011).
^{225}Ac (DDEP:2009, half-life updated in 2023; ENSDF: 2007).
^{211}At (DDEP:2011, ENSDF: 2011 (alpha decay), 2013 (Electron Capture))
^{149}Tb (ENSDF:2009 (alpha decay), 2022 (Electron Capture).
^{227}Th (ENSDF:2001).

There is a clear need for updated DDEP evaluations for nearly all the radionuclides on this list, considering that many of the existing evaluations are more than 12 years old. The availability of new published data and timelines for potential regulatory approval of radiopharmaceuticals containing TAT radionuclides could be used to prioritize when evaluations should be performed.

4.3. Needs to ensure availability of TAT radionuclides

Several presentations referred to the limited or unreliable availability of some radionuclides as being a factor impacting the pace of the development of TAT radiopharmaceuticals. This is particularly true for ^{211}At, which requires a cyclotron for production and detailed logistics to ensure timely delivery of this short-lived (several hours) radionuclide. Other radionuclides, such as ^{225}Ac, are in short supply because of limited supplies of ^{229}Th, from which most of the world's supply is derived. Efforts are underway to explore other, accelerator-based, production methods, but issues with radionuclidic impurities have slowed their acceptance (International Atomic Energy Agency (IAEA), 2024; Radchenko et al., 2021).

There is a strong need for continued investment in radionuclide production research from non-governmental organizations as well as the governmental and private sectors. This includes not only identifying and allocating additional resources for capital equipment such as cyclotrons, hot cells, and radiochemistry laboratory equipment, but also investments in distribution infrastructure and human resources. In particular, investments in training the next generation of engineers and nuclear scientists should be considered critical for ensuring the sustainability of the field.

4.4. Needs related to Quality Assurance and quality control of alpha-emitter-based radiopharmaceuticals

Several of the industrial presentations highlighted the companies' Quality Management Systems and the various types of instrumentation used for quality control and product release. These include radionuclide calibrators, NaI-based gamma well counters, HPGe detectors, and ancillary equipment such as high-performance liquid chromatography (HPLC) systems. Quite appropriately, the focus on the need for

traceability was for the radioactivity measurements made with the radionuclide calibrator. However, as pointed out in Section 3.3, the measurement of quantities beyond total contained activity is coming under increased scrutiny, and there is a need for reference sources that are appropriate for cross-calibrating other types of instrumentation. This leads to the following recommendations:

- *Whenever possible, all instrumentation used to measure radioactivity should be calibrated to the same reference, which is preferably traceable to a national measurement standard.*
- *The radionuclide metrology and radiopharmacy communities should work together to clearly define measurement requirements to validate critical quantities for radiopharmaceutical release that pertain to radioactivity, but that go beyond total contained activity (*e.g.*, impurities, standards for radio-HPLC, etc.). They should further collaborate to develop methods and protocols to calibrate the appropriate instrumentation and perform the required measurements in a way that preserves traceability.* This collaboration would most likely lead to the development of new secondary standards that assist in implementing those procedures.
- *Clear direction is needed from regulatory agencies regarding expectations for validating and documenting traceability for radioactivity measurements in the clinic and radiopharmacy, particularly those related to chemical stability and purity (radionuclidic impurities, effects of radiolysis, limits of detection/quantitation for impurities, etc.).*

4.5. Needs for the availability of secondary standards

One of the barriers that is often cited for bypassing the need for traceability or for not enforcing regulations requiring traceability is the perceived lack of availability of standards that are widely available, relatively inexpensive, or fit-for-purpose. For most NMIs, limited resources and a narrow mission to develop and maintain the primary standards for a country do not allow for the flexibility to develop or produce bespoke standards for each of the many communities they serve. Many of these issues can be alleviated through the implementation of secondary standards or the establishment of secondary standards networks. The following needs that could assist in the development and use of secondary standards and their dissemination were identified:

- *There is a strong need for guidance regarding the establishment of secondary standards laboratories, particularly those dedicated to providing measurement services to the nuclear medicine community.* Such guidance should include performance criteria, capability and resource requirements for a laboratory to be able to serve as a secondary standards laboratory, specific procedures for preparing and calibrating reference sources, and guidance on uncertainty assessment.
- *Because of the expanded need for standards in the medical community, especially secondary standards in geometries relevant to clinical measurements, laboratories with capabilities and capacity to produce and disseminate calibrated reference sources could provide a valuable service to the community by establishing traceability to a national standard and distributing secondary standards.*
- *Even if sources distributed by radiopharmacies, radiopharmaceutical manufacturers, and radionuclide producers are not intended for use as secondary standards, reported values of radioactivity content (or activity concentration) should be accompanied by an uncertainty assessment that includes, at a minimum, the most dominant uncertainty components.* These generally include, but are not limited to, the uncertainty on the primary standard with propagated uncertainties when calibrations are performed with derived sources, and uncertainties associated with any applied geometry corrections. Clear documentation with the activity values and uncertainties should be provided by the source supplier.
- When sources are intended for use as secondary standards, international guidance is available that specifies the type of documentation required on certificates or other similar statements of assay results (International Standards Organization (ISO), 2016). *These authoritative guidelines should be adopted by laboratories acting as distributors of secondary standards to provide greater clarity and consistency of information to the end user.*
- High-purity germanium (HPGe) detectors are being increasingly viewed as viable measurement instruments for radioactivity measurements, especially at the secondary standard level. However, discussions during the workshop highlighted the difficulty in maintaining a traceability chain for measurements using gamma-ray spectrometry as its basis. *For this reason, it is imperative that the radionuclide metrology community provide guidance on what measurement scenarios may be appropriate for gamma-ray spectrometry as a calibration tool, methods for accurate, traceable measurements using HPGe detectors, and conditions that must be met for a measurement result to be considered traceable.*

4.6. Needs to improve quantitative imaging and dosimetry

Effective implementation of dosimetry-guided alpha-emitter-based therapies as mandated by the Basic Safety Standards (International Atomic Energy Agency (IAEA), 2018; International Atomic Energy Agency (IAEA), 2014) requires end-to-end traceability to primary standards: from an accurate measurement of the activity administered to patients traceable to the relevant primary standard to the calculation of the absorbed doses, with robust uncertainty budgets. The optimization of TAT requires accurate and precise knowledge of the absorbed doses delivered to tumors and organs at risk to establish a safe amount of activity for administration. However, many challenges have been highlighted in recent years (Sgouros et al., 2021a, 2021b): the microscopic biodistribution of alpha particles, which can only be assessed *ex-vivo* via autoradiography, the small amount of activity administered to patients which leads to low counting statistics for *in-vivo* imaging with clinical SPECT, the long and complex decay chains with in-growth of long-lived progeny, or the potential separation of the decay progeny from the parent which can lead to increased toxicity levels. Despite poor clinical image quantification with SPECT for alpha particles, surrogate imaging using the relevant theranostic pair or beta-emitter analog does not provide information on the decay progeny that may separate from the target and lead to toxicity. Therefore, there is a need to improve *in-vivo* SPECT imaging quantification for alpha-emitters for treatment verification and adaptation of treatment planning of subsequent therapy cycles. Presently, SPECT using alpha-emitters is not well established, and its practicality and characterization in terms of accuracy, reproducibility, and measurement uncertainties need to be addressed to enable harmonization among centers. Pharmacokinetic models combining pre-clinical measurements, blood/urine samples, and imaging are used to improve clinical dosimetry models, but the potential impact of input parameters, as well as the accuracy of inputs required to obtain reliable dosimetry estimates, needs to be investigated. *Furthermore, dose conversion factors used in clinical dosimetry are based on assumptions of uniform distribution and no redistribution of the decay progeny; a framework to understand the error introduced by these assumptions when compared to a microdosimetric approach realistic to alpha-emitting radiopharmaceuticals is urgently needed.*

Given that the use of alpha-emitters is still in its early clinical stages as compared to established therapies using beta-emitting radiopharmaceuticals, there is a unique opportunity to address these measurement challenges before marketing authorization and wide routine clinical adoption of new alpha-emitter-based therapies. The following needs were highlighted:

- ***Traceability:*** Evaluation of the uncertainties through the clinical dosimetry workflow is essential for traceability, to provide confidence in the calculated absorbed doses, and to facilitate the

improvement of measurements. *To achieve this, guidelines and clinical software that enable the calculation of uncertainties are urgently needed.*

- ***Quantitative imaging optimization**: Optimization of quantitative SPECT with robust uncertainty budgets using clinical patient data, physical phantoms, and validated Monte Carlo models of the imaging systems to generate clinically realistic images.*
- ***Micro-to macro-dosimetry:** A framework is needed to assess the impact and errors associated with the assumptions made in macro-dosimetry calculations using autoradiography, pharmacokinetic modelling and microdosimetry calculations. This will require improvements to ex-vivo autoradiography methods which currently lack traceability and suffer from very large measurement uncertainties* (Chouin et al., 2013).
- ***Radiobiology:** A better understanding of the links between the macroscopic absorbed dose and the nano- and micro-dosimetric biological outcome is crucial to the development of optimized treatments.*
- ***Data sharing:** Publicly and freely available data and models will allow other researchers to optimize and develop methods to improve alpha-emitter-based therapies without the need to access an expensive supply of radionuclides, which is already struggling with low availability and high demand. Given the low number of treatments, data sharing will also enable the evaluation of novel artificial intelligence techniques to further improve these therapies.*
- ***Participation in interlaboratory comparison exercises:** International comparison exercises are required to assess the potential for harmonization for quantitative SPECT to enable more robust multi-center studies.*
- ***Quality Assurance:** The creation and use of reference traceable datasets are needed to validate software and benchmark quantitative imaging and dosimetry calculations.*

5. Conclusion

The recent International Workshop on Standards and Measurements for Alpha-Emitting Radionuclides in Therapeutic Nuclear Medicine successfully brought together researchers and practitioners from the clinical nuclear medicine, medical physics, radionuclide production, radiopharmacy, and radionuclide metrology communities to discuss how to advance the field of Targeted Alpha Therapy. Significant progress has recently been made in the development of several candidate radiopharmaceuticals, and there is continued optimism that several others may soon enter clinical use. To optimize their safety and effectiveness, however, care must be taken to ensure that the radioactivity measurements of the radiopharmaceuticals and the information derived from those measurements are the best that they can possibly be while still accomplishing clinical goals. It is hoped that the information and recommendations from this workshop will help guide the community to make this a reality.

CRediT authorship contribution statement

Brian E. Zimmerman: Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Ana M. Denis-Bacelar:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Jan Rušnák:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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.

Acknowledgments

The authors are indebted to all the Workshop attendees for their participation and input to the recommendations. Special thanks go to all the speakers who made the Workshop a success (see Appendix A) and to Dr. Vincent Gressier and the staff at the BIPM for logistical support.

The enthusiastic support from the AlphaMet Consortium for the workshop and its goals is greatly appreciated.

The project (22HLT03 AlphaMet) has received funding from the European Partnership on Metrology, co-financed from the European Union's Horizon Europe Research and Innovation Programme and by the Participating States. The National Physical Laboratory is funded by UKRI under the UK Government's Horizon Europe Guarantee scheme (no. 10117403). AMDB is supported by the UK's National Measurement System of the UK Government's Department for Science, Innovation and Technology (DSIT).

Appendix A. Final Agenda*

Workshop on Standards and Measurements for Alpha Emitting Nuclides in Therapeutic Nuclear Medicine

Thursday, February 22, 2024

9:00–9:15	**Welcome, overview of Workshop**	**Dr. Vincent Gressier, Director BIPM Ionizing Radiation Dept.; Dr. Brian Zimmerman, Chair CCRI Radionuclide Therapy and Quantitative Imaging Working Group; Dr. Jan Rušnák, Coordinator, EURAMET AlphaMet Project**
9:15–10:15	**Clinical Applications of Targeted Alpha Therapy (TAT): Present and Future** **Discussion**	**Prof. Mariza Vorster, College of Health Sciences, University of KwaZulu-Natal**
10:15–10:45	**Current status of therapeutic agents (radiopharmaceutical manufacturer perspective)**	
	Radiopharmaceutical research & development at Bayer	**Dr. Elisa Napoli, Bayer**
		Dr. Michael Schultz, Perspective Therapeutics
10:45–11:15	**Coffee**	
11:15–12:15	**Current status of therapeutic agents (radiopharmaceutical manufacturer perspective), continued**	
		Dr. Thomas Daniel-Robin, Orano Med
		Dr. Ben Fongenie, Blue Earth
		Dr. Aleysa Maruk, Oncoinvent
		Dr. Khaled Attia, Telix

(*continued on next page*)

(*continued*)

		Dr. Dan DeVries, NorthStar
	Discussion	
12:15–13:00	**Dosimetry and Patient Treatment Planning for TAT**	**Dr. Stig Palm, University of Gothenburg**
13:00–14:00	**Lunch**	
14:00–14:45	**Production and availability of alpha emitting nuclides for TAT**	
	PRISMAP, The European Medical Radioisotope Programme: an emphasis on alpha emitters in theranostics approaches	**Dr. Thierry Stora, PRISMAP Consortium**
	U.S. DOE Isotope Program Update and Perspective on Alpha-Emitters	**Dr. Ethan Balkin, US DoE Isotopes Program**
	Discussion	
14:45–15:45	**Measurement problems encountered in TAT clinical practice**	
	Targeted alpha therapy: when chemistry meets physics in the pharmacy	**Radiopharmacy – Dr. Janke Kleynhans, KU Leuven**
		Medical Physics - Dr. Astrid Delker, Ludwig-Maximilians Universität München
		Radiation Safety – Dr. Anna Sarnelli, IRCSS Istituto Romagnolo
15:45–16:15	**Coffee**	
16:15–17:15	**International metrology infrastructure for radioactivity measurement in nuclear medicine**	
	Overview: Metrology Hierarchy, the CCRI, and the Radionuclide Therapy and Quantitative Imaging Working Group	**Dr. Brian Zimmerman, Chair, CCRI Radionuclide Therapy and Quantitative Imaging Working Group**
	Equivalence and Comparisons for Nuclides of Interest to Medicine	**Dr. Romain Coulon, BIPM**
17:15–17:30	**Discussion, wrap-up Day 1**	**All participants**
17:30	**Adjourn**	

Friday, February 23, 2024

9:00–9:15	**Welcome, summary of Day 1**	**Dr. Brian Zimmerman, Chair CCRI Radionuclide Therapy and Quantitative Imaging Working Group**
9:15–10:15	**Traceability and Primary Standards for Alpha Emitters used in TAT**	**Dr. Denis Bergeron, NIST**
10:15–10:45	**Needs for nuclear data in TAT**	**Mr. Sean Collins, NPL**
10:45–11:15	**Coffee**	
11:15–11:45	**Dissemination of standards – needs from a clinical perspective; possible routes to secondary standards**	**Dr. Brian Zimmerman, NIST and Dr. Stephen Graves, University of Iowa**
11:45–12:30	**Additional aspects of dosimetry for TAT**	**Dr. Brian Miller, University of Arizona**
12:30–13:30	**Lunch**	
13:30–14:15	**IAEA programs for medical imaging physics in Member States**	**Dr. Peter Knoll, International Atomic Energy Agency**
14:15–14:45	**Overview of the EURAMET AlphaMet Project**	**Dr. Ana Denis-Bacelar, Impact WP Leader, AlphaMet Project**
14:45–15:00	**Overview of COST Action NOAR-** *Network for Optimized Astatine labeled Radiopharmaceuticals*,	**Dr. Stig Palm, University of Gothenburg**
15:00–15:15	**SECURE project overview**	**Dr. Govert de With (National Research and Consultancy Group) and Dr. Julien Bert (University of Brest)**
15:15–15:45	**Coffee**	
15:45–16:30	**Discussion – development of recommendations, needs statements**	**All participants**
16:30	**Adjourn**	

*Note: Presentation titles were tentative and served only to indicate the topic. Final titles can be seen in the on-line presentations.

Data availability

No data was used for the research described in the article.

References

Bergeron, D.E., Collins, S.M., Pibida, L., Cessna, J.T., Fitzgerald, R., Zimmerman, B.E., et al., 2021. Ra-224 activity, half-life, and 241 keV gamma ray absolute emission intensity: a NIST-NPL bilateral comparison. Appl. Radiat. Isot. 170, 109572.

Bergeron, D.E., Kossert, K., Collins, S.M., Fenwick, A.J., 2022. Realization and dissemination of activity standards for medically important alpha-emitting radionuclides. Appl. Radiat. Isot. 184, 110161.

Chouin, N., Lindegren, S., Frost, S.H.L., Jensen, H., Albertsson, P., Hultborn, R., et al., 2013. Ex vivo activity quantification in micrometastases at the cellular scale using the α-camera technique. J. Nucl. Med. 54, 1347–1353.

Collins, S.M., Pearce, A.K., Regan, P.H., Keightley, J.D., 2015. Precise measurements of the absolute γ -ray emission probabilities of ^{223}Ra and decay progeny in equilibrium. Appl. Radiat. Isot. 102, 15–28.

Collins, S.M., Keightley, J.D., Ivanov, P., Arinc, A., Fenwick, A.J., Pearce, A.K., 2019. The potential radio-immunotherapeutic α-emitter ^{227}Th – part II: absolute γ-ray emission intensities from the excited levels of ^{223}Ra. Appl. Radiat. Isot. 145, 251–257.

European Council, 2014. European Council Directive 2013/59/Euratom on basic safety standards for protection against the dangers arising from exposure to ionising radiation and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. Off. J. Eur. Union 1–73. Luxembourg: European Council.

Gadd, R., Baker, M., Nijran, K.S., Owens, S., Thomson, W., Woods, M.J., et al., 2006. Measurement Good Practice Guide No. 93: Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and Their Quality Control. Teddington, Middlesex, UK.

Galea, R., Moore, K., 2024. Primary standardization and half-life determination of ^{225}Ac at NRC. Appl. Radiat. Isot. 203, 111105.

Gear, J.I., Cox, M.G., Gustafsson, J., Gleisner, K.S., Murray, I., Glatting, G., et al., 2018. EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. Eur. J. Nucl. Med. Mol. Imag. 45, 2456–2474.

Gillings, N., Todde, S., Behe, M., Decristoforo, C., Elsinga, P., Ferrari, V., et al., 2020. EANM guideline on the validation of analytical methods for radiopharmaceuticals. EJNMMI Radiopharm Chem. 5, 7.

Helmer, R.G., 1999. International decay data evaluation project. Nucl. Instrum. Methods Phys. Res. 422, 518–524.

Hooijman, E.L., Radchenko, V., Ling, S.W., Konijnenberg, M., Brabander, T., Koolen, S.L. W., et al., 2024. Implementing Ac-225 labelled radiopharmaceuticals: practical considerations and (pre-)clinical perspectives. EJNMMI Radiopharm Chem 9, 9.

Humbert, D.P., Nichols, A.L., Schwerer, O., 2004. IAEA Nuclear Data Section: provision of atomic and nuclear databases for user applications. Appl. Radiat. Isot. 60, 311–316.

International Atomic Energy Agency (IAEA), 2006. Technical Report Series No 454: Quality Assurance for Radioactivity Measurement in Nuclear Medicine. Vienna, Austria.

International Atomic Energy Agency (IAEA), 2014. IAEA International Safety Standards Series No. GSR Part 3: Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards – General Requirements. International Atomic Energy Agency (IAEA), Vienna, Austria.

International Atomic Energy Agency (IAEA), 2018. IAEA Safety Standards Series No. SSG-46: Radiation Protection and Safety in Medical Uses of Ionizing Radiation. International Atomic Energy Agency (IAEA), Vienna, Austria.

International Atomic Energy Agency (IAEA), 2024. Production and Quality Control of Actinium-225 Radiopharmaceuticals. INTERNATIONAL ATOMIC ENERGY AGENCY, Vienna, Austria.

Jang, A., Kendi, A.T., Johnson, G.B., Halfdanarson, T.R., Sartor, O., 2023. Targeted alpha-particle therapy: a review of current trials. Int. J. Mol. Sci. 24, 11626.

Joint Committee for Guides in Metrology (JCGM), 2008. JCGM 100:2008 Evaluation of measurement data — guide to the expression of uncertainty in measurement. Sevres, France: Joint Committee for Guides in Metrology (JCGM) [Internet]. https://www.bipm.org/documents/20126/2071204/JCGM_100_2008_E.pdf/cb0ef43f-baa5-11cf-3f85-4dcd86f77bd6.

Judge, S.M., Coulon, R.M., Cox, M.G., Karam, L., Knoll, P., Michotte, C., et al., 2023. Traceability for nuclear medicine: the status of primary radioactivity standards. Metrologia 60, 012001.

Kossert, K., Grau Carles, A., 2010. Improved method for the calculation of the counting efficiency of electron-capture nuclides in liquid scintillation samples. Appl. Radiat. Isot. 68, 1482–1488.

Kossert, K., Mougeot, X., 2015. The importance of the beta spectrum calculation for accurate activity determination of 63 Ni by means of liquid scintillation counting. Appl. Radiat. Isot. 101, 40–43.

Kossert, K., Bokeloh, K., Dersch, R., Nähle, O., 2015. Activity determination of ^{227}Ac and ^{223}Ra by means of liquid scintillation counting and determination of nuclear decay data. Appl. Radiat. Isot. 95, 143–152.

Kossert, K., Marganiec-Gałązka, J., Mougeot, X., Nähle, O.J., 2018. Activity determination of 60 Co and the importance of its beta spectrum. Appl. Radiat. Isot. 134, 212–218.

Marouli, M., Lutter, G., Pommé, S., Van Ammel, R., Hult, M., Pierre, S., et al., 2019. Measurement of absolute γ-ray emission probabilities in the decay of ^{227}Ac in equilibrium with its progeny. Appl. Radiat. Isot. 144, 34–46.

Miederer, M., Benešová-Schäfer, M., Mamat, C., Kästner, D., Pretze, M., Michler, E., et al., 2024. Alpha-emitting radionuclides: current status and future perspectives. Pharmaceuticals 17, 76.

Mougeot, X., 2016. Systematic comparison of beta spectra calculations using improved analytical screening correction with experimental shape factors. Appl. Radiat. Isot. 109, 177–182.

Mougeot, X., 2017. BetaShape: a new code for improved analytical calculations of beta spectra. EPJ Web Conf. 146, 12015.

Pibida, L., Zimmerman, B., Fitzgerald, R., King, L., Cessna, J.T., Bergeron, D.E., 2015. Determination of photon emission probabilities for the main gamma-rays of ^{223}Ra in equilibrium with its progeny. Appl. Radiat. Isot. 101.

Pibida, L., Bergeron, D.E., Collins, S.M., Ivanov, P., Cessna, J.T., Fitzgerald, R.P., et al., 2024. Absolute emission intensities of the gamma rays from the decay of ^{224}Ra and ^{212}Pb progenies and the half-life of the 212 Pb decay. Appl. Radiat. Isot. 205, 111171.

Poty, S., Francesconi, L.C., McDevitt, M.R., Morris, M.J., Lewis, J.S., 2018. α-Emitters for radiotherapy: from basic radiochemistry to clinical studies—Part 1. J. Nucl. Med. 59, 878–884.

Radchenko, V., Morgenstern, A., Jalilian, A.R., Ramogida, C.F., Cutler, C., Duchemin, C., et al., 2021. Production and supply of α-particle–emitting radionuclides for targeted α-therapy. J. Nucl. Med. 62, 1495–1503.

Ratel, G., 2007. The Système International de Référence and its application in key comparisons. Metrologia 44, S7–S16.

Schwartz, J., Jaggi, J.S., O'Donoghue, J.A., Ruan, S., McDevitt, M., Larson, S.M., et al., 2011. Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody. Phys. Med. Biol. 56, 721–733.

Sgouros, G., Frey, E., Du, Y., Hobbs, R., Bolch, W., 2021a. Imaging and dosimetry for alpha-particle emitter radiopharmaceutical therapy: improving radiopharmaceutical therapy by looking into the black box. Eur. J. Nucl. Med. Mol. Imag. 49, 18–29.

Sgouros, G., Bolch, W.E., Chiti, A., Dewaraja, Y.K., Emfietzoglou, D., Hobbs, R.F., et al., 2021b. ICRU REPORT 96, dosimetry-guided radiopharmaceutical therapy. J. ICRU 21, 1–212.

Stokke, C., Gnesin, S., Tran-Gia, J., Cicone, F., Holm, S., Cremonesi, M., et al., 2024. EANM guidance document: dosimetry for first-in-human studies and early phase clinical trials. Eur. J. Nucl. Med. Mol. Imag. 51, 1268–1286.