Technical Protocol for a EURAMET Key Comparison of ^{225}Ac (EURAMET Project #)

1. Introduction

Targeted Alpha therapy (TAT) is a rapidly growing cancer treatment modality based on the use of alpha-emitting radionuclides. Due to the short penetration range and high linear energy transfer of alpha particles, which can cause more DNA damage than beta particles, TAT is showing promising efficacies and increased survival in early phase clinical trials. Presently, only $^{223}RaCl_2$ has regulatory approval. The AlphaMet project (Metrology for Emerging Targeted Alpha Therapies) is an ongoing European research project funded by the EURAMET R&I programme that brings together experts from National Metrology Institutes (NMIs), hospitals, academia and industry to support end-to-end traceability before wide routine adoption of TAT. In particular, the AlphaMet project aims at improving the metrological traceability of emerging α-emitting radiopharmaceuticals such as ^{211}At, ^{212}Pb/^{212}Bi and ^{225}Ac in order to accelerate their availability on the market.

This comparison is carried out in the framework of the AlphaMet project in order to link the participating NMIs (CEA/LNE-LNHB, CHUV/IRA, CMI, CIEMAT, ENEA, NPL, POLATOM/NCBJ) to the BIPM International Reference System (SIR) for the ^{225}Ac radionuclide.

2. Comparison protocol

2.1 Pilot laboratory: CEA/LNE-LNHB, France

Coordination:
Christophe BOBIN / Marie-Noëlle AMIOT
Address: LNE-Laboratoire national Henri Becquerel
CEA-Paris-Saclay
Bâtiment 602 / Point Courrier n° 111
F-91191 Gif-sur-Yvette Cedex, France
Tel : +33 1 68082964
E-mails: christophe.bobin@cea.fr; marie-noelle.amiot@cea.fr

Preparation of the ^{225}Ac solution and delivery to the participants: NPL, United Kingdom
Sean Collins
Address: National Physical Laboratory
Hampton Road
Teddington
Middlesex
TW11 OLW
E-mail: sean.m.collins@npl.co.uk

2.2 Participants

NMI	Country	Contact person	e-mail contact person
CEA/LNE-LNHB	France	Marie-Noëlle Amiot	marie-noelle.amiot@cea.fr
CHUV/IRA	Switzerland	Frédéric Juget	frederic.juget@chuv.ch
CMI	Czech Republic	Jana Sochorová Vladimir Dutka	jsochorova2@cmi.cz dutka@eurostandard.cz
CIEMAT	Spain	Miguel Roteta Ibarra	miguel.roteta@ciemat.es
ENEA	Italy	Marco Capogni	marco.capogni@enea.it
NPL	United Kingdom	Sean Collins	sean.m.collins@npl.co.uk
POLATOM/NCBJ	Poland	Justyna Marganiec-Gałązka	Justyna.Marganiec-Galazka@polatom.pl

2.3 Data of the ^{225}Ac master solution

Chemical composition of the solution: Actinium chloride (^{225}Ac(III)Cl_3) in 0.1 M hydrochloric acid
Approximate activity per unit mass of solution: 600 kBq g^{-1}
Container: Flame sealed ampoules
Approximate mass: 5 g

2.4 Measurand

The measurand for this comparison is the activity of ^{225}Ac per unit mass of the master solution.
The participants shall report their results at the following reference date and time:

4 October 2024 at 12:00 UTC

Recommended nuclear data: Decay Data Evaluation Project for ^{225}Ac [1] and its progenies and BetaShape calculations [2]
^{225}Ac half-life: $T_{1/2}$ = 9.9172 (21) d
^{221}Fr half-life: $T_{1/2}$ = 4.801 (5) min
^{217}At half-life: $T_{1/2}$ = 32.3 (4) 10^{-3} s
^{213}Bi half-life: $T_{1/2}$ = 45.59 (6) min
^{213}Po half-life: $T_{1/2}$ = 3.70 (5) 10^{-6} s
^{209}Tl half-life: $T_{1/2}$ = 2.161 (7) min
^{209}Pb half-life: $T_{1/2}$ = 3.277 (15) h

It is part of the exercise for the participant to identify and measure the activity of any possible impurity.

2.5 Schedule

For this comparison, ^{225}Ra as a salt will be shipped from CERN-MEDICIS. The chemical separation for the preparation of the ampoules with ^{225}Ac solution will be carried out at NPL.

The exercise shall start in September 2024 when an ^{225}Ac solution, with the chemical composition and approximate activity concentration reported above, will be prepared at NPL from the ^{225}Ra. The ^{225}Ac solution will be distributed in glass ampoules by NPL. Homogeneity between ampoules will be verified before shipment.

NPL will send to the BIPM, an appropriate ampoule filled with a ^{225}Ac solution having the same characteristics described above containing 3.6 g, in order to link the comparison results to the BIPM SIR for ^{225}Ac.

The following schedule for reporting is proposed:
Reporting opens: LNE-LNHB will announce the opening of the reporting period after LNE-LNHB results are submitted to the BIPM.

Reporting deadline:	January 31, 2025
Draft A sent to participants:	May 5, 2025
Draft A acceptance deadline:	May 26, 2025
Draft B sent to participants:	June 15, 2025
Draft B acceptance deadline:	July 18, 2025

LNE-LNHB will inform the participants of possible delays in the organisation of the comparison.

2.6 Shipment

Transport of the ^{225}Ac ampoules to the participants will be managed by NPL through their standard radioactive shipment arrangements. Participating institutes should send in advance all appropriate shipping, customs and special handling information to receive the package containing the ^{225}Ac solution in a glass ampoule.

Participating institutes must acknowledge receipt and shall check for any damage to the samples and report this to NPL and LNE-LNHB immediately upon receipt.

If delays occur, LNE-LNHB shall inform the participants and revise the schedule, if necessary.

2.7 Costs

The comparison is carried out in the framework of the funded EPM project AlphaMet.

The costs associated with the shipping of the ^{225}Ac comparison solutions from NPL to the participating institutes will be borne by LNE-LNHB.

Each participating institution is responsible for its own costs associated with the measurements, and any damage that may occur within their country.

2.8 Further information

To guarantee confidentiality, each participating institute will communicate its own results to the Executive Secretary of the CCRI(II), before the reporting deadline, using the standard reporting form for the BIPM SIR results [3] and describing the methods used for standardisation, the uncertainty budget, any additional information useful for the comparison, and the final results achieved in their own laboratory. In the case of several methods used, a unique final result by each participating NMI will be given to establish the degrees of equivalence.

A result from a participant will not be considered complete without an associated uncertainty and will not be included in the comparison report unless it is accompanied by an uncertainty supported by a complete uncertainty budget.

Participants must provide a list and evaluation of the principal components of the uncertainty budget based on the Guide to the Expression of Uncertainty in Measurement, published by the Joint Committee for Guides in Metrology (JCGM) [4]. In addition to the principal components of the uncertainty, common to all the participants, each individual institute should add any other components they deem necessary.

Uncertainties are assessed at a level of one standard deviation (k = 1) and information must be given on the number of effective degrees of freedom, required for a proper estimate of the level of confidence, where this is appropriate.

3. Preparation of the report on the comparison

According to the document “Measurement comparisons in the CIPM MRA” [5], the pilot laboratory, LNE-LNHB, is responsible for the preparation of the Draft-A comparison report, as in the schedule above.

During the comparison, the results will be kept confidential by the Executive Secretary of the CCRI(II) until all participants have completed their measurements and all the results have been completed, or until the deadline for reporting results (see 2.5). Only when these conditions are fulfilled, will the results be transmitted to LNE-LNHB, the pilot laboratory.

If, upon examination of the complete set of results, the pilot laboratory finds results that appear to be anomalous, the pilot laboratory will invite the corresponding institute to check their result for transcription or arithmetic errors but without indication about the magnitude or sign of the apparent anomaly. If no numerical error is found, the result will stand.

Draft-A is considered as confidential to all participants and will include the results, uncertainties, methods, the analysis carried out, the conclusions reached and other details transmitted by participants, identified by name. In particular, provisional degrees of equivalence for participating institutes shall also be stated, using the LNE-LNHB link to the SIR.

The pilot laboratory will circulate the Draft A to all participants for comments, with a reasonable deadline for reply. The date at which this draft is sent to participants is taken to be the end date for the comparison and is subsequently referred to as such. If any controversial comments are received by the pilot laboratory, discussions will continue until a consensus is reached.

Note that once all participants have been informed of the results, individual results and uncertainties may be changed or removed, or the complete comparison abandoned, only with the agreement of all participants and on the basis of some cause that renders the comparison or part of it invalid.

Due to the confidential character of the Draft A, copies will not be given to non-participants and graphs or other parts of the Draft A cannot be used in oral presentations without the specific agreement of all participants. The results may be the subject of an internal report if they are shown in relative terms and the names of participants hidden. At this stage, a participant may publish experimental techniques or new developments as long as no information or comments are made about the comparison results.

Once the final version of the Draft A is approved by the participants, the report is considered as the Draft B and shall be sent to the CCRI Executive Secretary who will make a preliminary technical and editorial revision before circulation through the KCWG(II) and the CCRI(II), for comments within a reasonable period of time. At this stage, the results are not considered confidential and can be used to support CMCs and used for presentations and publications, with the exception of the proposals for the reference value and degrees of equivalence.

The pilot laboratory shall take into account the comments received and revise the Draft B, obtaining the agreement of all participants if necessary. The revised Draft B will be considered as the Final Report and shall be sent to the CCRI Executive Secretary for verification purposes, uploaded into the KCDB and published in the Metrologia Technical Supplement series.

Successful participation in this comparison may support CMC claims for ^{225}Ac measured using the laboratory's method(s) applied in the comparison or methods calibrated by those used in the comparison. This comparison may also be used to support CMC claims for those radionuclides measured in the laboratory using the same method and having a degree of difficulty at or below that of the radionuclide measured in this comparison as reflected in the current Measurement Methods Matrix (MMM).

Christophe BOBIN, LNE-LNHB, July 2024

Sean COLLINS, NPL, July 2024

References

[1] Mougeot X., Huang X., Wang B., http://www.lnhb.fr/nuclides/Ac-225_tables.pdf
[2] Mougeot X. (2015) Erratum: reliability of usual assumptions in the calculation of β and ν spectra. Phys. Rev. C92, 059902.
[3] Reference Excel form BIPM/RI-SIR-F-05 (https://www.bipm.org/documents/d/guest/ri-sir-f-05)
[4] Evaluation of measurement data – Guide to the expression of uncertainty in measurement (JCGM 100:2008) and supplements.https://www.bipm.org/en/committees/jc/jcgm/publications
[5] Measurement comparisons in the CIPM MRA, CIPM-MRA-G-11 (version 1.1) https://www.bipm.org/utils/common/documents/CIPM-MRA/CIPM-MRA-G-11.pdf