

## Results of the EURAMET.RI(II)-K2.Ho-166 key comparison for the activity of the radionuclide $^{166}\text{Ho}$ per unit mass of aqueous solution

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### Abstract

This is the final report for the EURAMET.RI(II)-K2.Ho-166 key comparison of the activity of the radionuclide  $^{166}\text{Ho}$  per unit mass of aqueous solution which was organized in 2017 by Czech Metrology Institute (CMI) within the joint research project “Metrology for clinical implementation of dosimetry in molecular radiotherapy” (MRTDosimetry; 15HLT06) of the European Metrology Programme for Innovation and Research (EMPIR). The key comparison reference value of  $(2623.6 \pm 3.6) \text{ kBq} \cdot \text{g}^{-1}$  was determined from the results of three participants at the reference time of 1 December 2017 00:00 UTC. The details on the comparison are presented and analysed in this paper.

### Keywords

metrology, radioactivity, primary measurement, standardization, activity per unit mass,  $^{166}\text{Ho}$  radionuclide, molecular radiotherapy, MRT Dosimetry, EMPIR

### 1 Introduction

This international key comparison was carried out in order to compare mass activity measurement results from National Metrology Institutes (CMI, Czech Republic and NPL, United Kingdom) and Designated Institutes (LNE-LNHB, France and ENEA-INMRI, Italy) on the same  $^{166}\text{Ho}$  solution and to link those results to the International Reference System (SIR) of the Bureau International des Poids et Mesures (BIPM). The project was declared as an EURAMET.RI(II)-K2.Ho-166 key comparison and was registered in the EURAMET database under the number 1435. The pilot laboratory was CMI.

The presented work was carried out within the joint research project “Metrology for clinical implementation of dosimetry in molecular radiotherapy” (MRTDosimetry; 15HLT06) [1][2] of the European Metrology Programme for Innovation and Research (EMPIR). The project took place from 2016 to 2019 and its overall aim was to provide metrology for the clinical implementation of absorbed dose determination in molecular radiotherapy.

## 2 Participants

The comparison had four participants as specified in Table 1.

*Table 1: Participants of the comparison.*

Participant	Country	Contact person	Responsible person for activity measurements	Contact person e-mail
CMI	Czech Republic	Jaroslav Šolc	Jana Sochorová	<a href="mailto:jsolc@cmi.cz">jsolc@cmi.cz</a>
ENEA-INMRI	Italy	Marco Capogni	Marco Capogni	<a href="mailto:marco.capogni@enea.it">marco.capogni@enea.it</a>
LNE-LNHB	France	Christophe Bobin	Christophe Bobin	<a href="mailto:christophe.bobin@cea.fr">christophe.bobin@cea.fr</a>
NPL	United Kingdom	Andrew Fenwick	Andrew Fenwick	<a href="mailto:andrew.fenwick@npl.co.uk">andrew.fenwick@npl.co.uk</a>

## 3 Materials and Methods

### 3.1 $^{166}\text{Ho}$ radionuclide

Holmium-166 ( $^{166}\text{Ho}$ ) is a radionuclide with the half-life of about 26.8 h that disintegrates with 100 % emission probability through  $\beta^-$  decay [3]. The high energy of beta particles (maximum energy 1854.5 keV, average energy 667.3 keV) and the associated emission of 80.6 keV gamma photons with a yield of about 6.6 % makes this radionuclide interesting for health care. Its decay scheme is presented in Figure 1. Examples of  $^{166}\text{Ho}$  applications include direct intratumoral treatment injecting the radioactive compound directly into the tumour, selective internal radiation therapy with  $^{166}\text{Ho}$ -labelled microspheres, and targeted therapy with  $^{166}\text{Ho}$  labelled to antibodies or other tumour-seeking peptides. The imaging of distribution of the radionuclide in the patient body is possible with quantitative Single Photon Emission Computed Tomography (SPECT) and Magnetic Resonance Imaging (MRI). The full overview of current  $^{166}\text{Ho}$  medical applications is given in [4].

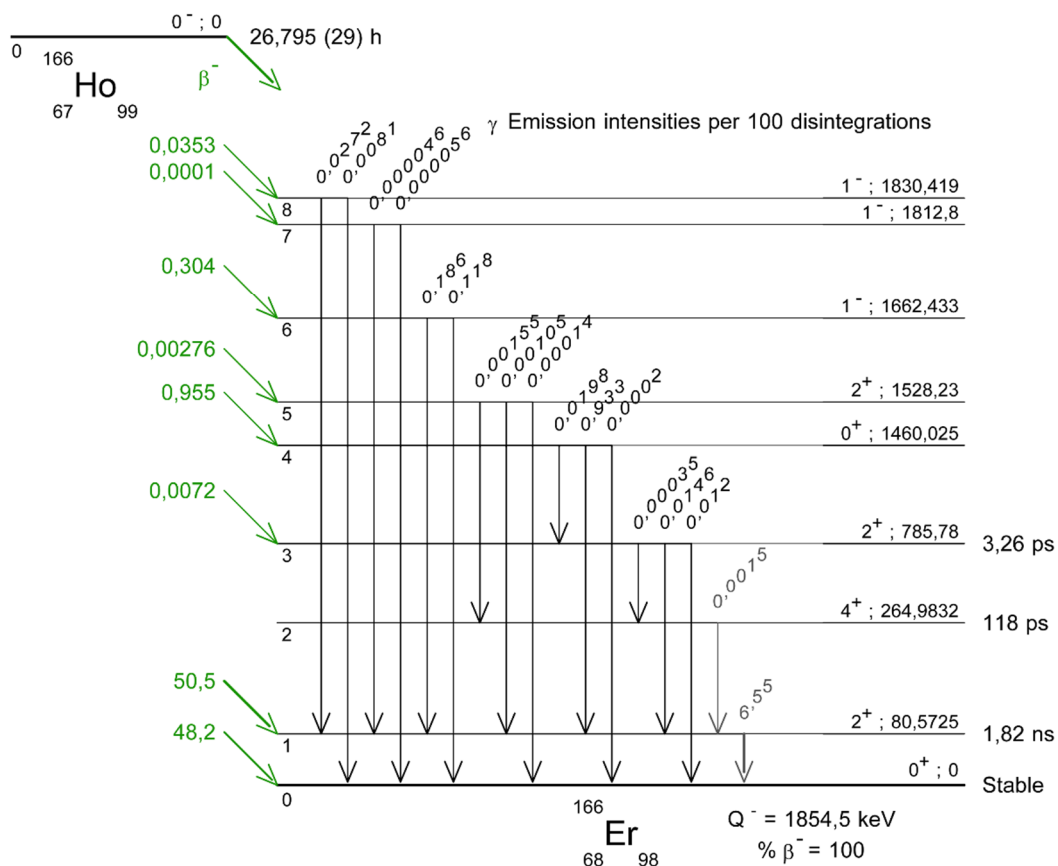


Figure 1:  $^{166}\text{Ho}$  decay scheme [3].

### 3.2 $^{166}\text{Ho}$ solution

The  $^{166}\text{Ho}$  for the comparison was produced by RadioMedic s.r.o., Czech Republic, by neutron irradiation of  $^{165}\text{Ho}$ . The  $^{166}\text{Ho}$  solution was purchased and delivered to CMI on 28 November 2017. The total ordered activity was 200 MBq that was high enough for the planned number of samples and for measurements of samples by participants within a few subsequent days. The radionuclide was dissolved in  $1 \text{ mol}\cdot\text{l}^{-1}$   $\text{HNO}_3$  in the total volume of  $1 \text{ cm}^3$ . No gamma-emitting radionuclide impurity was detected in the solution by  $\gamma$ -ray spectrometry method at CMI laboratory.

Samples for participants were obtained from the stock solution. The stock solution was prepared from 0.68312 g of master solution that was poured into 15.33018 g of the solution consisting of  $1 \text{ mol}\cdot\text{l}^{-1}$   $\text{HNO}_3$  and  $7.48 \text{ mg}\cdot\text{l}^{-1}$  of stable  $^{165}\text{Ho}$  carrier. This assured that the concentration of holmium did not change and the stability of the radionuclide in solution remained constant during the sample preparation. Chemical composition of the stock solution was  $15.9 \text{ mg}\cdot\text{l}^{-1}$   $\text{Ho}(\text{NO}_3)_3$  in  $1 \text{ mol}\cdot\text{l}^{-1}$   $\text{HNO}_3$  and the density was  $1.03 \text{ g}\cdot\text{cm}^{-3}$ .

The total of five samples in BIPM-SIR glass ampoules were prepared from the stock solution. Four ampoules were filled with 3.6 ml aliquots. Three of them were prepared for participants of the comparison - ENEA, LNE-LNHB and NPL. The fourth ampoule was prepared for BIPM to be measured in the SIR ionization chamber and link the results achieved in this comparison

to the BIPM.RI(II)-K1.Ho-166. These four ampoules were chosen from a set of ampoules in such a way to have the closest weight as possible, ranging from 4.2852 g to 4.3017 g, to minimize the influence of glass walls for ionization chamber calibration. The fifth ampoule was prepared for CMI and it was filled only with 1 cm<sup>3</sup> solution because the measurement in ionization chamber was not necessary (the other four ampoules were used instead). Smaller volume of solution required for CMI allowed to increase the activity per mass used for the comparison.

Weighing was performed with the calibrated balance (Sartorius type MSE 524S-1CE-DU, Germany) traceable to the SI (Système international d'unités) through the Czech national standard of weight. The uncertainty on weighing was 0.15 mg. Characteristics of SIR ampoules and sample solutions are presented in Table 2. The schematics of dilution is shown in Figure 2.

Table 2: SIR ampoules with <sup>166</sup>Ho solution

Institute	Ampoule identifier	Empty ampoule mass (g)	Solution mass (g)
BIPM	1679004	4.2949	3.7002
CMI	1679005 <sup>(1)</sup>	4.3136	1.0370
ENEA	1679003	4.2990	3.6996
LNE-LNHB	1679002	4.3017	3.7050
NPL	1679001	4.2852	3.6992

<sup>(1)</sup> not used for IC measurements.



Figure 2: Schematics of dilution. 1 - master solution, 2 - stock solution, 3 - BIPM-SIR ampoules.

The ampoules were flame-sealed and sent to the participants and to the BIPM on 29 November 2017 in the morning. The nominal activity of <sup>166</sup>Ho radionuclide per unit mass of the solution given in the source certificate on 28 November 2017 at 09:00 UTC was approximately 12.7 MBq·g<sup>-1</sup>. BIPM, LNE-LNHB and ENEA received their ampoules the same day, while NPL received the ampoule on 1 December due to logistics problems during the transfer at Brussels airport. The shipping paperwork and transport from CMI to Prague airport was organized by an external company.

### 3.3 Receipt of the results

The participants, including the leading laboratory, were asked to send their measurement reporting forms to the executive secretary of the CCRI in order to assure trustfulness of the

results of all participants. The deadline for the submission of the results was originally set to 31 March 2018.

However, ENEA was not able to perform the measurements using a primary method in 2017 due to the unavailability of the primary standard at that time. The primary standardization was planned for a few months later for which ENEA needed another  $^{166}\text{Ho}$  solution to make a link to the original measurements done with the CMI SIR ampoule. Unfortunately, there were serious problems to obtain a new solution, namely administrative issues, contamination of the solution with another radionuclide, reactor shutdown and COVID-19 lockdown. That is why the ENEA final results were sent to the CCRI executive secretary in July 2020.

LNE-LNHB and CMI submitted their results within the original deadline. NPL took advantage of the extended time period to recheck their data and sent the final results in January 2021.

After the results of all participants had been submitted, the CCRI executive secretary provided them to the pilot laboratory, CMI, for the evaluation and for the preparation of the comparison report.

### 3.4 Measurement methods

CMI, LNE-LNHB, and NPL standardized the  $^{166}\text{Ho}$  solutions using primary activity measurements techniques. ENEA standardized the solution by a relative method using an ionization chamber calibrated later by primary technique using another  $^{166}\text{Ho}$  solution provided by another manufacturer. Table 3 lists the measurement methods used by the participants while more detailed description of the used methods is given in the following sections.

*Table 3: Measurement methods*

<b>Participant</b>	<b>Acronym of the method</b>	<b>Description of the measuring system</b>
CMI	4P-PC-BP-NA-GR-CO	$4\pi\beta\text{-}\gamma$ coincidence counting using gas-flow proportional counter and NaI(Tl)
ENEA	4P-IC-GR-00-00-00 / 4P-LS-MX-00-00-TD	relative method <sup>(1)</sup> : $4\pi$ ionization chamber / linked to absolute method: liquid scintillation counting using TDCR
LNE-LNHB	4P-LS-MX-00-00-TD	liquid scintillation counting using TDCR
NPL	4P-LS-GH-BP-GR-CO	$4\pi\beta\text{-}\gamma$ coincidence counting with efficiency extrapolation using liquid scintillation and high-purity Germanium detectors

<sup>(1)</sup> Secondary method was used for the measurement of the intercomparison sample. The link to the primary standard was performed later with another  $^{166}\text{Ho}$  solution, see section 3.4.2.

#### 3.4.1 CMI primary measurement

At CMI the standardization of  $^{166}\text{Ho}$  was performed using the  $4\pi\beta\text{-}\gamma$  coincidence method [5] and the efficiency-extrapolation technique [6]. The detection system consisted of a stainless-steel cylindrical proportional counter (dimensions:  $2 \times$  (height: 18 mm, diameter: 64 mm)) operating with methane at atmospheric pressure in a gas flow arrangement. The discrimination threshold was set to 0.7 keV. A non-extending dead time of 5.995(5)  $\mu\text{s}$  was used. The  $\gamma$ -ray detection assembly is composed of two opposing NaI(Tl) detectors consisting of NaI crystals

with a diameter of 76.2 mm and a height of 76.2 mm each. The non-extending dead time of the gamma channel was set to 6.031(5)  $\mu\text{s}$ . For coincidence counting, a  $\gamma$ -window centred on the 80.6 keV was applied.

The source was prepared from the solution in the CMI ampoule by dilution so that its nominal activity per unit mass at the reference time was 300  $\text{kBq}\cdot\text{g}^{-1}$ . For coincidence counting, fifteen solid sources were prepared by deposition of 20 mg to 50 mg aliquots of diluted solution by deposition onto gold-coated VYNS films ( $\sim 40 \mu\text{g}\cdot\text{cm}^{-2}$ ) treated with Ludox and insulin. Different weights of solution were used in sample preparation to obtain a set of samples with different self-absorption. In addition, gold-coated VYNS foils were also used to cover solid sources in order to decrease the detection efficiency in the  $\beta$ -channel for the application of the efficiency-extrapolation technique. Analysis of data obtained by measurement of samples covered by various number of additional foils confirmed the expected extrapolation linearity for  $\frac{N_{\beta}N_{\gamma}}{N_c}$  as a function of  $(1 - \frac{N_c}{N_{\gamma}})/\frac{N_c}{N_{\gamma}}$ , where  $N_{\beta}$ ,  $N_{\gamma}$  and  $N_c$  are corrected count rates according to [7]. The highest counting efficiency in the proportional counter was found to be 99.5 %, and consequently, an efficiency extrapolation was applied. The resulting activity per unit mass was determined from the extrapolation with  $\frac{N_c}{N_{\gamma}}$  in the range of 0.98 – 0.995. The normalized extrapolation slope was 0.473(18).

### 3.4.2 ENEA relative and primary measurements

At the time of distribution of the  $^{166}\text{Ho}$  samples for the comparison, ENEA was not able to realize primary measurement of activity. Therefore, ENEA performed measurement using a secondary method that was later linked to the primary measurement performed with a different  $^{166}\text{Ho}$  solution.

#### 3.4.2.1 Secondary measurement with intercomparison $^{166}\text{Ho}$ solution

The  $^{166}\text{Ho}$  SIR ampoule (No. 1679003) received from CMI was measured in the ENEA-INMRI IG11 ionization chamber (IC). More than 10 measurement points were recorded. However, the IG11 IC was not calibrated for  $^{166}\text{Ho}$  at that time. Therefore the result could not be submitted and an additional effort to develop a primary standard of  $^{166}\text{Ho}$  solution activity had to be made.

#### 3.4.2.2 Establishment of ENEA $^{166}\text{Ho}$ activity primary standard

In the year 2019 a  $^{166}\text{Ho}$  mother solution was prepared by neutron irradiation of a pure metallic sample of  $^{165}\text{Ho}$  at the L.E.N.A reactor in Pavia, Italy. The liquid solution had similar chemical characteristics as the CMI sample used for the intercomparison. The glass ampoule utilized in 2019 was manufactured with the same geometry and dimensions as the BIPM SIR vials. It was a similar type of vials as the one received from CMI in 2017, however, it was not the same type as the ampoules provided by BIPM. The standardization of the  $^{166}\text{Ho}$  radioactive solution at ENEA-INMRI was carried out by liquid scintillation (LS) counting technique by the Triple-to-Double Coincidence Ratio (TDCR) method [8]. The measurements were performed using two high-performance standard glass vials filled with 10 mL of Ultima Gold as liquid scintillator mixed with aliquots of the radioactive solution ( $\sim 20$  mg). Two TDCR counters, owned by ENEA-INMRI, were used: the Hidex 300 SL ‘Metro’ version and the home-made portable TDCR [26], this last one made by 3 PMTs Hamamatsu R7600 U-200. A resolving time of 40

ns was used for the Hidex TDCR counter and of 140 ns for the portable TDCR. Due to the high-energy  $\beta^-$  emissions of the  $^{166}\text{Ho}$ , high TDCR values  $> 0.995$  were obtained in both TDCR counters. The efficiency for Double and Triple coincidences were obtained by Micelle code kindly provided by PTB. The activity of the two LS sources were calculated using a  $kB$  value equal to  $0.010 \text{ cm}\cdot\text{MeV}^{-1}$ . The final result of the activity concentration for the  $^{166}\text{Ho}$  solution was obtained as the average mean of the results of the two TDCR counters.

Thanks to the new  $^{166}\text{Ho}$  standard the below-mentioned actions were performed. These were the crucial points for the  $^{166}\text{Ho}$  activity standardization at ENEA-INMRI and the link to the BIPM SIR, as described later in the section 3.4.2.3.

- 1) The ENEA-INMRI high-energy resolution HPGe detector was calibrated by using a point-like solid source (mass of  $\sim 10$  mg) prepared from the same  $^{166}\text{Ho}$  mother solution. This allowed to calculate the  $^{166}\text{Ho}$  gamma ray intensities,  $I_\gamma$ , by using also the robust efficiency calibration curve of the ENEA-INMRI HPGe detector; the calculation of  $^{166}\text{Ho}$  gamma ray intensities helped to improved the determination of activity of  $^{166}\text{Ho}$  in the original CMI ampoule; geometry correction from CMI ampoule to the ampoule used for primary measurement was taken into account;
- 2) The ENEA-INMRI fixed well-type re-entrant Ionization Chamber (IC) IG11 was calibrated by using a standard glass ampoule filled with  $3.6 \text{ cm}^3$  of the same  $^{166}\text{Ho}$  mother solution. This ampoule was also measured by the ENEA-INMRI HPGe detector calibrated as in the point 1).

#### 3.4.2.3 Link of intercomparison sample to the primary standard

The link between the two  $^{166}\text{Ho}$  measurements, the one performed with the CMI SIR ampoule and the other with the standard ampoule filled with  $^{166}\text{Ho}$  radioactive solution prepared at L.E.N.A. reactor, were assured by the two ENEA-INMRI well calibrated secondary standards instruments: the IC IG11 and the HPGe spectrometer. However, only results obtained by the IC IG11 were used for the intercomparison because the IC results were considered more robust and the HPGe results were utilized for the sole purpose of an internal check on the two sets of measured data.

#### 3.4.3 LNE-LNHB primary measurements

The standardization of the  $^{166}\text{Ho}$  radioactive solution at LNE-LNHB was carried out by liquid scintillation (LS) counting using the Triple-to-Double Coincidence Ratio method (TDCR) [8]. The measurements were implemented on four standard glass vials filled with 10 mL Hionic Fluor mixed with aliquots of the radioactive solution ( $\sim 10$  mg). The detection apparatus is composed of three XP2020Q photomultipliers (Photonis) coupled to a MAC3 module [9] which was modified to set variable resolving time for TDCR counting. A resolving time equal to 80 ns was used. Due to the high-energy electrons emitted by  $^{166}\text{Ho}$ , high TDCR values greater than 0.996 were obtained. For each measured source, the detection efficiencies to double coincidences were calculated by means of the classical free-parameter statistical model [8]. For that purpose, the four main  $\beta^-$ -branches of  $^{166}\text{Ho}$  ( $\beta_{0,0}^-$ ,  $\beta_{0,1}^-$ ,  $\beta_{0,4}^-$  and  $\beta_{0,6}^-$ ) and their related probabilities were considered [10]. The corresponding  $\beta^-$ -spectra were calculated using the BetaShape code [11]. Regarding  $\gamma$ -transitions, only the highly-converted 80.6 keV transition

was taken into account in the analytical modelling. The related distribution of deposited energy in the scintillation cocktail (Hionic Fluor) by Compton scattering was determined by Monte Carlo calculations using the Geant4 simulation toolkit [12][13]. The activity of the four LS sources were calculated using a  $kB$  value equal to  $0.01 \text{ cm} \cdot \text{MeV}^{-1}$ .

#### 3.4.4 NPL primary measurements

The comparison sample was received on 1<sup>st</sup> December and following measurement on the NPL secondary standard ionisation chamber (Vinten 671 SN:3-5) was dispensed directly into ampoules (for measurement on ionisation chamber and high-purity germanium (HPGe) detectors), LS vials and a dilution bottle which was subsequently dispensed to further LS vials. Ampoules were prepared to confirm the gravimetric dilution factor by high-purity germanium measurements. Due to the short half-life of  $^{166}\text{Ho}$ , two sets of six LS vials containing 10 mL of Ultima Gold AB were prepared. The first set was prepared with approximately 70 kBq per source from the pre-dilution solution and the second set with the diluted solution using approximately 10 kBq per source at the reference time of 1 December 2017 12:00 UTC.

The LS vials were measured on the NPL  $4\pi(\text{LS})-\gamma$  digital coincidence counting (DCC) system [14]. The measurements were performed over the 4 December 2017 to 5 December 2017, with each vial being measured once. The coincidences were formed using the LS channel and the  $\gamma$ -gate set on the 80.6 keV  $\gamma$  ray emitted from the  $2^+ \rightarrow 0^+$  transition from the 80.6 keV excited level of  $^{166}\text{Er}$ . This transition is highly converted ( $\alpha_T = 6.9$ ) and thus there are significant X-rays emitted between 48 keV – 58 keV. A resolving time of 1  $\mu\text{s}$  was applied to the LS and  $\gamma$ -channels. To account for after-pulsing non-extending dead times of 20  $\mu\text{s}$  and 25  $\mu\text{s}$  were applied to the LS and  $\gamma$ -channels respectively.

The monitored ( $N_c/N_\gamma$ ) LS efficiency observed was 0.987, with the extrapolation performed over the range 0.897-0.982. The efficiency extrapolation was performed with the computer discrimination method [15],[16],[17] using the following function and maintaining  $N_0$ ,  $a_1$  and  $a_2$  as free parameters:

$$\frac{N_\beta}{\varepsilon_\beta} = N_0 + a_1 \left( \frac{1}{\varepsilon_\beta} - 1 \right) + a_2 \left( \frac{1}{\varepsilon_\beta} - 1 \right)^2 \quad (1)$$

### 3.5 Reference value

The results reported by the participants were analysed and evaluated using the power-moderated mean method [18]. This method is commonly used for calculating a key comparison reference value (KCRV) and its associated standard uncertainty. It allows technical scrutiny of data and correction or exclusion of extreme data. It uses a power-moderated mean that can calculate an efficient and robust mean from any data set and enables to obtain a good compromise between efficiency and robustness, while also providing a realistic uncertainty. The reported results were analysed with an Excel spreadsheet freely provided by the authors of the method in supplementary data to the paper [18] using the following parameters: Autoreject = FALSE, Autoalpha = FALSE, Criterion = 2.5, Alpha = 2. The Autoreject and Autoalpha setting allowed automatic rejection of analysed data and automatic setting of the Alpha value, respectively. The Criterion was used to indicate and exclude extreme data. It is a constant that multiplies the

standard uncertainty of the difference between the data and the reference value. Data outside are excluded. The Alpha defines the power of the uncertainties in the weighting factors. Its value equal to 2 means that the uncertainties are accurately known and the reported data are consistent [18]. Considering this set of data, all reported results would be accepted. However, the value reported by ENEA was not included in the KCRV because it was not coming from primary measurement method.

### 3.6 Reference time and $^{166}\text{Ho}$ half-life

The summary of available  $^{166}\text{Ho}$  half-lives published since 1989 is given in Table 4 and Figure 3. The current typically used half-life of  $^{166}\text{Ho}$  is 26.795 (29) h stated in the DDEP database (the Decay Data Evaluation Project) [3] but the value is heavily weighted towards two precise but discrepant measurements published before 1999 [19],[20], see also Figure 3. A new provisional evaluation for the MRTDosimetry project has been done [21] that considered additional measurement [22]. When preparing this comparison, the participants agreed to use the half-life value given by this evaluation. However, during the time period of analysis of the comparison results, a new evaluation of  $^{166}\text{Ho}$  half-life has been published as a result of the MRTDosimetry project which provided additional half-life value as a mean over five different measurements in three national metrology laboratories. Each laboratory used  $^{166}\text{Ho}$  solution obtained from another manufacturer [23] resulting in uncorrelated measurement of  $^{166}\text{Ho}$  half-life. Following the new half-life measurements, the evaluated result [21] seemed too high because it is biased by the value published in [19]. The selection of the  $^{166}\text{Ho}$  half-life used for the calculation of the KCRV was therefore not an easy task also keeping in mind that the half-life uncertainty could be the major uncertainty component in the uncertainty budgets. The  $^{166}\text{Ho}$  half-life value used in this comparison was selected in connection with the selection of the reference time, as described further.

Table 4: Relevant  $^{166}\text{Ho}$  half-life values reported in literature since 1989.

Number	$T_{1/2}$ (h)	Year	Reference
1	26.827 (5)	1989	[19]
2	26.7663 (44)	1992	[20]
3	26.794 (23)	2002	[24], update of [20]
4	26.795 (29) <sup>(1)</sup>	2004	[3]
5	26.824 (12)	2008	[25]
6	26.794 (50)	2014	[22], update of [24]
7	26.824 (30) <sup>(2)</sup>	2017	[21]
8	26.809 (14) <sup>(3)</sup>	2019	[23], used in this comparison

<sup>(1)</sup> strongly depends on [19] and [20];

<sup>(2)</sup> provisional evaluation for the MRTDosimetry project, originally proposed value for this comparison;

<sup>(3)</sup> arithmetic mean and its standard uncertainty determined from the five evaluations given in [23].

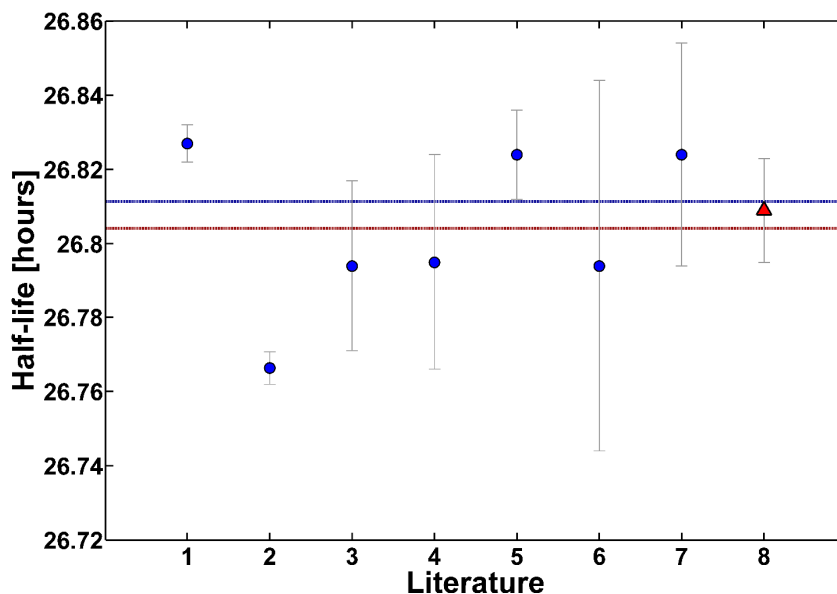


Figure 3: Graphical representation of relevant  $^{166}\text{Ho}$  half-lives reported in literature since 1989 (blue dots, red triangle) and the selected one for evaluation of this comparison (red triangle). The red line shows the arithmetic mean ( $T_{1/2} = (26.804 \pm 0.007) \text{ h}$ ; calculated from all values) and the blue line shows the power-moderated mean ( $T_{1/2} = (26.811 \pm 0.008) \text{ h}$ ; calculated from values 3-7 only. Values 1 and 2 were not included because they biased the result due to its very small uncertainty). 1 = [19], 2 = [20], 3 = [24], 4 = [3], 5 = [25], 6 = [22], 7 = [21], 8 = [23]. Values on x-axis correspond to Table 4.

The original reference time for the reported value of the activity per unit mass was set to 29 November 2017 11:00 UTC that was a day after the preparation and shipping of the  $^{166}\text{Ho}$  solution from the lead laboratory to the participants. However, two participants were able to perform the measurements as far as at the beginning of December that could lead to unduly bias of the participants' uncertainty due to the  $^{166}\text{Ho}$  half-life of up to 0.4 %.

To resolve these two problems with the undecided half-life and optimal reference time, the dependence of the KCRV and its uncertainty on these parameters was tested for several reference times set between 29 November and 3 December and three selected half-lives ranging from 26.795 (29) to 26.824 (30) h. It was found out that the KCRV has the weakest dependence on the half-life value when the reference time is set to 1 December 2017 0:00 UTC (Figure 4). This reference time also does not significantly bias the uncertainties reported by the participants due to the half-life uncertainty and, as a result, it allows to select any half-life within that range. Hence, the participants of the comparison jointly agreed to use the average value obtained from the five evaluations performed within the MRTDosimetry project [23]. Therefore, the KCRV of this key comparison is determined to **1 December 2017 0:00 UTC** using the  $^{166}\text{Ho}$  half-life of **(26.809 ± 0.014) h**.

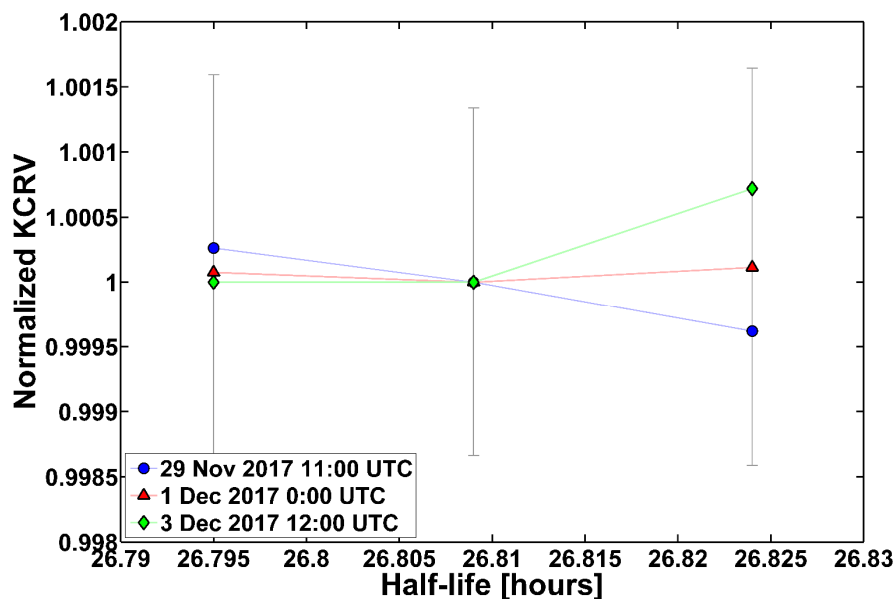


Figure 4: Dependence of the KCRV on  $^{166}\text{Ho}$  half-life and the reference time, normalized to the half-life selected for comparison. Only the uncertainties for the selected half-life are shown for picture clarity.

## 4 Results and discussion

### 4.1 Reported results and uncertainties

The reported results of the key comparison of activity of the radionuclide  $^{166}\text{Ho}$  per unit mass of aqueous solution at the participants' preferred reference time are presented in Table 5. The complete uncertainty budget of each participant is presented in Table 6. The combined uncertainty is expressed both with and without the component  $u(t_{ref})$  related to the decay between the reference time for the KCRV and the preferred reference time of each participant. It is clear that the selected reference time does not induce significant bias to the total uncertainty of any participant.

Table 5: Reported results of  $^{166}\text{Ho}$  activity per unit mass comparison at the reference time preferred by each participant.

Laboratory	Activity per unit mass (kBq·g <sup>-1</sup> )	Combined standard uncertainty (kBq·g <sup>-1</sup> )	Relative standard uncertainty (%)	Preferred reference time (UTC) by participants	Date of measurement
CMI	6827	11	0.16	29 Nov 2017 11:00	29-30 Nov 2017
ENEA	6950 <sup>(1)</sup>	97	1.38	29 Nov 2017 11:00	29 Nov 2017
LNE-LNHB	1925.5	6.5	0.34	1 Dec 2017 12:00	1-4 Dec 2017
NPL	160.8	0.5	0.29	5 Dec 2017 12:00	4-5 Dec 2017

<sup>(1)</sup> The result was obtained by the readings of the SIR ampoule received from CMI in 2017 in the IC-IG11 calibrated in 2019 by the new  $^{166}\text{Ho}$  standard developed at ENEA using a  $^{166}\text{Ho}$  solution provided by the LENA reactor in Pavia (see section 3.4.2 for details).

Table 6: Uncertainty budget of the participants.

Uncertainty component	Type	Laboratory:			
		CMI	ENEA	LNE-LNHB	NPL
		u (%)	u (%)	u (%)	u (%)
Counting statistics	A	0.06	0.25	0.2 <sup>(1)</sup>	0.120
Background	B	0.01	0.01	0.06	0.050
Weighing	B	0.01	0.01	0.1 <sup>(2)</sup>	0.100 <sup>(4)</sup>
Dilution	B	0.1			
Dead time	B	0.01	0.20	0.05 <sup>(3)</sup>	0.071 <sup>(5)</sup>
Counting time	B	0.01	0.01		
Statistical model	B		0.20		
Resolving time	B				0.100
Pile-up, afterpulse	B	0.01			0.028 <sup>(5)</sup>
Decay correction to preferred reference time <sup>(6)</sup>	B	0.08	0.25	0.20	0.01
Decay correction to reference time <sup>(7)</sup> , $u(t_{\text{ref}})$	B	0.05	0.05	0.02	0.15
Decay scheme parameters <sup>(8)</sup>	B		0.30		
Extra-/Inter-polation of efficiency curve	B	0.08	0.30		0.150
Reproducibility	B				0.100
Gate Selection (gamma)	B				0.100
Accidental coincidences	B				0.010
TDCR modelling	B			0.1	
Ampoule weighting	B			0.1	
IC calibration	B		0.50		
Variability from different TDCR counter	B		0.68		
Variability from different vials used for IC calibration	B		0.60		
Variability from different solution used (CMI solution and calibration solution)	B		0.70		
Combined standard uncertainty without $u(t_{\text{ref}})$		0.16	1.38	0.34	0.29
<b>Combined standard uncertainty</b>		<b>0.17</b>	<b>1.38</b>	<b>0.34</b>	<b>0.32</b>

- (1) st. dev. on 4 sources;
- (2) pycnometer technique;
- (3) live time technique;
- (4) including dilution;
- (5) liquid scintillation and gamma combined;
- (6) recalculation from measurement time to preferred reference time of each participant (Table 5); half-lives used: CMI, ENEA, LNHB: 26.824(30) h, NPL: 26.795(29) h;
- (7) recalculation from preferred reference time of each participant to the reference time of KCRV using a jointly agreed half-life 26.809(14) h given in chapter 3.6;
- (8) gamma emissions uncertainty due to corrections to the difference between the vial received by CMI and the one used later for the calibration of the ionization chamber.

### 4.3 The key comparison reference value

The participants' results recalculated to the reference time using the selected  $^{166}\text{Ho}$  half-life are summarized in Table 7 and graphically shown in Figure 5.

Table 7: Results of  $^{166}\text{Ho}$  activity per unit mass comparison and the KCRV at the reference time on 1 Dec 2017 00:00 UTC.

Laboratory	Activity per mass (kBq·g <sup>-1</sup> )	Combined standard uncertainty (kBq·g <sup>-1</sup> )	Relative standard uncertainty (%)		
			Total	Total without $u(t_{\text{ref}})^{(2)}$	Due to $u(t_{\text{ref}})^{(2)}$ only
CMI	2622.8	4.4	0.17	0.16	0.05
ENEA <sup>(1)</sup>	2670.1	36.9	1.38	1.38	0.05
LNE-LNHB	2626.0	8.9	0.34	0.34	0.02
NPL	2624.1	8.5	0.32	0.29	0.15
KCRV	2623.6	3.6	0.14	-	-

<sup>(1)</sup> The result was excluded from the KCRV;

<sup>(2)</sup> Uncertainty of the decay correction to the reference time.

The final key comparison reference value, including CMI, LNE-LNHB and NPL results, is  $(2623.6 \pm 3.6)$  kBq·g<sup>-1</sup> on 1 December 2017 0:00 UTC. As the ENEA result is not based on a primary measurement method, it is not included in the KCRV.

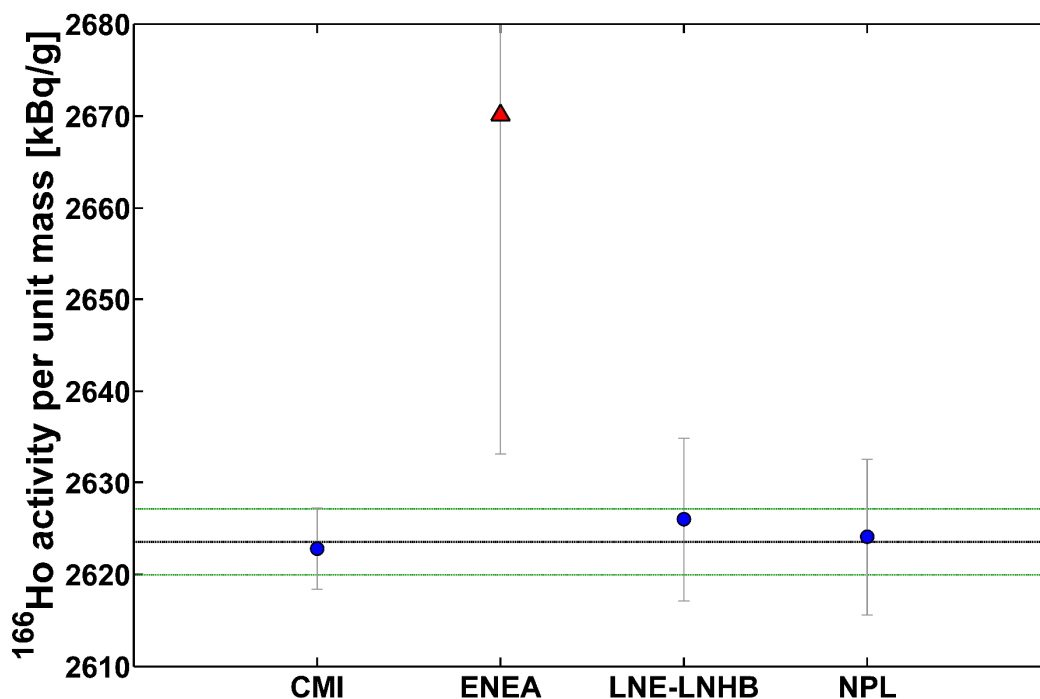


Figure 5: The comparison of  $^{166}\text{Ho}$  activity per unit mass of all participants at the reference time. Error bars represent the combined standard uncertainty. The power-moderated mean value is shown (black line) with its standard uncertainty (green lines). The value presented by a red triangle was excluded from the calculation of KCRV.

The  $\chi^2$  value equals to 0.054. The degree of equivalence of the participants' results, which represents the difference of the reported value from the KCRV, and its expanded uncertainty [18] equal to  $(-0.8 \pm 5.2) \text{ kBq}\cdot\text{g}^{-1}$  for CMI,  $(2.4 \pm 16.3) \text{ kBq}\cdot\text{g}^{-1}$  for LNE-LNHB, and  $(0.5 \pm 15.4) \text{ kBq}\cdot\text{g}^{-1}$  for NPL. The results are depicted in Figure 6.

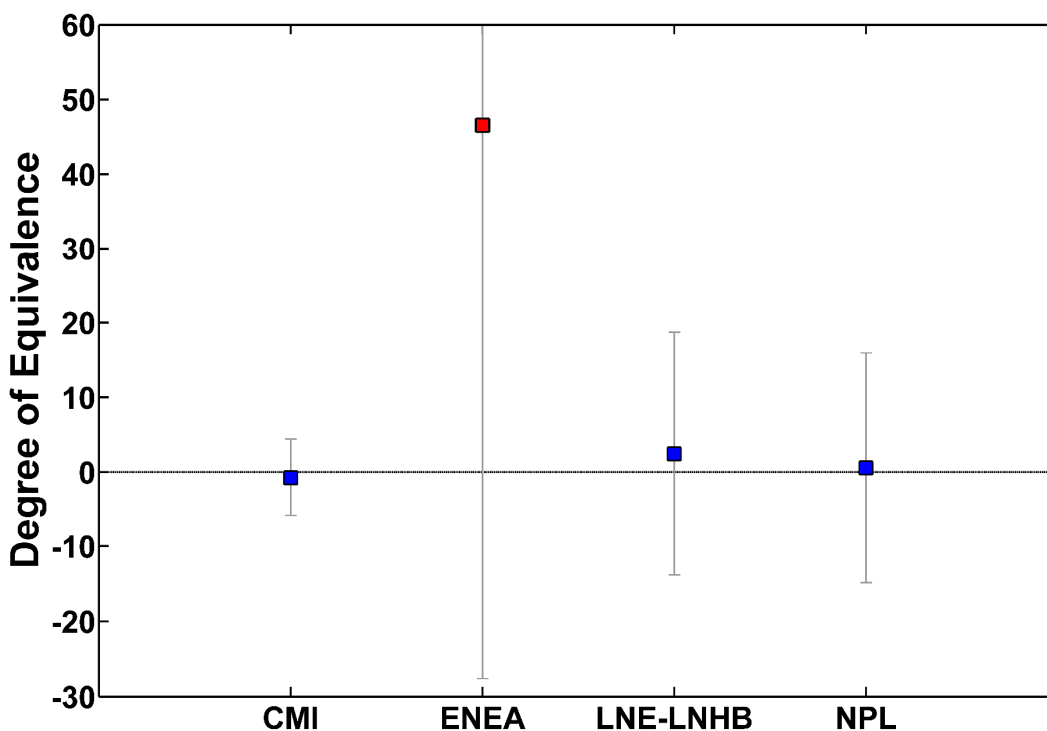


Figure 6: The degree of equivalence of the reported results. The value presented by a red square was excluded from the calculation of KCRV.

The ENEA result differs from the KCRV by about 1.8 % corresponding to the degree of equivalence of  $(46.5 \pm 74.1) \text{ kBq} \cdot \text{g}^{-1}$ . The authors assume that the difference is caused by adjunctive uncertainty components introduced by the used calibration chain, specifically by the remaining uncorrected difference in the measurement geometry between the vial received from CMI and the vial used later for the calibration of the ionization chamber.

## 5 Conclusions

The EURAMET.RI(II)-K2.Ho-166 key comparison of activity of  $^{166}\text{Ho}$  radionuclide per unit mass in aqueous solution, registered in the EURAMET database under the number 1435, was completed successfully with the participation of four European national metrology laboratories. The key comparison reference value of  $(2623.6 \pm 3.6) \text{ kBq} \cdot \text{g}^{-1}$  was determined from the results of three participants at the reference time of 1 December 2017 00:00 UTC. For this reference time, the result has the weakest dependence on the  $^{166}\text{Ho}$  half-life. The half-life used for the purpose of recalculation of the participants' results to this reference time was  $(26.809 \pm 0.014) \text{ h}$ .

The new standards of  $^{166}\text{Ho}$  radionuclide activity per unit mass of aqueous solution will improve metrology capabilities of the involved institutes and contribute to the decrease of uncertainty in dose assessment in the molecular radiotherapy applications.

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