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Primary standardization and determination of gamma ray emission intensities of Ho-166

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ABSTRACT

The procedure followed by the Nuclear Metrology Laboratory (LMN) at the IPEN-CNEN/SP, in São Paulo, for the primary standardization of ^{166}Ho is described. The activity of ^{166}Ho was determined by the efficiency extrapolation technique applied to a 4πβ(PC)-γ coincidence system using a gas flow proportional counter in 4π geometry coupled to a 76 × 76 mm NaI(Tl) crystal. The results for the γ-rays intensities at 80.57 and 1379.45 keV were 0.0651(11) and 0.00904(11), respectively.

1. Introduction

The radionuclide ^{166}Ho shows potential uses on selective internal radiation therapy such as in liver tumors (Nijsen et al., 2001) and in the treatment of patients with skeletal targeted radiotherapy using therapeutic agents such as ^{166}Ho-DOTMP, ^{166}Ho-TTHMP and ^{166}Ho-PAM that are bone-seeking radiopharmaceuticals and may play a role in the management of malignant disease localized in the bone or bone marrow.

The ^{166}Ho decay scheme is shown in Fig. 1 (Bé et al., 2004). It has a 26.8 h half-life and decays by 100% β^- emission to the excited states of ^{166}Er, with maximum beta energy of 1854.5 keV, followed by γ- and X-rays emissions. The 80.57 keV γ-ray has the maximum emission intensity (6.55%) among the gamma transitions in the decay scheme. There is also an important weak component (0.933%) at 1379.45 keV, which was considered in the primary standardization.

The β^- radiation have a maximum range of 8.7 mm in soft tissue and 3.8 mm in bone (Breitz et al., 2006). For this reason, ^{166}Ho is an excellent radionuclide for bone marrow treatment because these high energy β^- rays transfer sufficient absorbed dose to the bone (Yousefnia et al., 2014). Besides, its half-life is short enough to allow delivery of high-dose chemotherapy and cryopreserved peripheral blood stem cells transplantation within 6–10 days (Breitz et al., 2006).

Some publications concerning the primary activity, the absolute gamma-ray intensities and the decay data measurements for^{166}Ho are old (Sekine and Baba, 1981), (Ardisson et al., 1992), (Coursey et al., 1994). However, an excellent publication has been released recently concerning new measurements of this radionuclide (Bobin et al., 2019). In this publication, different primary standardization techniques have been used, absolute X- and γ-ray intensities were determined, as well as its half-life.

The Nuclear Metrology Laboratory (LMN) at the IPEN-CNEN/SP, in São Paulo, has performed primary measurements of activity for a wide range of radionuclides; in particular for some used in nuclear medicine such as ^{99m}Tc (Brito et al., 2012), ^{68}Ga (Koskinas et al., 2014), ^{111}In (Matos et al., 2014), ^{64}Cu (Yamazaki et al., 2018). Measurements of the activity of a^{166}Ho solution by primary methods, as well as the photon emission intensities per decay of its γ-rays have been carried out for the first time at the LMN in order to contribute to the current set of decay data measurements.

2. Experimental method

2.1. Sample preparation

A powder sample of Ho_2O_3, with 99.9% purity, supplied by British Drug Houses Ltd.(British Drug Houses Limited, 1996) was used. The isotope ^{166}Ho was produced by ^{165}Ho (n, γ) ^{166}Ho reaction, near the core of the IEA-R1 research reactor at the IPEN, operated at 4.5 MW, in a thermal neutron flux of 1.0×10^{13} cm^{-2} s^{-1}, for an irradiation time of 1 h and a cooling time of 24 h.

The sources were obtained by irradiating 3.5 mg Ho_2O_3 placed in a sealed polyethylene envelope and inserted into a cylindrical aluminum capsule. The irradiated sample was dissolved in 0.25 mL of 6.0 mol.L^{-1} hydrocloric acid solution and diluted in 1.0 mL of 0.1 mol.L^{-1}

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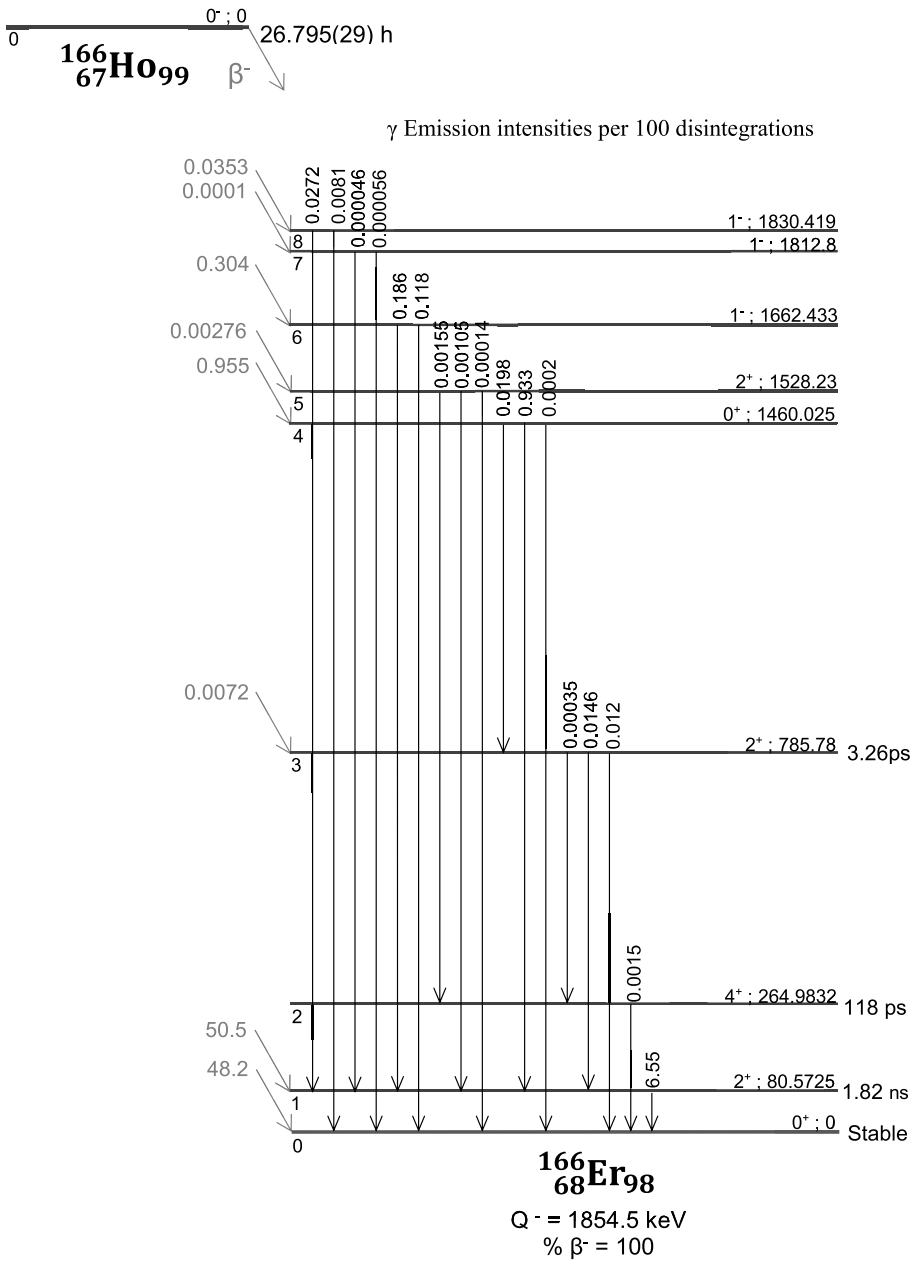

Fig. 1. Decay scheme of ^{166}Ho. [Bé et al., 2004]. All energies are in keV.

hydrochloric acid to form a stock solution. This stock solution was diluted 100 times with 0.1 mol.L^{-1} hydrochloric acid giving rise to a so-called "original" solution. This was the one used for preparing ^{166}Ho sources on thin collodion films, for the γ-ray emission intensity determination at 80.57 keV and 1379.45 keV, and one flamed-sealed ampoule with 1 mL solution for measuring the less intense γ-ray lines and check for impurities.

In addition, accurately weighed aliquots were taken from the original solution and diluted by a 4.5 dilution factor with 0.1 mol.L^{-1} hydrochloric acid and were used for preparing six ^{166}Ho sources with masses ranging from 9 to 50 mg, to be measured in the 4πβ(PC)-γ system.

These sources were prepared by dropping weighed aliquots on a collodion film 20 μg cm^{-2} thick. These films have been previously coated on each side with a 10 μg cm^{-2} thick gold layer, in order to render the film conductive. A seeding agent (CYASTAT SN) was used for improving the deposit uniformity and the sources were dried in a desiccator. The accurate source mass determination was performed by the pycnometer technique using a Mettler 56XP balance.

2.2. 4πβ-γ coincidence counting

The 4πβ−γ coincidence technique (Campion, 1959) was applied by means of a coincidence counting system composed by a 4π gas-flow proportional counter (PC), filled with P-10 gas mixture at 0.1 MPa, as the β channel, and by a 76 mm × 76 mm NaI(Tl) crystal, positioned above the PC counter, as the γ channel.

The ^{166}Ho source activities were determined by the extrapolation method (Baerg, 1973) from data acquired with a gamma window covering the 1379.45 keV full energy peak. The events were recorded by a software coincidence counting system (SCS), developed at the LMN (Toledo et al., 2007). This system digitalizes both beta and gamma amplified pulses registering the pulse height and the occurrence time for all pulses. It is based on a National Instruments PCI-6132 card (National Instruments, 2013). The activity calculation was performed by means of

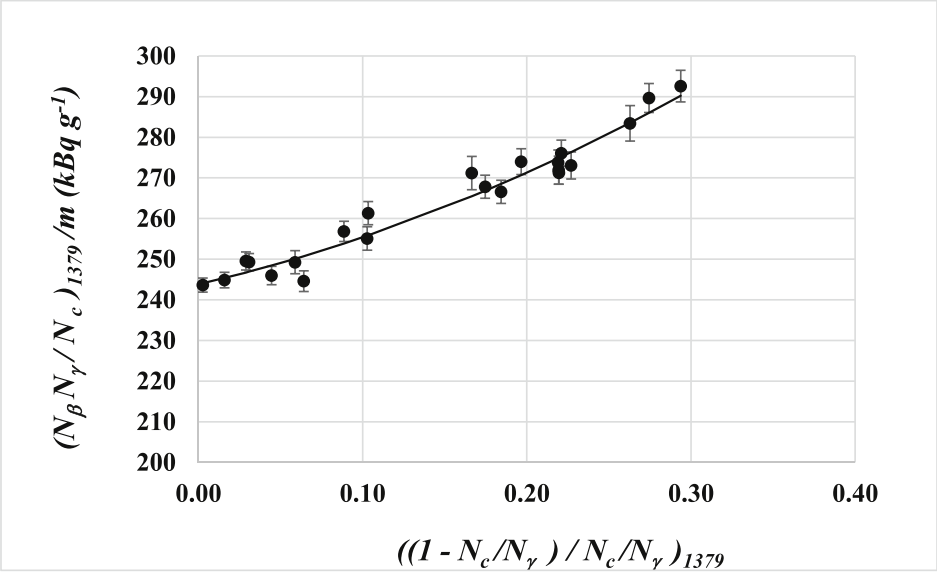

Fig. 2. Extrapolation curve for the 1379 keV γ-window obtained with the 4πβ−γ coincidence system. The black dots are experimental points; the continuous line corresponds to the fitting curve.

code SCTAC version 6.0 (Dias, 2010), developed at the LMN, which allows the selection of γ-ray window and other parameters, such as dead time and resolution time, after the data acquisition has been completed.

2.3. Gamma-ray intensities measurements

The determination of the γ-ray intensities was performed with a high purity germanium (HPGe) γ-ray spectrometer with a 500 μm thick Be window, having a 1.79 keV energy resolution at 1332.5 keV. The full energy peak efficiency was measured at a source-to-detector distance of 17.9 cm in the energy range from 80.57 keV to 1408.03 keV, using collodion sources and sealed ampoules.

The absolute γ-rays emission intensities of the 80.57 keV and 1379.45 keV lines were determined with ^{166}Ho collodion sources calibrated by the 4πβ(PC)-γ coincidence system, and a HPGe γ-ray spectrometer calibrated with collodion sources of ^{133}Ba, ^{60}Co, ^{152}Eu and ^{166m}Ho previously standardized in the 4πβ−γ coincidence system. In addition, ^{152}Eu, ^{60}Co, ^{133}Ba, ^{137}Cs flamed-sealed ampoules, filled with solutions standardized by the 4πβ-γ coincidence system, were used for calibrating the HPGe in order to measure the less intense lines, using an ampoule filled with ^{166}Ho original solution.

In order to avoid the high energy beta particles from entering the HPGe Be window, a 7.0 mm thick aluminum absorber was placed between the source and detector. The HPGe efficiency curve has been established considering the presence of this absorber.

The area under the peaks were calculated by code Alpino Version 4.0 developed at the LMN (Dias, 2001), which applies a sigmoidal background function as described by Dias et al. (2004). Dead time and pile-up corrections were applied by measuring a reference pulser located near the upper edge of the gamma-ray spectrum together with the sources (Debertin and Helmer, 1988).

The full energy peak efficiency curve for the adopted geometry was also calculated by means of Monte Carlo code MCNP6 (ORNL, 2013), in order to provide the efficiency above 1408.03 keV, due to the lack of experimental points. The average residual obtained between the experimental results and the calculated values was used for estimating

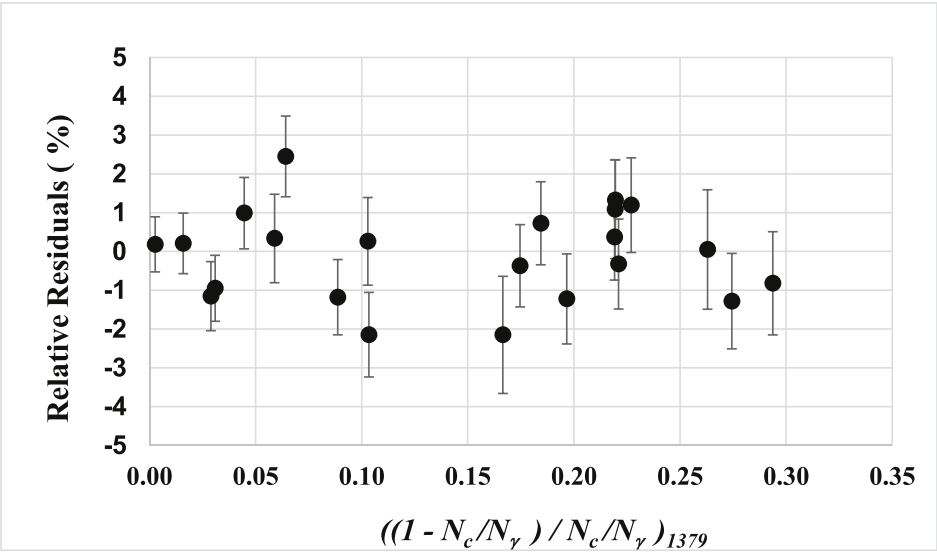

Fig. 3. Relative residuals between experimental and fitted values, in percent.

Table 1
Typical partial uncertainties in the 4πβ−γ coincidence system activity, in percent (k = 1).

Components	Uncertainty (%)
Counting statistics (included in fitting)	-
Dead time	0.05
Weight	0.10
Background (included in the fitting)	-
Decay	0.22
Resolving time	0.05
Extrapolation curve fitting	0.54
Combined uncertainty	0.60

the uncertainty for the MCNP6 calculated efficiencies above this energy. In addition, the calculated total and full energy peak efficiencies were used for obtaining the cascade summing corrections by means of code SUMCOR, developed at the LMN (Dias et al., 2018).

3. Results and discussion

The 4π(PC) beta efficiency was varied from 77.30% to 99.74% using a gamma-ray gate setting at 1379.45 keV by using external absorbers covering the sources on both sides. Fig. 2 shows the experimental extrapolation curve that yields the activity. This curve was fitted by a second-degree polynomial using code LINFIT (Dias, 1999) which incorporates the covariance matrix calculation. The relative residuals

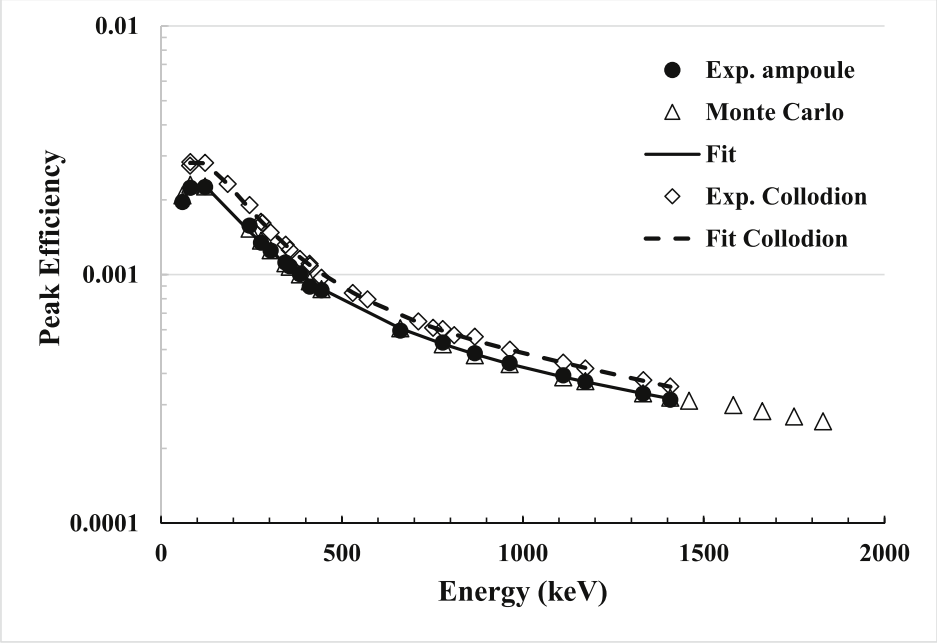

Fig. 4. Full energy peak efficiency curves for the HPGe spectrometer. The black dots are experimental data obtained with ampoules, and the continuous line is the fitting with these data; the triangles are Monte Carlo simulation obtained with ampoules; the diamonds are experimental data obtained with collodion sources, and the dashed line is the fitting with these data.

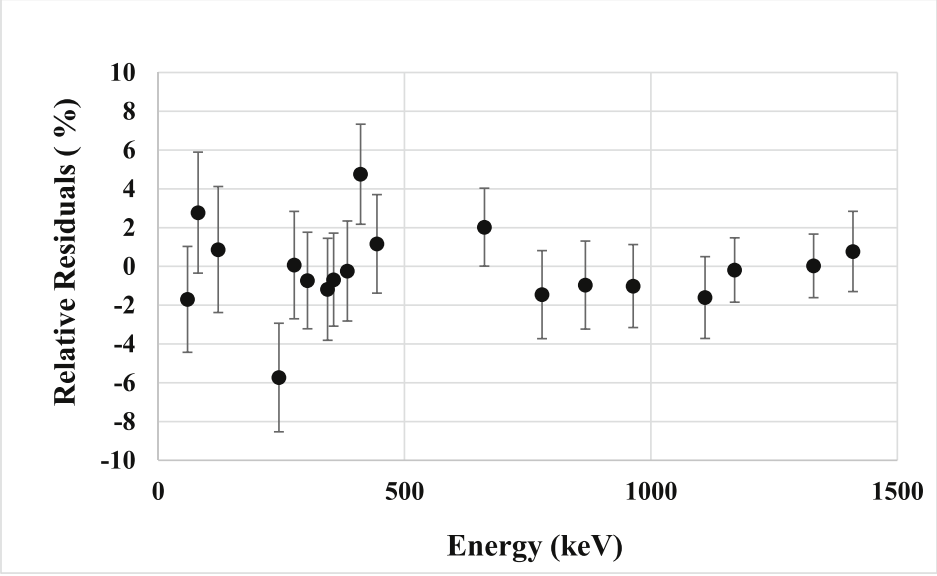

Fig. 5. Relative residuals between experimental and fitted HPGe efficiency values obtained by means of ampoules, in percent.

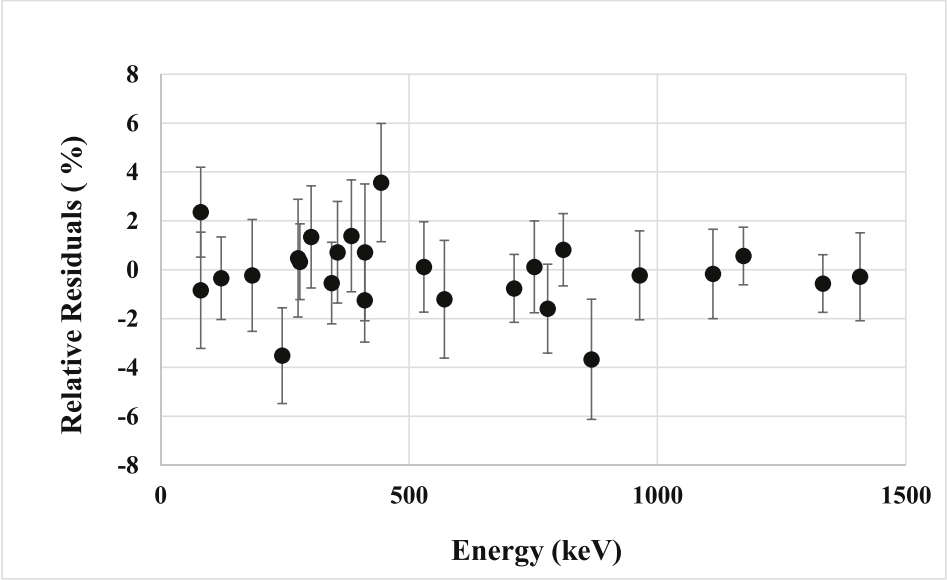

Fig. 6. Relative residuals between experimental and fitted HPGe efficiency values obtained by means collodion sources, in percent.

Table 2
Present results of ^{166}Ho γ-ray intensities in comparison with recent literature values *(Bobin et al., 2019) and evaluation (Bé et al., 2004), in percent.

γ Energy (keV)	This work	Evaluation	LNHB*	CMI*	NPL*
80.57	**6.51 (11)**	**6.55 (8)**	**6.61 (7)**	**6.636 (49)**	**6.618(51)**
674.24	**0.0204 (7)**	**0.0198 (17)**	**0.0193 (8)**		**0.02142 (68)**
705.21	**0.0143 (5)**	**0.0146 (12)**	**0.0134 (6)**		**0.01474 (65)**
785.78	**0.0126 (5)**	**0.0120 (3)**	**0.0118 (6)**		**0.01306 (58)**
1379.45	**0.904 (11)**	**0.933 (35)**	**0.896 (13)**	**0.904 (20)**	**0.9051 (69)**
1581.85	**0.175 (5)**	**0.186 (4)**	**0.180 (4)**	**0.180 (6)**	**0.1792 (24)**
1662.42	**0.114 (3)**	**0.118 (5)**	**0.114 (3)**	**0.1164 (41)**	**0.1157 (13)**
1749.84	**0.0255 (8)**	**0.0272 (10)**	**0.0259 (7)**		**0.02590 (48)**
1830.41	**0.0079 (3)**	**0.0081(2)**	**0.0080 (3)**		**0.00807 (26)**

between the experimental data and fitting are shown in Fig. 3. The distribution of points is quite uniform and does not show any noticeable trend.

Typical partial uncertainties for these activity measurements are presented in Table 1. The main uncertainties were counting statistics, dead time, gamma background and efficiency curve extrapolation.

Fig. 4 shows three different efficiency curves for the coaxial HPGe detector. The first one (black dots) was obtained with standard solutions in sealed ampoules; the second one (diamonds) was obtained with standard thin sources on collodion films, both calibrated in a 4πβ(PC)−γ coincidence system. These two sets of experimental data were fitted by the least square method using LOGFIT code (Dias and Moreira, 2005), which also incorporates the covariance matrix calculation. For ampoules and collodion sources, the reduced Chi-square values were 1.07 and 1.22, respectively, indicating satisfactory fits. The third curve shown in Fig. 4 (triangles) is a comparison between experimental points, obtained with ampoules, with a MCNP6 Monte Carlo calculation, performed in order to obtain efficiency values for γ-ray energies above 1408 keV. The optimized parameters used in this modeling were obtained by comparing the Monte Carlo results with the experimental ones at energies below 1408 keV.

Table 3
Typical uncertainty components of the γ-ray emission intensity, in percent (k = 1).

Component	80.57 keV[a] Uncertainty (%)	1379 keV[a] Uncertainty (%)	Less intense Uncertainty (%)
Statistics net peak area gamma-rays	**0.08**	**0.51**	**0.38–1.97**
Weight	**0.1**	**0.1**	**0.1**
Decay	**0.09**	**0.09**	**0.15**
Dead time	**0.29**	**0.29**	**0.30**
Activity 4πβ−γ coincidence system	**0.60**	**0.60**	**0.60**
Dilution factor	**014**	**0.14**	**0.14**
Activity of original solution	**0.62**	**0.62**	**0.62**
HPGe Efficiency	**1.62**	**0.89**	**1.04–1.40**
Ampoulegeometry			**1.74–2.25**
Combined uncertainty	**1.76**	**1.24**	**2.88–3.67**

[a] Absolute value obtained by means of collodion sources.

Fig. 5 shows the relative residuals between the fitted and experimental values for ampoules and Fig. 6 shows the relative residuals between the fitted and experimental values for collodion sources. No noticeable biases are shown in both distributions.

The absolute γ-ray intensities obtained by the HPGe spectrometer with 7.0 mm aluminum absorber are shown in Table 2. In this table, the values at 80.57 keV and 1379.45 keV are absolute and resulted (6.51 ± 0.11) % and (0.904 ± 0.011) %, respectively, obtained with collodion sources. The emission intensities for other γ rays, namely: 674.24 keV, 705.21 keV, 785.78 keV, 1581.85 keV, 1662.42 keV, 1749.84 keV and 1830.41 keV are also absolute and were obtained with a calibrated ampoule. These data are compared to the recommended values (Bé et al., 2004) and to the most recent (Bobin et al., 2019). There is a good agreement at all energies within the experimental uncertainties. Table 3 shows typical uncertainty components of the γ-ray emission intensity, in percent (with a coverage factor k = 1) involved in the final values, in order to obtain the combined uncertainty.

4. Conclusion

The primary standardization of ^{166}Ho in a 4πβ−γ coincidence

counting system, with a proportional counter associated with a Software Coincidence System (SCS) was performed, enabling the determination of the absolute γ-ray emission intensities of the 80.57 keV and 1379.45 keV γ lines by combining the results from the standardization system and a calibrated HPGe gamma-ray spectrometer. An aluminum absorber was used to prevent the high beta particles from crossing the Be HPGe window.

It was also possible to determine the emission intensity of other less intense γ-rays using a higher activity solution. The results are in good agreement with the literature within the experimental uncertainties.

Author contribution statements

M. F. Koskinas and M. S. Dias conceived of the presented idea; M. F. Koskinas and M. S. Dias developed the theory and performed the computations; M. F. Koskinas and I. M. Yamazaki contributed to sample preparation; I. M. Yamazaki D. S. Moreira, R. Semmler and F. Brancaccio carried out the experiment; D. S. Moreira. M. F. Koskinas and M. S. Dias contributed to the interpretation of the results. D. S. Moreira Designed the figures; M S. Dias made the Monte Carlo simulations All authors provided critical feedback and helped shape the research, analysis and manuscript.

Declaration of competing interest

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