Applied Radiation and Isotopes 70 (2012) 2006–2011

Contents lists available at SciVerse ScienceDirect

Applied Radiation and Isotopes

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

Standardization of Ga-68 by coincidence measurements, liquid scintillation counting and $4\pi\gamma$ counting

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ARTICLE INFO

Available online 25 February 2012

Keywords:
Ga-68
Ge-68
Radionuclide standardization

ABSTRACT

The radionuclide ^{68}Ga is one of the few positron emitters that can be prepared in-house without the use of a cyclotron. It disintegrates to the ground state of ^{68}Zn partially by positron emission (89.1%) with a maximum energy of 1899.1 keV, and partially by electron capture (10.9%). This nuclide has been standardized in the frame of a cooperation project between the Radionuclide Metrology laboratories from CIEMAT (Spain) and CNEA (Argentina). Measurements involved several techniques: $4\pi\beta-\gamma$ coincidences, integral gamma counting and Liquid Scintillation Counting using the triple to double coincidence ratio and the CIEMAT/NIST methods. Given the short half-life of the radionuclide assayed, a direct comparison between results from both laboratories was excluded and a comparison of experimental efficiencies of similar NaI detectors was used instead.

1. Introduction

The radionuclide ^{68}Ga deserves special interest in positron emission tomography (PET) because it is one of the few positron emitters that can be prepared in-house without the use of a cyclotron using a ^{68}Ge generator. It has important medical applications for neuroendocrine tumors. ^{68}Ga disintegrates to the ground state of ^{68}Zn with a half-life of 67.71 min, partially by positron emission (89.1%) with a maximum energy of 1899.1 keV, and partially by electron capture (10.9%) (Bé et al., 2004). Besides the main gamma transition (1077.35 keV) there are 13 weak gamma transitions from five excited levels in ^{68}Zn. A simplified decay scheme is given in Fig. 1.

There is only one reference describing the absolute standardization of this nuclide (Smith and Williams, 1971) and a few more about the ^{68}Ge/^{68}Ga mixture in equilibrium (Schonfeld et al., 1994; Grigorescu et al., 2004; Zimmerman et al., 2008). The standardization described in this paper involves several techniques and was the result of a cooperation project between the Radionuclide Metrology laboratories from CIEMAT (Spain) and CNEA (Argentina). An overall view of the complete standardization and comparison procedure followed at both laboratories is presented in Fig. 2. Given the short half-life of the nuclide, a direct comparison of sources could not be made and a comparison of experimental efficiencies of similar NaI detectors was used instead.

2. Standardization at CIEMAT

2.1. Material

A purified solution of ^{68}Ga was obtained by elution from a ^{68}Ge generator in HCl form. The solution was stabilized by adding a complexing agent (EDTA) to avoid Ga losses during source preparation, Purity tests were carried out by liquid scintillation counting (LSC) and indicated a ^{68}Ga/^{68}Ge activity ratio of $(2.10^6 \pm 0{,}5.10^6)$ at the elution time, and a factor of eight lower at the time of starting the measurements. This contribution had negligible influence in the standardization process. Gamma spectrometry measurements were also taken to check for impurities and showed no traces of contaminants as could be expected for a solution obtained from a generator.

Sources for all standardization methods were prepared by the pycnometer technique using a Mettler-Toledo MX5 balance.

2.2. $4\pi\beta-\gamma$ coincidence measurements

A set of three sources with masses between 11 and 16 mg were prepared onto metallized Vyns foils. The measurement setup included a pressurized proportional counter, with P10 counting gas at 450 kPa in the beta channel with separate preamplifiers for each body counter and a NaI (Tl) detector in the gamma channel, respectively. Both channels were equipped with spectroscopy amplifiers. The output signals were sampled by

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doi:10.1016/j.apradiso.2012.02.066

a 2-channels digital acquisition system, made by ULS-KOREA, at a rate of 100 MS s^{-1}. This unit generates a binary output file with information about all detected pulses. Pulse amplitudes and time stamps from both channels are registered in 10 ns time intervals. File post-processing with in-house software allows the selection of the energy threshold of the beta channel and the gamma windows as required by the coincidence method.

The standardization procedure was based in changing the efficiency in the β^+ channel by threshold variation. Coincidences between β^+ pulses and 511 keV annihilation photons were selected; therefore, the gamma window was selected around the full energy peak of 511 keV in the NaI (Tl) detector. This peak also includes a low proportion of Compton-scattered 1077 keV photons that does not interfere hardly in the measurements. The energies of the X-rays and Auger electrons following electron capture decay are around 8 keV. These electron capture particles are detected in the proportional counter but, as the lower discrimination level is set at 10 keV, they are not registered. With these setup settings, the standardization only depends on the branching ratio of the β^+ branch. A typical 3-dimensions coincidence spectrum is presented in Fig. 3.

The extrapolation was performed from a maximum β^+ efficiency of 94% to a minimum of 85%. When using this kind of discrimination method, the extrapolation to lower β^+ efficiencies is difficult given that the emission of annihilation photons from high energy positrons with low deposited energy takes place far away from the source. Corrections for dead time, accidental coincidences, background and

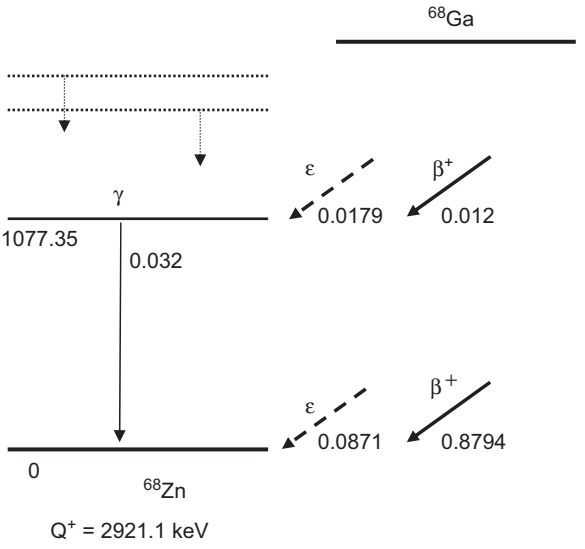

Fig. 1. Simplified decay scheme of ^{68}Ga. Data taken from Bé et al. (2004). Only the two lower energy levels are represented.

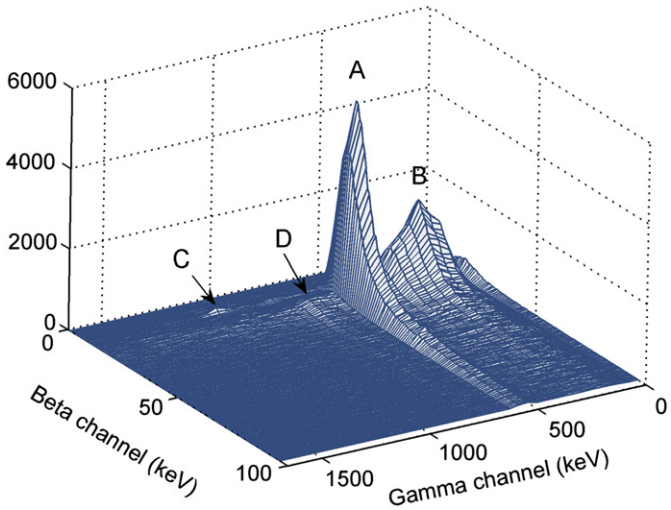

Fig. 3. 3-dimensions spectrum obtained at CIEMAT using a two-channel digital acquisition system. The main structures correspond to coincidences of positrons with: (A) the full absorption peak of 511 keV and (B) Compton-scattered 511 keV photons. Additional structures that can be identified are: coincidences between Auger electrons and 1077 keV photons (C) and between positrons and Compton-scattered 1077 keV photons (D).

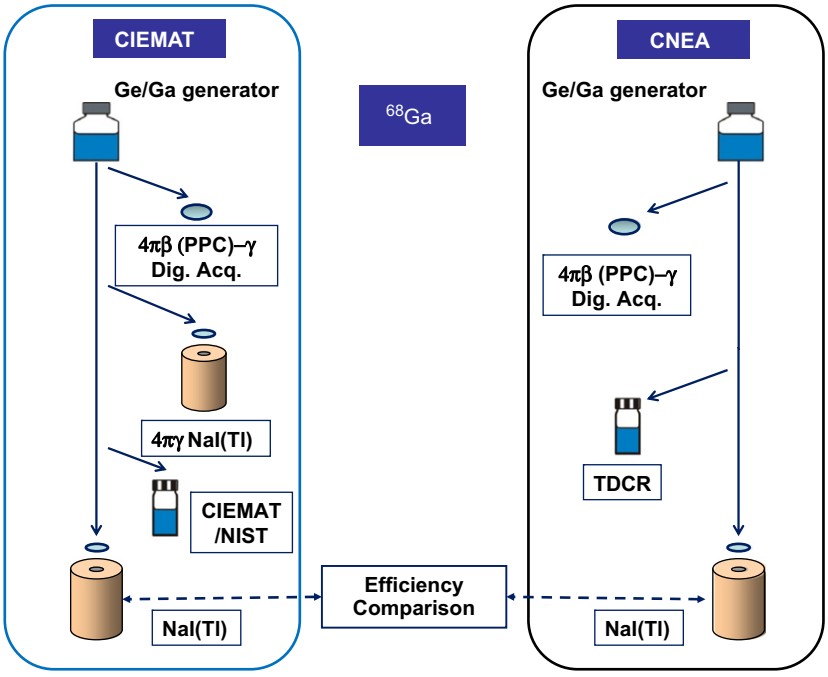

Fig. 2. Flowchart of the standardization of ^{68}Ga at CIEMAT and CNEA including the comparison procedure.

decay were performed using classical formulae (Gandy, 1963; Smith, 1978).

Activity concentration at the reference time was 1790 (11) Bq mg^{-1}. All uncertainty contributions, expressed in relative terms, are detailed in Table 1. The main component corresponds to counting statistics and extrapolation obtained in the fitting of the experimental results to a straight line. Its contribution, is $u_{rcs}=0.6\times10^{-2}$. As the standardization depends on the Auger electrons/β^+ ratio, there is an important contribution $u_{rnd}=0.16\times10^{-2}$ derived from the uncertainty in this nuclear parameter. A similar value corresponds to the effect of the half-life. The total combined relative uncertainty is $u_{rtot}=0.65\times10^{-2}$.

Additional coincidence measurements have been performed following the bidimensional extrapolation method described by Smith and Williams (1971) although they were not retained for the final results. In our setup, two gamma windows were selected around the 511 and 1077 keV full energy peaks and the efficiency was varied in the β^+ channel by threshold variation from 0 to 5 keV, an energy region that includes Auger electrons and low energy positrons. Using this method, the maximum computed β^+ efficiency was 99.5%. Nevertheless, results have a higher uncertainty than one-dimensional extrapolation for two main reasons: (1) the impossibility of varying independently the Auger and β^+ efficiency and (2) the low number of coincidences between Auger electrons or positrons and fully absorbed 1077 keV photons as a result of the low probability emission and low detection efficiency. In the Smith and Williams's implementation, the first problem was solved by adding absorbers and changing the counting gas.

2.3. $4\pi\gamma$ counting with a NaI (Tl) well-type detector

The basis of the standardization of sources of gamma emitters by integral gamma counting has been described in detail, among others, by Winkler and Pavlik (1983). The experimental equipment used at CIEMAT included a 7.5×7.5 cm NaI (Tl) well-type detector, a delay line amplifier and a fixed dead-time ADC. Four sources with masses between 10 and 12 mg were deposited onto polyethylene foils (75 micrometers thick) dried at room temperature and covered with a similar foil. They were placed inside the detector well and measured in two configurations: uncovered and between two Al disks, 1 mm thick, so that most positrons annihilate close to their emission point. Typical count rates varied between 800 and 2000 s^{-1}.

Implementing the $4\pi\gamma$ counting method for sources of positron emitters requires a detailed Monte Carlo simulation in order to accurately know the counting efficiency given that the emission of annihilation radiation can take place outside the radioactive source. The procedure followed in calculations was the same described in a previous paper on the standardization of ^{18}F and ^{22}Na (García-Toraño et al., 2007; Peyres and García-Toraño, 2011). For uncovered sources, calculated efficiencies were $\varepsilon_{\beta+}=0.886$ for the positron emitting branch and $\varepsilon_{ce}=0.0885$ for the electron capture branch, respectively. The total counting efficiency was obtained by adding the contribution of both branches:

$$\varepsilon = P_{\beta+}e_{\beta+}+P_{ec}e_{ce}=0.799(4)$$

where $P_{\beta+}$ and P_{ec} represent the emission probabilities for each branch. The measurement of covered sources was slightly less efficient ($\varepsilon=0.774$ (4)).

The activity concentration at the reference time was estimated as 1811 (10) Bq mg^{-1}. It corresponds to the mean of eight results, half of which correspond to covered sources and the other half to uncovered sources.

A detailed list of uncertainty components is presented in Table 1. The major contribution corresponds to the calculation of the counting efficiency whose components are: (a) the statistics of the simulation and (b) the numerical model. The relative component of the statistics was directly calculated by PENELOPE (Salvat et al., 2006) as $u_{rs}=0.26\times10^{-2}$. The contribution of the numerical model is difficult to evaluate, as it depends on the accuracy of the data provided by the detector manufacturer. From the measurement of covered and uncovered sources its relative contribution was conservatively estimated as $u_{rnm}=0.4\times10^{-2}$. Therefore the combined uncertainty for efficiency calculation was $u_{ref}=0.48\times10^{-2}$. An additional factor that affects the efficiency is the nuclear data parameters for which a separate contribution $u_{np}=0.13\times10^{-2}$ was estimated. Among the additional components, the half-life has the major contribution.

Table 1
Uncertainty components in the standardization of ^{68}Ga at CIEMAT and CNEA. The two first have been considered type "A" components and the remaining ones, type "B". Values are expressed in % of the Activity Concentration.

METHOD	CIEMAT-LMRI			CNEA-LMR	
Uncertainty component	**4πβ−γ coincidences**	**4πγ counting**	**LSC CIEMAT/NIST**	**4πβ−γ coincidences**	**TDCR**
Counting statistics		0.1	0.1		0.05
Extrapolation (inc. counting)	0.6			0.8	
Weighing	0.1	0.1	0.1	0.1	0.1
Dead time	0.05	0.05	0.02	0.05	0.02
Efficiency determination		0.48	0.35		0.5
Background	0.03	0.01	0.01	0.05	0.05
Pile up		0.01	0.01	–	–
Counting time	0.01	0.01	0.01	0.01	0.01
Impurities	–	–	–	–	0.04
Nuclear data	0.16	0.13	0.03	0.16	0.16
Quenching determination	–	–	0.1	–	–
k_B value	–	–	0.2	–	–
Half-life	0.16	0.16	0.16	0.16	0.16
Resolving time	0.04			0.04	–
Source stability	–	–	0.2	–	–
Combined uncertainty	**0.65**	**0.55**	**0.51**	**0.86**	**0.56**

2.4. Liquid scintillation counting measurements.

The CIEMAT/NIST method (Grau and García-Toraño, 1981) was used for liquid scintillation counting standardization. Four samples from the original solution with masses between 10 and 20 mg were added to vials containing 15 mL of Hisafe 3 scintillation cocktail. Since the quench factor of the sources was very low, small amounts of nitro-methane were added so that the measurements could match the tritium efficiency curve.

Measurements were carried out with a Quantulus Wallak counter in several cycles, with counting times of 1 min per vial, although accurate quench determination required additional 15 min counting times. Typical count rates varied between 500 and 3000 s^{-1}.

Efficiency calculation was carried out by a Monte Carlo simulation program using data from the NUCLEIDE database (Bé et al., 2004). The program randomly follows all decay paths and generates a cascade of particles and photons for each simulated disintegration. Atomic rearrangement for vacancies produced in K, L and M shells is also considered. A second program reads the output and simulates the photon interaction with the scintillator to determine the deposited energy. The counting efficiency is then computed using the classical

expression:

$$\varepsilon = \alpha \sum_i \left(1 - \exp\left(-\frac{\sum_k E_{ik} Q(E_{ik})}{2.m}\right)\right)^2$$

where each individual term in the outer sum represents the contribution of the ith cascade, α is a normalizing factor, m is the figure of merit, $Q(E_{ik})$ is the ionization quenching correction factor and $\{E_{ik}.Q(E_{ik})\}$ corresponds to the effective energy of the kth element in the ith cascade.

Counting efficiencies for β^+ and electron capture branches were dissimilar; the first being close to unity whiles the latter approached 0.7 for the experimental conditions of the measurements. The total counting efficiency, obtained by combining both contributions, was high, about 0.96.

The estimate of the activity concentration at the reference time was 1796 (10) Bq mg^{-1}. It corresponds to the mean of 11 results. A list of uncertainty components is presented in Table 1. The major contributor corresponds to the efficiency calculation, whose contribution was estimated by comparing the results of many simulation runs. Also related is the nuclear data contribution, although for LSC a low contribution is added given that counting efficiencies for both branches are closer than for other techniques. Source stability was also matter of concern and an additional term was added to account for it. Half-life value, counting statistics, k_B value and quenching determination complete the table.

2.5. Mean value

The final value for the activity concentration was 1799 (8) Bq mg^{-1}. It was obtained as the mean of three results, one for each standardization technique. This value was used for comparison purposes as described in Section 4.

3. Standardization at CNEA

3.1. Material

The used elution was obtained from a generator not being used for patient treatment and had a non negligible amount of ^{68}Ge. Therefore, the decay time correction, including decay during counting time, had to take into account its contribution. The ^{68}Ga/^{68}Ge activity ratio was $(1.28 \times 10^4 \pm 0.01 \times 10^4)$ at the time of elution, and decreased to $(7.13 \times 10^1 \pm 0.07 \times 10^1)$ at the start of measurements. Purity test were completed after measurements to allow secular equilibrium to be reached between ^{68}Ge and ^{68}Ga.

All sources were prepared by gravimetry using a Mettler-Toledo XP26 balance.

3.2. $4\pi\beta-\gamma$ coincidence measurement

For coincidence measurements, a set of five sources with masses between 11 and 15 mg were prepared onto metalized Vyns foils. The measurement equipment was similar to the one used at CIEMAT. A pressurized proportional counter working at 300 kPa and two NaI (Tl) detectors were used in the beta and gamma channel, respectively. The electronic equipment included, for the gamma channel, two preamplifiers, a double amplifier and a sum and invert module. For the beta channel, a single preamplifier followed by an amplifier was used. The equipment was completed with a digital acquisition system made by ULS similar to the one used at CIEMAT, which allowed an easy interchange of data files between both laboratories. The beta channel was set up in a way that the influence from the EC branch was eliminated and the activity was derived from the β^+ branching ratio. Coincidences were then selected between counter pulses excluding EC emissions, and a gamma gate around the 511 keV annihilation peak. Activity concentration at the reference time was 512.4 (44) Bq mg^{-1} (weighted mean of five results).

The major component of the uncertainty corresponds to counting statistics and extrapolation, performed with efficiency values typically between 0.95 and 0.7. Nuclear data as well as resolving time also add a significant contribution. The presence of ^{68}Ge in the sample, even if not detected, still affect the decay rate of ^{68}Ga so its contribution have been included in the decay correction.

3.3. TDCR measurements

Four sources were prepared using Ultima Gold-AB as scintillation cocktail. They were measured using a liquid scintillation counter with three tubes that has been described in detail in a previous paper (Arenillas and Cassette, 2006). The standardization methods was based on the counting of double and triple coincidences using the MAC3 module (Bouchard and Cassette, 2000) with efficiencies calculated according to the triple to double coincidence ratio (TDCR) model (Broda et al., 1988; Cassette et al., 2000).

The emission spectrum $S(E)$ of the nuclide can be written as:

$$S(E) = P_\beta \cdot S_\beta(E) + (1-P_\beta) * S_c(E)$$

where P_β is the beta emission probability, S_β (E) the normalized beta spectrum and $S_c(E)$ the normalized X and Auger spectrum.

The counting efficiency was calculated using a simplified model (Rodrígues, 2011) based on three assumptions: (a) Equal quantum efficiency (γ) of all photomultipliers; (b) very high beta efficiency and (c) monoenergetic emission (Ec) in the processes following electron capture (either emission of X-rays or Auger electrons).

From the monoenergetic assumption it follows that $S_c(E)=\delta(Ec)$. Let m denote the number of scintillating photons produced in the processes following electron capture. If we define: $\alpha(E)=1-exp(-\gamma \cdot m(E))$ and assuming that the counting efficiency for beta particles is unity, the TDCR relation becomes:

$$TDCR = \frac{\varepsilon_T}{\varepsilon_D} = \frac{P_\beta + (1-P_\beta)\cdot\alpha(Ec)^3}{P_\beta + (1-P_\beta)\cdot[3\alpha(Ec)^2 - 2\alpha(Ec)^3]}$$

Solving the above equation for α allows obtaining the efficiency for double coincidence counting.

Typical values were 0.970 (5) for ^{68}Ga and 0.725 (4) for ^{68}Ge efficiency, which were calculated from the denominator of the previous expression, where the term in brackets corresponds to the efficiency of the EC branch. Typical count rates for double coincidences, after correction by dead-time effects, varied between 3000 and 6000 s^{-1}.

In order to determine the ^{68}Ge contribution, a set of measurements were carried out after secular equilibrium was reached between this nuclide and its daughter ^{68}Ga. The net counting due to ^{68}Ga was obtained by subtracting the ^{68}Ge contribution to the initial set of measurements.

Activity concentration for ^{68}Ga at the reference time was 507.4 (29) Bq mg^{-1}. It corresponds to the weighted mean of four results.

The main component of the uncertainty budget presented in Table 1 is the counting efficiency for double coincidences, calculated for a typical triple to double coincidence ratio of 0.950 (2). Nuclear data and decay uncertainty also add significant contributions in this case. The contributions of the efficiency and activity

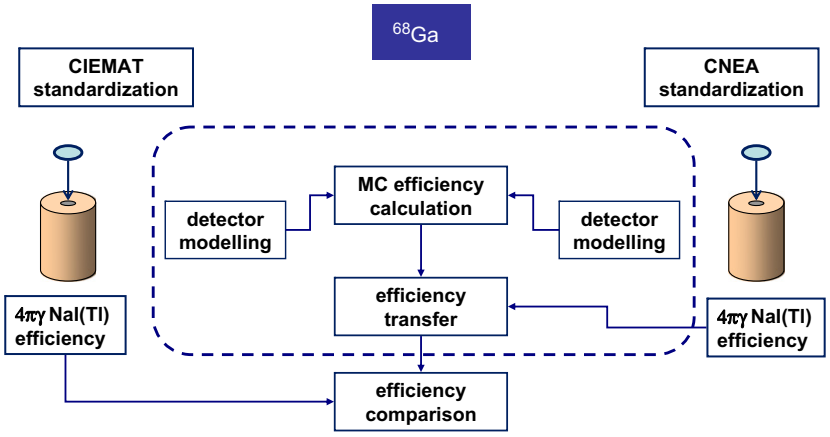

Fig. 4. Procedure followed to compare results from both laboratories. Calculation processes are represented inside the dashed box and experimental work outside it.

Table 2
Efficiency comparison in the measurement of ^{68}Ga with NaI(Tl) well-type detectors at CIEMAT and CNEA. In order to compare CIEMAT and CNEA values, Monte Carlo calculations have been used to correct the small efficiency differences between detectors at both laboratories.

	Experimental	MC calculation	MC efficiency ratio	Corrected experimental efficiencies
CIEMAT	0.804 (4)	0.799 (4)	1	0.804 (4)
CNEA	0.781 (5)	0.782 (5)	1.022 (4)	0.798 (6)

of ^{68}Ge were estimated together and added as an impurities component to the uncertainty budget.

3.4. Mean value

The final value for the activity concentration was 508.8 (36) Bq mg^{-1}. It was obtained as the mean of TDCR and coincidence counting results. This value was used for comparison purposes as described in Section 4.

4. Comparison of results between CIEMAT and CNEA

A direct comparison of the same material between both laboratories was not possible and an efficiency comparison exercise was setup instead. The procedure is depicted in Fig. 4 and relevant numerical results are presented in Table 2. As a first step, point sources whose activities were determined in the standardization processes were measured in both laboratories using similar well-type Na (Tl) detectors. Experimental efficiencies were then obtained as the ratio between the total counting rates and the source activities. Both detectors have same external dimensions (7.5 × 7.5 cm) but with slight differences in the well diameter (30.1 mm at CNEA model and 25.4 mm. at CIEMAT). Therefore, efficiencies were different (ε=0.804 (5) at CIEMAT and ε=0.781 (5) at CNEA) and could not be directly compared.

In a second step, detailed Monte Carlo simulations using the PENELOPE package allowed to establish the theoretical efficiency ratio between both detectors whose value was $\varepsilon_{CIEMAT}/\varepsilon_{CNEA}$= 1.022 (4). The uncertainty assigned to this factor only takes into account the statistics of the calculations given that both detectors are very similar and other effects would not play a significant role for this ratio. After correction by this factor, the efficiency of the CNEA detector becomes 0.798 (6), in good agreement with CIEMAT value.

5. Conclusion

Solutions of ^{68}Ga have been standardized in Metrology Laboratories at CIEMAT and CNEA by a variety of techniques. Since a direct comparison was not possible, results have been compared by measuring ^{68}Ga sources in similar detectors in both laboratories. Results are in good agreement within uncertainties.

Acknowledgments

Ciemat staff are grateful to the biomedical applications and pharmacokinetics unit, and particularly to Eduardo Romero, for providing the many ^{68}Ga solutions used in this project and for permanent advice; CNEA staff to the Nuclear Diagnostic Center Foundation for providing and transferring the radioisotope solution.

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