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Results of an international comparison for the activity measurement of ^{177}Lu

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ABSTRACT

An international Key Comparison of ^{177}Lu has recently been carried out. Twelve laboratories performed assays for radioactivity content on aliquots of a common master solution of ^{177}Lu, leading to eleven results submitted for entry into the Key Comparison Database of the Mutual Recognition Arrangement. A proposed Comparison Reference Value (CRV) was calculated to be 3.288(4) MBq/g using all eleven results. Degrees of equivalence and their uncertainties were calculated for each laboratory based on the CRV. Most of the values reported by the participating laboratories were within 0.6% of the CRV.

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1. Introduction

There has been increasing interest during the past 10 years in the use of ^{177}Lu for radionuclide-based radiotherapy for certain types of cancers (c.f., Rasaneh et al., 2011; Pan et al., 2009). Accurate administrations of drugs using this radionuclide require accurate standards against which instrumentation used in the clinics and radiopharmacies can be calibrated. Several new ^{177}Lu-based radiotherapy drugs are being investigated worldwide, which will cause an even greater need for such standards.

Lutetium-177 decays with three primary β^- branches ($E_{\beta max}$=177.0 keV (allowed), 385.4 keV (1st forbidden), and 498.3 keV (1st forbidden)) and has two reasonably strong γ-rays at 112.9 keV and 208.4 keV (Bé et al., 2004), making it suitable for analysis using a variety of techniques. Its relatively short half-life of 6.647(4) d (Bé et al., 2004) makes it an excellent candidate for therapeutic nuclear medicine applications, but presents many challenges for organizing an international comparison.

To date, the only previous comparison of ^{177}Lu that has been carried out was a bilateral comparison (BIPM-R(II)-K1.Lu-177) conducted between the National Institute of Standards and Technology (NIST) and the Physikalisch-Technische Bundesanstalt (PTB) in 2000 (Bureau International des Poids et Mesures (BIPM), 2011a). In that case, both laboratories were able to submit ampoules to the International Reference System (SIR) (Rytz, 1983) and report activity values based on liquid scintillation counting using the CIEMAT/NIST efficiency tracing method. The results indicated a difference of about 1.4% in the SIR equivalent activity. The short half-life of the ^{177}Lu did not allow for follow-up studies to be performed at that time.

Since 2000, several more national metrology institutes (NMIs) have standardized this radionuclide. In order to establish a link between primary standards of β-emitters in the NMIs and the SIR, as well as to provide a means for laboratories to substantiate Calibration and Measurement Capability (CMC) claims for β–γ emitting nuclides (Bureau International des

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Table 1
Laboratories participating in CCRI(II) Key Comparison CCRI(II)-K2.Lu-177 for ^{177}Lu.

Laboratory name	Acronym	Country	Regional Metrology Organization
Australian Nuclear Science and Technology Organisation	ANSTO	Australia	Asia-Pacific Metrology Programme (APMP)
Laboratório Nacional de Metrologia das Radiações Ionizantes, Instituto de Radioproteção e Dosimetria	LNMRI-IRD	Brazil	Inter-American Metrology System (SIM)
Instituto de Pesquisas Energéticas e Nucleares/Comissão Nacional de Energia Nuclear[a]	IPEN-CNEN	Brazil	SIM
European Commission-Joint Research Centre/Institute for Reference Materials and Measurements	IRMM	European Commission	European Collaboration of National Metrology Institutes (EURAMET)
Laboratoire national de métrologie et d'essais-Laboratoire national Henri Becquerel	LNE-LNHB	France	EURAMET
Physikalisch-Technische Bundesanstalt	PTB	Germany	EURAMET
Italian National Agency for New Technologies, Energy, and Environment–National Institute for Ionising Radiation Metrology	ENEA–INMRI	Italy	EURAMET
Institute of Atomic Energy POLATOM, Radioisotope Centre, Laboratory of Radioactivity Standards	POLATOM	Poland	EURAMET
National Institute of Research and Development for Physics and Engineering "Horia Hulubei"	IFIN-HH	Romania	EURAMET
National Metrology Institute of South Africa	NMISA	South Africa	Intra-Africa Metrology System (AFRIMETS)
National Physical Laboratory	NPL	United Kingdom	EURAMET
National Institute of Standards and Technology	NIST	United States of America	SIM

[a] The Instituto de Pesquisas Energéticas e Nucleares/Comissão Nacional de Energia Nuclear (IPEN-CNEN) is not the designated metrology institute for radioactivity in Brazil, but contributed a result that was combined with results from the Laboratório Nacional de Metrologia das Radiações Ionizantes, Instituto de Radioproteção e Dosimetria (LNMRI-IRD), which is the designated metrology institute for radioactivity, to arrive at a single final result for inclusion into the Key Comparison Database.

Poids et Mesures (BIPM), 2011b), a Key Comparison of ^{177}Lu was proposed in 2008.

2. Organization of the comparison

The participating laboratories of the comparison are listed in Table 1. As noted in the table, the Instituto de Pesquisas Energéticas e Nucleares/Comissão Nacional de Energia Nuclear (IPEN-CNEN) is not the designated radioactivity metrology institute for its country, but it submitted a value that was combined with data from the Laboratório Nacional de Metrologia das Radiações Ionizantes, Instituto de Radioproteção e Dosimetria (LNMRI-IRD) to arrive at a final submitted value from LNMRI-IRD (which is the national metrology institute for radioactivity in Brazil). Where appropriate, the final values from each institute are given separately, although only the combined value will appear in the Key Comparison Database (KCDB) (Bureau International des Poids et Mesures (BIPM), 2011a).

The agreed protocol called for the ^{177}Lu solutions to be prepared and distributed by NIST (which served as the pilot laboratory) from a single master solution. A flame-sealed ampoule containing 5 mL of solution having nominally 3.7 MBq of activity was sent to each participating laboratory on 17 April 2009. The carrier solution consisted of 20 μg Lu^{+3} per gram of solution in 1 mol L^{-1} HCl. Most participants received the vials within five days of shipment, although two laboratories received their samples more than a week later due to internal bureaucratic delays. These delays did not appear to have an influence on the measurement results.

According to the protocol, the participants were to report the activity concentration (in Bq g^{-1}) as of the reference time of 12:00 UTC 1 May 2009. The nuclear and atomic data in Bé et al. (2004) was to be used by every laboratory in their respective analyses.

3. Results and discussion

In addition to performing the activity determinations on the test solution, several laboratories were also able to send ampoules to the SIR so that the comparison can be linked through that system. According to Key Comparison rules (Bureau International des Poids et Mesures (BIPM), 2011c), the values that will appear in the KCDB and that will be used to calculate the Key Comparison Reference Value (KCRV) will be those derived from the SIR measurements in combination with the respondents' reported activities. Final degrees of equivalence (DoE) will be calculated from the KCRV and all those data will be published separately in the final report for the comparison. In order to provide a preliminary indication of the laboratories' performance, however, a CRV was calculated from the activity concentration data and interim DoEs calculated based on the proposed CRV.

In the initial screening of the data, all the individual results from all the laboratories were plotted and separated by technique in order to determine if there was any influence on the result from the measurement method used. This plot is given in Fig. 1. From the data, no such effect is apparent.

3.1. Proposed comparison reference value (CRV)

The results of each laboratory's measurements of the ^{177}Lu solution as of the reference time are summarized in Table 2 and Fig. 2. The uncertainties in both Table 2 and Fig. 2 are combined standard uncertainties as reported by each of the participants. The complete uncertainty budgets for all the submitted results are provided in Tables 1-12 in the Electronic Supplement that accompanies this paper and will be published in their entirety in the final comparison report.

The value submitted for LNMRI-IRD was originally calculated by that laboratory as being the median of six values: three coincidence measurements from LNMRI-IRD (using two different energy windows and two different extrapolation methods, giving values of 3.304(18) MBq g^{-1}, 3.285(18) MBq g^{-1}, and 3286(18) MBq g^{-1}), two anticoincidence measurements from LNMRI-IRD (using two different energy windows, giving values of 3.288(7) MBq g^{-1} and 3209(6) MBq g^{-1}), and one coincidence measurement from IPEN-CNEN (3.277(29) MBq g^{-1}). Following the advice of the Key Comparison Working Group of the Consultative Committee on Ionizing Radiation, Section 2: measurement of radionuclides (CCRI(II)), the results from the same technique were combined into a single value for each technique from each of the two institutions in order to investigate possible influences on the activity determination from measurement method. This now gives three results as follows: two values from LNMRI-IRD

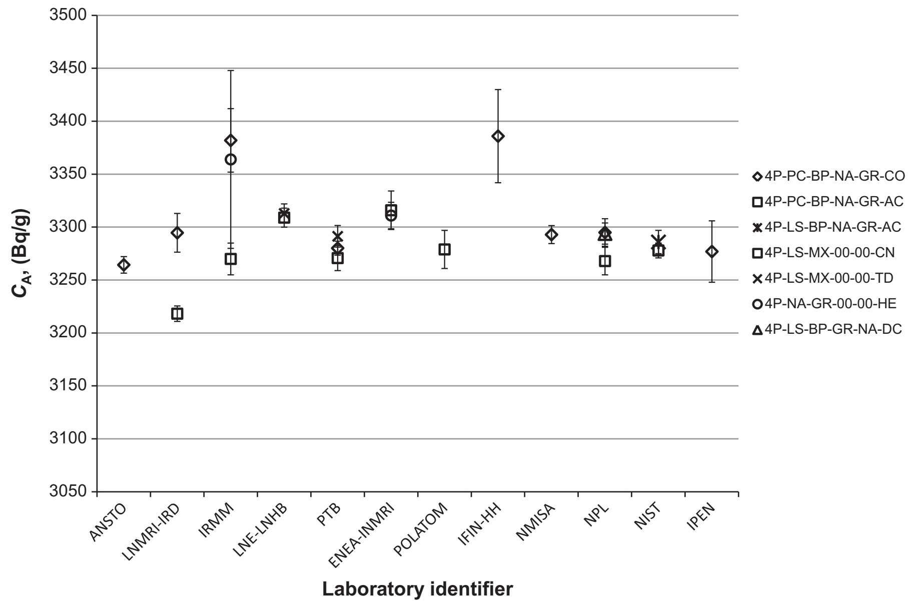

Fig. 1. Radioactivity concentration of the ^{177}Lu comparison solution as reported by the participants for all techniques. The uncertainty bars correspond to the combined standard uncertainty on each respondent's value.

Table 2
Specific activity, $C_{A,}$ of ^{177}Lu solution at the reference time of 12:00 UTC 1 May 2009 as reported by the participating institutions. The uncertainties, u_i, are the combined standard ($k=1$) uncertainties as reported by each participant. In cases in which more than one value was submitted, the one to be entered into the Key Comparison Database (KCDB) is given in parenthesis and the method used to arrive at that value (as reported by the laboratory) is specified. The acronyms used to describe the assay methods used conform to those used in the KCDB (Thomas, 2005).

Institution	C_A (MBq g^{-1})	u_i (MBq g^{-1})	Method
ANSTO	3.2644	7.8×10^{-3}	4P-PC-BP-NA-GR-CO
LNMRI-IRD	3.2183[a]	7.3×10^{-3}	4P-PC-BP-NA-GR-AC
	3.2947[a]	1.83×10^{-2}	4P-PC-BP-NA-GR-CO
	(3.2764)	(1.98×10^{-2})	Median of six values obtained from LNMRI/IRD and IPEN/CNEN (see text for details). U_c was calculated from the quadratic combination of the standard uncertainty of the median (0.34%) and a type B assessment of (0.50%) adopted from the result of the linear fit to the LNMRI-IRD coincidence data using the 113 keV gamma window
IPEN-CNEN[b]	3.277	2.9×10^{-2}	4P-PC-BP-NA-GR-CO
IRMM	3.270	1.5×10^{-2}	4P-LS-MX-00-00-CN
	3.382	3.0×10^{-2}	4P-PC-BP-NA-GR-CO
	3.364[c]	8.4×10^{-2}	4P-GR-NA-00-00-HE
	(3.320)	(5.4×10^{-2})	Partially weighted mean of first two values above (see text for details).
LNE-LNHB	3.309	9×10^{-3}	4P-LS-BP-NA-GR-AC
	3.313	9×10^{-3}	4P-LS-MX-00-00-TD
	(3.311)	(9×10^{-3})	Arithmetic mean of above results; U_c is the arithmetic mean of the standard uncertainties reported for each of the two values
PTB	3.2802	6.6×10^{-3}	4P-PC-BP-NA-GR-CO
	3.2914	1.02×10^{-2}	4P-LS-MX-00-00-TD
	3.2708	1.18×10^{-2}	4P-LS-MX-00-00-CN
	(3.2812)	(6.2×10^{-3})	Weighted mean of above results, taking correlations due to weighing into account; U_c is the calculated from the inverse of the square root of the sum of the weights
ENEA-INMRI	3.316	1.82×10^{-2}	4P-LS-MX-00-00-CN
	3.311	2.52×10^{-2}	4P-NA-MX-00-00-HE
	(3.3135)	(1.56×10^{-2})	Arithmetic mean of above results
POLATOM	3.279	1.8×10^{-2}	4P-LS-BP-NA-GR-CO/AC
IFIN-HH	3.386	4.4×10^{-2}	4P-LS-BP-NA-GR-CO
NMISA	3.293	8.5×10^{-3}	4P-LS-BP-NA-GR-CO
NPL	3.295	1.3×10^{-2}	4P-PC-BP-NA-GR-CO
	3.268	1.3×10^{-2}	4P-LS-MX-00-00-CN
	3.294	1.0×10^{-2}	4P-LS-BP-NA-GR-DC
	(3.286)	(1.0×10^{-2})	Arithmetic mean of above results; U_c is the standard deviation of the three measurements.
NIST	(3.286)	(1.1×10^{-2})	4P-LS-BP-NA-GR-AC
	3.278	7×10^{-3}	4P-LS-MX-00-00-CN

[a] Values obtained from multiple energy windows and extrapolation methods for the same technique have been averaged by the Pilot Laboratory to give a single value for each respective technique. See text for details.

[b] The Instituto de Pesquisas Energéticas e Nucleares-Comissão Nacional de Energia Nuclear (IPEN-CNEN) is not the designated metrology institute for radioactivity in Brazil, but contributed a result that was combined with results from the Laboratório Nacional de Metrologia das Radiações Ionizantes, Instituto de Radioproteção e Dosimetria (LNMRI-IRD), which is the designated metrology institute for radioactivity, to arrive at a single final result for inclusion into the Key Comparison Database.

[c] Technique was not considered by the participant to be a primary method and was not used in the calculation of their comparison value.

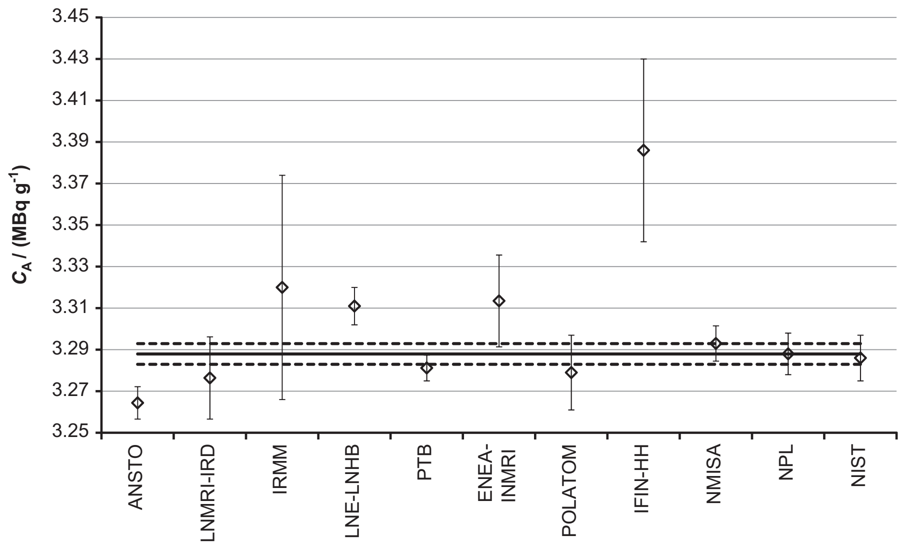

Fig. 2. Radioactivity concentration of the ^{177}Lu comparison solution as reported by the participants; only one result per participant, computed as explained in the text. The uncertainty bars correspond to the combined standard uncertainty on each respondent's value. The solid line represents the proposed Comparison Reference Value (CRV) of 3.288(4) MBq g^{-1} and the dashed lines represent the combined standard uncertainty on the CRV.

(one each for coincidence and anticoincidence counting) and one for IPEN-CNEN. These are the values given in Table 2. The final submitted value for inclusion in the KCDB however, was not recalculated and remains the same as that submitted by LNMRI-IRD.

In combining results from multiple measurement methods, an arithmetic (i.e., unweighted) mean was used by LNE-LNHB, ENEA–INMRI, and NPL, while PTB used a weighted mean to arrive at their final result. For the calculation of the final value for IRMM, a partially weighted mean of the results of the two methods considered by them to be primary (coincidence counting and liquid scintillation counting using the CIEMAT/NIST[1] efficiency tracing method) was calculated. For this calculation, an uncertainty of 72 kBq g^{-1} was first added to both results to give a Birge ratio (Birge, 1932) equal to 1.0. A partially weighted mean was then calculated with these new values using a power of 1 instead of 2 on the standard deviation. The high-efficiency NaI(Tl) method was not considered to be primary and was not included in the calculation.

The remaining laboratories based their comparison value on the results of measurements using a single technique. In the case of NIST, the comparison value was based on the anticoincidence measurement result because it was considered to be a pure primary measurement. The CIEMAT/NIST efficiency tracing result was provided as a confirmatory measurement only.

A visual inspection of the data in Fig. 2 suggests that no single data point appears to be an obvious outlier. However, using the weighted mean of 3.286(3) MBq g^{-1} for the entire data set ($n=11$) as a starting point, a Birge ratio of 1.56 was calculated, indicating that the data set is most likely inconsistent. Applying a normalized error test using a test value of 4 to the data set using an unweighted mean of 3.299(33) MBq g^{-1} as the CRV indicated that only the ANSTO result could be considered to be out of norm with a score value of 4.18, while a modified normalized error test with a test value of 2.5 indicated that only the value from IFIN-HH is an outlier candidate with a score value of 2.58. These two laboratories were contacted and given an opportunity to review their submissions for possible errors and both responded that none were found.

The fact that no single test could reveal a single point as being an outlier prompted the use of a technique that enables all the data in the set to be included in the calculation of the CRV. One such approach assumes that the uncertainty in each laboratory's result contains both within-laboratory and (generally unobserved) between-laboratory sources of variability (Crowder, 1992). In general, the magnitude of the within-laboratory variance is estimable and is reflected in the combined standard uncertainty reported by each laboratory along with their respective (mean) values of the activity concentration. The difficulty lies in the calculation of the magnitude of the between-laboratory variance. Once estimated, however, the combined variances can then be used to calculate the weighting factors that are ultimately used to calculate the consensus mean.

Several methods exist to estimate the magnitude of the between-laboratory variance (Rukhin, 2009; Vangel and Rukhin, 1999; Rukhin and Vangel 1998; DerSimonian and Laird, 1986; Paule and Mandel, 1982), with most of them relying on some sort of maximum likelihood analysis. The Consensus Mean module of the DATAPLOT program (Filliben, 1984) uses several approaches in addition to those referenced above to solve this problem and reports the consensus mean and magnitude of the between-laboratory variance for each technique. The means calculated with the 6 different implementations of this approach all agreed to within about 0.1% of each other and could be considered to be statistically identical. From the set of results, the one obtained with the Vangel–Rukhin Maximum Likelihood method (Vangel and Rukhin, 1999; Rukhin and Vangel 1998) was taken to be the most robust (Rukhin, 2009), leading to the proposal of a CRV of 3.288(4) MBq g^{-1}, where the quoted uncertainty corresponds to a standard ($k=1$) uncertainty interval that considers both within- and between-laboratory effects.

3.2. Impurity analyses

Analyses for possible radionuclidic impurities were carried out by all the laboratories, with most of the results having been obtained using calibrated high-purity germanium photon detectors. The ratios of activities of the identified impurities to the ^{177}Lu activity at the reference time are given in Table 3.

3.3. Degrees of equivalence

The degree of equivalence of each laboratory i with respect to the reference value is given by a pair of terms both expressed in

[1] CIEMAT is an acronym for Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, which is the National Metrology Institute of Spain.

Table 3
Relative activity of identified radionuclidic impurities in analyzed ^{177}Lu solution.

Laboratory	Impurities identified	Activities of impurities relative to ^{177}Lu at reference time	Method of analysis
ANSTO	^{177m}Lu	0.00030(3)	Gamma-ray spectrometry using HPGe detector
LNMRI-IRD	^{177m}Lu	0.000353(8)	Gamma-ray spectrometry using HPGe detector
IPEN-CNEN[a]	^{177m}Lu	0.00030(2)	Gamma-ray spectrometry using HPGe detector
IRMM	^{177m}Lu	0.0004(1)	Gamma-ray spectrometry using HPGe detector
LNE-LNHB	^{177m}Lu	0.00034(7)	Gamma-ray spectrometry using HPGe detector
PTB	^{177m}Lu	0.000309(15)	Gamma-ray spectrometry using HPGe detector
ENEA–INMRI	^{177m}Lu	0.000330(15)	Gamma-ray spectrometry using HPGe detector
		0.000310(56)	Gamma-ray spectrometry using NaI detector
POLATOM	^{177m}Lu	0.00033	Gamma-ray spectrometry using HPGe detector
IFIN-HH	^{177m}Lu	0.0004	Gamma-ray spectrometry using HPGe detector
NMISA	^{177m}Lu	0.00031	Ionization chamber with fits to chamber response and half-lives
NPL	^{177m}Lu	0.00033(3)	Gamma-ray spectrometry using HPGe detector
NIST	^{177m}Lu	0.000336(27)	Gamma-ray spectrometry using HPGe detector

[a] The Instituto de Pesquisas Energéticas e Nucleares-Comissão Nacional de Energia Nuclear (IPEN-CNEN) is not the designated metrology institute for radioactivity in Brazil, but contributed a result that was combined with results from the Laboratório Nacional de Metrologia das Radiações Ionizantes, Instituto de Radioproteção e Dosimetria (LNMRI-IRD), which is the designated metrology institute for radioactivity, to arrive at a single final result for inclusion into the Key Comparison Database.

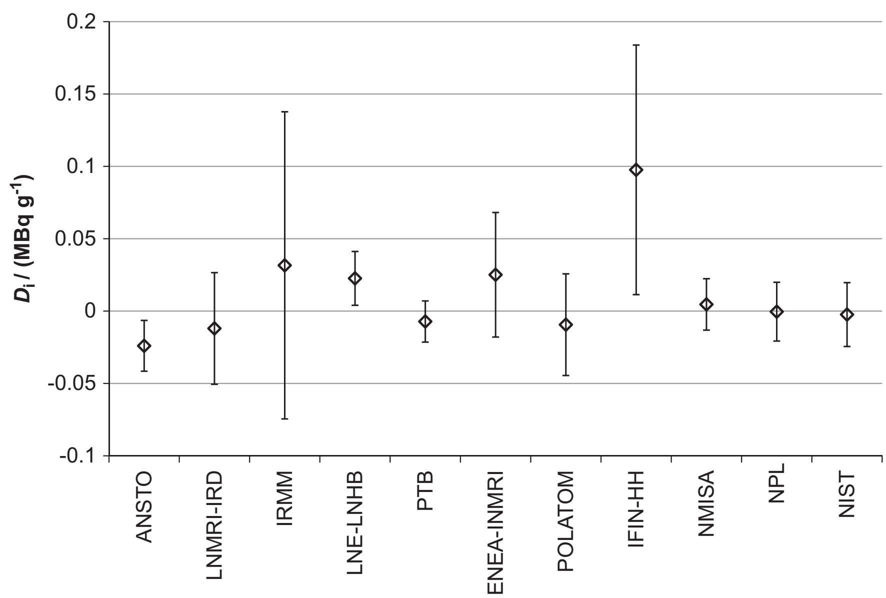

Fig. 3. Degrees of Equivalence, D_i, for participants in the CCRI Key Comparison CCRI(II)-K2-Lu-177. The value of D_i is computed as $x_i - x_{ref}$, where x_i is the laboratory reported result and x_{ref} is the proposed Comparison Reference Value of 3.288 MBq g^{-1}. The uncertainty bars (within the symbols) correspond to the expanded uncertainty, U_i, on D_i as calculated in Eq. (2).

the same units: the difference, D_i, and U_i, its expanded uncertainty ($k=2$). These quantities are expressed as

$$D_i = x_i - x_{ref} \quad (1)$$

where x_i and x_{ref} are each participant's result and the CRV, respectively. The uncertainty on D_i is given by (Ratel, 2005)

$$U_i = 2\left(\sqrt{(1-2w_i)u_i^2 + u_{ref}^2}\right) \quad (2)$$

where u_{ref} is the standard uncertainty on the reference value, u_i is the combined standard uncertainty as reported by each laboratory, and w_i are the normalized weighting factors given by

$$w_i = \frac{(1/(u_i^2 + u_b^2))}{\sum_{i=1}^{n}(1/(u_i^2 + u_b^2))} \quad (3)$$

The term u_b in Eq. (3) refers to the interlaboratory component of variability, which was calculated to have a magnitude of 0.34%

Table 4
Preliminary degrees of equivalence, D_i, and associated uncertainty, U_i, for all comparison participants. See text for explanation of terms. Final degrees of equivalence will be calculated with respect to measurements made in the International Reference System (SIR).

Laboratory	D_i (MBq g^{-1})	U_i (MBq g^{-1})
ANSTO	-0.024	0.017
LNMRI-IRD	-0.012	0.039
IRMM	0.032	0.106
LNE-LNHB	0.023	0.019
PTB	-0.007	0.014
ENEA–INMRI	0.025	0.043
POLATOM	-0.009	0.035
IFIN-HH	0.098	0.086
NMISA	0.005	0.018
NPL	-4×10^{-4}	0.020
NIST	-0.002	0.022

relative to the consensus mean value. The preliminary degrees of equivalence for participants in the comparison are presented graphically in Fig. 3 and numerically in Table 4. As previously discussed, final degrees of equivalence, as well as the final Key Comparison Reference Value (KCRV) will be calculated for the Draft B Report using measurements made in the International Reference System (SIR).

From the data in Table 4, it can be seen that the values of D_i range from -0.0235 MBq g^{-1} to 0.0981 MBq g^{-1}, which on a percentage basis corresponds to -0.71% to $+3.0\%$ of the CRV. Most of the submitted values, however, fall within 0.6% of the CRV. There do seem to be three values (ANSTO, LNE-LNHB, and IFIN-HH) whose uncertainty does not overlap with the CRV and its uncertainty. One possible cause, at least for the former two cases, could be that the uncertainties on the submitted value are grossly underestimated. This could also explain the fact that in at least one consistency or outlier test, each of these laboratories was indicated to be a possible contributor to the inconsistency in the extant data set. However, in the case of the IFIN-HH result, with such a large uncertainty already assigned, it is also likely that another effect is in play. This bears further investigation in a future comparison.

Although the official DoEs between the participating laboratories (as opposed to being referenced only to the CRV) will be based on the SIR data, a comparison of the NIST and PTB reported activity concentration values shows a difference of only 0.15%. This is well within the respective stated uncertainties and suggests that the 1.4% difference that was observed in the 2000 comparison has been resolved.

4. Conclusion

An international Key Comparison of ^{177}Lu has been successfully carried out. Although initial tests indicated that the data were not consistent, a single laboratory was not identified as being an outlier, prompting the use of a method that allowed for all the data from the participating laboratories to be included in the calculation of the CRV. Using the calculated CRV, it is demonstrated that most respondents reported values within 0.6% of the CRV.

Disclaimer

Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.apradiso.2012.02.014.

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