

**BIPM comparison BIPM.RI(II)-K1.Lu-177 of
activity measurements of the radionuclide ^{177}Lu**

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Abstract

Since 2000, two national metrology institutes (NMIs) have submitted two samples of known activity of ^{177}Lu to the International Reference System (SIR) for activity comparison at the Bureau International des Poids et Mesures. The activities were about 135 MBq. The degrees of equivalence between each equivalent activity measured in the SIR and the key comparison reference value (KCRV) have been calculated and the results are given in the form of a matrix for the two NMIs. A graphical presentation is also given. The results of this comparison have been approved by Section II of the Consultative Committee for Ionizing Radiation (CCRI(II)), comparison identifier BIPM.RI(II)-K1.Lu-177.

1. Introduction

The SIR for activity measurements of γ -ray-emitting radionuclides was established in 1976. Each NMI may request a standard ampoule from the BIPM that is then filled (3.6 g) with the radionuclide in liquid (or gaseous) form. The NMI completes a submission form that details the standardization method used to determine the absolute activity of the radionuclide and the full uncertainty budget for the evaluation. The ampoules are sent to the BIPM where they are compared with standard sources of ^{226}Ra using pressurized ionization chambers. Details of the SIR method, experimental set-up and the determination of the equivalent activity are all given in [1].

Since its inception until 31 December 2002, the SIR has measured 835 ampoules to give 606 independent results for 62 different radionuclides. The SIR makes it possible for national laboratories to check the reliability of their activity measurements at any time. This is achieved by the determination of the equivalent activity of the radionuclide and by comparison of the result with the key comparison reference value determined from the results of primary realizations. These comparisons are described as BIPM ongoing comparisons and the results form the basis of the BIPM key comparison database (KCDB) of the Mutual Recognition Arrangement (MRA) [2]. The comparison described in this report is known as the BIPM.RI(II)-K1.Lu-177 key comparison.

2. Participants

Two NMIs have submitted two ampoules for the comparison of ^{177}Lu activity measurements since 2000. The laboratory details are given in Table 1.

Table 1. Details of the participants in the BIPM.RI(II)-K1.Lu-177

NMI	Full name	Country	Regional metrology organization	Date of measurement at the BIPM
PTB	Physikalisch-Technische Bundesanstalt	Germany	EUROMET	2000-01-26
NIST	National Institute of Standards and Technology	United States	SIM	2000-02-15

3. NMI standardization methods

Each NMI that submits ampoules to the SIR has measured the activity either by a primary standardization method or by using a secondary method, for example a calibrated ionization chamber. In the latter case, the traceability of the calibration needs to be clearly identified to ensure that any correlations are taken into account.

A brief description of the standardization methods for each laboratory, the activities submitted and the relative standard uncertainties ($k = 1$) are given in Table 2. The list of acronyms used to summarize the methods is given in Appendix 3. Full uncertainty budgets have been requested as part of the comparison protocol only since 1998. When submitted by the NMIs, the uncertainty budgets are given in Appendix 1 attached to this report. Consequently, both the PTB and the NIST have provided detailed uncertainty budgets.

The half-life used by the BIPM is 6.646 (5) d [3].

Details regarding the solution submitted are shown in Table 3, including any impurities, when present, as identified by the laboratories. When given, the standard uncertainties on the evaluations are shown. Recently the BIPM has developed a standard method for evaluating the activity of impurities using a calibrated Ge(Li) spectrometer [4]. The CCRI(II) agreed in 1999 [5] that this method should be followed according to the protocol described in [6] when an NMI makes such a request or when there appear to be discrepancies [7].

Table 2. Standardization methods of the participants for ^{177}Lu

NMI	Method used and acronym (see Appendix 3)	Half-life / d	Activity A_i / kBq	Reference date YY-MM-DD	Relative standard uncertainty $\times 100$ by method of evaluation	
					A	B
PTB	LSC 4P-LS-MX-00-00-CN and $4\pi\beta\text{-}\gamma$ coincidence 4P-PC-BP-NA-GR-CO	6.646 (5) [3]	138 790	00-01-19 0 h UT	0.20	0.40
NIST	$4\pi\beta$ LS [8] 4P-LS-MX-00-00-CN	6.60 (1)	133 850	00-02-01 17 h UT	0.19	0.28

Table 3. Details of the solution of ^{177}Lu submitted

NMI	Chemical composition	Solvent conc. / (mol dm^{-3})	Carrier: conc. / ($\mu\text{g g}^{-1}$)	Density / (g cm^{-3})	Relative activity of $^{177}\text{Lu}^{\text{m}}$ impurity [†]
PTB	LuCl_3 in HCl	0.1	LuCl_3 : 20	0.999	$6.9 (6) \times 10^{-3} \%$
NIST	Lu in HCl	0.01	-	1.00	$27.1 (5) \times 10^{-3} \%$ *

[†] the ratio of the activity of the impurity to the activity of ^{177}Lu at the reference date.

* measured at the BIPM (see paragraph 4).

4. Results

All the submissions to the SIR since its inception in 1976 are maintained in a database known as the "mother-file". The activity measurements for ^{177}Lu arise from three ampoules and the SIR equivalent activity for each ampoule, A_{ei} , is given in Table 4 for each NMI, i . The dates of measurement in the SIR are given in Table 1.

The relative standard uncertainties arising from the measurements in the SIR are also shown. This uncertainty is additional to that declared by the NMI for the activity measurement shown in Table 2. Although activities submitted are compared with a given source of ^{226}Ra , all the SIR results are normalized to the radium source number 5 [1].

Measurements repeated at the BIPM after periods of up to twelve days later produced comparison results in agreement within SIR standard uncertainties for the PTB. These measurements confirm the validity of the half-life value used and the evaluation of the impurity corrections (1.0047 for the first measurement in the SIR).

Measurements repeated at the BIPM after periods of up to twelve days later produced comparison results showing a strong decrease for the NIST ampoule when using the

original impurity content as given by the NIST (0.022 (6) %). The level of $^{177}\text{Lu}^{\text{m}}$ impurity at the time of measurement in the SIR is about ten times higher than for the PTB, having in consequence a crucial influence on the SIR measurements. According to the protocol [6], impurity measurements were made at the BIPM and produced the activity ratio for $^{177}\text{Lu}^{\text{m}}$ given in Table 3. This reduced the decrease in the SIR results described above significantly and consequently the BIPM impurity measurements have been used to evaluate the impurity corrections for the final results of NIST.

More details on these ^{177}Lu submissions including the $^{177}\text{Lu}^{\text{m}}$ impurity are given in [7].

Table 4. Results of SIR measurements of ^{177}Lu

NMI	Activity submitted A_i / kBq	N° of Ra source used	SIR A_e / MBq	Relative uncertainty from SIR	Combined uncertainty $u_{c,i}$ / MBq
PTB	138 790	3	558.9	11×10^{-4}	2.8
NIST	133 850	3	551.2	16×10^{-4}	2.1

No recent submission has been identified as a pilot study so the result of each NMI is normally eligible for Appendix B of the MRA.

No international or regional comparison for this radionuclide has been held to date so no linking data are identified.

4.1 The key comparison reference value

The key comparison reference value is derived from the unweighted mean of all the results submitted to the SIR with the following provisions:

- a) only primary standardized solutions are accepted, or ionization chamber measurements that are directly traceable to a primary measurement in the laboratory;
- b) each NMI or other laboratory has only one result (normally the most recent result or the mean if more than one ampoule is submitted);
- c) any outliers are identified using a reduced chi-squared test and, if necessary, excluded from the KCRV using the normalized error test with a test value of four;
- d) exclusions must be approved by the CCRI(II).

The reduced data set used for the evaluation of the KCRVs is known as the KCRV file and is the reduced data set from the SIR mother-file. Although the KCRV may be modified when other NMIs participate, on the advice of the Key Comparison Working Group of the CCRI(II), such modifications are only made by the CCRI(II), normally during one of its biennial meetings.

Consequently, the KCRV for ^{177}Lu has been identified as 555.1 (3.9) MBq using the results from the PTB and the NIST.

4.2 Degrees of equivalence

Every NMI that has submitted ampoules to the SIR is entitled to have one result included in Appendix B of the KCDB as long as the NMI is a signatory or designated institute listed in the MRA. Normally, the most recent result is the one included. Any NMI may withdraw its result only if all the participants agree.

The degree of equivalence of a given measurement standard is the degree to which this standard is consistent with the key comparison reference value [2]. The degree of equivalence is expressed quantitatively in terms of the deviation from the key comparison reference value and the expanded uncertainty of this deviation ($k = 2$). The degree of equivalence between any pair of national measurement standards is expressed in terms of their difference and the expanded uncertainty of this difference and is independent of the choice of key comparison reference value.

4.2.1 *Comparison of a given NMI with the KCRV*

The degree of equivalence of a particular NMI, i , with the key comparison reference value is expressed as the difference between the results

$$D_i = A_{e_i} - \text{KCRV} \quad (1)$$

and the expanded uncertainty ($k = 2$) of this difference, U_i , known as the equivalence uncertainty, hence

$$U_i = 2u_{D_i}, \quad (2)$$

taking correlations into account as appropriate (see Appendix 2).

4.2.2 *Comparison of any two NMIs with each other*

The degree of equivalence, D_{ij} , between any pair of NMIs, i and j , is expressed as the difference in their results

$$D_{ij} = D_i - D_j = A_{e_i} - A_{e_j} \quad (3)$$

and the expanded uncertainty of this difference U_{ij} where

$$u_{D_{ij}}^2 = u_i^2 + u_j^2 - \sum_k (f_k u_{\text{corr},k})_i^2 - \sum_k (f_k u_{\text{corr},k})_j^2 \quad (4)$$

and any obvious correlations in the standard uncertainties for a given component, $u_{\text{corr},k}$, between the NMIs (such as a traceable calibration) are subtracted using an appropriate correlation coefficient, f_k , as are normally those correlations coming from the SIR.

The uncertainties of the differences between the values assigned by individual NMIs and the key comparison reference value (KCRV) are not necessarily the same uncertainties that enter into the calculation of the uncertainties in the degrees of equivalence between a pair of participants. Consequently, the uncertainties in the table of degrees of equivalence cannot be generated from the column in the table that gives

the uncertainty of each participant with respect to the KCRV. However, the effects of correlations have been treated in a simplified manner as the degree of confidence in the uncertainties themselves does not warrant a more rigorous approach.

Table 5 shows the matrix of all the degrees of equivalence as they will appear in Appendix B of the KCDB. It should be noted that for consistency within the KCDB, a simplified level of nomenclature is used with A_{ei} replaced by x_i . The introductory text is that agreed for the comparison. The graph of the first column of results in Table 5, corresponding to the degrees of equivalence with respect to the KCRV (identified as x_R in the KCDB), is shown in Figure 1. This representation indicates in part the degree of equivalence between the NMIs but does not take into account the correlations between the different NMIs. However, the matrix of degrees of equivalence shown in yellow in Table 5 does take the known correlations into account.

Conclusion

The BIPM ongoing key comparison for ^{177}Lu , BIPM.RI(II)-K1.Lu-177 currently comprises two results. These have been analysed with respect to the KCRV determined for this radionuclide, and with respect to each other. The matrix of degrees of equivalence has been approved by the CCRI(II) and is published in the BIPM key comparison database. Other results may be added as and when other NMIs contribute ^{177}Lu activity measurements to this comparison.

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References

- [1] Ratel G. The international reference system for activity measurements of γ -emitting radionuclides (SIR), *BIPM Monograph XX*, 2003, (in preparation).
- [2] MRA: *Mutual recognition of national measurement standards and of calibration and measurement certificates issued by national metrology institutes*, International Committee for Weights and Measures, 1999, 45 pp. <http://www.bipm.org/pdf/mra.pdf>.
- [3] Schötzig U. et al., Standardization and decay data of ^{177}Lu and ^{188}Re , *Appl. Radiat. Isot.*, **55** (2001) 89-96.
- [4] Michotte C., Efficiency calibration of the Ge(Li) detector of the BIPM for SIR-type ampoules, *Rapport BIPM-1999/03*, 15 pp.
- [5] *Comité Consultatif pour les Étalons de Mesures des Rayonnements Ionisants* 16th meeting (1999), 2001, CCRI(II) 81-82.

- [6] Michotte C., Protocol on the use of the calibrated spectrometer of the BIPM for the measurement of impurities in ampoules submitted to the SIR, *CCRI(II)/01-01*, 2001, 2 pp.
- [7] Michotte C. et al., First measurement of ^{177}Lu in the SIR, *CCRI(II)/01-02*, 2001, 5 pp.
- [8] Zimmerman B. et al., The standardization of ^{177}Lu by $4\pi\beta$ liquid scintillation spectrometry with ^3H -standard efficiency tracing, *Appl. Radiat. Isot.*, **54** (2001) 623-631.

Table 5. Table of degrees of equivalence and introductory text for ¹⁷⁷Lu

Key comparison BIPM.RI(II)-K1.Lu-177

MEASURAND : Equivalent activity of ¹⁷⁷Lu

Key comparison reference value: the SIR reference value x_R for this radionuclide is 555.1 MBq, with a standard uncertainty u_R of 3.9 MBq.

The value x_i is taken as the equivalent activity for laboratory i .

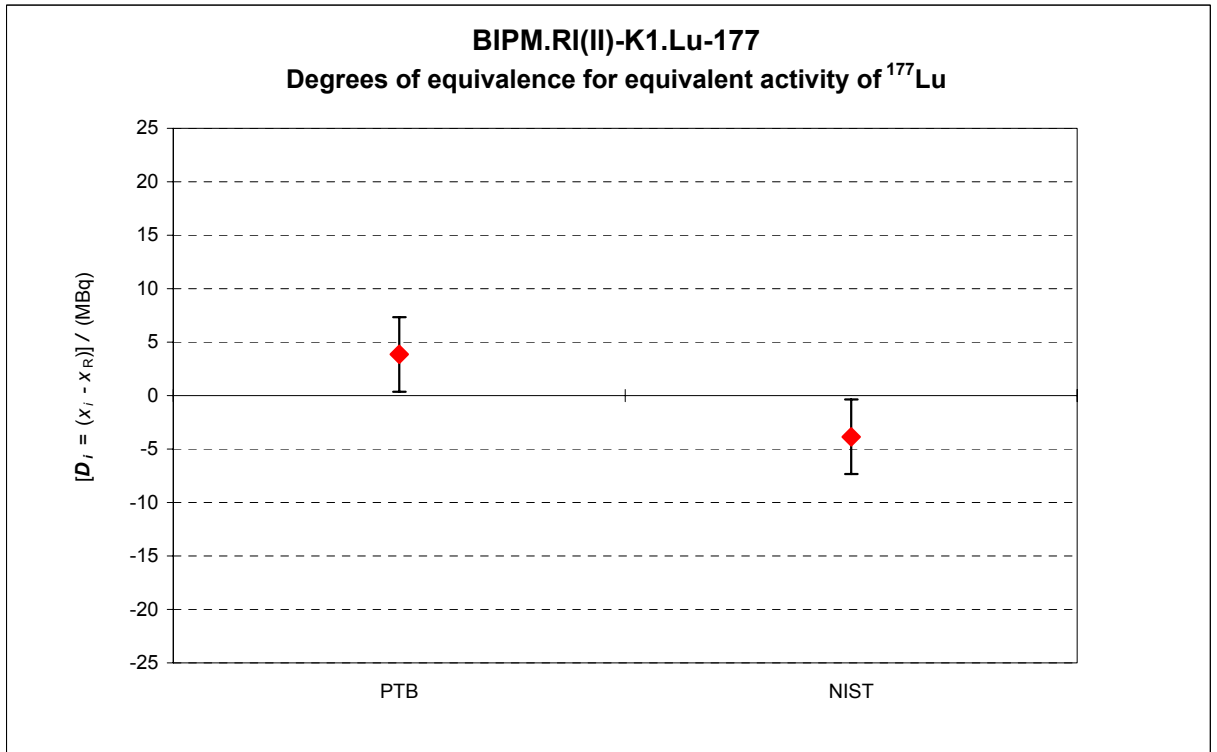
The degree of equivalence of each laboratory with respect to the reference value is given by a pair of terms: $D_i = (x_i - x_R)$ and U_i , its expanded uncertainty ($k = 2$), both expressed in MBq, and $U_i = 2((1 - 2/n)u_i^2 + (1/n^2)\sum u_i^2)^{1/2}$ when each laboratory has contributed to the calculation of x_R , with n the number of laboratories.

The degree of equivalence between two laboratories is given by a pair of numbers: $D_{ij} = D_i - D_j = (x_i - x_j)$ and U_{ij} , its expanded uncertainty ($k = 2$), both expressed in MBq.

The approximation $U_{ij}^2 \sim 2^2(u_i^2 + u_j^2)$ is used in the following table.

		Lab j →			
Lab i ↓		D_i	U_i	PTB	NIST
		/ MBq		D_{ij}	U_{ij}
	PTB	3.9	3.5	/ MBq	
NIST	-3.8	3.5	7.7	7.0	
			-7.7	7.0	

Figure 1. Graph of degrees of equivalence with the KCRV for ^{177}Lu (as it appears in Appendix B of the MRA)



Appendix 1. Uncertainty budgets for the activity of ^{177}Lu submitted to the SIR

The ^{177}Lu uncertainty budget for the PTB: ($4\pi\beta\text{-}\gamma$ -coincidence method)

Relative standard uncertainties	$u_i \times 10^4$ evaluated by method	
	A	B
counting statistics, $\nu = 59^\dagger$	20	
weighing, dilution		17
dead time		4
coincidence resolving time		2
background		4
timing		1
half-life		27
delay mismatch		2
extrapolation		22
correction applied to the ^{177}Lu activity		-
radionuclide impurities		3
Quadratic summation	20	40
Relative combined standard uncertainty, u_c	45	

† number of degrees of freedom

The ^{177}Lu uncertainty budget for the NIST:

Relative standard uncertainties	$u_i \times 10^4$ evaluated by method	
	A	B
Contributions due to		
LS measurement repeatability	14	–
LS cocktail variability and stability	13	18
Background measurement variability	0.2	–
^{177}Lu half-life	–	14
Gravimetric determinations	–	5
Dilution factor determination	–	14
^3H standard decay correction	–	1.9
^3H standard calibration	–	0.7
^3H standard gravimetric dilution	–	0.1
Gravimetric determination of ^3H LS samples	–	0.1
Live-time determinations for LS counting time intervals	–	7
^{177}Lu efficiency vs. figure of merit calculations	–	0.1
Determination of figure of merit, M	–	2.0
Radionuclide impurities	–	0.1
Quadratic summation	19	28
Relative combined standard uncertainty u_c	34	

Appendix 2. Evaluation of the uncertainty of the degree of equivalence

Table 5 indicates for each laboratory the degree of equivalence D_i with its associated uncertainty U_i . This appendix presents the procedure used to evaluate these uncertainties.

The degree of equivalence of one laboratory is defined as the difference between the individual value of the equivalent activity A_{ei} for an NMI i and a suitable reference value which has been evaluated by the KCDB Working Group and the expanded uncertainty of this difference. Currently, the reference value, KCRV, for a given radionuclide is calculated as the arithmetic mean value of the SIR experimental entries for this radionuclide. Briefly at least four situations can occur depending on the consistency of the experimental SIR data sets :

1. All data are consistent and contribute to the reference value; this is the general case;
2. The value obtained by a laboratory that no longer exists, is used as long as it fits the usual quality criteria; it is taken into account when evaluating the reference value but does not appear in the matrices of results;
3. A value, that has been identified for example as an outlier, is not taken into account for the evaluation of the reference value but, nevertheless, the corresponding laboratory appears in the matrices of results.

The situation where a laboratory that no longer exists but contributes to the reference value and where an outlier has been identified in the data set can occur. This is a combination of both situation 2) and situation 3). The results, deduced from these two preceding cases, are also presented here, case 4.

In the following, the expression of the uncertainty for these four cases is considered on the assumption that the uncertainties of the different equivalent activities A_{ei} are not correlated. For the sake of coherence with the definition of the variables used in the text, the following notation is used :

$x_i = A_{ei}$ and $u_i = u_{A_{ei}}$ its uncertainty.

Case 1. All n laboratories contribute to the reference value, and appear in Table 5. In this case obviously we have

$$x_{\text{ref}} = \bar{x} = \frac{\sum_{j=1}^n x_j}{n} \quad (\text{A-1})$$

$$D_i = x_i - x_{\text{ref}} \quad (\text{A-2})$$

$$D_i = x_i - \frac{\sum_{j=1}^n x_j}{n} = x_i \left(1 - \frac{1}{n}\right) - \frac{\sum_{j \neq i} x_j}{n} \quad (\text{A-3})$$

At this stage the uncertainty of D_i has to be calculated. Applying the method of Gauß for the propagation of the uncertainties it is necessary to calculate the partial derivatives of D_i with respect to the x_i .

$$\text{So } \frac{\partial D_i}{\partial x_i} = \left(1 - \frac{1}{n}\right), \text{ and} \quad (\text{A-4})$$

$$\frac{\partial D_i}{\partial x_j} = -\frac{1}{n}, (j \neq i). \quad (\text{A-5})$$

Then the total combined uncertainty becomes

$$u_{c_i}^2 = \left(\frac{\partial D_i}{\partial x_i}\right)^2 u_i^2 + \sum_{j \neq i} \left(\frac{\partial D_i}{\partial x_j}\right)^2 u_j^2 \quad (\text{A-6})$$

$$= \left(1 - \frac{1}{n}\right)^2 u_i^2 + \frac{1}{n^2} \sum_{j \neq i} u_j^2 \quad (\text{A-7})$$

or, after recombination

$$= \left(1 - \frac{2}{n}\right) u_i^2 + \frac{1}{n^2} \sum_{j=1}^n u_j^2. \quad (\text{A-8})$$

When a coverage factor of 2 is used (A-8) becomes

$$U_i^2 = 2^2 \left[\left(1 - \frac{2}{n}\right) u_i^2 + \frac{1}{n^2} \sum_{j=1}^n u_j^2 \right]. \quad (\text{A-9})$$

Case 2. A laboratory was used to evaluate the reference value but does not appear in Table 5.

Let us assign the subscript n to the additional laboratory that contributes to the reference value. The uncertainty of this laboratory will appear only in the second part of equation (A-9). Accordingly, equation (A-9) becomes

$$U_i^2 = 2^2 \left[\left(1 - \frac{2}{n}\right) u_i^2 + \frac{1}{n^2} \left(\sum_{j=1}^n u_j^2\right) \right], \text{ for } i = 1, n - 1. \quad (\text{A} - 10)$$

Case 3. The reference value was evaluated with all reported values except one.

For the sake of simplicity let us assign the subscript $n + 1$ to the ineligible laboratory so that the subscript for the other laboratories will run from 1 to n . Under this assumption the treatment of the ineligible laboratory will be slightly different and two formulae are deduced.

The ineligible laboratory does not contribute to the reference value, so the term $(1 - 2/n)$ in (A-9) reduces to 1 and the uncertainty is simply given by

$$U_{n+1}^2 = 2^2 \left[u_{n+1}^2 + \frac{1}{n^2} \sum_{j=1}^n u_j^2 \right]. \quad (\text{A} - 11)$$

In the evaluation of the uncertainty related to the n other laboratories the contribution from laboratory $n + 1$ disappears totally and the uncertainty remains given by the expression (A-10) without restriction over the subscript range i. e.

$$U_i^2 = 2^2 \left[\left(1 - \frac{2}{n}\right) u_i^2 + \frac{1}{n^2} \sum_{j=1}^n u_j^2 \right]. \quad (\text{A} - 12)$$

Case 4. A laboratory that no longer exists contributes to the reference value and an outlier has been identified for another laboratory.

Let us assign the subscript n to the defunct existing laboratory so that the expression for the mean (A-1) remains applicable. In addition the outlier will be labelled by $n + 1$. For the $(n - 1)$ first laboratories which contribute to the mean value and appear in Table 5 the uncertainty of D_i is given by

$$U_i^2 = 2^2 \left[\left(1 - \frac{2}{n}\right) u_i^2 + \frac{1}{n^2} \sum_{j=1}^n u_j^2 \right], \text{ for } i = 1, n - 1. \quad (\text{A} - 13)$$

For the laboratory $n + 1$ that is ineligible for the KCRV, its coefficient $(1 - 2/n)$ in (A-13) reduces to 1 and the expression of the uncertainty in Table 5 becomes

$$U_{n+1}^2 = 2^2 \left[u_{n+1}^2 + \frac{1}{n^2} \sum_{j=1}^n u_j^2 \right], \quad (\text{A} - 14)$$

similar to (A-11).

Appendix 3. Acronyms used to identify different measurement methods

Each acronym has six components, geometry-detector (1)-radiation (1)-detector (2)-radiation (2)-mode. When a component is unknown, ?? is used and when it is not applicable 00 is used.

Geometry	acronym	Detector	acronym
4π	4P	proportional counter	PC
defined solid angle	SA	press. prop counter	PP
2π	2P	liquid scintillation counting	LS
undefined solid angle	UA	NaI(Tl)	NA
		Ge(HP)	GH
		Ge-Li	GL
		Si-Li	SL
		CsI	CS
		ionization chamber	IC
		grid ionization chamber	GC
		bolometer	BO
		calorimeter	CA
		PIPS detector	PS
Radiation	acronym	Mode	acronym
positron	PO	efficiency tracing	ET
beta particle	BP	internal gas counting	IG
Auger electron	AE	CIEMAT/NIST	CN
conversion electron	CE	sum counting	SC
bremstrahlung	BS	coincidence	CO
gamma ray	GR	anti-coincidence	AC
X - rays	XR	coincidence counting with efficiency tracing	CT
alpha - particle	AP	anti-coincidence counting with efficiency tracing	AT
mixture of various radiation e.g. X and gamma	MX	triple-to-double coincidence ratio counting	TD
		selective sampling	SS

Examples	method	acronym
4π (PC) β - γ -coincidence counting		4P-PC-BP-NA-GR-CO
4π (PPC) β - γ -coincidence counting eff. trac.		4P-PP-MX-NA-GR-CT
defined solid angle α -particle counting with a PIPS detector		SA-PS-AP-00-00-00
4π (PPC)AX- γ (GeHP)-anticoincidence counting		4P-PP-MX-GH-GR-AC
4π CsI- β ,AX, γ counting		4P-CS-MX-00-00-00
calibrated IC		4P-IC-GR-00-00-00
internal gas counting		4P-PC-BP-00-00-IG