Applied Radiation and Isotopes 212 (2024) 111449

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

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

National programme for the reliability of ionizing radiation measurements based on inter-laboratory comparisons (ILCs): ILC n°2 'radiopharmaceutical activities'

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ARTICLE INFO

Keywords:
^{99m}Tc
^{18}F
^{177}Lu
Nuclear medicine
Activity comparison
Radionuclide calibrator

ABSTRACT

A national Inter-Laboratory Comparisons (ILCs) programme was organized in Italy in 2022 by the Italian National Institute of Ionizing Radiation Metrology (INMRI), belonging to ENEA (Italian National Agency for New Technologies, Energy and Sustainable Economic Development), under the auspices of the Ministry of Enterprises and Made in Italy (Mimit ex MiSe). Within this ILCs programme, six inter-laboratory comparisons were organized, including the ILC-2 which focused on activity measurements carried out with radionuclide calibrators commonly used in the nuclear medicine departments of the participants.

The focus was on three short-lived radionuclides - ^{99m}Tc, ^{18}F, ^{177}Lu - commonly employed in nuclear medicine for both diagnostic and therapeutic purposes. All presented results were compared with the reference values provided by ENEA-INMRI to ensure the traceability of measurements to the national primary activity standards. The observed deviation from the reference values of the measured activity were mainly within ± 10% (100% for ^{18}F, 91.7% for ^{99m}Tc, 100% for ^{177}Lu). The E_n statistical estimator was used to assess the participants' ability to estimate uncertainty in the provided activity values. The obtained values revealed that, in certain instances, the involved laboratories did not achieve the correct results for E_n (with failure rates of 22.7%, 16.7%, 12.5% for ^{18}F, ^{99m}Tc, ^{177}Lu, respectively), despite deviations from the reference values falling within the ± 10%. The aim of ILC-2 was to harmonize the activity measurements in the country within the field of nuclear medicine for the specific radionuclides studied and enhance the measurement capabilities of the participants.

1. Introduction

The ability to measure the activity of short-lived radionuclides of interest in nuclear medicine with high accuracy and precision, through the use of radionuclide calibrators, is a deeply felt need in Italy. This requirement is particularly significant due to the numerous nuclear medicine centers, across the country, that rely on radiopharmaceuticals for diagnostics and therapeutic purpose (Ferreira and Andrew, 2018) .

In nuclear medicine departments, devices known as radionuclide calibrators, also named "activity meters", are commonly used for measuring the activity of radiopharmaceuticals. These devices consist of gas-filled cylinders, working as an ionization chamber, featuring a well in the center where the radioactive source (i.e., the radiopharmaceutical) is placed. This particular geometry, close to 4π, maximises detection efficiency (Knoll, 2010).

In order to ensure successful therapies and high-quality imaging techniques, as well as to comply with radioprotection standards, accurate knowledge of the radioactivity content in the radiopharmaceuticals administered to patients is essential.

The International Atomic Energy Agency (IAEA) requires the calibration of sources and instruments employed for patient dosimetry (International Atomic Energy Agency, 2014). Criteria for accuracy in activity measurements using radionuclide calibrators vary from ± 5% to ± 10%, as reported in Park et al. (2019).

In 2022, the first Inter-Laboratory Comparison (ILC-2) was carried out in Italy, to measure the activity of radiopharmaceuticals as part of a scientific collaboration between ENEA-INMRI and the Italian medical community, some laboratory of which are linked to ENEA-INMRI through the MIRA project. MIRA is the research project 19NET04 of EMPIR, European Metrology Programme for innovation and Research

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https://doi.org/10.1016/j.apradiso.2024.111449
Received 30 June 2023; Received in revised form 15 July 2024; Accepted 17 July 2024
Available online 18 July 2024

Table 1
Results for ^{99m}Tc.

Lab Code	x_{lab} [MBq]	U (xl_{ab}) k = 1 [MBq]	x_{ref} [MBq]	U (x_{ref}) k = 1 [MBq]	Δ [%]	$\lvert E_n \rvert$ [−]
119	46.30	2.34	44.48	0.89	4.10	0.36
120	21.04	0.80	20.13	0.40	4.53	0.51
23	49.60	1.50	48.07	0.96	3.18	0.43
80	43.00	1.00	41.05	0.82	4.74	0.75
10	40.86	4.10	39.12	0.78	4.44	0.21
86	29.97	0.90	31.13	0.62	−3.74	0.53
60	42.00	0.07	40.97	0.82	2.52	0.63
82	40.30	0.10	37.79	0.76	6.64	1.65
70	48.30	1.40	45.47	0.92	6.23	0.85
42	48.20	1.40	46.45	0.93	3.78	0.52
43	45.50	1.40	43.45	0.87	4.71	0.62
100	46.25	2.77	45.71	0.92	1.17	0.09
44	45.16	0.21	41.53	0.83	8.73	2.12
27	41.73	1.25	43.95	0.88	−5.04	0.72
55	41.30	0.80	40.10	0.80	2.99	0.53
91	48.37	1.50	50.80	1.02	−4.79	0.67
85	39.56	0.03	38.23	0.77	3.48	0.87
88	40.00	0.10	38.46	0.77	4.00	0.99
79	40.73	1.22	40.11	0.80	1.55	0.21
8	42.20	0.90	36.57	0.73	15.38	2.43
134	49.95	1.00	107.72	2.16	−53.63	12.14
95	48.51	1.64	47.22	0.95	2.72	0.34
45	47.92	1.43	47.25	0.95	1.42	0.20
87	47.77	2.40	47.69	0.95	0.18	0.02

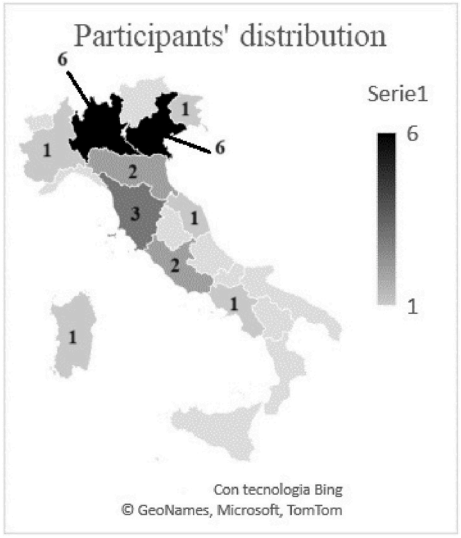


Fig. 1. - Participant's distribution in Italy.

EMPIR site, which aims to support for a European metrology network on the medical use of ionizing radiation MIRA site. Numerous hospitals in Italy were given the opportunity to participate in ILC-2, enabling them to assess the deviation of their instruments from the reference values provided by ENEA-INMRI for each radionuclide selected for the ILC-2. The collection of all results allowed to harmonize the activity measurements of radiopharmaceuticals across the country. Indeed, it is well known that comparison exercises, like the one described here, have been repeatedly shown to establish and improve the quality of measurements among participants. (Ciocanel et al., 1999; Joseph et al., 2003; MacMahon, 2007; Oropesa et al., 2003).

2. Interlaboratory comparison

A total of 24 Italian nuclear medicine centers joined the ILC-2 programme. The majority of these centers are located in northern Italy (16 centers), followed by the central Italy (6 centers). Finally, there is 1 center in the Campania region, located in southern Italy, and the last one is from the island of Sardinia (Fig. 1) .

Participants were not necessarily required to measure all three selected radionuclides. Instead, they were allowed to choose which radionuclides to include in their measurement capabilities test. The most frequently selected radionuclide was ^{99m}Tc, measured by all participants, followed by ^{18}F, measured by 22 of them. In contrast, only 8 participants provided measurement results for ^{177}Lu.

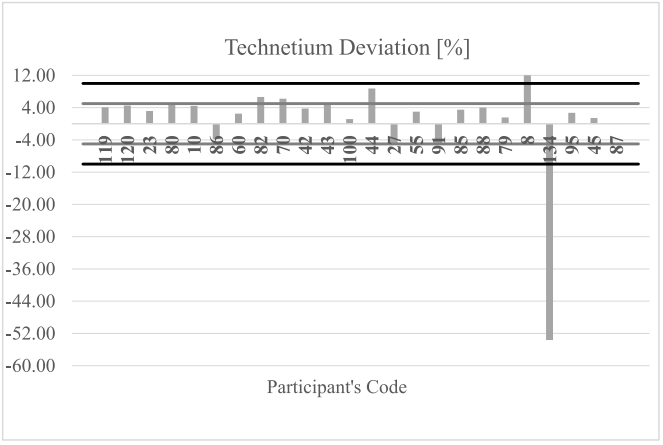
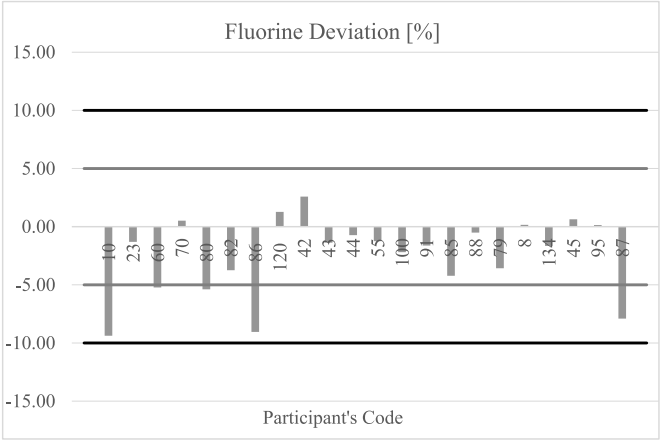
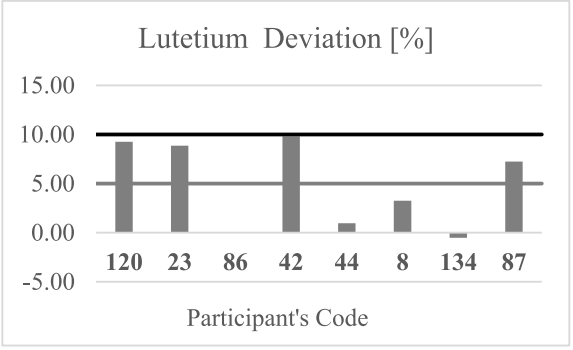


Fig. 2. ^{99m}Tc percentage deviation between the value declared by the Participant and the reference value provided by ENEA-INMRI.



Figs. 3. ^{18}F percentage deviation between the value declared by the Participant and the reference value provided by ENEA-INMRI.



Figs. 4. ^{177}Lu percentage deviation between the value declared by the Participant and the reference value provided by ENEA-INMRI.

Table 2
Results of ^{18}F.

Lab Code	x_{lab} [MBq]	U (xl_{ab}) $k = 1$ [MBq]	x_{ref} [MBq]	U (x_{ref}) $k = 1$ [MBq]	Δ [%]	$\|E_n\|$ [−]
10	40.52	4.00	44.71	0.45	−9.38	0.52
23	46.90	1.40	47.52	0.48	−1.30	0.21
60	47.80	0.03	50.44	0.51	−5.23	2.59
70	44.70	1.30	44.47	0.45	0.52	0.08
80	50.00	1.00	52.85	0.53	−5.39	1.26
82	45.39	0.01	47.15	0.47	−3.74	1.87
86	28.86	0.89	31.73	0.32	−9.05	1.52
120	29.95	1.20	29.57	0.30	1.28	0.15
42	41.10	1.20	40.06	0.42	2.59	0.41
43	44.80	1.30	45.43	0.46	−1.38	0.23
44	51.70	0.17	52.08	0.52	−0.72	0.34
55	41.20	0.80	41.72	0.42	−1.25	0.29
100	47.51	2.85	48.57	0.49	−2.19	0.18
91	46.99	1.40	47.77	0.48	−1.62	0.26
85	44.76	0.15	46.73	0.47	−4.22	2.00
88	48.00	0.10	48.25	0.48	−0.51	0.25
79	45.85	1.38	47.55	0.48	−3.57	0.58
8	40.20	0.70	40.14	0.42	0.16	0.04
134	45.75	1.00	46.52	0.47	−1.65	0.35
45	51.15	1.53	50.82	0.51	0.64	0.10
95	50.50	0.60	50.43	0.51	0.13	0.04
87	29.80	1.50	32.36	0.32	−7.90	0.83

Table 3
- Results of ^{177}Lu.

Lab Code	x_{lab} [MBq]	U (xl_{ab}) $k = 1$ [MBq]	x_{ref} [MBq]	U (x_{ref}) $k = 1$ [MBq]	Δ [%]	$\|E_n\|$ [−]
120	7.24	0.30	6.63	0.20	9.26	0.85
23	20.10	0.60	18.46	0.55	8.87	1.00
86	29.82	2.98	29.81	0.90	0.03	0.002
42	42.50	1.30	38.70	1.16	9.81	1.09
44	49.69	0.19	49.22	1.48	0.96	0.16
8	30.30	2.10	29.35	0.88	3.25	0.21
134	41.25	1.00	41.47	1.25	−0.52	0.07
87	28.96	1.40	27.00	0.81	7.24	0.60

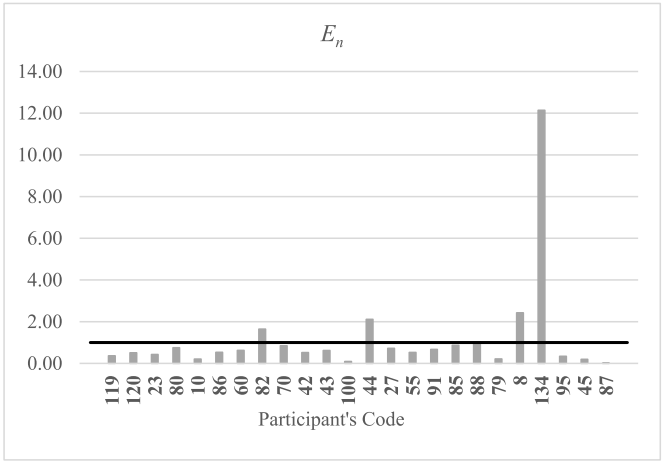


Fig. 5. ^{99m}Tc normalized error.

3. Methodology

As mentioned earlier, ILC-2 aimed to assess participants' proficiency in preparing and measuring a specified radiopharmaceutical source. Specifically, the ILC-2 scope involved the measurements within the activity [MBq] of the three radionuclides: ^{99m}Tc, ^{18}F and ^{177}Lu. The measurements were carried out using a Comecer VDC 606 commercial radionuclide calibrator, hereafter referred as 'VDC instrument', which

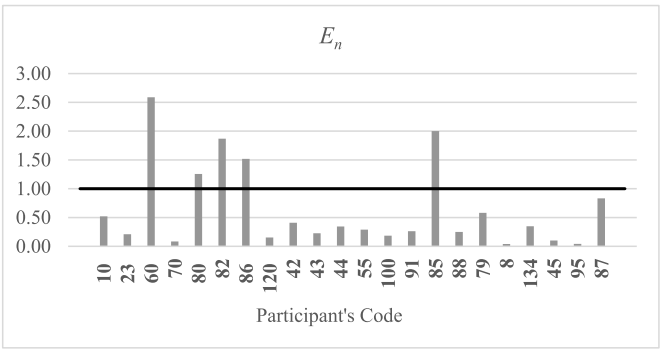
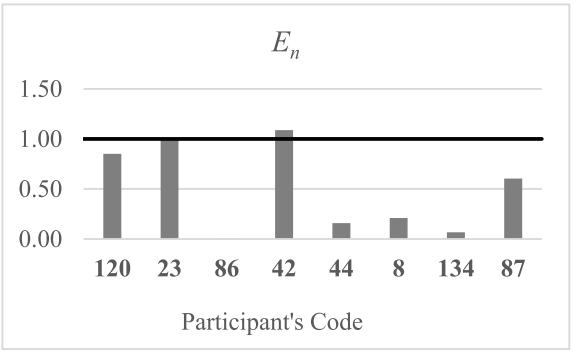


Fig. 6. ^{18}F normalized error.



Figs. 7. ^{177}Lu normalized error.

was provided by ENEA-INMRI and circulated among the participants.

In order to perform a blind comparison, the calibration factor applied for the VDC instrument was adjusted to a value known exclusively at ENEA-INMRI. In the presentation of results, participants are identified using blind codes to ensure anonymity.

The intercomparison process was structured according to the following.

1. The VDC instrument was dispatched to each participant. Upon receiving the instrument, participants were required to place it on a flat surface, away from sources of radiation, turn it on and wait for 3 h before starting the measurements;
2. The participant carried out the measurements, by:
   a. Preparing the source for each radionuclide by dispensing 4 cm^3 of aqueous solution, containing a radionuclide activity in the range 40–50 MBq, into a P6-type glass vial provided by ENEA-INMRI (height 54 ± 0.75 mm, diameter 21.75 ± 0.25 mm, wall thickness 1.2 ± 0.1 mm, maximum volume 13.8 ml);
   b. Measuring the source activity using their own instrument (hereafter called "laboratory value");
   c. Taking 5 VDC instrument activity readings of the background, with a 1-min interval between each reading;
   d. Taking10 VDC instrument activity readings of the source prepared as outlined in point a, with a 1-min interval between each reading;
   e. Taking 5 VDC instrument activity readings of the background, with a 1-min interval between each reading;
3. The participant reported the results (including reference and measurement times) on a data collection website, organized by ENEA-INMRI;
4. The received data were analyzed by ENEA-INMRI, taking into account the declared source activity (laboratory value) and the net readings of the VDC instrument;
5. ENEA-INMRI communicated the final results to each participant.

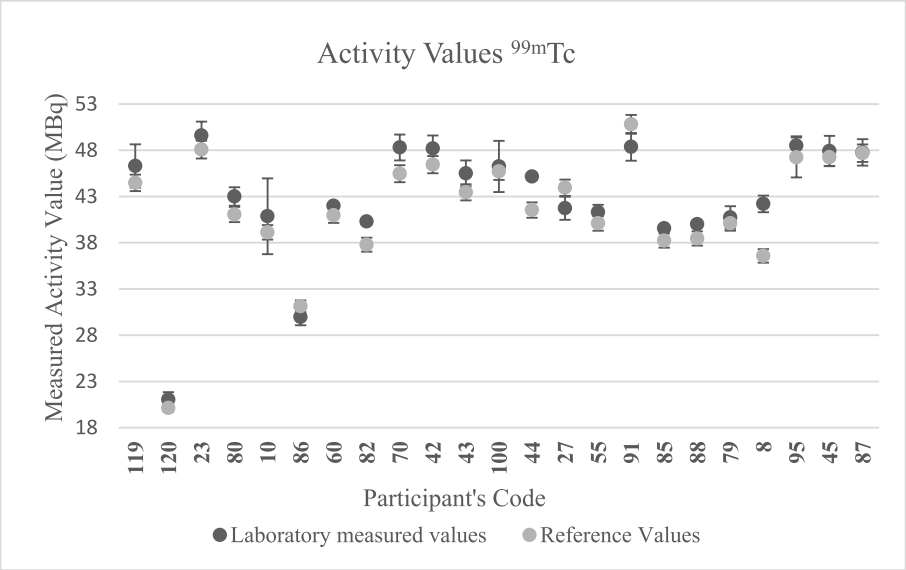


Fig. 8. Measured activity values from participants (excluding participant number 134) and the reference, along with their respective uncertainties for ^{99m}Tc.

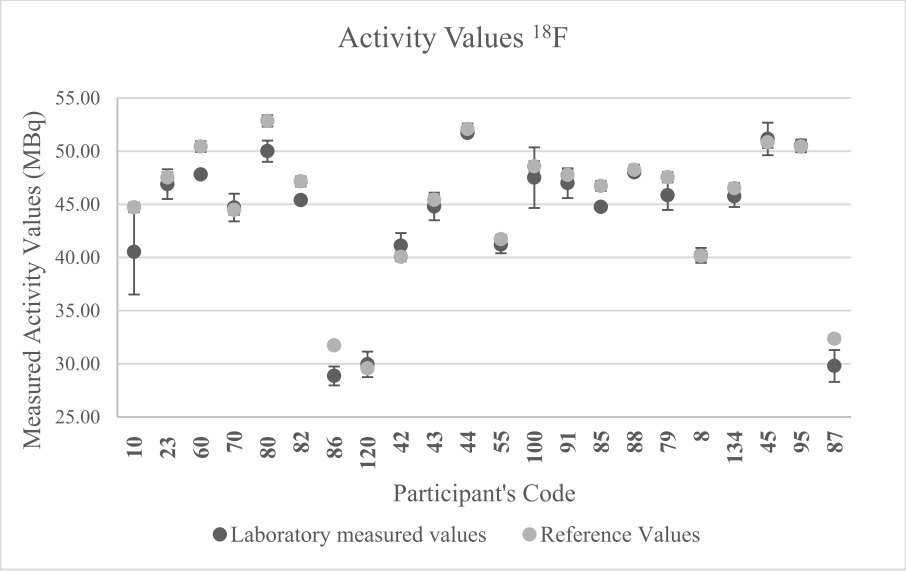


Fig. 9. Measured activity values from participants and the reference, along with their respective uncertainties for ^{18}F.

All the activity readings were performed in the nominal activity units of measurements, MBq, of the VDC instrument.

The above instructions were communicated to the participants through an informational note, while a website ENEA-INMRI Website developed by ENEA-INMRI was used for the collection of results.

During the intercomparison campaign, the ENEA-INMRI VDC instrument returned to ENEA-INMRI and its stability was tested by carrying out repeated measurements on a long-lived Ra-226 standard source with a known activity of (13.70 ± 0.16) MBq. Five measurements were taken within a 10-min timeframe, resulting in a standard deviation of 0.38%.

The linearity of the instrument was assessed one time before dispatching it to all participants, covering a range from 10 MBq up to 35 MBq with a ^{18}F source. The upper limit of 35 MBq was set based on the maximum activity (50 MBq) that ENEA-INMRI can receive on its own laboratory. The instrument displayed a linearity curve with an absolute deviation lower than 0.5%.

The obtained results fall within the typical acceptable tolerances for the field instruments, as outlined in Gadd et al. (2006).

4. Results and discussion

The analysis of the results was performed through a comparison of the laboratory values from each radionuclide by each participant, with the corresponding activity reference values calculated by ENEA-INMRI. The procedure to establish the reference was as follows: starting from the readings provided by each participant, using the VDC instrument, ENEA-INMRI calculated the average of these readings and subtracted the average of the background readings. The resulting values were then multiplied by the blind calibration factor to obtain the activity value. Finally, these values were reported at a specific reference time, incorporating decay corrections applied by ENEA-INMRI using the half-life of each radionuclide (Bé et al., 2004). This allowed for a comparison between the laboratory values provided by the participants, who measured each radioactive source using their own instrumentation, and the reference values calculated as described in the procedure above. The

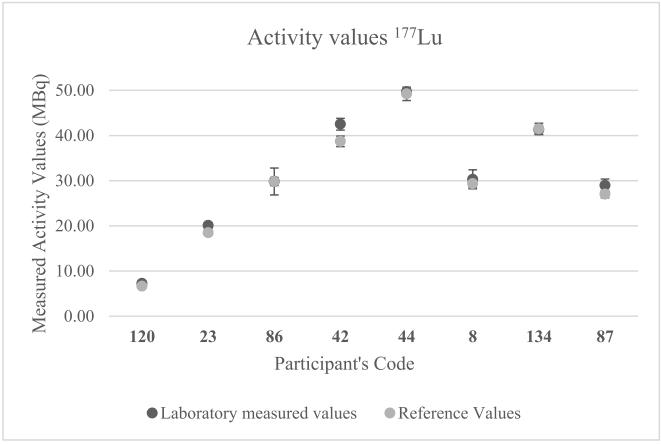


Fig. 10. Measured activity values from participants and the reference, along with their respective uncertainties for ^{177}Lu.

resulting deviations were analyzed taking into account the uncertainties reported by the participant and those declared by ENEA-INMRI.

The results of the comparison were analyzed using statistical indicators commonly employed in evaluation tests and inter-laboratory comparisons (Iwahara et al., 2001; UNI CEI EN ISOIEC 17043:2010 Valutazione della conformità – Requisiti generali per prove valutative interlaboratorio, 2010; International Organization for Standardization, 2015; Oliveira et al., 2016), namely percent deviation, $\Delta(\%)$, and normalized error, E_n, as defined below:

$$\Delta(\%) = \frac{x_{lab} - x_{ref}}{x_{ref}} \bullet 100$$

$$E_n = \frac{x_{lab} - x_{ref}}{\sqrt{U(x_{lab})^2 + U(x_{ref})^2}}$$

where x_{lab} and x_{ref} are the participants (laboratory) and ENEA-INMRI (reference) values, respectively, and $U(x_{lab})$ and $U(x_{ref})$ are the corresponding expanded uncertainties ($k = 2$). The combined standard uncertainty communicated by the participants to our institute is a total uncertainty without specifying the individual components. The normalized error, E_n, considered the expanded uncertainty associated with both the participant and reference values. The E_n score is particularly useful when assessing a participant's ability to achieve results close to the reference value within the claimed expanded uncertainty.

According to (UNI CEI EN ISOIEC 17043:2010 Valutazione della conformità – Requisiti generali per prove valutative interlaboratorio, 2010; International Organization for Standardization, 2015; Oliveira et al., 2016), the E_n should be interpreted with caution, as it involves ratios of two separate (but related) performance measures. The numerator is the deviation of the result from the assigned value. The denominator is a combined expanded uncertainty that should not be larger than the deviation in the numerator, if $U(x_{lab})$ and $U(x_{ref})$ were determined correctly.

Therefore.

- $E_n \geq 1$ or $E_n \leq -1$ could indicate a need to review the estimation of the uncertainty, or to provide a correction to a measurement issue;
- $-1 < E_n < 1$ should be taken as an indicator of successful performance only if the uncertainties are trustworthy and the deviation ($x_{lab} - x_{ref}$) is smaller than that needed by the participant's customers.

In ILC-2, we considered a result acceptable if Δ (%) fell within $\pm$10% and E_n within $\pm$1. The $\Delta(\%)$ boundary for ILC-2 was established based on the literature (American Association of Physicists in Medicine, 2012; Park et al., 2019), where these values generally range between 5% and 10%. Consequently, a $\pm$10% $\Delta(\%)$ for all three radionuclides was selected to determine the acceptability of the results.

The ILC-2 results for ^{99m}Tc, ^{18}F, and ^{177}Lu are reported in Tables 1–3 and in Figs. 2–10 respectively.

For ^{99m}Tc, only two participants exhibited a $\Delta(\%)$ greater than 10% (participants 8 and 134). These same had an E_n value greater than 1, and then can be considered outliers. Given the large discrepancy obtained by center number 134 in terms of $\Delta(\%)$, a bilateral comparison with the center on this radionuclide is currently being organized. However, it should be noted that the center does not use ^{99m}Tc in clinical practice, but only for quality control on their instruments. It is also evident that not all the participants who achieved a $\Delta(\%)$ less than 10% obtained a E_n value within $\pm$ 1. This discrepancy suggests that certain participants (participants 82 and 44) underestimated the uncertainty, as their declared uncertainties were smaller than those calculated by ENEA-INMRI.

For ^{18}F and ^{177}Lu, all participants obtained results with a $\Delta(\%)$ of less than 10%. However, not all participants achieved an acceptable result in terms of E_n. For example, participants numbered 60, 80, 82, 85 and 86 for ^{18}F and participant numbered 42 for ^{177}Lu did not meet the criteria, as indicated in Tables 2–3 and Figs. 6–7. This suggests that measurements reported with low uncertainty could mask issues related to uncertainty estimation, more precisely an underestimation of the uncertainty.

5. Conclusions

Based on the results obtained, it can be concluded that the participants who joined the project demonstrated proficient measurement skills.

All participants were able to measure the ^{18}F and the ^{177}Lu within a 10% deviation from the reference value, and the 91.7% could achieve the same for ^{99m}Tc within this interval. However, when considering a new interval with a $\Delta(\%)$ within 5%, the number of participants able to measure all three radionuclides within this range decrease of 77.3% for ^{18}F, 50% for ^{177}Lu and 79.2% for ^{99m}Tc.

Regarding outlier results, various factors such as poor calibration of instrumentation, interference during measurement, and inadequate sample preparation could have contributed. However, determining the primary source of error requires a bilateral comparison with the involved laboratory.

In conclusion, participants who obtained a result in $\Delta(\%)$ greater than 10% are strongly encouraged to verify the calibration of their radionuclide calibrator. Emphasizing the importance of a thorough evaluation of uncertainty in activity measurements, especially in routine applications, is also crucial.

Although the participation in ILC-2 was not mandatory, numerous nuclear medicine departments in Italy expressed significant interest in joining the intercomparison, driven by public concern regarding the use of radiation in the medical field.

The majority of participating centers in ILC-2 are located in northern Italy. In order to obtain a more comprehensive overview of the measurement capabilities across the country, it is advisable to prioritize recruiting nuclear medicine centers from other regions in Italy for future comparative studies.

CRediT authorship contribution statement

Lucrezia Spagnuolo: Writing – review & editing, Data curation. **Marco Capogni:** Supervision. **Aldo Antonio Fazio:** Supervision. **Pierino De Felice:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

The authors express their gratitude to the Italian Ministry for the Economic Development, MiSe (now Ministry of Enterprises and Made in Italy, Minit) for the funding provided, supporting both the ILC-2 and the fellowship payment for the corresponding author. Another heartfelt thank you is extended to the Symposium Company (located in Turin, Italy) for managing the shipment of the VDC instrument among the participants.

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