Published in final edited form as:

Appl Radiat Isot. 2018 September ; 139: 266–273. doi:10.1016/j.apradiso.2018.05.023.

Standardization of ^{64}Cu activity

D.E. Bergeron^{*}, J.T. Cessna, R. Fitzgerald, L. Pibida, and B.E. Zimmerman

Radiation Physics Division, National Institute of Standards and Technology, Gaithersburg, MD 20874, USA

Abstract

The complex decay scheme that makes ^{64}Cu promising as both an imaging and therapeutic agent in medicine also makes the absolute measurement of its activity challenging. The National Institute of Standards and Technology (NIST) has completed a primary activity standardization of a $^{64}\text{CuCl}_2$ solution using the $4\pi\beta(\text{LS})-\gamma(\text{NaI})$ live-timed anticoincidence (LTAC) counting method with a combined standard uncertainty of 0.51 %. Two liquid scintillation (LS) counting methods were employed for confirmatory measurements. Secondary measurements were made by high-purity germanium detectors, pressurized ionization chambers (IC), and a well-type NaI(Tl) counter. Agreement between the LTAC-based standard and standards from other laboratories was established via IC calibration factors. Poor agreement between methods and with theoretical IC responses may indicate a need for improved $\beta^{+/-}$ branching probabilities and a better treatment of $\beta^{+/-}$ spectra.

Keywords

Copper-64; beta-gamma coincidence method; anticoincidence; liquid scintillation; triple-to-double coincidence ratio; TDCR; efficiency tracing; Monte Carlo; ionization chamber; HPGe; nuclear decay data

1. Introduction

Because the Cu^{2+} ion binds stably to a very wide range of small molecules, peptides, and antibodies, copper radioisotopes are considered very promising as therapeutic and imaging agents in nuclear medicine (Smith, 2004). With a relatively long half-life (12.7004(20) h; Bé et al., 2011), ^{64}Cu has shown potential as a positron emission tomography (PET) imaging agent for monitoring molecular biological processes ranging from hypoxia to growth factor expression (see, e.g., Chen et al., 2004; Williams et al., 2005; Cai et al., 2006).

Increasingly, the importance of precise quantitation in molecular imaging is being recognized. Improved quantitative precision of image data brings confidence in the identification of weak uptakes or small changes necessary to monitor disease progression or response to therapy, or to meaningfully interpret biokinetic data. While the uncertainties on quantitative molecular imaging data are typically dominated by biological contributions, precise instrument calibration remains key to acquiring data that can be meaningfully

^{*} denis.bergeron@nist.gov.

compared to data acquired on different occasions and/or at different sites (see, e.g., Shankar, 2006; Boellaard, 2008; Scheuermann, 2009; Lockhart et al., 2011). Ideally, medical devices are calibrated to a common, national standard.

We report here the first standardization of ^{64}Cu activity by the National Institute of Standards of Technology (NIST), the national metrology institute (NMI) for the United States of America (USA). The primary standard was realized by live timed anticoincidence (LTAC) counting, with confirmatory measurements by two other liquid scintillation counting (LSC) based methods. The standardization is a challenging one due to the complex decay scheme, with significant β^+ and β^- branches accompanied by a 43.53(20) % electron capture branch that goes directly to the ^{64}Ni ground state. Other NMIs have previously standardized this radionuclide and a recent comparison under the auspices of the European Association of National Metrology Institutes (EURAMET) established accord between numerous European laboratories (Bé et al., 2012). As part of that exercise, a new evaluation of the decay scheme and nuclear data for ^{64}Cu was carried out. The calculation of detection efficiencies critical to standardization by typical LSC based methods was only possible using the new data (Kossert et al., 2014).

Though relatively long for nuclear medicine applications, the 12.7 h half-life of ^{64}Cu is far too short for shipping samples from Europe to the USA as part of a comparison exercise. The logistical hurdles that prevent distant laboratories from comparing standards for short-lived radionuclides have been recognized for some time. The transfer instrument of the international reference system (SIRTI) removes those hurdles (Michotte and Fitzgerald, 2010; Michotte et al., 2013). The ^{64}Cu standardization described herein was carried out in anticipation of the May 2016 visit from the SIRTI (Michotte et al., 2017).

2. Materials and Methods

2.1. Carrier solution

The carrier solution was prepared by dissolving CuCl_2 (99.995 %; Alfa Aesar, Ward Hill, MA¹) in 0.1 mol·L⁻¹ HCl to achieve a final Cu^{2+} concentration of 15.8(4) $\mu\text{g}\cdot\text{g}^{-1}$. This carrier composition was chosen based on the report of Wanke et al. (2010). Others have reported using slightly lower Cu^{2+} concentrations (Amiot et al., 2012).

2.2. Cu-64 solution dilutions

The measurements described herein were conducted during two separate experiments performed in November 2015 and March 2016. The dilution and source preparation schemes were similar in both experiments and are shown graphically in Figures S1 and S2. For the 2016 experiment, all containers (pycnometers, bottles, ampoules, etc.) used in source preparation were soaked in the CuCl_2 carrier for one week, rinsed with deionized water and ethyl alcohol, and allowed to dry for approximately one week before use.

¹Certain 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.

For each experiment, a solution containing nominally 1.1 GBq of ^{64}Cu in 0.1 mol·L⁻¹ HCl was received from the University of Wisconsin Cyclotron, where ^{64}Cu is produced by the $^{64}\text{Ni}(\text{p},\text{n})$ reaction (Avila-Rodriguez et al., 2007). One day after receipt of the material, the entire contents were diluted to approximately 20 mL to create a master solution which was subsequently dispensed into 5 mL ampoules and/or dose vials. Solution uniformity was verified by measuring the individual sources in a Vinten 671 ionization chamber (VIC) (serial number 3–2, Vinten Instruments, Surrey, UK), which is biased to –1500 V and is read by a Keithley 6517A electrometer (Keithley Instruments, Cleveland, OH).

Once the solution uniformity was confirmed, a solution with a nominal dilution factor of 10 was prepared and subsequently used to make counting sources. All gravimetric dilution factors were confirmed by ionization chamber and gamma spectrometry measurements to within 0.05 %.

2.3. Liquid scintillation sources

The diluted ^{64}Cu solution was used to prepare a series of liquid scintillation (LS) counting sources for use with the live-timed anticoincidence counting (LTAC), triple-to-double coincidence ratio (TDCR), and CIEMAT-NIST efficiency tracing (CNET) methods. Details of the application of each method are provided in Section 2.4.

In the 2015 LTAC experiments, hemispherical glass sources were prepared with Ultima Gold (UG; PerkinElmer, Waltham, MA) and Ultima Gold AB (UGAB; PerkinElmer, Waltham, MA). To 3 mL of scintillant, ^{64}Cu solution, cold Cu carrier solution, and water were added to give a total of 0.3 mL in the UGAB samples or 0.2 mL in the UG samples. A matched blank was prepared with each scintillant, with carrier substituted for the radioactive ^{64}Cu . In the 2016 experiments, only UG was used.

For the 2015 experiment, three cocktails for the TDCR measurements were prepared in 20 mL glass LS vials and consisted of nominally 10 mL of UGAB to which 0.9 mL of water was added. The amount of ^{64}Cu solution added ranged from 0.03 g to 0.08 g, so that reasonable count rates were achieved for all three sources by counting the weakest source first. CuCl_2 carrier solution was added to bring the total CuCl_2 content of all three sources to nominally 0.1 mL. A compositionally matched blank was also prepared and used for background subtractions. In 2016, the TDCR sources were prepared with compositions similar to the 2015 sources, but in 20 mL polyethylene vials. In addition to two unquenched sources, an additional set of three sources was chemically quenched with 0.04 mL to 0.25 mL of diluted nitromethane (10:1 ethanol:nitromethane by volume).

The CNET measurement sources were prepared the same way for both experiments and consisted of sets of five 20 mL glass LS vials containing 10 mL of UGAB, 1 mL of water, and 0.04 mL to 0.25 mL of diluted nitromethane. An additional five cocktails were prepared with 10 mL of UG, 0.7 mL of water, and 0.04 mL to 0.25 mL of diluted nitromethane. Nominally 0.04 g of ^{64}Cu solution was gravimetrically dispensed into each vial. For each ^{64}Cu series, a compositionally matched series of ^3H sources was also prepared. In addition, 2 blanks were prepared with compositions matching the most- and least-quenched sources for each series.

2.4. Methods

2.4.1. LTAC—Live-timed anticoincidence (LTAC) measurements were performed on the NIST LTAC system (Lucas, 1998; Fitzgerald and Schultz, 2008) for both the 2015 and 2016 experiments. Data were acquired simultaneously with analog and digital systems. Efficiency variation was achieved by changing the LS threshold. In the 2015 experiment, counts from three of the four sources were used in the activity determination, with 17 to 70 repeat determinations of 600 s (livetime) each. The fourth source was not counted before it had decayed to an activity too low to be measured. One source was measured twice.

In the 2016 experiment, counts from all three sources were used in the activity determination, with 45 to 100 repeat determinations of 600 s (livetime) each. One source was measured twice. To check for long-lived non-photon-emitting impurities, a decayed ^{64}Cu source was measured ≈ 2 weeks after the reference time; typical LS count rates differed from the blank rates by less than one standard deviation, indicating that no additional corrections were necessary.

2.4.2. TDCR—The triple-to-double coincidence ratio (TDCR) method of liquid scintillation counting was carried out in both experiments with the NIST TDCR system (Zimmerman et al., 2004) using both our MAC3- (Bouchard and Cassette, 2000) and field programmable gate array (FPGA)-based acquisition systems. Efficiency variation was achieved through the use of grey filters and, in 2016, by chemical quenching with nitromethane.

Each source was counted a minimum of three times with each of three grey filters on at least two occasions over the course of a three day counting period. The counting times varied between 300 s and 1200 s (live time) for each counting cycle and were adjusted according to count rate to provide a minimum of 10^6 counts in the triples counting channel.

Values for the triple-to-double coincidence ratio (K) of between 0.78 and 0.86 were observed in the two experiments. The logical sum of doubles efficiency (ϵ_D) as a function of K was calculated using the 2011 version of the MICELLE2 code (Kossert and Grau Carles, 2010) using the atomic data that accompany the code package, kB values of 0.0075 cm $\cdot$ MeV $^{-1}$ and 0.012 cm $\cdot$ MeV $^{-1}$, and nuclear data taken from the most recent Decay Data Evaluation Project (DDEP) evaluation (Bé et al., 2011). The MICELLE2 calculations were performed independently for each branch, and the results combined in a spreadsheet to calculate the total efficiencies.

2.4.3. CNET—The CIEMAT-NIST efficiency tracing (CNET) method of liquid scintillation counting (Grau Malonda and Garcia-Toraño, 1982; Coursey et al., 1986) was carried out on two counters in each experiment. The 2015 experiment used a Beckman LS 6500 (Beckman Coulter, Fullerton, CA) and an Aloka AccuFlex LSC-8000 (Hitachi, Tokyo, Japan). In the 2016 experiment, the Beckman counter was complemented by a Wallac 1414 Winspectral (PerkinElmer, Wesley, MA). Tracing efficiencies were calculated with the MICELLE2 code in the same manner as the TDCR efficiencies.

2.4.4. HPGe—Gamma-ray spectrometry measurements were carried out with four different HPGe detectors (both n-type and p-type detectors) with well-characterized efficiency curves (Pibida et al., 2006). Two ampoules were measured for photon-emitting impurities in each of the experiments. In addition, the 2015 measurements were used in a half-life determination, while the 2016 measurements focused on determining the emission probability of the main gamma-ray line (Pibida et al., 2017). Activities were calculated based on the 1346 keV gamma-ray peak and the 2011 DDEP evaluated emission probability (Bé et al., 2011). The HPGe detectors were also used to verify dilution factors in the source preparation process.

2.4.5. Ionization chambers—In both the 2015 and 2016 experiments, three ampoules were measured in the NIST automated ionization chamber (AutoIC), also known as “ICB” (Fitzgerald, 2010). Between each ^{64}Cu source, a ^{226}Ra reference source (RRS), and an empty sample holder for backgrounds were measured. The ratio (R) of the measured responses for ^{64}Cu and ^{226}Ra is related to the ^{64}Cu activity (A) by a calibration factor (K , which we commonly refer to as the K-value) by

$$K = A/R \quad (1)$$

where A in this case is taken to be the LTAC-determined activity.

As described above, each ampoule (and dose vial) that was prepared was measured in the VIC. Each measurement run consisted of 200 readings from the Keithley electrometer, sampled via a LabVIEW interface at 1.5 s or 2 s intervals. At least two measurement runs were performed for each source. Measured currents used in the K_{VIC} determinations ranged from approximately 91 pA to 97 pA for the 2015 experiment and approximately 106 pA to 126 pA for the 2016 experiment.

Sources were also measured on several commercial reentrant ionization chambers, i.e. “dose calibrators” (see Online Supplemental Material), and it was found that manufacturer-recommended calibration factors give activities within 2.4 % of the NIST standard.

2.4.6. Automatic well counter—Ampoules were measured in custom-built nylon centering sleeves on a PerkinElmer Wizard 2480 NaI(Tl) automatic gamma well counter (GWC) with an open counting window (nominally 20 keV to 2000 keV). In the 2015 experiment, GWC measurements were performed on ampoules originally prepared for ionization chamber and HPGe measurements. These ampoules were allowed to decay for ≈ 8.5 half-lives before any GWC measurements, so long-lived impurities dominated the observed count rates. In the 2016 experiment, ampoules were prepared specifically for GWC measurements (Figure S2). These measurements were part of a half-life determination (Pibida et al., 2017) and the data were also used to establish a calibration factor. The maximum net count rate was $\approx 2000 \text{ s}^{-1}$ and the count time was 600 s, so that the total counts were $> 1 \cdot 10^6$ in the first cycles. A 600 s background measurement was performed in each cycle, giving an average background count rate of 4.1 s^{-1} with a relative standard

deviation over 134 cycles of $< 2\%$. Impurity corrections were based on the HPGe determinations.

3. Results

3.1. Impurities

The impurities, expressed as a fraction, f , of the ^{64}Cu activity at the reference time (t_{ref} ; selected to fall in the middle of each measurement campaign), were determined by HPGe in each experiment and are given in Table 1. These data were used for impurity corrections in all LTAC, TDCR, CNET, ionization chamber, and gamma counting results. The short-lived ^{55}Co impurity was detected early in the experiments and its decay followed for several days (using the 931.1 keV and 1408.5 keV lines). The other impurities were determined after most of the ^{64}Cu had decayed using the main gamma-ray lines with emission probabilities larger than 7 % and energies larger than 40 keV.

The activity of the ^{57}Co impurity in the 2015 solution was confirmed to within 0.1 % by gamma spectrometry measurements performed more than one year after the reference time.

A check for long-lived beta-emitting impurities was performed by liquid scintillation counting in December 2016. Sources were prepared with ≈ 1 g of each master solution in 10 mL of UGAB. The net count rates were consistent with the rates predicted due to the ^{57}Co impurity, indicating no significant additional long-lived impurities.

After the primary standardization experiments discussed in this work, two additional studies with ^{64}Cu in May 2016 (SIRTI measurements; Michotte et al., 2017) and in June 2016 (positron emission tomography studies; Zimmerman et al., 2018) were carried out at NIST. These studies are relevant here because HPGe measurements of photon-emitting impurities have indicated batch-to-batch variability in the purity of the ^{64}Cu solution received from the University of Wisconsin. Figure 1 shows the impurity fractions decay corrected not to t_{ref} , which varied relative to the ^{64}Cu separation time (t_{sep}), but to a time $t'_{\text{ref}} \approx t_{\text{sep}} + 3$ d. For the four studies represented in Figure 1, t'_{ref} was 5 d to 12 d before t_{ref} . Analyzing the data in this way reveals that while the absolute activities of the impurities vary, the relative proportions of the different Co contaminants are roughly consistent from batch-to-batch, suggesting variability in the efficiency of the purification.

3.2. Primary activity determinations

3.2.1. LTAC— Cu-64 activities were calculated by extrapolation of data acquired with a gate set over the 1346 keV gamma-ray peak, as has been described by others (Kawada, 1986; Wanke et al., 2010; Sahagia et al., 2012; Bé et al., 2012; Havelka and Sochorová, 2014). Data acquired on analog and digital (with off-line analysis) systems returned activities that consistently agreed to $< 0.1\%$. In both experiments, extrapolations based on data acquired with a gate set over the annihilation photon peaks (511 keV or 1022 keV) underestimated the activity by $> 4\%$. Further, linear and quadratic extrapolations of these data gave intercepts that varied by several percent. These poor results when using the annihilation peaks for extrapolation are consistent with the findings of others (e.g. Sahagia et al., 2012; Wanke et al., 2010).

Figure 2 shows the residuals of linear and quadratic fits to the experimental data obtained with a gate over the 1346 keV gamma peak for the 2016 experiments. Residuals in the 2015 experiment were of similar magnitude and showed very similar trends. Monte Carlo simulations were performed in GEANT4 (Agostinelli et al., 2003) using a modified version of the package developed by Fitzgerald (2016), reproducing the general shape of the residuals. A full discussion has been presented separately (Bergeron and Fitzgerald, 2018), but some of the details are relevant here. The Monte Carlo simulations indicated a correction factor ($F = 0.9967$) for linear extrapolation of data collected with a gate over the 1346 keV gamma peak. Both correction factor and ‘scaling’ approaches were considered (Bergeron and Fitzgerald, 2018), along with alternative gate schemes; in all cases, the Monte Carlo treatment returned a similar result for the activity, but some schemes carried much more uncertainty than others.

The Monte Carlo model (referred to as MC2016 in Bergeron and Fitzgerald, 2018) initially used to analyze the LTAC data indicated a correction factor for linear extrapolation, but trends in the residuals indicated that the model was not properly capturing the experiment. At the time of the SIRTI comparison (Michotte et al., 2017), it was judged that the Monte Carlo simulations required further attention, and no correction was made. The primary activity standard adopted for the SIRTI comparison was based on the pure linear extrapolation of the LTAC data acquired with a gate over the 1346 keV gamma peak and over the range $Y = 0.31$ to 0.80 . This approach is consistent with the one adopted at other laboratories.

Table 2 gives the complete uncertainty budget for the LTAC-determined activity without a Monte Carlo-based correction. The 2016 data were used as the standard upon which the SIRTI comparison was based, but were consistent with the 2015 data and the individual uncertainty budgets were comparable. In both experiments, the two largest uncertainty components were the between-source variability and the extrapolation model uncertainty. The between-source variability could be interpreted as an indication of an incomplete uncertainty budget, rather than as a true source of uncertainty; we think that this uncertainty estimator contributes to a conservative estimate of the total combined uncertainty by accounting for otherwise hidden or unaccounted variances. This approach is widely adopted and well-established (Zimmerman and Collé, 1997). As reflected in Table 2, the model uncertainty was estimated from components including the difference between linear and quadratic extrapolations and the standard deviation on intercepts calculated from several different data domains, as discussed by Fitzgerald et al. (2015). Counting statistics in both experiments contributed $< 0.2\%$.

Following the SIRTI comparison, the Monte Carlo model was refined (referred to as “MC2017” in Bergeron and Fitzgerald, 2018). The new model better captured the experiment, and it became apparent that the indicated correction to the linear intercept ($F = 0.9967$) arose mostly due to the “Funck correction” (Funck and Nylandstedt Larsen, 1983).

3.2.2. TDCR—The calculated ϵ_D as a function of K for kB values of $0.0075\text{ cm}\cdot\text{MeV}^{-1}$ and $0.012\text{ cm}\cdot\text{MeV}^{-1}$ is presented in Figure 3. The TDCR curve displays the non-monotonic behavior typical of electron capture radionuclides (Broda et al., 2007). By varying the

efficiency and noting whether K increases or decreases with a reduction in detection efficiency (imposed by grey filters or chemical quenching), we were able to identify the lower part of the curve (with negative slope) as the one in which our measurements were made.

It was apparent early in the 2015 experiment that a large proportion of the measurements were being made very close to the inflection point of the efficiency curve ($K = 0.78$ to 0.81), despite using our entire set of available grey filters (see Figure S3). As a result, even small deviations in K lead to unstable ϵ_D . For this reason, only data with TDCR values above an arbitrary cutoff of $K = 0.793$ were used in the final activity calculations. In other words, the data collected with the highest counting efficiencies were not usable.

In the 2016 experiment, the LS sources were quenched with nitromethane to push the range of experimental efficiencies farther from the inflection point (i.e., lower). While higher K were achieved, it is clear from comparison with the LTAC results (*vide infra*) that ϵ_D and K did not scale according to the predictions of the MICELLE2 model. As a result, the uncertainty due to the quenching model was much higher with the lower counting efficiencies in 2016 than with the higher efficiency sources measured in 2015. Figure S3 shows that any differences in the quench curves obtained with different quenching mechanisms (i.e., chemical quenching with nitromethane v. gray filters) is within the scatter of the data. Moreover, the general shape of the efficiency curves and the approximate location of the inflection point are similar with glass and plastic LS vials, but the overall counting efficiency appears to be lower with plastic vials, counter to the expectation that dispersive vials should give improved efficiency (Cassette and Vatin, 1992). Finally, it appears that the bias in the calculated efficiencies at the lowest efficiency points is not completely captured in our uncertainty estimates. The difficulties in calculating LS efficiencies for ^{64}Cu were treated by Kossert et al. (2014) and will be discussed further in Section 4.2.

The estimated total combined uncertainties for the 2015 and 2016 experiments were 0.67 % and 1.0 %, respectively. Model dependence, arising from the experimental uncertainty on the determination of K and the estimated uncertainty on the calculated efficiencies, was the dominant source of uncertainty. As mentioned above, efficiencies near the inflection point are particularly sensitive to the input data, and we found here that the propagation of the uncertainties on the nuclear and atomic input data was the second largest component of uncertainty.

3.2.3. CNET—Since the counting efficiencies for ^3H and ^{64}Cu ($\epsilon_{\text{H-3}}$ and $\epsilon_{\text{Cu-64}}$) both decrease monotonically with increased quenching, the CNET method does not suffer from the complications of operating near an inflection point encountered in the TDCR exercise. Figure 4 shows the activities determined by CNET normalized by the average and plotted as a function of the added quenching agent. For UGAB, the MICELLE2 model gives a constant activity as a function of quenching. For UG, a slight increase in the measured activity with increased quenching is evident. Typically, this would be interpreted as an underestimation of the counting efficiency at higher quenching. Considering the TDCR results (discussed further in Section 4.2), we expect MICELLE2 to overestimate the counting efficiencies,

especially at higher quenching. It is possible that the unexpected quench-dependence is specific to the UG series. Indeed, the UGAB cocktails showed no sign of quench-dependence; all of the sources prepared for TDCR counting used UGAB.

Figure 4 also illustrates the between-counter variance observed in the 2016 CNET experiment.² NIST routinely measures sources on multiple counters to demonstrate that the measured activity is not dependent upon the specific operating conditions of a given instrument (e.g., Laureano-Pérez et al., 2007). In this case, measurements on the Beckman counter returned consistently higher activities than measurements on the Wallac. Within the data from each counter, no time-dependence in the measured activities was observed, suggesting that the variance is truly instrument-dependent. In the final uncertainty analysis, this variance (0.48 %) was the largest contributor to the combined standard uncertainty on the CNET-determined activity (0.55 %). The kB -dependence was relatively small (0.09 %), mostly because of the contributions of the high-efficiency $\beta^{+/-}$ branches.

3.2.4. HPGe—The ^{64}Cu activities determined by gamma ray spectrometry with HPGe detectors and based on the 2011 DDEP nuclear data (Bé et al., 2011), normalized by the corresponding LTAC-determined activities, are shown in Table 1. In the 2016 experiment, an evaluation specifically dedicated to determining the ^{64}Cu activity was added to the determinations carried out for impurities analyses. Using data from multiple samples and using two different software packages for peak fitting, an activity was determined with a 1.1 % combined standard uncertainty. The result normalized to the LTAC-determined activity was $A_{\text{HPGe}}/A_{\text{LTAC}} = 0.988(11)$ where the largest component in the stated uncertainty is the uncertainty on the DDEP gamma ray emission probability, followed by the uncertainty on A_{LTAC} . These data were also used to calculate new emission probabilities (Pibida et al., 2017).

3.3. Ionization chamber calibration factors

For ICB, the combined standard uncertainty on the adopted K-value (determined experimentally in the 2016 experiment) is 0.58 %. The uncertainty on the LTAC-determined activity is the largest component, followed by experiment-to-experiment variability ($s_{\text{ev}} = 0.29 \%$), defined as the standard deviation on the K-values determined in the two experiments. This uncertainty estimator, like the source-to-source variability described in Section 3.2.1, contributes to a conservative estimate for the total combined uncertainty by accounting for otherwise hidden variances between experiments.

The energy-dependent response of ICB has been characterized, and a Monte Carlo simulation of the detector developed using the EGSnrc user code DOSRZnrc (Rogers et al., 2010). Unknown physical parameters were fixed by minimizing the residuals of the shape of the response curve to the relative experimental responses to 14 radionuclides. The overall normalization was then fixed to the response to ^{60}Co . The ratio of the theoretical K-value to the experimental (2016) K-value was 1.017(15) where the stated uncertainty is the

²CNET results from the 2015 experiment were similar to the 2016 results. However, the data acquired with the Aloka counter could not be properly interpreted because the instrument's timestamp is reported with one minute precision, which is inadequate for short half-life radionuclides like ^{64}Cu .

combination of the combined standard uncertainty on the experimental value and the average absolute residual for the Monte Carlo fit. The residuals near 511 keV were on the order of 1.5 %. Previous calculations for other positron-emitters (^{18}F and $^{68}\text{Ge}/^{68}\text{Ga}$) gave better agreement (ratios of 1.003(11) and 1.008(12)) with experiment than we see for ^{64}Cu .

For the VIC, the 2015 and 2016 experiments found $K_{\text{VIC}} = 1.937(11) \text{ pA}\cdot\text{MBq}^{-1}$ and $= 1.952(10) \text{ pA}\cdot\text{MBq}^{-1}$, respectively. For both experiments, the largest contributor to the uncertainty on K_{VIC} was the uncertainty on the ^{64}Cu activity. The final adopted $K_{\text{VIC}} (= 1.952(14) \text{ pA}\cdot\text{MBq}^{-1})$ was the 2016 value with an additional uncertainty component for the experiment-to-experiment variability ($s_{\text{ev}} = 0.51 \%$). Instrumental drift could be mostly ruled out as a contributor to s_{ev} since VIC response to a ^{226}Ra check source differed by only 0.14(11) % between the experiments. In addition, the data used to calculate K_{VIC} were acquired with nearly identical currents in both experiments (see section 2.4.5), so non-linearity of electrometer response does not contribute to s_{ev} .

A Monte Carlo simulation of the VIC was developed using PENELOPE (Salvat et al., 2001) and based on detailed engineering drawings and a series of x-ray computed tomography images acquired at NIST. The number of ion pairs per eV for nitrogen, $W_{\text{N}_2} = 34.8(2) \text{ eV}$, was taken from ICRU Report 31 (1993). The N_2 pressure in the chamber was adjusted in the simulation to reproduce the experimental response to ^{18}F (Fitzgerald et al., 2014). For ^{64}Cu , the calculated K_{VIC} was $1.920(27) \text{ pA}\cdot\text{MBq}^{-1}$, so the ratio of the theoretical K_{VIC} to the experimental K_{VIC} was 0.984(16). The simulation was also used to calculate K_{VIC} for $^{68}\text{Ge}/^{68}\text{Ga}$, giving much better agreement with experiment (0.999(15)).

3.4. GWC calibration factor

In the 2016 experiment, ampoules counted in home-built centering nylon sleeves with an open counting window gave a detection efficiency of approximately 0.14 counts per decay of ^{64}Cu . This efficiency is, of course, specific to the unique counting geometry employed at NIST. The ampoules were measured repeatedly for more than 3 d, providing data for a new half-life determination, the details of which are reported separately (Pibida et al., 2017).

4. Discussion

4.1. Link to the NPL

The Vinten 671 ionization chamber (VIC) at NIST (Serial No. 3–2) has a known response relationship (NPL, 1984) with sister chambers at various national metrology institutes, including the one at the National Physical Laboratory (NPL) in Teddington, UK (“NPL master chamber”, Serial No. 3–5). Because the chambers give consistent responses to $< 0.23 \%$, calibrations based on standards at NIST and NPL can be indirectly compared. Using the K_{VIC} (and volume correction factors) communicated by colleagues at the NPL (Fenwick, 2015), the LTAC-based activities from the 2015 and 2016 experiments can be normalized ($K_{\text{NIST}}/K_{\text{NPL}}$) to give 1.0041(58) and 0.9968(51), respectively (see Figure 5). The stated uncertainties are from the LTAC activities only, neglecting uncertainty contributions from the VIC measurements and from the NPL $K_{\text{VIC}} (= 0.9 \%)$. Both the 2015 and 2016 values for K_{VIC} agree with the NPL value to within its stated uncertainty. Agreement with the NPL

K_{VIC} can also be interpreted as an indirect confirmation of agreement with the EURAMET comparison (Bé et al., 2012).

The Monte Carlo-corrected results are also shown in Figure 5. The uncertainties shown include modifications to the “model uncertainty” component described in Table 2: the difference between Monte Carlo-corrected linear and quadratic extrapolations (0.31 %) was estimated and an additional uncertainty component reflecting the residuals of a fit of Monte Carlo calculations to the experimental data was included. A complete assessment of the uncertainty on F would require a full propagation of the nuclear data uncertainties and has not been carried out here; so the uncertainties on the Monte Carlo-corrected points in Figure 5 may be slightly underestimated.

4.2. Between-method agreement

For ease of comparison, activities determined by LTAC, CNET, TDCR, and HPGe were normalized by the activity determined in each experiment using the NPL value for K_{VIC} (Figure 5). The LTAC-determined activities were consistently higher than those determined by other methods. Other labs have reported lower activities with TDCR and CNET than with coincidence counting methods, but with better agreement between methods than we see here (Bé et al., 2012).

In the TDCR measurements, other laboratories tend to use only the highest-efficiency (unquenched) sources in their activity assessments. Further, some laboratories use lower total aqueous fractions, which can result in higher counting efficiency. We found that lower counting efficiencies resulted in increased model bias (Section 3.2.2). However, since the highest achievable counting efficiencies were near the inflection point of the K v. ϵ_D curve, they were attended by increased uncertainty. In addition to the uncertainty attending the severe slope of the K v. ϵ_D curve, Amiot et al. (2012) added that near the inflection point, the calculated K and ϵ_D are particularly sensitive to the nuclear data. In summary, efficiency calculations for ^{64}Cu , as for other electron capture nuclides with complex decay schemes, remain challenging, especially at lower counting efficiencies. It is currently unclear whether the challenge may owe partially to non-linearities in the low-energy response of TDCR systems, but it is clear that the tradeoff between bias and uncertainty makes the TDCR method non-ideal for the standardization of ^{64}Cu . Indeed, it is clear (Figure 5) that our estimated uncertainties do not fully account for the bias in calculated efficiencies for the lowest efficiency data.

In general, the calculated ϵ_D were too high. The difficulties in calculating efficiencies for ^{64}Cu in particular were discussed by Kossert et al. (2014) in their description of some extensions to the MICELLE2 model. They noted that gamma- and x-ray scattering from the optical chamber can produce a non-negligible increase in the probability of interaction in the scintillant (as demonstrated by Cassette et al., 2006), that positron annihilation in flight—occurring with ≈ 0.6 % probability for ^{64}Cu positrons—reduces the energy deposited in the scintillant, and that screening and exchange effects may need to be considered in the calculation of the ^{64}Cu $\beta^{+/-}$ spectrum shapes. Kossert and Mougeot (2015) demonstrated the potential importance of screening and exchange corrections very clearly in the case of ^{63}Ni , and Kossert et al. (2014) suggested they may also be important in the ^{64}Cu case. We have

previously noted that when this problem arises, it is more pronounced at lower counting efficiencies (Bergeron et al., 2016), which is consistent with our current results.

The efficiency curves for CNET are not plagued by inflection points, and for UGAB appeared to be free of trending with counting efficiency. The method adopted by other laboratories of using only the highest efficiency data would not result in significantly higher recovered activities; in fact, considering the UG data, this approach would give a slightly lower activity. The high instrument-dependent variability may arise due to small differences in the low-energy thresholds of the different counters, though this might be expected to introduce more quench-dependence than we observe.

4.3. Possible bias in $P_{\beta^+/-}$

For both ICB and VIC, Monte Carlo simulations underestimate the instrument response (recall that K-values for ICB are expressed in Bq and K_{VIC} are given as pA·MBq⁻¹).³ Nearly all of the IC response will be due to the β^+ branch. If the 0.9 % uncertainty on the adopted P_{β^+} is considered, then the agreement between the simulations and experiments seems better. The adopted P_{β^+} is based on theoretical calculations, and critically depends on the adopted P_{β^-} (Bé et al., 2011). The adopted P_{β^-} , in turn, relies crucially on the value reported by Christmas et al. (1983), which uses a $4\pi\beta(\text{LS})\text{-}\gamma$ coincidence method. Gating on the 511 keV peak, the coincidence method does not provide a reliable extrapolation (see section 3.2.1 and Bergeron and Fitzgerald, 2018), calling into question the weight of the Christmas value on P_{β^-} . A lower estimate for P_{β^-} , as would be derived from a consideration of the other evaluated data, would result in a higher estimate for P_{β^+} , which would also be more in keeping with the experimental data (Bé et al., 2011). In short, the discrepancy between our calculated and measured IC responses points to a possible bias in the adopted P_{β^+} , which we suspect may be the result of a bias in the adopted P_{β^-} .

Assuming bias in $P_{\beta^+/-}$, we must consider how the between-method agreement discussed in the preceding section (4.2) is affected. Neither the TDCR nor CNET method would be much affected since any decrease in P_{β^-} would be offset by an increase in P_{β^+} and both branches have very high LS efficiency. In fact, TDCR efficiencies calculated in MICELLE2 with an estimate for the increase in P_{β^+} gave slightly worse agreement between TDCR and LTAC, suggesting that the β spectrum shape in the MICELLE2 model may require modification. Since the HPGe determined activity is based on the 1346 keV gamma ray peak, a reevaluation of $P_{\beta^+/-}$ would impact the result insofar as the electron capture branching ratio, P_{ec} , is calculated directly from P_{β^+} (Be et al., 2011). An increase in P_{β^+} would thus result in a decrease in P_{ec} , bringing the HPGe determined activity into improved accord with LTAC.

It is our conclusion that the ⁶⁴Cu nuclear decay data deserve further scrutiny.

³The manufacturer-recommended dial settings for some commercial “dose calibrators” are based on empirical or Monte Carlo calculations using available nuclear data. As described in the Online Supplemental Material, those calculations also systematically underestimate instrument responses.

5. Conclusions

NIST has completed a primary standardization of ^{64}Cu activity. The standard is based on live-timed anticoincidence (LTAC) counting, gating on the 1346 keV gamma-ray peak. Ionization chamber calibration factors allowed an indirect comparison of the LTAC-based standard with standards from other laboratories and accord was demonstrated. Measurements with two model-based liquid scintillation counting techniques, CIEMAT-NIST efficiency tracing (CNET) and triple-to-double coincidence ratio (TDCR) counting, were problematic and provided only limited confirmatory data.

Discrepancies between theoretical and experimental ionization chamber responses may indicate bias in the adopted $\beta^{+/-}$ branching ratios for ^{64}Cu . A new mass spectrometry experiment might be useful.

In May 2016, NIST participated in a SIRT comparison of ^{64}Cu , demonstrating good agreement with other laboratories. Incorporating the Monte Carlo-based correction (which includes the Funck correction) would shift our standard farther from the reference value, but we have suggested that submissions to the comparison that used coincidence counting without the Funck correction—including our own—are systematically biased.

The corrected LTAC-based standard has been transferred to several NIST-maintained secondary standard ionization chambers. In the future, ^{64}Cu calibrations at NIST can be carried out on these chambers with expected uncertainties $< 0.6\%$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Mark Tyra and Jerry LaRosa (NIST) for meticulously preparing the carrier solution and Lynne King (NIST) for assisting with HPGe measurements. We thank Ron Collé (NIST) for insights on LS counters.

References

- Agostinelli S, Allison J, Amako E, et al., 2003 GEANT4 – a simulation toolkit. Nucl. Inst. Meth. Phys. Res. A 506, 250–303.
- Amiot MN, Bé MM, Branger T, Cassette P, Lépy MC, Ménesguen Y, Da Silva I, 2012 Standardization of ^{64}Cu using an improved decay scheme. Nucl. Inst. Meth. A 684, 97–104.
- Avila-Rodriguez MA, Nye JA, Nickles RJ, 2007 Simultaneous production of high specific activity ^{64}Cu and ^{61}Co with 11.4 MeV protons on enriched ^{64}Ni nuclei. Appl. Radiat. Isot 65, 1115–1120. [PubMed: 17669663]
- Bé M-M, Chisté V, Dulieu C, Mougeot X, Chechev MP, Kuzmenko NK, Kondev FG, Luca A, Galán M, Nichols AL, Arinc A, Pearce A, Huang X, Wang B, 2011 Table of Radionuclides, BIPM Monographie 5, Vol. 6 ISBN: 13 978–92-822–2234-8.
- Bé M-M, Cassette P, Lépy MC, Amiot M-N, Kossert K, Nähle OJ, Ott O, Wanke C, Dryak P, Ratel G, Sahagia M, Luca A, Antohe A, Johansson L, Keightley J, Pearce A, 2012 Standardization, decay data measurements and evaluation of ^{64}Cu . Appl. Radiat. Isot 70, 1894–4899. [PubMed: 22406222]
- Bergeron DE, Fitzgerald R 2018 Monte Carlo modelling of live-timed anticoincidence (LTAC) counting for Cu-64. Appl. Radiat. Isot, 134, 280–285. [PubMed: 28974327]

- Bergeron DE, Galea R, Laureano-Pérez L, Zimmerman BE, 2016 Comparison of ^{14}C liquid scintillation counting at NIST and NRC Canada. *Appl. Radiat. Isot* 109, 30–35. [PubMed: 26585641]
- Boellaard R, Oyen WJG, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT, Arends B, Verzijlbergen FJ, Zijlstra J, Paans AM, Comans EFI, Pruim J, 2008 The Netherlands protocol for standardization and quantification of FDG whole body PET studies in multi-centre trials. *Eur. J. Nucl. Med. Mol. Imag* 35, 2320–2333.
- Bouchard J, Cassette P, 2000 MAC3: an electronic module for the processing of pulses delivered by a three photomultiplier liquid scintillation counting system. *Appl. Radiat. Isotop* 52, 669–672.
- Broda R, Cassette P, Kossert K, 2007 Radionuclide metrology using liquid scintillation counting. *Metrologia* 44, S36–S52.
- Cai W, Chen K, Mohamedali KA, Cao Q, Gambhir SS, Rosenblum MG, Chen X, 2006 PET of vascular endothelial growth factor receptor expression. *J. Nucl. Med* 47, 2048–2056. [PubMed: 17138749]
- Cassette P, Vatin R, 1992 Experimental evaluation of TDCR models for the 3 PM liquid scintillation counter. *Nucl. Inst. Meth. A* 312, 95–99.
- Cassette P, Ahn GH, Alzitzoglou T, Aubineau-Lanière I, Bochud F, Garcia Torano E, Grau Carles A, Grau Malonda A, Kossert K, Lee KB, Laedermann JP, Simpson BRS, van Wyngaardt WM, Zimmerman BE, 2006 Comparison of calculated spectra for the interaction of photons in a liquid scintillator. Example of ^{54}Mn 835 keV emission. *Appl. Radiat. Isot* 64, 1471–1480. [PubMed: 16600600]
- Chen X, Hou Y, Tohme M, Park R, Khankaldyyan V, Gonzales-Gomez I, Bading JR, Laug WE, Conti PS, 2004 Pegylated Arg-Gly-Asp peptide: ^{64}Cu labeling and PET imaging of brain tumor $\alpha_v\beta_3$ -integrin expression. *J. Nucl. Med* 45, 1776–1783. [PubMed: 15471848]
- Christmas P, Judge SM, Ryves TB, Smith D, Winkler G, 1983 The decay scheme of ^{64}Cu . *Nucl. Inst. Meth* 215, 397–408.
- Coursey BM, Mann WB, Grau Malonda A, Garcia-Toraño E, Los Arcos JM, Gibson JAB, Reher D, 1986 Standardization of carbon-14 by $4\pi\beta$ liquid scintillation efficiency tracing with hydrogen-3. *Appl. Radiat. Isot* 37, 403–408.
- Fenwick A, 2015 Personal correspondence
- Fitzgerald R, 2010 An automated ionization chamber for secondary radioactivity standards. *Appl. Radiat. Isot* 68, 1507–1509. [PubMed: 20031425]
- Fitzgerald R, Schultz MK, 2008 Liquid-scintillation-based anticoincidence counting of Co- 60 and Pb-210. *Appl. Radiat. Isot* 66, 937–940. [PubMed: 18342524]
- Fitzgerald R, Zimmerman BE, Bergeron DE, Cessna JC, Pibida L Moreira DS, 2014 A new NIST primary standardization of ^{18}F . *Appl. Radiat. Isot* 85, 77–84. [PubMed: 24384397]
- Fitzgerald R, Bailat C, Bobin C, Keightley JD, 2015 Uncertainties in $4\pi\beta\text{-}\gamma$ coincidence counting. *Metrologia* 52, S86–S96.
- Fitzgerald R, 2016 Monte Carlo based approach to the LS-NaI $4\pi\beta\text{-}\gamma$ anticoincidence extrapolation and uncertainty. *Appl. Radiat. Isot* 109, 308–313. [PubMed: 27358944]
- Funck E, Nylandstedt Larsen A, 1983 The influence from low energy x-rays and Auger electrons on $4\pi\beta\gamma$ coincidence measurements of electron-capture-decaying nuclides. *Appl. Radiat. Isot* 34, 565–569.
- Grau Malonda A, Garcia-Toraño E, 1982 Evaluation of counting efficiency in liquid scintillation counting of pure β -ray emitters. *Appl. Radiat. Isot* 33, 249–253.
- Havelka M, Sochorová J, 2014 Standardisation of ^{64}Cu using a software coincidence counting system. *Appl. Radiat. Isot* 87, 203–206. [PubMed: 24332340]
- ICRU Report: Average energy required to produce an ion pair, Report No. 31, International Commission on Radiation Units and Measurements, Washington, D.C.: ICRU Publications, ISBN 0–913394-25–4, 1979, reprinted 1993.
- Kawada Y, 1986 Decay data measurements of ^{64}Cu by $4\pi\beta\text{-}\gamma$ coincidence technique and photon spectrometry. *Appl. Radiat. Isot* 37, 7–12.

- Kossert K, Grau Carles A, 2010 Improved method for the calculation of the counting efficiency of electron-capture nuclides in liquid scintillation samples. *Appl. Radiat. Isot* 68, 1482–1488. [PubMed: 20022256]
- Kossert K, Cassette Ph., Grau Carles A, Jörg G, Gostomski CLV, Nähle O, Wolf Ch., 2014 Extension of the TDCR model to compute counting efficiencies for radionuclides with complex decay schemes. *Appl. Radiat. Isot* 87, 242–248. [PubMed: 24296068]
- Kossert K, Mougeot X, 2015 The importance of the beta spectrum calculation for accurate activity determination of ^{63}Ni by means of liquid scintillation counting. *Appl. Radiat. Isot* 101, 40–43. [PubMed: 25827946]
- Laureano-Pérez L, Collé R, Fitzgerald R, Outola I, Pibida L, 2007 A liquid-scintillation-based primary standardization of ^{210}Pb . *Appl. Radiat. Isot* 65, 1368–1380. [PubMed: 17766125]
- Lockhart CM, MacDonald LR, Alessio AM, McDougald WA, Doot RK, Kinahan PE, 2011 Quantifying and reducing the effect of calibration error on variability of PET/CT standardized uptake value measurements. *J. Nucl. Med* 52, 218–224. [PubMed: 21233174]
- Lucas LL, 1998 Calibration of the Massic Activity of a Solution of ^{99}Tc . *Appl. Radiat. Isot* 49, 1061–1064.
- Michotte C, Fitzgerald R, 2010 Activity measurements of the radionuclide $^{99\text{m}}\text{Tc}$ for the NIST, USA in the ongoing comparison BIPM.RI(II)-K4.Tc-99m. *Metrologia* 47, Tech Suppl. 06027.
- Michotte C, Nonis M, Bobin C, Altizoglou T, Sibbens G, 2013 The SIRT: a new tool developed at the BIPM for comparing activity measurements of short-lived radionuclides world-wide. *Rapport BIPM-2013/02*
- Michotte C, Nonis M, Bergeron D, Cessna J, Fitzgerald R, Pibida L, Zimmerman B, Fenwick A, Ferreira K, Keightley J, Da Silva I, 2017 Activity measurements of the radionuclides ^{18}F and ^{64}Cu for the NIST, USA in the ongoing comparisons BIPM.RI(II)-K4.F-18 and BIPM.RI(II)-K4.Cu-64. *Metrologia* 54, Tech Suppl. 06011.
- NPL, 1984 Certificate of Measurement of Model 671 Ionization Chambers, Reference R509.
- Pibida L, Hsieh E, Fuentes-Figueroa A, Hammond MM, Karam L, 2006 Software studies for germanium detectors data analysis. *Appl. Radiat. Isot* 64, 1313–1318. [PubMed: 16564692]
- Pibida L, Zimmerman B, Bergeron DE, Fitzgerald R, Cessna JT, and King L, 2017 Determination of photon emission probabilities for the main gamma-ray and half-life measurements of ^{64}Cu . *Appl. Radiat. Isot* 129, 6–12.
- Rogers DWO, Kawrakow I, Seuntjens JP, Walters BRB, and Mainegra-Hing E, 2010 NRC User Codes for EGSnrc, NRC Report PIRS–702(RevB), Ottawa.
- Sahagia M, Luca A, Antohe A, Ivan C, 2012 Standardization of ^{64}Cu and ^{68}Ga by the $4\pi(\text{PC})\beta\text{-}\gamma$ coincidence method and calibration of the ionization chamber. *Appl. Radiat. Isot* 70, 2025–2030. [PubMed: 22417699]
- Salvat F, Fernandez-Varea JM, Acosta E, Sempau J, 2001 PENELOPE, A code system for Monte Carlo simulation of electron and photon transport. *Proceedings of a Workshop/Training Course, OECD/NEA 5–7 November 2001 NEA/NSC/DOC(2001)19* ISBN:92–64-18475–9.
- Scheuermann JS, Saffer JR, Karp JS, Levering AM, Siegel BA, 2009 Qualification of PET scanners for use in multicenter cancer clinical trials: The American College of Radiology Imaging Network experience. *J. Nucl. Med* 50, 1187–1193. [PubMed: 19525463]
- Shankar LK, Hoffman JM, Bacharach S, Graham MM, Karp J, Lammertsma AA, Larson S, Mankoff DA, Siegel BA, Van den Abbeele A, Yap J, Sullivan D, 2006 Consensus recommendations for the use of ^{18}F -FDG PET as an indicator of therapeutic response in patients in national cancer institute trials. *J. Nucl. Med* 47, 1059–1066. [PubMed: 16741317]
- Smith SV, 2004 Molecular imaging with copper-64. *J. Inorg. Biochem* 98, 1874–1901. [PubMed: 15522415]
- Wanke C, Kossert K, Nähle OJ, Ott O, 2010 Activity standardization of ^{64}Cu . *Appl. Radiat. Isot* 68, 1297–1302.
- Williams HA, Robinson S, Julyan P, Zweit J, Hastings D, 2005 A comparison of PET imaging characteristics of various copper radioisotopes. *Eur. J. Nucl. Med. Mol. Imag.* 32, 1473–1480.

- Zimmerman BE, Collé R, 1997 Standardization of ^{63}Ni by $4\pi\beta$ liquid scintillation spectrometry with ^3H -standard efficiency tracing. J. Res. Natl. Inst. Stand. Technol 102, 455–477. [PubMed: 27805155]
- Zimmerman BE, Collé R, Cessna JT, 2004 Construction and implementation of the NIST triple-to-double coincidence ratio (TDCR) spectrometer. Appl. Radiat. Isot 60, 433–438. [PubMed: 14987681]
- Zimmerman BE, Bergeron DE, Edgerton JP, 2018 Assessing the absolute quantitative accuracy of Positron Emission Tomography for Cu-64 using traceable calibrated phantoms. Appl. Radiat. Isot 134, 68–73. [PubMed: 28974328]

Figure 1. Impurity fractions, f , for ^{55}Co (circles), ^{57}Co (triangles), and ^{58}Co (diamonds) determined by HPGe for four ^{64}Cu solutions at t'_{ref} , a reference time that is approximately fixed with respect to the ^{64}Cu separation time. Uncertainty bars represent standard combined uncertainties on the fractions. See text for additional details.

Figure 2.

Fit residuals r , normalized by the linear extrapolation intercept, N_0 , as a function of the inefficiency (Y) for linear (open circles) and quadratic (open triangles) extrapolations of the LTAC data acquired with one source in the 2016 experiment. Uncertainty bars represent the standard deviation on 81 measurements.

Figure 3.

Plot of calculated logical sum of doubles efficiency, ϵ_D , as a function of K for Ultima Gold using kB values of $0.0075 \text{ cm} \cdot \text{MeV}^{-1}$ (closed circles) and $0.012 \text{ cm} \cdot \text{MeV}^{-1}$ (open squares), as calculated by the 2011 version of the MICELLE2 code (Kossert and Grau Carles, 2010) with default atomic data and the most recent evaluated nuclear data Bé et al., 2011. The open circles (with uncertainty bars, mostly smaller than the symbols, indicating standard deviations on repeated measurements) are the 2015 experimental data calculated as efficiencies based on the LTAC-determined activity.

Figure 4. Massic activities (C_A) recovered by CNET in the 2016 experiment, normalized by the average ($\bar{C}_A$) and plotted against the amount of added quenching agent. The Ultima Gold (circles) and Ultima Gold AB (triangles) series were measured on the Beckman (closed symbols) and Wallac (open symbols) counters.

Figure 5.

Comparison of the activities determined with different measurement methods. For ease of comparison, results from both the 2015 (circles) and 2016 (triangles) experiments are normalized by the activity determined using the VIC with the volume-corrected calibration coefficient (K_{VIC}) determined by the NPL. The Monte Carlo-corrected LTAC results are shown with open circles and triangles. The gray dashed lines show the standard combined uncertainty on the NPL K_{VIC} . Uncertainty bars represent combined standard uncertainties.

Table 1

Impurities detected by HPGe measurements with half-lives ($T_{1/2}$) from DDEP (Bé et al., 2011). Impurity fractions ($f = A_i / A_{\text{Cu-64}}$; where A_i and $A_{\text{Cu-64}}$ are the impurity and ^{64}Cu activities determined by HPGe) and uncertainties are given at the reference time (t_{ref}). The agreement between the HPGe- and LTAC-determined activities for ^{64}Cu is represented in the $A_{\text{HPGe}}/A_{\text{LTAC}}$ ratio.

	ID	nuclide	$T_{1/2}$ / d	f at t_{ref}	$A_{\text{HPGe}}/A_{\text{LTAC}}$	
2015	A2-R1	Cu-64	0.529183(83)		0.9901	
		Co-55	0.7304(12)	$5.4(7) \cdot 10^{-5}$		
	A2-R1	Cu-64	0.529183(83)		0.9869	
		Co-56	77.234(26)	$2.72(38) \cdot 10^{-6}$		
		Co-57	271.8(1)	$3.47(49) \cdot 10^{-5}$		
		Co-58	70.85(3)	$1.23(17) \cdot 10^{-5}$		
		Cu-67	2.576(5)	$9(1) \cdot 10^{-6}$		
	2016	A2-R1	Cu-64	0.529183(83)		0.9865
			Co-55	0.7304(12)	$3.9(8) \cdot 10^{-6}$	
		A1	Cu-64	0.529183(83)		0.9962
Co-56			77.234(26)	$1.06(26) \cdot 10^{-6}$		
Co-57			271.8(1)	$4.38(11) \cdot 10^{-5}$		
Co-58			70.85(3)	$1.00(25) \cdot 10^{-5}$		
Cu-67			2.576(5)	$6(2) \cdot 10^{-5}$		

Table 2

Uncertainty budget for the activity measured by LTAC in the 2016 experiment.

Uncertainty Component	%
Counting statistics: Typical standard deviation of the mean for repeated activity determinations ($N = 45$ to 102) on a single source on a single measurement run (4 runs with 3 sources; one source measured on two occasions, with recovered activity consistent to 0.03 %)	0.12
Between source: Standard deviation on the activities determined for 3 sources	0.34
Model uncertainty: Estimated by combining the typical difference on the activities recovered with a linear and a quadratic extrapolation (0.32 %) with the standard deviation on the activities recovered from 13 linear extrapolations using domains of $N = 7$ to 12 efficiency points (0.06 %)	0.32
Mass determinations	0.05
Live Time: Estimated based on previous work	0.10
Background: Estimated by propagating the standard deviation of the mean for repeated ($N = 10$) measurements of the matched blank	0.10
Impurities: Uncertainty on impurity corrections for ^{55}Co , including estimated uncertainty on activity (20 %), LS efficiency (10 %), and half-life (0.2 %)	6E-04
Half-life: From DDEP (2010), 12.7004(20) h	0.02
Combined standard uncertainty ($u_c = (\sum u_i^2)^{1/2}$)	0.51