



Standardization of ^{64}Cu activity

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HIGHLIGHTS

- The activity of a ^{64}Cu solution was measured by live-timed anticoincidence (LTAC) counting.
- Liquid scintillation counting with efficiency tracing or triple-to-double coincidence ratio provided confirmatory measurements.
- Between-method discrepancies may indicate a need for revisiting recommended nuclear data.

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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.

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 compared to data acquired on different occasions and/or at different sites (see, e.g.,

Shankar et al., 2006; Boellaard et al., 2008; Scheuermann et al., 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.,

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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 $15.8(4) \mu\text{g g}^{-1}$. 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 Figs. 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.

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 $^{64}\text{Ni}(p,n)$ 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 6517 A 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-ray 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 0.04–0.25 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 0.04–0.25 mL of diluted nitromethane. An additional five cocktails were prepared with 10 mL of UG, 0.7 mL of water, and 0.04–0.25 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 17–70 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 45–100 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

¹ Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

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