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Dose calibrator manufacturer-dependent bias in assays of ^{123}I

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HIGHLIGHTS

- Dose calibrator calibration factors were determined for ^{123}I.
- The NIST standard was indirectly linked to the SIR.
- Manufacturer-dependent biases result in a spread of 11.3 % in measured activity.

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ABSTRACT

Calibration factors for commercial ionization chambers (i.e. dose calibrators) were determined for a solution of ^{123}I; the activity was based on the 1976 NBS standard. A link between the NIST standard and the International Reference System (SIR) was established. The two major U.S. dose calibrator manufacturers recommend oppositely biased calibration factors, giving a spread of 11.3% in measured activities. With modern quantitative imaging techniques capable of $\leq$ 10% accuracy, this bias for a SPECT nuclide is highly significant.

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1. Introduction

With a clinically useful half-life (13.2234 $\pm$ 0.0037 h), a photon energy well-suited for modern gamma cameras and collimators (158.97 keV), and a decay scheme (83.25 photons per decay in the main gamma channel) (Bé et al., 2004) that allows for excellent counting rates with minimal burden to the thyroid, ^{123}I has been referred to as "almost a designer radioiodine for thyroid scanning" (Park, 2002). The same properties make ^{123}I, when complexed to imaging agents such as the norepinephrine analog, metaiodobenzylguanidine (MIBG), an ideal single photon emission computed tomography (SPECT) nuclide, used extensively in qualitative and semi-quantitative cardiac and brain imaging. For promising applications such as measurement of disease progression or response to therapy, differentiation and assessment of Lewy body dementia, and monitoring the efficacy of neuroprotective treatments, absolute quantitation of uptake becomes essential (Soret et al., 2003).

The first measurement in any approach to quantitative molecular imaging is of the activity dosage to be administered to the patient. This measurement is typically performed using a commercial "dose calibrator" which incorporates a reentrant ionization chamber (IC). Dose calibrators provide readings in activity units (Bq or Ci), giving the correct reading for a specific nuclide when the correct calibration factor or "dial setting" is selected by the user. Ideally, the imaging system (PET or SPECT) is calibrated with phantoms prepared from sources measured on the same dose calibrator. As quantitative accuracy in imaging becomes increasingly important, and especially as quantitative results are compared from site-to-site as in multi-center trials, absolute traceability to national standards becomes increasingly desirable (Zimmerman and Judge, 2007). The difficulties specific to SPECT multi-center trials have recently been discussed in Dickson et al. (2012), but this report considers only scanner performance, and does not directly address the additional difficulties that would arise in a comparison of absolute activity measurements. We have recently reported on the methodology behind an international comparison involving absolute image quantification in SPECT (Zimmerman et al., 2013). The comparison, which has not yet been completed, uses phantoms containing traceable quantities of ^{133}Ba (a surrogate for ^{131}I). Past comparisons of activity measurements

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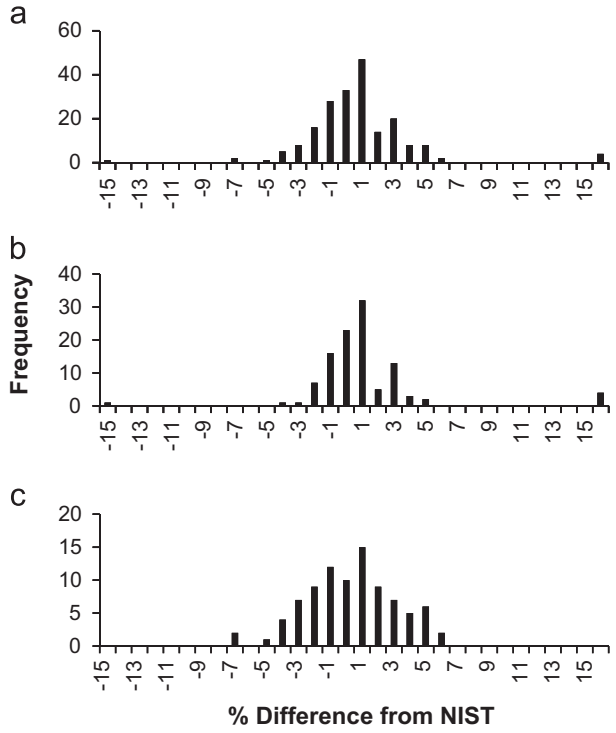

Fig. 1. Histogram of results reported by participants in the NRMAP for measurements of ^{123}I activity. The relative difference between the reported activities and the NIST value is calculated, and the results are binned in increments of 1%. The histogram shows the number of results in each bin. The results are presented as (a) all methods combined, (b) IC measurements only, and (c) non-IC measurements. Since most participants have submitted measurements in the past, their measurement protocols have been optimized for agreement with NIST. See Sections 1 and 4.1 for additional discussion.

(using dose calibrators, not SPECT) have indicated that ^{123}I and other nuclides with relatively low energy photon emissions have presented measurement challenges to clinical nuclear medicine sites (dos Santos et al., 2004; Zimmerman and Judge, 2007).

For the radiopharmaceutical industry in the United States, traceability of activity measurements to national standards is achieved through the NIST Radioactivity Measurement Assurance Program (NRMAP; Cessna and Golas, 2012). In this voluntary program, participants engage in proficiency exercises to demonstrate traceability (for individual measurements) to the National Institute of Standards and Technology (NIST). As an important radiopharmaceutical, ^{123}I has been distributed as part of the program in the past. More recently, it has been a regular "open month" submission; that is, program participants have submitted samples in NIST ampoules and their measurement results to NIST for calibration/comparison. In Fig. 1, results from distributions in 1977 and 1980 are combined with open month submissions from 2000 to 2012. The results are from seven different participants with a total of 197 reported values; 108 of which were IC measurements (chamber type was not always reported, and calibration factors were only very rarely disclosed). Non-IC measurements were mostly gamma ray spectrometry (HPGe, Ge(Li), or NaI(Tl) detectors). The histograms in Fig. 1 show that the IC results and the results from other methods are centered on the NIST value; excluding outliers ($>20\%$ error), the respective means were 0.06% (Fig. 1b) and -0.16% (Fig. 1c). In addition, Fig. 1 shows that the IC results are slightly more concentrated about the NIST value than the other methods; the respective standard deviations were 1.6% and 2.8%.

A recent open month submission to the NRMAP precipitated an evaluation of dose calibrator dial settings, which we report here.

Table 1
The NIST-maintained representative set of commercial reentrant ICs ("dose calibrators").

Model	Manufacturer	SN
CRC-12	Capintec	12561
CRC-15R	Capintec	155544
CRC-25PET	Capintec	270224
CRC-35R	Capintec	350267
CRC-1.8 atm	Capintec	570029
AtomLab-400	Biodex (electrometer)	12090302
	Sun Nuclear (chamber)	76652058
AtomLab-500	Biodex (electrometer)	12090718
	Sun Nuclear (chamber)	76652069
NPL-type	Keithley 2514 (electrometer)	0732149
	Vinten 671 (chamber)	3-2

This is the first time that NIST has determined calibration factors for its commercial ICs. Results are reported with complete uncertainty evaluations, and we examine differences between the calibration factors recommended by the manufacturers and those determined in this study. Finally, we describe an indirect link between the primary standardization performed at NIST in 1976 and the International Reference System (SIR).

2. Experiment

The massic activity of an ^{123}I solution (^{123}I as NaI in 0.1 mol L^{-1} NaOH) was determined by measuring a NIST standard 5 mL ampoule containing nominally 5 g of solution in the NIST "4π"γ ionization chamber (Calhoun, 1987). The calibration factor was initially determined by $4\pi\ \beta-\gamma$ coincidence counting as part of a primary standardization performed in June 1976 (NIST, 1976a and 1976b). The primary standardization included confirmatory gamma ray spectrometry measurements using a Ge(Li) detector; the two techniques agreed to within 0.21%. The nuclear decay data used in the standardization were taken from Martin (1976). In the present study, an additional correction factor ($1.5\pm0.5\%$) was applied to the original calibration factor to account for chamber height effects, as described by Fitzgerald (2012). The combined standard uncertainty on the massic activity of the solution was 0.60% ($k=1$).

Because of the short half-life of ^{123}I, NIST has never submitted an ampoule of this nuclide to the SIR, making direct comparison of the NIST standard to the standards of other National Metrology Institutes (NMIs) impossible. However, we can offer an indirect (via the NPL-type Vinten 671 ionization chamber (Woods, et al., 1983),[1] vide infra) comparison that suggests our standard is consistent with others.

The ampoule, with known standard activity (700–800 MBq at the time of measurement), was measured on each of the NIST-maintained commercial dose calibrators (for dose calibrator details, see Table 1). The "calibration curve" method of dial setting determinations used here has been described previously (Zimmerman and Cessna, 2000). Briefly, measurements were performed at 13 dial settings and the chamber readouts and measurement times were recorded. The readings were decay corrected, normalized to the standard activity, and plotted against the dial settings. Fits (see Table 2 for equations) of the resulting curves were then used to calculate the correct dial setting for each chamber. Calibration factors in terms of current (pA MBq^{-1})

[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.