Certification of Standard Reference Material® 955d
Toxic Elements and Metabolites in Frozen Human Blood

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Abstract

Standard Reference Material (SRM) 955d is intended for use in validating analytical methods for measuring toxic elements and mercury species in human blood, and in value assigning locally produced control materials analyzed using the validated methods. A unit of SRM 955d consists of six vials of frozen human blood with two vials at each of three mass concentration levels. Each vial contains nominally 1.6 mL of whole blood. This publication documents the production, analytical measurements, and statistical evaluations leading to the certification of the SRM.

Key Words

Human blood; Standard Reference Material (SRM); Arsenic (As); Cadmium (Cd); Chromium (Cr); Cobalt (Co); Lead (Pb); Manganese (Mn); Mercury (Hg); Selenium (Se); Uranium (U); Ethylmercury (EtHg); Inorganic Mercury (iHg); Methylmercury (MeHg); Thyroglobulin (Tg); Blood spot testing

Technical Information Contact for these SRMs

Please address technical questions about these SRMs to srms@nist.gov where they will be assigned to the appropriate Technical Contact responsible for support of this material. For sales and customer service inquiries, please contact srminfo@nist.gov.

Table of Contents

List of Tables

Purpose and Description

This Standard Reference Material (SRM) is intended for use in validating analytical methods for measuring toxic elements and mercury species in human blood and in value assigning locally produced control materials analyzed using the validated methods. A unit of SRM 955d consists of six vials of frozen human blood with two vials at each of three mass concentration levels. Each vial contains nominally 1.6 mL of whole blood.

NIST is guided by and adheres to the ethical principles set forth in the Belmont Report [1]. SRM 955d was developed after an appropriate human subjects' research determination.

Warning: SRM 955d is a Human-Sourced Material

SRM 955d is a human-sourced material. *Handle as a biohazardous material capable of transmitting infectious disease.*

SRM 955d was prepared from whole blood units obtained from a commercial blood bank in Tennessee, USA. Each donor unit of blood used in the preparation of this product was tested by FDA-licensed tests and found to be negative for human immunodeficiency virus (HIV), HIV 1 antigen, hepatitis B surface antigen, and hepatitis C. However, no known test method can offer complete assurance that hepatitis B virus, hepatitis C virus, HIV, or other infectious agents are absent from this material. Accordingly, this human blood-based product should be handled at the Biosafety Level 2 [2].

Introduction

The toxicity of lead affects nearly every system in the body, and the most accurate biomarker for lead exposure is the lead level in blood. SRM 955 was developed in the early 1980s to provide accuracy and traceability in clinical measurement and biomonitoring of population exposure to lead poisoning. The subsequent iterations of the SRM saw bovine blood or caprine blood being used as matrices because animal dosing facilitated the introduction of endogenous lead at desired levels while animal blood is potentially less susceptible to carry human pathogens. Human blood was used in the production of SRM 955d because commutability is emerging as the primary concern for standards in clinical measurements. The scope of the intended use of the standard has been expanded to include the assessment of the corrosion of implantable devices and measurement of nutritional biomarkers. Consequently, the name of the SRM has been updated to "Toxic Elements and Metabolites in Frozen Human Blood" to reflect the expanded functionality of the standard. The target levels of analytes in SRM 955d were established based on the principle of preserving to the maximum extent the values in SRM 955c, while adjusting outdated levels to the 50th percentile or 95th percentile distributions of the 2011/2012 National Health and Nutrition Examination Survey [3]. The final production of SRM 955d took place at the Centers for Disease Control and Prevention (CDC) cleanroom facility of the Inorganic and Radiation Analytical Toxicology Branch, Division of Laboratory Sciences, National Center for Environmental Health in Atlanta, GA, from February 8, 2016 through February 10, 2016. The production of SRM 955d was a joint effort between NIST and CDC. Value assignment of the SRM was based on measurements made at NIST, CDC, Mayo Clinic (Rochester, Minnesota), and Division of Environmental

Health Sciences, Laboratory of Inorganic and Nuclear Chemistry, Wadsworth Center, New York State Department of Health (NYSDOH, Albany, NY).

Preparation[1]

Dipotassium ethylenediaminetetraacetic acid (K₂EDTA) stabilized human whole blood, packaged in 500 mL units, was obtained from Tennessee Blood Services Corp (TBS) in Memphis, TN. All units were shipped on dry ice to CDC in Atlanta, GA, and stored at -80 °C until use. Units of blood were screened for Pb, Cd, Cr, Co, Mn, Hg, and Se before they were combined in three pre-cleaned 15 L high-density polyethylene (HDPE) bottles to form the Level 1 to Level 3 pools for SRM 955d. Each pool contained 12.55 L of blood. The mass concentrations of analyte elements and mercury species in the pools were adjusted to the target levels by spiking with appropriate amounts of NIST SRM 3100 series single-element standard solutions and commercial high-purity uranium, ethylmercury (EtHg), and methylmercury (MeHg) solutions. The contents of each pool were homogenized with a magnetic stirrer for 24 h prior to dispensing into individual pre-screened 2 mL polypropylene cryovials. The product was stored at −80 °C prior to shipment to NIST on dry ice. The first, the last, and every tenth vial of the production sequence were selected for use in homogeneity assessment and value-assignment measurement.

Storage and Use

SRM 955d is shipped frozen (on dry ice) and, upon receipt, must be stored frozen at temperatures below −60 °C in the original packaging until use. SRM 955d should be thawed at room temperature. The material should be used within 4 h after being thawed. The blood in each vial of the SRM should be homogenized by gently inverting the sealed vial several times before a test portion is removed. A minimum test portion of 0.1 mL should be used for the values provided in this publication to be valid. Unused or remaining material should be discarded after 4 h. The certification does not apply to contents of previously opened material, because the stability of the analytes has not been investigated under such conditions. SRM 955d is not intended as a calibration standard, particularly not for the calibration of Pb in anodic stripping voltammetry (ASV) measurements, because the mass fractions of Pb in the SRM were adjusted to the target levels using lead ions. For validation of ASV measurement of Pb, sample preparation must free all protein-bound Pb before the measurement for the certified values to be valid.

Analytical Methods

Measurements of toxic elements and mercury species in SRM 955d were made at NIST, CDC, Mayo Clinic, and NYSDOH. The density of the three levels of SRM 955d at 22 °C was measured at NIST using an Anton Paar DMA 5000 M density meter. Thyroglobulin in Level 1 of SRM 955d was measured at ETH Zurich using an enzyme-linked immunosorbent assay (ELISA) [4]. All measurements performed are traceable to the International System of Units (SI) either through Certified Reference Materials (CRMs) that state traceability to the SI or

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[1] Certain commercial equipment, instrumentation, or materials are identified in this document to adequately specify the experimental procedure. Such identification does not imply recommendation or endorsement 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.

through the SRM 3100 series single element standard solutions that are traceable to the SI, except for the measurement of thyroglobulin.

NIST Measurement Methods: Pb, Cd, and Cr were measured by isotope dilution inductively coupled plasma mass spectrometry (ID-ICP-MS). Hg was measured by isotope dilution cold vapor (ID-CV) ICP-MS. EtHg, inorganic mercury (iHg), and MeHg were measured by NIST personnel at the CDC site using triple spike isotope dilution gas chromatography (ID-GC) ICP-MS. As, Co, Mn, Se, and U were measured by ICP-MS.

ID-ICP-MS measurement of Pb, Cd, and Cr: For the determination of Pb and Cd, test portions of approximately 1.6 g were digested with accurately weighed aliquots of enriched ^{206}Pb and ^{111}Cd solutions using nitric acid (HNO_3) in a closed-vessel microwave system. Isotopic measurements were made using a quadrupole ICP-MS. Pb was measured in standard mode, and Cd was measured in collision cell mode with kinetic energy discrimination using 8 % hydrogen in He as a collision gas [5, 6]. For the determination of Cr, test portions of 1 g were mixed with enriched ^{53}Cr isotope in a diluent consisting of 0.1 % ammonium hydroxide (NH_4OH), 0.1 % Triton X-100, 1.5 % methanol (MeOH), and 0.02 mmol/L EDTA with water as the balance. All dilutions were by volume unless stated otherwise. O_2 was used as the reaction gas and the analyte was measured in MS/MS mode as $^{52}Cr^{16}O^+$ and $^{53}Cr^{16}O^+$ using a triple quadrupole ICP-MS. Quantitative determinations of Pb, Cd, and Cr are traceable to the SI through the certified values assigned to the SRM 3100 series single element standard solutions.

ID-CV-ICP-MS measurement of Hg: Test portions of 0.25 g to 0.50 g were digested in HNO_3 with accurately weighed aliquots of enriched ^{201}Hg solution in single use disposable borosilicate glass vessels with caps using a single-mode microwave cavity system. Hg isotopes were measured in time-resolved analysis mode using cold vapor generation coupled with ICP-MS [7]. Quantitative determinations are traceable to the SI through the certified values assigned to the SRM 3100 series single-element standard solutions.

ICP-MS measurement of As, Co, Mn, Se, and U: Test portions of 1 g were digested in a mixture of HNO_3 and H_2O_2 at 90 °C in polypropylene tubes. An appropriate amount of Rh was added as an internal standard, and the analytes were measured in collision cell mode with hydrogen as the collision gas. The method of standard addition was used to quantify the analytes. Quantitative determinations of As, Co, Mn, and Se are traceable to the SI through the certified values assigned to the SRM 3100 series single-element standard solutions. Quantitative determinations of U are traceable to the SI through the certified values assigned to High-Purity Standards (HPS, Charleston, SC) CRM 100 64-1.

ID-GC-ICP-MS measurement of EtHg, iHg, and MeHg: Test portions of 0.1 mL were weighed into clean 2 mL polypropylene micro-centrifuge tubes using a calibrated five-place analytical balance. A 100 μL aliquot of a spike mixture, consisting of Et^{198}Hg, i^{199}Hg, and Me^{201}Hg (in 2 % volume fraction HCl, 3 % volume fraction acetic acid, and 1 % volume fraction MeOH) was added gravimetrically to the sample. The mixture was vortexed to homogenize the sample and spike. The mercury species were solubilized by adding 500 μL of 25 % mass fraction tetramethylammonium hydroxide (TMAH). Following the addition of the TMAH, the samples

were placed into a convection oven at 80 °C for 18 h. After the samples were cooled to the room temperature, they were placed back into the biosafety hood and transferred to clean 20 mL glass solid phase micro-extraction SPME analysis vials, followed by the addition of 7.7 mL of 0.1 mol/L sodium acetate buffer, pH 4.75, bringing the final pH to between 5 and 6. The samples were then derivatized by adding 250 µL of 0.2 % mass concentration sodium tetra(n-propyl) borate (NaBPr$_4$) reagent, to promote volatility of the mercury species for GC separations. A Perkin Elmer Elite-5 capillary column was used to separate the Hg species. The samples were analyzed by GC-ICP-MS in Dynamic Reaction Cell (DRC) mode of a Perkin Elmer DRCII using Ar as a collision gas [8-10]. Quantitative determinations of EtHg, iHg, and MeHg are traceable to the SI through the certified values assigned to CRMs IES-EtHg198, 199Hg010025, and IES-MMHg201 from Innovative Solutions in Chemistry S.L. (ISC, Oviedo, Spain).

CDC Measurement Methods: Pb, As, Cd, Cr, Co, Mn, Hg, Se, and U were measured by ICP-MS. EtHg, iHg, and MeHg were measured by triple spike ID-GC-ICP-MS.

ICP-MS measurement of Pb, Cd, Mn, Hg, and Se for homogeneity and value assignment: The measurement of these elements was made in accordance with Division of Laboratory Sciences (DLS) Method 3016.8 on PerkinElmer ELAN DRC II instruments [11, 12]. A test portion of 50 µL was diluted in a ratio of 1 part sample, 1 part water, and 48 parts diluent prior to analysis. The sample diluent contained 5 µg/L each of Ir, Rh, and Te as internal standards in 0.4 % TMAH, 1 % ethyl alcohol (EtOH), 0.01 % ammonium pyrrolidine dithiocarbamate (APDC), and 0.05 % Triton X-100. Pb and Cd were measured in vented mode. Mn, Hg, and Se were measured in DRC mode. O$_2$ was the reaction gas used for Mn and Hg measurements while methane (CH$_4$) was the reaction gas used for the Se measurement. Matrix-matched and weighted linear external calibration was used to quantify the analytes. Quantitative determinations of Pb, Cd, Mn, Hg, and Se are traceable to the SI through the certified values assigned to HPS CRM SM-2107-042.

ICP-MS measurement of Pb, Cd, Mn, Hg, and Se for stability assessment: The measurement was made in accordance with a method to be published as DLS Method 3040.1-02 on Agilent 8900 triple-quadrupole instruments. A test portion of 50 µL was diluted in a ratio of 1 part sample, 1 part water, and 18 parts diluent prior to analysis. The sample diluent contained 5 µg/L each of Ir, Rh, and Te as internal standards in 1 % TMAH, 1 % EtOH, 0.01 % APDC, and 0.05 % Triton X-100. All analytes were measured in the MS/MS mode using a mixture of H$_2$ and O$_2$ as the cell gas. All analytes were measured on-mass except Se, which was measured as ^{80}Se^{16}O$^+$. Matrix-matched and weighted linear external calibration was used to quantify the analytes. Quantitative determinations of Pb, Cd, Mn, Hg, and Se are traceable to the SI through the certified values assigned to HPS CRM SM-2107-057.

ICP-MS measurement of As and U for homogeneity assessment and value assignment: A test portion of 50 µL was diluted in a ratio of 1 part sample, 1 part water, and 48 parts diluent prior to analysis on PerkinElmer ELAN DRC II instruments. The sample diluent contained 5 µg/L each of Ir, Rh, and Te as internal standards in 0.4 % TMAH, 1 % EtOH, 0.01 % APDC, and 0.05 % Triton X-100. U was measured in vented mode. Arsenic was measured as ^{75}As^{16}O$^+$ in DRC mode using O$_2$ as the reaction gas. Matrix-matched and weighted linear external

calibration was used to quantify the analytes. Quantitative determinations of As are traceable to the SI through the certified values assigned to HPS CRM 10003-1 and Inorganic Ventures (IV, Christiansburg, VA) CRM CGAS1. Quantitative determinations of U are traceable to the SI through the certified values assigned to IV CRM CGU1 and SPEX (Metuchen, NJ) CRM CLU2-1BY.

ICP-MS measurement of As and U for stability assessment: A test portion of 50 µL was diluted in a ratio of 1 part sample, 1 part water, and 18 parts diluent prior to analysis on Agilent 8900 triple-quadrupole instruments. The sample diluent contained 5 µg/L each of Ir, Rh, and Te as internal standards in 1 % TMAH, 1 % EtOH, 0.01 % APDC, and 0.05 % Triton X-100. U was measured in vented mode. Arsenic was measured as $^{75}As^{16}O^+$ in MS/MS mode using O_2 as the reaction gas. Matrix-matched and weighted linear external calibration was used to quantify the analytes. Quantitative determinations of As are traceable to the SI through the certified values assigned to HPS CRM 10003-1. Quantitative determinations of U are traceable to the SI through the certified values assigned to IV CRM CGU1.

ICP-MS measurement of Cr and Co: A test portion of 250 µL was diluted in a ratio of 1 part sample, 1 part water, and 18 parts diluent prior to analysis. The diluted sample contained 20 µg/L each of Ga and Sc as internal standards in 0.4 % TMAH, 1 % EtOH, 0.01 % APDC, and 0.05 % Triton X-100. Cr and Co were measured in Kinetic Energy Discrimination (KED) mode of a Thermo iCAP Q-a using He as a collision gas. Matrix-matched and weighted linear external calibration was used to quantify the analytes. Quantitative determinations of Cr are traceable to the SI through the certified values assigned to HPS CRM 100012-6, SPEX CRM CLCR2-2Y, and IV CRM CGCR(3)1. Quantitative determinations of Co are traceable to the SI through the certified values assigned to HPS CRM 100013-1, SPEX CRM PLCO2-2Y, and IV CRM CGCO1.

ID-GC-ICP-MS measurement of EtHg, iHg, and MeHg: A test portion of 100 µL was spiked with enriched $^{199}HgCl_2$, $CH_3^{200}HgCl$ and $C_2H_5^{201}HgCl$ isotopic standards. The mixture was vortexed prior to being solubilized with 500 µL TMAH. After TMAH had been added, the samples were placed into an 80 °C convection oven for 24 h. A 200 µL test portion of the solubilized sample was transferred to a 20 mL glass solid phase microextraction (SPME) analysis vial and 7.7 mL of 0.1 mol/L sodium acetate (NaOAc) buffer (pH 4.75) was added to bring the final pH to between 5 and 6. A 250 µL aliquot of $NaBPr_4$ derivative agent at 0.2 % mass concentration was added to promote volatility of the mercury species. A Perkin Elmer Elite-5 capillary column was used to separate the Hg species. The samples were analyzed by GC-ICP-MS in DRC mode using Ar as a collision gas [8-10]. Quantitative determinations of EtHg, iHg, and MeHg are traceable to the SI through the certified values assigned to ISC CRMs IES-EtHg198, IES-Hg199, and IES-MMHg201.

Mayo Clinic Measurement Methods: Pb, As, Cd, Cr, Co, Mn, and Hg were measured by ICP-MS.

ICP-MS measurement of Pb, As, Cd, and Hg: A test portion of 100 µL was diluted to 2.5 mL with a solution containing Ga, Ir, Lu, and Rh as internal standards in dilute HCl diluent. Pb, As, Cd, and Hg were measured in KED mode using He as the collision gas. Matrix-matched

external calibration was used to quantify the analytes. Quantitative determinations of Pb, As, Cd, and Hg are traceable to the SI through the certified values assigned to IV custom standards.

ICP-MS measurement of Cr and Co: A test portion of 100 µL was diluted to 2.5 mL with a solution containing enriched Ga and ^{6}Li as internal standards in dilute EDTA diluent. Cr was measured in DRC mode using NH_3 as the reaction gas. Co was measured in KED mode using He as the collision gas. Matrix-matched external calibration was used to quantify the analytes. Quantitative determinations of Cr and Co are traceable to the SI through the certified values assigned to IV custom standards.

ICP-MS measurement of Mn: A test portion of 100 µL was diluted to 2.5 mL with a solution containing Ga and ^{6}Li as internal standards in dilute EDTA diluent. Mn was measured in DRC mode using NH_3 as the reaction gas. Quantitative determinations of Mn are traceable to the SI through the certified values assigned to IV CRM CGMN1.

NYSDOH Measurement Methods: Pb, As, Cd, Cr, Co, Mn, Hg, Se, and U were measured by ICP-MS. The measurements were made in accordance with NYSDOH Method DOH-LINC-431. A test portion of 200 µL was diluted in a ratio of 1 part sample, 1 part 1 % HNO_3, and 48 parts of a diluent consisting 2 µg/L each Ga, Ir, Rh, and Y as internal standards in 0.5 % HNO_3, 1 mg/L Au, and 0.005 % Triton-X 100. Pb, Cd, Co, Hg, and U were measured in standard mode. Mn was measured in standard mode at high resolution. As, Cr, and Se were measured in KED mode using 7 % H_2 in He as a reaction gas. Matrix-matched external calibration was used to quantify the analytes. Quantitative determinations of Pb, Cd, and Hg are traceable to the SI through the certified values assigned to HPS CRM SM-2017-007. Quantitative determinations of As, Cr, Co, Mn, Se, and U are traceable to the SI through the certified values assigned to HPS CRM SM2326-003.

Results and Discussion

Homogeneity: At each level, there were two production lines for SRM 955d. The first, the last, and ten randomly selected vials from the set of vials collected from every tenth vial of the production sequence of each production line were used for homogeneity assessment. Thus, a total of 24 vials were measured in duplicate. This is a two-way nested ANOVA design with two factors, A = lines and B = vials. Vials are nested within lines. The ANOVA model equation is described in detail in [13]. Briefly,

$$y_{ijk} = \mu + \tau_i + \beta_{j(i)k} + E_{j(i)k}, \; i = 1, \ldots, a, \; j = 1, \ldots, b, \; k = 1, \ldots, n \qquad (1)$$

$a = 2 =$ number of lines

$b = 12 =$ number of vials/line

$n = 2 =$ number of replicates

The constant μ denotes the common mean analyte concentration. The subscript $j(i)$ indicates that the jth level of factor B is nested within the ith level of A. τ_i represents

the effect of A at the ith level; $\beta_{j(i)k}$ is the effect at the jth level of factor B within the ith level of A at the kth replicate; and $E_{j(i)k}$ is error. We made the following assumptions: A is fixed and B is random, $\sum_{i=1}^{a} \tau_i = 0$, $\beta_{j(i)k} \sim N(0, \sigma_\beta)$, and $E_{j(i)k} \sim N(0, \sigma_E)$.

Tests:

H_0: All $\tau_i = 0$ versus Not all $\tau_i = 0$ (Lines are the same)

H_0: All $\sigma_\beta = 0$ versus $\sigma_\beta \neq 0$ (Vials are the same (homogeneity test))

The test results are given in Table 1. According to these data one cannot reject the hypothesis that there is no vial to vial effect, although there seems to be a line effect in some instances.

Table 1. Analysis of Variance for Homogeneity of Analytes in SRM 955d

Analytes	P-value Lines	P-value Vials
CdLev1	9.6E-01	8.0E-01
CdLev2	2.9E-05	3.6E-01
CdLev3	6.1E-02	1.6E-01
MnLev1	8.6E-07	7.1E-01
MnLev2	1.6E-05	5.6E-01
MnLev3	7.7E-04	6.2E-01
PbLev1	1.5E-08	6.9E-01
PbLev2	2.0E-07	4.0E-01
PbLev3	9.9E-01	3.5E-01
SeLev1	8.3E-02	7.8E-01
SeLev2	7.0E-04	1.2E-01
SeLev3	1.1E-02	2.0E-01
HgLev1	1.0E-09	6.1E-01
HgLev2	4.1E-01	4.6E-01
HgLev3	9.3E-01	2.1E-01
AsLev1	2.0E-01	7.3E-01
AsLev2	7.9E-01	1.5E-01
AsLev3	1.4E-01	8.7E-01
ULev1	2.5E-01	3.8E-01
ULev2	5.8E-01	8.5E-03
ULev3	4.6E-03	5.5E-01
CoLev1	9.1E-01	4.7E-01
CoLev2	9.0E-01	2.5E-01
CoLev3	3.0E-02	9.3E-01
CrLev1	4.4E-01	2.8E-01
CrLev2	5.3E-01	6.2E-01
CrLev3	6.8E-01	7.1E-01
MeHgLev1	2.5E-02	1.1E-01
MeHgLev2	8.2E-01	2.3E-01
EtHgLev1	2.6E-01	4.4E-01
EtHgLev2	4.2E-01	2.7E-01
iHgLev1	6.2E-01	9.3E-01
iHgLev2	9.1E-01	2.2E-01

Certified Values: A NIST certified value is a value for which NIST has the highest confidence in its accuracy in that all known or suspected sources of bias have been fully investigated or accounted for [14]. Collaborating laboratories were instructed to analyze one vial per level per day with a new calibration performed each new day. A minimum of eight and a maximum of ten vials were analyzed by each participating laboratory. The results of the participants were combined using the NIST Consensus Builder (DerSimonian Laird procedure) [15-17]. Only the NIST lab analyses contained Type B components of standard uncertainty [18-19]. The NIST combined standard uncertainty (obtained from Type A and Type B standard uncertainties) was used in the NIST Consensus Builder along with the other labs' standard uncertainties of their means [17].

Datasets obtained from participating laboratories were analyzed, and the results of the statistical analyses are summarized in Table 2 to Table 34. The 95 % Student's t-distribution confidence intervals are used about the mean value $\bar{X}$ for each analyte with a standard deviation of the mean value (StdMean, $\sigma_{\bar{X}}$) that includes Type B standard uncertainty when available, and with associated effective degrees of freedom (ν_{eff}) specified in the tables. The combined standard uncertainty for the consensus value is obtained from the NIST Consensus Builder [17]. Briefly, the summary measurements ($\bar{X}_j$, $\sigma_{\bar{X}_j}$, ν_j), j =1,2,3,4, of the participating laboratories, CDC, Mayo, NYSDOH and NIST, are assumed to be connected by a common measurand, μ, ~~in~~ by the following relation.

$$\bar{X}_j = \mu + B_j + \varepsilon_j \tag{2}$$

($\nu_j = \nu_{\text{eff}}$) listed in the tables below. The term B_j is a normal random variable with mean 0 and standard deviation τ and is a measure of between lab variation. The term ε_j represents random error which is assumed to be normally distributed with mean 0 and standard deviation σ_ε. The B_j's and ε_j's are all independent. The Consensus Builder is an algorithm that takes the summary measurements and produces an estimate of μ and an uncertainty value for this estimate. The estimate the Consensus Builder produces is a nonuniform weighted average. There are three options for this calculation: a DerSimonian–Laird procedure, a hierarchical Bayesian procedure and a Linear Pool procedure. The DerSimonian–Laird procedure was chosen. In the DerSimonian–Laird procedure, τ is estimated as follows

$$\tau^2 = \max\left\{0, \frac{\sum_{j=1}^{p} \sigma_{\bar{X}_j}^{-2}(\bar{X}_j - \tilde{X})^2 - p + 1}{\sum_{j=1}^{p} \sigma_{\bar{X}_j}^{-2} - \sum_{j=1}^{p} \sigma_{\bar{X}_j}^{-4}\left(\sum_{k=1}^{p} \sigma_k^{-2}\right)^{-1}}\right\}, \qquad \tilde{X} = \frac{\sum_{j=1}^{p} \bar{X}_j \sigma_{\bar{X}_j}^{-2}}{\sum_{j=1}^{p} \sigma_{\bar{X}_j}^{-2}} \tag{3}$$

where p represents the number of labs measuring the element. Note that $\tilde{X}$ is the classical variance weighted mean estimate of μ. The DerSimonian–Laird consensus estimate is

$$\hat{\mu} = \frac{\sum_{j=1}^{p} \frac{\bar{X}_j}{\tau + \sigma_{\bar{X}_j}^2}}{\sum_{j=1}^{p} \frac{1}{\tau + \sigma_{\bar{X}_j}^2}} \tag{4}$$

The uncertainty of $\hat{\mu}$ is obtained by Monte Carlo, i.e., the summary values ($\bar{X}_j$, $\sigma_{\bar{X}_j}$, ν_j), j =1,2,3,4 are regenerated using equation (2) and the assumed normal distributions. An

estimate $\hat{\mu}$ from (4) is recreated at each Monte Carlo run. The uncertainty is the sample standard deviation of the Monte Carlo sample of $\hat{\mu}$'s.

Tables 2 to 13 list the results for Pb, As, Cd, Cr, Co, Mn, Hg, Se, U, EtHg, iHg, and MeHg in SRM 955d Level 1. Tables 14 to 25 list the results for Pb, As, Cd, Cr, Co, Mn, Hg, Se, U, EtHg, iHg, and MeHg in SRM 955d Level 2. Tables 26 to 34 list the results for Pb, As, Cd, Cr, Co, Mn, Hg, Se, and U in SRM 955d Level 3. Tables 35 to 37 list the certified values, expanded uncertainties (U), coverage factors (k), and effective degrees of freedom (ν_{eff}) for analytes in Level 1 to Level 3 of SRM 955d. Certified values were calculated by multiplying the consensus standard uncertainty ($\sigma\bar{x}$) by the coverage factor corresponding to the 95 % Student's t-distribution confidence intervals determined by the degrees of freedom of $\sigma\bar{x}$.

Table 2. Statistical Analysis of Lead Measurements (Pb, µg/dL) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	1.474	1.493	1.483	1.493	1.520	1.507	1.498	1.461
2	1.497	1.552	1.524	1.539	1.515	1.527	1.482	1.456
3	1.503	1.493	1.498	1.585	1.516	1.551	1.473	1.462
4	1.508	1.495	1.502	1.491	1.509	1.500	1.436	1.460
5	1.557	1.451	1.504	1.470	1.472	1.471	1.493	1.459
6	1.505	1.512	1.509	1.484	1.457	1.471	1.420	1.457
7	1.656	1.602	1.629	1.482	1.475	1.479	1.430	1.460
8	1.495	1.506	1.501	1.441	1.463	1.452	1.460	1.456
9							1.423	1.455
10								1.460
Mean			1.519			1.495	1.457	1.459
StdMean			0.016			0.012	0.010	0.00073

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	Pb	1.519	0.016	7
2	Pb	1.495	0.012	7
3	Pb	1.457	0.010	8
4	Pb	1.459	0.0083	> 60
Consensus	**Pb**	**1.480**	**0.013**	**> 60**

Table 3. Statistical Analysis of Arsenic Measurements (As, µg/L) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	6.616	6.288	6.452	5.396	5.771	5.584	4.648	5.890
2	6.438	6.151	6.295	4.653	4.844	4.749	4.660	5.210
3	6.619	5.770	6.195	5.979	5.596	5.788	4.551	5.680
4	5.915	5.887	5.901	5.227	5.222	5.225	4.487	5.910
5	5.377	5.421	5.399	5.688	5.662	5.675	4.168	5.590
6	5.379	5.701	5.540	5.411	5.446	5.429	4.296	6.090
7	5.234	5.304	5.269	4.765	5.040	4.903	3.969	6.090
8	5.021	5.420	5.221	4.868	5.414	5.141	4.094	6.080
Mean			5.784			5.311	4.359	5.818
StdMean			0.17			0.13	0.094	0.11

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	ν_{eff}
1	As	5.78	0.17	7
2	As	5.31	0.13	7
3	As	4.36	0.094	7
4	As	5.82	0.11	7
Consensus	**As**	**5.31**	**0.39**	**> 60**

Table 4. Statistical Analysis of Cadmium Measurements (Cd, µg/L) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	0.2908	0.2779	0.2844	0.3942	0.4593	0.4268	0.3472	0.3322
2	0.3383	0.3500	0.3442	0.3998	0.4280	0.4139	0.3206	0.3259
3	0.3008	0.3085	0.3047	0.3887	0.3142	0.3515	0.3070	0.3285
4	0.2662	0.2025	0.2344	0.2882	0.3322	0.3102	0.3240	0.3348
5	0.3402	0.3326	0.3364	0.3461	0.3016	0.3239	0.3386	0.3244
6	0.3073	0.2836	0.2955	0.3238	0.3309	0.3274	0.3132	0.3232
7	0.3793	0.3437	0.3615	0.2753	0.3348	0.3051	0.3010	0.3256
8	0.3716	0.3682	0.3699	0.3418	0.3915	0.3667	0.3356	0.3263
9							0.3120	0.3269
10								0.3303
Mean			0.3163			0.3532	0.3221	0.3278
StdMean			0.0160			0.0164	0.0052	0.0012

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	Cd	0.3163	0.0160	7
2	Cd	0.3532	0.0164	7
3	Cd	0.3221	0.0052	8
4	Cd	0.3278	0.0088	> 60
Consensus	**Cd**	**0.3260**	**0.0052**	**> 60**

13

Table 5. Statistical Analysis of Chromium Measurements (Cr, µg/L) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	0.333	0.489	0.411	0.948	0.872	0.910	0.848	0.810
2	0.699	0.844	0.771	0.867	0.891	0.879	0.999	0.680
3	0.640	0.575	0.608	0.804	1.365	1.084	0.995	0.836
4	0.956	0.878	0.917	0.857	0.870	0.863	0.993	0.757
5	0.885	0.881	0.883	0.935	1.093	1.014	0.860	0.921
6	1.036	0.973	1.005	1.017	0.908	0.962	0.871	0.842
7	0.924	0.888	0.906	0.815	0.851	0.833	0.977	0.922
8	1.001	1.034	1.017	0.915	0.948	0.932	0.963	0.729
9								0.794
Mean			0.815			0.935	0.938	0.810
StdMean			0.074			0.029	0.023	0.027

Set	Analyte	$\overline{X}$	$\overline{\sigma x}$	ν_{eff}
1	Cr	0.815	0.074	7
2	Cr	0.935	0.029	7
3	Cr	0.938	0.023	7
4	Cr	0.810	0.034	11
Consensus	**Cr**	**0.886**	**0.035**	**> 60**

Table 6. Statistical Analysis of Cobalt Measurements (Co, µg/L) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	0.3336	0.3230	0.3283	0.3635	0.3362	0.3499	0.3536	0.5410
2	0.3281	0.3184	0.3233	0.3506	0.3735	0.3621	0.3788	0.4520
3	0.3242	0.3170	0.3206	0.3215	0.5758	0.4487	0.3994	0.4340
4	0.3022	0.2914	0.2968	0.3505	0.6020	0.4763	0.3910	0.4060
5	0.3196	0.2788	0.2992	0.3339	0.3119	0.3229	0.3472	0.4230
6	0.3452	0.3189	0.3320	0.4629	0.3483	0.4056	0.3478	0.4780
7	0.3200	0.3108	0.3154	0.3719	0.4999	0.4359	0.3634	0.4710
8	0.3679	0.3410	0.3544	0.3562	0.3369	0.3466	0.3830	0.4340
Mean			0.3213			0.3935	0.3705	0.4549
StdMean			0.0065			0.0198	0.0072	0.0149

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	ν_{eff}
1	Co	0.321	0.0065	7
2	Co	0.393	0.020	7
3	Co	0.371	0.0072	7
4	Co	0.455	0.015	7
Consensus	**Co**	**0.384**	**0.026**	**> 60**

Table 7. Statistical Analysis of Manganese Measurements (Mn, μg/L) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	47.00	46.70	46.85	48.47	49.69	49.08	47.94	50.09
2	50.35	51.44	50.89	49.59	49.00	49.30	47.74	49.83
3	50.92	49.99	50.46	46.67	47.75	47.21	47.63	49.39
4	48.59	48.53	48.56	48.08	47.68	47.88	46.68	49.38
5	52.90	49.24	51.07	47.26	48.96	48.11	48.74	49.14
6	51.15	50.46	50.80	48.12	47.04	47.58	46.57	49.60
7	53.12	51.38	52.25	46.99	47.48	47.24	47.81	50.07
8	49.90	50.69	50.30	48.12	46.71	47.42	47.45	49.78
Mean			50.15			47.98	47.57	49.66
StdMean			0.59			0.29	0.25	0.12

Set	Analyte	$\bar{X}$	$\bar{\sigma_x}$	ν_{eff}
1	Mn	50.15	0.59	7
2	Mn	47.98	0.29	7
3	Mn	47.57	0.25	7
4	Mn	49.66	0.13	10
Consensus	**Mn**	**48.79**	**0.64**	**> 60**

Table 8. Statistical Analysis of Mercury Measurements (Hg, µg/L) in Level 1

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	1.364	1.404	1.384	1.321	1.298	1.310	1.269	1.352
2	1.461	1.361	1.411	1.576	1.558	1.567	1.337	1.352
3	1.486	1.553	1.520	1.477	1.370	1.424	1.320	1.359
4	1.468	1.438	1.453	1.363	1.352	1.358	1.295	1.362
5	1.568	1.470	1.519	1.163	1.450	1.307	1.306	1.360
6	1.508	1.454	1.481	1.264	1.239	1.252	1.306	1.342
7	1.532	1.451	1.491	1.189	1.286	1.238	1.287	1.346
8	1.579	1.546	1.562	1.529	1.468	1.499	1.252	1.347
Mean			1.478			1.369	1.297	1.353
StdMean			0.021			0.042	0.0096	0.0026

Set	Analyte	$\bar{X}$	$\bar{\sigma_x}$	ν_{eff}
1	Hg	1.478	0.021	7
2	Hg	1.369	0.042	7
3	Hg	1.297	0.010	7
4	Hg	1.353	0.016	> 60
Consensus	**Hg**	**1.373**	**0.041**	**> 60**

Table 9. Statistical Analysis of Selenium Measurements (Se, µg/L) in Level 1

Data		Set1		Set2	Set3
Vials		Replicates	Combined	Replicates	Replicates
1	212.2	212.7	212.5	194.3	208.9
2	213.6	217.3	215.4	195.6	213.4
3	216.1	216.0	216.1	192.4	211.2
4	210.2	213.0	211.6	201.8	207.2
5	209.4	210.6	210.0	202.7	213.8
6	213.4	212.1	212.7	199.0	202.8
7	216.1	213.8	215.0	186.9	211.0
8	217.2	221.8	219.5	191.0	209.7
Mean			214.1	195.5	209.8
StdMean			1.1	1.9	1.3

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	v_{eff}
1	Se	214.1	1.1	7
2	Se	195.5	1.9	7
3	Se	209.8	1.4	10
Consensus	**Se**	**206.6**	**4.9**	**> 60**

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Table 10. Statistical Analysis of Uranium Measurements (U, µg/L) in Level 1

Data	Set1		Combined	Set2	Set3
Vials	Replicates		Combined	Replicates	Replicates
1	0.01010	0.01300	0.01155	0.00800	0.01220
2	0.01510	0.01700	0.01605	0.01140	0.01080
3	0.01700	0.01490	0.01595	0.01160	0.01270
4	0.01270	0.01220	0.01245	0.01060	0.01480
5	0.00785	0.01080	0.00933	0.00940	0.00950
6	0.01240	0.00968	0.01104	0.01060	0.01080
7	0.00782	0.00437	0.00610	0.01140	0.01320
8	0.00980	0.00910	0.00945	0.00980	0.01440
Mean			0.01149	0.01035	0.01230
StdMean			0.00119	0.00044	0.00065

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	v_{eff}
1	U	0.01149	0.00119	7
2	U	0.01035	0.00044	7
3	U	0.01230	0.00101	9
Consensus	**U**	**0.01108**	**0.00064**	**> 60**

Table 11. Statistical Analysis of Ethylmercury Measurements (EtHg, µg/L) in Level 1

Data	Set1		Combined	Set2
Vials	Replicates		Combined	Replicates
1	0.302	0.328	0.315	0.3325
2	0.397	0.440	0.418	0.3524
3	0.470	0.449	0.460	0.3147
4	0.326	0.359	0.343	0.3280
5	0.313	0.295	0.304	0.3190
6	0.319	0.333	0.326	0.3099
7	0.360	0.335	0.347	0.3394
8	0.402	0.378	0.390	0.3238
Mean			0.363	0.3275
StdMean			0.019	0.0049

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	v_{eff}
1	EtHg	0.363	0.019	7
2	EtHg	0.327	0.012	> 60
Consensus	**EtHg**	**0.342**	**0.017**	**> 60**

Table 12. Statistical Analysis of Inorganic Mercury Measurements (iHg, µg/L) in Level 1

Data	Set1			Set2
Vials	Replicates		Combined	Replicates
1	0.309	0.352	0.330	0.3995
2	0.352	0.353	0.353	0.4004
3	0.369	0.330	0.349	0.4202
4	0.438	0.441	0.440	0.4048
5	0.418	0.432	0.425	0.4105
6	0.442	0.475	0.459	0.4053
7	0.454	0.515	0.485	0.3919
8	0.425	0.428	0.426	0.3964
Mean			0.408	0.4036
StdMean			0.020	0.0031

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	iHg	0.408	0.020	7
2	iHg	0.404	0.015	> 60
Consensus	**iHg**	**0.405**	**0.012**	**> 60**

Table 13. Statistical Analysis of Methylmercury Measurements (MeHg, µg/L) in Level 1

Data	Set1			Set2
Vials	Replicates		Combined	Replicates
1	0.644	0.571	0.608	0.6147
2	0.639	0.767	0.703	0.6247
3	0.614	0.617	0.616	0.5941
4	0.628	0.626	0.627	0.5825
5	0.585	0.625	0.605	0.6081
6	0.629	0.679	0.654	0.5859
7	0.596	0.630	0.613	0.6206
8	0.599	0.640	0.619	0.6256
Mean			0.631	0.6070
StdMean			0.012	0.0061

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	MeHg	0.631	0.012	7
2	MeHg	0.607	0.023	> 60
Consensus	**MeHg**	**0.626**	**0.010**	**> 60**

Table 14. Statistical Analysis of Lead Measurements (Pb, μg/dL) in Level 2

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	4.912	4.870	4.891	5.099	5.044	5.071	4.962	4.8890
2	4.990	4.957	4.973	5.037	5.021	5.029	4.880	4.8700
3	5.224	5.099	5.162	5.006	4.958	4.982	4.940	4.8910
4	5.124	5.203	5.163	5.054	5.031	5.042	4.953	4.8850
5	4.927	5.123	5.025	4.846	4.952	4.899	4.884	4.8860
6	5.025	5.069	5.047	4.837	4.860	4.849	4.853	4.8800
7	5.255	5.159	5.207	4.990	4.921	4.955	4.701	4.8910
8	5.038	5.361	5.199	4.925	4.957	4.941	4.821	4.9100
9							4.733	
Mean			5.083			4.971	4.858	4.8878
StdMean			0.0160			0.0164	0.0052	0.0012

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	Pb	5.083	0.041	7
2	Pb	4.971	0.027	7
3	Pb	4.858	0.031	8
4	Pb	4.888	0.027	> 60
Consensus	**Pb**	**4.947**	**0.043**	**> 60**

Table 15. Statistical Analysis of Arsenic Measurements (As, µg/L) in Level 2

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	297.5	286.8	292.1	277.0	277.1	277.1	276.2	276.80
2	282.8	291.8	287.3	274.8	277.7	276.3	276.3	278.10
3	276.1	276.8	276.4	281.5	273.8	277.7	257.3	276.30
4	271.9	271.4	271.7	276.4	278.4	277.4	277.7	275.10
5	281.9	278.8	280.4	285.4	287.3	286.4	253.6	281.20
6	288.9	293.2	291.0	284.7	280.2	282.5	251.7	276.50
7	298.5	293.8	296.2	282.7	278.6	280.7	253.3	278.40
8	294.0	288.9	291.5	281.2	284.8	283.0	254.5	275.10
Mean			285.8			280.1	262.6	277.19
StdMean			3.1			1.3	4.2	0.71

Set	Analyte	$\bar{X}$	$\overline{\sigma_x}$	ν_{eff}
1	As	285.8	3.1	7
2	As	280.1	1.3	7
3	As	262.6	4.2	7
4	As	277.2	0.75	8
Consensus	**As**	277.5	2.4	**> 60**

Table 16. Statistical Analysis of Cadmium Measurements (Cd, µg/L) in Level 2

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	5.460	5.372	5.416	5.430	5.410	5.420	5.382	5.397
2	5.341	5.268	5.305	5.490	5.440	5.465	5.408	5.331
3	5.424	5.429	5.426	5.440	5.280	5.360	5.097	5.339
4	5.456	5.420	5.438	5.380	5.250	5.315	5.249	5.403
5	5.319	5.415	5.367	5.190	5.170	5.180	5.329	5.310
6	5.464	5.530	5.497	5.450	5.230	5.340	5.339	5.356
7	5.482	5.408	5.445	4.930	4.920	4.925	5.232	5.331
8	5.315	5.597	5.456	5.140	5.100	5.120	5.312	5.294
9							5.416	
Mean			5.419			5.266	5.307	5.345
StdMean			0.021			0.063	0.034	0.014

Set	Analyte	$\overline{X}$	$\overline{\sigma x}$	ν_{eff}
1	Cd	5.419	0.021	7
2	Cd	5.266	0.063	7
3	Cd	5.307	0.034	8
4	Cd	5.345	0.082	> 60
Consensus	**Cd**	**5.343**	**0.042**	**> 60**

Table 17. Statistical Analysis of Chromium Measurements (Cr, μg/L) in Level 2

Data	Set1			Set2			Set3	Set4
Vials		Replicates	Combined		Replicates	Combined	Replicates	Replicates
1	1.778	1.643	1.711	2.073	2.004	2.039	1.960	2.050
2	2.205	2.363	2.284	1.996	2.011	2.004	2.078	1.927
3	1.783	1.749	1.766	1.910	1.933	1.922	1.936	2.060
4	2.251	2.253	2.252	2.005	2.064	2.035	2.207	1.889
5	2.589	2.338	2.464	2.095	2.132	2.114	1.960	2.033
6	2.253	2.457	2.355	2.004	2.027	2.016	1.946	1.978
7	2.239	2.296	2.267	1.935	1.816	1.876	2.056	2.060
8	2.258	2.355	2.307	1.983	2.026	2.005	2.077	1.954
Mean			2.176			2.001	2.027	1.994
StdMean			0.098			0.026	0.033	0.023

Set	Analyte	$\overline{X}$	$\overline{\sigma_X}$	ν_{eff}
1	Cr	2.176	0.098	7
2	Cr	2.001	0.026	7
3	Cr	2.027	0.033	7
4	Cr	1.994	0.032	10
Consensus	**Cr**	**2.012**	**0.019**	**> 60**

Table 18. Statistical Analysis of Cobalt Measurements (Co, µg/L) in Level 2

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	1.650	1.662	1.656	1.590	1.548	1.569	1.642	1.642
2	1.685	1.715	1.700	1.589	1.588	1.589	1.592	1.699
3	1.626	1.635	1.631	1.495	1.574	1.535	1.588	1.699
4	1.545	1.500	1.523	1.428	1.523	1.476	1.595	1.715
5	1.611	1.595	1.603	1.466	1.612	1.539	1.589	1.619
6	1.610	1.633	1.622	1.494	1.512	1.503	1.578	1.684
7	1.576	1.562	1.569	1.515	1.462	1.489	1.591	1.670
8	1.700	1.728	1.714	1.611	1.500	1.556	1.618	1.775
Mean			1.627			1.532	1.599	1.688
StdMean			0.0065			0.0198	0.0072	0.0149

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	ν_{eff}
1	Co	1.627	0.023	7
2	Co	1.532	0.014	7
3	Co	1.599	0.0073	7
4	Co	1.688	0.019	9
Consensus	**Co**	**1.610**	**0.028**	**> 60**

Table 19. Statistical Analysis of Manganese Measurements (Mn, µg/L) in Level 2

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	48.23	47.88	48.05	51.41	50.09	50.75	49.82	51.94
2	51.40	50.99	51.20	52.28	51.71	51.99	50.50	52.60
3	54.87	53.87	54.37	49.65	49.53	49.59	49.28	52.78
4	50.95	52.15	51.55	50.98	49.16	50.07	50.08	52.04
5	52.33	54.48	53.40	49.53	50.98	50.25	51.33	51.74
6	52.82	53.09	52.96	50.71	50.13	50.42	48.33	51.94
7	54.46	53.82	54.14	49.05	49.88	49.47	50.20	52.38
8	51.75	56.34	54.04	51.36	49.88	50.62	50.19	51.78
Mean			52.46			50.40	49.97	52.15
StdMean			0.76			0.28	0.31	0.14

Set	Analyte	$\bar{X}$	$\bar{\sigma_{x}}$	ν_{eff}
1	Mn	52.46	0.76	7
2	Mn	50.40	0.28	7
3	Mn	49.97	0.31	7
4	Mn	52.15	0.15	9
Consensus	**Mn**	**51.18**	**0.66**	**> 60**

Table 20. Statistical Analysis of Mercury Measurements (Hg, µg/L) in Level 2

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	6.677	6.654	6.665	7.132	6.760	6.946	6.557	7.014
2	6.884	6.958	6.921	6.770	8.183	7.476	6.473	6.931
3	6.927	6.848	6.887	6.717	6.788	6.753	6.573	6.880
4	6.747	7.180	6.964	7.299	7.299	7.299	6.566	7.018
5	7.076	6.827	6.952	6.376	6.632	6.504	6.510	6.922
6	6.852	6.885	6.869	7.228	6.927	7.077	6.229	6.981
7	7.706	7.074	7.390	7.083	6.714	6.898	6.250	6.984
8	6.893	7.357	7.125	6.863	6.652	6.758	6.279	6.949
9								6.995
10								7.240
11								7.278
12								6.805
13								6.993
14								6.938
15								6.979
Mean			6.972			6.964	6.430	6.994
StdMean			0.075			0.111	0.053	0.031

Set	Analyte	$\bar{X}$	$\sigma\bar{x}$	ν_{eff}
1	Hg	6.97	0.075	7
2	Hg	6.96	0.11	7
3	Hg	6.43	0.053	7
4	Hg	6.99	0.087	> 60
Consensus	**Hg**	**6.83**	**0.17**	**> 60**

Table 21. Statistical Analysis of Selenium Measurements (Se, µg/L) in Level 2

Data		Set1		Set2	Set3
Vials		Replicates	Combined	Replicates	Replicates
1	274.2	282.2	278.2	244.6	266.0
2	271.3	265.8	268.6	248.2	270.0
3	287.7	277.0	282.3	238.3	270.9
4	273.1	277.1	275.1	249.2	274.4
5	278.4	267.8	273.1	257.0	268.7
6	268.0	271.5	269.7	242.2	277.0
7	272.3	274.8	273.5	230.4	268.2
8	274.3	302.0	288.2	236.1	264.5
Mean			276.1	243.3	270.0
StdMean			2.3	3.0	1.5

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	Se	276.1	2.3	7
2	Se	243.3	3.0	7
3	Se	270.0	1.6	10
Consensus	**Se**	**263.2**	**8.3**	**> 60**

Table 22. Statistical Analysis of Uranium Measurements (U, µg/L) in Level 2

Data	Set1		Combined	Set2	Set3
Vials		Replicates	Combined	Replicates	Replicates
1	0.1098	0.1137	0.1118	0.0870	0.1016
2	0.1235	0.1174	0.1204	0.0904	0.1017
3	0.1002	0.1052	0.1027	0.0886	0.0909
4	0.1210	0.1034	0.1122	0.1016	0.1027
5	0.1102	0.1014	0.1058	0.1024	0.1034
6	0.1047	0.1098	0.1072	0.0896	0.1015
7	0.0981	0.1008	0.0994	0.0884	0.1073
8	0.1090	0.1151	0.1120	0.0958	0.1148
Mean			0.1090	0.0930	0.1030
StdMean			0.0023	0.0022	0.0024

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	U	0.1090	0.0023	7
2	U	0.0930	0.0022	7
3	U	0.1030	0.0025	9
Consensus	**U**	**0.1016**	**0.0048**	**> 60**

Table 23. Statistical Analysis of Ethylmercury Measurements (EtHg, µg/L) in Level 2

Data	Set1		Combined	Set2
Vials		Replicates	Combined	Replicates
1	0.658	0.607	0.632	0.670
2	0.715	0.589	0.652	0.648
3	0.707	0.738	0.722	0.684
4	0.602	0.635	0.618	0.667
5	0.557	0.573	0.565	0.650
6	0.640	0.599	0.620	0.650
7	0.648	0.595	0.622	0.638
8	0.731	0.684	0.707	0.675
Mean			0.642	0.660
StdMean			0.018	0.0056

Set	Analyte	$\bar{X}$	$\sigma_{\bar{x}}$	ν_{eff}
1	EtHg	0.642	0.018	7
2	EtHg	0.660	0.024	> 60
Consensus	**EtHg**	**0.649**	**0.014**	**> 60**

Table 24. Statistical Analysis of Inorganic Mercury Measurements (iHg, µg/L) in Level 2

Data	Set1			Set2
Vials	Replicates		Combined	Replicates
1	2.968	2.041	2.504	2.092
2	1.996	1.868	1.932	2.127
3	1.992	2.022	2.007	2.215
4	1.933	1.771	1.852	2.182
5	2.178	2.686	2.432	2.081
6	1.933	2.290	2.112	2.175
7	2.076	2.178	2.127	2.097
8	2.093	1.843	1.968	2.125
Mean			2.117	2.137
StdMean			0.083	0.017

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	v_{eff}
1	iHg	2.117	0.083	7
2	iHg	2.137	0.023	22
Consensus	**iHg**	**2.135**	**0.022**	**> 60**

Table 25. Statistical Analysis of Methylmercury Measurements (MeHg, µg/L) in Level 2

Data	Set1			Set2
Vials	Replicates		Combined	Replicates
1	3.989	3.838	3.914	3.628
2	4.031	3.942	3.987	3.695
3	3.828	3.787	3.807	3.709
4	3.854	3.888	3.871	3.698
5	3.967	4.009	3.988	3.761
6	3.595	3.703	3.649	3.743
7	3.714	3.797	3.755	3.723
8	3.820	3.905	3.862	3.819
Mean			3.854	3.722
StdMean			0.041	0.020

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	v_{eff}
1	MeHg	3.854	0.041	7
2	MeHg	3.722	0.138	> 60
Consensus	**MeHg**	**3.844**	**0.039**	**> 60**

Table 26. Statistical Analysis of Lead Measurements (Pb, µg/dL) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	44.65	43.94	44.29	42.92	42.72	42.82	42.20	41.51
2	42.23	41.76	41.99	42.65	42.39	42.52	42.08	41.58
3	43.36	43.71	43.54	42.18	41.99	42.09	41.25	41.48
4	44.07	43.77	43.92	42.62	42.52	42.57	42.37	41.51
5	42.18	42.53	42.35	41.72	42.25	41.99	42.02	41.50
6	44.86	44.39	44.62	40.97	40.92	40.94	42.18	41.47
7	43.38	44.34	43.86	41.73	41.55	41.64	40.01	41.48
8	42.04	42.19	42.12	41.63	41.80	41.71	42.14	41.48
9							42.54	
Mean			43.34			42.03	41.87	41.50
StdMean			0.37			0.22	0.26	0.012

Set	Analyte	$\overline{X}$	$\sigma_{\overline{x}}$	ν_{eff}
1	Pb	43.34	0.37	7
2	Pb	42.03	0.22	7
3	Pb	41.87	0.26	8
4	Pb	41.50	0.21	> 60
Consensus	**Pb**	**42.13**	**0.32**	**> 60**

31

Table 27. Statistical Analysis of Arsenic Measurements (As, μg/L) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	772.2	766.2	769.2	779.8	780.6	780.2	780	785.2
2	797.6	769.7	783.7	786.0	785.1	785.5	789	773.5
3	771.4	765.8	768.6	776.8	772.2	774.5	724	759.5
4	753.8	747.1	750.4	780.1	781.0	780.6	777	757.3
5	776.3	779.6	777.9	796.7	806.4	801.6	718	771.0
6	816.8	816.7	816.7	781.0	788.9	784.9	728	755.7
7	806.9	788.1	797.5	800.7	784.7	792.7	749	778.7
8	799.7	794.8	797.2	787.6	786.7	787.2	719	776.6
Mean			782.7			785.9	748	769.7
StdMean			7.4			2.9	11	3.9

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	ν_{eff}
1	As	782.7	7.4	7
2	As	785.9	2.9	7
3	As	748.0	10.6	7
4	As	769.7	3.9	7
Consensus	**As**	**773.7**	**6.7**	**> 60**

Table 28. Statistical Analysis of Cadmium Measurements (Cd, µg/L) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	11.374	11.005	11.189	10.512	10.553	10.532	10.625	10.607
2	10.317	10.379	10.348	10.323	11.019	10.671	10.666	10.541
3	10.316	10.750	10.533	10.690	10.430	10.560	10.245	10.548
4	10.532	10.563	10.548	10.556	10.291	10.423	10.194	10.519
5	10.412	10.418	10.415	10.578	10.464	10.521	10.405	10.481
6	11.251	10.989	11.120	10.198	10.289	10.244	10.471	10.656
7	10.864	11.090	10.977	10.181	9.994	10.088	10.072	10.629
8	10.508	10.327	10.418	10.089	10.589	10.339	10.778	10.527
9							10.471	
Mean			10.694			10.422	10.436	10.564
StdMean			0.122			0.067	0.078	0.021

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	ν_{eff}
1	Cd	10.694	0.122	7
2	Cd	10.422	0.067	7
3	Cd	10.436	0.078	8
4	Cd	10.564	0.097	> 60
Consensus	**Cd**	**10.500**	**0.056**	**> 60**

Table 29. Statistical Analysis of Chromium Measurements (Cr, μg/L) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	42.67	42.48	42.57	41.49	39.84	40.67	43.61	42.51
2	45.69	44.79	45.24	40.42	41.25	40.84	44.38	43.40
3	43.90	43.06	43.48	40.28	40.28	40.28	41.35	43.03
4	44.20	43.81	44.01	40.84	39.03	39.94	40.67	42.84
5	43.24	42.90	43.07	42.93	42.31	42.62	40.49	42.78
6	46.13	46.16	46.14	40.67	40.88	40.77	40.13	42.49
7	44.99	45.18	45.09	40.13	41.25	40.69	41.47	42.40
8	47.02	47.08	47.05	42.58	42.29	42.43	40.20	42.66
Mean			44.58			41.03	41.54	42.76
StdMean			0.55			0.34	0.57	0.12

Set	Analyte	$\bar{X}$	$\bar{\sigma_{x}}$	v_{eff}
1	Cr	44.58	0.55	7
2	Cr	41.03	0.34	7
3	Cr	41.54	0.57	7
4	Cr	42.76	0.20	> 60
Consensus	**Cr**	**42.45**	**0.66**	**> 60**

Table 30. Statistical Analysis of Cobalt Measurements (Co, µg/L) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	31.30	31.57	31.43	31.63	31.15	31.39	32.34	32.83
2	34.21	33.43	33.82	31.71	33.02	32.37	31.16	32.29
3	32.51	32.49	32.50	31.48	31.45	31.47	32.16	31.40
4	31.09	31.30	31.20	31.64	30.34	30.99	31.45	31.88
5	32.16	31.60	31.88	31.99	31.31	31.65	30.30	32.04
6	34.47	34.52	34.50	30.79	31.14	30.97	31.33	31.73
7	33.70	33.22	33.46	32.01	31.94	31.98	31.29	32.47
8	34.45	34.53	34.49	32.06	32.47	32.26	30.76	32.61
Mean			32.91			31.63	31.35	32.16
StdMean			0.47			0.19	0.24	0.17

Set	Analyte	$\overline{X}$	$\overline{\sigma_X}$	v_{eff}
1	Co	32.91	0.47	7
2	Co	31.63	0.19	7
3	Co	31.35	0.24	7
4	Co	32.16	0.17	7
Consensus	**Co**	**31.91**	**0.26**	**> 60**

Table 31. Statistical Analysis of Manganese Measurements (Mn, µg/L) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	78.17	76.89	77.53	73.65	74.00	73.82	75.43	77.92
2	77.17	75.18	76.18	76.22	75.18	75.70	73.76	77.61
3	79.49	81.10	80.30	74.04	73.06	73.55	74.55	76.23
4	77.08	77.51	77.29	72.36	75.05	73.70	71.31	75.92
5	77.55	78.23	77.89	74.39	74.30	74.35	74.89	77.64
6	82.54	82.09	82.31	75.08	75.19	75.14	72.91	75.98
7	80.67	83.08	81.88	74.66	73.61	74.14	74.09	77.72
8	77.18	76.84	77.01	73.39	74.32	73.86	71.79	78.35
Mean			78.80			74.28	73.59	77.17
StdMean			0.83			0.27	0.52	0.34

Set	Analyte	$\bar{X}$	$\bar{\sigma}_{\bar{x}}$	ν_{eff}
1	Mn	78.80	0.83	7
2	Mn	74.28	0.27	7
3	Mn	73.59	0.52	7
4	Mn	77.17	0.35	7
Consensus	**Mn**	**75.9**	**1.0**	**> 60**

Table 32. Statistical Analysis of Mercury Measurements (Hg, μg/L) in Level 3

Data	Set1			Set2			Set3	Set4
Vials	Replicates		Combined	Replicates		Combined	Replicates	Replicates
1	57.37	57.48	57.43	54.95	55.45	55.20	52.44	56.34
2	57.80	56.49	57.15	56.05	56.58	56.31	53.61	55.07
3	55.08	57.83	56.46	54.13	53.85	53.99	53.79	57.04
4	57.38	60.77	59.08	55.45	55.90	55.67	54.12	56.38
5	56.12	53.84	54.98	54.95	54.84	54.89	54.16	55.98
6	57.48	56.93	57.20	53.17	53.45	53.31	53.62	54.76
7	55.49	58.71	57.10	55.19	55.97	55.58	51.58	58.02
8	52.96	54.22	53.59	56.97	56.57	56.77	53.62	57.47
9							54.28	
Mean			56.62			55.22	53.47	56.38
StdMean			0.59			0.41	0.30	0.40

Set	Analyte	$\overline{X}$	$\overline{\sigma x}$	ν_{eff}
1	Hg	56.62	0.59	7
2	Hg	74.28	0.27	7
3	Hg	53.47	0.30	8
4	Hg	56.38	0.76	> 60
Consensus	**Hg**	**55.35**	**0.79**	**> 60**

Table 33. Statistical Analysis of Selenium Measurements (Se, µg/L) in Level 3

Data	Set1			Set2	Set3
Vials		Replicates	Combined	Replicates	Replicates
1	829.8	828.0	828.9	681.9	786.7
2	831.7	810.1	820.9	712.4	773.2
3	799.7	823.7	811.7	674.8	755.9
4	786.7	818.1	802.4	685.9	761.9
5	794.8	767.9	781.3	689.9	761.3
6	814.4	809.0	811.7	688.9	749.1
7	769.1	783.6	776.4	651.9	773.1
8	773.1	774.9	774.0	656.3	756.1
Mean			800.9	680.3	764.7
StdMean			7.5	6.9	4.3

Set	Analyte	$\bar{X}$	$\sigma\bar{x}$	ν_{eff}
1	Se	800.9	7.5	7
2	Se	680.3	6.9	7
3	Se	764.7	4.3	7
Consensus	**Se**	**749**	**32**	**> 60**

Table 34. Statistical Analysis of Uranium Measurements (U, μg/L) in Level 3

Data	Set1			Set2	Set3
Vials	Replicates		Combined	Replicates	Replicates
1	1.090	1.067	1.078	1.005	1.064
2	1.128	1.059	1.093	0.896	1.040
3	0.987	1.003	0.995	0.945	1.043
4	1.083	1.108	1.096	0.933	1.038
5	1.047	1.056	1.051	0.945	1.056
6	1.097	1.090	1.094	0.998	1.068
7	1.050	1.029	1.040	0.927	1.048
8	1.086	1.113	1.099	0.945	1.073
Mean			1.068	0.949	1.054
StdMean			0.013	0.013	0.0048

Set	Analyte	$\bar{X}$	$\bar{\sigma x}$	ν_{eff}
1	U	1.068	0.013	7
2	U	0.949	0.013	7
3	U	1.054	0.0058	15
Consensus	**U**	**1.024**	**0.033**	**> 60**

Table 35. Certified Values of Analytes in SRM 955d Level 1 (μg/L)[1]

Analyte	Mean	U	k	ν_{eff}
Pb[1]	1.480	0.026	1.98	1.3E+02
As	5.31	0.76	1.96	2.5E+03
Cd	0.326	0.010	1.96	7.9E+04
Cr	0.886	0.069	1.97	2.8E+02
Co	0.384	0.051	1.96	1.5E+03
Mn	48.8	1.3	1.97	4.0E+02
Hg	1.373	0.081	1.96	5.0E+05
Se	206.6	9.5	1.96	4.0E+04
U	0.0111	0.0013	1.97	3.9E+02
EtHg	0.342	0.034	1.96	8.5E+02
iHg	0.405	0.024	1.96	8.0E+02
MeHg	0.626	0.020	1.96	1.0E+05

[1]Pb values are in μg/dL units

Table 36. Certified Values of Analytes in SRM 955d Level 2 (µg/L)[1]

Analyte	Mean	U	k	v_{eff}
Pb[1]	4.947	0.085	1.96	2.5E+03
As	277.5	4.8	1.96	3.0E+03
Cd	5.343	0.082	1.96	7.0E+04
Cr	2.012	0.037	1.96	8.0E+05
Co	1.610	0.057	1.96	1.5E+03
Mn	51.2	1.3	1.96	2.9E+03
Hg	6.83	0.33	1.96	7.9E+04
Se	263	16	1.96	2.7E+03
U	0.1016	0.0095	1.96	9.0E+04
EtHg	0.649	0.028	1.96	1.0E+05
iHg	2.135	0.043	1.96	8.0E+04
MeHg	3.844	0.077	1.96	2.5E+03

[1]Pb values are in µg/dL units

Table 37. Certified Values of Analytes in SRM 955d Level 3 (µg/L)[1]

Analyte	Mean	U	k	v_{eff}
Pb[1]	42.13	0.63	1.96	9.5E+03
As	774	13	1.96	7.5E+03
Cd	10.50	0.11	1.96	1.0E+04
Cr	42.5	1.3	1.96	7.0E+04
Co	31.91	0.50	1.96	8.5E+04
Mn	75.9	2.0	1.96	2.6E+03
Hg	55.3	1.6	1.96	2.5E+03
Se	749	62	1.96	2.6E+03
U	1.024	0.065	1.96	8.5E+04

[1]Pb values are in µg/dL units

Reference Density Values: A reference value is a noncertified value that is the best estimate of the true value where all known or suspected sources of bias have not been fully investigated by NIST [14]. The densities of the three levels of SRM 955d were measured using an Anton Paar DMA 5000 M Density Meter. Eight randomly selected vials at each level of the SRM were measured. The densities of the three levels of the SRM are summarized in Table 38.

Table 38. Reference Values of Density for the Three Levels of SRM 955d (g/mL)

SRM 955d	Level 1	Level 2	Level 3
Density	**1.052147**	**1.052118**	**1.051285**
Type A standard uncertainties	0.000037	0.000005	0.000016
Type B standard uncertainties	0.000005	0.000006	0.000008
Combined standard uncertainty, u_c	0.000037	0.000008	0.000018
Degrees of freedom, ν_{eff}	7	44	10
Coverage factor, k	2.365	2.015	2.228
Expanded uncertainty, U	**0.000088**	**0.000017**	**0.000040**

Information Value: An information value is a non-certified value that is considered to be of interest to the SRM user, but insufficient information is available to assess the uncertainty associated with the value, or only a limited number of analyses were performed [14]. To support the applications in dried blood spot (DBS) testing of metabolites, thyroglobulin (Tg) in SRM 955d Level 1 was measured by the collaborating laboratory at the Human Nutrition Laboratory, Institute of Food Nutrition and Health, Swiss Federal Institute of Technology (ETH) in Switzerland. An enzyme-linked immunosorbent assay was used for the Tg measurement [4]. The results for Tg are listed in Table 39.

Table 39. Information Values of Thyroglobulin (Tg) in SRM 955d Level 1 (µg/L)

Vial	Tg
1	35.6
2	30.2
3	30.9
4	32.7
5	27.4
6	35.4
7	31.1
8	27.9
9	25.7
10	22.5
Mean	**29.9**
s	4.2
RSD (%)	14 %

Conclusions

SRM 955d was developed for use in validating measurement procedures for toxic elements and mercury species in whole human blood or similar matrices. It was jointly produced by NIST and CDC to supersede SRM 955c. The analytes of SRM 955d were determined to be homogeneous for the intended purpose. Measurements leading to the certification of SRM 955d were made at CDC, Mayo Clinic, New York State Department of Health, and NIST. The analytes in SRM 955d are stable based on historical experience with these analytes in blood matrix SRMs, particularly the 955 series of SRMs. As part of quality assurance, NIST will monitor the stability of the analytes throughout the certification period of the SRM.

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