Journal of ASTM International, Jan. 2006, Vol. 3, No. 1
Paper ID: JAI13171
Available online at: www.astm.org

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Opportunities for Development of Reference Materials for Beryllium

ABSTRACT: Reference materials provide the foundation for assessment of analytical chemistry methods, accurate quantification of occupational and environmental exposures, and conduct of in vitro and in vivo toxicology studies for health effects research. Although the National Institute of Standards and Technology (NIST) supplies industry, academia, government, and other users with over 1300 reference materials of the highest quality and metrological value, the number of beryllium reference materials is limited. Currently available beryllium reference materials include standard spectroscopy solutions of beryllium and copper-beryllium alloy in the form of blocks, chips, and rods. Beryllium is present as a trace element in some standard soil-sludge, coal fly ash, and urine reference materials. Beryllium on filter media was available at one time, but is not currently available. A number of opportunities exist for identification and development of needed beryllium reference materials for beryllium-containing ores, beryllium oxide, beryllium metal, beryllium metal-matrix materials, beryllium-containing alloys, and beryllium in biological samples. These opportunities will require multi-disciplinary and multi-organizational collaboration. Needed actions include consensus on the relevant chemical and physical forms of beryllium; market analyses of demand for the materials; identification of candidate industrial or laboratory-produced samples of the materials; selection of samples that meet criteria for uniformity, physical form, measured quantities, and continued availability; development of production protocols for collection and preparation of the materials, including adequate provisions for occupational health and environmental protection; incorporation of these materials into a supply, distribution, and cost-recovery infrastructure; and continued feedback and information sharing to ensure that the reference materials are meeting user needs or are modified as necessary. Lessons from other major initiatives for reference materials of lead, silica, and similar materials provide guidance on how to optimize and implement an enhanced program for beryllium reference materials.

KEYWORDS: beryllium, reference materials, certified reference materials, standard reference materials, traceability

Nomenclature

Certified Reference Material (CRM)—Reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence [1].

Measurand—Particular quantity subject to measurement [2].

Reference Material (RM)—Material or substance one or more of whose property values are sufficiently homogeneous, stable, and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials [1].

Manuscript received April 14, 2005; accepted for publication June 30, 2005; published Jan. 2006.
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Standard Reference Material® (SRM)—A certified reference material (CRM) issued by the National Institute of Standards and Technology (NIST). An SRM is a well characterized material produced in quantity to improve measurement science. It is certified for specific chemical or physical properties, and is issued by NIST with a certificate that reports the results of the characterization and indicates the intended use of the material.

Traceability—The property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties [2].

Introduction

Reference materials play a critical role in occupational health efforts to understand and prevent disease from toxic materials such as beryllium. Reference materials provide the foundation for assessment of analytical chemistry methods, for accurate quantification of occupational and environmental exposures, and for the conduct of empirical and mechanistic health effects research. Reference materials are also critical components of material science, engineering, and production.

Although the National Institute of Standards and Technology (NIST) supplies industry, academia, government, and other users with over 1300 reference materials of the highest quality and metrological value, the number of beryllium materials is limited. Currently available beryllium reference materials include standard spectroscopy solutions of beryllium and copper-beryllium in the form of blocks, chips, and rods. Beryllium is also present as a trace element in some standard soil-sludge, coal fly ash, and urine reference materials. Beryllium on filter media was available at one time, but is not currently available.

A number of opportunities exist for identification and development of needed beryllium reference materials for beryllium-containing ores, beryllium oxide, beryllium metal, beryllium metal-matrix materials, beryllium-containing alloys, and beryllium in biological samples. These opportunities will require multi-disciplinary and multi-organizational collaboration. The purpose of this paper is to summarize the terminology and qualification procedures for reference materials, present examples of relevant reference materials, and discuss the possible next steps for development of new beryllium reference materials.

Types of Reference Materials

A *Reference Material (RM)* is a material or substance one or more of whose property values are sufficiently homogeneous, stable, and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials [1]. Figure 1 illustrates the hierarchy among all materials in our workplaces and general environment and the subsets of materials that qualify as various types of reference materials.

A "material of interest" becomes a reference material by being selected and prepared in an appropriate manner:

$$\begin{pmatrix}\text{A material}\\ \text{of interest}\end{pmatrix} + \begin{pmatrix}\text{Adequate Preparation}\\ \text{(homogeneity, uniformity, etc)}\end{pmatrix} = \begin{pmatrix}\text{A Reference}\\ \text{Material (RM)}\end{pmatrix}$$

A reference material qualifies as a *Certified Reference Material (CRM)* when a metrology laboratory (national or commercial) issues a certificate stating that one or more of its property values are certified by a procedure which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence [1]. Thus:

$$\begin{pmatrix}\text{A Reference}\\ \text{Material (RM)}\end{pmatrix} + \begin{pmatrix}\text{Certified}\\ \text{measurand}\\ \text{values}\end{pmatrix} = \begin{pmatrix}\text{A Certified}\\ \text{Reference}\\ \text{Material}\\ \text{(CRM)}\end{pmatrix}$$

The differences between an RM and a CRM are that (1) the CRM requires metrological efforts by the producer to ensure the traceability of the certified results for the CRM and (2) the CRM requires the issuance of a certificate by that producer taking responsibility for the reported values. To conform to an accreditation program or to gain wider acceptance, CRM producers often adhere to the general requirements for the competence of reference material producers as stated in ISO Guide 34 [3] and to the general and statistical principles for the certification of reference materials as stated in ISO 35 [4], and ensure that their certificates fulfill the requirements of ISO Guide 31 [5], which defines the contents of certificates and labels for reference materials.

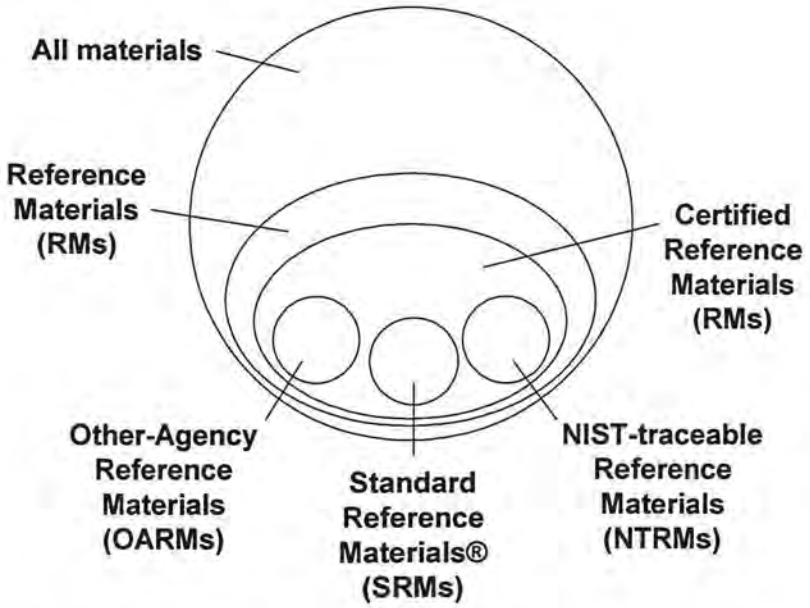

FIG. 1—*Relationships among all materials in our workplaces and environment and the subsets of those materials that have been designated as different categories of reference materials.*

To improve measurement science, NIST produces and distributes CRMs under the registered name *Standard Reference Material® (SRM)*. Thus, an SRM is a CRM that is issued by NIST. An SRM is certified for specific chemical or physical properties and is issued by NIST with a certificate that reports the results of the characterization and indicates the intended use of the material. The three technical categories of SRMs are chemical composition, physical properties, and engineering materials. The NIST Technology Services website (http://www.nist.gov/srm) describes the SRM program in detail.

NIST also prepares and characterizes CRMs under specific agreements with other agencies. These are known as *Other Agency Reference Materials (OARMs)*. Under such agreements, the entire lot of materials and the accompanying reports are transferred to the contracting agency. OARMs meet the ISO requirements for CRMs.

A *NIST Traceable Reference Material (NTRM)* is a CRM produced by a commercial supplier with a well defined traceability to the values of standards maintained by NIST. This traceability is established via criteria and protocols defined by NIST that are tailored to meet the needs of the metrological community to be served. The NTRM concept was established to allow NIST to efficiently respond to the increasing needs for high-quality reference materials. Reference material producers adhering to these requirements are allowed to use the NIST "NTRM" trademark to identify their products. NTRMs meet the ISO requirements for CRMs.

The first example of an NTRM was in the area of gas metrology. The gas NTRM program was established in 1992 in partnership with U.S. Environmental Protection Agency (EPA) and specialty gas companies as a means for providing end-users with the wide variety of certified gas standards needed to implement the "Emissions Trading" provision of the 1990 Clean Air Act. Gas NTRMs are produced and distributed by specialty gas companies with NIST oversight of the production and maintenance and direct involvement in the analysis. The gas standards prepared according to this program are related, within known limits of uncertainty, to specific gaseous primary standards maintained by NIST.

"Make-Your-Own" Reference Materials (MYOMs) are a new concept in CRMs that are made and evaluated (for the most part) outside the primary NIST laboratories for the specific purposes of the user. This type of reference material results from the complete blending of two other gravimetically aliquoted reference materials. Figure 2 illustrates the relationships between an existing reference material (or set of reference materials) and a MYOM. The certified or reference values for a MYOM are calculated using the corresponding values for the parent materials and the gravimetric dilution factor. To preserve the uncertainty levels of the parent materials in the MYOM, the uncertainty component associated with weighing and blending must be small compared to the uncertainties in the parent materials. MYOMs meet the ISO requirements for CRMs.

Types of Values and Modes of Certification

Each particular analyte, chemical or physical property, or quantity that is subject to measurement is referred to as a *measurand* [2]. For SRMs prepared by NIST, there are three levels of *values* that can be established for a particular measurand:

- A NIST Certified Value represents 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 by NIST. Certified values have associated uncertainties.

- A NIST Reference Value is a best estimate of the true value provided by NIST where all known or suspected sources of bias have not been fully investigated by NIST. Reference values have associated uncertainties.
- A NIST Information Value is a value that will be of interest and use to the SRM/RM user, but insufficient information is available to assess the uncertainty associated with the value. Information values do not have associated uncertainties.

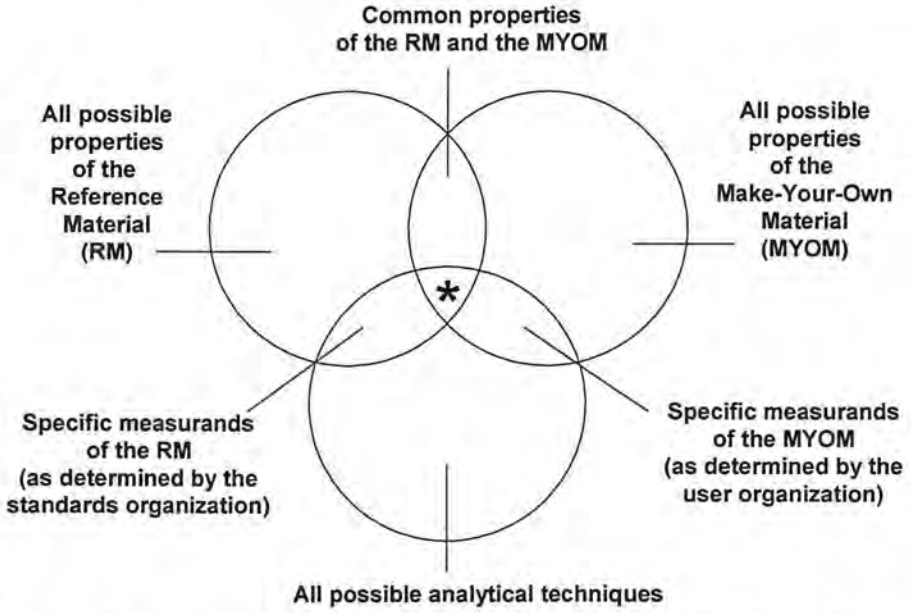

FIG. 2—*Relationships between an existing reference material (or set of reference materials) and a "Make-Your-Own" Reference Material (MYOM).*

The use and interpretation of certified values, reference values, and information values are related to an SRM user's requirements that his or her results be "*traceable to NIST.*" Although the phrase "traceable to NIST" is commonly used, it is strictly incorrect because results or values can only be traceable to stated reference results or values, not to institutes. Traceability is the property of the *result* of a measurement or the *value* of a standard whereby the result or value can be related to *stated references*, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties [2]. Thus, the phrase "traceable to NIST" can be thought of as "traceable to the results of measurements or the values of standards at NIST." Because the definition of traceability requires an unbroken chain of comparisons all having stated uncertainties, only certified values and reference values can be used as "stated references." Information values do not qualify as stated references, because they do not have uncertainties associated with them.

Table 1 summarizes the characteristics of seven *modes* by which certified values, reference values, and information values, or all three, can be developed [6]. The choice of mode(s) to be used in the value-assignment for any SRM for chemical measurements is based on previous experiences and knowledge of the specific matrix, analyte(s) of interest, current measurement

capabilities, the quality of the analytical method's results, and the intended use of the material. The final designation of an assigned value for an SRM as a NIST certified value, NIST reference value, or NIST information value is based on the specific value-assignment mode used and the assessed quality of the resulting data relative to the intended use of the material.

TABLE 1—*Relationships between the seven modes of certification recognized by NIST and the type(s) of value (certified, reference, or information) that can be assigned by each certification mode [6].*

		Type of Value		
Mode	Description	Certified	Reference	Information
1.	Certification at NIST Using a Single Primary Method with Confirmation by Other Method(s)	•		
2.	Certification at NIST Using Two Independent Critically Evaluated Methods	•	•	
3.	Certification/Value-Assignment Using One Method at NIST and Different Methods by Outside Collaborating Laboratories	•	•	
4.	Value-Assignment Based On Measurements by Two or More Laboratories Using Different Methods in Collaboration with NIST		•	•
5.	Value-Assignment Based on a Method-Specific Protocol		•	•
6.	Value-Assignment Based on NIST Measurements Using a Single Method or Measurements by an Outside Collaborating Laboratory Using a Single Method		•	•
7.	Value-Assignment Based on Selected Data from Interlaboratory Studies		•	•

Certified Values

As summarized in Table 1, certified values result from any of Modes 1, 2, or 3, wherein either a *primary* method or two *independent* methods are used to determine an analyte.

- The concept of a *primary method* has been described by Moody and Epstein [7] as a "definitive method" and more recently articulated by the Consultative Committee for Amount of Substance (CCQM) as a method having the highest metrological properties, whose operation can be completely described and understood, for which a complete uncertainty statement can be written down in terms of units belonging to the International

System of Units (SI) [8]. In practice, a primary method has all of its potentially significant sources of error evaluated explicitly for the application of the method and the matrix under investigation [7]. NIST always combines primary methods with some means of confirmatory analysis. Such confirmation can be accomplished by the re-determination of certified constituents in other SRMs or CRMs of similar matrix and constituent concentration range, or by using a second method with appropriate controls. Confirmatory methods can be carried out either in NIST laboratories or by collaborating laboratories with appropriate experience.

- Methods are considered to be *independent* if they have completely different sources of error and variability. In practice this is rarely the case, but methods can usually be chosen so that the most significant sources of error are different. For example, where material dissolution might be a significant challenge to the analytical process, different sample preparation methods can be selected to minimize the chance that similar errors will be incurred. Instrumental methods can be considered to be independent if they rely on different physical, spectroscopic, or chemical phenomena to generate their respective analytical response. In all cases, the design of the certification plan ensures that all methods have the appropriate precision and accuracy for measurement of the target analyte(s) in the matrix.

Certification Mode 1 involves the use of a single primary method at NIST with confirmation by another method (or methods).

Certification Mode 2 involves the use of two or more critically evaluated *independent* NIST methods [9].

Certification Mode 3 is used when NIST does not have a suitable second independent method, and outside laboratories are selected to collaborate on the certification process. In such cases, NIST works very closely with the outside laboratory analysts to ensure that the details of the measurement protocol, data analysis, and reporting requirements are carried out according to NIST specifications.

Reference Values

Even though Modes 2 and 3 can result in a certified value, if the results of the methods do not agree sufficiently, NIST designates the assigned value as a reference value. Reference values can result from certification Modes 2–7.

Information Values

Certification Modes 4–7 can also result in a NIST information value. Such is the case when the agreement among data from multiple methods is not sufficient to estimate a reliable uncertainty. Information values provide users with supplemental information about the SRM composition. Certified values and reference values have corresponding uncertainties. Information values do not have corresponding uncertainties.

Application-Related Issues for Reference Materials

Reference Materials for Calibration

Reference materials used for the calibration of instruments or analytical methods are, in general, relatively simple mixtures of analytes whose concentrations are very well known. Often such reference materials are solutions, prepared from pure materials by highly accurate and precise means at high concentration. They are intended to be diluted either by volumetric or gravimetric procedures producing one or more working mixtures so that the resulting series of analyte concentrations spans the range of the intended analysis. Analyte concentrations in calibration reference materials are known to have such high accuracy and precision that they can be used to establish instrumental response calibration curves where the error can be assumed to reside predominantly in the instrumental readings. Minimizing uncertainty in the analyte concentration (the independent variable in the calibration procedure) avoids mathematical model complications known as the "error-in-X" case [10]. The assumption that error resides predominantly in the instrument reading (the dependent variable) is necessary, for instance, to estimate the slope and intercept of a straight line using simple linear regression.

Calibration reference materials can be the key to ensuring the quality of results for chemical analysis results provided that the chief source of error is in the calibration step of the analytical method. This is not often the case for the determination of beryllium in industrial materials or environmental samples. In these cases, the chemical matrix and physical form of the sample present far more significant sources of error due to incomplete chemical dissolution, interferences, and matrix effects. However, calibration reference materials can be effective tools in these cases when they are used in standard additions, internal standard, and matrix-matching schemes to correct for analytical bias.

Reference Materials for Method Validation

Reference materials intended to validate the entire analytical method are designed to represent, as faithfully as possible, the chemical matrix, physical form, and analyte levels of the target sample. By testing the validity of the entire analytical method, such reference materials ensure to a greater degree the quality of analytical results for real samples. For all their benefits, however, matrix reference materials are much more difficult to develop. Before one can begin to design the certification procedures for a matrix reference material, the process of selecting, processing, and accepting a candidate material must be addressed.

It is almost paradoxical that one must know a fair amount about real-world samples before the relevant matrix reference materials can be developed to qualitatively and quantitatively verify such knowledge. The target analytes in industrial and environmental samples can take on many forms, and one must understand and clearly state the physical and chemical form of the intended measurand. For example, free and bound forms of beryllium must be identified if a matrix reference material is to adequately challenge sample preparation steps. Some sort of screening analysis has to be used to characterize the chemical matrix of interest. In many cases, the sample collection method itself adds to the list of concomitant species that must be included in the design of the reference material. Industrial hygiene evaluations often employ air filters and wipe materials, which can interfere with either the sample preparation steps or can add to the list of species interfering with the detection of the analyte.

Some methods of analysis are intended to reproduce the action of natural environmental conditions. For instance rainwater and groundwater leaching effects can be mimicked by the extraction of analytes and interfering matrix species as an analysis preparation step. Not only do such applications require that reference materials and real samples be of a similar chemical matrix, but they must also be of similar physical form. Moreover, careful design work is necessary for reference materials to present the same challenges to the analytical chemistry process as the real samples. One straightforward way to ensure that a reference material matches all the critical parameters of the target sample types is to collect real material at a site of known contamination. A practical matter arises when the need to document the origin of a reference material conflicts with the site owner's desire to remain unidentified.

General Properties of Beryllium

Beryllium and its oxide are used in a wide variety of materials to take advantage of a number of its unique properties. As an alloying constituent, beryllium lends a high degree of dimensional stability and wear resistance to metals. Its superior transmittance to X-rays makes beryllium foil a good choice for spectrometer windows. Beryllium is also used in ceramics and in the nuclear industry for reactor moderation. Mining, extracting, and refining beryllium involves the production of fine powders, which potentially pose airborne and skin contact health risks. Evaluations of health effects, degrees of exposure, and the effectiveness of remediation measures depend on the accurate determination of beryllium using metrologically sound analytical chemistry methodologies.

Existing Beryllium Reference Materials

The information presented below on existing beryllium SRMs has been excerpted directly from the *NIST Certificate of Analysis* for each SRM described. The certificates of analysis routinely describe how the SRMs were intended to be used, how the SRMs were prepared, how uncertainties in the metrological properties were determined, the time period of the certifications for each of the materials, the manner in which NIST will maintain the certification, and instructions for use. If appropriate, an SRM is also accompanied by a *Material Safety Data Sheet (MSDS)* containing sections on material identification, hazardous ingredients, physical/chemical characteristics, fire and explosion hazard data, reactivity data, health hazard data (including emergency and first aid procedures), precautions for safe handling and use, and source data and other comments.

Beryllium Solution SRM

SRM 3105a is intended for use as a primary calibration standard for the quantitative determination of beryllium by analytical methods such as inductively coupled plasma spectrometry (both optical and mass) and atomic absorption spectrometry [11]. Each sales unit of SRM 3105a consists of five 10 mL sealed borosilicate glass ampoules each containing a 10 % nitric acid solution of beryllium prepared gravimetrically to contain a known mass fraction of beryllium. The current certified value of beryllium in SRM 3105a is 10.83 mg/g ± 0.07 mg/g [11]. That value is based on (1) gravimetric preparation and (2) inductively coupled plasma optical emission spectrometry (ICP-OES) using three independently prepared primary standards.

The uncertainty in the certified value is calculated as $U = (2\mu_c + B)$ mg/g where μ_c is the combined standard uncertainty calculated according to the ISO and NIST guidelines [12,13] and the procedure of Schiller and Eberhardt [14] for combining independent analytical methods. The value of μ_c is intended to represent, at the level of one standard deviation, the combined effect of uncertainty components associated with the gravimetric preparation and the analytical determinations. The quantity B is an allowance for between-method differences.

Note that the relative expanded uncertainty of the certified value for SRM 3105a is less than 0.7 %. This low level of uncertainty results from a combination of dissolution and gravimetric preparation using ultra-pure beryllium metal as well as the high-accuracy comparison of the candidate SRM solution with independently prepared NIST standard beryllium solutions. Besides the uncertainty components of these two methods of beryllium determination, the beryllium metal purity and its uncertainty were also taken into account. The use of two independent methods for the certification of beryllium in SRM 3105a represents one of the seven modes (Table 1) that NIST uses for value assignment of chemical reference materials.

Expiration of Certification—The current certificate of analysis for SRM 3105a states that the certification of SRM 3105a Lot No. 892707 is valid, within the measurement uncertainty specified, until 15 December 2006, provided the SRM is handled in accordance with the "Instructions for Use" given in the certificate. It is further stated that the certification is nullified if the SRM is damaged, contaminated, or modified.

Maintenance of Certification—The certificate describes how the certification will be maintained by NIST. NIST will monitor representative solutions from this SRM lot over the period of its certification. If substantive changes occur that affect the certification before the expiration of certification, NIST will notify the purchaser. Purchasers are advised to facilitate notification by returning the registration card that accompanies the certification.

Traceability to this SRM—The certificate states that calibration of analytical instruments or procedures for the determination of beryllium should be performed using standards that are traceable to this SRM. The traceability of standards to this SRM must be established through an unbroken chain of comparisons, each having stated uncertainties [2]. Comparisons are based on physical or chemical measurements proportional to the beryllium concentration. These may include various spectroscopic or classical methods of analysis. The gravimetric and volumetric dilution preparations are also considered to be methods of comparison. The uncertainties assigned to such traceable standards must include the uncertainty of this SRM appropriately combined with the uncertainties of all comparison measurements.

Instructions for Use Caution—The certificate cautions the user to handle the SRM in a safe manner (i.e., wear gloves and avoid accidental breakage or spillage during handling of acid solution SRMs that are contained in tip-sealed borosilicate glass ampoules with pre-scored stems).

Instructions for Preparation of Working Standard Solutions—The certificate describes how working standard solutions should be prepared by mass or by volume.

Blocks, Chips, and Rods of Beryllium-Copper Alloy

SRMs for beryllium in various solid copper alloys have been available from NIST since the early 1980s. High-purity copper was melted with several minor and trace elements to produce SRMs 1121, C1121, 1122, C1122, 1123, and C1123. The materials with the "C" designation were the chill-cast SRMs. Samples of the chill-cast material were 32 mm (1.25 in.) square by 19 mm (0.75 in.) thick. Wrought samples were 32 mm (1.25 in.) in diameter by 19 mm (0.75 in.) thick. Beryllium ranged from a certified value of 0.46 % in SRMs 1123 and C1123 to 1.92 % in C1121. Only SRM C1122, with beryllium at 1.75 %, is presently available for sale. The others in this series have been sold out and discontinued. This form of the alloy is intended primarily for calibration of X-ray and optical emission spectrometers.

Beryllium-copper alloys in chip form are intended for chemical analysis. SRMs 458, 459, and 460 are copper alloys with beryllium at 0.360 % in SRM 458, at 1.82 % in SRM 459, and at 1.86 % in SRM 460. They were prepared in cooperation with ASTM International and are in the form of chips sized between 0.50 mm and 1.18 mm sieve openings (35 mesh and 16 mesh). Certified values are also provided for the concentrations of aluminum, chromium, cobalt, iron, lead, magnesium, nickel, silicon, tin, and zinc in these SRMs. Cooperative analyses for certification were performed at the following laboratories: Armco Research and Technology, Armco, Inc., Middletown, OH; Brush Wellman, Inc., Elmore, OH; Colonial Metals Company, Columbia, PA; NGK Insulators Ltd., Handa City, Japan; NGK Metals Corp., Reading, PA; and Teledyne Wah Chang, Albany, OR. Information values are provided for the concentrations of antimony, copper, manganese, silver, sulfur, titanium, and zirconium.

Beryllium as a Trace Element

Beryllium is listed as a trace element in some standard NIST soil and sludge SRMs (e.g., SRM 1646a Estuarine Sediment, SRM 1944 New York/New Jersey Waterway Sediment, and SRMs 2586 and 2587 Trace Elements in Soil). Beryllium is assigned a reference value of 1.6 mg/kg with an expanded uncertainty of 0.3 mg/kg in SRM 1944. Concentrations of beryllium in the other SRMs are information values ranging from less than 1mg/kg to over 9 mg/kg.

Beryllium is also listed as information values in three coal fly ash materials (SRMs 2689, 2690, and 2691) as well as in SRM 1632c Bituminous Coal. The range of values is from about 1 mg/kg in the coal to 21 mg/kg in SRM 2689.

An information value of 5 μg/L is listed for beryllium in one of the series of toxic elements in urine SRMs (SRM 2670a).

Beryllium on Filter Media SRM (No Longer Available)

Beryllium on filter media was available at one time as SRM 2677a, but the certification of this SRM expired on 30 September 1999 and was not extended because the demand for these samples was low and the amount of laboratory effort to prepare the samples was high. SRM 2677a was intended primarily as an analytical standard for use in the determination of beryllium and arsenic in industrial atmospheres [15].

The filters were of the mixed cellulose ester type, and were 37 mm in diameter with a pore size of 0.8 μm. Each filter was prepared by depositing a 50 μL aliquot of an appropriate composite solution of Be and As onto the filter, followed by drying. The composite solutions were prepared gravimetrically by mixing together appropriate amounts of a standard beryllium

solution (prepared from high-purity Be metal) and a standard arsenic solution (prepared from SRM 83d, As_2O_3). In the preparation of the arsenic standard, As^{+3} was oxidized to As^{+5} with bromine and was expected to be present on the filters as the arsenate. The blank filters were prepared by adding a 50 μL aliquot of the dilute mixed acid (HNO_3 and H_2SO_4) solution to each filter.

SRM 2677a consisted of a set of ten membrane filters (two at each concentration level), packaged in five Petri dishes, with each Petri dish containing two (i.e., duplicate) filters from one of the following five ranges of concentrations (in micrograms per filter): Level I (0.129 ± 0.003 Be and 0.269 ± 0.006 As), Level II (0.643 ± 0.015 Be and 2.69 ± 0.065 As), Level III (2.58 ± 0.06 Be and 26.92 ± 0.65 As), Level IV (0.050 ± 0.001 Be and 0.101 ± 0.002 As), and Blank (≤ 0.0005 Be and ≤ 0.0005 As).

The certified values for SRM 2677a were based on gravimetric measurements made during the production of four stock solutions used to impregnate the filters and on measurements of the amount of stock solution deposited on the filters. The listed uncertainties were expressed as two standard deviations for a single filter, and included the uncertainties of the stock solutions used in the preparation of the filters.

The certificate for SRM 2677a noted that, in all instances, an entire filter must be dissolved for each set of measurements because the metals may not be uniformly distributed on the filter.

Insights and Examples from Non-Beryllium Reference Materials

Understanding the preparation methods used over the years by NIST for soils, dusts, and other materials gives an indication of the range of strategies that might be used to prepare new beryllium SRMs. There are both specific and general lessons to be learned. A general lesson is related to ensuring SRM homogeneity. For example, reference material preparation methods should be designed to ensure homogeneity of the material at whatever minimum aliquot size is required. For bulk materials like soils and sediments, the minimum sample size can be in the hundreds of milligrams range. However, when sampling schemes for real samples involve the wiping of surfaces, sample sizes can be in the microgram range, presenting a very difficult challenge to ensuring homogeneity of the reference material. Examples of historically important and relevant NIST SRMs are given below.

An Urban Particulate Matter SRM

Originally certified in 1978, SRM 1648 Urban Particulate Matter still sells at a rate of over 100 units (2 g of material per bottle) per year. This SRM was prepared from airborne ambient dust collected from the St. Louis area using a bag house specifically designed for the purpose. Collection took place over a period in excess of twelve months. The material was removed from the filter bags, combined into a single lot, screened through a fine-mesh sieve to remove extraneous materials, and thoroughly blended in a V-blender. In this case, the collected material was already in the same physical form as the intended sample.

A Lead Contamination Indoor Dust SRM

When the candidate reference material is mixed with other undesirable material, more extensive physical preparation steps are necessary. SRM 2584 is a dust material that was collected from interior living spaces. Approximately 65 % of the material was obtained from

households involved in lead poisoning intervention programs in which vacuum cleaners with high efficiency air filters were used to remove dust and other surface debris from homes where cases of lead poisoning had occurred. This material was mixed with low-lead-level material taken from conventional vacuum cleaner bags from households not identified as having a lead contamination problem. All dust bags and their contents were radiation-sterilized. The material from each bag was then mixed and tumbled in a modified food processor using chopping blades and a compressed air jet. While still tumbling, the dust was separated from unwanted debris by vacuuming through a series of screens into a clean HEPA vacuum cleaner. The dust collected in this manner was then screened through a 90 μm stainless steel sieve using vibration and a vacuum. Processed sub-lots of approximately 5 kg each were set aside and analyzed for lead by X-ray fluorescence in order to develop a blending protocol for the target lead concentration. Selected high- and low-level sub-lots were blended in a cone blender and then bottled.

Soils and Sediments SRMs

For candidate materials that are collected in bulk, a change in the physical form and particle size distribution, or both, is often necessary. For soils and sediments, extensive grinding, milling, and sieving may be required to prepare the material for blending. Effective homogenization requires a narrow particle size distribution; however, the material becomes less useful for bulk physical properties performance measures. For natural-matrix reference materials, the emphasis at NIST is usually on chemical composition, so most materials undergo extensive treatments to obtain homogeneous samples with small mean particle sizes.

For example, NIST and the U.S. Geological Survey (USGS) collaborated in 1992 to produce a series of three SRM soil materials: SRM 2709 San Joaquin Soil, SRM 2710 Montana Soil with highly elevated trace element concentrations, and SRM 2711 Montana Soil with moderately elevated trace element concentrations. Each of these materials is certified for over 25 elements, with information values for more than 30 elements and leachable concentrations using U.S. EPA Method 3050 for flame atomic absorption spectrometry (FAAS) and inductively coupled plasma optical emission spectrometry (ICP-OES). To ensure homogeneity at the 250 mg sample size, the material for these SRMs was subjected to a series of preparation steps, including gross physical separation from debris and pre-drying in an air oven and for three days at room temperature. The material was then passed over a vibrating 2 mm screen to remove plant material, rocks, and large chunks of aggregated soil. Material remaining on the screen was disaggregated and rescreened. The combined material passing the screen was ground in a ball mill to pass a 74 μm screen and blended for 24 h.

Biological Matrix SRMs

The concentrations of key elements in biological and botanical matrix SRMs are often so low that special techniques are needed to reduce the size of particles and narrow their size distribution while avoiding contamination from the preparation equipment. SRM 1566b Oyster Tissue is an example of such a material. This material was initially freeze-dried, broken into small pieces, and blended in a mixer with titanium blades. The final step took place in a jet mill specially designed for this purpose. The sample was entrained in two high-speed streams directed at each other so that the sample collided with itself, fracturing the particles without abrasion from foreign material.

Air Sampling or Wipe Sampling SRMs

Many environmental and industrial hygiene sampling protocols specify sampling using air filters or wipes. Over the years, NIST has investigated ways to deposit candidate material on filters and wipes with some success. SRM 2783 Air Particulate on Filter Media and SRM 2679a Quartz on Filter media were both prepared by suspending homogeneous particulate material in a liquid, depositing a measured amount on each filter blank, and carefully drying under clean conditions. The process is quite tedious, and the loaded filter must be handled very carefully. While binders could be used to improve the physical stability of these materials, they can introduce chemical matrix effects not encountered in real samples.

Steps for New Beryllium Reference Materials

Figure 3 illustrates the total life cycle process for reference materials. Necessary actions for preparing new reference materials include consensus on the desired chemical and physical forms of beryllium; market analyses of demand for the materials; identification of candidate industrial or laboratory-produced samples of the materials; selection of samples that meet criteria for uniformity, physical form, measured quantities, and continued availability; development of production protocols for collection and preparation of the materials, including adequate provisions for occupational health and environmental protection; incorporation of these materials into a supply, distribution, and cost-recovery infrastructure; and continued feedback and information sharing to ensure that the reference materials are meeting user needs or are modified as necessary. Issues for applying each of these steps to beryllium are discussed below.

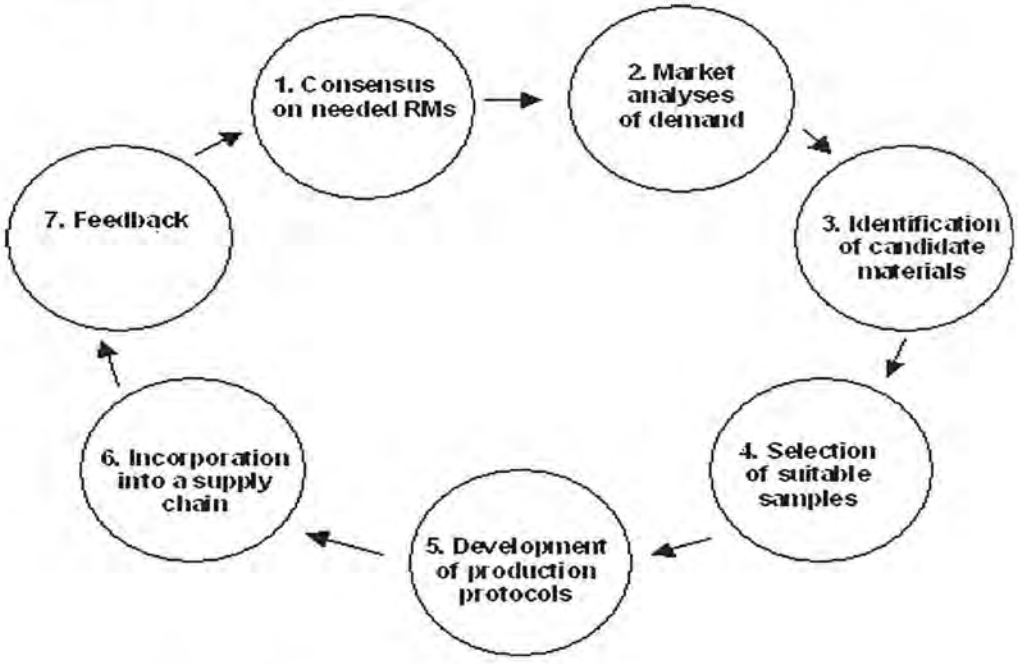

FIG. 3—*Overview of the integrated life cycle process for reference materials.*

Step 1: Consensus on Candidate Beryllium Reference Materials

As noted above, current beryllium SRMs are limited to standard spectroscopy solutions; blocks, chips, and rods of copper-beryllium alloy; and beryllium as a trace element in some standard soil-sludge, coal fly ash, and urine reference materials. Beryllium on filter media was available at one time, but is not currently available. It would be useful to have SRMs for beryllium-containing ores, beryllium oxide, beryllium metals, beryllium-containing alloys, and beryllium in biological samples. Continued dialogues involving the beryllium industry, regulatory, and research stakeholder communities are needed to develop and prioritize a complete list of candidate reference materials.

Step 2: Market Analyses of Demand

Decisions on which beryllium materials should be developed into reference materials first (or ever) are likely to be driven by two types of market analyses of demand for the materials, in combination with feasibility considerations for how, where, and by whom the reference materials will be made.

The first analysis involves simple economics: How quickly will projected revenues meet or exceed projected costs? In its normal decision making, NIST uses a cost-recovery formula by evenly dividing the costs of production over the number of SRM units that are expected to sell in five years. If the economics are favorable, the decision to proceed would simply require the expertise and input to complete all remaining steps of the reference material lifecycle process.

The second analysis disregards simple economics and focuses on what materials are needed to answer critical health and safety questions. Costs of producing and distributing the reference materials would most likely have to be underwritten by sponsoring agencies. In such cases, feasibility issues (how, where, by whom) would still be the final deciding factors.

Step 3: Identification of Candidate Materials

Identification of candidate industrial or laboratory-produced samples of beryllium materials has recently focused on two materials: well characterized powders of product type I-400 beryllium metal, which includes particles in the respirable size range, and well characterized powders of product type UOX-125 beryllium oxide, which consists of aggregates of 200 nm diameter primary particles. Additional information about these two candidate materials can be found in recent publications by Stefaniak et al. [16,17,18]. Additional discussion and research will be required to identify candidate materials of beryllium-containing ores; beryllium oxide in the form of larger, compact particles; beryllium-containing alloys, including copper, nickel, aluminum, and other materials; and beryllium in biological samples, including lung, skin, and other organs and tissues.

Step 4: Selection of Suitable Samples

Selection of samples that meet acceptable criteria for uniformity, physical form, measured quantities, and continued availability would be straightforward for the proposed beryllium metal and beryllium oxide materials. Type I-400 beryllium metal and type UOX-125 beryllium oxide are industrial products, have defined production pedigrees, have been extensively characterized (as noted above), and can be obtained in large quantities (i.e., more than tens of kilograms).

They can be size-separated in the laboratory using well established and published techniques [19].

Step 5: Development of the Production Protocol to Establish and Document the Pedigree of the Reference Material

Production protocols would specify precisely how the material would be prepared so that the pedigree of the material is appropriately established and documented. This would include the specification of the required measurands and the procedures for determining the measurands. Development of production protocols for collection, preparation, and characterization of the new beryllium reference materials would involve not only aerosol and materials science considerations, but also substantial attention to adequate provisions for occupational health and environmental protection. Original preparation of size-selected samples of the I-400 and UOX-125 beryllium materials was done in the 1980s and 1990s in projects sponsored by the U.S. Department of Energy (DOE) in the specialized and highly controlled inhalation toxicology research laboratories at Lovelace Respiratory Research Institute (LRRI) in Albuquerque, New Mexico. The beryllium aerosol facilities at LRRI have been decommissioned and the facilities have been turned to other uses. NIST has some capabilities for working with toxic materials, but does not currently have the capacity to undertake production of beryllium powder SRMs. Interagency discussions of how and where beryllium reference materials could be produced are underway among representatives of interested federal agencies including NIST, NIOSH, and DOE. The production options for new beryllium CRMs include the categories of Standard Reference Materials, NIST-traceable reference materials, or Other-Agency Reference Materials.

Once a candidate material has been accepted and its homogeneity assessed, the design of the certification program can be determined, keeping in mind the intended use of the material and the capabilities of the analytical methods. If the material were made and evaluated (for the most part) outside the primary NIST laboratories, it might have the attributes of a "Make-Your-Own" reference material as described in Fig. 2. For example, as is done currently, the specific surface area of the new beryllium reference material would be determined by comparison to existing NIST surface area SRMs (none of which are beryllium); the density of the beryllium reference material would be determined in comparison to non-beryllium reference materials; and the particle physical size would be determined from microscopy that is calibrated with non-beryllium materials. Properties such as crystalline structure would be determined by comparison to known beryllium references.

Note that, as with all materials, many of the measurands for beryllium reference materials can be experimentally determined by more than one technique. For example, beryllium particle solubility can be assessed in simulated lung fluid or in simulated phagolysosomal fluid, as well as by observation of dissolution behavior in beryllium-exposed laboratory animals. Similarly, particle "size" can be assessed by cascade impaction (aerodynamic diameter), by diffusion (thermodynamic diameter), by light-scattering, or by electrical mobility. These techniques are based on fundamentally different processes, requiring differing interpretation or leading to different results. When such information is communicated, in addition to any normally reported degree of confidence or data distribution that may be quoted, it will be critical to state the means by which the information was derived or determined.

Step 6: Incorporation into a Supply Chain

Incorporation of new beryllium reference materials into a supply, distribution, and cost-recovery infrastructure will require designation of a responsible organization or network of organizations. Preparation, packaging, and shipping could be done by an organization different from the organization responsible for listing the available materials, taking orders, and conducting billing.

Step 7: Feedback

Continued feedback and information sharing is critical to ensuring that the reference materials are meeting user needs or are modified as necessary. It is likely that applications of any new reference materials will contribute to a better understanding of the needs for other reference materials. In addition, the results of laboratory studies and field applications of the reference materials may increase the number and quality of the certified, reference, and information values for measurands of interest for these materials.

Conclusion

A number of opportunities exist for identification and development of new beryllium reference materials. Taking advantage of these opportunities will require multi-disciplinary and multi-organizational collaboration. Past experiences can be built upon and new relationships and capabilities can be conceived and implemented. Beryllium is not the only toxic material for which a broader spectrum of reference materials would be useful. Lessons from new initiatives in beryllium can inform our strategies for dealing with other toxic agents over a broad spectrum of organizational and disciplinary lines.

Acknowledgments

The authors gratefully acknowledge the many individuals presently or formerly at NIST who participated in the preparation, statistical assessment, certification, and issuance of the many SRMs described in this report, including T. A. Butler, T. C. Rains, T. A. Rush, L. L. Yu, L. J. Wood, and B. S. MacDonald.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute of Standards and Technology or the National Institute for Occupational Safety and Health.

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