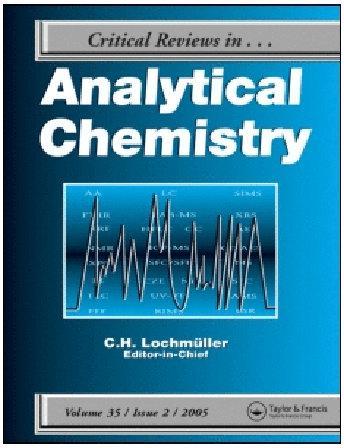

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THE ROLE OF REFERENCE MATERIALS AND REFERENCE METHODS IN CHEMICAL ANALYSIS*

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TABLE OF CONTENTS

I. INTRODUCTION

A. Scope and Purpose of the Review

The purpose of this paper is to provide a brief overview and review of the role of reference materials and reference methods in chemical analysis. Our primary concern is with the use of reference materials and reference methods in transferring accuracy and precision throughout large multilaboratory measurement networks. Although reference materials and reference methods can be effectively used to assure accuracy and precision within an individual laboratory, the great demand for compatible national measurement systems has led to their increased utilization in a total systems approach to accurate measurements in a variety of areas of chemical analysis. This paper first describes the concepts that provide the basis for the use of reference methods and reference materials to achieve measurement compatibility in multilaboratory networks. The basic concepts necessary to understand the measurement process itself are described. A conceptual systems model involving a hierarchy of reference materials and analytical methods which are utilized to transfer accuracy from a primary measurement standards laboratory into the field is presented. The basic philosophical and technical concepts underlying the systems approach to accurate measurement are evaluated and described without the use of detailed mathematical or statistical models. The role of federal laboratories, regulatory agencies, voluntary standards organizations, professional societies, and individual analytical laboratories is described in the context of a reference material-analytical method hierarchy. Criteria and guidelines that should be used for the selection and evaluation of reference materials and reference methods are reviewed. A comprehensive, technical evaluation of all the applications of reference materials and reference methods to chemical measurement systems is beyond the scope of any single review. However, some examples of recent applications of reference methods and materials are presented from the areas of industrial materials analysis (primarily metals), clinical analysis, and environmental analysis. Elemental analysis is emphasized. However, analogous conclusions can be drawn for other applications in chemical analysis. Some future needs for the development and utilization of reference materials and reference methods are presented. Also discussed is the growing need to establish mechanisms for achieving traceability of field measurements to primary reference materials and reference methods, and the role of federal laboratories, regulatory agencies, and commercial laboratories in helping to assure traceability.

B. Importance of Chemical Analysis

The last 75 years have seen a tremendous growth in both the variety and numbers of chemical analyses made in the U.S. At the turn of the century, the analytical chemist was largely concerned with elemental analysis of bulk constituents in important industrial materials (e.g., metals and ores) as well as agricultural chemicals such as fertilizers. Subdisciplines of analytical chemistry such as environmental and clinical analysis were yet to be formally established. Trace elemental analysis at the part per million level was virtually unknown as was quantitative organic trace analysis.[1] In the period 1900 to 1950, method sensitivity for the detection of most chemical constituents was improved from a level of several percent to the 0.01% level while at the same time, accuracy and precision requirements were also increasing.

In the last 25 years, the advent of rapid, highly sensitive, and precise instrumental techniques — many operating in a comparative mode — has contributed to a tremendous increase in the number of chemical measurements now being made each year in the U.S. In the area of clinical chemistry alone, the number of laboratory tests exceeded 5 billion in 1975 at a cost of nearly $9 billion.[2] Nearly 50% of such tests can be categorized as chemical analyses. In the area of industrial materials analysis, the number and variety of chemical tests has also grown dramatically as a myriad of important new materials have been introduced into the economy and more rigid trade specifications for such materials have required improved production quality control procedures.

To place an economic value on the contribution of chemical analyses to the U.S. economy would be exceedingly difficult. What is certain, however, is that chemical measurements result in considerable value added to goods being produced and thus make a substantial contribution to the gross national product (GNP) of the U.S. as well as the economies of other industrialized nations. Almost all materials in commerce today have been analyzed at least once in the progression from raw material to consumer product.

In the 1960s, R. D. Huntoon first enunciated the concept of the National Measurement System[3,4] and pointed out the critical role of measurement in the U.S. economy. In a more recent study, Seed and Pawlick[5] have estimated that in 1973, the U.S. GNP generated by measurement related activity, exceeded $70 billion in over 80 agricultural, mining, manufacturing, transportation, communications, and service-oriented economic categories. Because many of these categories are directly concerned with the production of raw materials and finished products — where the composition of a material must be rigidly controlled — chemical measurements make up a significant fraction of the value of the measurements being made each year. For example, the steel industry alone is estimated to perform more than one half billion chemical analyses each year, most of which are carried out by rapid spectrographic techniques at an average cost of approximately $2/measurement.[6]

Chemical analyses provide much of the basis for equitable treatment of producer and consumer in the commerce of raw materials and finished products and are critical to industrial quality control, as well as for assessing the performance and assuring the reliability of materials in service. They provide quantitative data on the composition and other important properties of materials. Reliable data are essential for effective communication among scientists from different laboratories and across language barriers. A strong argument could be made that chemical analyses directly provide the fundamental measurement basis for a large fraction of the world's economic output.

During the last decade, a number of sociopolitical events have resulted in an increased awareness of the importance of chemical measurements. This is particularly true in such areas as medical diagnosis[7] and environmental analysis,[8] where government regulations and/or voluntary action on the part of industrial organizations or professional societies have resulted in extensive use of chemical measurements for regulatory compliance as well as testing, monitoring, and laboratory (personnel) certification purposes. Analytical chemistry is also making vital contributions to many other areas such as food packaging,[9] forensic chemistry,[10] and art conservation.[11] Such uses of chemical analyses have placed equally rigid requirements on the quality of the measurements being made, particularly with respect to the precision and accuracy of individual measurements, as well as the proficiency of multilaboratory networks. Never before have so many critical decisions involving health, safety, and economics depended on the quality of chemical analytical data.

The importance of developing reliable analytical techniques as well as reference materials was also recognized in the early 1900s. At that time, the evaluation and standardization of chemical analytical methods had already started through the efforts of such organizations as the Association of Official Agricultural Chemists (the forerunner of the Association of Official Analytical Chemists, AOAC) and the American Society for Testing and Materials (ASTM). The latest reference manuals[12,13] published by these two organizations list hundreds of evaluated methods of chemical analysis for a wide variety of materials ranging from ores to pesticides. We will return to these and other standards organizations later in this paper. At approximately the same time as standard analytical methods were first being developed in the U.S., the National Bureau of Standards (NBS) was founded (in 1901). NBS first provided reference materials, then known as standard samples, in 1906. In 1911, NBS offered only 23 certified reference materials[14] In 1977, nearly 1000 Standard Reference Materials (SRMs) are offered for sale by NBS, with approximately 700 of these intended for use in chemical analysis.[15] Literally thousands of additional reference materials are available from other national laboratories,[16a-c] as well as commercial sources.[17a-c]

II. THE USE OF REFERENCE MATERIALS AND REFERENCE METHODS TO ACHIEVE MEASUREMENT COMPATIBILITY

A. Important Characteristics of the Analytical Measurement Process

Measurement processes have been studied extensively from both an experimental and a statistical point of view. Statistical quality control of industrial goods originated with the work of Shewhart[18] who introduced the concept of control charts over 50 years ago. In 1946, Wernimont[19] applied the use of control charts to chemical analysis. The tremendous post-World War II expansion of industrial and space-related technology led to an unprecedented demand for better measurement technology. In the period 1945 to 1965 many staff members of the NBS devoted considerable effort to the systematic evaluation of the critical statistical parameters that describe measurement processes, including precision, systematic error, and accuracy. Also developed were a number of important statistical concepts used in experimental design, interlaboratory testing, the description of functional relationships, and the evaluation of experimental data. NBS Special Publication 300[20] contains a collection of over 30 papers covering these topics along with an excellent set of general references on measurement science and statistics. Particularly relevant to chemical analysis are the following papers contained in this reference manual:

1. C. Eisenhart's two papers on precision and accuracy of instrument calibration systems, and the expression of the uncertainties of final results

2. A series of papers by W. J. Youden on uncertainties in calibration, instrumental drift, experimental design, and interlaboratory testing

3. M. A. Natrella's paper on planning of experiments

4. The paper by J. Mandel and T. W. Lashof on interlaboratory evaluation of test methods

5. The paper on accuracy in chemical

analysis using linear calibration curves by J. Mandel and F. J. Linnig.

(For further examination of these topics, References 21 to 25 are also recommended.)

Shewhart[26] enunicated the fundamental concept that all measurement processes consist of two operational aspects described as qualitative and quantitative. The quantitative aspect of measurement requires some type of scale, which is used to acquire an estimate of the numerical value of a property of a material such as the composition of a specific element. The qualitative aspect of measurement consists of a method or procedure for applying the scale to the property being measured. The end result of applying a method plus a scale is to arrive at a numerical value for the property under consideration by means of a measurement-property relationship.[22]

Our purpose here is not to present a detailed discussion involving the statistical analysis of experimental data, but rather to point out the key measurement concepts necessary to establish the validity of analytical data and, in particular, to establish accuracy on a national scale. An important goal of the work cited above is to develop measurement systems that will allow meaningful communication among different measurement stations over long periods of time and large geographical distances. This leads us to the concept of measurement compatibility. If measurements are to be useful in fostering meaningful economic or scientific communication between two or more parties, the different parties must agree on the results of the measurement and the meaning of the numbers associated with the measurement.[6,27,28] This agreement should take into consideration any imprecision and inaccuracies in the measurement process under consideration. Huntoon,[29] in an extension of his earlier work[3,4] defining the National Measurement System concept, has also cited the importance of measurement compatibility and described the general role of reference materials in achieving compatibility.

If a measurement process is to be meaningful, then the data obtained should be both precise and free of systematic error within agreed upon end-use requirements of uncertainty. In this paper, we define an accurate measurement to be both precise and free of systematic error. Accurate measurement systems are necessarily compatible. Additional requirements for measurement processes, such as wide dynamic range, high sensitivity, or rapid operation, might also be desirable. However, such requirements are not necessary in achieving accuracy but rather represent practical considerations. If a measurement system is accurate, the numerical value obtained for the properties being measured are "true values" within the uncertainties of the measurement processes being used.

The true value determined by measurement processes is referred to as the "quaesitum" by Dorsey and Eisenhart and extensively discussed in their paper on absolute measurements.[30] A pragmatic operational definition of the "true value" of a property is the value determined by precise measurement methods that are free of systematic error, i.e., an accurate method. Such values should ultimately be experimentally traceable to the base units of measurement such as mass, length, and time (see Section II.B.2.b).

B. Transferring Accuracy Throughout Large Measurement Networks

1. Different Mechanisms for Achieving Compatibility

There are a number of different ways to achieve measurement compatibility and transfer accuracy between two or more laboratories.[6,27-29] The most prevalent of these include the following.

a. Calibration Services

In this type of measurement system, a central (primary) standards laboratory such as NBS[31] calibrates instruments or other artifacts (e.g., gauge blocks) sent to it by other laboratories in the measurement network. The calibrated instruments are then returned for use as "secondary" standards. In this manner, a hierarchy of primary and secondary standards laboratories is established to transfer accuracy from the primary standards laboratory to a remote field installation. The calibration service mode of achieving measurement compatibility has proven to be particularly useful for transferring the accuracy of physical measurement parameters such as length, mass, volume, voltage, frequency, and magnetic field intensity.

b. Standard Reference Data

This mechanism for accuracy transfer utilizes critically evaluated data on the properties of well-characterized materials or systems. If the reference data are available together with well-characterized materials, preparation procedures, and measurement methods, the user can then reproduce the data directly or reproduce the original measurements. For example, temperature measurements can be made compatible through the use of reference data defining the melting point of pure substances. The purity of the material is very crucial in such an application. The Standard Reference Data program of the NBS was authorized by Congress[32] to coordinate the production and dissemination of critically evaluated physical and chemical reference data on a national scale. In cooperation with the American Physical Society and the American Chemical Society, this program publishes a Journal of Physical and Chemical Reference Data containing critical data compilations.

c. Standard Reference Signals

A very efficient mechanism for achieving interlaboratory measurement compatibility for such parameters as time or frequency is to use accurate, stable radio signals generated by a central source (e.g., the time signals generated by the NBS Radio Station WWV in Boulder, Colorado). The number of measurement parameters to be made compatible through this mode is obviously limited.

d. Reference Materials

A fourth way to achieve measurement compatibility is through the use of reference materials as transfer devices. In the context of measurement compatibility, a reference material is considered to be any material, device, or physical system for which definitive numerical values can be associated with specific properties and that is used to calibrate a measurement process. In this sense, the "reference material" could be a set of weights used for mass measurements, a chemical system that emits an accurate and reproducible amount of a substance (e.g., gas generators[33]), or a homogeneous, stable metal alloy containing, for example, a known amount of chromium. It is through the use of reference materials that compatibility in the field of chemical analysis can be most easily achieved, when the reference materials in turn are components of a fully integrated compatible measurement system, which utilizes accurate methods and good measurement quality control throughout.

e. Reference Methods

Reference methods provide an additional mechanism for achieving measurement compatibility. A reference method of analysis is a method that has had its accuracy rigorously demonstrated through experimental validation, as will be discussed later. Reference methods are being increasingly used in conjunction with reference materials to assure measurement compatibility, as will also be discussed later.

2. Definition of Terms and Concepts

Below are a series of definitions and brief descriptions of some terms and concepts to be used extensively in this paper. These terms will be used to describe an accuracy-based measurement system which represents a conceptual systems model for achieving compatibility of chemical measurements on a national scale. These terms are defined from the framework and according to current practices of the NBS and are definitions commonly accepted in the field of chemical analysis.

a. Reference Materials

Primary reference materials — The term reference materials is used to describe a generic class of well-characterized, stable, homogeneous materials, produced in quantity and having one or more physical or chemical properties experimentally determined within stated measurement uncertainties. Primary reference materials are reference materials having properties certified by a recognized national standards laboratory or standards agency such as the NBS in the U.S. or the National Physical Laboratory in England. Primary reference materials are certified using the most accurate and reliable measurement techniques available consistent with end-use requirements. International standards organizations such as the International Union of Pure and Applied Chemistry (IUPAC) and the International Standards Organization (ISO) have recommended the use of the term "Certified Reference Material" along with the abbreviation CRM to describe primary reference materials. Thus, in the U.S., Standard Reference Materials (SRMs) are certified primary reference materials produced by the NBS. In this paper, the terms primary reference materials and SRM will be used interchangeably.

Secondary reference materials — The distinction between primary and secondary reference materials is somewhat arbitrary and is best made in terms of end use. Secondary reference materials are generally considered to be those produced by commercial organizations or by individual laboratories for direct use as working standards. The working standards may then be used to assess small changes[34] in analytical procedures on a daily basis. In many cases, the secondary reference materials are directly related to SRMs or other primary reference materials. For example, NBS issues SRMs for use in clinical analysis, e.g. cholesterol, uric acid, and glucose. These are highly pure materials generally issued in crystalline or solid form. Many commercial medical-materials suppliers use NBS SRMs as primary calibration standards to control the production of secondary reference materials in which the constituent of interest is present in a serum matrix. The College of American Pathologists (CAP) also produces secondary reference materials for use in laboratory survey programs. A paper by Hanson[35] describes the relationship of the CAP reference solutions to NBS SRMs.

A primary reference material is normally produced by a national standards laboratory or other organization having legal authority to issue such materials. Primary reference materials are generally produced in much smaller quantities and have much more rigorous certification requirements than secondary reference materials of a similar nature. Secondary reference materials are usually developed for use in high-volume day-to-day field operations where low operating cost and moderate accuracy are important considerations. Primary reference materials are intended for use where accuracy is the most important requirement, regardless of cost. At NBS, SRMs are certified using definitive methods of analysis whenever possible (see Section c. below) and in many cases, also provide the accuracy basis for the development of reference methods described in Section d., below.

b. Basic Measurements Units

Anyone who has had the misfortune to be simultaneously enrolled in two different courses in physics and/or chemistry in which two distinct systems of measurements units were used realizes the confusion that occurs in attempting to communicate simultaneously in two separate scientific languages. In principle, as long as both systems of units provide self-consistent measurement scales, they can be accurately related to each other through exact physico-chemical equations. In practice, scientific communication will be considerably more effective if everyone is utilizing the same system of measurement units. Most of the nations of the world have now agreed to use the system of units referred to as the "Systeme International d'Unites" or the "International System of Units" abbreviated as SI and usually referred to as the "Metric System." The U.S. will be gradually converting to the SI units for general use during the next decade. The SI system of units has been the overwhelming choice of most analytical chemists for decades.

The SI system of units includes the seven base units: mass, length, time, electric current, thermodynamic temperature, luminous intensity, and the amount of substance, i.e., the mole. Using the basic equations of physics, one may describe the approximately 50 derived units (e.g., volume, density, frequency, and viscosity) in terms of the base units.[36] The derived units, together with the base units, form the basis for the other experimental measurement parameters which are normally determined in physics and chemistry laboratories (e.g., absorbance, nuclear cross-section, spectral intensity, pH, etc.). It is not always possible to relate the experimentally determined parameters to the basic units without the use of extensive approximations or inexact equations. These approximations may lead to large uncertainties in the determination of the experimental parameters through the introduction of systematic errors.

c. Definitive Methods

Dorsey and Eisenhart in their classic paper on absolute measurements[30] state the following:

> By an absolute measurement of a physical quantity, such as the velocity of light, is meant the determination of the value of that quantity in terms of the significant fundamental units of length, mass, time, etc., and of those constant parameters that characterize the accepted system of theoretical equations that connect the several pertinent quantities.

Analogously, in the field of chemical analysis, an absolute measurement of a chemical property such as composition is generally made by a method (either instrumental or manual in nature) in which the property in question is either directly evaluated in terms of the fundamental units of measurement or indirectly related to the base units via exact mathematical equations. Many of the chemical methods of analysis based on such techniques as gravimetry or coulometry fall within this definition.

Definitive methods of chemical analysis are those that have a valid and well-described theoretical foundation, have been experimentally evaluated so that reported results have negligible systematic errors, and have high levels of precision. Such methods, with high reliability, give "true values" and are thus the chemical analogues of the absolute physical methods described by Dorsey and Eisenhart. They are the most accurate methods available to measure a given chemical property. The term definitive method was first used by Young[37] in the sense described here while applying some of these measurement compatibility concepts to the field of clinical analysis.

Definitive methods provide the fundamental basis for accuracy in chemical analysis. Such methods usually require highly skilled personnel and are time-consuming as well as expensive to perform. Thus, they are generally uneconomical for field use. Two excellent examples illustrating the development of definitive methods are reviewed by Cali and Reed.[38] These two definitive methods are the determination of calcium in serum by isotope dilution mass spectrometry (IDMS) developed by Moore and Machlan[39] and the determination of the combustion energy of benzoic acid in terms of electrical units developed by Churney and Armstrong.[40] The application of the IDMS definitive method to the determination of Pb, U, Th, T, and Ta in NBS Trace Element Glass SRMs is described by Barnes et al.[41]

In the case of the IDMS method for trace inorganic analysis, one relates the concentration of unknown samples directly to the actual weights of spike solutions and the isotopic atomic fraction of the spike and unknown sample as measured by mass spectrometry, using the following equation:[38]

$$\text{Concentration of sample (wt)} = \frac{W_{sp}\,C[A_{sp} - RB_{sp}]}{BR - A} \cdot \frac{M}{W_s}$$

where

W_{sp} = Weight of spike solution, grams
C = Concentration of spike, μmol/g of solution
A_{sp} = Atomic fraction of isotope A in spike
B_{sp} = Atomic fraction of isotope B in spike
A = Atomic fraction of isotope A in sample
B = Atomic fraction of isotope B in sample
R = Experimentally measured ratio of A/B in sample
M = Atomic weight of analyte
W_s = Weight of sample, grams

In terms of accuracy, the power of the IDMS technique results from the fact that chemical manipulations are carried out on a direct weight basis and the mass spectrometric determinations involve isotopic ratios rather than absolute isotopic determinations, obviating the need for instrumental corrections. Thus, systematic errors are essentially eliminated. This technique automatically and directly results in determination of experimental parameters in terms of base units of measurement.

The small measurement uncertainty obtainable by this technique is illustrated by the measurement of trace uranium in the glass SRM cited above. The relative uncertainty of the IDMS measurements was less than 0.25% for U concentrations in the range of 0.8 to 460 μg/g and only 1.8% at a U concentration of 0.07 μg/g. In this case, the uncertainties included method imprecision, possible unknown systematic error, and material variability. When available, definitive methods are preferred by NBS to certify SRMs.

d. Reference Methods

Cali et al.[6,28] have defined a reference method to be "a method of proven and demonstrated accuracy." The accuracy of the reference method should be demonstrated[38] by direct comparison with a definitive method or with a primary reference material as is described in Section III.B. The term reference method of analysis has come into extensive use since the development of the first reference method for analysis of Ca in blood serum.[42] Some, but not all, of the analytical methods commonly referred to by such terms as standard method, unique method, official method, or referee method (see for example References 12 and 13) may be properly described as reference methods in terms of the above definition and criteria to be discussed in Section III.B.

Reference methods are one of the key components of a chemical measurement system and represent the primary mechanism for transferring the accuracy of a definitive method or an SRM into widespread use in the field. Since reference methods, like definitive methods, may also be moderately sophisticated, they may not always be acceptable for routine field use where time and cost are important considerations. Like SRMs, and in many cases in association with SRMs, reference methods can be used to develop and/or assess field methods, evaluate secondary reference materials, and control the accuracy of quality assurance procedures.

e. Field Methods

The term field method denotes any method of chemical analysis used in an application requiring large numbers of individual measurements to be made on a routine basis. In modern analytical laboratories, such measurements are usually made by a technician using automated instrument systems capable of producing highly precise (but not necessarily accurate) data. Many of these instruments utilize comparative methods and thus require the use of reference materials to correct for systematic biases inherent in the technique. Examples of field methods are the multielement X-ray fluorescence spectrometers commonly used in industrial quality control laboratories and the multianalysis automated spectroscopic analyzers used in many clinical laboratories.

f. Traceability

Traceability is a term that is coming into increased usage at the present time, especially in the regulatory area. Basically, traceability implies the assurance of the transfer of accuracy and/or precision from one to another of the above-named components of measurement systems. For example, a field method should be demonstrated to be traceable to a reference method and a reference method demonstrated to be traceable to a definitive method. The exact requirements and procedures necessary to insure traceability depend on the specific problem being addressed. A number of traceability protocols are currently being developed, primarily resulting from the needs of regulatory agencies. Some of these will be described later. Each laboratory or organization going from one level to the next in the measurement hierarchy is expected to be able to demonstrate the traceability of its measurements back to the next higher level. The development of well-defined traceability protocols which will assure proper transfer of accuracy may be a necessary, if not always simple, procedure. A recent workshop has discussed the development of traceability protocols for gas analyses to meet environmental regulations.[43]

3. The Systems Approach to Measurement Compatibility

a. The Measurement Method/Reference Material Hierarchy

A great deal has been written about the need for a "systems" approach to achieve compatible measurements on a national (or international) scale. Many of the previously cited references discuss in great depth the various systems concepts for achieving measurement compatibility. Cali[44,45] and other members of the NBS staff[6,28,38] have applied these concepts, particularly to the areas of clinical analysis and trace chemical analysis. As far as chemical analysis is concerned, the systems approach to compatible measurement can be best described in terms of six necessary technical components of an accuracy-based measurement system. These components which were defined in the previous section are:

1. Basic measurement units
2. Definitive measurement methods
3. Primary reference materials
4. Reference measurement methods
5. Secondary reference materials
6. Field methods

To properly utilize those distinct, readily identifiable components of chemical measurement systems, there is also an essential need for adequate intralaboratory (internal), and interlaboratory (external) quality assurance procedures. The relationships between each of the components in this idealized accuracy-based measurement network are schematically shown in Figure 1.

Figure 1 represents a hierarchial system of analytical methods and reference materials each coupled to the other in the manner shown. The function of each component (I to VI) is to transfer accuracy to the level immediately below it and to provide traceability to the level immediately above it, thus assuring measurement compatibility in the overall system. This schematic represents an idealized system which, however, closely approximates a number of operative systems in the U.S. As we proceed from top to bottom, accuracy requirements diminish at the expense of increased measurement efficiency. In such a system, a typical field method accuracy requirement of 5 to 10%

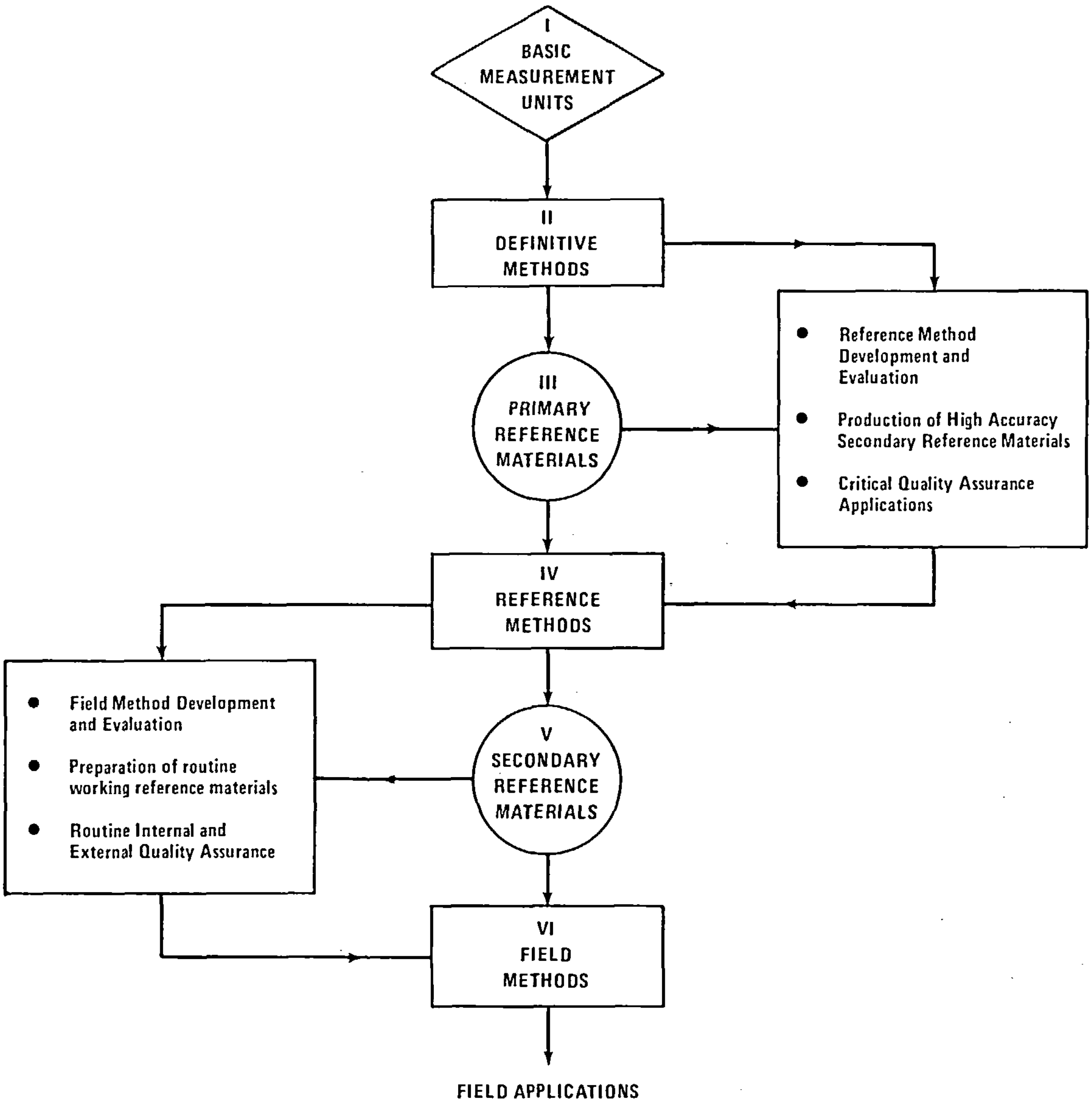


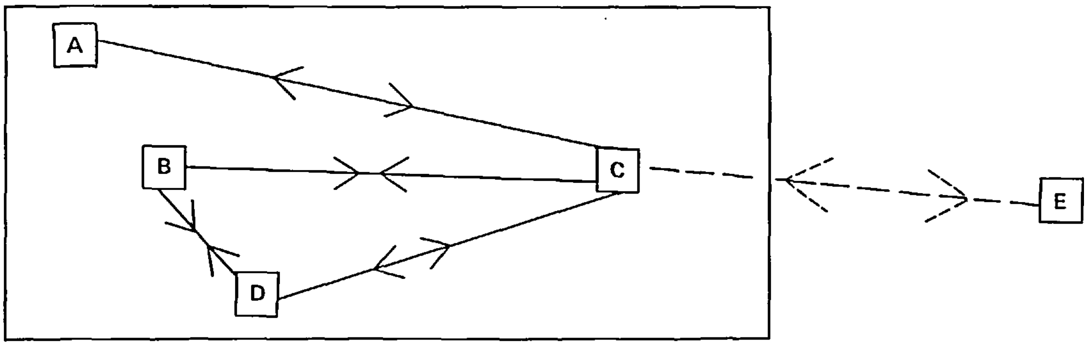
FIGURE 1. Schematic illustrating the relationship among the different technical components of an "idealized" accuracy-based chemical measurement system.

would require the accuracy of reference method to be in the range of 1 to 3%. The definitive method and primary reference material should then have accuracies in the 0.1 to 1.0% range.

b. Use of Precision Alone

In principle, reference materials and "standardized" methods can be used to achieve measurement compatibility on the basis of precision alone[27] if all laboratories in a network use identical measurement methods and reference materials. This is schematically illustrated in Figure 2. All laboratories (A through D) within the network are using the same methods and reference materials. The laboratories within the network (A through D) may use homogeneous reference materials and analytical methods having inherent systematic errors but good precision and still agree on the results of these measurements. Buyer-seller transactions and exchange of scientific data can be meaningful providing the transactions occur among laboratories A through D. However, if one of the laboratories has to compare results with a laboratory outside the network (e.g., C with E),

- All laboratories (A–D), in universe using same methods and reference materials



- Hence, compatibility within immediate universe of users

- What happens when "C" attempts to communicate with "E" who is using different methods and reference materials?

FIGURE 2. Schematic illustrating how measurement compatibility may be achieved by use of precision alone in closed laboratory networks.

and the outside laboratory is using a different measurement method and/or reference material, then measurement compatibility may be difficult or impossible to achieve. The problem of measurement incompatibility can usually be overcome by the use of accuracy-based measurement systems in which all measurement methods and reference materials in use throughout the network are rigorously characterized in terms of accuracy. Systematic errors are either eliminated or adjustments are made to correct for such errors.

c. The Need for Measurement Quality Assurance

Although not explicitly shown as a unique component of the measurement system illustrated in Figure 1, experience has shown that formal quality assurance procedures are necessary if accuracy is to be maintained in measurement systems over long periods of time. There are two fundamentally distinct but equally important types of formal measurement quality assurance procedures used to establish or maintain precision and accuracy in chemical measurement networks. The first is commonly referred to as intralaboratory (internal) quality assurance (IQA), whereby each individual laboratory maintains a formal set of experimental and statistical protocols designed to establish and maintain the precision and/or accuracy of its own measurement processes. Such quality assurance programs usually involve the use of control charts and reference samples used as controls together with statistical models for interpretation of data as is described by Shewhart[18] and Wernimont.[19] A recent special symposium on the validation of the measurement process at the April (1976) meeting of the American Chemical Society (ACS) in New York City presented a series of papers by G. Wernimont, R. C. Rhodes, J. J. Filliben, and S. Denning, which will be published as a Special ACS Monograph.[25] The papers treat such topics as statistical control, ruggedness tests, sampling errors, interlaboratory testing, and their application to chemical analysis. The point to be stressed here is that, unless carefully and continuously monitored, measurement processes tend to get out of statistical control, i.e., they lose their predictability. Without statistical control of measurement processes in individual laboratories, reference methods and reference materials may be of little value in establishing and maintaining accuracy in multilaboratory networks.

Although each individual laboratory must ultimately be responsible for its own measurement assurance, there are a number of formal external mechanisms designed to aid laboratories with respect to long-term quality assurance. These have been established by various government agencies, professional societies and standards organizations. These are usually referred to as interlaboratory (external) quality assurance programs (EQA). In EQA programs, the sponsoring organization usually provides a set of uniform well-characterized test specimens or reference materials to a large number of participating laboratories to be measured as unknowns. The participating laboratories analyze the test specimens and submit the data to the sponsor for detailed analysis. The sponsor then supplies each laboratory with quantitative statistical data such as:

1. The precision and/or accuracy of the method used by the participating laboratory
2. The precision and/or accuracy of the data obtained by the other participating laboratories using the same method
3. The precision and/or accuracy of the alternative types of methods used to measure the same properties
4. Usually some statement concerning the acceptability of the individual laboratory results, when compared to group averages

Examples of large interlaboratory quality assurance programs are those sponsored by such organizations as the College of American Pathologists[46] and the U.S. Environmental Protection Agency.[47] The existence of definitive methods, reference methods, and SRMs provides a convenient and reliable mechanism for establishing the accuracy of test specimens used in such quality assurance programs.[44,48]

The measurement method/reference-materials hierarchy illustrated in Figure 1 is designed to provide what Cali[28,38] has called "a systems approach to accurate measurement," whereby the accuracy of measurements in the field can be rigorously established and ultimately traced to definitive methods of analysis, which in turn are experimentally evaluated in terms of the uncertainties inherent in determining the base units of measurement. Several points should be stressed. Standard Reference Materials and reference methods play an important role in transferring accuracy from a central standards laboratory into the field. However, these two components by themselves are not sufficient to assure accuracy throughout the total system. The measurement chain illustrated in Figure 1 is only as strong as its weakest link. High quality secondary reference materials, reliable field methods, as well as good internal and external quality assurance programs are also necessary to assure accuracy of the overall system. It is the ultimate responsibility of individual chemists and laboratory managers to assure that the measurements being made in his or her laboratory are effectively coupled into the various technical components of the total measurement system. This raises the issue of the role of the various private-sector and government organizations which make up the organizational components of a measurement system and what they can do to assist individual field laboratories in achieving accuracy.

d. The Role of Public and Private-Sector Organizations

If the operation of most private and government organizations in the area of measurement standards in the U.S. were to be described by one word, it would be voluntary. With few exceptions (such as the regulation of basic weights and measures by state government agencies), the development of material and product specifications, standardized analytical methods, and reference materials is carried out in the U.S. under a so-called "Voluntary Standards System."[49] In general, material specifications and measurement methods achieve legal status or are made mandatory only when incorporated into contracts between producer and consumer. This mode of operation of measurement systems in the U.S. is quite different from that of other nations where the use of specifications, analytical methods, or even reference materials may be mandated by law. Only in recent years have measurement-system requirements been made mandatory in the U.S. as a result of legislation such as that aimed at controlling environmental pollution, improving the operation of clinical laboratories, or assuring the safety of consumer products. Thus, federal agencies such as the Environmental Protection Agency, the Food and Drug Administration, the Center for Disease Control, the Consumer Product Safety Commission, and the Department of Transportation have currently legislated responsibilities for assuring the reliability of measurements in areas central to their regulatory missions. Numerous examples could be cited of the establishment of rules and regulations that involve chemical analysis and require use of specified analytical methods.[50-52] Regulatory agencies have recently started to require the use of SRMs (or secondary reference materials traceable to SRMs) together with standardized analytical methods.[53] Pending legislation before Congress[54] could add further to regulatory requirements for chemical measurement systems.

In spite of the recent trend toward increased

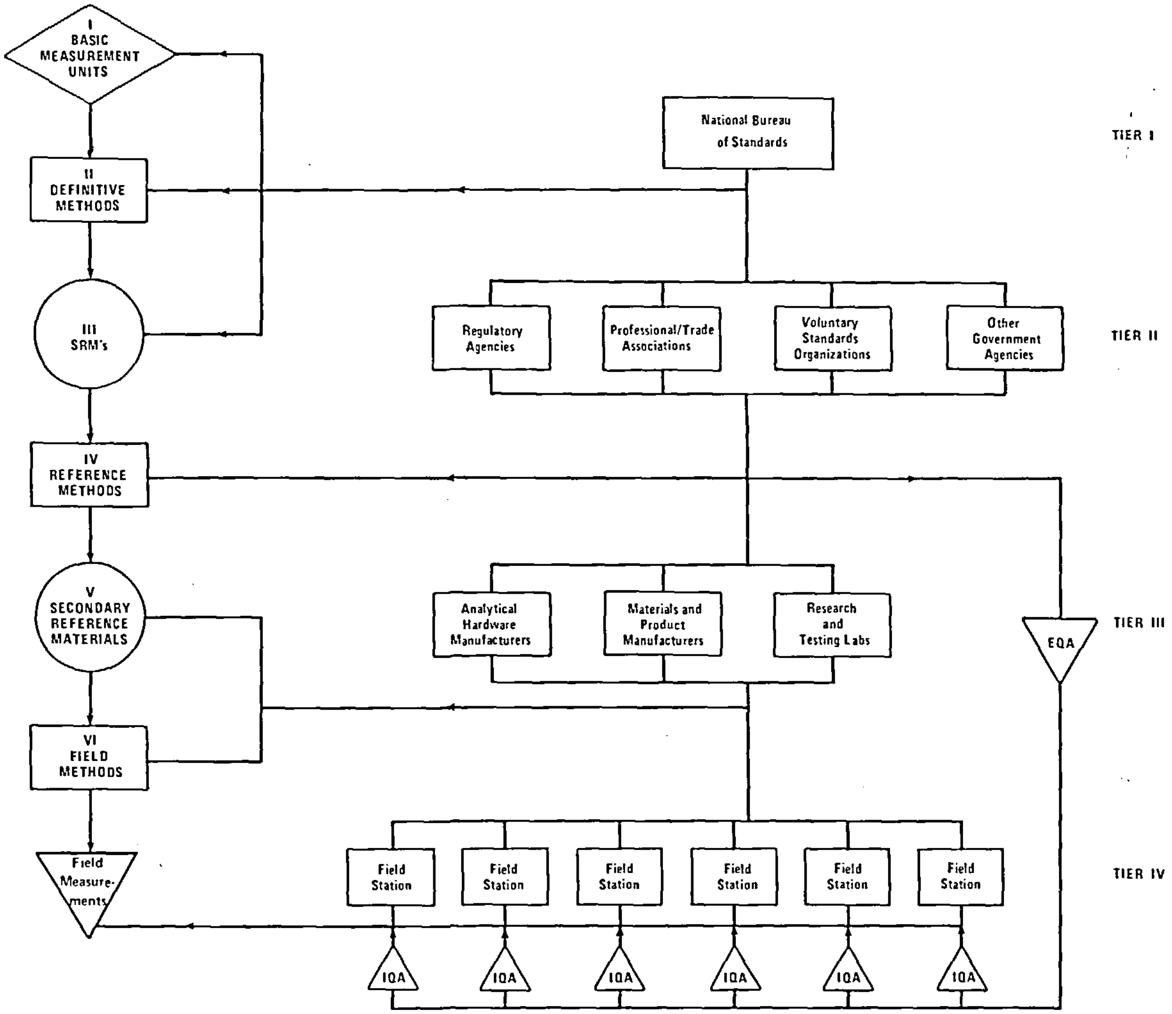


FIGURE 3. Schematic illustrating the relationships between the various organizational and technical components of an idealized accuracy-based measurement system.

regulation, the measurement standards process in the U.S. is still basically voluntary in nature and dependent on the cooperation of numerous government agencies, standards organizations, trade associations, and professional societies. A recent NBS publication[55] lists nearly 600 private and government organizations involved in some area of measurement standards development or promulgation. Many of these organizations are involved in some phase of standardization related to chemical analysis or in the development of materials and product specifications or codes requiring the measurement of chemical properties. The many interactions between the various organizations participating in one or more phases of a measurement system are too numerous and complex to describe in any comprehensive way. Here, we attempt to draw some general conclusions with respect to the role of various public and private organizations vis-à-vis with the accuracy based measurement network described in Figure 1.

Figure 3 is a schematic illustration describing the different types of organizations making up a typical chemical measurement system in the U.S. Depending on the specific analytical application, the technical and organizational components of the measurement system will vary. Not all components of the system may be necessary to promulgate accuracy for all measurement applications. However, Figure 3 is believed to be a reasonable representation of a typical chemical measurement system. The major coupling points of each organizational component to the various functional components of the measurement system described in Figure 1 are also shown. The role of each organization can be described in terms of a four-tiered organizational hierarchy.

Tier I – primary standards laboratory – Tier I consists of the primary standards laboratory, which is the NBS for most of the chemical measurements made in the U.S. In some countries, the primary standards laboratory is represented by a network of government-owned or government-sanctioned laboratories reporting to a central office such as the National Board for Quality Control and Measures of Poland or the State Committee on Standards of the Soviet Union. In the U.S., a major function of NBS as the primary standards laboratory is to develop the three most fundamental components of the chemical measurement systems: basic units of measurement, definitive methods of analysis, and primary reference materials. NBS also cooperates with Tier II organizations in the development of reference methods. The Tier II organizations have the major responsibility for reference-method development and evaluation. Thus, reference methods represent a major mechanism for transferring the accuracy of the definitive chemical measurements performed at the NBS to the measurements made by the thousands of individual laboratories within the U.S.

Tier II – regulatory and voluntary standards bodies – Depending on the specific application, the second tier consists of a consortium of organizations such as government regulatory agencies, professional or trade associations, and voluntary standards groups. For example, in the area of chemical analysis of steels, organizations such as the American Society for Testing Materials (ASTM), the American Iron and Steel Institute, the Steel Founders Society of America, and the Office of Pipeline Safety (Department of Transportation) are all involved in the development of specifications for metallurgical products. The specifications might require the use of "standardized" test methods and reference materials. In the field of clinical analysis, Tier II organizations consist of such groups as the Center for Disease Control, the Food and Drug Administration, the College of American Pathologists, the American Association of Clinical Chemists, and the National Committee for Clinical Laboratory Standards (NCCLS). The trade associations, professional societies, and government agencies in Tier II are either directly responsible for developing reference methods of chemical analysis or work within voluntary standards organizations such as ASTM or NCCLS to develop and promulgate such methods. Tier II organizations represent the prime organizational interface between NBS and individual field laboratories or companies. In a few cases, Tier II organizations also produce secondary reference materials which may be used for compliance monitoring, interlaboratory quality assurance, or be provided directly to field laboratories for use in internal quality assurance. Individual companies and chemical testing laboratories are extensively represented on the committees of the voluntary standards organizations. Thus, Tier II organizations also obtain information from the field and thus provide considerable feedback to NBS concerning field measurement problems.

Tier III – individual companies or research laboratories – Tier III consists of three separate subgroups. First are the instrument manufacturers, chemical supply houses, and related commercial organizations acting as individual entities. This subgroup is responsible for the development of the vast majority of analytical instrumentation as well as the production of most of the secondary reference materials used as working standards. This subgroup represents, in part, the major "hardware" suppliers in the field of chemical analysis.

The second subgroup in Tier III consists of the producers and manufacturers of the tens of thousands of different materials and products that are produced in our industrialized economy. These companies represent the major users of the analytical hardware produced by other organizations in Tier III. This group also depends on Tier II organizations to help develop standardized analytical methods as well as material and product specifications.

The third subgroup in Tier III consists of individual research laboratories such as those at nonprofit institutions or universities and also commercial testing laboratories. These organizations are also involved in the development of analytical hardware and software as well as development of materials and products. In many cases, these organizations serve as subcontractors of the other organizations in Tier III. They also serve as referees to resolve measurement disputes which sometimes arise between other Tier III organizations.

Tier IV – individual field measurement

stations – This tier consists of the tens of thousands of individual measurement stations making literally billions of chemical measurements per year. For example, depending on the measurements being made, Tier IV might consist of individual clinical laboratories, individual air pollution monitoring stations, or possibly the dozens of individual quality control measurement stations within a single steel company. These field laboratories depend on Tier III organizations for the majority of their analytical hardware needs (and on occasion to referee measurement disputes) and depend on Tier II organizations for some software needs (e.g., reference methods and external quality assurance). Many of these laboratories directly utilize the SRMs and information on methods provided by NBS as part of their internal quality assurance programs. Thus, one sees that Figure 3 represents an integrated, self-consistent system. In principle, such a system could serve to assure both compatibility of measurements within the U.S. and traceability of measurements back to the definitive methods and SRMs developed by the NBS.

III. CRITERIA FOR THE DEVELOPMENT AND EVALUATION OF REFERENCE MATERIALS AND REFERENCE METHODS

A. Reference Materials

In this section, we discuss the most important factors that must be considered in the selection and evaluation of reference materials used in chemical analysis. Generalizations are difficult to make because each reference material presents a unique set of requirements with respect to such factors as accuracy, form, or stability. A detailed discussion on the preparation and evaluation of SRMs appears elsewhere[6,56,57] Here, we identify some of the most important requirements and criteria which are taken into consideration at NBS during the development of SRMs. These should be considered minimum requirements necessary for the establishment of guidelines for development and evaluation of primary reference materials. Similar considerations should also be taken into account in the development of secondary reference materials. However, depending on the application, technical requirements for secondary reference materials may be much less rigid.

1. End-use Requirements

The first consideration is to assess the technical requirements that will dictate the end use of the reference material. End use will largely govern the establishment of important certification requirements such as accuracy, stability or homogeneity, as well as determine the final form of the SRM (e.g., chip, solid, or solution). The most accurately certified, stable, homogeneous reference material that technology can produce would be of limited value if the material is not delivered in a form consistent with end-use requirements.

2. General Certification Requirements

At NBS, there is a legal aspect of the SRM certification process. NBS SRMs carry the full weight and authority of NBS and the U.S. Department of Commerce as they are specifically authorized by federal legislation. However, more important are the technical aspects of the certification process which necessarily involves the concepts of "accuracy" and "uncertainty" of the values determined for the properties being certified.

If at all possible, NBS attempts to certify all SRMs used for chemical analysis on the basis of accuracy. Thus, a certified value is the present, best estimate of the "true" value. The certified value is not expected to deviate from the "true" value by more than the stated measurement uncertainty. The stated uncertainty of the value of a property must take into account any systematic errors and imprecision inherent in the measurement process as well as any material variability. Three principal measurement modes are used for certification at NBS. In order of preference, they are

1. Measurement at NBS by a definitive method, as defined previously, usually performed by two or more analysts working independently; frequently, an accurately characterized backup method is employed to provide additional assurance that the data are correct
2. Measurement at NBS by two or more independent reference methods having small estimated inaccuracies relative to the end-use certification requirement
3. Measurement by a qualified network of laboratories using both methods of proven accuracy and existing SRMs as controls. This mode is frequently used for renewal of compositional SRMs. When high accuracy is the goal, the

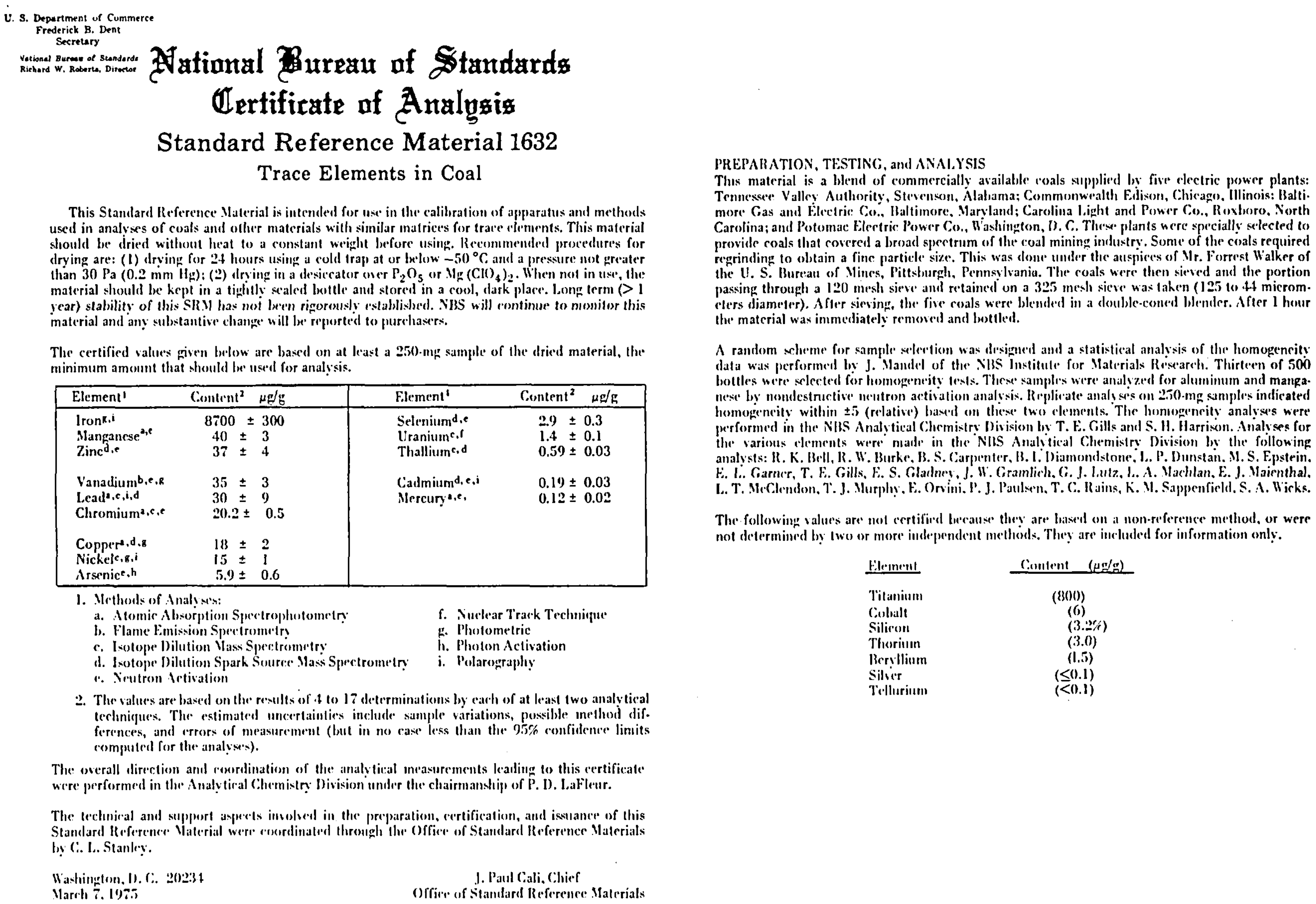
consensus approach to certifying reference materials should be implemented with extreme caution. The mean value of the results of a large number of laboratories may not necessarily represent an accurate value even when between laboratory and within laboratory imprecisions are small.

The rigid measurement certification criteria utilized by NBS have been found to result in high accuracy and reliability of certified data. The adherence to such criteria necessarily results in high costs and a lengthy certification process that may take months (or years) to complete. For example, a typical multielement trace compositional SRM might involve certification using a dozen different reference methods and/or definitive methods as well as several dozen analysts. Many trade-offs must be made between achieving high accuracy as opposed to minimizing certification time and costs. Since NBS SRMs serve as primary reference materials, an accuracy three to ten times greater than the end-use requirements must generally be attained even though the resulting SRMs may be costly. (U.S. Government policy requires all NBS SRM production costs to be recovered through sales.) In many cases, secondary reference materials may not have such stringent accuracy requirements. Thus, costs of producing secondary reference materials may be reduced through using less rigorous measurement certification criteria. Every case must be considered on its own merits.

Figures 4, 5a, and 5b are copies of two typical certificates for trace element compositional SRMs (for analysis of coal and unalloyed copper) recently issued by NBS. These certificates illustrate the different measurement modes used for certification at NBS. For all certified values, the stated measurement uncertainty includes method imprecision, method biases, and material variability. The stated uncertainties take into account the subjective judgment of the analysts as well as the results of statistical analysis. The judgment of the analyst is particularly important in evaluating systematic errors. In cases where the values obtained by networks of cooperating laboratories or by analysts using different methods cannot be reconciled, the values cannot be certified. Such values might be given for informational purposes but are clearly segregated and identified as such on the certificate. For example, the data contained in the Copper SRM certificate (page 2) are recommended values.

3. Material Variability

Considerable time and money would be wasted if analytical certification measurements were made on candidate reference materials which were later found to be inhomogeneous with respect to the properties of interest. The homogeneity of a material is a measure of the spatial variation of the value of the property in question, e.g., the variation of the composition of an element as a function of distance along a solid rod or between containers of a gas or liquid. A material is homogeneous with respect to a specific property if the measured value of that property in a specimen of minimum size (or weight) is identical, within end-use measurement uncertainty requirements, to the measured value of that property in another portion of the material of the same minimum size. The end use uncertainty requirements should include the measurement method imprecision and systematic error as well as material variability. It is absolutely essential that carefully designed experimental and statistical procedures be used to assess homogeneity of a material before certification experiments begin. The establishment of homogeneity is particularly important for metallic and other solid materials. Beeghley et al.[57] point out that homogeneity requirements may differ dramatically depending on end use. For chemical methods of analysis, homogeneity at about the 0.1 to 0.5-g level is normally required. For techniques such as electron microprobe and mass spectrometry, homogeneity at the 1-μm level is desired but may be difficult to achieve in practice. Fortunately, the homogeneity of materials is usually relatively easy to establish once an adequate statistical sampling plan has been designed. Only relative measurements using precise rather than accurate techniques are normally required. Thus, highly precise rapid instrumental methods such as X-ray fluorescence or neutron activation analysis can be employed to evaluate material variability without having to be concerned with the evaluation of systematic errors. A series of NBS publications[58-63] describe the considerable effort expended on the evaluation of SRM homogeneity for a series of metal-alloy reference materials. The information contained on the two certificates in Figures 4 and 5 indicates that these particular SRMs are homogeneous to within the



U. S. Department of Commerce
Frederick B. Dent
Secretary

National Bureau of Standards
Richard W. Roberts, Director

National Bureau of Standards
Certificate of Analysis
Standard Reference Material 1632
Trace Elements in Coal

This Standard Reference Material is intended for use in the calibration of apparatus and methods used in analyses of coals and other materials with similar matrices for trace elements. This material should be dried without heat to a constant weight before using. Recommended procedures for drying are: (1) drying for 24 hours using a cold trap at or below −50 °C and a pressure not greater than 30 Pa (0.2 mm Hg); (2) drying in a desiccator over P_2O_5 or $Mg(ClO_4)_2$. When not in use, the material should be kept in a tightly sealed bottle and stored in a cool, dark place. Long term (> 1 *year) stability of this SRM has not been rigorously established. NBS will continue to monitor this* material and any substantive change will be reported to purchasers.

The certified values given below are based on at least a 250-mg sample of the dried material, the minimum amount that should be used for analysis.

Element[1]	Content[2] µg/g	Element[1]	Content[2] µg/g
Iron[g,i]	8700 ± 300	Selenium[d,e]	2.9 ± 0.3
Manganese[a,e]	40 ± 3	Uranium[c,f]	1.4 ± 0.1
Zinc[d,e]	37 ± 4	Thallium[c,d]	0.59 ± 0.03
Vanadium[b,e,g]	35 ± 3	Cadmium[d,e,i]	0.19 ± 0.03
Lead[a,c,i,d]	30 ± 9	Mercury[a,e,]	0.12 ± 0.02
Chromium[a,c,e]	20.2 ± 0.5		
Copper[a,d,g]	18 ± 2		
Nickel[c,g,i]	15 ± 1		
Arsenic[e,h]	5.9 ± 0.6		

1. Methods of Analyses:
   - a. Atomic Absorption Spectrophotometry
   - b. Flame Emission Spectrometry
   - c. Isotope Dilution Mass Spectrometry
   - d. Isotope Dilution Spark Source Mass Spectrometry
   - e. Neutron Activation
   - f. Nuclear Track Technique
   - g. Photometric
   - h. Photon Activation
   - i. Polarography
2. The values are based on the results of 4 to 17 determinations by each of at least two analytical techniques. The estimated uncertainties include sample variations, possible method differences, and errors of measurement (but in no case less than the 95% confidence limits computed for the analyses).

The overall direction and coordination of the analytical measurements leading to this certificate were performed in the Analytical Chemistry Division under the chairmanship of P. D. LaFleur.

The technical and support aspects involved in the preparation, certification, and issuance of this Standard Reference Material were coordinated through the Office of Standard Reference Materials by C. L. Stanley.

Washington, D. C. 20234
March 7, 1975

J. Paul Cali, Chief
Office of Standard Reference Materials

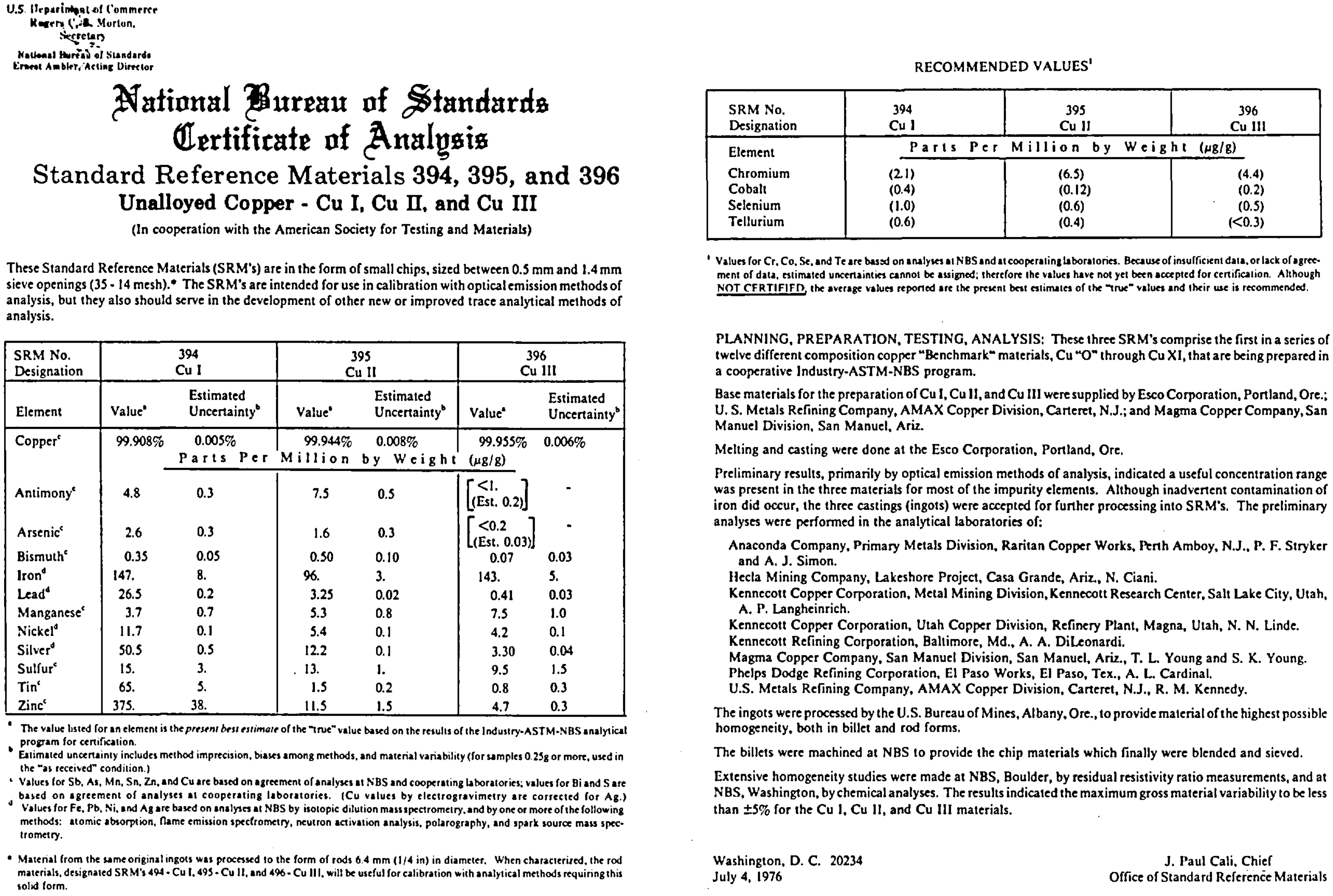
PREPARATION, TESTING, and ANALYSIS
This material is a blend of commercially available coals supplied by five electric power plants: Tennessee Valley Authority, Stevenson, Alabama; Commonwealth Edison, Chicago, Illinois; Baltimore Gas and Electric Co., Baltimore, Maryland; Carolina Light and Power Co., Roxboro, North Carolina; and Potomac Electric Power Co., Washington, D. C. These plants were specially selected to provide coals that covered a broad spectrum of the coal mining industry. Some of the coals required regrinding to obtain a fine particle size. This was done under the auspices of Mr. Forrest Walker of the U. S. Bureau of Mines, Pittsburgh, Pennsylvania. The coals were then sieved and the portion passing through a 120 mesh sieve and retained on a 325 mesh sieve was taken (125 to 44 micrometers diameter). After sieving, the five coals were blended in a double-coned blender. After 1 hour the material was immediately removed and bottled.

A random scheme for sample selection was designed and a statistical analysis of the homogeneity data was performed by J. Mandel of the NBS Institute for Materials Research. Thirteen of 500 bottles were selected for homogeneity tests. These samples were analyzed for aluminum and manganese by nondestructive neutron activation analysis. Replicate analyses on 250-mg samples indicated homogeneity within ±5 (relative) based on these two elements. The homogeneity analyses were performed in the NBS Analytical Chemistry Division by T. E. Gills and S. H. Harrison. Analyses for the various elements were made in the NBS Analytical Chemistry Division by the following analysts: R. K. Bell, R. W. Burke, B. S. Carpenter, B. I. Diamondstone, L. P. Dunstan, M. S. Epstein, E. L. Garner, T. E. Gills, E. S. Gladney, J. W. Gramlich, G. J. Lutz, L. A. Machlan, E. J. Maienthal, L. T. McClendon, T. J. Murphy, E. Orvini, P. J. Paulsen, T. C. Rains, K. M. Sappenfield, S. A. Wicks.

The following values are not certified because they are based on a non-reference method, or were not determined by two or more independent methods. They are included for information only.

Element	Content (µg/g)
Titanium	(800)
Cobalt	(6)
Silicon	(3.2%)
Thorium	(3.0)
Beryllium	(1.5)
Silver	(≤0.1)
Tellurium	(<0.1)

FIGURE 4. Copy of the certificate for the NBS Trace Element in Coal SRM.



U.S. Department of Commerce
Rogers C. B. Morton,
Secretary
National Bureau of Standards
Ernest Ambler, Acting Director

National Bureau of Standards Certificate of Analysis

Standard Reference Materials 394, 395, and 396

Unalloyed Copper - Cu I, Cu II, and Cu III

(In cooperation with the American Society for Testing and Materials)

These Standard Reference Materials (SRM's) are in the form of small chips, sized between 0.5 mm and 1.4 mm sieve openings (35 - 14 mesh).[e] The SRM's are intended for use in calibration with optical emission methods of analysis, but they also should serve in the development of other new or improved trace analytical methods of analysis.

SRM No. Designation	394 Cu I		395 Cu II		396 Cu III	
Element	Value[a]	Estimated Uncertainty[b]	Value[a]	Estimated Uncertainty[b]	Value[a]	Estimated Uncertainty[b]
Copper[c]	99.908%	0.005%	99.944%	0.008%	99.955%	0.006%
	Parts Per Million by Weight ($\mu g/g$)					
Antimony[c]	4.8	0.3	7.5	0.5	[<1. (Est. 0.2)]	-
Arsenic[c]	2.6	0.3	1.6	0.3	[<0.2 (Est. 0.03)]	-
Bismuth[c]	0.35	0.05	0.50	0.10	0.07	0.03
Iron[d]	147.	8.	96.	3.	143.	5.
Lead[d]	26.5	0.2	3.25	0.02	0.41	0.03
Manganese[c]	3.7	0.7	5.3	0.8	7.5	1.0
Nickel[d]	11.7	0.1	5.4	0.1	4.2	0.1
Silver[d]	50.5	0.5	12.2	0.1	3.30	0.04
Sulfur[c]	15.	3.	13.	1.	9.5	1.5
Tin[c]	65.	5.	1.5	0.2	0.8	0.3
Zinc[c]	375.	38.	11.5	1.5	4.7	0.3

[a] The value listed for an element is the *present best estimate* of the "true" value based on the results of the Industry-ASTM-NBS analytical program for certification.

[b] Estimated uncertainty includes method imprecision, biases among methods, and material variability (for samples 0.25g or more, used in the "as received" condition.)

[c] Values for Sb, As, Mn, Sn, Zn, and Cu are based on agreement of analyses at NBS and cooperating laboratories; values for Bi and S are based on agreement of analyses at cooperating laboratories. (Cu values by electrogravimetry are corrected for Ag.)

[d] Values for Fe, Pb, Ni, and Ag are based on analyses at NBS by isotopic dilution mass spectrometry, and by one or more of the following methods: atomic absorption, flame emission spectrometry, neutron activation analysis, polarography, and spark source mass spectrometry.

[e] Material from the same original ingots was processed to the form of rods 6.4 mm (1/4 in) in diameter. When characterized, the rod materials, designated SRM's 494 - Cu I, 495 - Cu II, and 496 - Cu III, will be useful for calibration with analytical methods requiring this solid form.

RECOMMENDED VALUES[1]

SRM No. Designation	394 Cu I	395 Cu II	396 Cu III
Element	Parts Per Million by Weight ($\mu g/g$)		
Chromium	(2.1)	(6.5)	(4.4)
Cobalt	(0.4)	(0.12)	(0.2)
Selenium	(1.0)	(0.6)	(0.5)
Tellurium	(0.6)	(0.4)	(<0.3)

[1] Values for Cr, Co, Se, and Te are based on analyses at NBS and at cooperating laboratories. Because of insufficient data, or lack of agreement of data, estimated uncertainties cannot be assigned; therefore the values have not yet been accepted for certification. Although NOT CERTIFIED, the average values reported are the present best estimates of the "true" values and their use is recommended.

PLANNING, PREPARATION, TESTING, ANALYSIS: These three SRM's comprise the first in a series of twelve different composition copper "Benchmark" materials, Cu "O" through Cu XI, that are being prepared in a cooperative Industry-ASTM-NBS program.

Base materials for the preparation of Cu I, Cu II, and Cu III were supplied by Esco Corporation, Portland, Ore.; U. S. Metals Refining Company, AMAX Copper Division, Carteret, N.J.; and Magma Copper Company, San Manuel Division, San Manuel, Ariz.

Melting and casting were done at the Esco Corporation, Portland, Ore.

Preliminary results, primarily by optical emission methods of analysis, indicated a useful concentration range was present in the three materials for most of the impurity elements. Although inadvertent contamination of iron did occur, the three castings (ingots) were accepted for further processing into SRM's. The preliminary analyses were performed in the analytical laboratories of:

Anaconda Company, Primary Metals Division, Raritan Copper Works, Perth Amboy, N.J., P. F. Stryker and A. J. Simon.
Hecla Mining Company, Lakeshore Project, Casa Grande, Ariz., N. Ciani.
Kennecott Copper Corporation, Metal Mining Division, Kennecott Research Center, Salt Lake City, Utah, A. P. Langheinrich.
Kennecott Copper Corporation, Utah Copper Division, Refinery Plant, Magna, Utah, N. N. Linde.
Kennecott Refining Corporation, Baltimore, Md., A. A. DiLeonardi.
Magma Copper Company, San Manuel Division, San Manuel, Ariz., T. L. Young and S. K. Young.
Phelps Dodge Refining Corporation, El Paso Works, El Paso, Tex., A. L. Cardinal.
U.S. Metals Refining Company, AMAX Copper Division, Carteret, N.J., R. M. Kennedy.

The ingots were processed by the U.S. Bureau of Mines, Albany, Ore., to provide material of the highest possible homogeneity, both in billet and rod forms.

The billets were machined at NBS to provide the chip materials which finally were blended and sieved.

Extensive homogeneity studies were made at NBS, Boulder, by residual resistivity ratio measurements, and at NBS, Washington, by chemical analyses. The results indicated the maximum gross material variability to be less than ±5% for the Cu I, Cu II, and Cu III materials.

Washington, D. C. 20234
July 4, 1976

J. Paul Cali, Chief
Office of Standard Reference Materials

A

FIGURE 5. Copy of the certificate for the NBS Copper Benchmark SRMs, CuI–CuIII.

Chemical analyses for certification were made on composite samples representative of the entire lot for each material.

Cooperative analyses were performed in the following analytical laboratories:

Anaconda American Brass Company, Research and Technical Center, Waterbury, Conn., J. T. McCrackan and V. M. Horrigan.
Bridgeport Brass Company, Bridgeport, Conn., A. W. Young.
Carpenter Technology Corporation, Research and Development Center, Reading, Pa., C. T. Polinko.
International Nickel Company of Canada, Limited, J. Roy Gordon Research Laboratory, Sheridan Park, Mississauga, Ontario, Canada, St. J. H. Blakeley.
Kennecott Copper Corporation, Metal Mining Division, Kennecott Research Center, Salt Lake City, Utah, A. P. Langheinrich.
Kennecott Copper Corporation, Utah Copper Division, Refinery Plant, Magna, Utah, N. N. Linde.
Kennecott Refining Corporation, Baltimore, Md., A. A. DiLeonardi.
National Research Council of Canada, Division of Chemistry, Ottawa, Canada, D. S. Russell.
Phelps Dodge, Copper Products Company, Elizabeth, N.J., J. R. Conniff.
Phelps Dodge Refining Corporation, El Paso Works, El Paso, Tex., A. L. Cardinal.
Phelps Dodge Refining Corporation, Laurel Hill Works, Maspeth, N.Y., W. D. Charles and R. Kretschmann.
Revere Copper and Brass Incorporated, Rome, N.Y., S. Glessner.
Scovill, Metals Division, Waterbury, Conn., E. D. Wade.
Southwire Company, Copper Division, Carrollton, Ga., G. S. Bowers.

Analyses were performed in the NBS Analytical Chemistry Division by the following: I. L. Barnes, D. A. Becker, R. K. Bell, R. W. Burke, B. I. Diamondstone, L. P. Dunstan, M. S. Epstein, E. L. Garner, T. E. Gills, J. W. Gramlich, E. F. Heald, L. A. Machlan, E. J. Maienthal, T. J. Murphy, P. J. Paulsen, T. C. Rains, T. A. Rush, and M. J. Seward.

The overall direction and coordination of the preparation and fabrication aspects for these materials were performed initially by R. P. Reed, M. B. Kasen, and J. G. Hust, with the latter assuming full responsibility for the project (NBS, Boulder, Colo.).

The overall coordination of the NBS analytical measurements leading to certification was under the direction of I. L. Barnes.

The technical and support aspects involved in the preparation, certification, and issuance of these Standard Reference Materials were coordinated through the Office of Standard Reference Materials by R. E. Michaelis.

ADDITIONAL INFORMATION: Details concerning the planning, preparation, testing, and analysis of these copper "Benchmark" materials are to be published in an NBS Special Publication (260 Series). Information that should be of immediate interest to the user laboratories follows:

Analysts should use the chip materials in the "as received" condition.

Some surface oxidation (discoloration) is present on the chip materials, but the amount is not analytically significant for the elements certified. The analyst should keep the container tightly capped when not in use.

To achieve a compatible measurement system, the analyst is expected to use the certified (or recommended) value listed for an element irrespective of the estimated uncertainty associated with that value. If the certified value should change for any reason, such as new or improved methodology, analysts should be able to calibrate accordingly and on a unified basis.

Elements other than those certified or recommended may be present in these materials as indicated below. These are *not certified* but are given as additional information on the composition.

SRM No. Designation	Cu I 394	Cu II 395	Cu III 396
	Parts per Million by Weight (ug/g)		
Elements Detected			
Oxygen	(230)	(435)	(270)
Cadmium	(0.5)	(0.4)	(0.6)
Gold	(0.07)	(.13)	(<0.05)
Magnesium	(<0.1)	(<0.1)	(<0.1)
Elements not Detected (Conservative "upper limits")			
Aluminum	(<0.2)	(<0.2)	(<0.2)
Calcium	(<0.1)	(<0.1)	(<0.1)
Silicon	(<0.3)	(<0.3)	(<0.3)
Titanium	(<0.3)	(<0.3)	(<0.3)

FIGURE 5B

stated limits for 250-mg samples. Thus, these SRMs should be useful for chemical methods of analysis as well as some spectrochemical techniques.

4. *Material Stability*

The ideal primary reference material is physically and chemically stable for an indefinite period of time. The certifying agency should establish the stability of the material and include any critical information concerning long-term stability or special storage requirements on the certificate. If a reference material is not stable over time, its use for applications involving long-term internal or external quality control of measurement systems could be considerably limited. For example, the certificate for the Trace Element in Coal SRM (Figure 4) indicates that the stability of this material beyond 1 year has not been established, but is being monitored by NBS. The user of the unalloyed copper SRM is warned of possible surface oxidation if the container is not kept tightly capped. Reference-material users must pay strict attention to such requirements to assure proper utilization if long-term accuracy is to be maintained. Secondary reference materials may have much less rigid stability requirements, especially when used in short-term quality assurance applications.

5. *Physical Form*

The physical form of the material is also dictated mainly by end-use requirements.[57] For example, metal SRMs intended to be used with optical emission or X-ray spectrochemical techniques are usually supplied in solid disk form. Since many of the rapid instrumental methods such as X-ray fluorescence are subject to interferences (i.e., "matrix effects"), the SRM matrix should be similar to that of normal test specimens being analyzed by such techniques. Mathematical models have been developed[64] to correct for matrix effects, but care must be taken in selecting the form and composition of any reference materials used in such applications. The degree to which a reference material may be used to establish accuracy or compatibility depends on how closely it corresponds to the specimens being analyzed.

Taylor[65] has proposed a classification system for reference materials based on the similarity of the reference material to specimens being analyzed. We recommend classifying SRMs and secondary reference materials according to four different categories similar to those proposed by Taylor as follows.

Matrix reference materials – Matrix reference materials are essentially identical to the actual samples being measured. The coal and unalloyed copper SRMs in Figures 4 and 5 represent examples of matrix SRMs, provided they are used in applications involving the analysis of coal and refined copper products. For many industrial materials such as steels or refractories, an extremely close correspondence between reference material and test specimen can usually be achieved. This may not be the case in other areas such as environmental or clinical analysis where the "real world" specimens may be exceedingly complex and variable. Thus, the actual properties of test specimens may be difficult to reproduce or duplicate in a reference material.

Simulated reference materials – Simulated reference materials are those having properties close to the test specimens and are used to simulate analytical problems in the field. An example of a simulated SRM is the trace element in water standard now under preparation at NBS. This SRM will contain over 15 different trace elements in a fresh-water matrix. It is being prepared by spiking distilled water with trace elements and, thus, will only simulate rather than duplicate fresh-water samples collected in the field.

Synthetic reference materials – Synthetic reference materials are those that require the user to perform some type of operation to transform the material to a more appropriate form before use. This introduces the possibility of added uncertainties beyond those inherent in the reference material certification or the measurement method being used. The SO_2 and NO_2 permeation-tube SRMs provided by NBS (SRMs 1625 through 1627, 1629) for use in air pollution analysis fall within this category. In the case of permeation-tube SRMs, the user is required to maintain stringent temperature controls and an accurate gas flow system to synthesize a reliable gas mixture that is in turn used to establish reference values. The paper by Hughes[66] describes the precautions that must be taken in preparing and using permeation tubes and other gas mixture SRMs.

Surrogate reference materials – Surrogate reference materials are those having little or no correspondence with actual test specimens, except that they may contain some constituent of mutual interest. An example of a surrogate SRM would be a metal matrix SRM used to standardize or evaluate methods for determining trace elements in blood serum or human tissue. In principle, this can be accomplished[67,68] as long as one takes into account the limitations imposed by use of the surrogate material. One must be able to transform the surrogate SRM to a form whereby the matrix effects are eliminated or minimized and the accuracy of the standard is maintained. The additional chemical manipulations inherently result in additional uncertainties being brought into the measurement process.

6. Publication of Reference Material Utilization Software

Huntoon[29] stresses the importance of supplying adequate "how to" software along with any reference material to help assure proper utilization. Any information that is critical to the proper utilization of the reference material should obviously be contained on the certificate of analysis. For example, the Trace Element in Coal SRM certificate (Figure 4) contains recommended procedures to assure proper sample drying before use. In many cases, detailed information concerning material preparation, homogeneity testing, or measurement certification procedures may also prove to be extremely helpful to users involved in a particularly critical experiment such as the evaluation of the accuracy or precision of "state-of-the-art" methods. To aid in such critical applications, NBS has devoted a special series of monographs (denoted as the NBS 260 Series) which are intended to provide the users of particular classes of SRMs with detailed information on development and certification procedures, as well as comprehensive information on such subjects as homogeneity and stability testing. References 69 through 96 list the NBS 260 Special Publications which are particularly relevant to chemical analysis, in addition to those cited previously. These particular monographs only cover a limited number of areas of chemical analysis in which SRMs are currently being used. We are aware of very few analogous publications describing reference materials produced by other organizations, although the need for such documentation has been recognized by producers of primary reference materials in a number of countries. Producers of reference materials should aim to increase the number and scope of such reference documents in the future. In critical applications of primary reference materials in particular, the documentation describing the preparation and evaluation of the material may prove to be as important as the reference material itself.

Table 1 summarizes the major differences between primary and secondary reference materials in terms of selection and evaluation criteria. The major end uses of primary and secondary reference materials are also given. Some examples illustrating these uses are given in Section IV.

B. Reference Methods

1. Accuracy Requirements

In this section, we discuss the most important factors to be considered in the selection and evaluation of reference methods for chemical analysis. We should point out that the term reference method is currently used in various contexts by a number of different standards organizations or government agencies. As will be shown in Section IV, many of the so-called reference methods may not meet the criteria to be discussed here, and thus, should probably be denoted by other terms, such as standardized methods or compliance methods, in order to eliminate unnecessary confusion.

In Section II, a reference method was defined as a method that provides accurate numerical values of the property being measured, with the accuracy being rigorously demonstrated by direct experimental comparison with a definitive method or a primary reference material. If the accuracy of a method has not been rigorously demonstrated, it should not be considered as a reference method. The requirement of demonstrated accuracy is of major importance if a reference method is to perform its major function – that of transferring accuracy from definitive methods and primary reference materials to secondary reference materials and field methods as illustrated in Figures 1 and 3. Only recently has it been formally recognized that reference methods may be effectively used to transfer accuracy. They are rapidly

TABLE 1

Comparison of Primary and Secondary Reference Materials

	Primary reference materials	Secondary reference materials
Producer	Usually a national standards laboratory or other organization having legal authorization	Commercial manufacturers, professional societies, trade associations, etc; attain legal status when incorporated into contracts
Preferred mode of certification	1. Definitive method using two independent analysts; 2. two or more independent reference methods; 3. measurement by qualified laboratory network using previously issued primary reference materials as controls	At least one highly reliable reference method
Quantity produced	10^2 to 10^3 units for most applications in chemical analysis; 6–10 year supply providing stability is no problem	Might be produced at the rate of about 10^3-10^6 per year when used in routine quality assurance applications
Accuracy requirements	Highest attainable accuracy consistent with economic constraints and end-use requirements; strive for a factor of 3 to 10 better accuracy than end-use requirement	Should be factor of 3 to 10 higher accuracy than field use requirements; for some applications, accurate certification not necessary
Homogeneity and physical form	Depends on end-use requirements	Depends on end-use requirements
Stability	Preferably as long as possible; minimum of 1–2 years should be guaranteed	Might be as short as a few weeks if materials are used immediately
Major end-use	Development/evaluation of reference methods Development of secondary reference materials Critical field applications where high accuracy is major requirement	Development/evaluation of field methods Day-to-day intralaboratory quality assurance, e,g., analytical controls Interlaboratory quality assurance and proficiency testing
Cost to user (typical reference material)	\$50–\$300	\$1–\$100

increasing in both their number and their applicability. The criteria given below have been developed over the past several years and have been found to be sufficient for a range of application areas.

In many cases, such as within a closed measurement network illustrated in Figure 2, the distinction between a reference method and a standardized method will be found to be of no particular consequence. As long as all members of the closed measurement network are using identical measurement methods (and reference materials) and are never required to communicate outside of their network, measurement compatibility can be achieved even though the measurement methods may have an inherent bias or systematic error. As long as all measurement stations achieve the same bias, all stations will agree on the results of their measurements and can carry out business in a rational manner. If they are working in a buyer-seller framework, a price structure for a commodity can still be established in an "equitable manner" even if the transaction involves a different quantity of material than measured by the buyer and seller. The price is agreed upon and the quantity is mutually measured to be the same value by the two parties. However, such a closed measurement system is rare. Even if one were to exist for a limited period of time, the introduction of new measurement technology or such factors as regulatory requirements would inevitably lead to disputes that could not be resolved without introducing accuracy into the system.

In principle, the accuracy of a reference method can be established on the basis of first principles, such as is done with definitive methods (Section II.B.2.c). However, a more practical approach to verifying the accuracy of a reference method is by direct comparison with primary reference materials or definitive methods through interlaboratory testing by highly qualified laboratories.

The demonstration of accuracy by a single laboratory could be sufficient. However, in practice, evaluation of the method by a series of laboratories provides a better characterization of the overall uncertainty of the method because information on between laboratory precision (reproducibility) as well as within laboratory precision (repeatability) is obtained. This also permits the evaluation of the reference method in a variety of experimental situations within different laboratories and with different operators. In this manner, documentation is improved and procedural errors are identified and eliminated. Experience has shown that a careful review of the method procedure documentation is required before an analyst who is unfamiliar with the method can obtain accurate results. Examples of reference methods being evaluated in this manner within the field of clinical chemistry will be discussed in Section IV of this paper. Many of the ASTM measurement methods can also be considered reference methods according to these criteria and are also discussed later. In these cases, the validation of the reference method has been accomplished by both of the modes described above. A direct comparison is being made with definitive methods in the case of a series of clinical reference methods under development. In the case of many of the ASTM methods, evaluations have been based on comparison with primary reference materials.

2. *Demonstration of Accuracy*

A recent paper by Cali and Reed[38] describes five major steps involved in the establishment of the accuracy of a reference method. With minor variations, the following basic procedure is the one used for most reference methods developed to this time:

1. Establish the accuracy goal of the method, or alternatively, the limit of the inaccuracy to be allowed from the "true value." Rather than aiming for the highest achievable accuracy, the goal should be established on the basis of end-use requirements such as cost, ease of performance, and application. Typically, the accuracy goal of the reference method is set at least a factor of three higher than dictated by end-use requirements. An interlaboratory test protocol is then designed so that the accuracy of the candidate reference method can be verified through appropriate statistical analysis. The protocol must consider such factors as the number of collaborating laboratories, the number and type of materials to be sent to each collaborator, and the number and sequence of measurements to be made by each collaborator.[97] Ultimately, the accuracy (and precision) of the method will be verified through statistical analysis and, thus, the statistical design of the test protocol is critical.[98]

2. Choose the candidate method which when demonstrated to produce accurate results,

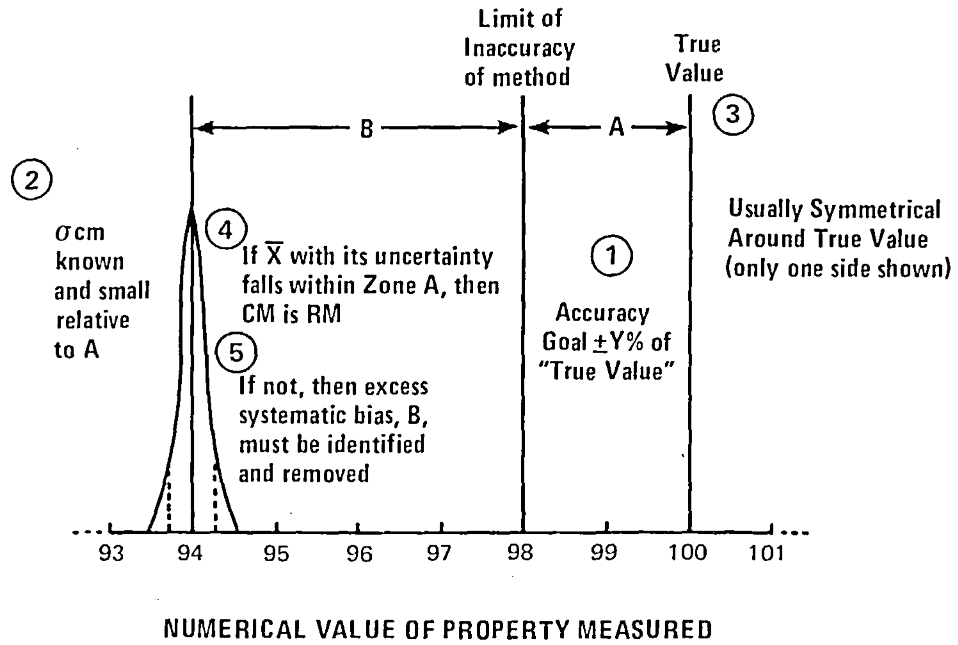


FIGURE 6. Demonstrating the accuracy of a reference method. (See text for meaning of circled numbers.) (From Cali, J. P. and Reed, W. P., The Role of National Bureau of Standards SRM's in Accurate Trace Analysis, National Bureau of Standards, Special Publication, No. 422, U.S. Government Printing Office, Washington, D.C.)

becomes the reference method. If possible, the candidate method should be one that has been previously evaluated in terms of both precision and systematic error and should inherently be one of high precision. The detailed measurement protocol should clearly describe the experimental procedures as well as the statistical design considerations.

3. Determine the "true value" of the property under consideration in a homogeneous, stable lot of material similar to the matrix, which would normally be analyzed by the reference method. This may be accomplished through comparison with values obtained by a definitive method or, alternatively, a series of primary matrix reference materials may be used for this purpose. If available, the use of existing primary reference materials is preferred because of time and cost savings. However, for this particular application, the primary reference material must be a matrix reference material as defined previously.

4. Determine the numerical value of the property under study by using the candidate method protocol (i.e., the step-by-step experimental and statistical procedure) together with the samples in Step 3. The statistical procedures incorporated into the protocol are used to calculate a mean value, $\bar{x}$, from the data obtained by the participating laboratories. If the precision of the method is known or demonstrated to be small relative to any systematic error, the deviation of $\bar{x}$ from the true value is a measure of the bias of the candidate method. If this bias is less than the reference method accuracy goal, then the candidate method becomes the reference method.

5. If the systematic error is greater than required by the reference method goal, further study of the candidate method is required to identify and eliminate (or correct) sources of systematic error until the condition stated in Step 4 is reached.

These five steps are graphically illustrated in Figure 6. The circled numbers 1 through 5 correspond to the five steps described above. The following should be noted:

1. Accuracy goals are usually set symmetrically around the "true value." Figure 6 shows only the negative bias side. A mirror image of the figure to the right of the true value line exists but is not shown.

2. In this figure, the accuracy goal refers to the accuracy goal of the reference method (RM). Here, the numerical value of the mean (for the property under analysis) shall be within plus or minus 2% of the "true value."

3. At 2 on the figure, a typical normal distribution is shown for the values of a large number of replicate determinations using the candidate method (CM). The precision of the CM should be considerably less than the width of the limit of inaccuracy as shown.

4. The "true value" point (100 in this figure) is determined independently using a definitive method or taken to be the certified value of a primary reference material.

The discussion above is meant to illustrate a systematic procedure for demonstrating the accuracy of a reference method. Experience with reference method development has shown that the validation of the method may involve three or four iterations of the above process before the described accuracy goals can be reached. What is important is that reference methods be accurate and that the accuracy be verified through actual experiments and evaluated with proper statistical procedures.

IV. THE APPLICATION OF REFERENCE MATERIALS AND REFERENCE METHODS TO LARGE MEASUREMENT NETWORKS

A. Reference Materials

1. Major Uses of Reference Materials

a. Production or Evaluation of Secondary Reference Materials

One common use of SRMs and other primary reference materials is to provide an accurate reference basis for the production or evaluation of secondary reference materials. Analogously, secondary reference materials may also be used to develop "in-house" or "tertiary" reference materials. For example, NBS produces over 40 SRMs consisting of gas mixtures certified for trace and bulk chemical constituents, such as oxides of nitrogen or carbon. Many commercial specialty gas manufacturers use NBS SRMs as primary reference standards during the production of secondary reference materials. The less expensive secondary standards are then directly used in the field. In this manner, the accuracy of the field measurements can in principle be related back to NBS measurements without NBS having to directly supply hundreds or thousands of field installations with SRMs. In such an application, the existence of a reliable measurement protocol for relating the accuracy of the secondary reference material to the SRM is essential. In the case of gas analysis, the EPA is working with NBS and commercial gas manufacturers to develop protocols for establishing the traceability of secondary gas reference materials to NBS SRMs. For example, a draft protocol for establishing traceability of calibration gases used with continuous source emission monitors has been developed for EPA and is currently undergoing technical evaluation and review.[43]

A recent example of the application of an SRM to the evaluation of secondary reference materials is in standardization of temperature measurements in the clinical laboratory. The accurate measurement and control of temperature is essential for assuring the reliability of many clinical measurements (e.g., enzyme analysis). At the request of the College of American Pathologists, Mangum and Wise of NBS[93,99] developed a series of precision thermometer SRMs (NBS SRMs 933 and 934) to be used as primary temperature reference standards for clinical laboratories. Because these SRMs are considerably more costly than ordinary thermometers, they should not be used for routine field applications. The National Committee for Clinical Laboratory Standards (NCCLS) has developed a tentative standard practice[100] for temperature calibration of temperature sensors which incorporates the NBS SRMs into the measurement protocol. Ween[101] has also published a procedure for using NBS SRMs (or other high accuracy commercial temperature standards) to evaluate thermometers used in routine clinical laboratory applications. This example is an excellent illustration of three different tiers of the measurement hierarchy described in Figure 3 — the primary standards laboratory (NBS), the voluntary standards organization (NCCLS), and a manufacturer of commercial reference materials — all working together to transfer accuracy from the primary standards laboratory into the field and to assure the traceability of temperature measurements throughout the different components of the clinical measurement system.

b. Direct Primary Standardization in the Field

Many comparative field methods of chemical analysis such as the spectrochemical or X-ray fluorescence techniques commonly used to analyze metals and alloys are capable of achieving high accuracy when SRMs are used directly as calibration standards. For example, many of the standard methods developed by ASTM Committee E-2 on Emission Spectroscopy are in widespread field use. Since some of these rapid methods are essentially nondestructive, SRMs or other primary reference materials can be directly used in the field for calibration purposes without great additional costs. For example, ASTM Standard Method E322-67 is used for analyzing low-alloy steels by X-ray fluorescence.[102] The NBS D-800 and 1200 series of low-alloy steel SRMs are recommended for use as primary standards with this method. In cases where the direct use of an SRM may be costly, the quality control laboratory may use the SRM to control the production of less costly secondary standards produced internally.

Accurately characterized primary or secondary reference materials are essential to establishing the accuracy of many rapid comparative field methods. Such methods may give results that are highly matrix dependent. Normally, a large series of reference materials for instrument calibration is required to cover each material class or type under investigation over a wide range of compositions. Many thousands of different materials and compositional levels would be needed to satisfy all needs in industrial materials processing, research applications, environmental monitoring, and the like. The need for trace element reference materials is particularly critical.[103] Recognizing this dilemma, the NBS Office of Standard Reference Materials has initiated a program to produce a limited number of so-called benchmark SRMs to serve as the anchor points for the calibration of many instrumental measurement systems. Commercial suppliers should use the benchmark SRMs to control the production of secondary reference materials.

Table 2 summarizes the trace analytical SRMs currently available from NBS. These are intended to serve as benchmarks for the analysis of metal, inorganic, botanical, and biological as well as environmentally significant matrices. In principle, the interchangeability of the various trace element SRM matrix systems is limited only to the chemical talents available. With present-day sophistication in chemical manipulations and understanding of the basic chemical principles underlying various measurement techniques, the matrix, per se, may often be eliminated, or matrix interferences may be minimized by such means as separations, extractions, preconcentrations, or instrumental background corrections. The final critical requirement is that the chemical procedure used to measure both the test specimens and the SRMs be identical with respect to all variables that could influence the measurement.

Irons et al.[104] recently used a series of NBS biological trace element SRMs as benchmarks for the production of working reference materials which had compositional levels intermediate to that of the available SRMs. This was accomplished through appropriate mixing of the SRMs. The intermediate-composition reference materials in turn were used to evaluate the sensitivity, precision, and accuracy of energy-dispersive X-ray spectroscopy and inductively coupled plasma emission spectrometry for routine analysis of biological materials. Since matrix independence is never fully achievable in practice, a sizable number of trace elemental SRMs for major matrix classes will probably always be required. An objective of a primary standards laboratory should be to make the primary reference materials as broadly applicable as possible. Producers of secondary reference materials should extend the range of concentrations covered by the primary reference materials whenever feasible.

c. Method/Instrument Development and Evaluation

SRMs and other reference materials are being increasingly used in the development or evaluation of analytical methods and instrumentation. Such applications of SRMs are widely reported in the literature. For example, a review of the journal *Analytical Chemistry* during the 18-month period ending December 1976 identified over 40 research articles[105-147] citing the use of SRMs in the development or evaluation of a wide variety of different methods for chemical analysis and in particular for trace elemental analysis. Table 3 summarizes and illustrates the variety of applications of SRMs in these recent papers. Particular note should be taken of those papers using SRMs to establish or verify the accuracy, precision, and/or sensitivity of the methods being developed. This use of SRMs not only results in a better

TABLE 2

NBS Trace Element SRMs

SRM No.	Name	Certified values[a]
		Botanical/biological standards
1570	Spinach	12 trace elements, 3 major constituents
1571	Orchard leaves	14 trace elements, 5 major constituents
1573	Tomato leaves	9 trace elements, 4 major constituents
1575	Pine needles	12 trace elements, 5 major constituents
1565	Oyster meat	9 trace elements, 3 major constituents
1569	Brewers yeast	Cr is certified at 2.12 μg/g
		Environmental standards
1601–1603	CO_2 in nitrogen	~300–400 ppm
1604–1609	Oxygen in nitrogen	~1.5 ppm–21 mol%
1610–1613	Hydrocarbons in air	~1–1000 ppm
1625–1627	SO_2 permeation tubes	Permeation rate ~0.6–2.8 μg/min over 20–30°C
1629	NO_2 permeation	Permeation rate ~1.5 μg/min at 25°C
1630	Trace mercury in coal	0.13 ppm
1632	Trace metals in coal	13 trace elements
1633	Trace metals in fly ash	13 trace elements
1634	Trace metals in fuel oil	Ni, Pb, V, Zn, Fe, as well as S
1636–1638	Lead in reference fuel	Pb at 12, 20, 28, and 773 μg/g
1641–1642	Mercury in water	1.49 μg/ml and 1.18 ng/ml
1658–1660	Methane in air	1–10 ppm (SRM 1660 contains 4 ppm methane and 1 ppm propane)
1661–1664	SO_2 in nitrogen	~500–2500 ppm
1665–1669	Propane in air	~3–500 ppm
1677a–1681a	CO in nitrogen	~10–1000 ppm
1683a–1687a	NO in nitrogen	~50–1000 ppm
2611–2614	CO in air	~1–45 ppm
2671	Fluorine in freeze-dried urine	0.8 mgF^-/l and 7.1 mgF^-/l
2672	Mercury in freeze-dried urine	0.05 mg Hg/l and 0.29 mg Hg/l
2675–2676	Toxic metals on filters	Be, Cd, Pb, Zn, and Mn at trace levels
		Industrial standards – metals, ores, glasses
608–619	Trace element glasses	Graded series of 36 trace elements
607	Potassium feldspar	Rb, Sr content, Sr isotopic ratio
685	High purity gold	Cu, Fe, In
680–681	High purity platinum	12 trace elements
682–683	High purity zinc	6 trace elements
726	Intermediate purity selenium	24 trace elements
394–396	Unalloyed copper	12 trace elements
991	Lead-206 spike, assay and isotopic solution	0.32 μmol Pb 206/g
993	Uranium-235 spike, assay and isotopic solution	28.270 μmol U^{235} g
1261–1265 661–665 461–468	Low alloy steels; electrolytic iron	Over 30 trace and bulk constituents
1089–1099	Various steel alloys	Certified for trace levels of oxygen and nitrogen

[a] The units used in the table correspond to those used on the certificates of analysis.

TABLE 3

Examples of Use of SRMs for Method Development and Evaluation

Method application	SRMs used	Ref.
Determination of Hg in petroleum products by acid decomposition and cold-vapor atomic absorption at 5–10 ng/g	SRM 1630 (coal) used as spike	105
Determination of trace Cd in petroleum by atomic absorption at 10 ng/g level	SRM 1053a (cadmium cyclohexane butyrate)	106
Analysis of chemical oxygen demand in waste waters in the range of 3–900 mg/l	SRM 84h (acid potassium phthalate) in solution as working standard	107
Determine As and Sb in environmental samples using gas chromatography with microwave emission spectrometry at ppm levels	SRM 1571 (orchard leaves), SRM 1577 (bovine liver), SRM 1632 (coal), SRM 1633 (fly ash) used to establish accuracy of method	108
Multielement analysis using rf cavity ion source and mass spectrometry	SRM 804a (basic electric steel) used to establish reproducibility	109
Trace element analysis of fluids by proton-induced X-ray fluorescence	SRM 1571 (orchard leaves) to establish accuracy	110
Simultaneous determination of tellurium and uranium using neutron activation analysis	SRM's U0002 and U010 (uranium oxides) used in standard solutions, SRM 1571 (orchard leaves), SRM 1632 (coal), and SRM 1633 (fly ash) used to establish accuracy	111
Determination of iodine-129 at natural levels using neutron activation and isotopic separation	SRM 4949 (iodine-129) used as internal standard	112
Determined trace mercury in environmental samples using a new Zeeman method for atomic absorption spectrophotometry	SRM 1571 (orchard leaves) and SRM 1633 (coal) used to establish accuracy	113
Titrimetric determination of fluorine following volatilization	SRM 120b (phosphate rock) used to establish accuracy	114
Determination of silicon in glasses and minerals in the range of 14–94% using atomic absorption spectrometry	SRM 1a (limestone), SRM 70a (fieldspar, potash), SRM 77 (burnt refractory), SRM 78 (burnt refractory), SRM 89 (lead barium glass), SRM 91 (opal glass), SRM 93 (high boron glass), SRM 97 (flint clay), SRM 98 (plastic clay), SRM 99 (feldspar, soda), SRM 102 (silica brick) used to establish accuracy over wide concentration range	115
Evaluation of sample pretreatments for mercury determination using neutron activation analysis	SRM 1577 (bovine liver), SRM 1571 (orchard leaves), and SRM 1630 (coal) used to establish accuracy of method	116
Determination of trace carbon and boron using quasi-prompt charged particle activation analysis	SRM 610 (glass), SRM 612 (glass), SRM 1571 (orchard leaves), and SRM 1143 (blast furnace iron) to establish accuracy of method	117
Determination of arsenic, selenium, antimony, and tellurium in foods using rapid hydride evolution and atomic absorption spectrometry	SRM 1571 (orchard leaves) and SRM 1577 (bovine liver) used to establish accuracy of method	118
Determination of mercury by cold-vapor atomic absorption	SRM 1571 (orchard leaves) and SRM 1577 (bovine liver) used to establish accuracy of method	119
Used internal standardization in a vidicon flame spectrometer to analyze magnesium in serum	SRM 1577 (bovine liver) used to establish accuracy	120
Multielement analysis using charged particle activation analysis with X-ray counting	SRM 610 (glass), SRM 612 (glass), and SRM 614 (glass) used to establish accuracy	121
Trace element analysis using multielement isotope dilution with a coaxial cathode ion source	SRM 461 (low alloy steel) used to establish sensitivity and precision for certain isotopes	122
Calcium analysis using a wavelength-modulated filter flame photometer	SRM 19 (limestone) used to establish accuracy of method	123
Evaluated gas phase exponential dilution as a calibration technique for gas detector	SRM's 1666–1668 (propane in air) used to calibrate flame ionization detectors and to evaluate accuracy of direct calibration with exponential dilution flasks	124
Analysis of low alloy steels by secondary ion mass spectrometry	SRMs 461, 465, and 466 (low alloy steels) used to evaluate sensitivity and applicability for quantitative analysis	125

TABLE 3 (continued)

Examples of Use of SRMs for Method Development and Evaluation

Method application	SRMs used	Ref.
Spectrophotometric determination of vanadium (V) by extraction with *N*-[*p*-*N*,*N*-Dimethylanilino)-3-methoxy-2-naphtho] hydroxamic acid	SRM 67 (manganese metal) and SRM 117 ferrotitanium) used to establish accuracy of method	126
Analysis of low alloy steels with the ion microprobe mass analyzer	SRM 466 (low alloy steel) used to evaluate method and to correct for carbide formation in the matrix	127
Analysis of refractory oceanic-suspended materials using a decomposition technique	SRM 98a (plastic clay) used to evaluate elemental recovery	128
Determination of uranium in natural waters by neutron activation analysis	SRM 950a (uranium oxide) used in standard solutions	129
Determination of lead using Zeeman atomic absorption with a dual chamber furnace	SRM 1577 (bovine liver) used to establish accuracy of method	130
Determination of selenium (IV) by anodic stripping voltammetry in flow system with ion exchange separations	SRM 1261 (low alloy steel), SRM 1571 (orchard leaves), SRM 1577 (bovine liver), SRM 1632 (coal), and SRM 1633 (fly ash) used to establish accuracy of method	131
Development of a continuum source atomic absorption spectrometer with high resolution and wavelength modulation	Used prototype NBS tomato leaves and pine needle SRMs to compare 3 different methods of analysis for copper	132
Determination of lead, cadmium, and zinc using Zeeman effect in atomic absorption spectrometry	SRM 1577 (bovine liver) used to establish accuracy of lead determinations	133
Evaluation of the local thermal equilibrium model for quantitative analysis of secondary ion mass spectrometry	Used data obtained on SRM 661 (low alloy steel), SRM 121d (stainless steel), and SRM 162a (monel) to evaluate models	134
Assay of Boron-10 enriched elemental boron by isotope dilution mass spectrometry	Used SRMs 951–952 (boric acid) as isotopic spikes	135
Development of a low flux multielement instrumental neutron activation analysis method for archaeometry	SRM 1632 (coal) and SRM 1633 (fly ash) used to establish accuracy of method	136
Determination of nanogram levels of chromium using coupled gas chromatography atomic absorption	SRM 1571 (orchard leaves) used to evaluate extraction procedure	137
Trace element analysis of solid materials by laser probe mass spectrometry	SRM 611 (glass) and SRM 464 (low alloy steel) used to evaluate accuracy	138
Direct analysis of metals and alloys using atomic absorption	Used NBS Brass and zinc SRMs (unidentified) to establish detection limits and reproducibility	139
Quantitative detection of NO_2 in nitrogen using laser magnetic resonance at 1616 cm^{-1}	Used SRM 1629 (NO_2 permeation tube) as a calibration standard	140
Detection of lead via lead-207m using a cyclic activation and a modified sum-coincidence system	SRM 1571 (orchard leaves) used in evaluation of sensitivity	141
Development of a neutron activation analysis program for multielement trace analysis with absolute counting	SRM 4216 (mixed radionuclide) used to calibrate detector efficiency	142
Trace elemental analysis by heavy ion-induced X-ray emission	SRM 1577 (bovine liver) and SRM 1571 (orchard leaves) used to evaluate accuracy	143
Determination of toxic elements in environmental samples using radiochemical separation prior to gamma-ray spectrometry	SRM 1632 (coal), 1633 (fly ash), SRM 1577 (bovine liver), and SRM 1571 (orchard leaves) used as calibration standards	144
Detection and characterization of aerosols containing transuranic elements with the nuclear track technique	Used NBS trace element glass SRMs to measure neutron dose	145
Determination of boron and cadmium in environmental materials by nondestructive thermal neutron-prompt gamma-ray spectrometry	SRM 1632 (coal), SRM 1633 (fly ash), SRM 1571 (orchard leaves), SRM 610 (glass), SRM 614 (glass), SRM 1093 (valve steel), SRM 1262 (low alloy steel), and SRM 1264 (low alloy steel) used to establish accuracy of method	146
Determination of tin in the concentration range 0.002–1.0% with 4,5 Dihydroxyfluorecein by differential absorptrometry	SRMs 443 and 444 (stainless steel) used to establish accuracy of method	147

understanding of the limitations of the method, but also makes it easier to compare the accuracy, precision, or sensitivities of different methods used to measure the same properties.

An excellent recent example of the use of SRMs for method evaluation is the study of Ondov et al.[148] in which four laboratories used instrumental neutron activation analysis, instrumental photon activation analysis, and natural radioactivity counting to measure 37 different elements in NBS SRM 1632 (coal) and 41 elements in SRM 1633 (fly ash). Their results were compared to values for the 12 elements certified by NBS and considerable data are presented for over 20 elements not certified by NBS. This study showed that the accuracy and interlaboratory dispersion of data obtained by nuclear methods of analysis was superior to several other methods used by the participating laboratories.

In spite of the rather large use of SRMs and other primary reference materials in method evaluation as indicated in Table 3, there are an equally large number of papers published in the literature that do not utilize primary reference materials to evaluate such factors as accuracy or sensitivity when such reference materials are readily available. The value of newly developed methods would be considerably enhanced if researchers would more often establish and/or verify the accuracy of their results relative to values produced by other methods via comparison with SRMs. Such use would also help to assure the traceability of the results of individual researchers to other components of the measurement hierarchy.

d. Quality Assurance

Another major application of reference materials is to provide a common reference basis in measurement quality assurance. A detailed discussion of intralaboratory and interlaboratory quality assurance is beyond the scope of this paper. The reader is referred to the publications of Wernimont,[19,25] Shewhart,[18,26] Youden,[21] and Mandel[22] for a discussion of some statistical and experimental methods used in internal and external quality-control programs. In many internal quality assurance applications, the use of accurately characterized primary reference materials may be unnecessary. The major concern may be to monitor the repeatability of measurements from a single measurement station or the reproducibility of measurements between different stations within a single laboratory or company. The daily use of SRMs may be too costly for such purposes. In such applications, a sufficient quantity of a reasonably stable material similar in nature to the matrix of the specimens being analyzed can be used as a reference material. Eckert and Mongan[149] have described such an internal quality control program. They use materials prepared in-house as reference materials to monitor the long-term precision of stations that are monitoring lead contamination in air and water. Winter[47] has also described the use of reference materials in the quality assurance program of the EPA Environmental Monitoring and Support Laboratories in Cincinnati. Previous reference was made to the extensive use of secondary reference materials in the laboratory survey programs of the College of American Pathologists.

An excellent example of the use of SRMs to establish the precision and/or accuracy of measurements made through interlaboratory testing is represented by ASTM Standard Methods E-350, E351a, E352, E353, and E354 which are intended for use in the chemical analysis of a variety of iron and steel products for several dozen elements over broad concentration ranges.[150] In this case, a variety of NBS SRMs and primary reference materials produced in England were used to evaluate the accuracy, reproducibility, and repeatability of these standard methods. For example, Table 4 shows data obtained for the analysis of manganese over the range of 0.01 to 2.5% by the method specified in ASTM E350 (a photometric determination after treatment with periodate). The certified values of the NBS and British primary reference materials are shown in parentheses. The within laboratory precision (R_1) and the between laboratory precision (R_2) are shown in absolute percent of manganese. These values are determined by the procedure specified in ASTM Standard E173, *Recommended Practice for Conducting Interlaboratory Studies of Methods for the Chemical Analysis of Metals.*[12] Good accuracy and precision is obtained for all but the lowest concentration by this method. In this case, the use of accurately characterized, homogeneous primary reference materials was critical to establishing the precision and accuracy of the method. Once accuracy and precision are established, such methods may then be used to evaluate secondary reference materials or standards prepared in-house to be routinely used in quality assurance applica-

TABLE 4

Determination of Manganese in Low Alloy Steels Using ASTM Standard Method E350[a]

Test specimen	Manganese found (%)	Repeatability[b] (R_1)	Reproducibility[b] (R_2)
Alloy steel (BCS 252, 0.016 Mn)	0.022	0.004	0.006
Alloy steel (BCS 255/1 0.16 Mn)	0.161	0.004	0.010
Low-alloy steel (NBS 72f, 0.545 Mn)	0.551	0.010	0.020
Low-alloy steel (NBS 139a, 0.780 Mn)	0.780	0.009	0.030
Alloy steel (NBS 159, 0.807 Mn)	0.819	0.010	0.034
Low-alloy steel (NBS 13f, 0.889 Mn)	0.892	0.015	0.027
Low-alloy steel (NBS 1006, 1.89 Mn)	1.91	0.02	0.04

Note: BCS = British Chemical Standard, NBS = NBS Standard Reference Materials.

[a] From Part 12 of *1976 Annual Book of ASTM Standards,* 582. Reprinted by permission of the American Society for Testing and Materials, Copyrighted.

[b] Repeatability and reproducibility defined in ASTM Standard Recommended Practice E-173, Conducting Interlaboratory Studies for Chemical Analysis of Metals, *1976 Annual Book of ASTM Standards,* 464, Part 12.

tions. The E350 Standard Methods of ASTM meet the criteria specified for the development of reference methods (Section III.B.) and these methods, in fact, serve as good examples of reference methods.

Waasdorp[151] has described a comprehensive internal quality-control program for chemical analysis in steel plants. This particular internal quality control program utilizes systematic measurement protocols for maintaining both short-term and long-term control of the accuracy of measurement processes used in steel production. In the long-term control system, the reference materials used consist of a random selection of specimens obtained from recent production runs which are submitted for analysis by accurate chemical methods. Periodically (i.e., twice each year), the results of the routinely used production-line method (spectrochemical analysis) are compared with results obtained from the more accurate chemical analytical methods. Figure 7 compares data obtained for the analysis of phosphorous at the 0.015% level by both methods for a 6-month period ending in March 1975. Data are shown for samples from two different Basic Oxygen Furnaces (BOF). In this manner, Waasdorp is able to monitor the long-term accuracy of the routine spectrochemical techniques relative to the more accurate chemical methods.

In the short-term quality control system, Waasdorp utilizes samples, as reference materials, which have previously been analyzed by the accurate chemical method. Once during each 8-hr work shift, the reference materials are analyzed on each spectrometer on duty. This permits immediate identification of measurement problems, such as instrument drift, so that rapid corrective action can be taken, if necessary. Figure 8 illustrates the type of control chart used by Waasdorp to monitor the short-term variability of the spectrochemical measurements as a function of shift changes within the plant. The heavy vertical line on the charts represents the value obtained for the reference material using the accurate chemical method. E(σ) is the standard deviation (precision) of the chemical procedure. $\bar{X}$ and S denote the mean value and standard deviation respectively, of the data taken as a function of time using the spectrochemical technique. Thus, both the precision and accuracy of the spectrochemical field method can be monitored on a daily (hourly) basis. If the chemical methods of analysis are similar to the methods described in the ASTM E350 series, Waasdorp could, in principle, establish the traceability of his measurements to NBS SRMs.

The rigorous internal quality-control procedures described by Waasdorp are illustrative of the rigorous quality-control procedures used throughout the steel industry. Woodruff and Bendure[152] have recently described an extensive quality assurance program used by another steel

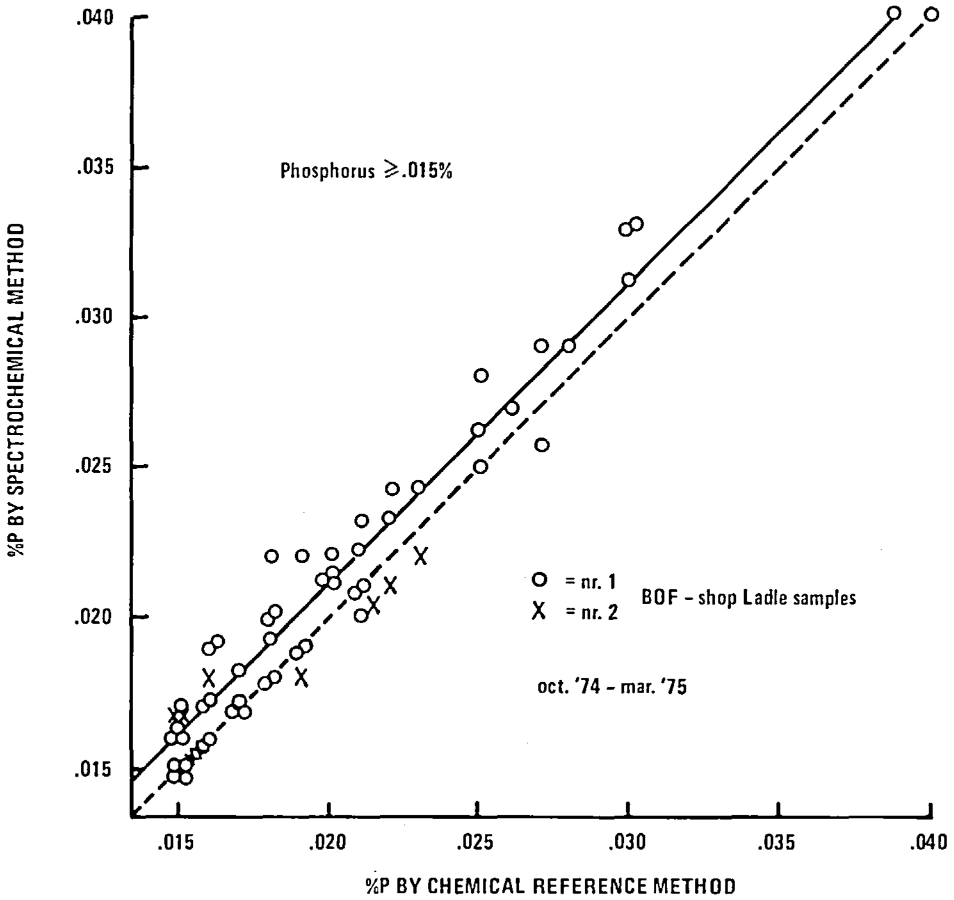


FIGURE 7. Comparison of data from the measurement of phosphorus in steel using an accurate chemical method as a reference method to control the long-term accuracy of a spectrochemical field method. (From Waasdorp, A., Rapid Quality Control Analysis in the Steel Plant, paper presented at the 1976 Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Cleveland, 1976.)

company. These authors describe a quality assurance system in which the various plant laboratories are evaluated periodically and rated according to their performance over a long period of time.

e. A Case Study – The Determination of SO_2 Using the Pararosaniline Method

Chapter 13 of *The Statistical Analysis of Experimental Data* by Mandel[22] is concerned with the statistical evaluation of measuring processes, including a comprehensive treatment of the analysis of variances of data obtained from interlaboratory testing. Mandel emphasizes the potential advantage of using reference materials to reduce the between-laboratory variability of data obtained by different laboratories using the same measurement method.

An example of the use of reference materials to reduce between-laboratory variability in a large network of participating laboratories is also described elsewhere by Mandel.[153] This application of reference materials involved an Environmental Protection Agency survey[154] of 96 laboratories to evaluate the pararosanaline method[155] for determination of sulfur dioxide in air. This method measures the concentration of sulfur dioxide in a sample of air by the spectrophotometric determination of the color intensity of the dye resulting from the chemical reaction between sulfur dioxide and pararosanaline. A series of five concentration levels of powder samples consisting of sodium sulfate dispersed in mannitol were prepared and analyzed by NBS[156] to serve as test specimens (unknowns) for the interlaboratory survey.

Mandel recommends a procedure for analyzing data from interlaboratory surveys. A linear rela-

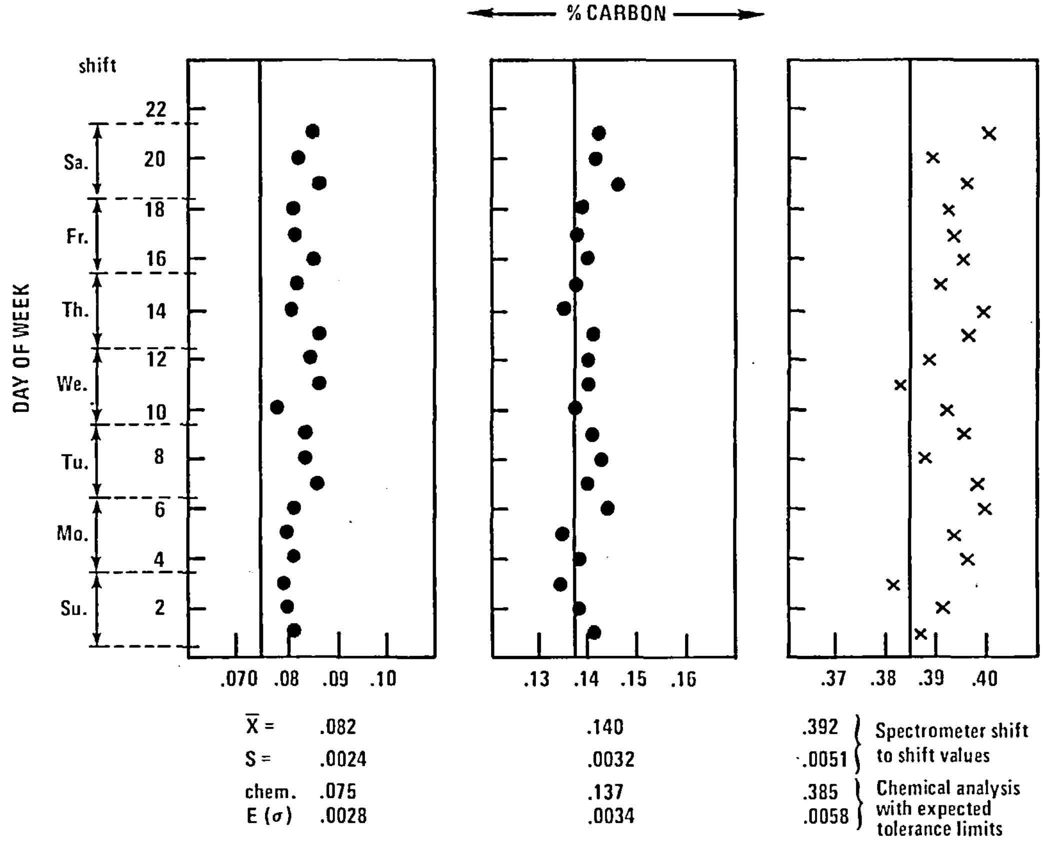


FIGURE 8. Control charts used to monitor the short-term accuracy and precision of spectrochemical methods for carbon analysis of steel. (From Waasdorp, A., Rapid Quality Control Analysis in the Steel Plant, paper presented at the 1976 Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Cleveland, 1976.)

tionship is assumed between the value of the parameter being measured (in this case absorbance) and the property being determined (concentration of SO_2). The test results obtained by each laboratory are plotted against the corresponding average values of the property obtained by all laboratories[157] or against other reference values (e.g., the "true" values, if such values are known). In this manner, one obtains a set of straight lines (referred to as calibration lines). Each line represents the data from a single laboratory. Mandel cites two important cases that typically occur. These correspond respectively to a collection of parallel lines (Figure 9a) or a bundle of lines concurrent at the origin (Figure 9b). In either case, considerable improvement in the between-laboratory precision of the method can be accomplished if some mechanism could be found to bring the lines representing each laboratory closer together. This may be accomplished through the use of reference materials to adjust the data of each laboratory.

In the case of parallel calibration lines (Figure 9a), a simple vertical displacement of each line to make it connect with the bisector of the axes would eliminate the additional variability between laboratories. Each laboratory could correct for its own bias by using a reference material to determine the difference between its measured value and the certified value. The laboratory can then displace its calibration line to compensate for its bias. If this adjustment is made by all laboratories, the between-laboratory precision of the method should be considerably improved. For the case of parallel calibration lines, the choice of the concentration level of the reference material is immaterial, i.e., any point on the x-axis would be appropriate.

Such is not the case when all the lines are concurrent, as in Figure 9b. In this case, all lines

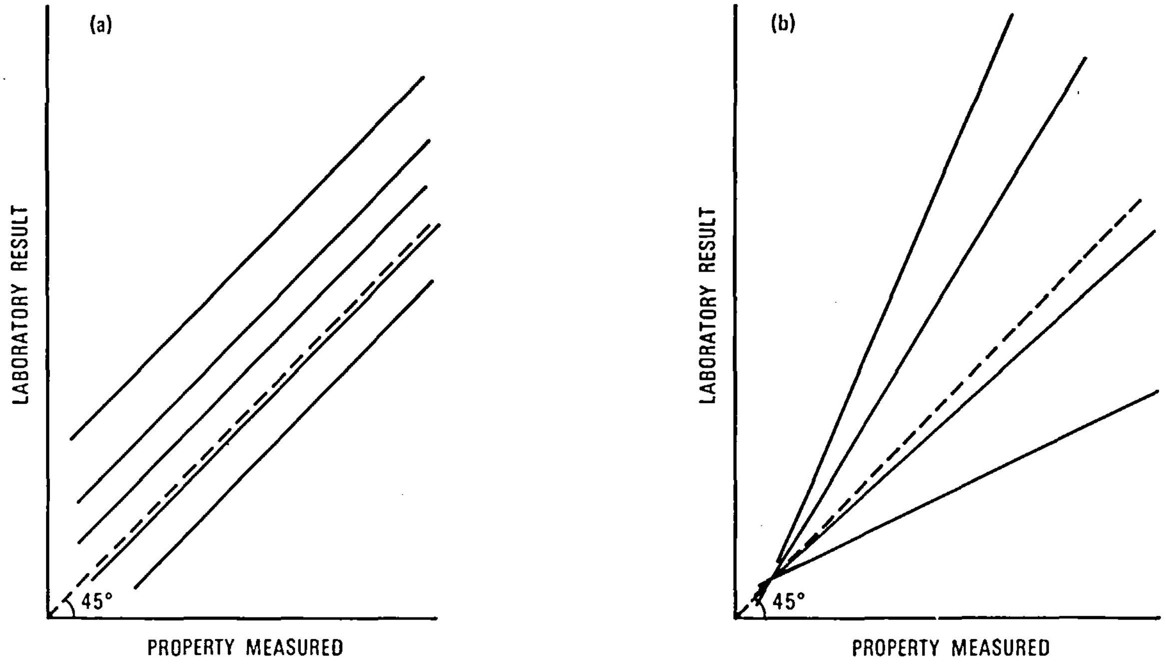


FIGURE 9. Schematic illustrating typical calibration lines obtained when plotting laboratory results against the actual values of the properties measured. Two typical cases are obtained: (a) parallel lines and (b) concurrent lines through the origin. These are discussed in text. (From Mandel, J., *Statistics and Standard Reference Materials*, National Bureau of Standards, Special Publication, No. 408, U.S. Government Printing Office, Washington, D.C., 1975.)

have different slopes but go through a common point (the origin). Thus, the laboratory biases are multiplicative rather than additive. This means that all values obtained by an individual laboratory are too high or too low, by a multiplicative constant (the slope of the line). In such a case, the most advantageous choice of concentration level for the reference material would be at a level far removed from the point of concurrence of the lines. In the case of concurrent lines, each laboratory must adjust its data by dividing each of its values by the ratio of the measured value of a reference material to the assigned value of the reference material. In the more general case where the calibration lines cross each other at random, two reference materials at different concentration levels are required to make the corrections.

We now describe the application of this statistical model to the EPA SO_2 survey because it illustrates the fact that large reductions in between-laboratory variability can be obtained through the use of reference materials.

Table 5 gives the values for all five concentrations (A through E) of the test specimens as measured by each of the 96 laboratories participating in the survey. Table 6 summarizes the mean value and standard deviation for each of the five concentration levels of the survey test specimens as determined by NBS. In addition to making an accurate determination of the SO_2 levels in each of the five test specimen series, NBS also carried out considerable stability and homogeneity testing[156] to assure proper characterization of the materials. Thus, the test specimens were, in essence, well-characterized reference materials. In this case, the standard deviation is a measure of the variability of the levels of SO_2 between ampoules in the same series. Comparison of the results of Table 5 and Table 6 indicate that the variability of the test results between laboratories was an order of magnitude larger than could be accounted for by the variability between ampoules.

The values obtained at each of the five concentration levels for each of the 96 laboratories was then plotted against the accurate values obtained by NBS. Each laboratory's results were represented by a straight line, fitted by the method of least squares to the five points of each plot. This resulted in a set of 96 straight lines for which the abscissa values were the same in all cases (i.e., those of the NBS values). This analysis revealed

TABLE 5

Determination of SO_2 by Pararosaniline Method Interlaboratory Survey Results – All Values in $\mu g/m^3$

Lab.	A	B	C	D	E	Lab.	A	B	C	D	E	Lab.	A	B	C	D	E
1	50.0	121.7	341.7	545.0	676.7	35	30.0	120.1	390.4	390.4	450.5	69	90.1	180.2	468.5	897.9	967.0
2	53.4	135.0	366.0	598.0	745.0	36	60.1	150.2	390.4	540.5	570.6	70	60.1	150.2	420.4	660.7	840.8
3	45.6	121.5	370.4	611.2	762.9	37	10.0	90.0	306.7	563.3	610.0	71	60.1	150.2	420.4	690.7	900.9
4	45.8	130.8	354.4	619.0	751.0	38	55.2	121.3	327.2	493.3	634.2	72	46.6	186.6	478.1	711.3	816.2
5	40.0	134.0	316.7	600.7	773.3	39	50.0	133.3	413.3	676.7	866.7	73	27.3	100.3	377.0	549.0	734.3
6	66.6	182.0	523.0	732.0	853.0	40	33.2	104.0	309.8	513.4	643.1	74	38.0	122.0	403.0	490.0	650.0
7	36.3	135.3	428.3	676.6	841.2	41	39.5	117.0	324.0	521.0	640.0	75	4.1	10.2	28.5	48.9	53.0
8	60.1	180.2	450.5	630.6	870.9	42	60.1	180.2	450.5	660.7	810.8	76	60.1	210.2	420.4	750.8	900.9
9	43.5	143.6	398.6	659.6	855.3	43	4.7	11.5	32.2	50.5	62.4	77	55.0	142.0	381.0	646.0	800.0
10	15.9	35.5	80.5	108.2	126.2	44	75.2	211.0	453.0	773.0	946.0	78	58.3	142.0	417.0	583.0	804.0
11	33.3	79.0	184.4	359.0	411.1	45	25.3	65.9	130.0	142.7	146.3	79	533.0	133.0	28.3	450.0	533.0
12	15.0	39.0	108.1	183.2	219.2	46	3.0	9.0	18.0	27.0	54.1	80	39.2	144.0	366.0	533.0	639.0
13	83.0	127.0	333.0	573.0	680.0	47	42.3	140.1	393.6	623.1	773.1	81	58.3	130.0	360.0	513.0	606.7
14	42.0	129.1	432.4	735.7	822.8	48	1.3	52.0	180.7	280.7	298.7	82	43.7	126.7	333.0	550.0	756.0
15	55.0	141.0	210.0	202.0	348.0	49	53.0	212.0	483.0	711.0	742.0	83	41.7	130.0	315.0	527.0	660.0
16	39.0	122.0	333.0	522.0	712.0	50	71.7	220.0	600.0	983.3	1266.6	84	7.4	22.2	57.3	70.2	109.1
17	60.1	120.1	360.4	630.6	720.7	51	0.8	2.4	5.2	102.2	125.8	85	9.0	30.0	78.1	168.2	237.2
18	57.1	150.2	408.4	729.7	849.9	52	24.1	104.2	343.5	480.9	687.2	86	35.0	97.1	303.8	554.5	777.0
19	73.0	96.0	245.2	511.2	547.8	53	30.0	150.2	360.4	510.5	660.7	87	60.1	150.2	420.4	660.7	870.9
20	49.5	104.5	335.5	536.3	753.5	54	60.1	150.2	390.4	540.5	690.7	88	54.1	216.2	360.4	636.6	825.8
21	30.0	150.2	420.4	690.7	840.8	55	39.0	112.0	638.0	794.3	1002.6	89	37.0	112.0	272.0	490.0	603.0
22	22.5	73.2	115.5	185.8	250.0	56	69.1	156.2	438.4	669.7	726.7	90	75.1	195.2	480.5	774.8	985.0
23	111.1	216.2	630.6	1111.1	1261.3	57	45.0	127.9	224.9	376.8	461.1	91	51.1	156.2	435.4	642.6	837.8
24	28.3	100.8	280.0	450.0	567.0	58	280.0	870.0	217.0	358.0	415.0	92	60.1	150.2	360.4	630.6	780.8
25	37.0	69.0	157.0	246.0	290.0	59	60.1	171.2	426.4	702.7	828.8	93	180.2	390.4	1891.9	2702.7	3903.9
26	50.0	139.7	341.0	732.1	883.5	60	416.3	187.3	445.4	777.1	961.5	94	42.0	114.1	201.2	402.4	585.6
27	40.3	133.0	340.0	577.0	743.0	61	22.9	114.5	352.5	535.7	673.9	95	90.0	220.0	721.0	1050.0	1400.0
28	33.2	127.3	363.8	392.7	696.8	62	30.0	120.1	390.4	570.6	720.7	96	57.0	137.0	389.0	593.0	743.0
29	62.0	157.0	434.0	509.0	641.0	63	51.7	128.3	362.5	575.0	700.0						
30	202.4	297.6	988.0	1487.9	1928.3	64	51.2	115.5	313.7	573.0	727.7	Avg.	60.72	143.10	396.28	586.06	735.43
31	53.0	150.0	385.0	605.0	757.0	65	55.4	97.0	317.2	452.4	543.4						
32	40.0	132.0	436.0	580.0	860.0	66	50.5	134.8	397.1	567.4	839.9						
33	150.2	510.5	1291.3	2222.2	2582.6	67	17.0	23.0	74.0	132.0	174.0	NBS	44.7	131.3	383.0	595.0	767.3
34	60.1	120.1	390.4	600.6	750.8	68	54.1	177.2	210.2	381.4	453.5						

From Mandel, J., Statistics and Standard Reference Materials, National Bureau of Standards, Special Publication No. 408, U.S. Government Printing Office, Washington, D.C., 1975.

TABLE 6

Determination of SO_2 by Pararosaniline Method (National Bureau of Standards' results)

Test specimen series	SO_2 values ($\mu g/m^3$)	
	Mean value	Standard deviation[a]
A	44.4	6.0
B	131.3	13.3
C	383.0	23.0
D	595.0	32.3
E	767.3	31.3

[a]Between ampoules of the same series; based on a random sample of 20 ampoules.

From Mandel, J., Statistics and Standard Reference Materials, National Bureau of Standards, Special Publication, No. 408, U.S. Government Printing Office, Washington, D.C., 1975.

that values obtained by four laboratories (58, 60, 79, and 93) showed excessive scatter about their fitted lines, indicating serious problems with statistical control of their measurement process. The data from these laboratories were eliminated, and the subsequent analysis was confined to data from the remaining 92 laboratories.

Figure 10 represents the linear plot of a typical laboratory (laboratory 11). The height, H, is the ordinate of the fitted line at the point $\bar{x}$, where $\bar{x}$ represents the average of the NBS values plotted along the abscissa. The slope, B, for laboratory 11 is 0.5442 and the standard deviation of scatter about the line, S, is 25.3. Further analysis indicated that the bundle of lines corresponding to all 92 laboratories was essentially concurrent at the origin. Thus, the structure of the data is similar to that described in Figure 9b. This important conclusion allowed the evaluation of the effectiveness of using one of the samples (i.e., sample E) as a reference material and adjusting all the data at the other four concentration levels for each laboratory by use of the NBS "certified" value.

This adjustment was made for each laboratory by dividing each of their values obtained for test specimens A through D by the ratio:

$$\frac{\text{Measured Value for Series E}}{\text{NBS Assigned Value for Series E}}$$

Table 7 contains the data for series A through D that have been adjusted by the reference-material values. A comparison of values in this table with the corresponding unadjusted values in Table 5 shows the considerable improvement of between-laboratory precision through the use of the specimen E as a reference material. Table 8 shows the standard deviations between laboratories for each of the series A through D for the original and adjusted data. In the case of test specimen series A, the between-laboratory standard deviation was reduced by 25%, while for series D the between-laboratory variability was reduced by 80%. This illustrates the considerable improvement in measurement compatibility which can, in principle, be achieved through the use of reference materials. By comparing the grand mean of the values for all laboratories before and after the data adjustment, one sees that the overall accuracy of the laboratories (as measured by the relative deviations of the mean of all laboratories from the NBS values) has also improved by use of the reference material, particularly at the lowest concentration level.

Mandel[22] has stressed that a reference material may be used to improve the compatibility of measurements only to the extent that within-laboratory imprecision is small in comparison to the between-laboratory imprecision. This implies that each individual measurement station has attained statistical control over its own measurement process. Fortunately, good within-laboratory precision may be obtainable with many instrumental field methods. In cases where proper internal quality-control procedures have not sufficiently reduced within-laboratory imprecision, reference materials may not be very useful in helping to reduce the variability of measurements between laboratories.

A case in point is the interlaboratory study carried out by NBS to evaluate methods used to determine mercury in water at the 0.2 to 5.0 ppb range. The results of this study are described by Uriano and Cali.[27] The data indicated that neither the between-laboratory precision nor the accuracy of the laboratories was improved to any great extent by the use of reference materials. In that particular study, there was considerable evidence of lack of internal quality control for many of the participating laboratories to the extent that within laboratory imprecisions were large. Reference methods are useful in such cases to provide an evaluation of the suspected field methods. An

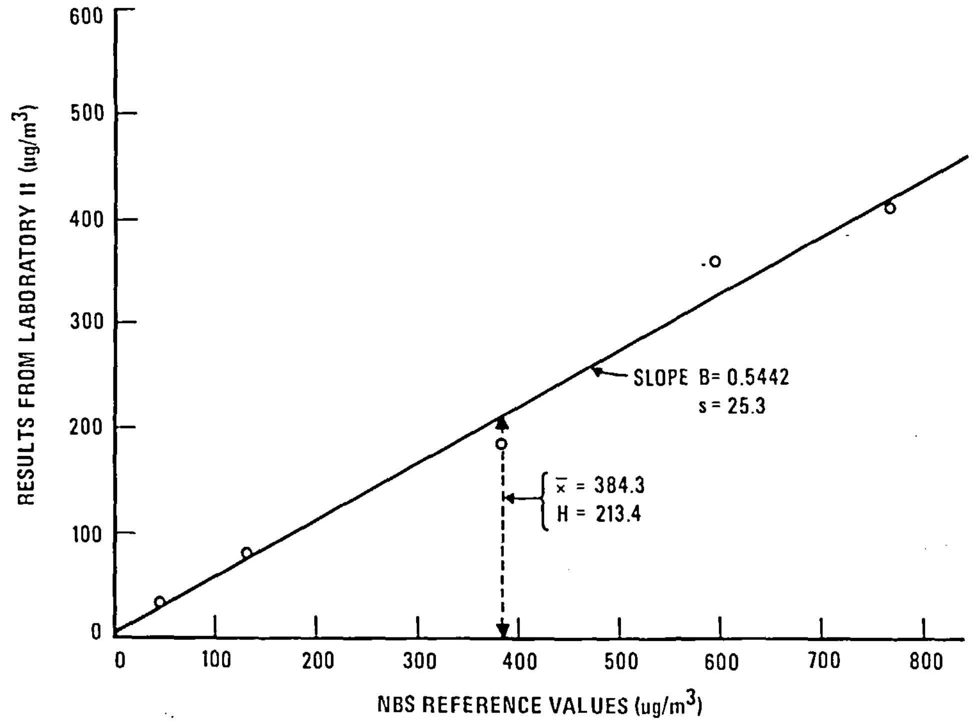


FIGURE 10. Calibration line for laboratory 11 in the multilaboratory survey of the pararosanoline method for SO_2 measurements. (From Mandel, J. Statistics and Standard Reference Materials, National Bureau of Standards, Special Publication, No. 408, U.S. Government Printing Office, Washington, D.C., 1975.)

example from clinical chemistry is presented later in this paper.

These two examples again provide evidence that reference materials alone are not sufficient to assure compatible measurements between laboratories if a state of internal statistical quality control has not first been obtained within each laboratory. Thus, in addition to making proper use of reference materials, good analytical methods under strict quality control are absolutely essential.

3. Application to Industrial Chemical Analysis

An important component of any industrial standardization system is the development of "specifications" and/or "codes" which aim to define the essential properties of a material or product and possibly the requirements for the performance of the product in service.[158] Standard codes and specifications might include performance specifications for use of the material in a given application. The chemical composition as well as values for other chemical or physical properties may also be specified. Industrial codes and specifications are established mainly through the consensus process in the U.S. Such specifications are implemented by a variety of voluntary standards organizations. These specifications essentially govern the commerce of materials and products in the U.S. Material or product specifications might also require testing by a standard analytical or reference method, which in turn should be calibrated through the use of specified primary or secondary reference materials.[57] For example, the set of ASTM standard methods of analysis for low-alloy steels and related materials (E350 series), which was cited previously, is used to analyze products covered by over 500 specifications established by ASTM, the Society for Automotive Engineers, and the American Iron and Steel Institute.

As materials are developed for use in high-performance applications, the specifications for materials become more rigid. This, in turn, leads to a greater demand for better characterized reference methods and reference materials. For example, the typical NBS compositional SRM for use in the steel industry in the 1920s was certified for

TABLE 7

Determination of SO_2 by Pararosaniline Method-adjusted Data for Series A to D – All Values in $\mu g/m^3$

Lab.	A	B	C	D	Lab.	A	B	C	D	Lab.	A	B	C	D
1	56.7	138.0	387.4	618.0	32	35.7	117.8	389.0	517.5	65	78.2	137.0	447.9	638.8
2	55.0	139.0	377.0	615.9	33	44.6	151.7	383.7	660.2	66	46.2	123.1	362.8	518.3
3	45.8	122.2	372.6	614.8	34	61.4	122.8	399.0	613.8	67	75.0	101.4	326.3	582.1
4	46.8	139.8	362.1	632.4	35	51.2	204.6	665.0	665.0	68	91.5	299.8	355.7	645.4
5	39.7	133.0	314.2	596.0	36	80.8	201.9	525.0	726.9	69	71.5	143.0	371.7	712.5
6	59.9	163.7	470.5	658.5	37	12.6	113.2	385.7	708.6	70	54.8	137.0	383.7	602.9
7	33.1	123.4	390.7	617.2	38	66.8	146.8	395.9	596.9	71	51.2	127.9	358.1	588.3
8	52.9	158.8	396.9	555.6	39	44.3	118.0	365.9	599.1	72	43.9	175.4	449.4	668.7
9	39.0	128.8	357.6	591.7	40	39.7	124.1	369.6	612.6	73	28.5	104.8	393.9	573.7
10	96.8	215.5	489.6	657.7	41	47.4	140.3	388.5	624.6	74	44.9	144.0	475.7	578.4
11	62.2	147.5	344.2	670.0	42	56.8	170.5	426.3	625.2	75	58.7	147.8	413.0	708.6
12	52.5	136.7	378.4	641.2	43	57.5	141.4	395.7	621.1	76	51.2	179.0	358.1	639.4
13	93.7	143.3	375.8	646.6	44	61.0	171.1	367.4	627.0	77	52.8	136.2	365.4	619.6
14	39.2	120.4	403.3	686.1	45	132.6	345.7	682.0	748.3	78	55.6	135.5	398.0	556.4
15	121.3	310.9	463.0	621.8	46	42.6	127.9	255.8	383.7	80	47.1	172.9	439.5	640.0
16	42.0	131.5	358.9	562.5	47	42.0	139.0	390.6	618.4	81	73.8	164.4	455.3	649.3
17	63.9	127.9	383.7	671.4	48	3.4	133.6	464.2	721.1	82	44.3	128.6	338.0	558.2
18	51.5	135.6	368.7	658.9	49	54.8	219.2	499.5	735.2	83	48.5	151.1	366.2	612.7
19	102.3	134.5	343.5	716.1	50	43.4	133.3	363.5	595.7	84	52.3	156.1	403.0	493.7
20	50.4	106.4	341.6	546.1	51	4.8	14.4	32.0	623.4	85	29.1	97.1	252.5	543.9
21	27.4	137.0	383.7	630.3	52	26.8	116.4	383.5	537.0	86	34.6	95.9	300.0	547.6
22	69.1	224.7	354.5	570.3	53	34.9	174.4	418.5	592.9	87	52.9	132.3	370.4	582.1
23	67.6	131.5	383.7	676.0	54	66.7	166.8	433.7	600.5	88	50.2	200.9	334.8	591.5
24	38.3	136.4	378.9	609.0	55	29.9	85.7	488.3	607.9	89	47.1	142.5	346.1	623.5
25	97.9	182.6	415.4	650.9	56	72.9	164.9	462.9	707.0	90	58.5	152.1	374.3	603.6
26	43.4	121.3	296.2	635.8	57	74.9	212.8	374.3	626.9	91	46.8	143.0	398.8	588.5
27	41.6	137.4	351.1	595.9	59	55.6	158.5	394.8	650.5	92	59.0	147.6	354.1	619.7
28	36.5	140.2	400.6	432.4	61	26.1	130.4	401.4	610.0	94	55.1	149.5	263.6	527.3
29	74.2	187.9	519.5	609.3	62	32.0	127.9	415.6	607.5	95	49.3	120.6	395.2	575.5
30	80.5	118.4	393.1	592.1	63	56.6	140.7	397.4	630.3	96	58.9	141.5	401.7	612.4
31	53.7	152.0	390.2	613.2	64	54.0	121.8	330.8	604.2					
										Avg.	53.91	148.39	389.62	615.16

From Mandel, J., Statistics and Standard Reference Materials, National Bureau of Standards, Special Publication, No. 408, U.S. Government Printing Office, Washington, D.C., 1975.

TABLE 8

Determination of SO_2 by Pararosaniline Method Standard Deviation Between Laboratories[a]

Test specimen series	SO_2 Values ($\mu g/m^3$)	
	Original data	Adjusted data
A	28	21
B	66	44
C	181	76
D	292	59

[a]For a single determination in each laboratory ($\mu g/m^3$).

From Mandel, J. Statistics and Standard Reference Materials National Bureau of Standards, Special Publication, No. 408, U.S. Government Printing Office, Washington, D.C., 1975.

about a half dozen bulk constituents. Now, over 40 elements, many of them at the part per million level, must be certified to provide sufficient information to evaluate metallurgical properties such as ductility or corrosion resistance. In many cases, the bulk constituents should be certified at accuracies of 0.1% or less, while the trace constituents can hopefully be certified to accuracies of several percent or better.

To illustrate how reference materials and reference methods are utilized in a typical industrial measurement system, we cite the current activities in the U.S. aimed at improving the analysis of trace elements in unalloyed copper.[103] As part of the trace element benchmark SRM program, NBS has been cooperating with industrial laboratories and ASTM in an effort to produce a series of unalloyed copper SRMs certified for chemical composition and eventually containing the useful concentration ranges for 25 to 30 important trace elements. Impurity elements and their concentration levels in refined copper have a profound effect on such properties as electrical conductivity and thus on product performance in a number of energy-related applications. For example, the presence of as little as 50 $\mu g/g$ of Fe in copper wire can reduce the electrical conductivity by as much as 4%. Chemical composition specifications for unalloyed copper products have become so severe that disputes among producers and consumers have resulted. To promote measurement compatibility and standardization in this multibillion dollar a year industry, NBS was asked to provide accurately characterized trace element SRMs. ASTM is also in the process of developing standard methods for the analysis of unalloyed copper.[159] The development of the new NBS copper benchmark SRMs should greatly aid in the evaluation of the accuracy of the proposed standard methods and eventually lead to nationally accepted reference methods.

Together with existing copper ore SRMs, the new copper benchmark SRMs will provide coverage of nearly all the copper materials cycle from the mining through fabrication stages. Figure 11 illustrates the different stages in the copper materials cycle. Analytical measurements are important for quality and process control at many different points in the cycle. The four copper ore SRMs previously issued by NBS (SRMs 330 [copper millheads], 331 [copper milltails], 332 [copper concentrate], and 333 [molybdenum concentrate]) are for use at the critical points of cycle involving ore concentration and beneficiation. In addition to copper composition, several trace elements are of major concern at this stage of the cycle. For example, there are the important precious metal by-products (rhenium, gold, and silver). Table 9 shows the NBS certified and information values for the constituents of interest in the copper ore SRMs. For example, rhenium is certified and covers the range from 0.4 ppm in the copper milltails to 869 ppm in the molybdenum concentrate. The certified values are at levels typical of those found in actual ores and concentrates.

The unalloyed copper benchmark trace elemental SRMs are designed to be used with measurements made during the smelting, refining, casting, and fabrication stages of the copper materials cycle. More than 70 participants cooperated with NBS in the planning stage of this major project, with 16 companies providing the base materials and 22 laboratories cooperating in the analytical program for certification. The program now has active participation from Canada, South America, the European Economic Community, and a major effort from both industrial and government groups in South Africa (coordinated through the South African Bureau of Standards).

In the case of the unalloyed copper benchmarks, a series of different materials eventually will be developed covering the composition

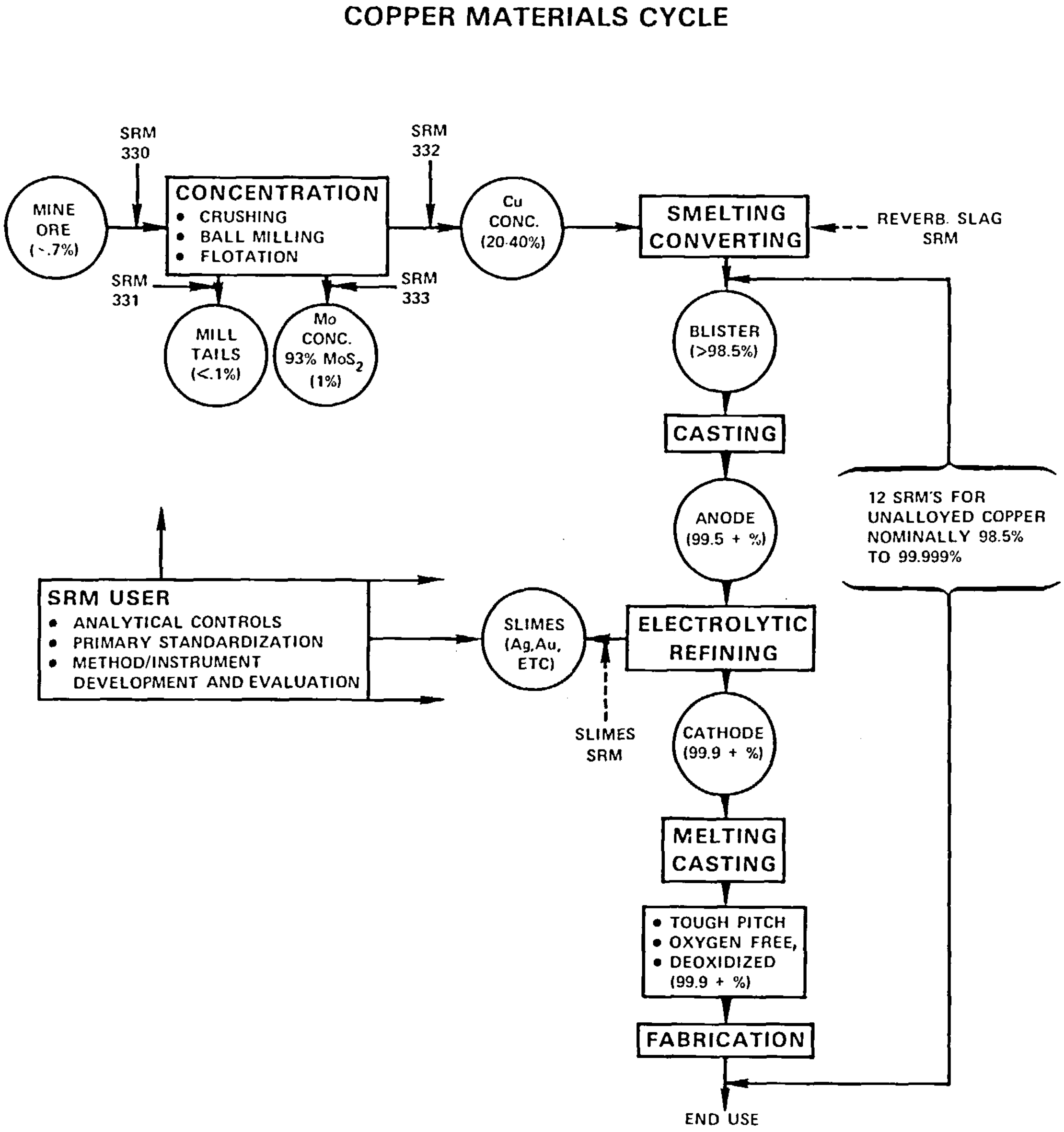


FIGURE 11. Illustration of the use of various NBS Copper SRMs at different points in the Copper Materials Cycle.

range of the products of blister through electrolytic copper (see Table 10). Some of these materials will be processed into different forms, e.g., chips or rods. This set of SRMs will contain between 25 and 30 elements, generally covering the concentration range of from 0.1 to 500 ppm. For example, Bi should cover the range from less than 0.1 ppm up to 35 ppm, and Fe should cover the range 0.1 to 350 ppm. Total copper will cover the range from approximately 99 to 99.999+%.

The first three SRMs in this series, designated as SRMs 394 (CuI), 395 (CuII) and 396 (CuIII), are now available to the public. The SRMs are in the form of small chips for chemical and spectrochemical methods of analysis. Certified values together with estimated uncertainties are given in Figures 5A and 5B. These three SRMs cover the range of copper concentration from 99.908 to 99.955%. The corresponding rod forms of these materials will be issued during 1977 and will be denoted as SRMs 494, 495, and 496.

The analytical program for certification of the Cu benchmarks has been one of the most difficult ever attempted at NBS. The main reason was that

TABLE 9

Certified Values for NBS Copper Ore SRMs

SRM no. designation	330 mill heads	331 mill tails	332 Cu concentrate	333 Mo concentrate
Element		Certificate values		
Cu (wt %)	0.84 ± 0.01	0.091 ± 0.001	28.4 ± 0.1	1.04 ± 0.01
Mo (wt. %)	0.018 ± 0.001	0.0022 ± 0.0002	0.64 ± 0.01	55.3 ± 0.1
Re (ppm)	0.30 ± 0.06	0.04 ± 0.02	10.2 ± 0.2	869 ± 10
		Information values		
Au (ppm)	0.085	0.015	1.8	10
Ag (ppm)	1.20	0.28	36	21

TABLE 10

Target Concentration Ranges for NBS Copper Benchmark SRMs

Element	Probable range (ppm)
Sn	0.1–550
Pb	0.1–325
Bi	<0.1–35
Ni	0.1–550
Sb	0.1–150
Fe	0.1–350
Te	0.1–200
Au	<0.05–100
Ag	0.1–550
Cr	0.1–150
Mn	0.1–500
Zn	0.1–150
Co	0.1–300
Se	0.1–400
O	15–1000
As	0.1–350
Si	<0.1–400
Al	<0.1–400
Mg	<0.05–5
Cd	<0.1–50
Ti	<0.1–300
Li	<0.1–5
B	<0.1–40
Zr	<0.1–300
P	~1–400
Be	<0.01–300
S	9–25
Cu	99.0–99.999+%

some trace analytical methods generally applicable to other matrices were not directly applicable for use with a copper matrix. NBS analysts had to undertake an extensive method-development program before these SRMs could be certified. Several significant developments and observations were made in the course of the certification program. For example, the limit of detection of both As and Sb by spectrochemical methods used in the field appears to be far lower than previously believed (see Table 11). In the case of arsenic, the two completely independent analytical methods used by NBS (spectrophotometry and spark source mass spectrometry) resulted in lower values than the average of the cooperating laboratories. The cooperating laboratories used spectrochemical methods. In the case of SRM 396, NBS estimates the arsenic value to be 0.03 ppm as opposed to the 1.5 ppm average of the cooperating laboratories.

Large discrepancies between NBS results and those of the cooperating laboratories have also occurred in the case of Fe. This is shown clearly in Table 12 which summarizes data taken on SRM 396. The three NBS methods agreed very well, while the cooperating data showed considerable variation. The variability of the cooperating laboratory data, obtained in most cases by spectrochemical techniques, implies a need for improved field methodology for these particular trace elements as well as the critical need for the development of a reference method. The data in Tables 11 and 12 also illustrate the potential danger in using a consensus interlaboratory testing approach to certify reference materials when reference methods are not available for use by the laboratories to control accuracy.

Iron has also proved to be most difficult with respect to homogeneity, especially at the higher concentrations. When 1-g samples are employed, the SRMs have been found to be homogeneous to about 1% relative. When the sample size is reduced to 0.25 g, the inhomogeneity increases to about

TABLE 11

NBS Copper Benchmark SRMs (comparison of data)

	Values by weight (ppm)			
	Average of cooperating labs		NBS values	
SRM	As	Sb	As	Sb
SRM 394 (CuI)	3.0	5.6	2.6	4.8
SRM 395 (CuII)	2.2	7.0	1.6	7.5
SRM 396 (CuIII)	1.5	2.0	0.03 (est.)	0.2 (est.)

TABLE 12

Comparison of NBS Data on Fe (μg/g) in SRM 396 (CuIII)

NBS	
Isotopic dilution	143.1 (1 g)
Mass spectrometry	144.2 (1/4 g)
Polarography	142.1
Activation analysis	140
Cooperators	
Lab B	142.5
Lab C	100.0
Lab E	70–100
Lab F	85
Lab G	120
Lab H	125
Lab J	71
Lab K	138
Lab L	122
Lab M	100
Lab N	150

5% (relative). This material variability is yet to be explained. More details on the NBS methods and certification procedures will be presented in two special monographs to be part of the 260 Series of SRM publications cited previously.

The rod form of Cu(I)-Cu(III) will be issued during mid 1977, thus completing Phase I of this project. Phase II consists of six additional materials, two of which Cu(0) and Cu(XI) will be issued in chip form only. The other four, Cu(IV)-Cu(VII) will be issued in both rod and chip form. These SRMs should be available during late 1977. The issuance of a series of phosphorized copper SRMs, in disk form only, will complete the project during 1978.

The arrows on Figure 11 indicate the points in the copper materials cycle at which the copper SRMs are intended to be used. The need for additional SRMs to be used at two other critical points in the cycle are being evaluated: an SRM to be used in the evaluation of copper slimes (refining by-products that are rich in precious metals) and an SRM for the analysis of slag from reverberation furnaces (one of the critical stages in the copper processing cycle). These points are shown as dotted arrows in Figure 11.

The unalloyed copper SRM project is illustrative of the many important industrial applications of reference materials to trace chemical analysis. The various trace analytical SRMs now available from NBS for analysis of industrial materials are shown in Table 2.

B. Reference Methods

Since reference methods as defined herein are a considerably newer accuracy transfer mechanism than reference materials, the number of examples which might be cited to illustrate their use are quite limited. The ASTM E-350 series of methods discussed previously represent reference methods for use in the industrial area. The determination of total calcium in serum[42] is the only clinical chemistry reference method which has been published to date. A modified version of this method is under development by NCCLS at this time. A reference method for glucose in serum[160] is nearing completion and eight additional methods including serum albumen, bilirubin, lead, and cholesterol are currently under development by the American Association of Clinical Chemists Committee on Standards.[161] Boutwell[162] and Brown[163] have both discussed the impact that the introduction of the calcium in serum reference method has made with respect to the accuracy of field methods. The bias of field measurements was reduced by approximately a factor of three. Several field methods were identified as requiring modification, and the discontinued use of several other methods was also recommended.

In addition to the methods given above, there are a number of standardized analytical methods given in the literature that meet some if not all of the recommended criteria for the development of reference methods. Many ASTM standard methods have been evaluated by interlaboratory testing by members of the ASTM committee or by other cooperating laboratories. However, not all of these methods are evaluated by comparison with definitive methods of known accuracy or with primary reference materials and, thus, should not be considered reference methods in the sense used in this paper. In some cases, data evaluating the accuracy of these standard methods may have been collected during their development. However, since such data are not published with the method, it is not possible for the data to be independently verified. A simple procedure of just publishing such data when available might serve to upgrade some of the standard methods to accurately characterize reference methods. This is not meant to imply that standard methods which have not been characterized for accuracy are not useful. However, data characterizing method precision and accuracy are of paramount importance, especially when the use of such methods will provide the basis for critical economic, health, or environmental decisions.

The value of accurately characterized measurement methods has become increasingly important in the enforcement of environmental regulations. Thus, agencies such as the EPA are placing great emphasis on the development and publication of measurement methods for use in environmental monitoring. For example, in the area of air pollution analysis, the EPA specifies measurement methods which must be used to demonstrate that regulatory standards are being met. These measurement methods are also referred to as reference methods by the Environmental Protection Agency, but in all cases may not meet the reference method criteria defined in this paper. The criteria used in developing EPA air pollution reference methods are given by Clements.[50] Only a single method for a pollutant is designated as an EPA reference method. The method, so designated, must have acceptable accuracy and precision. Further, it must have been scientifically and statistically validated by a multiple laboratory collaborative test under a variety of anticipated user conditions. In addition, these methods require that the equipment used be readily available in most laboratories.

Clements outlines a two-step process to qualify a method as a reference method. The first step is a single laboratory investigation where the method is examined against reference materials to determine its efficiency and to verify the absence of interferences. At the same time, the proposed calibration system is also studied. During this first step, operational details and operating manuals are developed. Reagents are checked for stability, and the performance of the method over the entire range of expected pollutant concentration is evaluated. Those methods that meet the single laboratory investigation requirements are then tested by a series of participating laboratories at a common site while making simultaneous measurements of the existing ambient air. In some additional cases, spike samples of ambient air with additional amounts of pollutant are measured by all the collaborators. This technique is well illustrated by the procedure used in the ASTM Project Threshold.[50] It is important to point out that EPA's reference methods are used to determine compliance with regulatory standards. In most cases, an attempt is made to select the most accurate method, but that is not always the case and not a prime criteria for selection. Ease of analysis and performance with common laboratory instrumentation are considered more important criteria. In the context of this paper, the EPA reference methods might be better referred to as compliance methods for field use.

In the case of methods for chemical analysis of water and waste, the Environmental Protection Agency publishes a series of EPA-recommended methods which are also used for compliance purposes.[164] We present here a brief description of the criteria used by EPA for selection of these water and waste methods. The method should measure the desired property or constituent with precision, accuracy, and specificity sufficient to meet the analytical needs of EPA in the presence of interferring materials typically expected to be present. The method should utilize equipment and skills available in typical modern water-pollution control laboratories. The method must currently be in use in a number of laboratories or have been sufficiently tested to establish its validity. The method should be rapid enough to permit routine use for examination of a large number of samples. In addition, precision and accuracy statements are provided where such data are available; these, however, are not required. Thus, in some cases the water-analysis methods may not meet the reference method criteria suggested in this paper.

We now turn to a brief description of additional standard methods which in some cases are referred to as reference methods but may not necessarily meet the criteria outlined in this paper. These are the numerous federal supply test methods developed by the General Services Administration (GSA) and a large number of measurement methods pertaining to procurement of hardware through the use of military specifications. In many cases, these test methods are adapted from ASTM measurement methods and in other cases are developed and carefully described in GSA and military specification documents. However, in most cases, accuracy and precision data are not provided and in many cases have not been determined. Rather, reproducibility and ease of performance of the analyses are the most important criteria. The federal hardware procurement system is an example of one in which all measurements are being made according to specific, well-defined methods by a closed network of measurement laboratories in such a way that systematic errors may not be of major importance. This is not to imply that the methods are inaccurate but only that inaccuracies within a closed-loop buyer-seller arrangement may not always be of major consequence. Compatibility in such cases may be assured by precision alone.

There are also a number of standard analytical methods published by the American Association of Clinical Chemists.[165] In the past, the procedure used in the certification of these methods was as follows. Methods which may have been developed by a single analyst were submitted to a review board in much the same way as publications are usually submitted to the editor of journals. The method was carefully described in the submitted publication along with data pertinent to its accuracy and precision, if such was available. The method was then submitted to a series of participating laboratories which agreed to test the method under field conditions. This procedure assured that methods were at least evaluated for such factors as clarity of protocol or precision but did not necessarily assure evaluation with respect to accuracy. Recently, the policy of the AACC has changed to require a more thorough evaluation of methods. Under the new policy, a well-characterized method will be published in the journal *Clinical Chemistry*. For the next year, it will be subject to criticism and suggestions for modification and possible independent verification of the data. If able to withstand this scrutiny, the method will then be published in *Standard Methods of Clinical Chemistry*. The first paper submitted under the new policy was "Reference Method for Serum Calcium" by Cali, Bowers, and Young.[42]

Many other examples could be cited concerning recent attempts to develop more accurately characterized analytical methods or to strengthen the procedures used to standardize methods by various government or private-sector organizations. In the accuracy-based measurement system described in Figure 3, the reference method represents the key component in transferring the accuracy inherent in definitive methods (or primary reference materials) into widespread field use. There is no question that much remains to be accomplished in reference-method development in all areas of chemical analysis. Improved mechanisms for assessing the traceability of measurements back to primary reference materials or definitive methods also represent a major challenge to the analytical community.

V. FUTURE NEEDS

In this section we will briefly present our views concerning future needs in the areas of reference materials and reference methods. As has been previously emphasized throughout this paper, there is a growing awareness on the part of a wide range of industrial and technical organizations of the need for more accurate analytical measurements. The traditional needs for measurement accuracy to help assure equity in commerce have been complemented by critical regulatory requirements in areas such as health, environmental control, nuclear safeguards, and occupational safety. Many chemical measurement systems are being heavily impacted by regulatory requirements. What were previously relatively closed communities of analysts have now become open-ended measurement systems whereby individual measurement stations may now be required to report test results to federal, state, and local government agencies, as well as to private-sector, professional, standards, or trade organizations. The needs of such organizations are best served if such data are accurate. This has resulted in unprecedented demands to develop primary and secondary reference materials, definitive methods, reference methods, as well as improved field methods. The increased demands are taxing the available resources of many of the organizational components of the measurement hierarchy. All organizational components of chemical measurement systems must work even closer together in the future to provide the tools to assure measurement accuracy in an efficient manner.

Many segments of the government and private-sector laboratory communities are beginning to recognize the need to improve the quality of measurements made in the field. There are literally thousands of commercial laboratories in the U.S. that test and evaluate products or perform chemical analyses. To evaluate the capabilities of these testing laboratories, many government and private organizations have initiated their own laboratory inspection and proficiency-testing programs. Such programs generally operate independently, serve limited constituencies, and use widely varying criteria for accrediting laboratories. Most also lack national or international acceptance so that the approval of a laboratory by one jurisdiction does not guarantee approval by another.

To meet the need for a national system of testing laboratory accreditation, the Department of Commerce has established the National Voluntary Laboratory Accreditation Program (NVLAP). Final procedures for the utilization and operation of the program were published by the Secretary of Commerce in the Federal Register on February 25, 1976 (15 CFR-Part 7). It is expected that several of the laboratory accreditation programs to be established over the next 5 years could involve chemical analyses. The specific criteria to be used for accrediting laboratories will depend on the type of analyses under consideration. The use of reference materials and reference methods by the laboratory, as well as use of quality control procedures to help establish "proof" of reliable performance, will undoubtedly be among the factors taken into consideration in any accreditation process.

The concept of traceability, previously defined and discussed, may also become of paramount importance in the future and is already being incorporated into some federal and state regulations. However, there has been relatively little effort devoted to defining what is meant, by traceability, although at least one workshop[43] and several papers discuss this concept.[166,167] Traceability implies that each level in a hierarchical tier of measurement systems should be able to relate and trace its measurements results back to the next higher level in the tier, such that there is a logical progression of accuracy from the field method of analysis all the way back up through the system to primary national (or possibly international) standards. One system for achieving traceability is through the establishment of definitive methods of analysis, primary standard reference materials, reference methods, secondary reference materials, and field methods of analysis, coupled to each other as in Figure 3. An accuracy-based measurement network aids in assuring traceability between levels. The development of improved traceability criteria is essential to the establishment of fair and effective regulations and is also needed to enhance the use of secondary reference materials.

At the present time, it appears that requirements for traceability, especially those specified by the EPA, are utilizing written traceability protocols. Thus, specific protocols are being developed to provide a mechanism of traceability from secondary standard suppliers back to primary standard reference materials. In principle, it is not necessary that a unique protocol procedure be followed to assure traceability. The ultimate proof of traceability is the actual performance of one level in the system relative to another.[166] No protocol can guarantee good performance. Good performance must be established through experimental validation of the accuracy and statistical control (stability) of each measurement process.

The last several decades have seen an increasing emphasis on the development of trace analytical techniques for the analysis of a wide variety of materials. The development of well-characterized trace elemental primary reference materials certified on the basis of accuracy has been one of the most important recent contributions to standardization in analytical chemistry. As detection sensitivities continued to increase over the coming years, there will be a need to extend the scope of existing reference materials to cover the added range of sensitivities. However, there are still many gaps in the coverage of concentration ranges and matrix types which can be filled in using available definitive methods to certify additional primary reference materials.

Several areas of industrial analysis in particular require immediate attention. For example, a series of trace element primary reference materials for the analysis of nickel and cobalt-based metal alloys used in high temperature applications (e.g., "superalloys" used in jet engines) are critically needed. Trace element SRMs are also needed for analysis of a number of other industrially important materials such as the lead alloys used in batteries and the stoichiometric compounds used in semiconductor applications. In additional, there is considerable work to be done in extending the range of botanical/biological reference materials to cover other matrices and concentration ranges for elements of trace toxic and nutritional significance. There is also a considerable need to accurately certify not only the total concentration of elements but also the levels of various chemical species. Reference method development should follow the development of primary reference materials in each of these areas.

If the last 10 years could be referred to as the decade of accurate trace elemental analysis, the next 10 years may well be referred to as the decade of accurate trace organic analysis. Recent developments[168] in gas chromatography-mass spectrometry and other chromatographic techniques point to the eventual use of such methods for high-accuracy quantitative organic analysis. In the area of clinical analysis, the expected rapid growth in the development of sensitive immunoassay techniques will also require the development of accurately characterized organic substances to serve as reference materials.

High on any priority list of future organic reference materials would be environmentally important substances such as polynuclear aromatics, chlorinated pesticides, organophosphorus pesticides, phenols, triazines, and uracils. Clinically important substances such as enzymes, individual proteins, and therapeutic drugs are also important. The development of definitive methods for analyzing such substances is a prerequisite to primary reference material and reference-method development. The actual development of matrix-type primary reference materials containing such substances at trace levels and in a form similar to normal test specimens is a challenge yet to be met. NBS has recently completed the research and development phase of a project aimed at producing a series of SRMs for drugs used in the treatment of epilepsy. The SRMs will consist of four drugs (dilantin, ethosuximide, phenobarbital, and primidone) contained in a human serum matrix at subtherapeutic, therapeutic, and toxic levels (ranging from approximately 2 to 180 μg/ml). If the production of this SRM is successful, it will represent the first trace organic SRM produced by NBS and should help to improve the compatibility of clinical tests used in the treatment of epilepsy.[169] Hopefully, the completion of this SRM will be rapidly followed by the development of a number of additional trace organic SRMs in the areas cited above and the subsequent development of reference methods for trace organic analysis.

VI. CONCLUSION

The establishment of compatible accuracy-based chemical measurement systems is becoming increasingly essential. There are a number of important technical components of a compatible chemical measurement system. They are 1.) a self-consistent system of base measurement units; 2.) accurately characterized definitive, reference, and field methods; and 3.) accurately characterized primary and secondary reference materials. In addition, strict measurement protocols designed to establish intralaboratory and interlaboratory measurement quality control as well as traceability between the various technical components of the system are also necessary to assure compatibility. Such a system can only be effective if each organizational component of the system understands its role with respect to the others as well as to the various technical components of the system. The measurement network described in Figure 3 is only as strong as its weakest link. All technical and operational components of the system are vital to the functioning of the total system.

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SUBJECT INDEX

CRC Critical Reviews in Analytical Chemistry

Volume 6 Issues 1–4

Page Numbers for Issues: Issue 1, 1–130; Issue 2, 131–222; Issue 3, 223–324; Issue 4, 325–414