

# Standard Reference Material<sup>®</sup> 3294

## Multielement Tablets

### CERTIFICATE OF ANALYSIS

**Purpose:** This Standard Reference Material (SRM) is intended for the evaluation of analytical methods for the determination of elements in dietary supplement tablets and similar matrices and for quality assurance when assigning values to in-house control materials.

**Description:** A unit of SRM 3294 consists of five bottles, each containing 30 tablets. The SRM is delivered as whole tablets because grinding may compromise stability. Each tablet weighs approximately 1.5 g.

The development of SRM 3294 was a collaboration between the National Institute of Standards and Technology (NIST) and the National Institutes of Health, Office of Dietary Supplements (NIH ODS).

**Certified Mass Fraction Values:** A NIST certified value is a value for which NIST has the highest confidence in its accuracy in that all known or suspected sources of bias and variability have been taken into account [1].

Table 1. Certified Mass Fraction Values (Dry-Mass Basis) for Elements in SRM 3294<sup>(a)</sup>

Element <sup>(b,c)</sup>	Mass Fraction (mg/g)		Element <sup>(b,c)</sup>	Mass Fraction (mg/kg)	
Boron (B)	0.141	± 0.007	Arsenic (As)	0.132	± 0.044
Calcium (Ca)	110.7	± 5.3	Cadmium (Cd)	0.08015	± 0.00086
Chloride (Cl)	53.0	± 2.3	Chromium (Cr)	93.7	± 2.7
Copper (Cu)	1.40	± 0.17	Lead (Pb)	0.2727	± 0.0024
Iodine (I)	0.1327	± 0.0066	Molybdenum (Mo)	70.7	± 4.5
Iron (Fe)	12.35	± 0.91	Nickel (Ni)	8.43	± 0.30
Magnesium (Mg)	67.8	± 4.0	Selenium (Se)	17.42	± 0.45
Manganese (Mn)	1.44	± 0.11			
Phosphorus (P)	75.7	± 3.2			
Potassium (K)	53.1	± 7.0			
Zinc (Zn)	10.15	± 0.81			

<sup>(a)</sup> Values are expressed as  $x \pm U_{95\%}(x)$ , where  $x$  is the certified value and  $U_{95\%}(x)$  is the expanded uncertainty of the certified value. The true value of the analyte is believed to lie within the interval  $x \pm U_{95\%}(x)$  with 95 % confidence. To propagate this uncertainty, treat the certified value as a normally distributed random variable with mean  $x$  and standard deviation  $U_{95\%}(x)/2$  [2–4]. The results in Table 1 are expressed as mass fractions in units of milligrams analyte per gram sample (mg/g) or milligrams analyte per kilogram sample (mg/kg). Metrological traceability is to the International System of Units (SI) unit for mass [2] through the purity evaluations and gravimetric procedures used in the preparation of calibration solutions.

<sup>(b)</sup> Determined at NIST as described in Appendix B.

<sup>(c)</sup> Determined by collaborating laboratories as described in Appendices B and C.

**Non-Certified Values:** Non-certified values for elements in SRM 3294 are provided in Appendix A.

**Period of Validity:** The certified values delivered by **SRM 3294** are valid within the measurement uncertainty specified until **30 June 2031**. The certified values are nullified if the material is stored or used improperly, damaged, contaminated, or otherwise modified.

**Maintenance of Certified Values:** NIST will monitor this SRM to the end of the period of validity. If substantive technical changes occur that affect the certification before the expiration of this certificate, NIST will notify the purchaser. Registration (see attached sheet or register online) will facilitate notification.

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**Safety:** SRM 3294 IS INTENDED FOR RESEARCH USE; NOT FOR HUMAN CONSUMPTION.

**Storage and Handling:** The material should be stored at controlled room temperature (20 °C to 25 °C), in an unopened bottle, until required for use. Freshly ground powder was observed to gain an average of 0.075 % of its original mass in 3 h after grinding. After 24 h, the average gain was 0.11 % of its original mass at 44 % relative humidity and a temperature of 21 °C.

**Use:** At least 15 tablets must be ground to obtain a homogeneous sample prior to removal of a test portion for analysis. Individual tablets should not be analyzed because of tablet-to-tablet variability. The variation of measured element mass fractions from tablet to tablet ranges from approximately 15 % to 25 %, therefore these instructions for use must be followed. NIST analysts used two methods to grind tablets to a powder prior to analysis: (1) thirty tablets were ground in a disk mill, which involved shaking in an orbital pattern for 6 min; (2) batches of 15 tablets, 20 tablets, or 30 tablets were ground for 10 min using an automated mortar and pestle. (Note that 6 min of shaking in a disk mill did not grind the tablets, particularly the coating material, as finely as did technique (2).) For mass fraction values to be valid, test portions of the powder equal to or greater than 0.2 g for As, Ca, Cr, Co, Cu, Fe, I, La, Mg, Mn, Mo, Na, Sb, Se, V and Zn should be used, test portions equal to or greater than 0.25 g for B, Cd, Ni, and Sn should be used, test portions equal to or greater than 0.35 g for K and P should be used, test portions equal to or greater than 0.5 g for Pb should be used, test portions equal to or greater than 0.75 g for Cl and Ti should be used, and test portions equal to or greater than 4.5 g for Si and Sr should be used (see Appendix B for additional information). Test portions should be analyzed as-received and results converted to a dry-mass basis by determining moisture content (described below) on a separate test portion.

**Determination of Moisture:** Moisture content of SRM 3294 was determined at NIST in ground tablets (see instructions for “Storage and Handling” and “Use”) by (1) freeze-drying to constant mass over 8 d; (2) drying over magnesium perchlorate in a desiccator at room temperature for 5 d, 7 d, and 12 d; and (3) drying for 4 h in a forced-air oven at 80 °C. Unweighted results obtained using all three techniques were averaged to determine a dry-mass proportion of  $(0.9863 \pm 0.0051)$  gram dry mass per gram as-received mass; the uncertainty shown on this value is an expanded uncertainty. The conversion factor used to convert data from an as-received to a dry-mass basis is the inverse of the dry-mass proportion. A relative uncertainty component for the conversion factor (0.26 %) obtained from the moisture measurements is incorporated in the uncertainties of the certified and reference values, reported on a dry-mass basis, that are provided in this certificate.

**Material Acquisition and Preparation:** A manufacturer of multivitamin/multielement tablets prepared a non-commercial batch of tablets according to their normal procedure. These tablets are a direct-compression tablet formulation produced by blending a vitamin and a mineral pre-mix with the remaining bulk of the formulation, compression, and tablet film coating. The film coating consisted of triethyl citrate, polysorbate 80, yellow #6 aluminum-lake, hypromellose, and titanium dioxide.

## REFERENCES

- [1] Beauchamp, C.R.; Camara, J.E.; Carney, J.; Choquette, S.J.; Cole, K.D.; DeRose, P.C.; Diewer, D.L.; Epstein, M.S.; Kline, M.C.; Lippa, K.A.; Lucon, E.; Molloy, J.; Nelson, M.A.; Phinney, K.W.; Polakoski, M.; Possolo, A.; Sander, L.C.; Schiel, J.E.; Sharpless, K.E.; Toman, B.; Winchester, M.R.; Windover, D.; *Metrological Tools for the Reference Materials and Reference Instruments of the NIST Material Measurement Laboratory*; NIST Special Publication (NIST SP) 260-136, 2021 edition; U.S. Government Printing Office: Washington, DC (2021); available at <https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.260-136-2021.pdf> (accessed Nov 2021).
- [2] Thompson, A.; Taylor, B.N.; *Guide for the Use of the International System of Units (SI)*; NIST Special Publication 811; U.S. Government Printing Office: Washington, DC (2008); available at <https://www.nist.gov/pml/special-publication-811> (accessed Nov 2021).
- [3] JCGM 100:2008; *Evaluation of Measurement Data — Guide to the Expression of Uncertainty in Measurement (GUM 1995 with Minor Corrections)*; Joint Committee for Guides in Metrology (JCGM) (2008); available at <https://www.bipm.org/en/publications/guides> (accessed Nov 2021); see also Taylor, B.N.; Kuyatt, C.E.; *Guidelines for Evaluating and Expressing the Uncertainty of NIST Measurement Results*; NIST Technical Note 1297; U.S. Government Printing Office: Washington, DC (1994); available at <https://www.nist.gov/pml/nist-technical-note-1297> (accessed Nov 2021).
- [4] JCGM 101:2008; *Evaluation of Measurement Data — Supplement 1 to the “Guide to the Expression of Uncertainty in Measurement” — Propagation of Distributions Using a Monte Carlo Method*; Joint Committee for Guides in Metrology (JCGM) (2008); available at <https://www.bipm.org/en/publications/guides> (accessed Nov 2021).
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- [6] Sieber, J.; Broton, D.; Fales, C.; Leigh, S.; MacDonald, B.; Marlow, A.; Nettles, S.; Yen, J.; *Standard Reference Materials for Cements*; *Cem. Concr. Res.*, Vol. 32, pp. 1899–1906 (2002).

*Certain commercial equipment, instruments, or materials may be identified in this Certificate of Analysis to adequately specify the experimental procedure. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.*

*Users of this SRM should ensure that the Certificate of Analysis in their possession is current. This can be accomplished by contacting the Office of Reference Materials 100 Bureau Drive, Stop 2300, Gaithersburg, MD 20899-2300; telephone (301) 975-2200; e-mail [srminfo@nist.gov](mailto:srminfo@nist.gov); or the Internet at <https://www.nist.gov/srm>.*

\* \* \* \* \* End of Certificate of Analysis \* \* \* \* \*

# APPENDIX A

**Non-Certified Values:** Non-certified values are suitable for use in method development, method harmonization, and process control but do not meet the NIST criteria for certification [1] and are the best estimates of the true values based on available data. The values are provided with an uncertainty that may reflect only measurement reproducibility, may not include all sources of uncertainty, and/or may reflect a lack of sufficient statistical agreement among multiple analytical methods. Non-certified values should not be used to establish metrological traceability to the International System of Units or other higher-order reference system.

Non-certified mass fraction values for analytes in SRM 3294, reported on a dry-mass basis, are provided in Table A1 and are the mean of results provided by NIST measurements. Values are expressed as  $x \pm U_{95\%}(x)$ , where  $x$  is the non-certified value and  $U_{95\%}(x)$  is the expanded uncertainty of the non-certified value. The method-specific value of the analyte lies within the interval  $x \pm U_{95\%}(x)$  with 95 % confidence. To propagate this uncertainty, the non-certified value should be treated as a normally distributed random variable with mean  $x$  and standard deviation  $U_{95\%}(x)/2$  [3,4].

Table A1: Non-Certified Mass Fraction Values (Dry-Mass Basis) for Analytes in SRM 3294

Element <sup>(a)</sup>	Mass Fraction (mg/kg)
Antimony (Sb)	0.159 ± 0.008
Cobalt (Co)	0.81 ± 0.01
Lanthanum (La)	0.70 ± 0.01
Silicon (Si)	2010 ± 10
Sodium (Na)	330 ± 20
Strontium (Sr)	29.8 ± 0.2
Tin (Sn)	11.1 ± 0.9
Titanium (Ti)	5400 ± 300
Vanadium (V)	8 ± 2

<sup>(a)</sup> Determined at NIST as described in Appendix B.

**Period of validity:** The non-certified values are valid within the measurement uncertainty specified until **30 June 2031**. The value assignments are nullified if the material is stored or used improperly, damaged, contaminated, or otherwise modified.

**Maintenance of Non-Certified Values:** NIST will monitor this material to the end of its period of validity. If substantive technical changes occur that affect the non-certified values during this period, NIST will update this Appendix. Before making use of any of the values delivered by this material, users should obtain the most recent version of this documentation, available free of charge through the <https://www.nist.gov/srm> website.

\*\*\*\*\* End of Appendix A \*\*\*\*\*

# APPENDIX B

## SOURCE, PREPARATION AND ANALYSIS

**Analytical Approach for Determination of Elements:** Value assignment of the mass fractions of the elements in SRM 3294 was based on the combination of measurements from several different analytical methods at NIST and in an interlaboratory comparison exercise involving GMA FIACC laboratories. NIST provided measurements by using prompt gamma activation analysis (PGAA), instrumental neutron activation analysis (INAA), radiochemical neutron activation analysis (RNAA), X-ray fluorescence spectrometry (XRF), and inductively coupled plasma optical emission spectrometry (ICP-OES) or inductively coupled plasma mass spectrometry (ICP-MS) with isotope dilution (ID) in some cases. GMA laboratories used their usual methods. Tables B1 and B2 list the methods used for measurement of the elements.

### **NIST Analyses for As, B, Cd, Cu, Hg, I, K, Mo, Ni, P, Pb, Se, Sn, V, and Zn by Using ICP-OES and ICP-MS:**

Tablets were ground as described above in "Use". Copper, molybdenum, nickel, phosphorus, potassium, vanadium, and zinc were measured by ICP-OES in duplicate test portions (0.35 g to 0.4 g) taken from each of six bottles of the SRM. Samples for ICP-OES analysis were digested in Teflon beakers in nitric, perchloric, and hydrofluoric acids. Arsenic, boron, iodine, nickel, selenium, and tin were measured by ICP-MS in single test portions (0.25 g to 0.45 g) taken from each of six or ten bottles. Except for samples in which iodine was measured, samples for ICP-MS and ID-ICP-MS analyses were digested in microwave systems; samples in which arsenic, boron, nickel, selenium, and tin were measured were digested in nitric and hydrofluoric acids, samples in which cadmium was measured were digested in nitric and hydrofluoric acids, and samples in which lead was measured were digested in nitric acid. Samples in which iodine was measured were digested in an alkaline solution of sodium hydroxide and sodium sulfite and were measured by ICP-MS with standard additions. Cadmium was isolated from interferences (Mo and Sn, in particular) by solid-phase extraction and measured by ID-ICP-MS in collision-cell mode in single test portions (0.25 g) taken from each of ten bottles. Lead was measured by ID-ICP-MS in single test portions (0.5 g) taken from each of six bottles. Mercury was measured by using ID cold vapor ICP-MS (ID-CV-ICP-MS) in two 0.5 g test portions taken from a single bottle. Samples for mercury analysis were digested in a mixture of nitric acid and hydrogen peroxide. The mass fraction of mercury was too low for quantitation. Quantitation for ICP-OES and non-ID-ICP-MS analyses was based on the method of standard additions.

### **NIST Analyses for Ca, Co, Cr, Cu, Fe, I, La, Mg, Mn, Mo, Na, Sb, Se, V, and Zn by Using INAA:**

Tablets were ground as described above, and antimony, calcium, cobalt, chromium, copper, iodine, iron, lanthanum, magnesium, manganese, molybdenum, selenium, sodium, vanadium, and zinc were measured using INAA. Individual disks were prepared from 0.2 g test portions taken from each of eight bottles; a duplicate was prepared from one of the bottles. Disks were formed using a stainless steel die and hydraulic press. Standards were prepared by transferring a weighed portion of a solution containing a known amount of each element onto filter papers or from pure elements or compounds of known purity. For analysis of short-lived nuclides (calcium, copper, iodine, magnesium, manganese, sodium, and vanadium), samples, standards, and controls were packaged individually in clean polyethylene bags and irradiated individually at 20 MW. For analysis of long-lived nuclides (antimony, cobalt, chromium, iron, lanthanum, molybdenum, selenium, and zinc), samples, standards, and controls were irradiated for 3 h; irradiation capsules were then inverted 180°, and materials were irradiated another 3 h. Short-lived nuclides were counted for 5 min after a 2 min decay and again for 20 min following a 15 min decay. For the long-lived irradiations, a 4 h count followed a 5 d decay and an 8 h count followed a 25 d decay.

### **NIST Analyses for B, Cl, Cu, Fe, K, and Ti by Using PGAA:**

Tablets were ground as described above, and boron, chlorine, copper, iron, potassium, and titanium were measured using PGAA. Individual disks were formed from 0.75 g test portions taken from each of six bottles and duplicate test portions taken from each of two bottles of the SRM. Disks were formed using a stainless steel die and hydraulic press. Standards were prepared by transferring a weighed portion of a solution containing a known amount of each element onto filter papers. Disks were formed from the dried filter papers. Samples, standards, and controls were packaged individually in clean polyethylene bags and irradiated individually at 20 MW, which provided a neutron fluence rate of  $3.0 \times 10^8 \text{ cm}^{-2}\text{s}^{-1}$ . The following  $\gamma$ -ray lines were used for quantitation: 477 keV line from  $^{10}\text{B}$  (corrected for  $^{10}\text{B}$  in the background and for  $^{23}\text{N}$  at 472 keV from the sample), 770 keV line from  $^{39}\text{K}$ , 6111 keV line from  $^{35}\text{Cl}$ , 341 keV and 1381 keV lines from  $^{48}\text{Ti}$ , 278 keV line from  $^{63}\text{Cu}$ , and 352 keV line from  $^{56}\text{Fe}$ .

### **NIST Analyses for As by Using RNAA:**

Tablets were ground as described above, and arsenic was measured by using RNAA. Individual disks were formed from 0.2 g test portions taken from each of five bottles of the SRM. Disks were formed using a stainless steel die and hydraulic press. Standards were prepared by transferring a weighed portion of a solution containing a known amount of arsenic onto filter papers. Disks were formed from the dried filter papers. Samples, standards, and controls were packaged individually in clean polyethylene bags and irradiated in

one polyethylene irradiation vessel for 2 h at 20 MW, which provided a neutron fluence rate of  $1.0 \times 10^{14} \text{ cm}^{-2}\text{s}^{-1}$ . Samples and controls were combined with  $^{77}\text{As}$  tracer and digested in nitric and perchloric acids. Arsenic was sequestered on hydrated manganese dioxide resins, which were then counted. The 559 keV line from decay of  $^{76}\text{As}$  was used for quantitation. The 239 keV line from decay of  $^{77}\text{As}$  was evaluated for yield determination.

**NIST Analyses for Ca, Cr, Fe, K, Mg, Mn, Mo, P, Si, and Sr by Using XRF:** Tablets were ground as described above, and calcium, chromium, iron, magnesium, manganese, molybdenum, phosphorus, potassium, silicon, and strontium were measured by using XRF in duplicate or triplicate test portions of 4.5 g taken from each of six bottles. Samples were prepared by borate fusion, and samples were cast as 40 mm diameter beads. (Average loss on fusion at 975 °C was 53.2 % of the average (as-received) mass.) The K-L<sub>2,3</sub> characteristic X-ray lines of calcium, chromium, iron, magnesium, manganese, molybdenum, phosphorus, potassium, silicon, and strontium were used for quantitation. Sample beads were bracketed with at least four synthetic standards for calibration [5,6].

**Homogeneity Assessment:** The homogeneity of various elements was assessed at NIST by using ICP-OES, INAA, PGAA, and XRF. Analysis of variance did not show inhomogeneity for the test portions analyzed. All measurands were treated as though they were homogeneously distributed, although homogeneity of all measurands was not assessed.

Table B1. NIST Methods Used for Elemental Determinations<sup>(a)</sup>

Element	NIST Analytical Methods
Antimony (Sb)	INAA
Arsenic (As)	ICP-MS, RNAA
Boron (B)	ICP-MS, PGAA
Cadmium (Cd)	ID-ICP-MS
Calcium (Ca)	INAA, XRF
Chlorine (Cl)	PGAA
Chromium (Cr)	INAA, XRF
Cobalt (Co)	INAA
Copper (Cu)	ICP-OES, INAA, PGAA
Iron (Fe)	INAA, PGAA, XRF
Iodine (I)	ICP-MS, INAA
Lanthanum (La)	INAA
Lead (Pb)	ICP-MS, ID ICP-MS
Magnesium (Mg)	INAA, XRF
Manganese (Mn)	INAA, XRF
Molybdenum (Mo)	ICP-OES, INAA, XRF
Nickel (Ni)	ICP-OES, ICP-MS
Phosphorus (P)	ICP-OES, XRF
Potassium (K)	ICP-OES, PGAA, XRF
Selenium (Se)	ICP-MS, INAA
Silicon (Si)	XRF
Sodium (Na)	INAA
Strontium (Sr)	XRF
Tin (Sn)	ICP-MS
Titanium (Ti)	PGAA
Vanadium (V)	ICP-OES, INAA
Zinc (Zn)	ICP-OES, INAA

<sup>(a)</sup> ICP-OES Inductively coupled plasma optical emission spectrometry  
 ICP-MS Inductively coupled plasma mass spectrometry  
 ID-ICP-MS Isotope dilution inductively coupled plasma mass spectrometry  
 INAA Instrumental neutron activation analysis  
 PGAA Prompt gamma-ray activation analysis  
 XRF X-ray fluorescence spectrometry

Table B2. Summary of GMA FIACC Analytical Methods Used for Measurement of Elements.

Element	Methods <sup>(a,b,c)</sup>
Calcium (Ca)	ICP-OES (4), FAAS (1)
Chloride (Cl <sup>-</sup> )	Potentiometric titration (2)
Copper (Cu)	ICP-OES (3), FAAS (1)
Iron (Fe)	ICP-OES (4), FAAS (1)
Magnesium (Mg)	ICP-OES (4), FAAS (1)
Manganese (Mn)	ICP-OES (3), FAAS (1)
Phosphorus (P)	ICP-OES (3), Colorimetry (1)
Potassium (K)	ICP-OES (4), FAAS (1)
Zinc (Zn)	ICP-OES (4), FAAS (1)

<sup>(a)</sup> Not all laboratories reported methods used.

<sup>(b)</sup> Number in ( ) corresponds to number of laboratories using the method.

<sup>(c)</sup> ICP-OES Inductively coupled plasma optical emission spectrometry  
 FAAS Flame atomic absorption spectroscopy

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# APPENDIX C

## Collaborating Laboratories Contributing Data to Value Assignment of Elemental Determinations

Laboratories participating in an interlaboratory comparison exercise organized by the Grocery Manufacturers Association (GMA) Food Industry Analytical Chemists Committee (FIACC) that provided results are:

Campbell Soup Company (Camden, NJ),  
Covance (Madison, WI),  
General Mills, Inc., James Ford Bell Technical Center (Golden Valley, MN),  
Krueger Food Laboratories, Inc. (Billerica, MA),  
Novartis Nutrition Corporation (St. Louis Park, MN).

The GMA FIACC interlaboratory comparison exercise was coordinated by I.-P. Ho of GMA (Washington, DC).

\*\*\*\*\* End of Appendix C \*\*\*\*\*