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Standard Test Method for Analysis of Multiple Elements in Cannabis Matrices by Inductively Coupled Plasma Mass Spectrometry (ICP-MS)[1]

This standard is issued under the fixed designation D8469; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This test method uses inductively coupled plasma mass spectrometry (ICP-MS) to determine multiple trace elements in cannabis and cannabis-related matrices following sample preparation using microwave-assisted acid digestion. This test method is applicable to the quantification of trace levels of elements in dried plant materials, concentrates, oils, extracts, tinctures of cannabis and cannabis-related products. Other matrices may be added provided that the lab validates the extra matrices using Practice D8282. Details are provided on the validation of both the sample preparation procedure and analytical method using certified reference materials (CRMs) and validation of the analytical method using spike recovery testing of several cannabis based samples.

1.2 This test method should be used by analysts experienced in the use of microwave digestion and ICP-MS, matrix interferences, and procedures for their correction or reduction, and should only be used by personnel trained in the handling, preparation, and analysis of samples for the determination of trace elements in cannabis and cannabis products (**1**).[2] This test method was developed using a single quadrupole ICP-MS equipped with a collision/reaction cell (CRC) that can be pressurized with helium (He) gas for the removal of polyatomic interferences using kinetic energy discrimination (KED). This test method can also be run using a triple quadrupole or "tandem" mass spectrometer (MS/MS) ICP-MS instrument, which is fitted with CRC technology. The ICP-MS method accounts for polyatomic interferences, which are the most common spectral overlaps in ICP-MS, isobaric interferences, and any potential doubly-charged ion interferences (M^{2+}) that may arise from the presence of rare earth elements (REEs) in the samples, as the REE^{2+} ion interferences can affect the accuracy of the measurement of arsenic (As) and selenium (Se) in the samples. Table 1 lists elements for which the test method applies along with recommended analytical masses, and secondary masses for some elements. The priority toxic elements arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb), also sometimes referred to as the "big four" toxic trace elements are listed separately because of their toxicity, as discussed in 5.1.

1.3 Certified reference materials (CRMs) should be matrix matched as closely as possible to the cannabis/plant matrix. In-house reference materials (RMs) are acceptable if no CRM is available and/or the in-house RM is well characterized, but CRMs are preferred. NIST 1575a Pine Needles, NRC HEMP-1, and a NIST hemp sample (NIST number not assigned yet) were analyzed to verify method bias. The RM/CRMs should have a recovery between 80 % to 120 % when concentrations are above the limit of quantification (LOD) or within the concentration uncertainty (converted to percent relative uncertainty) supplied on the certificate, whichever is greater. If acceptable values are not obtained, the analytical solution may be reanalyzed once. If acceptability is still not met, recalibrate and reanalyze the entire analytical sequence and/or prepare and digest new analytical portions.

1.4 *Multi-laboratory Validation (MLV)*—This test method was tested by analyzing an NRC hemp CRM, a NIST hemp SRM, and a NIST plant control sample (NIST 1575a Pine Needles) by four laboratories each running a single quadrupole ICP-MS.

1.5 Gravimetric dilution (weight/weight), volumetric dilution (volume/volume), or a combination of the two techniques (weight/volume) are acceptable methods for ICP-MS sample preparation.

1.6 *Units*—The values stated in SI units are to be regarded as the standard. No other units of measurement are included in this standard.

1.7 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.8 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the*

[1] This test method is under the jurisdiction of ASTM Committee D37 on Cannabis and is the direct responsibility of Subcommittee D37.03 on Laboratory.

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[2] The boldface numbers in parentheses refer to the list of references at the end of this standard.

TABLE 1 Recommended Masses for Each Element and Some Secondary Masses

Priority Elements	Recommended Analytical Mass	Secondary Analytical Masses
Arsenic (As)	75	...
Cadmium (Cd)	111	114
Lead (Pb)	208[A]	...
Mercury (Hg)	201	200, 202
Other Elements	**Recommended Analytical Mass**	
Sodium (Na)	23	...
Aluminum (Al)	27	...
Potassium (K)	39	...
Vanadium (V)	51	...
Chromium (Cr)	52	53
Manganese (Mn)	55	...
Iron (Fe)	56	54
Cobalt (Co)	59	...
Nickel (Ni)	60	58, 62
Copper (Cu)	63	65
Zinc (Zn)	66	67, 68
Selenium (Se)	78	77, 80
Molybdenum (Mo)	95	98
Silver (Ag)	107	...
Antimony (Sb)	121	...
Barium (Ba)	137	...
Thallium (Tl)	205	...
Thorium (Th)	232	...
Uranium (U)	238	...

[A] Lead is measured as the sum of the three most abundant isotopes, 206, 207, and 208: (208) = M(206) + M(207) + M(208).

Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.

2. Referenced Documents

2.1 *ASTM Standards:*[3]

D1193 Specification for Reagent Water

D8270 Terminology Relating to Cannabis

D8282 Practice for Laboratory Test Method Validation and Method Development

E177 Practice for Use of the Terms Precision and Bias in ASTM Test Methods

E691 Practice for Conducting an Interlaboratory Study to Determine the Precision of a Test Method

2.2 *Other Standards:*

U.S. Environmental Protection Agency (EPA) standard methods 200.8 and 6020B **(2, 3)**

FDA EAM 2.2 Food Homogenization **(4)**

3. Terminology

3.1 For definitions of terms related to cannabis, see Terminology D8270.

3.2 *Definitions:*

3.2.1 *analytical solution, n*—a cannabis sample that has been prepared for analysis per 11.3.

3.2.2 *calibration blank (CalBK), n*—volume of Type 1 reagent water containing the same amount of acid matrix as is in the calibration standards.

3.2.3 *calibration standards (CalSTD), n*—a standard having an accepted value (reference value) for use in calibrating a measurement instrument or system.

3.2.4 *calibration stock solution, n*—solution prepared from the stock standard solution(s) to verify the instrument response with respect to analyte concentration.

3.2.5 *cannabidiol (CBD), n*—a cannabinoid found in cannabis plants.

3.2.6 *collision/reaction cell (CRC), n*—device used to remove polyatomic interfering ions through reaction or collision with a gas added to the cell.

3.2.7 *interlaboratory study (ILS) or multi lab validation (MLV), n*—study in which collaborators in multiple laboratories use a defined method of analysis to analyze identical portions of homogeneous materials to assess the performance characteristics obtained for that method of analysis.

3.2.8 *internal standard (ISTD), n*—pure element(s), which is not one of the analyte elements and is not present in the sample, added in known amount(s) to a solution.

3.2.9 *laboratory duplicate (DUP), n*—two aliquots of the same sample taken in the laboratory and analyzed separately with identical procedures; analyses of laboratory duplicate 1 and laboratory duplicate 2 indicate precision associated with laboratory procedures, but not with sample collection, preservation, or storage procedures.

3.2.10 *limit of detection (LOD), n*—the minimum concentration of an analyte that can be identified, measured, and reported with 99 % confidence that the analyte concentration is greater than zero.

3.2.11 *method blank (MBK), n*—use 0.5 g Type 1 water for method blanks.

3.2.12 *relative standard deviation (RSD), n*—the measure of deviation of the measured analytical concentrations around the mean—used to express the precision of the results.

3.2.13 *spike solution, n*—an aliquot of cannabis sample to which known quantities of the method analytes are added in order to check if the sample matrix contributes bias to the analytical results; the background concentrations of the analytes in the sample matrix must be determined in a separate aliquot and the measured values in the spiked sample corrected for background concentrations—see 14.2.

3.2.14 *tuning solution, n*—a solution which is used to determine acceptable instrument performance before calibration and sample analyses—see 13.1.

4. Summary of Test Method

4.1 This test method describes the multi-element determination of multiple trace elements by ICP-MS in cannabis and cannabis-based samples and matrices. The digested sample is introduced into the ICP (plasma) as an aerosol by passing the liquid sample through a simple pneumatic nebulizer. The largest aerosol droplets are removed from the gas stream by a

[3] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

spray chamber, and about 2 % to 3 % of the remaining smaller droplets are swept into the central channel of the plasma via the torch. It is recommended to use a thermoelectric (Peltier) cooled spray chamber to reduce signal drift caused by localized temperature change. A cooled spray chamber also reduces the water vapor content of the aerosol, resulting in a hotter plasma and so improving matrix tolerance, increasing ionization, reducing suppression, and reducing formation of oxides and other matrix based polyatomic ion overlaps. The sample aerosol enters the plasma, which is generated in a stream of argon contained in a torch. The torch is surrounded by a coil or plate to transfer RF energy into the plasma. The argon plasma temperature (up to 10 000 K maximum and around 7500 K in the central channel) rapidly dries the aerosol droplets, which are then decomposed, vaporized, atomized, and ionized by the removal of one electron from each atom. The positively charged ions that are produced in the plasma are extracted into the vacuum system via a series of interface cones. To maintain the high vacuum around the mass spectrometer, the orifices of the cones are small, typically 1 mm diameter or less. An ion focusing system or "lens" is used to focus the ions into the entrance aperture of a quadrupole mass spectrometer (MS). The quadrupole uses a combination of DC (direct current) and AC (alternating current) electrical fields to separate the ions based on their mass-to-charge ratio (*m/z*). The electron multiplier (EM) detector detects each ion as it exits the quadrupole. Singly charged ions (M^+) with an *m/z* equal to the ion's mass are detected by the EM detector. The detector electronics count and store the total signal for each mass (*m/z*), creating a mass spectrum.

4.2 A weighed portion (approximately 0.5 g is typical) of a thoroughly homogenized cannabis sample is digested using a mixture of HNO_3 and HCl using closed-vessel digestion apparatus. The digests are then diluted using Type 1 reagent water to 50 g. Blanks and CRMs are prepared in the same way. Internal standards are added to the solutions to compensate for variations in sample introduction efficiency and element ionization efficiency in the plasma. The solutions are typically introduced to the ICP-MS instrument via an autosampler. By comparing measured *m/z* peak intensities of elements in the sample with *m/z* peak intensities measured with the calibration standards, the concentrations of elements in the sample can be calculated.

5. Significance and Use

5.1 Medical and/or recreational marijuana (cannabis) has been legalized for adult use in many countries and states within the USA (**5**). Many jurisdictions that permit the use of medicinal and recreational marijuana require testing of cannabis and associated products to ensure safety from contaminants, especially the toxic "big four" elements such as As, Cd, Hg, and Pb (**6**), and other metals worthy of consideration (**6**). These heavy metals can accumulate in plants grown in polluted soils or contamination can occur during the manufacturing process (**7**). In addition to ensuring product safety, the analysis of mineral and other trace elements is required for labeling purposes when these products are sold as nutritional supplements. Trace element analysis of plant and nutritional supplement materials is a well-established application (**8**). Following acidic digestion to break down the plant-based samples' primary components, ICP-MS is often used for quantitative analysis because of its multi-element capability, high sensitivity, speed, robustness, and wide dynamic range.

5.2 This test method covers the rapid determination of multiple elements in cannabis sample digests. The elements include the priority toxic elements (As, Cd, Hg, and Pb), as well as elements required by some states and elements of interest in the cannabis community (V, Cr, Cu, Zn, Sb, Ba, Se, Ag, Na, Al, K, Mn, Fe, Co, Ni, Mo, Tl, Th, and U). Irrespective of the number of elements being measured, test times are approximately a few minutes per test specimen, and detectability for most elements is in the low- to sub-ppb range.

6. Interferences

6.1 *Spectral Interferences*—Polyatomic ions that have the same *m/z* as an analyte ion are the main source of spectral interferences in ICP-MS. A list of typical polyatomic ions that are derived from the plasma gas (Ar), reagents, or sample matrix is shown in Table 2. If a high plasma temperature is maintained, the level of many polyatomic interferences will be reduced. The robustness of the plasma can be determined by measuring the CeO/Ce ratio. The oxide ratio shows the plasma's ability to break apart the Ce-O molecule. Since the Ce-O molecule is strongly bound, it is a good indicator of decomposition of the sample matrix and other molecular ions. Comparing the signal for CeO^+ at *m/z* 156 to Ce^+ at *m/z* 140 allows a quick assessment of the plasma's capability to decompose the matrix. A more robust plasma (lower CeO/Ce ratio) is beneficial for analyzing the high and variable matrix levels encountered in typical batches of cannabis samples. The typical CeO/Ce ratio that can be achieved varies for different ICP-MS designs, but operators should be aware of the analytical benefits of better matrix tolerance, higher ionization, and lower levels of polyatomic interferences that are provided by optimizing to a lower CeO/Ce ratio, ideally as close as possible to 1 %. Often polyatomic ion interferences can be avoided by the selection of an alternative analytical isotope. If that is not appropriate, some ICP-MS systems provide a simple and reliable solution to resolve common polyatomic interferences using a CRC that is operated in helium collision mode, often referred to as He mode. He mode uses KED to filter out polyatomic ions while allowing atomic ions to pass through the cell to the detector. KED is a physical process that makes use of the fact that polyatomic (molecular) ions have a larger ionic cross-section than the atomic ions at the same *m/z*. Due to their larger size, the polyatomic ions collide more frequently with the helium cell gas, and so lose more energy than the (smaller) analyte ions do. Because of their greater energy loss during passage through the cell, the polyatomic ions can be rejected using a bias voltage at the cell exit. He mode is effective for many polyatomic ion overlaps, so it works for many elements, and it can be applied to a wide range of typical ICP-MS sample types, even varied samples with complex and unknown matrices. Common, matrix-based polyatomic interferences are removed, allowing access to the preferred isotopes of all

TABLE 2 Common Polyatomic and Potential Elemental Interferences in Typical Cannabis Matrix Samples

Priority Analytes	Polyatomic Interferences	Elemental Interferences
^{75}As	$^{40}Ar^{34}SH$, $^{40}Ar^{35}Cl$, $^{40}Ca\ ^{35}Cl$, $^{37}Cl_2H$	$^{150}Sm^{++}$, $^{150}Nd^{++}$
^{111}Cd	$^{95}Mo^{16}O$, $^{94}Zr^{16}OH$	...
$^{206,\ 207,\ 208}Pb$	$^{190}Pt^{16}O$, $^{191}Ir^{16}O$, $^{192}Pt^{16}O$	...
^{201}Hg	...	...
Other Analytes	**Polyatomic Interferences**	**Elemental Interferences**
^{23}Na	$^{7}Li^{16}O$	$^{46}Ti^{++}$
^{27}Al	$^{12}C^{15}N$, $^{13}C^{14}N$, $H^{12}C^{14}N$	...
^{39}K	^{38}ArH	$^{78}Se^{++}$
^{51}V	$^{35}Cl^{16}O$, $^{37}Cl^{14}N$, $^{34}S^{16}OH$	...
^{52}Cr	$^{36}Ar^{16}O$, $^{40}Ar^{12}C$, $^{35}Cl^{16}OH$,$^{37}Cl^{14}NH$, $^{34}S^{18}O$	...
^{55}Mn	$^{37}Cl^{18}O$, $^{23}Na^{32}S$, $^{23}Na^{31}PH$	$^{110}Cd^{++}$
^{56}Fe	$^{40}Ar^{16}O$, $^{40}Ca^{16}O$	$^{112}Cd^{++}$
^{59}Co	$^{40}Ar^{18}OH$, $^{43}Ca^{16}O$, $^{23}Na^{35}ClH$	$^{118}Sn^{++}$
^{60}Ni	$^{44}Ca^{16}O$, $^{23}Na^{37}Cl$	$^{120}Sn^{++}$, $^{120}Te^{++}$
^{63}Cu	$^{40}Ar^{23}Na$, $^{12}C^{16}O^{35}Cl$, $^{12}C^{14}N^{37}Cl$, $^{31}P^{32}S$, $^{31}P^{16}O_2$	$^{126}Te^{++}$, $^{126}Xe^{++}$
^{66}Zn	$^{34}S^{16}O_2$, $^{32}S^{34}S$, $^{33}S_2$, $^{48}Ca^{18}O$	$^{132}Xe^{++}$, $^{132}Ba^{++}$
^{78}Se	$^{40}Ar\ ^{38}Ar$, $^{62}Ni^{16}O$	^{78}Kr, $^{156}Gd^{++}$, $^{156}Dy^{++}$
^{95}Mo	$^{40}Ar^{39}K^{16}O$, $^{79}Br^{16}O$	...
^{107}Ag	$^{91}Zr^{16}O$	...
^{121}Sb	$^{105}Pd^{16}O$	...
^{137}Ba	$^{97}Mo^{40}Ar$	...
^{205}Tl	...	...
^{232}Th	...	...
^{238}U	$^{201}Hg^{37}Cl$	...

typical analytes. He mode also removes the common polyatomic overlaps on secondary isotopes. Measuring secondary isotopes can be used to confirm the result reported using the primary isotope. For severe background interferences, a reactive cell gas may be suitable as an alternative to He collision mode. However, reactive cell gases need to be treated with caution on single quadrupole ICP-MS, as their use can lead to analyte signal loss, and the creation of unpredictable new cell-formed product ion overlaps, unless the CRC mass stability boundaries and reactive gas flows are optimized correctly. But a reaction gas may give more complete removal of certain predictable and consistent interferences, such as Ar_2 on Se at mass 78 and 80. Correction equations within ICP-MS instrument software can also be used to correct for polyatomic interferences, although they can be less reliable than using a CRC in KED/He mode of operation. Interference equations involve determining the signal for another isotope of the interfering element and subtracting the appropriate signal from the analyte isotope signal.

6.2 *Isobaric Molecular and Doubly-charged Ion Interferences*—Isobaric molecular and doubly-charged ion interferences can affect ICP-MS measurements of some analytes, as shown in Table 2. Isobaric overlaps occur when an analyte is measured at an isotope mass where an isotope of a different element is also present. Most isobaric interferences that could affect ICP-MS determinations have been well studied in the literature and are not unique to this method (**1**, **2**). These overlaps are easy to avoid by choosing the default, preferred analytical isotope for each element of interest. Doubly-charged ions can affect quadrupole ICP-MS measurements because a quadrupole mass spectrometer separates ions based on their *m/z*, rather than their true atomic mass. So, if an atom loses two electrons—giving it a double-positive charge (M^{2+}) rather than the usual single-positive charge (M^{+}), it will appear at half its true mass. For example, arsenic can suffer a doubly-charged ion interference from the REE, samarium ($^{150}Sm^{++}$) and neodymium ($^{150}Nd^{++}$). Other examples of potential elemental interferences are listed in Table 2. Some instrument manufacturer's software includes an automatic software routine to correct for doubly-charged ion interferences. The same correction can be set up manually, following manufacturer guidelines.

6.3 *Physical Interferences*—Physical interferences occur during sample introduction, processes in the plasma, and the transmission of ions through the instrument's interface and may lead to differences in instrument responses for the sample and the calibration standards. Physical interferences can occur when the viscosity and surface tension of a sample solution is different compared to the low matrix, synthetic calibration standards. The difference can cause variation in the solution flow through the uptake tubing, the nebulization (aerosol droplet formation) process, and the transport and evaporation rate of the aerosol droplets. These variations lead to a change in the overall transport of aerosol droplets to the plasma and therefore a change in the overall signal. Since these effects influence all elements the same, internal standard correction can be used to effectively compensate for the signal differences. If samples contain high levels of total dissolved solids (TDS) and the plasma is not optimized for good robustness, undissociated sample matrix material may deposit on the interface cones, affecting ion transmission. Typically, for ICP-MS, it is advised that TDS should not exceed 0.2 % (w/v), so samples that contain higher TDS levels would typically be diluted before being analyzed. However, instruments that are equipped with aerosol dilution technology use an additional argon gas flow to dilute the aerosol before it reaches the torch. This technology enables samples with percent level TDS to be analyzed routinely by ICP-MS over extended periods of time. Internal standardization or standard addition may be effectively used to compensate for many physical interference effects and

long term drift. Internal standards should have similar analytical behavior to the elements being determined.

6.4 *Memory Interferences*—To minimize carryover of isotopes of elements in one sample contributing to the signals of subsequent samples, ensure that the elements are stabilized in solution (for example, by adding HCl) and flush the system with a rinse blank(s) between samples. Blanks should be analyzed periodically to check that they are free from memory effects. The possibility of memory effects should be acknowledged, and suitable rinse times should be employed. The required rinse time for a particular element varies and should be determined before the analysis. This can be done by aspirating the highest calibration standard containing the elements of interest for a normal sample analysis period, followed by analysis of the rinse blank multiple times afterwards. Track the rinse blank for any carry-over. The length of time required to reduce analyte signals to within a factor of 10 of the limit of detection should be noted. If available, an intelligent rinse function can be used to optimize rinse times by monitoring the elemental signals and terminating the rinse step early if the monitored element signals fall below a set threshold. If the analytical solution concentrations are higher than the highest standard concentration, dilute the analytical solution. The new concentration should ideally be at the midpoint of the calibration curve for that element. If the concentration of the injected unknown sample is higher than the highest calibration standard, then check all samples following that high sample. Make sure to check for carry-over by checking the RSD of replicate concentrations of all samples following the sample that was higher than the highest calibration curve. If RSD exceeds 10 %, determine if it is due to carry-over and remedy before proceeding.

7. Apparatus

7.1 *Balance*—Top loading or analytical, with automatic tare, capable of weighing to 0.0001 g, with sufficient capacity to weigh prepared solutions.

7.2 *Volumetric tubes*—For volumetric dilution, use 15 mL or 50 mL tubes that are class A calibrated, so the volume mark can be used for final dilution in the vials.

7.3 *Inductively coupled plasma mass spectrometer (ICP-MS)*—The ICP-MS must be capable of scanning *m/z* range 5 μ to 240 μ with a minimum resolution better than 0.5 μ at 10 % peak height. The ICP-MS should be equipped with a CRC or equivalent that provides consistent and reliable control of typical polyatomic ion overlaps. In many routine applications, the CRC is pressurized with helium, acting as a collision gas. Polyatomic overlaps on analyte ions are removed through the physical process of KED. On single quadrupole ICP-MS instruments, reactive cell gases may be suitable for addressing some spectral overlaps. See manufacturers' instruction manual for operation of the ICP-MS.

7.3.1 The instrument should be configured with a typical sample introduction system such as a nebulizer, spray chamber, quartz torch, and interface cones. Sample uptake and introduction to the ICP-MS is done with a peristaltic pump.

7.4 *Microwave digestion system*—A microwave capable of reaching 210 °C should be used.

8. Reagents and Materials

8.1 *Purity of reagents*—Reagent grade chemicals shall be used in all tests. Unless otherwise indicated, it is intended that all reagents shall conform to the specifications of the committee on Analytical Reagents of the American Chemical Society, where such specifications are available (**9**).[4] Other grades may be used, provided it is pure enough to be used without lessening the accuracy of the determination.

8.2 *Purity of water*—Unless otherwise indicated, references to water shall be understood to mean reagent water as defined by Type 1 of Specification D1193.

8.3 *Purity of acids*—Trace metal grade or better chemicals of nitric acid and hydrochloric acid should be used for microwave digestion and preparing diluted acid for sample preparation and analysis.

8.4 *Diluent*—Made with 1 % (v/v) HNO_3/0.5 % (v/v) HCl solution in Type 1 water.

8.5 *ICP-MS tuning, calibration, and internal standards*—The stock standards used for tuning and calibrating the ICP-MS, and the internal standard solution used for the preparation of the samples are detailed in Table 3.

8.5.1 *Blank solutions*—Prepare calibration blank (1 % HNO_3/0.5 % HCl in ASTM Type 1 Water or 2 % HNO_3/0.5 % HCl in ASTM Type 1 Water) and a rinse blank (same composition as calibration blank) solutions on the same day as analysis.

8.5.1.1 *Method blanks (MBK)*—A minimum of two MBKs must be included in each digestion batch to verify the absence of contamination that may arise from the vessels.

[4] *Reagent Chemicals, American Chemical Society Specifications*, American Chemical Society, Washington, DC. For suggestions on the testing of reagents not listed by the American Chemical Society, see *Analar Standards for Laboratory Chemicals*, BDH Ltd., Poole, Dorset, U.K., and the United States *Pharmacopeia and National Formulary*, U.S. Pharmacopeial Convention, Inc. (USPC), Rockville, MD.

TABLE 3 Solutions Used in Method Development

Solution	Elements
Initial Calibration Verification Standard (Second source standard from the Environmental Calibration Standard)	10 μg/mL of Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn, Th, U; 1000 μg/mL of Fe, K, Ca, Na, Mg, Sr
Environmental Spike Mix	100 μg/mL Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn, U. 1000 μg/mL Fe, K, Ca, Na, Mg
Environmental Calibration Standard	10 μg/mL of Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn, Th, U; 1000 μg/mL of Fe, K, Ca, Na, Mg
Internal Standard	100 μg/mL of ^{6}Li, Sc, Ge, Lu, In, Tb, Rh, Bi
Tuning Stock Solution	10 μg/mL of Li, Co, Ce, Y, Tl
Mercury (Hg)	1000 μg/mL of Hg
Hg Calibration Solution	10 μg/mL of Hg

8.5.2 *Calibration standard solutions*—Prepare these weekly in a 50-mL polypropylene centrifuge tube: Working Environmental Calibration Standard: 1 mg/L Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn, Th, U. 100 mg/L Fe, K, Ca, Na, Mg in 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Add 5 mL of Environmental Calibration Standard to 45 mL of 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Mercury (Hg) Stock Calibration Standard A: 10 mg/L Hg in 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Prepare by adding 0.5 mL of 1000 µg/mL Hg Standard to 49.5 mL of 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Mercury (Hg) Working Solution A: 0.1 mg/L in 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Prepare by adding 0.5 mL of Hg Stock Calibration Standard A (see previous text) to 49.5 mL of 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution.

8.5.3 *Calibration standards*—Prepare the multi-element calibration standards listed in Section 12 from the calibration stock solutions. Prepare the standards on the same day as sample analysis, make each standard in a 50 mL polypropylene centrifuge tube.

8.5.4 *Internal standard and QC standards*—Prepare the following standard solutions and sample solutions in 50 mL polypropylene centrifuge tubes:

8.5.4.1 *Internal standard (ISTD) working solution for on-line addition*—2 mg/L ^{6}Li, Sc, Ge, Lu, In, Tb, Rh, Bi in 1 % HNO_3. Prepare by adding 1 mL of Internal Standard Mix to 49 mL of 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. ISTD solution may be prepared volumetrically. The exact concentration is less important than the same concentration over an entire analytical sequence.

8.5.4.2 *Mercury (Hg) working solution B*—1.0 mg/L Hg in 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Prepare by adding 5.0 mL of 10 µg/mL Hg Standard to 45 mL of 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Prepare independent solutions from Working Hg Solution A. Use independent Hg standard from Hg Stock Calibration Standard A.

8.5.4.3 *Initial calibration verification (ICV) solution*—0.05 mg/L Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Sr, Tl, V, Zn, Th, U. 5 mg/L Fe, K, Ca, Na, Mg. 0.001 mg/L Hg in 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Prepare by adding 0.25 mL of Initial Calibration Verification Standard and 0.05 mL of 1 mg/L Working Hg Solution B to 49.7 mL of 1 % (v/v) HNO_3 and 0.5 % (v/v) HCl solution. Prepare independent solutions from the Continuing Calibration Verification solution.

8.5.4.4 *Continuing calibration verification (CCV) solution*—Use a mid-level calibration standard (Std 5 in Section 12).

8.5.4.5 *Certified reference materials (CRM)*—Add the details of the CRM your laboratory has selected and fill in the QC information in the ICP-MS software. Analyze at least one CRM sample such as NIST 1547a Peach Leaves, NIST 1573a Tomato Leaves, NIST 1575a Pine Needles, NRC HEMP-1, or NIST Hemp SRM (available in 2022). Digest them with the other samples.

8.5.4.6 *Laboratory duplicates (DUP)*—Select a sample from the batch to be analyzed. Remove two 15 mL aliquots of the sample solution and place each aliquot in a separate 50 mL polypropylene test tube.

8.5.4.7 *Spike solution*—Prepare the spike solutions and add to the chosen cannabis samples before closed-vessel microwave digestion. Prepare the standards on the same day as sample digestion. One spiked analytical solution per sample type is recommended.

8.5.4.8 *Mercury (Hg) Spike Stock Solution A*—100 mg/L Hg in 1% (v/v) HNO_3 solution. Prepare by adding 5 mL of 1000 mg/L Hg Standard to 45 mL of 2% (v/v) HNO_3 solution in a 50 mL polypropylene test tube. The Hg spike stock solution is prepared without HCl and should therefore be freshly prepared each month or more frequently if the stability of the standard cannot be confirmed.

8.5.4.9 *Working spike solution – High*—1 mg/L Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Hg, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn, Th, U. 10 mg/L Fe, K, Ca, Na, Mg. in 2 % (v/v) HNO_3 solution. Prepare by adding 0.5 mL of Environmental Spike Mix and 0.5 mL of Hg Spike Solution A (see above) to 49 mL of 2 % (v/v) HNO_3 solution in a 50 mL polypropylene test tube.

8.5.4.10 *Working spike solution – Low*—100 µg/L Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Hg, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn, Th, U. 0.1 mg/L Fe, K, Ca, Na, Mg. in 2 % (v/v) HNO_3 solution. Prepare by adding 5 mL of Working Spike Solution – High (see above) to 45 mL 2 % (v/v) HNO_3 solution in a 50 mL polypropylene test tube.

9. Hazards

9.1 The use of laboratory equipment and chemicals exposes the analyst to several potential hazards. Good laboratory technique and safety practices should be used at all times. Safety glasses and acid resistant gloves should be worn at all times when handling samples or reagents, or when near others handling these items, especially when handling standards containing elements such as As, Cd, Hg, Pb, Cr, Cu, Zn, Sb, Ba, Se, Ag, Na, Al, K, Mn, Fe, Co, Ni, Mo, Tl, Th, and U. Also, proper ventilation and other physical safeguards should be in place when handling these standards. Analysts should consult, and must be familiar with, their laboratory's chemical hygiene and safety plan and Safety Data Sheets for all reagents and standards listed.

9.2 ICP-MS instruments require a supply of argon gas that can be provided from compressed argon gas cylinders or bottles, or from a liquid argon Dewar. Liquid argon represents a potential cryogenic and suffocation hazard and leaks from a compressed argon cylinder can also represent a suffocation hazard. Safe handling procedures should be employed at all times when handling compressed gas cylinders, liquid argon tanks, and fittings, and appropriate gas monitoring equipment should be installed in laboratories where such gases are stored and used. Many ICP-MS instruments are fully interlocked to prevent user exposure to harmful electrical voltages, radio frequency emissions, ultraviolet radiation, high temperatures, and other hazards. The operator should never attempt to disable

these interlocks or operate the instrument if any safety interlocks are suspected to have been disabled. Refer to instrument manuals for safety precautions regarding use.

9.3 All additional company safety practices and procedures should be followed at all times. Spilled samples and reagents should be cleaned up from instrument and laboratory surfaces immediately. Acid spills should be neutralized with sodium bicarbonate solution before cleanup. The acidification of samples containing reactive materials may result in the release of toxic gases, such as cyanides or sulfides. Acidification (and disposal) of samples should be done in a fume hood.

10. Sampling, Test Specimens, and Test Units

10.1 The method was developed and tested on the cannabis and hemp samples listed in Table 4.

10.2 *Sample Homogenization*—This test method assumes that all samples have been collected and homogenized accordingly per production batch size and physical form of the product. The aim of sample collection is to obtain a representative sample of the entire production batch while the aim of homogenization is to obtain an analytical sample representative of the collected sample. Follow state protocol for cannabis sampling and homogenization, or refer to ASTM Committee D37 Sample Preparation Group documents (under development) for reference on homogenization approaches. Depending on the type of sample, the homogenization procedure should be such that it provides uniform and repeatable results using instrumentation that is easy to clean and maintain, is adapted to hold various sample sizes, and, preferably, that is metal free, to reduce the risk of contamination of the sample.

11. Preparation of Apparatus

11.1 *ICP-MS*—Consult the manufacturer's instructions for operating the instrument.

11.2 The ICP-MS operating parameters used for verifying this method for the analysis of cannabis and hemp-matrices are shown in Table 5. Optimal operating parameters for this test method may vary by specific ICP-MS system models. The instrument used included a CRC operating in helium collision mode and aerosol dilution technology. See Section 13 for more details.

11.3 Typical microwave digestion operating parameters used for the preparation of cannabis and hemp-matrices are shown in Table 6. Optimal operating parameters for this method may vary by specific microwave digestion system models. These digestion conditions were optimized for batches of mixed samples of various degrees of decomposition difficulty. If digesting only plant material, for example, less acid volume may be used. When using less acid volume or lower digestion temperatures, a complete digestion should still be achieved. In most cases, a clear and colorless solution upon dilution with no particulate constitutes a complete digestion. Check for matrix enhancements and suppressions by monitoring spike recovery data and by examining the internal standard signal.

TABLE 4 Cannabis Sample Categories and Samples

Sample Category	Sample
Inhaled	Hemp flower
Oral	Hemp butter
Topical	Cannabis-based pain relief cream
Manufacturing	CBD crude extract

TABLE 5 Example ICP-MS Parameters

Parameter	Value
RF power (W)	1600
Sampling depth (mm)	10
Carrier gas (L/min)	0.80
Aerosol dilution gas (L/min)	0.15
Aerosol dilution setting	4
Helium cell gas (mL/min)	4.3
Energy discrimination (V)	3.0

TABLE 6 Example Microwave Digestion Parameters

Example Digestion	
Sample weight	0.5 g
HNO_3	9 mL
HCl	1 mL
Oven Program	
Ramp (to 210 °C)	20 min
Hold (at 210 °C)	15 min
Cool down	10 min
Final Dilution	
Reagent water	Add to 50 g
Total dilution factor	100×

12. Calibration and Standardization

12.1 The ICP-MS system should be calibrated using a calibration blank and a minimum of four calibration standards using a linear curve fit. Up to seven multi-element standards were used in this test method (Table 7). Using pipettes to make calibration standards, and then recording the weights is common.

12.2 *Calibration*—At the beginning of the analysis of each batch of samples, perform a calibration consisting of the blank and all calibration standards appropriate for the range. Use the CCV check standard to determine if each element is in calibration. When the results obtained with the CCV are within 10 % of the expected concentrations for all elements to be analyzed, proceed with test specimen analyses. Otherwise, make any adjustments to the instrument that are necessary and repeat the calibration for those elements that failed the QC check. Repeat this procedure with the check standard every 10 to 20 samples.

12.3 ICP-MS instruments use software that automatically performs the calculations to establish the calibration curve. See Section 15 for details of the calculations.

12.4 The limits of detection (LODs) are calculated by analyzing a low-level spike solution: LOD = 3 × SD (low-level spike) × 100 (dilution factor). Analytical limits will vary depending on the specific instrumentation, dilution factor, and blank quality. Achieving the lowest analytical limits requires careful attention to operating conditions and the highest level of quality control.