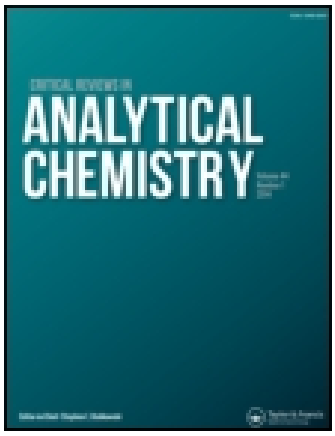


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# Validation and Quality Control of an ICP-MS Method for the Quantification and Discrimination of Trace Metals and Application in Paper Analysis: An Overview

Ion Gh. Tanase[a], Dana Elena Popa[a], Gabriela Elena Udriştioiu[a], Andrei A. Bunaciu[b] & Hassan Y. Aboul-Enein[c]

[a] Department of Analytical Chemistry, Faculty of Chemistry, University of Bucharest, Bucharest, Romania

[b] SCIENT (by CROMATEC_PLUS SRL), Research Center for Instrumental Analysis, Bucharest, Romania

[c] Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo, Egypt

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# Validation and Quality Control of an ICP-MS Method for the Quantification and Discrimination of Trace Metals and Application in Paper Analysis: An Overview

**Ion Gh. Tanase,[1] Dana Elena Popa,[1] Gabriela Elena Udriştioiu,[1] Andrei A. Bunaciu,[2] and Hassan Y. Aboul-Enein[3]**

*[1]Department of Analytical Chemistry, Faculty of Chemistry, University of Bucharest, Bucharest, Romania*
*[2]SCIENT (by CROMATEC_PLUS SRL), Research Center for Instrumental Analysis, Bucharest, Romania*
*[3]Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo, Egypt*



**Questioned documents analysis includes: handwriting comparison, analysis of the ink and the printer used in the production of the documents, and the physical and chemical characterization of the cellulosic substrate (paper) of the documents. In many situations in life, for financial, social, and personal concerns, we depend on different documents. Therefore, over time, various analytical methods have been developed in order to determine their authenticity, source, and age or to differentiate various papers. In this study a quantitative analytical method for the determination of eight trace level chemical elements (Al, Ba, Fe, Mg, Mn, Pb, Sr, Zn) from document paper samples using inductively coupled plasma-mass spectrometry (ICP-MS) was validated and applied. The evaluation of the performance parameters of the method (applicability, fitness for purpose, linearity, working range, limit of detection and limit of quantification, sensitivity, accuracy, and precision) was accomplished. An overview of the validation parameters are presented and discussed in detail.**

**Keywords** Inductively coupled plasma-mass spectrometry, paper analysis, quality control, trace metals, validation

## INTRODUCTION

An important atomization and excitation source in atomic emission spectrometry is plasma: direct current plasma, alternating current plasma, inductively coupled plasma, capacitively coupled plasma. It presents various advantages over the electrical arc or electrical spark and underlies inductively coupled plasma-atomic emission spectrometry (ICP-AES) (Broekaert, 2002; Garbarino and Taylor, 1985; Greenfield et al., 1964; Reed, 1961; Tănase, 2001, 2007; Wendt and Fassel, 1965).

Inductively coupled plasma-mass spectrometry (ICP-MS) has been used for both highly sensitive multielement analysis and the independent measurement of specifically stable isotopes (Beauchemin et al., 2000; Becker, 2007; Broekaert, 2002; Hill, 2006; Montaser, 1998; Nelms, 2005; Taylor, 2000; Vanhaecke and Köllensperger, 2003). Usually, the detection limit is $10^{-9}$ g, but it may be lowered down to $10^{-12}$ g (Date and Gray, 1989; Douglas and French, 1981; Houk et al., 1980).

Inductively coupled plasma as an excitation source was introduced by Reed (1961), but the first practical uses reported were by Greenfield et al. (1964) and Wendt and Fassel (1965).

ICP-MS proved to possess an effective combination of precision, accuracy, a large number of elements that can be determined, and good detection limits (Bacon et al., 1999; Date and Gray, 1989; Haraguchi, 1999).

Inductively coupled plasma offers high ionization efficiency; it operates at atmospheric pressure and at high temperatures, while a mass spectrometer requires vacuum conditions and ambient temperature, so it is therefore necessary to introduce an interface to reduce both temperature and pressure. The most common interface consists of two cones made of copper or nickel, with millimeter or submillimeter apertures (Broekaert, 2002; Garbarino and Taylor, 1985).

To summarize the many scientific papers on the analysis of trace-level elements various reviews have been published. Bacon et al. (1999) published a general review about atomic mass spectrometry. Haraguchi (1999) reviewed multielement profiling analyses of biological, geochemical, and

Address correspondence to Hassan Y. Aboul-Enein, Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo 12311, Egypt. E-mail: haboulenein@yahoo.com

environmental samples. Mach et al. (1996) published a review for metals speciation. Bersier et al. (1994) compared some advanced electroanalytical techniques with atomic absorption spectrometry (AAS), ICP-AES, and ICP-MS in environmental analysis. In 1994 Lobinski (Lobinski, 1994) presented the status of speciation analysis using gas chromatography (GC) with mass spectrometry detection. Cresser et al. (1993) published a general review of atomic spectrometry for environmental analysis.

From 1992 to 1997 other reviews were also published: general applications of ICP-MS to environmental analysis (Broekaert, 1995; Byrdy and Caruso, 1994; Grosser and Wolf, 1997; Tomlinson et al., 1995; Uden, 1995), and application of ICP-MS to radionuclides (Crain, 1996), rare earth compounds (Daolio et al., 1992), biological and environmental samples (Sah, 1995), and geoanalysis and hydrology (Brenner and Taylor, 1992). Some other reviews discuss hyphenated methods: chromatography and ICP-MS (Ellis and Roberts, 1997; Hill et al., 1993).

A couple of reviews from 1998 covered general applications of ICP-MS for elemental speciation studies (Zoorob et al., 1998) and applications of ICP-MS to cosmo-chemistry, geochemistry, and paleoceanography (Halliday et al., 1998).

Between 2000 and 2012, reviews were published on trace metal determination using ICP-MS in various fields: environment and life sciences (Richardson, 2001), elemental speciation (B'Hymer and Caruso, 2006; Leykin and Yakimovich, 2012; Moldovan et al., 2004; Ray et al., 2004; Rodríguez-Gonzalez et al., 2005; Rosen and Hieftje, 2004; Sanz-Medel et al., 2003; Shah and Caruso, 2005; Waddell et al., 2005), biological systems (Schaumlöffel and Lobinski, 2005), metalloprotein analysis (Hagege et al., 2004), oyster analysis (Sneddon and Vincent, 2008), food (Cubadda, 2004) and beverage (Meija et al., 2004) analysis, precious metals (Balcerzak, 2002, 2003), brain science (Ha et al., 2011), biomedicine (Qin et al., 2011), soils and agriculture (Wei and Yang, 2010), and bullet alloys (Ulrich et al., 2004).

Furthermore, in the past decade, some reviews and books that cover various aspects of ICP-MS have been published (Agatemor and Beauchemin, 2011; Ammann, 2007; Beauchemin, 2010; Chace, 2001; Linge and Jarvis, 2009; McLuckey and Wells, 2001; Tomer, 2001; Vestal, 2001; Zhou, 2005).

For multielement trace analysis, several ICP-MS methods have been developed (Eiden et al., 1999; Hattendorf and Günther, 2000, 2003; Held et al., 1995; McCurdy and Potter, 2001; Morrison et al., 2000; Tanner et al., 2000; Vaughan et al., 1987) and validated (Brouwers et al., 2006; Demuth and Heumann, 2001; Voica et al., 2009, 2012), and measurement uncertainty was estimated (Clough et al., 2003; Ruth, 2004).

ICP-MS has proved to be a fast, precise, and sensitive technique for multielement analysis of document paper (bank certificates, bills, personal documents, etc.). Spence and Francis (Spence et al., 2002) quantified nine elements (Na, Mg, Al, Mn, Sr, Y, Ba, La, and Ce) within questioned documents (a threatening letter), and the study was used to assist in a criminal investigation. Wagner et al. (1999) studied ink corrosion in the written area of some ancient manuscripts, revealing that the content of iron and copper varies significantly between written and non-written areas. They used laser ablation ICP-MS to define the distribution patterns of iron and copper on the surface of the manuscript. McGaw et al. (2009) used ICP-MS to determine the concentration of nine elements (Mg, Al, Mn, Fe, Sr, Y, Ba, Ce, and Nd) from paper samples provided by two different vendors. Based on the significant differences of some element concentrations, they differentiated reams of paper from the same vendor. They were also able to differentiate the paper purchased from the two different vendors.

In a previous study Udrişţioiu and coworkers (Tănase et al., 2012; Udrişţioiu, 2012) optimized an ICP-MS method for the quantitative determination of eight trace-level elements (Al, Ba, Fe, Mg, Mn, Pb, Sr, and Zr) in sheets of paper from five different brands of white A4 photocopy paper. The results of the study proved that this method can be used for the discrimination of paper from different brands.

The objective of the present work is to present a detailed validation and overview for the quality control in a single laboratory of the method for the determination of trace elements (Al, Ba, Fe, Mg, Mn, Pb, Sr, Zn) in five different brands of white A4 photocopy paper using ICP-MS.

For the validation of the method several parameters have been taken into account and evaluated, namely: applicability, fitness for purpose, selectivity and specificity, fitness of the calibration function, linearity range, sensitivity, detection limit, quantification limit, accuracy, precision, and the uncertainty of the analytical measurement results.

## EXPERIMENTAL SECTION

ICP-MS is an analytical technique used for quantitative determination of trace chemical elements in various gaseous, liquid, and solid samples, among which are paper samples.

Virtually all chemical elements can be determined with high sensitivity and low background signal by ICP-MS. The technique provides very good detection limits and thanks to the quadrupole analyzer, multielement measurement takes only a few minutes for each sample. The ion population depends on the plasma temperature (5,000–9,000 K) and the ionization potential (3.89 eV for Cs and 10.43 eV for Hg).

To discriminate paper samples based on the element concentrations measured by ICP-MS, the elements must meet several conditions, namely:

- Their concentration in the paper samples must be above the detection limit of the instrument;
- They must be uniformly distributed in the sheets and in each ream;
- They should not be affected by spectral interference;

- They should have a significant concentration change from one manufacturer to another.

## Reagents and Materials

All the reagents and solvents were of analytical grade: nitric acid (Merck, Suprapur) and hydrogen peroxide (30% AnalR). Ultrapure deionized water from a Milli-Q analytical reagent-grade water purification system (Millipore, USA) was used.

To ensure the continuity of operating parameters a multielement solution was used (PerkinElmer Co., Beaconsfield, Bucks, UK, which contains Be, Co, In, Ge, Tl, and U, 10 ppb for each element), prepared in 2% $HNO_3$.

In order to prepare calibration standard solutions and internal standard solutions a certified reference material (ICP Multi Element Standard Solution, Merck, 25 elements of 10 ppm each) was used as a stock solution. The calibration standard solutions were prepared in 2% $HNO_3$ and their concentrations lay between 5 and 100 ppb.

The paper chosen for analysis was office document paper: white, A4 (210/297 mm), 80 $g \cdot m^{-2}$ printer/copy paper labeled acid- and chlorine-free. Five different brands of paper were used: 1, Storaenso, multilaser; 2, Xerox, business; 3, Uni Copy, laser copier; 4, Navigator, universal; and 5, Sky Copy, paper.

## Apparatus and Optimization

The analyses were performed using a NexION 300 ICPMS (PerkinElmer Co., Beaconsfield, Bucks, UK) with an S10 auto sampler. The spectral data were processed with Chromera software (PerkinElmer Co., Beaconsfield, Bucks, UK). A microwave digestion unit (MW 3000 PerkinElmer) was used for the digestion of the samples.

For the optimization of ICP-MS the aspects that must be taken into consideration are: the highest power of detection, minimal spectral interference, signal increase, and highest precision. The most important parameters are the power of the ICP, the flow of the gas, the burner geometry, the position of the sampler, and the ion optics parameters because they determine the ion yield and transmission and the intensities of the analyte and interference signals.

Optimization of carrier gas flow, ion sampling location, and the power is critical in ICP-MS. Changes in the nebulizer gas flow influence the formation and breakdown of cluster ions. Therefore, it is also necessary to consider optimization for minimum spectral interference.

The carrier gas flows influence the ion energies (Broekaert, 2002; Raeymaekers et al., 1989) and the geometry of the aerosol channel. The aerosol gas flow must be optimized together with the power and the position of the sampler.

The transmission for a certain ion can be optimized by changing the voltages at the different ion lenses. Thus, the optimization of its detection limit and the minimization of interference are accomplished. In multielement determinations a compromise must be always made.

The instrumentation and data acquisition optimized parameters were presented in a previous paper (Tănase et al., 2012).

In a daily operation the instrument was tuned for the analysis using the above-mentioned multielement solution. The purpose of this operation was to:

- Optimize the vertical and horizontal position of the torch to achieve a maximum signal for indium;
- Optimize the position of the lens for a maximum signal for one of the ascertained masses (lithium, indium or uranium);
- Adjust nebulizer flow to achieve a maximum signal for beryllium, indium, and uranium simultaneously with a minimum ratio for oxides.

After this, the instrument was calibrated using the calibration standard solutions.

## Procedure

The used procedure was detailed described in the previous study (Tănase et al., 2012).

## Validation of the Analytical Method

Method validation is essential in the assessment of a laboratory's competence to provide reliable analytical results. The concept of method validation is in close relation to quality control and quality assurance, and it is extensive; the method validation should include all the stages from sampling to the final result, not only the instrumental one (van Zoonen et al., 1999). The first step consists in assessment of the performance criteria.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) gave characteristic definitions and requirements for validation in two guidelines (ICH, 1994, 1996). The first guidelines present the validation characteristics required for different types of testing procedures. The second covers experimental data and some statistical interpretations. These guidelines provide support for both the authorities and industry and emphasize the importance of a suitable validation process.

They provide only a basis for a general discussion about validation parameters, their calculation, and interpretation. The analyst has the responsibility to identify the parameters that are relevant for the performance of the analytical procedure. Therefore, he or she must clearly understand the background of the validation parameters and the consequences of their values.

The evaluation of performance criteria is closely related to the "fitness for purpose" concept, defined in the International Union of Pure and Applied Chemistry (IUPAC) "Orange Book" (Inczédy et al., 1998) as "the degree to which the data

produced by a measurement process enables a user to make technically and administratively correct decisions for a stated purpose," For this reason it is important first to consider the requirements related to the problem and second to choose the analytical method that best fits their needs and, ultimately, to assess.

The Eurachem guide *The Fitness for Purpose of Analytical Methods* (Eurachem, 1998) describes how important it is that the analytical performance and the analytical problem be suitable. It discusses the importance of the analytical method validation. "Fitness for purpose" involves the applicability and suitability criteria (Thompson et al., 2002), which require the assessment of the operational and time constraints, as well as other parameters such as reuse or automation opportunities. "Fitness for purpose" represents the degree to which the performance of an analytical method meets the criteria that the analyst and the end user of the data have agreed on (Massart et al., 1997; Taverniers et al., 2004).

In the *Handbook of Chemometrics and Qualimetrics* Massart et al. (1997) presented two types of performance criteria: primary and secondary. Accuracy, precision, trueness, and limit of detection belong to the first group, while the other parameters that can influence these primary criteria belong to the second group (linearity, working range, quantification limit, selectivity, sensitivity, robustness).

The validation of analytical methods is the process of establishing the performance characteristics and their limitations, as well as identifying the parameters that may influence these characteristics. Currently, there are a variety of guides and guidelines on method validation in different areas (pharmaceutical, food, environmental).

The U. S. Food and Drug Administration (FDA) has published two guides to the validation of analytical (U.S. Department of Health and Human Services et al., 2000) and bioanalytical (U.S. Department of Health and Human Services et al., 2001) methods and IUPAC has published guidance for validation of analytical methods (Thompson et al., 2002). Eurachem has published the most detailed guide, both theoretically and practically (Eurachem, 1998) and AOAC has published a guide about how to meet the ISO 17025 requirements (Analytical Laboratory Accreditation Criteria Committee [ALACC], 2007). Huber (2007) published a validation reference book. Other authors have also addressed the validation of analytical methods (Ermer and Miller, 2005; Tănase et al., 2007; Viswanathan et al., 2007).

Analytical method validation along with measurement uncertainty estimation and concentration profiles can provide a way to verify the "fitness for the purpose" of the method in terms of meeting legal requirements (Thompson et al., 2002).

## RESULTS AND DISCUSSIONS

After studying the literature data, in order to discriminate the different types of paper the following 28 chemical elements have been taken into consideration : Li, Na, Mg, Al, K, Sc, Ti, V, Mn, Cr, Rb, Fe, Co, Ni, Cu, Zn, Sr, Y, Zr, Ag, Cd, Sb, Ba, La, Ce, Nd, Pb, and Th. Twenty-five trace elements were analyzed using ICP-MS. From these 25 chemical elements:

- 7 (Li, Rb, Co, La, Ce, Nd, Th) were removed from the list because their concentrations are below the background level;
- 4 (V, Zr, Y, Lidup) were removed from the list because the relative standard deviation (%RSD) values were greater than 15% (see Table 1);
- 6 (Na, K, Cr, Ni, Ti, Cu) were removed from the list because they can lead to interference;
- 2 (C, Ca) were removed from the list because they have high concentrations in the paper due to paper's cellulose (80%) and calcium carbonate content.

Therefore, the selected chemical elements to be determined from the paper samples were: Mn, Sr, Al, Mg, Ba, Fe, Zn, and Pb, and they served for method validation in a single laboratory.

## Performance Parameters of the Method and Their Characterization

### *Applicability of the Analytical Method*

Applicability as a typical performance characteristic after validation should provide: the performance specifications; information about the identity of the analyte, the concentration range, and the type of validation matrices; a comprehensive protocol; and the intended application (Thompson et al., 2002).

Applicability must always follow the rules of the method validation (Massart et al., 1997): all the steps should be validated, not only the measurement one; validation must be for the entire specified concentration range; and validation is necessary for all the types of matrices that the method will be applied on.

To identify the appropriate items in order to discriminate the paper samples the following algorithm was developed:

- Literature study to identify the trace elements found in the paper using various analytical techniques;
- Achievement of complete scans of paper samples that were disaggregated;
- Comparison of the results of the full scan data with those obtained from the literature in order to eliminate those items due to interference that may come from different stages of preparing samples for analysis;
- Calculation of the%RSD for each of the selected elements. Those elements with%RSD values greater than 15% were not taken into consideration in further studies (these high values indicate nonuniformities along the analyzed paper pages).

TABLE 1
Detection limit and instrument precision for 25 chemical elements determined in the five paper samples

| | Paper 1 | | Paper 2 | | Paper 3 | | Paper 4 | | Paper 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Chemical element | LOD ($\mu$g/g) $n = 10$ | %RSD $n = 5$ | LOD ($\mu$g/g) $n = 10$ | %RSD $n = 5$ | LOD ($\mu$g/g) $n = 10$ | %RSD $n = 5$ | LOD ($\mu$g/g) $n = 10$ | %RSD $n = 5$ | LOD ($\mu$g/g) $n = 10$ | %RSD $n = 5$ |
| Li | 0.05 | 15 | 0.05 | 15.4 | 0.05 | 14.8 | 0.05 | 14.8 | 0.05 | 16.2 |
| Na | 6 | 3.1 | 6 | 3.5 | 6 | 4.9 | 6 | 2.1 | 6 | 2.4 |
| Mg | 1 | 1.6 | 1 | 1.2 | 1 | 2.6 | 1 | 2.7 | 1 | 1.2 |
| Al | 1 | 1.4 | 1 | 1.1 | 1 | 1.1 | 1 | 1.2 | 1 | 1.9 |
| K | 0.7 | 5.1 | 0.7 | 5.7 | 0.7 | 4.1 | 0.7 | 4.6 | 0.7 | 4.3 |
| Ti | 0.5 | 4.8 | 0.5 | 4.6 | 0.5 | 4.9 | 0.5 | 4.1 | 0.5 | 5.7 |
| V | 0.02 | 15.7 | 0.02 | 16.3 | 0.02 | 15.0 | 0.02 | 14.9 | 0.02 | 16.2 |
| Cr | 0.3 | 11.2 | 0.3 | 11.9 | 0.3 | 10.7 | 0.3 | 10.7 | 0.3 | 9.8 |
| Mn | 0.1 | 1.9 | 0.1 | 1.3 | 0.1 | 1.4 | 0.1 | 1.1 | 0.1 | 1.4 |
| Fe | 1 | 2.3 | 1 | 2.1 | 1 | 2.1 | 1 | 2.8 | 1 | 2.9 |
| Co | <0.01 | 3.4 | <0.01 | 3.8 | <0.01 | 4.3 | <0.01 | 2.9 | <0.01 | 2.9 |
| Ni | 0.1 | 2.4 | 0.1 | 2.6 | 0.1 | 1.9 | 0.1 | 2.2 | 0.1 | 2.1 |
| Cu | 0.2 | 11.2 | 0.2 | 11.0 | 0.2 | 10.3 | 0.2 | 11.8 | 0.2 | 9.5 |
| Rb | <0.01 | 5.7 | <0.01 | 4.8 | <0.01 | 5.1 | <0.01 | 7.6 | <0.01 | 5.3 |
| Zn | 0.1 | 4.9 | 0.1 | 5.2 | 0.1 | 4.6 | 0.1 | 4.5 | 0.1 | 4.7 |
| Sr | 0.1 | 1.7 | 0.1 | 1.8 | 0.1 | 1.3 | 0.1 | 0.7 | 0.1 | 1.1 |
| Y | <0.01 | 15.2 | <0.01 | 15.9 | <0.01 | 14.8 | <0.01 | 16.0 | <0.01 | 16.0 |
| Zr | 0.2 | 16.2 | 0.2 | 16.7 | 0.2 | 15.3 | 0.2 | 15.8 | 0.2 | 15.1 |
| Ba | 0.1 | 1.1 | 0.1 | 1.9 | 0.1 | 1.4 | 0.1 | 1.7 | 0.1 | 1.8 |
| Pb | 0.01 | 1.5 | 0.01 | 1.9 | 0.01 | 1.9 | 0.01 | 1.9 | 0.01 | 1.0 |
| La | <0.01 | 3.6 | <0.01 | 3.3 | <0.01 | 3.8 | <0.01 | 3.7 | <0.01 | 3.2 |
| Ce | <0.01 | 5.1 | <0.01 | 5.8 | <0.01 | 5.6 | <0.01 | 4.7 | <0.01 | 3.6 |
| Nd | <0.01 | 8.2 | <0.01 | 8.3 | <0.01 | 8.6 | <0.01 | 8.9 | <0.01 | 5.9 |
| Th | <0.01 | 16.1 | <0.01 | 16.9 | <0.01 | 15.6 | <0.01 | 16.9 | <0.01 | 15.0 |
| U | <0.01 | 15.2 | <0.01 | 15.6 | <0.01 | 16.1 | <0.01 | 15.0 | <0.01 | 15.7 |



*Fitness for Purpose*

The significance and the importance of the fitness for purpose were discussed above.

It must be mentioned that the requirements of an analytical method and the required quality of the analytical result (its accuracy) refer to the fitness for purpose of the analytical method.

It is very important that the test sample be representative of the entire stack of paper studied. It is necessary that a sheet of paper randomly selected from the stack contain elements with levels of concentrations very close to those found in other sheets from the same ream. Since often there are only a very small number real paper samples available and target elements exist in trace level concentrations, it is important to prove that the analytical method is able to reliably determine the trace level analytes, that is, it is fitted for the purpose.

*Selectivity, Specificity, and Interference*

In a method validation process the first performance characteristics that are discussed are selectivity and specificity. A compulsory condition is to make sure that a given signal is owed only to an analyte in an analyzed sample.

Selectivity is defined as "the extent to which it can determine particular analyte(s) in a complex mixture without interference from other components in the mixture" (Vessman et al., 2001). Specificity is the "highest selectivity" (Vessman et al., 2001). IUPAC recommends not using the term specificity.

Both selectivity and specificity provide an idea about the reliability of the analytical method.

Mass spectra represent a complete, precise, and efficient source of information for the determination of atomic and molecular weights, for qualitative and quantitative analysis of various compound mixtures, as well as of the biological compounds, and for the analysis of high-purity materials and the surface analysis.

In the normal analytical range the spectral background of the inductively coupled plasma is relatively simple, especially in the spectral range between 190 and 300 nm, where the analytical spectral lines of metals lie. This simple spectral

background consists mainly in the lines of argon and other weak emission bands of $HO^-$, $NO_3^-$, and $CN^-$.

The inter-element effects are relatively small when using ICP. These effects, known as *matrix effects* or *interferences*, are those phenomena that interfere in the relationship intensity (abundance)-analyte concentration due to the presence of other components in the plasma. They can be divided in two categories: *physical* and *spectral*.

Different properties of the sample (sample volatility) and their modifications (viscosity changes) related to the sample introduction method and ionization of the sample in the plasma lead to *physical interferences*.

It is hard for the standards matrix to match the samples matrix, and the variability between the various samples must also be mentioned.

Considering these aspects, in order to obtain genuine results some corrections are required. In ICP-MS obtaining valid analytical data is often done applying internal standardization. The internal standard added to all the solutions (standards and samples), which also corrects the instrumental drift, must meet some conditions: not present spectral interferences, not be an analyte in the sample, have a mass close to those of the analytes, be mono-isotopic, and have an ionization energy similar to that of to the analytes.

It is recommended to select more internal standards in order to cover a wide range of masses (Sc for the small mass elements and Rh for heavy elements) (Broekaert, 2002).

*Spectral interferences* arising in ICP-MS are a consequence of the low resolution of the quadrupole mass filters; there are *isobaric* and *polyatomic interferences*.

The *isobaric interferences* appear when an isotope of an element overlaps with an isotope of another element with the same nominal mass. These are known different possible isobaric overlaps (Prichard et al., 1996). This type of interference is predicted when basic information about the sample is available, and it can be corrected automatically with software.

*Polyatomic interferences* appear due to the molecular ions formed either in the high-temperature plasma or in the interface region between the plasma and the mass filter. The most common polyatomic species and the isotopes causing interferences are cited in the literature (Prichard et al., 1996). This phenomenon may be reduced by the operating conditions that are used and the sample preparation step.

It must be emphasized that the correct interpretation of a mass spectra is done knowing and correlating all the information about the sample and the interferences.

The selectivity evaluation of the method for trace multielement determination in the paper samples by ICP-MS was performed by analyzing the calibration samples and the paper samples, obtaining the mass spectra. Five sheets of paper from each producer were randomly selected. Mass spectra were used to create a database called "Paper mass spectrometry." By comparing the spectra the probabilities of the paper samples' spectra matching with the database were obtained. At probabilities between 80 and 90%, it was determined that the elements chosen (Al, Ba, Fe, Mg, Mn, Pb, Sr, Zr) were present in the paper samples.

TABLE 2
Spectral interference due to the influence of sample matrix

| m/z | Analyte (% abundance) | Possible interference |
|---|---|---|
| 23 | Na (83.2) | $^{12}C^{11}B^+$ |
| 39 | K (93.1) | $^{27}Al^{12}C^+$ |
| 48 | Ti (73.9) | $^{48}Ca^+$ |
| 49 | Ti (5.5) | $^{48}CaH^+$ |
| 52 | Cr (83.8) | $^{12}C^{40}Ar^+$ |
| 53 | Cr (9.5) | $^{13}C^{40}Ar^+$ |
| 58 | Ni (68.3) | $^{40}Ca^{18}O^+$ |
| 60 | Ni (26.2) | $^{44}Ca^{16}O^+$ |
| 63 | Cu (69.2) | $^{23}Na^{40}Ar^+$ |
| 65 | Cu (30.8) | $^{25}Mg^{40}Ar^+$ |

Experimentally it has been found that the paper items that may provide spectral interference are Na, K, Ti, Cr, Ni, and Cu (see Table 2). These elements were removed from the list of items that can be used in discriminating the sheets of paper from different manufacturers.

## Linearity and Assessment of the Calibration Function

When a physical or a physicochemical investigated property is associated with a given measured signal, the dependence between these quantities must be determined. A linear dependence is the most common in analytical chemistry. In the calibration step the output signals are assigned to the corresponding analyte concentrations, and the dependence between them is usually determined using the linear regression method (Danzer and Currie, 1998; Konieczka and Namieśnik, 2009).

A calibration function is determined from values of the measurement response at given concentrations. Depending on the type of correlation between the analyte concentration and the measurement response, different mathematical or statistical tools can be used.

The linearity of an analytical procedure is its ability to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample (ICH, 1994). The linearity must be demonstrated directly on the analyte or on spiked samples using at least five concentrations over the whole working range.

The most frequently used method of determining linearity is a graph of measuring instrument calibration. Appropriate statistical calculations are also recommended, such as a linear regression. The slope and the intercept, the residual sum of squares, the coefficient of correlation, and a graphical presentation of the residuals should be reported.

Usually, the following calibration models are used:

- The model of the linear regression is the classical model for calibration; it assumes a linear correlation between the measured values and the corresponding concentrations and requires the normal distribution of the responses (International Organization for Standardization, 1990). It has limited applicability because the homogeneity of variances is given in a working range of only one or two orders of magnitude of concentration.
- The model of nonlinear second-order calibration functions should be considered when the linear model is not adequate (European Commission, 2009; International Organization for Standardization, 2001). This model has the same limitations: the normal distribution of the responses and the homogeneity of variances over the working range.
- The model of weighted regression consists of weighting each value with the reciprocal variance, and it should be applied when the other models are not suitable.

Usually the calibration function in the chosen working range is a priori supposed to be linear, but this should be verified in the course of the validation study.

Numerical parameters of the regression are meaningful only for evaluating the performance of the analytical procedure after the verification of a linear response function.

The coefficient of correlation is often misused since it is neither a proof of linearity nor a suitable general quantitative measure. On the contrary, it requires linearity as a prerequisite (Tănase et al., 2007). The correlation coefficient requires random scatter around the linear regression line to have a quantitative meaning at all, but even then the numerical values cannot be properly compared, because they depend on the slope (Baumann, 1997), as well as on the number of determinations and the regression concentration range (Ermer and Miller, 2005). Therefore, this parameter is not suitable as a general acceptance criterion for the performance of an analytical procedure.

Chan (2004) emphasized that at least five concentration levels should be used and the slope, the residual sum of squares, and the *y*-intercept must be reported. The slope of the regression line is correlated with the sensitivity, and the *y*-intercept provides an estimate of the variability of the method.

In the present study the calibration function and the performance characteristics of the analytical procedure were determined for a working range between 5 and 100 ppb for each of the eight elements determined by ICP-MS. Six concentration levels and one blank were used, with five replicates. This corresponds to 33 degrees of freedom. The linear and nonlinear (second order) regression the results are presented in Tables 3 and 4.

As a characteristic process quantity, sensitivity is determined for the middle of the working range. From this, the process standard deviation and the relative process standard deviation were calculated.

## Assessment of the Linearity Model

*Maximum Allowable Standard Deviation of the Slope*

The maximum relative standard deviation of the slope is calculated according to:

$$s_b(\%) = (s_b/b) \times 100 \quad (1)$$

TABLE 3
Linear regression; 6+1 (blank) concentration levels, five replicates, 33 degrees of freedom

| | Element | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Linear regression parameter | Al | Ba | Fe | Mg | Mn | Pb | Sr | Zn |
| Slope, $b$ | 4206.14 | 1774.90 | 6722.38 | 2855.78 | 7505.67 | 17495.12 | 9446.50 | 1053.46 |
| Standard deviation of the slope, $SD_b$ | 97.62 | 23.38 | 38.25 | 37.05 | 38.18 | 71.12 | 45.05 | 8.31 |
| Relative standard deviation of the slope, $RSD_b$ (%) | 2.32 | 1.32 | 0.57 | 1.30 | 0.51 | 0.41 | 0.48 | 0.49 |
| *y*-intercept, $a$ | 38988.06 | 10278.57 | 204936.00 | 12689.01 | 7398.46 | 8524.41 | 9277.97 | 8087.53 |
| Standard deviation of the *y*-intercept, $SD_a$ | 5224.46 | 1251.07 | 2047.34 | 1982.75 | 2043.33 | 3806.47 | 2411.17 | 444.57 |
| Correlation coefficient, $r$ | 0.9912 | 0.9972 | 0.9996 | 0.9972 | 0.9996 | 0.9997 | 0.9996 | 0.9990 |
| Determination coefficient, $r^2$ | 0.9825 | 0.9943 | 0.9989 | 0.9944 | 0.9991 | 0.9995 | 0.9992 | 0.9980 |
| Residual standard deviation of the calibration curve, $SD_{y1}$ | 20534.78 | 4917.33 | 8047.09 | 7793.22 | 8031.30 | 14961.36 | 9477.14 | 1747.39 |
| Standard deviation of the blank, $SD_{blank}$ | 172.17 | 121.72 | 2130.37 | 80.27 | 39.45 | 90.95 | 47.64 | 235.04 |
| $F$ test | 1856.53 | 5765.08 | 30880.35 | 5941.96 | 38647.44 | 60506.9 | 43964.35 | 16083.22 |

TABLE 4
Nonlinear (second-order) regression; 6+1 (blank) concentration levels, five replicates, 32 degrees of freedom

| Second-order regression parameters | Element | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Ba | Fe | Mg | Mn | Pb | Sr | Zn |
| *y*-intercept, *a* | 29459.7 | 11331.85 | 198118 | 11204.4 | -203.24 | 1398.91 | 919.56 | 7157.71 |
| Standard deviation of the *y*-intercept, $SD_a$ | 6016.64 | 1558.95 | 1656.15 | 2480.89 | 1318.46 | 4358.12 | 1827.02 | 494.16 |
| Linear coefficient, *b* | 5095.66 | 1676.57 | 7358.88 | 2994.38 | 8215.33 | 18160.32 | 10226.79 | 1140.26 |
| Standard deviation of the linear coefficient, $SD_b$ | 349.28 | 90.50 | 96.14 | 144.02 | 76.54 | 252.99 | 106.06 | 28.69 |
| Quadratic coefficient, *c* | –9.09 | 1.01 | –6.51 | –1.42 | –7.26 | –6.80 | –7.98 | –0.89 |
| Standard deviation of the quadratic coefficient, $SD_c$ | 3.45 | 0.89 | 0.95 | 1.42 | 0.76 | 2.50 | 1.05 | 0.28 |
| Correlation coefficient, *r* | 0.9928 | 0.9973 | 0.9998 | 0.9973 | 0.9999 | 0.9998 | 0.9999 | 0.9992 |
| Determination coefficient, $r^2$ | 0.9857 | 0.9945 | 0.9996 | 0.9946 | 0.9998 | 0.9996 | 0.9997 | 0.9984 |
| Residual standard deviation of the calibration curve, $SD_{y2}$ | 18902.48 | 4897.76 | 5203.11 | 7794.20 | 4142.20 | 13691.90 | 5739.95 | 1552.51 |
| Sensitivity in the center of the working range, *E* $E = b + c \cdot \overline{x}$ | 4368.01 | 1757.01 | 6838.21 | 2881.00 | 7634.81 | 17616.17 | 9588.491 | 1069.257 |
| Standard deviation of the method $SD_{xo}$ $SD_{xo} = SD_y/E$ | 4.33 | 2.79 | 0.76 | 2.71 | 0.54 | 0.78 | 0.60 | 1.45 |
| Relative variation coefficient of the method, *V* $V = (SD_{xo}/\overline{x}) \cdot 100$ | 10.82 | 6.97 | 1.90 | 6.76 | 1.36 | 1.94 | 1.50 | 3.63 |
| *F* test | 1097.98 | 2906.42 | 36955.49 | 2970.73 | 72690.18 | 36127.19 | 59954.13 | 10192.03 |



where $s_b$ is the standard deviation of the slope and *b* is the slope of the calibration curve.

The standard deviation of the slope should not exceed 8% for specialized techniques (MS detection) (European Commission, 2009). The data presented in Table 2 show that in this study the condition is fulfilled.

*Maximum Allowable Residue for Different Calibration Levels*

The maximum acceptable residues for each calibration level is method dependent, so it should be specified during the validation study and should be set up as a criterion for future assessment of the calibration curves produced in routine analysis (AOAC International, 1993). The maximum acceptable residue for the first level of calibration could be much higher for the other levels.

The graphic representations of the residues depending on the concentrations of the eight elements (Al, Ba, Fe, Mg, Mn, Pb, Sr, Zn) for which the calibration curve was realized by ICP-MS are presented in Figure 1. It can be seen that at low levels of concentration values several residues lie between 15 and 20% and for all the other concentrations the residue values are below 10% and even below 5%.

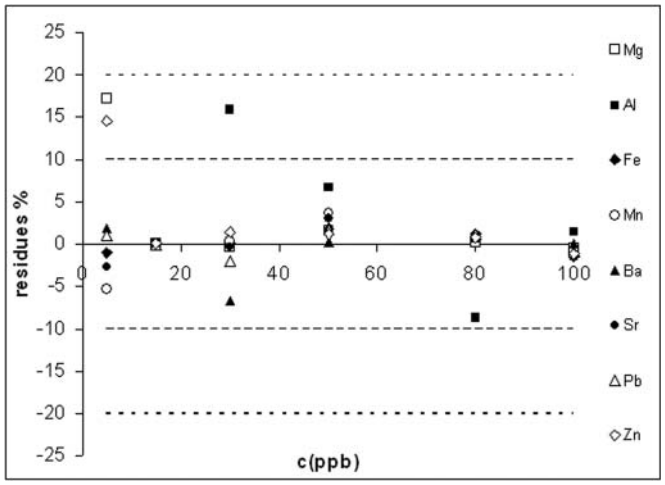


FIG. 1. Graphic representation of the residues% vs. concentration.

*Assessment of the Adequateness of the Linearity Model by Statistical Tests*

To verify linearity different statistical tests can be used (European Commission, 2009).

*ANOVA for Lack of Fit*

The test for adequateness of the linearity model allows the validity of the regression model and the chosen working range to be verified. The ANOVA lack of fit model is based on the comparison of the tabulated $F$ of Fisher values with the observed $F$ of Fisher calculated on the basis on the experimental results and on the sums of squares.

The observed $F$ values relative to the calibration function ($F_{cal.function}$) and to the lack of fit ($F_{lack\ of\ fit}$) were calculated on the basis of the ratio between the variance due to the linearity and that due to nonlinearity and the variance due to the residue, using the relations:

$$F_{cal.function} = \frac{s^2_{cal.function}(y)}{s^2_{pureerror}(y)} \tag{2}$$

$$\mathrm{F_{lackoffit}} = \frac{\mathrm{s^2_{lackoffit}}(y)}{\mathrm{s^2_{pureerror}}(y)} \tag{3}$$

where

$$\mathrm{s^2_{cal.function}}(y) = \frac{\mathrm{SSD_{cal.function}}(y)}{1} \tag{4}$$

$$\mathrm{s^2_{lackoffit}}(y) = \frac{\mathrm{SSD_{lackoffit}}(y)}{\mathrm{p-2}} \tag{5}$$

$$\mathrm{s^2_{pureerror}}(y) = \frac{\mathrm{SSD_{pureerror}}(y)}{\mathrm{p(n-1)}} \tag{6}$$

$$\mathrm{SSD_{cal.function}} = \mathrm{SSD_{total}} - \mathrm{SSD_{residual}} \tag{7}$$

$$\mathrm{SSD_{lackoffit}} = \mathrm{SSD_{residual}} - \mathrm{SSD_{pureerror}} \tag{8}$$

where $n$ is the number of replicates ($n = 5$), $p$ is the number of calibration levels ($p = 7$), ($p$–2) represents the number of degrees of freedom relative to the error of the model (nonlinearity), $p(n–1)$ represents number of degrees of freedom relative the residual, $s^2$ is the variance, and SSD represents the sum of squares.

In Table 5, the representative values calculated for the evaluation of the linearity are presented.

*Plot of the Residues*

The graphic representation of the residues versus the corresponding concentration values or the fitted value is a way to verify the two assumptions of linearity and constant residual standard deviation. If these two assumptions are confirmed, then the figure should display a plot of randomly distributed points centered on zero (Figure 2). If the model is not linear, a systematic pattern between the residuals and the concentration values can be seen.

As can be observed in Figure 2, the residuals are distributed normally, which proves that the linear model was correctly chosen.

*Mandel's Test*

Mandel's test is based on the assumption that relatively large deviations of measured values from a straight line are caused by nonlinearity and may be reduced through the selection of a "better" regression model, e.g., a second-order function.

Mandel's test value (MTV) (Table 6) is calculated using the residual standard deviation from the first-order calibration function and from the second-order calibration function:

$$\mathrm{MTV} = ((\mathrm{n}-2)\cdot \mathrm{s^2_{y1}} - (\mathrm{n}-3)\cdot \mathrm{s^2_{y2}})/\mathrm{s^2_{y2}} \tag{9}$$

and is compared with the value obtained from the $F$ table (1, 32, 99%) = 7.50.

## Acceptability Criteria for ANOVA for Lack of Fit Approach

*Validity of the Regression Model*

If the $F$ of the Fisher value, relative to the linear regression, calculated on the basis of the experimental results, is higher than the $F$ of the tabulated Fisher value ($F$(1, 16, 99%) = 8.53), the regression model could be considered as acceptable at the risk level of 1% (European Commission, 2009). If $F$ is between 8.53 and 4.49 ($F$(1, 16, 95%) = 4.49) the model can be considered as acceptable at the risk level of 5%. If $F$ is lower then 4.49 the model cannot be used to prove linearity.

The calculated F values are presented in Table 3. All of them are higher than 8.53, so the linear regression model is validated.

*Validity of the Chosen Calibration Range*

If the nonlinearity $F$ value is lower than the $F$ of the tabulated Fisher value $F$(1, 16, 95%) = 2.74, the chosen working range is validated, within the possible error at level of 5%. If the value is between 2.74 and 4.20 $F$(6, 16, 99%) = 4.20, the chosen working range is validated, with the possible error at level of 1%.

*Working Concentration Range*

The working concentration range is the range in which the method is validated and that gives acceptable trueness and precision. It should be distinguished from the calibration range in which the regression model for calibration (most frequently a linear one) is established and verified. The lowest limit of the working range is the lowest limit of the calibration range. However, the upper limit of the working range could be not only the highest point in the calibration curve for which the regression model is validated, but also a higher concentration

TABLE 5
ANOVA lack of fit model applied to test the linearity of the calibration curves obtained for Al, Ba, Fe, Mg, Mn, Pb, Sr, and Zn using ICP-MS

| | ELEMENT | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Parameter | Al | Ba | Fe | Mg | Mn | Pb | Sr | Zn |
| $SSD_{cal.function}$ | 782855168049.80 | 139400140154.36 | 1999676632068.88 | 360880820556.21 | 2492830199715.87 | 13543998655740.10 | 3948706101148.04 | 49107780589.36 |
| $SSD_{residual}$ | 13915351503.79 | 797943264.33 | 2136935824.66 | 2004232357.68 | 2128560102.70 | 7386793278.87 | 2963931336.93 | 100760743.61 |
| $SSD_{pureerror}$ | 931989947.00 | 686978473.00 | 310064067.00 | 1601119169.00 | 175552837.00 | 2869720677.00 | 345594512.00 | 9809208.00 |
| $SSD_{total}$ | 796770519553.60 | 140198083418.69 | 2001813567893.54 | 362885052913.89 | 2494958759818.57 | 13551385449019.0 | 3951670032484.97 | 49208541332.97 |
| $SSD_{lackoffit}$ | 12983361556.79 | 110964791.33 | 1826871757.66 | 403113188.68 | 1953007265.70 | 4517072601.87 | 2618336824.93 | 90951535.61 |
| $s^2_{cal.function}$ | 782855168049.81 | 139400140154.36 | 1999676632068.88 | 360880820556.21 | 2492830199715.87 | 13543998655740.10 | 3948706101148.04 | 49107780589.36 |
| $s^2_{lackoffit}$ | 2596672311.36 | 22192958.27 | 365374351.53 | 80622637.74 | 390601453.14 | 903414520.37 | 523667364.99 | 18190307.12 |
| $s^2_{pureerror}$ | 33285355.25 | 24534945.46 | 11073716.68 | 57182827.46 | 6269744.18 | 102490024.18 | 12342661.14 | 350328.86 |
| $F_{cal.function}$ | 23519.51 | 5681.70 | 180578.63 | 6311.00 | 397596.80 | 132149.43 | 319923.40 | 140176.24 |
| $F_{tab}(1, 28, 95\%)$ | 4.20 | | | | | | | |
| $F_{tab}(1, 28, 99\%)$ | 7.64 | | | | | | | |
| $F_{lackoffit}$ | 78.01 | 1.11 | 32.99 | 1.41 | 62.30 | 8.81 | 42.43 | 51.92 |
| $F_{tab}(5, 28, 95\%)$ | 2.56 | | | | | | | |
| $F_{tab}(5, 28, 99\%)$ | 3.75 | | | | | | | |

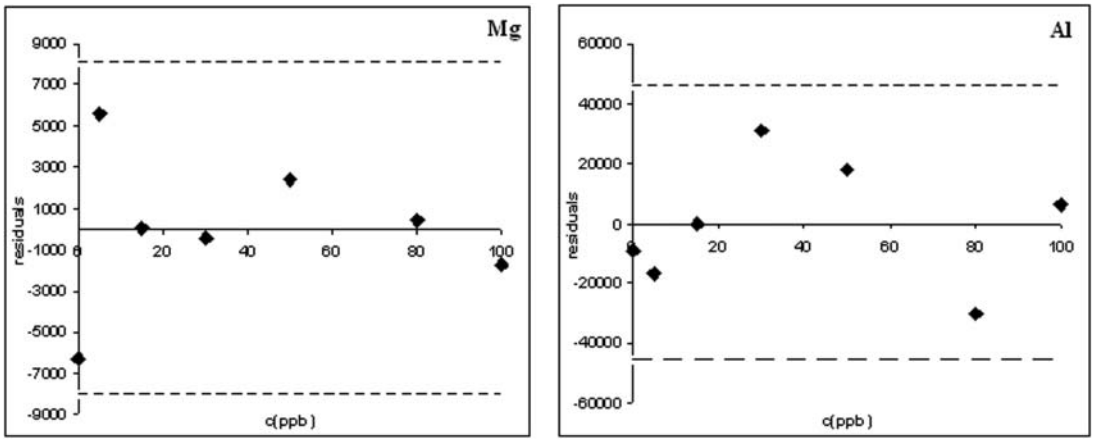


FIG. 2. Graphic representation of the residues vs. concentration.



at which acceptable trueness can be proven (e.g., by comparing with the test the results of a diluted upper limit concentration with a concentration inside the calibration range).

Since in paper analysis the concentration of target elements is very low the working concentration range was established between 5 and 100 ppb.

*Limit of Detection and Limit of Quantification*

Among the parameters that need to be determined are the limit of detection (LOD) and the limit of quantification (LOQ); they play a significant role in the validation of the analytical procedures. Although the meaning of these parameters and their understanding do not raise questions, the determination of their values is sometimes problematic due to the large number of definitions describing the notions of both the LOD and the LOQ and to the practical difficulties in univocally determining the magnitude of the noise level in a given measuring instrument.

There are several ways of determining the LOD and LOQ, based on: the determinations of the blank samples, the numerical value of the S/N ratio, a graphical method, and the standard deviation of the signals and the slope of the calibration curve.

In the present study the last approach was used. The LOD was calculated with the formula:

$$\mathrm{LOD} = \frac{3.3 \cdot SD}{b} \tag{10}$$

where $b$ is the slope of the calibration curve.

Standard deviation was determined in two ways: as a standard deviation of results obtained for the series of blank samples ($SD_{blank}$) and as a standard deviation of the intercept of the obtained calibration curve ($SD_a$). The calculated LODs obtained in these ways and the mean values are presented in Table 7.

The correctness of the calculated LODs is verified because the mean values fulfill the following conditions:

$$10 \cdot \mathrm{LOD} > c_{min} \tag{11}$$

$$\mathrm{LOD} < c_{min} \tag{12}$$

where $c_{\min}$ is the analyte concentration in the standard solution with the lowest concentration.

The LOQ was calculated with the formula

$$\mathrm{LOQ} = 3 \cdot LOD \tag{13}$$

and the obtained values are presented in Table 7.

*Sensitivity*

Sensitivity is the relationship of change in the output signal of a measuring instrument to the change in the analyte concentration that produces it (Konieczka and Namieśnik, 2009). Sensitivity shows the smallest difference in the analyte concentration that can be ascertained using a specific method.

The values of the calibration curves slopes for the eight trace elements (Al, Ba, Fe, Mg, Mn, Pb, Sr, Zn) determined by

TABLE 6
Mandel's test value (MTV) calculated for the eight target elements

| | Element | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Ba | Fe | Mg | Mn | Pb | Sr | Zn |
| Mandel's test value (MTV) | 6.95 | 1.26 | 46.93 | 0.99 | 92.06 | 7.40 | 57.96 | 9.80 |

TABLE 7
Limit of detection (LOD) and limit of quantification (LOQ) calculated for the eight target elements

| Parameter | Element | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Al | Ba | Fe | Mg | Mn | Pb | Sr | Zn |
| $LOD_{SDblank}$, ppb | 0.14 | 0.23 | 1.05 | 0.09 | 0.02 | 0.02 | 0.02 | 0.74 |
| $LOD_{SDa,}$ ppb | 4.10 | 2.33 | 1.01 | 2.29 | 0.90 | 0.72 | 0.84 | 1.39 |
| $\overline{LOD}$, ppb | 2.12 | 1.28 | 1.03 | 1.19 | 0.46 | 0.37 | 0.43 | 1.06 |
| $LOQ_{SDblank}$, ppb | 0.41 | 0.68 | 3.14 | 0.28 | 0.05 | 0.05 | 0.05 | 2.21 |
| $LOQ_{SDa}$, ppb | 12.30 | 6.98 | 3.02 | 6.87 | 2.70 | 2.15 | 2.53 | 4.18 |
| $\overline{LOQ}$, ppb | 6.35 | 3.83 | 3.08 | 3.58 | 1.37 | 1.10 | 1.29 | 3.19 |

ICP-MS are presented in Table 3. Note that, with one exception, the values of the slopes are of the same order of magnitude and they are quite different, proving different sensitivities for each of these elements.

*Accuracy*

Accuracy is studied as two components: *trueness* and *precision* (International Organization for Standardization, 1994).

The *accuracy* of an analytical method is defined as the degree of closeness between a test result and the accepted reference value (International Organization for Standardization, 1994). This represents the systematic deviation of the results from the real value. The accuracy of a method is also a guide to the utility and applicability of the method to real samples.

*Precision* expresses how close the independent test results are to each other. The results are obtained from measurements of more samples originating from the same homogeneous sample under stipulated conditions (International Organization for Standardization, 1994). Precision is usually expressed as standard deviation (SD), relative standard deviation (RSD), or percentage relative standard deviation (%RSD). The precision of an analytical method can be assessed on three levels: repeatability, intermediate precision (one laboratory reproducibility), and reproducibility.

Repeatability represents the analytical variability in the same conditions of measurement within short intervals of time (between the measurements and during these), by the same operator using the same equipment and method.

Intermediate precision represents the analytical variability over a long period of time of the measurement process when replicate measurements are realized in the same laboratory, using two or more different instruments and different operators. It is determined by comparing the results obtained in one laboratory during a certain number of weeks. The objective of intermediate precision is to verify if, in the same laboratory, the method will provide the same results once the method development phase is completed.

Reproducibility is the precision between different laboratories. This is determined by analysis of aliquots from homogeneous lots in different laboratories by different operators in different environmental and operational conditions, using different equipment, but within specific parameters of the method.

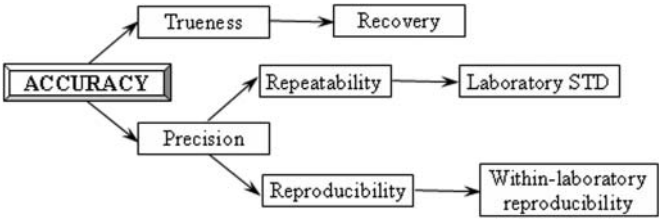


FIG. 3. Accuracy components.

From the practical point of view the constancy of the nebulizer gas flow is essential for the precision achievable in ICP-MS. After stabilizing the nebulizer gas flow, the relative standard deviations can be below 1%. They can be improved still further by internal standardization.

*Trueness* represents the closeness of agreement between the average value obtained from a large series of test results and an accepted reference value (International Organization for Standardization, 1994). Trueness is usually expressed in terms

TABLE 8
Repeatability estimation for the eight elements

| Element | Concentration (ppb) | *SD* (ppb) | %RSD | *r* (ppb) |
|---|---|---|---|---|
| Al | 15 | 0.019 | 0.13 | 0.054 |
| | 50 | 0.231 | 0.43 | 0.646 |
| | 100 | 0.246 | 0.24 | 0.690 |
| Ba | 15 | 0.346 | 2.31 | 0.969 |
| | 50 | 0.217 | 0.43 | 0.608 |
| | 100 | 0.669 | 0.67 | 1.874 |
| Fe | 15 | 0.035 | 0.23 | 0.097 |
| | 50 | 0.378 | 0.73 | 1.057 |
| | 100 | 0.923 | 0.94 | 2.584 |
| Mg | 15 | 0.062 | 0.41 | 0.173 |
| | 50 | 0.240 | 0.47 | 0.672 |
| | 100 | 0.419 | 0.42 | 1.174 |
| Mn | 15 | 0.059 | 0.40 | 0.166 |
| | 50 | 0.041 | 1.79 | 2.561 |
| | 100 | 0.483 | 0.49 | 1.352 |
| Pb | 15 | 0.041 | 0.28 | 0.116 |
| | 50 | 0.997 | 1.98 | 2.791 |
| | 100 | 1.028 | 1.03 | 2.878 |
| Sr | 15 | 0.342 | 1.12 | 0.468 |
| | 50 | 0.361 | 0.70 | 1.012 |
| | 100 | 0.342 | 0.35 | 0.959 |
| Zn | 15 | 0.423 | 2.82 | 1.185 |
| | 50 | 0.376 | 0.74 | 1.053 |
| | 100 | 0.803 | 0.81 | 2.249 |

of bias (the total systematic error as contrasted to random error). There may be one or more systematic error components contributing to the bias (International Organization for Standardization, 1994).

Another expression of accuracy is the uncertainty of measurement. It is calculated combining bias and its relative standard deviation (calculated for the assessment of trueness) and the standard deviation of the reproducibility assessment. Figure 3 presents the accuracy components.

Standard deviation can be calculated in several ways: at least nine independent determinations in the whole measuring range (three independent determinations for three concentration levels) (ICH, 1994, 1996); six independent determinations of an analyte in standard samples for the concentration level corresponding to the concentration of a real sample (ICH, 1994, 1996); ten independent determinations at a certain concentration level (Eurachem, 1998). Standard solutions and blanks spiked at different concentrations within the working range were analyzed.

In the present study, ten independent determinations (with three replicates each) for three concentration levels were performed. This approach was chosen because the precision is different depending on the concentration level.

After realizing the determinations, the standard deviations (*SD*), percentage relative standard deviations (%RSD), and repeatability limits (*r*) were calculated (Table 8).

The repeatability limit expresses the maximum acceptable difference between two results obtained under repeatability conditions with a probability of 95%. It was calculated using the relation:

$$r = t \cdot \sqrt{2} \cdot s_r \cong 2.8 \cdot s_r \tag{14}$$

where $t$ is the two-tailed Student $t$ value at the 95% confidence level and $s_r$ is the repeatability standard deviation. Once the $r$ value is fixed, it should always be higher than the difference between duplicate analyses. This allows verifying the consistency of the results and deciding whether the difference between duplicate analyses of a sample, determined under repeatability conditions, is significant.

In the absence of paper reference materials or a collaborative study, the bias was investigated by spiking and recovery.

TABLE 9
Recovery values and statistical parameters for the eight elements from samples provided by five manufacturers

| Sample | Element / Parameter | Al | Ba | Fe | Mg | Mn | Pb | Sr | Zn |
|---|---|---|---|---|---|---|---|---|---|
| Paper 1 | $\overline{R}\%$ | 100.42 | 103.43 | 101.72 | 97.44 | 96.92 | 98.08 | 97.74 | 98.32 |
| | $SD_R$ | 0.70 | 0.68 | 1.48 | 0.81 | 0.28 | 0.28 | 1.14 | 0.23 |
| | $RSD_R\%$ | 0.70 | 0.66 | 1.45 | 0.83 | 0.29 | 0.29 | 1.17 | 0.23 |
| | $u_R$ | 0.41 | 0.39 | 0.85 | 0.47 | 0.16 | 0.16 | 0.66 | 0.13 |
| | $t_{calc}$ | 0.01 | 0.09 | 0.02 | 0.05 | 0.19 | 0.12 | 0.03 | 0.13 |
| Paper 2 | $\overline{R}\%$ | 97.31 | 102.22 | 99.63 | 97.45 | 96.43 | 97.66 | 96.79 | 96.85 |
| | $SD_R$ | 0.47 | 0.23 | 1.69 | 1.54 | 0.40 | 0.04 | 0.96 | 0.05 |
| | $RSD_R\%$ | 0.48 | 0.23 | 1.70 | 1.58 | 0.42 | 0.04 | 0.99 | 0.05 |
| | $u_R$ | 0.27 | 0.13 | 0.98 | 0.89 | 0.23 | 0.02 | 0.55 | 0.03 |
| | $t_{calc}$ | 0.1 | 0.17 | 0.01 | 0.03 | 0.15 | 1.12 | 0.06 | 0.11 |
| Paper 3 | $\overline{R}\%$ | 101.01 | 102.42 | 98.37 | 102.00 | 97.28 | 97.44 | 98.05 | 96.47 |
| | $SD_R$ | 0.81 | 0.37 | 0.64 | 1.77 | 0.37 | 0.33 | 1.06 | 1.44 |
| | $RSD_R\%$ | 0.80 | 0.36 | 0.65 | 1.73 | 0.38 | 0.34 | 1.08 | 1.50 |
| | $u_R$ | 0.47 | 0.21 | 0.37 | 1.02 | 0.21 | 0.19 | 0.61 | 0.83 |
| | $t_{calc}$ | 0.02 | 0.11 | 0.04 | 0.02 | 0.13 | 0.13 | 0.03 | 0.04 |
| Paper 4 | $\overline{R}\%$ | 102.48 | 103.75 | 97.30 | 97.25 | 97.50 | 97.13 | 101.54 | 95.89 |
| | $SD_R$ | 0.84 | 0.91 | 0.51 | 0.56 | 0.36 | 0.03 | 0.71 | 0.20 |
| | $RSD_R\%$ | 0.82 | 0.87 | 0.52 | 0.58 | 0.37 | 0.03 | 0.70 | 0.20 |
| | $u_R$ | 0.49 | 0.52 | 0.29 | 0.33 | 0.21 | 0.01 | 0.41 | 0.11 |
| | $t_{calc}$ | 0.05 | 0.07 | 0.09 | 0.08 | 0.12 | 1.98 | 0.04 | 0.36 |
| Paper 5 | $\overline{R}\%$ | 103.99 | 105.85 | 102.55 | 97.50 | 97.75 | 97.05 | 98.26 | 94.71 |
| | $SD_R$ | 0.38 | 1.56 | 1.25 | 0.56 | 1.35 | 0.35 | 0.36 | 1.05 |
| | $RSD_R\%$ | 0.36 | 1.47 | 1.22 | 0.57 | 1.38 | 0.36 | 0.37 | 1.11 |
| | $u_R$ | 0.22 | 0.90 | 0.72 | 0.32 | 0.78 | 0.20 | 0.21 | 0.61 |
| | $t_{calc}$ | 0.18 | 0.06 | 0.04 | 0.08 | 0.03 | 0.15 | 0.08 | 0.09 |

A typical test paper sample was analyzed before and after spiking.

To determine the recovery (the difference between the two results as a proportion of the added portion), experiments using spiked blank matrix were carried out as follows:

- From the reproducibility study on three different spiking concentrations (low, medium, and high) from the working range analyzed in three different batches under reproducibility conditions, a calculation is performed on the mean concentration for each concentration investigated,
- Using the equation below, the recovery is calculated for each spiking concentration level:

$$R\% = \frac{(\overline{c} - c_i)\cdot 100}{c_{spike}} \qquad (15)$$

- where $\overline{c}$ is the mean concentration determined in the spiked sample, $c_i$ is the concentration of the analyte in the sample before spiking the blank sample, and $c_{spike}$ is the spiked concentration.

After the digestion procedure of the paper samples (140–150 mg of sample in 100 mL solution) the sample matrix "concentration" is quite high. Thus, it is possible to increase or decrease the signal for some elements. To check the influence of the sample matrix the recovery was determined by adding a multielement standard solution to the digested sample. The results obtained for the eight elements (Al, Ba, Fe, Mg, Mn, Pb, Sr, Zn) from five types of paper are shown in Table 9. Analyzing these recovery values, ranging from 94.71% to 105.85%, it can be concluded that: the matrix effects are minimal and for this type of analysis is not necessary to use an internal standard.

A significance test (European Commission, 2009) is used to determine whether the mean recovery for the working range is significantly different from 1.0. The test statistic $t$ is calculated using the following equation:

$$t_{calc} = \frac{|1 - (\overline{R}/100)|}{s_{rec}\cdot\sqrt{1/n}} = \frac{|1 - (\overline{R}/100)|}{u_{\overline{R}}} \leq t_{crit} \qquad (16)$$

where $\overline{R}$ is the mean recovery, $u_{\overline{R}}$ is the uncertainty of the mean recovery value, and $s_{rec}$ is the standard deviation of the recovery.

The value of $t_{calc}$ is compared with the critical value $t_{crit\ (n-1,\ 95\%)} = t_{crit\ (2,\ 95\%)} = 2.92$. All the obtained results are presented in Table 9. As can be seen, in all cases the calculated value is smaller than critical one, $t_{calc} < t_{crit}$, which means that the recovery is not significantly different from 1.

## CONCLUSIONS

In this single-laboratory validation study, an ICP-MS analysis method for the quantitative determination of trace elements in document paper was developed, validated, and applied. ICP-MS is considered an excellent technique for detailed characterization of the elemental composition of paper samples. The analytical procedure developed for determining the mass fraction of eight trace elements in paper allowed the consideration and evaluation of most performance parameters for method validation: applicability, fitness for purpose, linearity, working range, limit of detection and limit of quantification, sensitivity, accuracy, and precision. The values of these parameters indicated that the analytical procedure is rapid, sensitive, linear, accurate, and precise for the determination of all eight trace level elements and therefore is validated. The results of the analysis showed that paper samples from five different manufacturers can be discriminated on the basis of element concentrations. Also, it could be concluded that each paper type has a specific micronutrient "footprint" (based on which the paper can be identified and characterized).

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