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Simultaneous Determination of As, Cu, Cr, Se, Sn, Cd, Sb and Pb Levels in Infant Formulas by ICP-MS after Microwave-Assisted Digestion: Method Validation

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Abstract

The growing importance of chemical measurements has greatly pressured the development of measures to improve the quality of analytical results and to guarantee quality to the end users. In this work an ICP-MS method was validated for the simultaneous determination of essential trace elements (Chromium, Selenium and Copper) and non-essential toxic elements (Cadmium, Antimony, Arsenic, Tin and Lead) in infant formula available in Sicily. The extraction of samples was performed by a microwave assisted digestion with HNO3 to stabilize these elements. Several parameters have been taken into account and evaluated for the validation of method: selectivity/specificity, trueness by recovery, repeatability and within-laboratory reproducibility at three levels of concentration, instrumental detection limit, limit of determination (LOD), limit of quantification (LOQ), range of linearity, standard measurement uncertainty. Results indicate that this method could be used in the laboratory for the routine determination of these 8 essential and non-essential elements in infant formulas with acceptable analytical performance.

Keywords: Validation process; ICP-MS; Infant formula; Heavy metals; Trace elements; Toxic food contamination; Microwave digestion

Introduction

Infant formulas such powder and liquid milk, fruit juice, homogenized, and cookies are a mixture of ingredients that have been proven suitable for infant feeding. The nutritional safety and adequacy of infant formula shall be scientifically demonstrated to support growth and development of infants; consequently, there is the need to determine very low concentration of elements that may be present in trace and ultratrace levels.

Trace elements and minerals are essential for biological processes and play an important role in normal growth and development but can be toxic when taken in excess [1]; both toxicity and necessity vary from element-to-element. With increasing industrialization and environmental pollution, a heavy metal exposure assessment study is necessary [2-6]. The heavy metals enter the human body through inhalation and ingestion and it is well established that children are more sensitive to heavy metals such as Pb and Cd than adults [7]. Infant growth and development critically depend on the provision of an appropriate diet. Analytical measurements are essential to maintain control processes and products quality, both in manufacturing, trade and research. Quadrupole Inductively Coupled Plasma Mass Spectrometry (ICP-MS) has been widely employed for the detection of elements at very low concentration, as requested for these products [8-10]. Gases such as H_2 or He are then bled into the collision/reaction cell, which consists of an octapole, operated in the rf-only mode. The rf-only mode focuses the ions, which then collide and react with molecules of the collision/reaction gas. By a number of different mechanisms, polyatomic interfering ions like 40 Ar 16O, and 38 ArH will be converted to harmless non-interfering species.

The aim of this study is to validate a method for the simultaneous determination of essential trace elements such Chromium (Cr), Selenium (Se), Copper (Cu) and non-essential elements such Cadmium (Cd), Antimony (Sb), Arsenic (As), Tin (Sn) and Lead (Pb), potentially toxic for the consumers in infant formula available in Sicily according to the Commission Decision 2002/657/EC, UNI CEI EN ISO/IEC 17025/2005, Commission Regulation (EC) n° 333/2007, Commission Regulation (EC) n° 836/2011 for acceptability criteria of the method and taking into account the Commission Regulation (EC) n° 488/2014 and the Commission Regulation (EC) n° 1881/2006 for the maximum acceptable levels [11-26].

Materials and Methods

Instrumentation

The elements were determined by using ICP-MS (7700x series, Agilent Technologies, Santa Monica CA, USA). The sample solution were pumped by a peristaltic pump from tubes arranged on a autosampler ASX-500 Series (Agilent Technologies, Santa Monica (CA), USA), that was combined with a quartz cyclonic spray chamber (water cooled 2°C). The instrumental setting and operative conditions are reported in Table 1.

Fast and efficient sample digestion was achieved by a microwave-assisted nitric acid procedure. Samples digestion was carried out using a microwave digestion system Multiwave 3000 (Anton-Paar, Graz, Austria) equipped with a rotor for eight MF100 PTFE-TFM (poly-tetrafluoroethylene-tetrafluoroethylene) vessels.

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Parameter	Setting
RF-Power (W)	1550
Reflected power	<5
Carrier gas flow (mL/min)	1.0
Plasma gas flow (L/min)	15
Auxiliary gas flow (mL/min)	1.0
Spray chamber	Water cooled double pass
Spray chamber temperature (°C)	2
Lens voltage (V)	6.25
Mass range (amu)	6-209
Mass resolution	0.7
Integration time points/ms	3
Points per peak	3
Replicates	3

Table 1: ICP-MS instrumental parameters.

Reagents and gases

All solutions were prepared with analytical reagent ultra-pure grade.

- Water for chromatography LiChrosolv® was purchased from Merck KgaA (Darmstadt, Germany).

- Ultrapur nitric acid 60% was purchased from Merck KgaA (Darmstadt, Germany).

- Standard solution: the multielement calibration solutions were prepared at different concentration leves (0.001-50 µg/L) from 1000 mg/L single element ICP-MS grade standard, traceable to NIST, were purchased from VWR International LTD. (Randon, Pennsylvania, USA).

- To optimize the performance of ICP-MS before use, a Tuning Solution for ICP-MS, capable of covering a wide range of masses (Ce, Co, Li, Mg, Tl and Y 1 µg/l) was purchased from Agilent Technologies, Santa Monica, CA, USA).

- Internal Standard solution: 100 mg/L standard stock solution of scandium (Sc), yttrium (Y), indium (In), terbium (Tb), rhodium (Rh), lutetium (Lu), Lithium (Li^6), indium (In), germanium (Ge) and bismuth (Bi) was purchased from Agilent Technologies (Santa Monica, CA, USA).

- Ultrapure grade carrier gas (argon (Ar), 99.9995% pure) was purchased from SOL S.p.a. (Monza, Mi, Italy).

- Ultrapure grade diluition gas (helium (He), 99.9995% pure) was purchased from SOL S.p.a. (Monza, Mi, Italy).

- Ultrapure grade diluition gas (hydrogen (H_2), 99.9995% pure) was purchased from SOL S.p.a. (Monza, Mi, Italy).

Quality assurance

The accuracy of the analysis was verified by analyzing the Certified Reference Materials (Fapas® test material, infant cereal, reference number T07183QC) and the concentration for each of the samples were typically within the certified range of 10% of the certified value, demonstrating the validity of the above methods, as presented in Table 2.

Sampling collection and samples preparation

A total of 10 samples of commercially available infant formulas liquid milk were collected from local supermarkets all over Sicily between February/March 2015. The samples represented four popular brands available on the market. All brands were represented by only liquid milk products, targeted for infants aged 6 to 12 month. All the samples were kept in their original packages and transferred to the laboratory by an ice box, properly labelled and stored in refrigerator than processed for analysis within one week of their purchase, well before the expiry date.

The sample digestion procedure was performed according to the UNI EN 13805:2002; 1 g of the representative samples were transferred into previously decontaminated vessels with 3 mL of Ultrapure nitric acid 60% (V/V) and 5 mL of water. The digestion procedure is reported in Table 3.

Method validation

Instrumental/method detection and quantification limits: In order to calculate the instrumental/method limits of detection and quantification (LoDs and LoQs), the 3σ and 10σ approach were employed. The following formulas were used:

$$LoD = \frac{3sd\,C_{spike}}{I_{spike} - I}$$

$$LoQ = \frac{10sd\,Cd_{spike}}{I_{spike} - I}$$

Where:

C=Concentration expressed in µg L^{-1}

Sd=Standard deviation

I=Signal intensity of the element

A number of 15 pool reagents blanks/digested samples and 15 pool reagents blanks/digested samples spiked with 0.01 µgL^{-1} of As, Cd, Pb, Sb and 5.00 µgL^{-1} of Se, Cr, Sn and Cu were prepared and analyzed. The reagent blanks were used for the calculation of instrumental LoDs and LoQs, while digested samples was used for the calculation of method LoDs and LoQs. For method LoDs and LoQs, weight (≈ 1 g) of samples is taken into account to calculate the final values. The Requirement for LOD and LOQ, set in European Regulations are reported in Table 4.

Range of the linearity and calibration curve: Although ICP-MS is well known for benefiting from a wide linear concentration range, this parameter was evaluated by checking the linear regression coefficient (r^2) of a calibration curve constructed with 8 standard additions (BlankCal - 0.01-0.05-0.1-0.5-1-5-10-50 µg/L). A pool of digested samples was used for this test. The linearity of the calibration curve was considered acceptable when $r^2>0.999$. In the whole validation, the calibration curve for the measurements was always prepared with at least five points (BlankCal not included).

Recovery study: Trueness of the method was assessed by using the recovery of the three concentration levels. All samples were spiked with the right amount of concentration in according to the scheme of Table 5, digested according to the pre-established MW program and then analyzed. The recovery was calculated as follow:

$$recovery\% = \frac{100C}{spiked\ concentration}$$

Where, *C* is the element concentration found. An acceptance limit between 90 and 110% was selected.

Repeatability and within-laboratory reproducibility: The repeatability and within-laboratory reproducibility were calculated as percentage variation coefficient (CV%), analyzing the same samples

Element (µg/Kg)	Certified (mg/Kg)	Measured (mg/Kg)
Cadmium	0.047 ± 0.005	0.048 ± 0.003
Chromium	0.135 ± 0.020	0.132 ± 0.010
Lead	0.066 ± 0.010	0.067 ± 0.004
Selenium	0.085 ± 0.010	0.084 ± 0.009

Table 2. Results of elemental analyses for certified reference materials.

Ph (Fase)	Power (W)	Ramp (min)	Hold (min)	Fan
1	600	10:00	40:00	1
2	0	0	15	3

Table 3. Microwave parameters.

Element	ML (mg/Kg)	LOD (mg/Kg)	LOQ (mg/Kg)
Cd	≤ 0.005	≤ 0.001	≤ 0.002
Pb	≤ 0.020	≤ 0.004	≤ 0.008
Sn	≤ 50	≤ 5	≤ 10

Table 4: Requirement for LOD and LOQ are set in Commission Regulation (EC) n° 836/2011 for Cadmium, Lead and Inorganic tin; ML: maximum permitted level according to Commission Regulation (EC) n° 1881/2006 and Commission Regulation (EC) n° 488/2014.

used for recovery study in three different days. As concerns the within-laboratory reproducibility, in particular, the first day not applied no change, the operator and the instrument and different kind of matrix were changed in the second and in the third day.

Ruggedness study: The ruggedness study is strongly recommended when a method is being subjected to the validation process. It has to be carried out by selecting and varying any factor that may influence the result of the measurement.

Measurement uncertainty: A laboratory has to demonstrate the quality of the results produced and its fitness for purpose by giving a measure of the confidence that can be placed on the result. All possible sources of uncertainty have to be carefully identified. In this study, the following contributions to combined measurement uncertainty were selected: the preparation of the standard solutions (u_f), the standard uncertainty associated to the recovery (u_{rec}) and the within-laboratory reproducibility of the measurements (u_m); each component was calculated as follows in order to validate the method:

$$u_{rec} = \frac{rsd}{\sqrt{n}}$$

where *rsd* is the ratio between the standard deviation of the mean recovery and the mean recovery value and *n* is the number of spiked samples; the uncertainty u_f associated with the preparation of the standard solutions was considered by the sum of the contributes: pipettes volume, scale and stock solutions:

$$\frac{u_f}{C} = \sqrt{\left(\frac{u_v}{V}\right)^2 + \left(\frac{u_b}{M}\right)^2 + \left(\frac{u_{cal}/\sqrt{3}}{Cal}\right)^2}$$

where u_v is the standard uncertainty of the pipettes volume, u_{cal} is the standard uncertainty of the stock standard solutions and u_b is the standard uncertainty of the scale. Then, the combined uncertainty (u_C) was calculated as the square sum of the three contributes:

$$\frac{u_c}{C} = \sqrt{u_m^2 + u_{rec}^2 + u_f^2}$$

While, the expanded measurement uncertainty *(U)* was:

$$U = u_c\left(x\right)^k$$

where *k* is the coverage factor of 2, which considers a normal distribution of measurements with a 95% confidence level.

Results and Discussion

In this study only liquid milk was chosen for the method validation because is the infant formula with the lowest admissible level of non-essential toxic elements imposed by the Commission Regulation (EC) n° 488/2014 and Commission Regulation (EC) n° 1881/2006. The sensitivity of the instrumentation used for the validation of the method has achieved all the objectives that Commission Regulation (EC) n° 836/2011 requires us to the determination of cadmium, lead, and tin to be used in official food control.

Figure 1 and 2 show the calibration curves of all analytes, the equation of the straight line, DL (instrumental detection limit) and BEC (background equivalent concentration). The statistical tests were derived from the analysis of variance applied to the least-squares regression (according to the Fischer tests). Results indicated that the linear regression model was acceptable for the 8 analytes in the defined range with a satisfactory correlation coefficient ($r^2 \geq 0.999$). The values of LoDs and LoQs are shown in Table 6; results from LoD and LoQ detection comply with the Commission Regulation (EC) n. 333/2007, laying down the methods of sampling and analysis for the official control of heavy metals levels in foodstuff.

The performance studies show range of recovery between 96% e 105%. To calculate the limit of repeatability a number of 15 pool reagents digested samples spiked with 0.1 - 1.00 - 10.00 μgL^{-1} of As, Cd, Pb, Sb and 10.00 - 20.00 - 50.00 μgL^{-1} of Se, Cr, Sn and Cu were prepared and analyzed. For the within-laboratory reproducibility, five different parameters were changed and tested: (a) analytical standards; (b) operator; (c) day; (d) torch; (e) micropipette; (f) peristaltic pump rate. The major contributions are detected; a good estimate of the measurement uncertainty can be made by concentrating effort on the largest and most significant contributions. Afterwards, the uncertainty components are quantified and the combined uncertainty is calculated (Table 7). All the possible sources of uncertainty have to be carefully identified and taken into account.

While measuring the concentrations by ICP-MS with external standard, fluctuations in the measurement of ionic currents occurring as a result of the electrical noise in the detector, instabilities in plasma discharge, instabilities of the electrical parameters of the analyzer, lead to uncertainties in the determination of the parameters of the calibration line [27]. The values obtained produces standard measurement uncertainties (u_f) less than the maximum standard measurement uncertainties (u_m), calculated with the formula reported in point C.3.3.2 of the Commission Regulation (EC) n° 836/2011 to the applicability of the methods for the official control (Table 8). All concentration levels showed Horrat values of repeatability and reproducibility lower than 2 as specified by the Commission Regulation (EC) n° 836/2011.

Conclusion

ICP-MS is a very useful technique, particularly for food safety. This new instrumentation application combines sensitivity, specificity and speed and only requires a few amount of sample. The proposed method showed to be reliable for the determination of eight elements in infant formula and in according to the performance criteria and

Element	Level 1 (mg/Kg)	Level 2 (mg/Kg)	Level 3 (mg/Kg)
As	0.005	0.05	0.5
Cd	0.005	0.05	0.5
Pb	0.005	0.05	0.5
Sb	0.005	0.05	0.5
Se	0. 50	1.00	2.5
Cr	0. 50	1.00	2.5
Sn	0.50	1.00	2.5
Cu	0.50	1.00	2.5

Table 5. Concentration levels for the analytes (10 replicates for level).

Element	LoD (mg/Kg)	LoQ (mg/Kg)	Applicability range (mg/Kg)
As	0.001	0.002	0.002 – 2.50
Cd	0.0008	0.001	0.001 – 2.50
Pb	0.002	0.006	0.006 – 2.50
Sb	0.003	0.008	0.008 – 2.50
Se	0.50	1.00	1.00 – 2.50
Cr	0.50	1.00	1.00 – 2.50
Sn	0.50	1.00	1.00 – 2.50
Cu	0.50	1.00	1.00 – 2.50

Table 6: Method detection and quantification limits and applicability range.

	Pb			Cd		
Parameters (µg/kg)	5.00	50.0	500	5.00	50.0	500
Recovery (%)	98	101	100	97	103	101
Limit of repeatability (µg/kg)	0.45	7.22	34.10	0.35	2.62	23.2
Within-laboratory reproducibility (µg/kg)	0.62	8.61	53.71	0.55	3.81	45.4
Expanded uncertainty (µg/kg)	± 2.20	± 5.90	± 40.3	± 0.75	± 4.90	± 50.5
	As			**Sb**		
Parameters (µg/kg)	5.00	50.0	500	5.00	50.0	500
Recovery (%)	102	102	102	96	98	102
Limit of repeatability (µg/kg)	0.62	8.50	41.8	0.91	8.28	50.2
Within-laboratory reproducibility (µg/kg)	0.83	10.2	59.2	1.85	10.5	70.3
Expanded uncertainty (µg/kg)	± 1.25	± 10.3	± 61.8	± 1.86	± 9.73	± 80.2
	Se			**Cr**		
Parameters (mg/kg)	0.5	1	2.5	0.5	1	2.5
Recovery (%)	98	101	98	101	101	100
Repeatability (mg/Kg)	0.02	0.03	0.16	0.03	0.05	0.12
Within-laboratory reproducibility (mg/Kg)	0.03	0.05	0.22	0.04	0.07	0.19
Expanded uncertainty (mg/Kg)	± 0.08	± 0.10	± 0.22	± 0.06	± 0.14	± 0.21
	Cu			**Sn**		
Parameters (mg/kg)	0.5	1	2.5	0.5	1	2.5
Recovery (%)	102	99	100	105	101	98
Repeatability (mg/Kg)	0.03	0.05	0.16	0.05	0.09	0.2
Within-laboratory reproducibility (mg/Kg)	0.05	0.07	0.19	0.06	0.10	0.3
Expanded uncertainty (mg/Kg)	± 0.08	± 0.10	± 0.22	± 0.10	± 0.15	± 0.45

Table 7: Method performance for all the analysed elements.

Element	Concentration µg/Kg		
	5.00	**50.0**	**500**
As	u_m=1.09	u_m=4.09	u_m=50.6
	u_f=1.12	u_f =9.01	u_f=90.0
Cd	u_m=1.01	u_m=4.00	u_m=50.3
	u_f=1.07	u_f=9.00	u_f=90.0
Pb	u_m=2.25	u_m=4.76 u_f=9.05	u_m=48.8 u_f=90.0
	u_f=1.41		
Sb	u_m=1.50 u_f=1.80	u_m=9.07 u_f=9.12	u_m=80.3 u_f=90.01

Element	Concentration mg/Kg		
	0.5	**1.00**	**2.50**
Se	u_m=0.08 u_f=0.26	u_m=0.11 u_f=0.28	u_m=0.23 u_f=0.39
Cr	u_m=0.06 u_f=0.26	u_m=0.14 u_f=0.28	u_m=0.21 u_f=0.39
Sn	u_m=0.10 u_f=0.26	u_m=0.15 u_f=0.28	u_m=0.45 u_f=0.39
Cu	u_m=0.08 u_f=0.26	u_m=0.10 u_f=0.28	u_m=0.22 u_f=0.39

Table 8: Performance criteria set out by the EC Regulation n° 836/2011.

the requirements set in the regulations of the European Union for method validation to be used in official food control. Furthermore, the present method offers satisfactory detection limits due to the powerful spectrometric analytical technique employed and provides a precise and accurate method with high sample throughput for determination of As, Cd, Sb, Pb, Cr Se Sn and Cu in infant formula.

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