Investigation of Uncertainty Contributions for Elemental Analysis of Sesized Street Heroin by ICPMS

AURA LICSANDRU[1]*, VERONICA NACEA[2], RICA BOSCENCU[2]

[1]General Inspectorate of Romanian Police, Central Laboratory for Drug Analysis and Profiling, 13-15, Stefan cel Mare Blvd., 020123, Bucharest, Romania

[2]„Carol Davila" University of Medicine and Pharmacy, Faculty of Pharmacy, Inorganic Chemistry Departament, 6, Traian Vuia Str., 020956, Bucharest, Romania

The aim of the study was the identification and quantification of uncertainty sources associated with heroin elemental analysis by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) following sample dissolution through microwave assisted acid digestion. The percentage contribution of each source to the relative combined uncertainty was also calculated.The "bottom-up" approach was used to estimate the measurement uncertainty, while weighing of samples, analyte recovery, sample volume, calibration curve and repetability were considered for uncertainty sources. The range of expanded uncertainties was 5.71-14.87% (using a coverage factor k = 2, which gives a level of confidence of approximately 95%) for Al, Mg, Cu and Co concentration and obtained data indicate major contribution to the uncertainty budget originating from the calibration curve and also from the preparation of calibration standards. We found that the uncertainties caused by samples weighing, sample preparation and repeatability of ICP-MS measurement have no dominant contribution to the overall uncertainty and the uncertainty due to recovery was below 10%.

Keywords: heroin, ICP-MS, Ishikawa Diagram, uncertainty sources, uncertainty budget

The main objective of quantitative analysis is to obtain the most reliable analytical results, which must reflect unambiguously true and clear values of sample composition [1]. But the results can only approximate the value of the specific quantity subject to measurement [2] and thus they are not complete and cannot be properly interpreted unless they are accompanied by a quantitative statement of their uncertainty [3].

As measurement uncertainty estimation is considered an important part of the method validation procedure, the list of guidelines and works dedicated to this topic is getting longer every year. Previous studies about uncertainty determination in drugs of abuse analysis referred mostly to chromatographic techniques such as GC-FID [4], GC-MS [5,6] HPLC [7,8] HPLC-MS/MS [9], which were applied for the separation and quantification of organic analytes.

The level of inorganic impurities in seized drugs was also investigated [10-15] in order to evaluate the potential importance of major and trace metals content in sample comparision and/or origin determination, but neither uncertainties associated with elements concentration determination nor disscussions about uncertainty sources were included.

In what method validation and, particularly, measurement uncertainty estimation are concerned, there is a gap in the area of illicit drug elemental analysis by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Our study aimed to evaluate the uncertainty related to determination of metal content in seized heroin by ICP-MS. The contribution of each uncertainty source was investigated in order to identify solutions for the improvement of the combined measurement uncertainty.

Experimental part

Reagents and calibration standards

Acid digestion of the samples was carried out with a mixture of nitric acid (60% volume concentration of HNO_3 ultrapure Merck) and hydrogen peroxide (30% volume concentration of H_2O_2 p.a., Fluka).

Multi-element calibration Standard 3 (Ag, Al, As, Ba, Be, Bi, Ca, Cd, Co, Cr, Cs, Cu, Fe, Ga, In, K, Li, Mg, Mn, Na, Ni, Pb, Rb, Se, Sr, Ti, V, U, Zn, for each 10 μg/mL) and Yttrium solution (1000 μg/mL) from Perkin Elmer were employed for calibration of the instrument and internal standardization respectively. Single element standard solutions (Al, Co, Cu, Mg, for each 1000 μg/mL) were used for the fortification of blank and sample solutions. All solutions were prepared or diluted with double deionized water (specific resistance 18.2 MΩcm^{-1}) from a Milli-Q Millipore water purification system.

Preparation of standard solutions

Standard solutions were prepared just before analysis through a serial dilution method (fig. 1) on the same stock solution (Standard 3). The calibration curves for Mg and Al (two of the major elements in illicit heroin) were generated using STD 1 (1000 μg/L), STD 2 (500μg/L), STD3 (200μg/L) and STD4 (100 μg/L), whereas STD 7 (1μg/L), STD 6 (10 μg/L), STD 5 (50 μg/L) and STD 4 were selected for Co and Cu (trace elements in illicit heroin) calibration curves. All solutions were prepared using the same volumetric glassware: three graduated pipettes (with 1, 5 and 10 mL capacity) for larger volumes and an autopipette (20-200 μL) for small volumes. Dilutions were performed in volumetric flasks (50 mL) by filling to the mark with ultrapure water.

Sample preparation

Heroin samples were weighed using a CP224S-0CE Sartorius electronic analytical balance and a microwave oven decomposition system (Multiwave 3000 with Rotor 8SXQ80, Anton Paar GmbH, Graz) was involved for samples microwave assisted acid digestion following a particular procedure described in our prior published work [16].

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* *email: aura_licsandru@yahoo.com; Tel.: +40742285994*

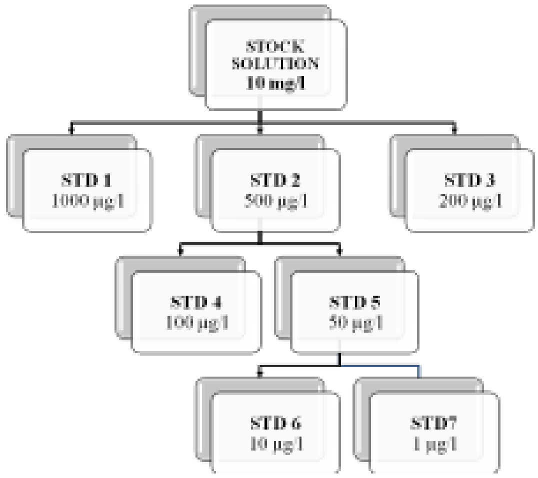

Fig. 1. Scheme of standard solution preparation

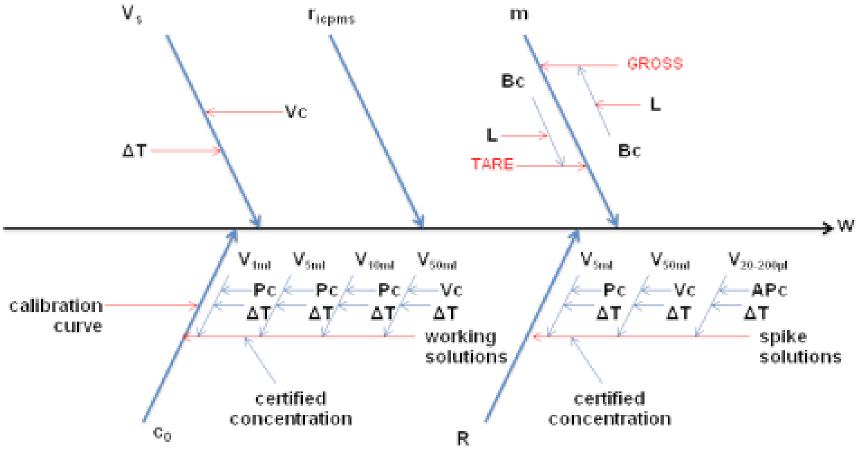

Fig. 2. The Ishikawa Diagram showing the influence of individual parameters of the analytical procedure on the combined uncertainty of analyte content determination, where: Pc = pipette calibration, Vc = volumetric flask calibration, APc = autopipette calibration, Bc = balance calibration, L = balance linearity, ΔT = temperature effect

Sample analysis

Elemental analysis of heroin samples was performed on a Perkin Elmer ELAN DRC-e ICP-MS quadrupole spectrometer (working as described in our previous paper [16]). The detector ran either in Analog or Dual mode of operation, depending on the level of metals concentration in the heroin samples, and the instrument calibration was carried out for each element being analysed prior to the measurement.

Estimation of measurement uncertainty

The uncertainty related to analysis of heroin street samples by ICP-MS was estimated following the “step-by step” or “bottom-up” approach [17], which demands a clear description of what being measured (measurand), as well as its relationship with the potential variables that can have an impact on it. The values of the input quantities and their associated standard uncertainties were propagated through the model to provide an estimate (value) of the output quantity and its associated standard uncertainty. The uncertainties of the final results were expressed as standard deviations (standard uncertainty) or by multiples of standard deviations (expanded uncertainty) with a specified numerical factor (coverage factor). The modeling of measuring process is particularly useful when evaluate the contribution of reference value uncertainties to the combined uncertainty associated with the final measurement results.

Results and discussions

Identification of uncertainty sources

The chemical element concentration in the digestion solutions were determined by ICP-MS software and the further calculation of the element contents in the solid sample was done by means of equation (1):

$$w = \frac{c_0 \times V_s}{m} \times d \qquad (1)$$

where:

w = the analyte concentration in the sample (stated in mg/kg),

c_0 = the analyte concentration in the digestion solution (stated in µg/L),

V_s = the volume of digestion sample (stated in l),

m = the mass sample mineralized by microwave acid digestion (stated in g) and d represents the dilution factor.

Equation (1) stands for the measurement function which describes the relationship between the output and the input quantities. Hence, the uncertainty of the measurand has several components. Some of the uncertainty components are A-type and they are evaluated by statistical methods, while others fall into B-type category, whose evaluation is usually based on scientific judgment [11] (i.e. manufacturer’s specifications, data provided in calibration reports, uncertainties assigned to reference data taken from handbooks).

The relationship between the measurand and all factors that influence can be graphically illustrated in a cause-effect diagram, known also as Ishikawa Diagram (after Kaoru Ishikawa, a *Japanese* quality control *statistician*) [18]. For the nonce, the predicted concentration of the analyte (w) (fig. 2) is affected by the final volum of the sample (Vs), the sample weight (m), the calibration curve (c_0), the recovery of the analyte (R) and the repetability of the measurement (r_{ICPMS}). Because the sample solution was not diluted prior to ICP-MS analysis, the contribution of this factor was not considered in further calculations.

After the separately identification and quantification of relevant uncertainty sources, the combined uncertainty of analyte content determination can be calculated according to the law of error propagation [19] by means of equation (2).

$$u_c(w) = w \times \sqrt{u_{rel}(m)^2 + u_{rel}(V_s)^2 + u_{rel}(c_0)^2 + u_{rel}(r_{ICPMS})^2 + u_{rel}(R)^2} \qquad (2)$$

Estimation of uncertainty due to sample weighing, u(m)

Weighing vessel was placed on the balance and the heroin sample was transferred subsequently inside it (without removing it from the balance). The net weight calculated for the powder material was 0.260 g. The balance liniarity (as from the calibration certificate) was ±0.2 mg. We assumed a rectangular distribution when convert the liniarity contribution to a standard uncertainty. The contribution was counted twice as the weighing process involved a difference. The numeric calculation gives: $u(m) = \sqrt{(0.2/\sqrt{3})^2 \times 2} = 0.16330mg$ and $u_{rel}(m)$ = 0.16330 / 260 = 0.00063

Estimation of uncertainty associated with the preparation of sample solution, u(Vs)

At the end of the digestion procedure, solutions were quantitatively transfered into clean 50 mL volumetric flask, and then diluted to volume with ultrapure water. In order to calculate the uncertainty, two components are considered and combined (3): calibration data as specified by the manufacturer (in terms of tolerance interval), and uncertainty of the volume due to difference from calibration temperature (the laboratory temperature does not differ from 20°C by more than 4 degrees). For volume calibration (±0.06 mL) a triangular distribution was supposed and only liquid's volume expansion caused by temperature variation was taken into account (γ_{water} = 2.1 . 10^{-4} °C^{-1}, coefficient of volume expansion). The uncertainty of the temperature effect was calculated using the assumption of a rectangular distribution (4) and the numeric results for relative uncertainty $u_{rel}(V_s)$ are summarized in table 1.

$$u(V_s) = \sqrt{u(V)^2 + u(T)^2} \qquad (3)$$

$$u(T) = \frac{4 \times \gamma \times V}{\sqrt{3}} \qquad (4)$$

Estimation of uncertainty related to analyte concentration, $u(c_0)$

The concentration of the analyte in the solution of unknown sample (c_0) was calculated from the best-fit calibration equation (5) (via inversion of the calibration equation) [20] after measuring the response (I_0) for the solution of unknown sample:

$$c_0 = \frac{I_0 - b}{a} \qquad (5)$$

where:

a = the instrument response factor, evaluated as the slope of the best-fit line,

b = the intercept.

In order to quantify the uncertainty for calibration curve the standard uncertainty of regression equation for calibration curve ($u_{calibration}$) and standard uncertainty of concentration of standard solutions for calibration curve *($u(c_{STD})$)*were considered (6).

$$u_{rel}(c_0) = \sqrt{u_{rel}(c_{STD})^2 + (u_{calibration}/c_0)^2} \qquad (6)$$

After the estimation of all uncertainty components, as further described below, the relative uncertainty related to determination of analyte concentration based on calibration curve was found: $u_{rel}(c_o)$=0.02989

Uncertainty due to the preparation of standard solutions, $u(c_{STD})$

The uncertainty associated with the volumetric glassware used for preparation of calibration standards has two sources of uncertainty: one resulting from the calibration of inner volume of the volumetric flask and graduated pipettes, and the other due to the laboratory temperature variation from the temperature calibration (20°C). There are other two components which influence the final results, as well: the uncertainty associated with analyte concentration in the stock solutions (±0.5 mg/L for each element), and the uncertainty of working solutions measurement repeatability (*$u(RSD_{STD})$*) for n = 3 replicates of each calibration standard (7).

$$u_{rel}(c_{STD}) = \sqrt{u_{rel}(c_{element})^2 + \sum_{i=1}^{n} u_{rel}(V)^2 + \sum_{i=1}^{n}\left(\frac{RSD_{STD}}{\sqrt{n}}\right)^2} \qquad (7)$$

Four calibration standards with a concentration 100, 200, 500 and 1000 μg/L were prepared for generating Al calibration curve. The results we got from the calculation of relative uncertainty arisen from the preparation of all calibration standards are resumed in table 2.

Uncertainty associated with calibration curve, $u_{calibration}$

This uncertainty component was quantified based on calibration curve obtained for Al (8), following EURACHEM recommendation [17].

$$y(Al) = 0.00354177 . x(Al) + 0.00028308 \qquad (8)$$

The amount of Al in the solution of unknown sample was determined by a mean of three replicates, leading to a concentration c_0 = 187.09 μg/L. The uncertainty associated with the linear square fitting procedure curve was calculated by means of equations (9) and (10) [17]. The calibration standards were measured three times each

Description	Value, x, (ml)	Distribution	Factor	Standard uncertainty, u(x)
calibration of volumetric flask	0.06	triangular	$\sqrt{6}$	0.02449
temperature variation	0.042	rectangular	$\sqrt{3}$	0.02425
relative uncertainty, $u_{rel}(V_s)$				**0.00069**

Table 1

UNCERTAINTY CALCULATION ARISING FROM PREPARATION OF SAMPLE SOLUTION IN 50 mL VOLUMETRIC FLASK

calibration standards	$u_{rel}(V)$	$RSD_{STD}/\sqrt{n}$	$u_{rel}(c_{element})$	$u_{rel}(c_{STD})$
STD1	0.00259	0.00153	0.02551	**0.02687**
STD2	0.00497	0.00320		
STD3	0.00259	0.00273		
STD4	0.00340	0.00129		

Table 2

UNCERTAINTY CALCULATION RELATED TO THE PREPARATION OF CALIBRATION STANDARDS

Table 3
CALIBRATION RESULTS

c_{STD}, mg/l	I_{exp} (cps) 1	2	3	s_r	$\sum_{j=1}^{n}(c_j-\overline{c})^2$	$u_{calibration}$	$u_{calibration}/c_0$
0.1	0.366	0.365	0.364	0.01203	1.47	2.31345	**0.01237**
0.2	0.706	0.702	0.710				
0.5	1.762	1.760	1.747				
1.0	3.554	3.553	3.540				

Table 4
EXPERIMENTAL RESULTS FOR RECOVERY STUDY

c_{spike}, µg/l	c_{native}, µg/l 1	2	3	c_{obs}, µg/l 1	2	3	s_{native}	s_{obs}
300	186.201	187.908	187.159	469.654	466.144	463.708	0.86	2.99
		187.089			466.502			

Table 5
UNCERTAINTY CALCULATION RELATED TO ANALYTE RECOVERY

Description	x	u(x)	u(x)/x
volumetric flask (50ml) calibration	0.06	0.03447	0.00069
graduated pipette (5ml) calibration	0.03	0.01249	0.00250
micropipette (20-200µl) calibration	0.0006	0.00026	0.00170
certified concentration (Al, 1000 µg/ml)	3.00	1.53061	0.00153
$u_{rel}(c_{spike})$		**0.00346**	
$u_{rel}(R)$		**0.00771**	

and the values for signal intensity as recorded by ICP-MS instrument are displayed in table 3.

$$u_{calibration}=\frac{s_r}{a}\sqrt{\frac{1}{p}+\frac{1}{n}+\frac{(c_0-\overline{c})^2}{\sum_{j=1}^{n}(c_j-\overline{c})^2}} \quad (9)$$

$$s_r=\sqrt{\frac{\sum_{j=1}^{n}\left[I_j-(b+a\times c_j)\right]^2}{n-2}} \quad (10)$$

where:

s_r = the residual standard deviation,

$\overline{c}$ = the mean value of different calibration standards,

p = the number of repeated measurements to determine c_0,

n = the number of measurements for the calibration,

j = the index for the number of measurements to generate the calibration curve.

Estimation of uncertainty related to analyte recovery achieved with microwave-assisted acid digestion, u(R)

Determination of metal concentration by ICP-MS depends to a great extent on the sample preparation. Microwave assisted acid digestion was performed for seized street heroin. Recovery rate was used in order to evaluate the accuraccy of dissolution procedure [16]. As certified reference materials able to mimic the matrix of heroin samples are unavailable, the recovery of the analyte was estimated by studying the recovery of an added compound that is regarded as a surrogate for the native analyte [21].

Heroin samples were spiked with known quantities of four analytes (Mg, Al, Cu, Co) before mineralization, and then analized in 3 replicates. The analyte recovery and its associated standard uncertainty were calculated using equations (11) and (12) [22]. The experimental results are presented in table 4.

$$R=\frac{\overline{c}_{obs}-\overline{c}_{native}}{c_{spike}} \quad (11)$$

$$u(R)=R\times\sqrt{\frac{\frac{s^2_{obs}}{n}+s^2_{native}}{(\overline{c}_{obs}-\overline{c}_{native})^2}+\left(\frac{u(c_{spike})}{c_{spike}}\right)^2} \quad (12)$$

where:

$\overline{c}_{native}$ = the mean value of the analyte concentration in the unspiked sample,

$\overline{c}_{obs}$ = the mean value of the analyte concentration in the spiked sample,

c_{spike} = the analyte concentration in the spiked blank,

s_{native} = the standard deviation of the results from the replicate analyses of the unspiked samples

s_{abs} = the standard deviation of the results from the replicate analyses of the spiked samples.

The Al spike solution (100 mg/L) was prepared by dilution of a stock solution using a 50 mL volumetric flask and a 5 mL graduated pipette. Aliquots of 150µL from Al solution (micropipette 20-200µL capacity, ±0.0006µL) were transferred to blanks and heroin samples prior digestion, so that final Al concentration in digestion blank solutions to be 300µg/L.

In addition to the serial dilution and the concentration of Al stock solution (1000µg/mL ± 3µg/mL), the temperature effect was also taken into account in the calculation of uncertainty associated with the preparation of the spike solution. The numeric results are summarised in table 5.

Estimation of uncertainty related to repetability of ICPMS determination, u (r_{ICPMS})

This uncertainty component covers the contributions of instrument stability, and precision of calibration [23]. The repeatability determination of analyte concentration by ICP-MS was assessed for six replicates of the sample. The standard uncertainty due to repeatability was calculated as: $u(r_{ICPMS})=conc_{SD}/\sqrt{6}$. Finally, for the relative uncertainty related to determination repeatability we found u_{rel} (r_{ICPMS}) = 0.00187

Combined uncertainty and extended uncertainty

Aluminium content in the solid sample was calculated by means of equation (1) providing w = 35.98 µg / g. Uncertainty of the final result was estimated by combining all the uncertainty components using equation (2) and we obtained $u_c(w)/w$ = 0.03.

Table 6
UNCERTAINTY BUDGET FOR METALS DETERMINATION IN HEROIN SAMPLES

SOURCE OF UNCERTAINTY	Al		Mg		Co		Cu	
	u_{rel}	p%*	u_{rel}	p%*	u_{rel}	p%*	u_{rel}	p%*
mass weighing	0.00063	**0.04**	0.00063	**0.05**	0.00063	**0.03**	0.00063	**0.01**
preparation of sample solution	0.00069	**0.05**	0.00069	**0.06**	0.00069	**0.03**	0.00069	**0.01**
preparation of standard solutions	0.02721	**76.81**	0.02703	**89.10**	0.02897	**58.28**	0.02754	**13.72**
calibration	0.01237	**16.28**	0.00260	**0.82**	0.02362	**38.74**	0.06850	**84.85**
analyte recovery	0.00771	**6.32**	0.00879	**9.42**	0.00668	**3.10**	0.00863	**1.35**
ICPMS measurement repetability	0.00187	**0.37**	0.00053	**0.03**	0.00018	**0.00**	0.00103	**0.02**
SUM OF THE SQUARES	0.00096		0.00082		0.00144		0.00553	
Combined uncertainty	1.11		3.94		0.18		0.25	
Expanded uncertainty	2.22		7.88		0.36		0.50	

* $\frac{u^2}{\sum_{i=1}^{k} u_i^2} \times 100$

The extended uncertainty was calculated by multiplying the combined uncertainty by the coverage factor k = 2, in order to achieve a level of confidence of approximately 95%: $U(w) = u_c(w) \times k = 1.11 \times 2\ 2.22$ μg/g (in percentage, expressed as ± 6.19%).

The same algorithm described above for Al determination in seized heroin samples was also applied for Mg, Cu and Co. The results are presented in table 6.

As the uncertainty budget is commonly used as a qualitative tool to detect the dominant terms contributing to measurement uncertainty [24], the relative contribution of each factor was also calculated for the elements of interest, but we chosed to replace the relative standard uncertainty related to element concentration $u_{rel}(c_o)$ with its components, $u_{rel}(c_{STD})$ and respectively $u_{rel\ calibration}$.

We found that the uncertainties caused by sample weighing and sample preparation are almost negligible, so that they can be considered of lower importance. The repeatability of the ICP-MS measurement has also no dominant contribution to the overall uncertainty, as it is less than 0.5%.

Comparable contributions to the combined uncertainty come from the recovery rate, not only for trace elements (Cu, Co), but also for Mg and Al, identified as major elements in heroin samples. In all cases, the uncertainty due to recovery was below 10%.

At the same time, the determination of analyte concentration $u(c_o)$, bring the highest contribution, regardless of the elements or their concentrations in solutions. Moreover, taking into account the two components of $u(c_o)$, u_{rel}, u_{STD} and $u_{rel\ calibration}$ respectively, they show different contribution when details of experimental determination are put side by side.

If we consider the case of Mg, a calibration curve with the correlation coefficient R = 0.999981 and a linearity range from 100 μg/L to 1000 μg/L was used as reference to find c_0 = 717.73 μg/L. The contribution of the uncertainty due to calibration curve was in this case 0.82%, while the uncertainty associated with the preparation of calibration standards was 89.10%. Within the same linearity range, the calibration curve for Al, the other major element in heroin samples, had a correlation coefficient R = 0.999969. We found c_0 = 187.09 μg/L. Contributions of calibration curve and preparation of working solutions were in turn 16.28%, and 76.81%, respectively. As the determinations involved standard solutions for calibration with the same concentration, we found $u_{rel}(c_{STD}) \approx 0.03$ and depending significantly on the volume calibration of glassware. The increasing of the contribution of uncertainty related to calibration in parallel with the decreasing of uncertainty associated with standard preparation is presumably caused by the small values of Al concentration, near the low end of the calibration range.

For the other two metals found in trace amounts in heroin samples we find the same situation: the estimated values of uncertainty due to preparation of calibration standards are almost identical for Co and Cu, but their contributions to the global uncertainty are quite different (58.28% for Co and 13.72% for Cu). Lower contribution of Cu is a result of significant increase of uncertainty related to calibration curve for the measuring of concentration near the limits of the calibration range.

Conclusions

The uncertainty related to major and trace metal determination in seized street heroin was estimated following the "bottom-up" approach, and the uncertainty budget was used to evaluate the contribution of each component to combined and expanded uncertainty.

We found out that three uncertainty components of a total of six considered for study are less than 10% of the highest component, and thus have little impact on the overall uncertainty. Hence, the uncertainties caused by sample weighing, sample preparation and ICP-MS measurement repeatability can be possibly omitted from calculation.

For all metals taken into consideration (Al, Mg, Co and Cu), the uncertainty related to the metal concentration showed the biggest influence on the overall uncertainty in terms of its components. However, the uncertainty due to the calibration curve as well as that associated with the preparation of calibration standards brought different contributions, depending on the metal concentrations, the former being dominating over the uncertainty budget near the limits of the calibration range.

Therefore, further quantitative analyses require a particular attention on the concentration range of analytes and a better control over the whole process, which may include a *semi-quantitative* elemental screening by ICP-MS, as well as periodic instrument calibrations, so that predicted concentrations of major and trace metals to be properly undertaken throughout the calibration range.

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