

A comparison in the evaluation of measurement uncertainty in analytical chemistry testing between the use of quality control data and a regression analysis

João A. Sousa · Alexandra M. Reynolds ·
Álvaro S. Ribeiro

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Abstract The evaluation of measurement uncertainties has been widely applied to the calibration of measurement instruments, whereas its application to tests, despite increasing requirements, is a more recent phenomenon. The generalization of the evaluation of measurement uncertainties to tests has been a gradual process, in line with changes in the requirements of the normative framework that regulates the accreditation of tests laboratories and also as the perceived good practices have evolved. The sole identification of the relevant sources of uncertainty was followed by the requirement to provide a simplified estimate of the measurement uncertainty, and it is now an accepted requirement to properly evaluate the expanded measurement uncertainty associated with any tests. In this study, the evaluation of measurement uncertainty associated with the determination of sulfate in water will be attempted using a procedure that includes linear regression, with the regression parameters provided with associated uncertainties, and a Monte Carlo method applied as a

validation tool of the conventional mainstream evaluation method, concerning the approximations in terms of linearization of the model and the assumed shape of the output distribution introduced by this approach.

Keywords Measurement uncertainty · Chemical metrology · Regression analysis · Monte Carlo method · GUM uncertainty framework

Introduction

The gradual process of measurement uncertainty evaluation being applied to testing, from the sole identification of sources of uncertainty to the full evaluation of the expanded measurement uncertainty, was naturally also extended to chemical metrology, where accredited tests laboratories now fully comply with the requirement of evaluating the measurement uncertainty for each chemical parameter being tested [1].

As a consequence, guides have been published [2], in an attempt to provide a common ground to the evaluation of uncertainty in chemistry, mainly to comply with the views expressed in the Guide to the Expression of Uncertainty in Measurement [3] (GUM), and it is still very common in analytical chemistry to find evaluation methods based on different uncertainty frameworks depending on the information available, for example on data from collaborative studies, measurements on certified reference materials (CRM) and recovery tests, as the main indicators. Thus, it is relevant to compare different approaches commonly used in chemical laboratories to evaluate measurement uncertainties, and to validate some of these procedures with an accepted validation tool as specified in the Supplement 1 to the GUM [4].

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J. A. Sousa (✉)
Laboratório Regional de Engenharia Civil, IP-RAM,
9000-264 Funchal, Portugal
e-mail: jasousa@lrec.pt

A. M. Reynolds
Investimentos e Gestão da Água, S.A.,
9000-082 Funchal, Portugal
e-mail: xana@iga.pt

Á. S. Ribeiro
Laboratório Nacional de Engenharia Civil,
1700-066 Lisboa, Portugal
e-mail: asribeiro@lnec.pt

Among common features in chemical metrology, the use of the least squares method (LSM) to obtain a straight-line regression and the comparison between quantities expressed in the form of ratios are very common and need therefore to be adequately evaluated. The calibration curves based on LSM are profusely used in analytical chemistry, being, in some cases, the main source of uncertainty associated with the measurands. It follows that a systematic procedure to adequately evaluate the uncertainty entailed by the use of the calibration curve would be a clear advantage to those working in this field. The mathematical formulation based on ratios is also very common, for example, to express the concentration of a substance, and due to its possible nonlinearity, it should have its evaluation validated [5].

Unfortunately, there are cases of laboratories whose scope is the physical–chemical and microbiological characterization of samples, for example, in accordance with techniques and methods that integrate water monitoring programs, where the current practice when working with calibration curves is to obtain a straight-line regression and use it without consideration of the uncertainty associated with estimates of the regression parameters, despite correct methodologies being available from different sources for some time [2]. This is clearly inadequate since the estimates of the input quantities, that is, the measured data, have themselves associated uncertainty, and there is correlation associated with the estimates a and b of the two regression parameters, which need to be accounted for in the subsequent use of the calibration curve to propagate the uncertainties in the conventional equation relating an independent variable x to a dependent variable y [6], through the expression $x = (y - a)/b$. Moreover, in the case of the ratios, they also require validation as the relative values of uncertainties in the numerator and denominator may greatly influence the final value of measurement uncertainty [7].

In this work, the evaluation of measurement uncertainty will be applied to the determination of sulfates in a water sample using an analytical method based on the methylthymol blue method [8]. A comparison will be established between different approaches for the evaluation of uncertainties, namely data validation (internal and external quality control), GUM and Monte Carlo method (MCM) as described in the GUM supplement [4]. It should be pointed out that the difference between the GUM and MCM is from the computational point of view rather than a conceptual point of view. They address the same problem, that is, the propagation of uncertainties from inputs to an output using an input–output model, the measurement equation. However, given the input distributions, they have different computational approaches to evaluate the summary information about the output distribution. The GUM

introduces approximations in terms of the linearization of the model and the assumed shape of the output distribution, whereas the MCM makes no linearizing or shape assumptions and from this point of view can be regarded as a more accurate computational approach to the uncertainty evaluation problem based on the measurement equation. In this sense, the MCM can be used to determine whether the assumptions/approximations made in the GUM approach are reasonable (but can say nothing about whether the assigned input distributions are reasonable or not).

In summary, this study aims to evaluate the measurement uncertainties in the area of analytical chemistry testing, with application to other fields of science, using experimental data from tests in water samples and appropriate statistical tools. This objective is in line with the growing necessity of evaluating measurement uncertainties in testing, according to the international standard NP EN ISO/IEC 17025:2005, and may represent a useful step to the generalized application of this methodology to other areas.

Determination of sulfates in a water sample

The application will focus on an analytical methodology followed by the LQA-Madeira Regional Laboratory for Water Quality Control, in the determination of sulfate in water based in the methylthymol blue method.

In the automated procedure for the determination of sulfate, based on the methylthymol blue method [8], a constant volume of the sample is pumped through peristaltic pumps to the analyzer where the sample is passed through a sodium form cation exchange column to remove multivalent metal ions. The sample containing sulfate is then reacted with an alcohol solution of barium chloride and methylthymol blue at pH of 2.5–3.0 to form barium sulfate. The combined solution is raised to a pH of 12.5–13.0, so that excess barium reacts with methylthymol blue. The uncomplexed methylthymol blue color is grey; if it is chelated with barium, the color is blue. The amount of uncomplexed methylthymol blue is measured at 460 nm, in a segmented flow analyzer (SFA) shown in Fig. 1, which provides the results in digital units (DU).

The analytical method involves several volumetric operations, preparation of the calibration standards and instrumental monitoring and quantification (analytical calibration). The sequence of analytical procedure includes the following steps, more relevant to the estimation of the calculation of uncertainties: (a) takes 3 mL/min of the sample; (b) preparation of the calibration standards and control; and (c) instrumental quantification.

One fundamental step in many analytical methods, as referred, is the construction of a calibration curve, so that it



Fig. 1 Segmented flow analyzer and volumetric equipment used in the tests

can be used to predict a value of the quantity X corresponding to a specific value of the quantity Y . This study will attempt to implement an adequate methodology to extract an uncertainty value from the calibration curve that can reflect the variability due to the uncertainty parameterization. This, in turn, will simplify the overall procedure of uncertainty evaluation. Especially in this test of determining the sulfate content in water samples, the importance of the calibration curve is enhanced by the absence of many manipulation steps, for example digestions and distillations, common to other tests.

Uncertainties associated with the construction of calibration curves

Some applications of the least squares method to obtain linear regression parameters do not include, in its formulation, the information related to the measurement uncertainties of the quantities used to build the curve, for example the uncertainties associated with the volumetric material used for the determination of mass concentrations and the repeatability associated with the instrument indications. In order to be able to carry out a so-called inverse evaluation (or prediction), in which for a given estimate value of Y , and its associated measurement uncertainty, a corresponding value of X and its associated measurement uncertainty will be estimated, one requires the uncertainties of the regression parameters. To obtain these, it is required to account for the uncertainties of y and x , and possible correlations if applicable, to avoid unnecessary approximations. The importance of this methodology arises from the fact that, in practice, the uncertainty related to the calibration curve is known, from the use of several standards solutions, to be significant.

Uncertainties in the input data

In the system of coordinates of the calibration curve, there are values of equipment signal, in digital units (DU), in the ordinates and values of mass concentration, in mg/L, in the abscissas. The uncertainty values in DU were obtained from different sets of experimental data, assuming a normal distribution at each concentration level. The mass concentration levels are taken as 10, 20, 30, 40 and 50 mg/L SO_4 .

The uncertainties associated with each concentration level are related to the process of dilution undertaken by the main solution. The calibration solutions are prepared in volumetric flasks previously decontaminated with type II water (high degree of purity). In order to obtain the required levels of concentration of SO_4 , a piston pipette is used to dilute 100, 200, 300, 400 and 500 μL volume levels in the same 100-mL volumetric flask. The main steps are:

- Weighing of 14.786 g of Na_2SO_4 and dilution in a 1000-mL vessel to obtain a mass concentration of 10000 mg/L of SO_4 , where mass concentration C_{MS} is a common quantity varying the amount provided by the piston pipette;
- Preparation of standards 10, 20, 30, 40 and 50 mg/L SO_4 for the calibration curves, for example $C_{10} = 100 \mu\text{L} C_{\text{MS}}/100 \text{ mL} = 100 \mu\text{L} \times (10000 \text{ mg/L})/100 \text{ mL} = 10 \text{ mg/L}$. Repeat for 200, 300, 400 and 500 μL using the same piston pipette and the same 100-mL volumetric flask;
- Determination of equation of calibration curve; and
- Using the calibration curve to obtain a value of mass concentration corresponding to an unknown water sample used in the segmented flow analyzer.

The input uncertainty data, taken from calibration certificates or product specifications, and the assumed distributions can be summarized in Table 1 below.

Table 1 Input uncertainties for the evaluation of measurement uncertainties associated with the mass concentration values used for the calibration function

Equipment	Uncertainty	Distribution
Balance	0.50 mg	Rectangular
Volumetric flask 1000 mL	0.40 mL	Rectangular
Volumetric flask 100 mL	0.10 mL	Rectangular
Piston pipette 100 µL	0.24 µL	Normal
Piston pipette 200 µL	0.28 µL	Normal
Piston pipette 300 µL	0.32 µL	Normal
Piston pipette 400 µL	0.36 µL	Normal
Piston pipette 500 µL	0.40 µL	Normal

Following the methodology stated in the GUM the uncertainties will be propagated from the preparation of the main solution $C_{MS} = 10000$ mg/L of SO_4 to the different concentrations of the standards of the calibration curve. The main equation is, for example, for the 20 mg/L SO_4 standard

$$C_{20} = \frac{V_{PP}C_{MS}}{V_{VF}} = \frac{200 \mu\text{L} \times 10000 \text{ mg/L}}{100 \text{ mL}}$$

where PP stands for piston pipette, MS stands for main solution and VF stands for volumetric flask. Applying the GUM uncertainty framework, where in practice the input quantities can be considered to be independent, the uncertainty associated with C_{20} is estimated according to the expression

$$u(C_{20}) = \sqrt{\left(\frac{\partial C_{20}}{\partial V_{PP}}\right)^2 u^2(V_{PP}) + \left(\frac{\partial C_{20}}{\partial C_{MS}}\right)^2 u^2(C_{MS}) + \left(\frac{\partial C_{20}}{\partial V_{VF}}\right)^2 u^2(V_{VF})}$$

where the partial derivatives represent the sensitivity coefficients of each quantity in the mathematical model. Strictly speaking, a covariance term should, obviously, have been used, but it was considered to be negligible. Using the values of Table 1 yields the standard uncertainties for each standard used in the calibration curve, illustrated in Table 2.

The uncertainties associated with the digital units provided by the equipment (indications) are calculated

Table 2 Standard uncertainties for each standard of the calibration curve

Concentration SO_4 (mg/L)	Standard uncertainty (mg/L)
10	1.3×10^{-2}
20	1.8×10^{-2}
30	2.4×10^{-2}
40	3.0×10^{-2}
50	3.6×10^{-2}

Table 3 Standard uncertainties for each indication in digital units (DU)

Indication (DU)	Standard uncertainty (DU)
227	6.3
457	9.3
683	15
905	22
1125	26

assuming a rectangular distribution between limits found from different experiments with the equipment. Table 3 summarizes those values.

The calibration function with associated uncertainties

Having the uncertainty values of Tables 2 and 3, one is able to apply the prescribed methodology [6] in order to obtain the straight-line regression equation with their regression parameters and associated uncertainties.

This case corresponds to the one described of the statistical model

$$x_i = X_i^* + d_i, \quad y_i = Y_i^* + e_i, \quad Y_i^* = A^* + B^*X_i^*, \quad i = 1, \dots, m$$

where d_i and e_i are realizations of independent random variables with expectations zero and variances $u^2(x_i)$ and $u^2(y_i)$, respectively. In this model, (x_i, y_i) represent the measured coordinates of the (unobserved) point (X_i^*, Y_i^*) lying on the line $Y = A^* + B^*X$.

Having uncertainties associated with x_i , besides the more common uncertainties associated with y_i , was obviously taken into consideration in the procedure to determine the calibration curve. The problem of determining a and b in this context is known as orthogonal distance regression or generalized distance regression [6]. The estimates a and b are those that minimize the sum of squares

$$\sum_{i=1}^m \left[v_i^2 (x_i - X_i)^2 + w_i^2 (y_i - A - BX_i)^2 \right]$$

in relation to A, B and X_i , for weights $v_i = 1/u(x_i)$ and $w_i = 1/u(y_i)$. Each solution estimate x_i^* , along with a and b , specifies the estimate (x_i^*, y_i^*) , $y_i^* = a + bx_i^*$, of (X_i^*, Y_i^*) in the statistical model.

The minimization process associated with the solution of this mathematical model involves an iterative process of two steps, determining first an optimized value x_i^* based on approximations to a and b , and then as functions of these x_i^* new approximations are determined for a and b that reduce the sum of squares above.

The main results to be obtained from the implementation of this procedure, including the vector \mathbf{a} of dimension 2×1 containing the regression parameters and the associated covariance matrix U_a of dimension 2×2 :

$$\mathbf{a} = \begin{bmatrix} a \\ b \end{bmatrix}, \quad \mathbf{U}_a = \begin{bmatrix} u^2(a) & u(a,b) \\ u(a,b) & u^2(b) \end{bmatrix}$$

In our specific application, the obtained values corresponding to these are as follows:

$$\mathbf{a} = \begin{bmatrix} 2.08 \\ 22.61 \end{bmatrix}, \quad \mathbf{U}_a = \begin{bmatrix} (9.21)^2 & -3.60 \\ -3.60 & (0.46)^2 \end{bmatrix}$$

This provides the required data to evaluate the value and associated uncertainty in mass concentration of SO_4 that would result from the use of the calibration curve with a specific indication. For example, having a sample with value $y = 750$ DU and $u(y) = 17.03$ DU would lead to a SO_4 concentration value of $x = 33.1$ mg/L and $u(x) = 0.84$ mg/L.

Uncertainty evaluation according to data-based method validation and quality control

The quantification of uncertainty of measurement data-based validation and/or quality control method is the combination of standard uncertainties associated with the overall performance of the analytical method. These components can be combined as independent components of a multiplicative expression or an additive expression, depending on the range of concentration (varied or fixed) in which they work.

It should be noted that this process for the evaluation of measurement uncertainty is only valid when the analytical method is properly validated and is under statistical control. Bearing this in mind, it provides an estimated uncertainty that corresponds to the real uncertainty of the method and permits to overcome some shortcomings of more detailed and theoretical methods when there are steps whose uncertainty is difficult to estimate. In this procedure, the uncertainty associated with the intermediate precision is usually dominant.

Quantification of measurement uncertainty associated with precision

The standard uncertainty associated with the precision of the method was calculated from the sample standard deviation of the intermediate precision, with a variability of M intermediate precision factors (changing test conditions, e.g., operators, time and standard solutions) and n replicates

$$s_{I(M)} = \sqrt{\frac{1}{n-1} \sum_{k=1}^n (y_k - \bar{y})^2}$$

Since there is the need to work with a range of concentrations, it is common practice to use the relative standard uncertainty, which is estimated as follows [9],

$$u'_{I(M)} = \frac{s_{I(M)}}{\bar{y}}$$

Quantification of measurement uncertainty associated with accuracy

The quantification of the measurement uncertainty associated with the accuracy of the method is evaluated by analysing fortified samples (samples to which are added known amounts of analyte, commonly called recovery tests).

The standard uncertainty of recovery is therefore estimated by the standard deviation of the mean recoveries

$$u(\bar{R}_m) = s_{\bar{x}} = \frac{s_{\bar{R}_m}}{\sqrt{n}} \bar{R}_m$$

where the standard deviation of mean recoveries is divided by the number of recovery tests and multiplied by the mean recovery, due to the use of several samples at different concentrations [9]. The uncertainty associated with the preparation of the sample is considered negligible.

Quantification of the expanded measurement uncertainty

The calculation of the combined measurement uncertainty is based on the law of propagation of uncertainties (LPU). The relative standard uncertainty components, evaluated from the validation and quality control data of the method, are accounted as independent components of a multiplicative expression since the laboratory operates in different concentration ranges.

The combined standard uncertainty is given by the following expression:

$$u(y) = y \sqrt{(u'_{I(M)})^2 + (u'_R)^2}$$

Finally, the expanded measurement uncertainty, U , is obtained by multiplying a coverage factor corresponding to a confidence level of 95%, using the Welch–Satterthwaite formula [3] for the determination of the number of effective degrees of freedom of a Student's t -distribution.

$$U(y) = k u(y)$$

The effective number of degrees of freedom associated with k was $\nu_{\text{eff}} = 11$ in this case (resulting from a number of degrees of freedom for each uncertainty component of 10 and 11, for the precision and accuracy components, respectively).

Discussion of results

Results from the procedure associated with the validation and quality control method (QCM) were compared with

results from a methodology able to estimate the uncertainties associated with the use of a calibration curve produced by a limited number of experimental data, with the corresponding input uncertainties evaluated by the GUM method and MCM.

The comparison will be established for mass concentrations of SO_4 of 10 and 25 mg/L. Results from the QCM are displayed in Table 4.

It is worth pointing out that the value related to the SO_4 concentration of 10 mg/L was obtained in repeatability conditions, that is, same calibration curve, on the same day, with 10 independent flasks. On the other hand, the value related to the SO_4 concentration of 25 mg/L was obtained in conditions of intermediate precision along the year, from several calibration curves, thus reflecting a wider variability.

Applying the mathematical model developed for the calibration curve framework shows very similar results for the GUM and MCM approaches, which, for this application, validates the GUM uncertainty framework and its assumption of a Gaussian PDF for the measurand. This validation is pertinent according to previous reasoning, see also [5, 7]. Results are shown below in Table 5.

A comparison between Tables 4 and 5 clearly shows that there is a concentration level of SO_4 with comparable results, for the 25 mg/L value, and another concentration level, at the lower level of the concentration range, where the results differ significantly. This latter fact, however, is in line with previous caution remarks and is consistent with the theory of the least square method. In fact, as pointed out above, the QCM results for the 10 mg/L value were acknowledged as underestimated since they were only based on repeatability conditions associated with one calibration curve, whereas the other level of concentration reflected a much wider variability of conditions over a longer period of time. Moreover, a larger uncertainty near the extremes of the calibration curve and lower uncertainty

Table 4 Expanded measurement uncertainties evaluated by the QCM

Mass concentration SO_4 (mg/L)	Expanded uncertainty ($k = 2.25$) (%)	Expanded uncertainty ($k = 2.25$) (mg/L)
10	4.2	0.42
25	5.0	1.3

Table 5 Expanded measurement uncertainties evaluated from the calibration curve

Mass concentration SO_4 (mg/L)	Expanded uncertainty ($k = 2.00$) (%)	Expanded uncertainty ($k = 2.00$) (mg/L)
10	7.8	0.78
25	4.7	1.2

on the middle region of the calibration curve are expected, which is consistent with the results obtained.

One important point related to the application of the least squares method is that the observed chi-squared value, based on the sum of the squares of residuals from the linear regression, as shown in Figs. 2 and 3, is well below the 95% quantile of the chi-squared distribution for the same number of degrees of freedom, thus validating the assumption of a straight-line model. The residuals in x are too small to be shown in Fig. 2.

Another important point relates to the input uncertainty associated with digital signal of the equipment. Since our estimative was based on a limited number of readings, the assumed distribution should have been a Student's t -distribution instead of a normal distribution. The MCM can readily accommodate this change, and in Figs. 4 and 5, those differences are well illustrated. The different vertical scales in the two figures do not affect the comparison and conclusion to be drawn from them, regarding the shape of the distribution.

Figure 5 shows the normal distribution assumed in the simulations of the present study. The reason for this choice is related to the assumption of normality usually linked with least squares applications in the context of measurement, on the one hand, and also to the fact that it was not clear how to treat the available experimental data, since a rectangular distribution could also have been envisaged, having 10 sets of experimental data. Could one have worked with a smaller sample, with 5 data points, say? The difference in the output uncertainty value between a normal distribution and two possible Student's t -distributions with 4 or 9 degrees of freedom was evaluated and is about 9% when using the 5 data points set or about 2.7% for the 10 data points case, when the expanded uncertainty is obtained

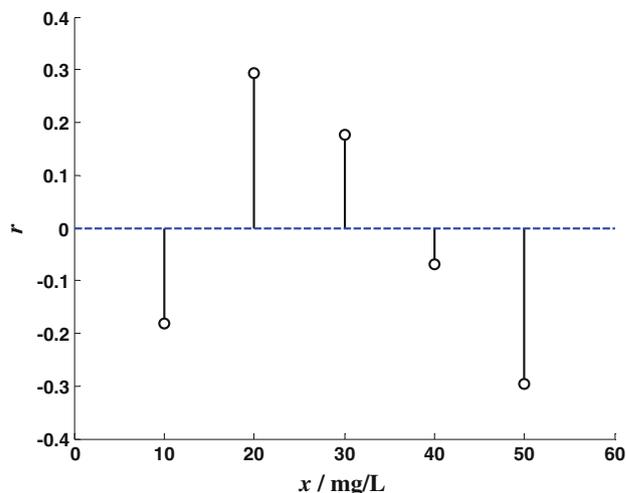


Fig. 2 Residuals from the linear regression assumption

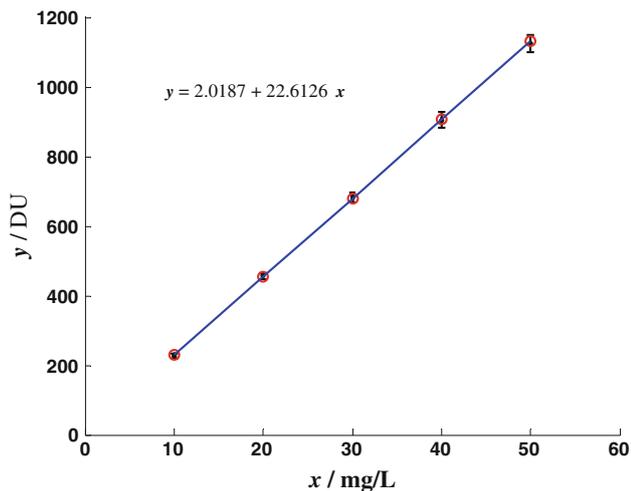


Fig. 3 Calibration curve obtained

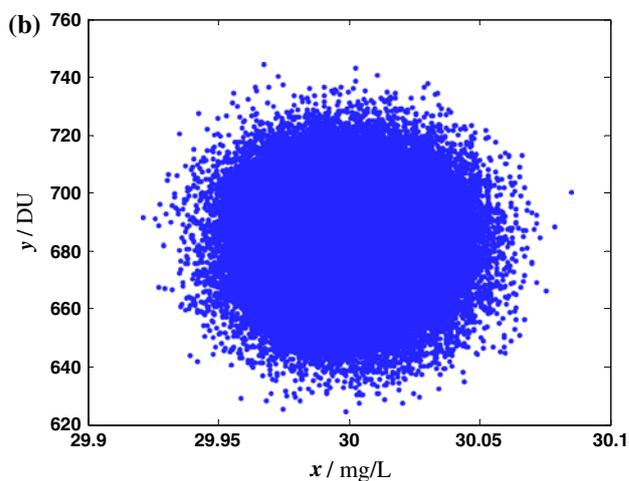
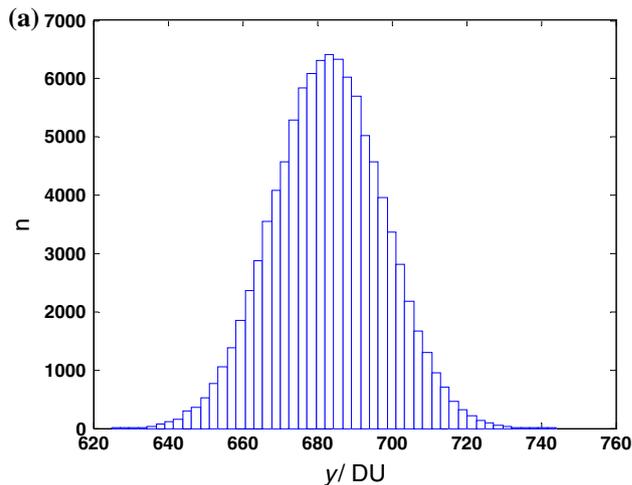


Fig. 5 a Histogram resulting from input normal uncertainty distribution for y. b Scatter points for both x and y input uncertainty distributions for 30 mg/L of SO₄

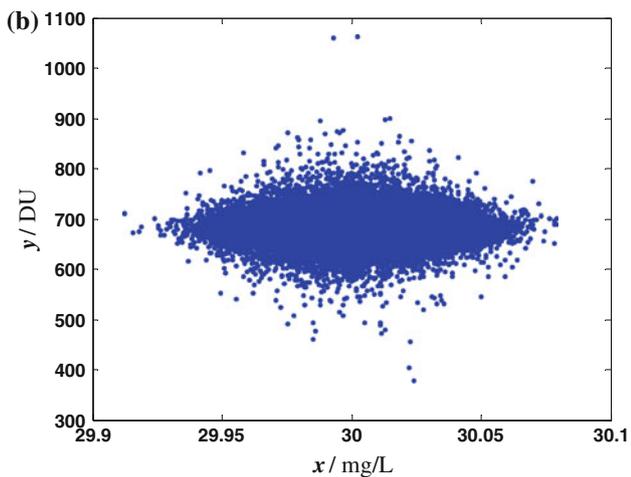
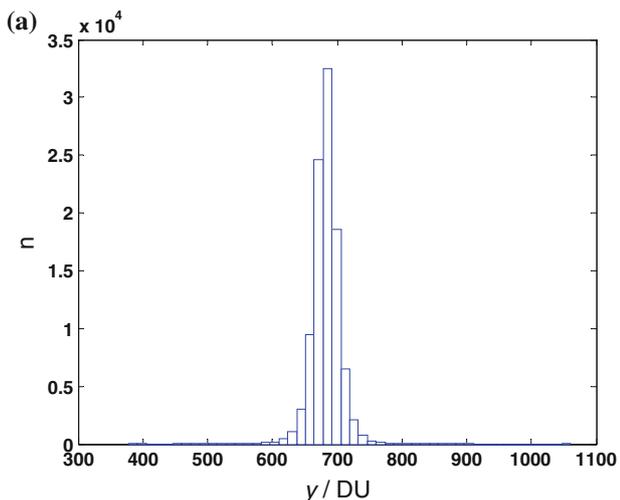


Fig. 4 a Histogram resulting from input uncertainty Student's *t*-distribution for y with 4 degrees of freedom. b Scatter points for both x and y input uncertainty distributions for 30 mg/L of SO₄

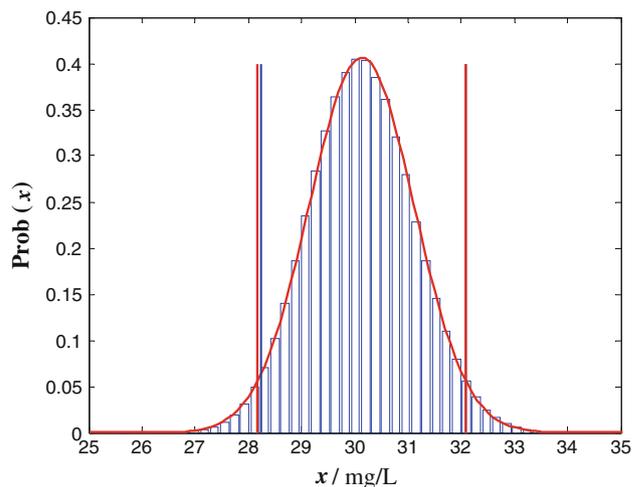


Fig. 6 Probability density function x based on a normal input distribution of y

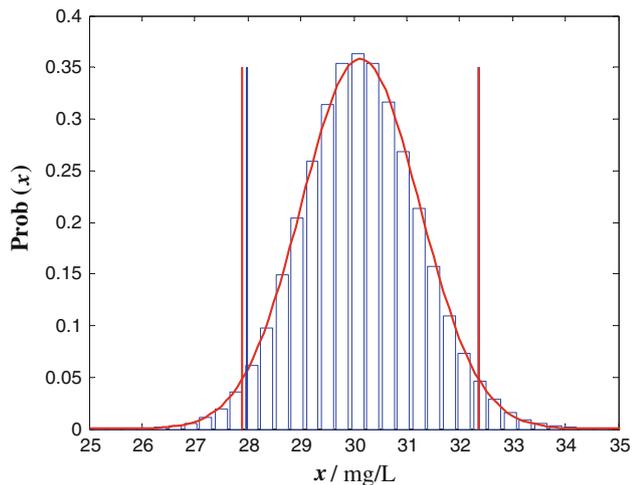


Fig. 7 Probability density function x based on a Student's t -input distribution of y with 9 degrees of freedom

by a coverage factor of $k = 2$, which is acceptable for this purpose.

The distribution assumed for the output quantity x is obviously normal, in line with the GUM uncertainty framework, but this assumption requires confirmation using a MCM technique, for both cases of a normal or a Student's t -input uncertainty associated with the input quantity y , as illustrated in Figs. 6 and 7. The impact on the output distribution is apparent, and it illustrates well one of the advantages of MCM. The assumption of normality can be misleading, and in the case of ratios, a validation procedure is mandatory, especially if the input distributions are not Gaussian [7]. In our case, the wider shape and wider tails of a Student's t -distribution are clearly shown, and although the mean value of the distribution is almost identical, there is a difference in the expanded uncertainty interval of about 10%, which indicates that the number of readings used to estimate the input uncertainty associated with the y values should be selected carefully, on the one hand, and that the GUM uncertainty framework can underestimate the expanded confidence interval if the output distribution departs from a Gaussian condition.

Conclusions

The present study was able to implement an adequate methodology to evaluate the measurement uncertainties entailed by the use of calibration curves. The application was supported by experimental data supplied by analytical

chemistry testing of sulfate in water samples, and the results clearly show the adequacy of the implemented procedure.

This relatively simple procedure requires a reliable estimate of the uncertainties characterizing the variability of values in both coordinate axes and is able to produce results comparable to methods requiring much longer periods of time in testing and are therefore more costly.

The GUM uncertainty framework can be applied to the type of mathematical formulation found in this example, but the number of readings on which the uncertainty of the equipment digital signal is evaluated should always be kept above 10 and should, preferably, be increased to guarantee that the input distributions have a normal or quasi-normal distribution.

This study will be extended to include second-order calibration curves and exponential calibration curves and also analytical processes with greater manipulation stages, for example samples digestion and distillation, in order to characterize the influence of these in the overall measurement uncertainty.

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